ECTRIMS 2022 – ePoster

Clinical aspects of MS - Diagnosis and differential diagnosis

EP0800

Diagnostic wandering in multiple sclerosis highlights the need for increased physicians' alertness

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Introduction: Multiple sclerosis (MS) is a highly heterogeneous disease in terms of clinical and MRI presentation, as well as prognosis for individual people. Timely diagnosis is of importance in MS, as it is linked with favorable long-term outcomes.
Aim - Objectives: To describe the patients' diagnostic wandering, that is, the care pathway of patients until the diagnosis of MS, to measure the delays in the diagnosis, as well as to identify the factors that contribute to diagnostic delay in MS
Methods: An online questionnaire was administered by the Hellenic Academy of Neuroimmunology (HEL.A.NI.) site regarding demographics, self-reported patient determined disease steps (PDDS) score, year of diagnosis, diagnostic delay and number and the specialty of medical health providers implicated prior to the diagnosis by a Neurologist.
Results: Eighty-five people with MS (PwMS) (m:f 24:61, mean age ± standard error of mean: 41.32 ± 1.17) participated. MS was diagnosed from 1980 to 2021. The mean diagnostic delay was 7.04 ± 1.71 months [range 0.5–84]. The year of diagnosis exhibited a negative correlation with the diagnostic delay (Spearman's rho: -0.244; p=0.026). Twenty-two (26%) of PwMS visited physicians of at least two other medical specialties prior to their referral to a Neurologist. Binary logistic regression indicated that initial examination from medical providers other than neurologists was linked with diagnostic delay equal to or longer than 6 months (for the overall model R square: 0.167, p=0.061, for initial examination from other specialties p=0.035).
Conclusions: We hereby provide evidence of an overall reduction in diagnostic delay in MS over time. However, physicians need to be highly alert in order to timely refer the patient to a Neurologist, following the initial evaluation.

Disclosure
All authors have nothing to disclose.

EP0801

Limited diagnostic utility of serologic testing in the evaluation for multiple sclerosis and its mimics: a single-center observational study

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Background: The clinical evaluation of a new diagnosis of MS typically includes serologic testing to evaluate for its many mimics, yet there is little data to guide approaches to such testing.
Methods: In a single MS subspeciality center retrospective study, new patient evaluations for MS over the course of a year were identified, and the results of serologic testing and diagnostic evaluation extracted. Retrospective longitudinal diagnostic assessment was performed to confirm the accuracy of initial of serological testing assessments.
Results: 150 patients were identified. 823 serologic tests were completed.73 (49%) patients were diagnosed with a demyelinating disorder. There were 40 (5%) positive tests, 38(95%) were assessed as false positives, and two true positives occurred in patients with known pre-existing rheumatologic diagnoses. Positive serologic testing results led to an additional 117 serum tests, 10 radiographs and 2 biopsies. There was no change in diagnosis in any patient as the result of serologic testing.
Conclusions: Serologic testing in the clinical assessment for MS resulted in unnecessary diagnostic delay, additional testing, and considerable healthcare cost.Optimal approaches to diagnostic serologic testing in MS may be best guided by the identification of clinical and radiographic "red flags" suggestive of specific disorders.

Disclosure
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Colin Lyness, MD,**Jessica Piche, MD**, and **Benjamin Stewart, MD**, have no reportable conflicts of interest.

EP0802

Potential use of biomarkers in the family members of new untreated relapsing-remitting multiple sclerosis for early diagnosis of multiple sclerosis

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Introduction: Multiple sclerosis is a neuroinflammatory autoimmune disorder of the central nervous system. The pathogenic function of Receptor for advanced glycation end products (RAGE), Apolipoprotein A1 (Apo-AI), and High mobility group box1 (HMGB1) in the breakdown of the blood barrier, and neuroinflammatory diseases such as multiple sclerosis have been reported.
Objectives: This research aimed to use an enzyme-linked immunosorbent assay (ELISA) to measure plasma levels of S100A12, Apo-A1, and western blot to measure HMGB1plasma levels. Thirty-five new cases of untreated patients with deterministic relapsing-remitting multiple sclerosis (RRMS) according to the McDonald criteria, twenty-four healthy controls (HC), and twenty-six family members of untreated RRMS (termed them as a high-risk group) were entered into the study.
Aims: Achieve a proposed method for early assessment and diagnosis of MS in people at high risk before the onset of the disease.
Results: In the new cases of untreated RRMS ($P<0.05$; 0.045) and high-risk ($P<0.05$; 0.001) groups, the plasma level of S100A12 was dramatically lower. Although the plasma level of Apo-A1 decreased markedly in the high-risk group ($P<0.05$; $P=0.003$) compared to the HC group, there was no significant difference in the untreated RRMS patients ($P=0.379$). The plasma level of HMGB1 was significantly higher in the untreated RRMS patients ($P<0.05$; $P=0.063$) compared to the HC group, but there was no notable difference in the untreated RRMS patients ($P=0.571$). Vitamin D3 was considerably reduced in both RRMS and high-risk groups.
Conclusion: Our findings suggested that these biomarkers could be one of the contributing elements in the pathogenesis of MS, based on an earlier study that revealed their significance in inflammatory processes and plasma alterations in family members based on our research. However, their practical applicability as a prognostic biomarker will take more research and testing.

Disclosure
Mahsa Samangooei declares that she has no conflict of interest.
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EP0803

Blood platelet RNA as biomarker for the detection of early stage multiple sclerosis

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Introduction: We previously demonstrated aberrant blood platelet RNA profiles in multiple sclerosis (MS), providing a potential biomarker for distinguishing MS patients from healthy individuals. However, the utility of blood platelet RNA profiling in detecting early stage MS versus other (neuroinflammatory) disorders that mimic MS has not been investigated.
Objectives: This prospective validation study examines the diagnostic capacity of spliced blood RNA platelet profiles in a cohort of patients with early stage MS, non-MS patients with diagnoses that mimic MS and healthy controls (HCs).
Methods: Patients were selected from a population that was referred to the Amsterdam MS Center for a second opinion regarding possible diagnosis of MS. Platelet RNA of blood samples from 61 MS patients, 21 non-MS patients and 24 HCs were isolated and sequenced. In the first step of our approach, ANOVA analysis was used to determine differentially expressed genes ($FDR < 0.05$) which were visualized in a heatmap using unsupervised clustering, and subsequently analysed using a PCLDA model. Additional analysis will be conducted.
Results: The ANOVA comparing MS patients with HCs yielded 2546 genes, while non-MS versus HCs identified 3377 genes. The ANOVA comparing MS patients and non-MS patients yielded no genes with an $FDR < 0.05$, therefore we opted for a p-value < 0.05 yielding 143 genes. PCLDA modelling generated three models: HCs versus MS patients (accuracy/ROC: 1.0/1.0), HCs versus non-MS patients (accuracy/ROC: 1.0/1.0) and MS patients versus non-MS patients using a p-value cutoff (accuracy/ROC: 0.833/0.868).
Conclusions: Our preliminary data suggests that spliced platelet RNA is of potential diagnostic value for the detection of early stage multiple sclerosis. However, the current dataset contains a low number of samples in the non-MS and healthy donor groups. Further analysis will be conducted aimed at increasing the number of non-MS patients and HCs included to further investigate the

ability of spliced platelet RNA to differentiate between MS and non-MS patients.

Disclosure
FL, EP, MB report no disclosures. TW is shareholder of Illumina. JK reports speaker and consulting fees and grants from Biogen, Celgene, Genzyme, Immunic, Merck, Novartis, Roche, Sanofi and Teva. This work was funded by a grant from Merck.

EP0804

Leber hereditary optic neuropathy-plus syndrome mimicking a neuro-inflammatory disorder

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Introduction: Leber Hereditary Optic Neuropathy (LHON) is a mitochondrial disorder that leads to vision loss. LHON-Plus (+) describes a variant with features that can mimic neuroinflammation.
Objectives: To discuss LHON+ syndrome mimicking neuro-inflammatory disease.
Aims: N/A
Methods: Diagnostic use of Rapid Genome Sequencing in the Critical Care Unit.
Results: A 17-year-old male presented with 2 months of progressive vision and hearing loss. Workup of optic neuritis included Brain Magnetic Resonance Imaging (MRI) showing symmetric, non-enhancing T2 hyperintensities of the area postrema (AP), pontine reticular formation, and periaqueductal gray matter. Neuromyelitis Optica (NMO) and Myelin Oligodendrocyte Glycoprotein (MOG) testing were negative. Some clinical improvement without full recovery occurred concomitant with a five-day course of intravenous (IV) methylprednisolone. One year later the patient presented with transient severe hypertension, acute headache, and worsening vision associated with focal seizure activity. Imaging revealed progression of brainstem lesions and new bilateral vasogenic edema consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Imaging findings improved after five days of IV methylprednisolone; however, he had persistent bilateral dense central scotomas and dyschromatopsia. Cerebral spinal fluid infectious studies were negative. Autoimmune encephalopathy panel, repeat NMO and MOG cell-based assays were negative. Because of a family history of visual loss of unclear etiology in a paternal grandfather, rapid genomic sequencing testing was sent and identified homozygous nonsense variants in the nuclear-encoded mitochondrial DNAJC30 gene (c.24G>A; p.W8X) associated with LHON. Treatment with idebenone was initiated. This case shows that LHON+ syndromes can mimic neuro-inflammatory conditions with neuroimaging findings including brainstem T2 hyperintensities with AP involvement. To our knowledge, only three patients with DNAJC30 variants have previously been reported to have MRI brain abnormalities. LHON+ mimicking NMO has previously been reported with a mitochondrial genome variant (m.14484T>C). RPLS with LHON has been previously reported associated with m.11778G>A.
Conclusions: LHON+ should be considered in patients with atypical progressive optic neuropathy and concomitant non-enhancing symmetric imaging findings involving the AP, particularly if symptoms are unresponsive to immunotherapy.

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EP0805

Anti-neurochondrin antibody as a potential biomarker in primary autoimmune cerebellar ataxia – a case report

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Introduction: Primary autoimmune cerebellar ataxia (PACA) is a rare disease. In a subgroup of patients, neuronal autoantibodies can support the diagnosis.
Objectives: Presenting a case of anti-neurochondrin antibody associated PACA.
Methods: Written informed consent for this case report was given.
Results: A 33-year-old male first noticed 05/20 a reduced control of the right leg. At first consultation at our hospital 09/21, he complained of gait imbalance, fine motor skill deficits, intention tremor, intermittent diplopia and slurred speech. Clinically, he presented a pancerebellar syndrome with stance, gait and limb ataxia, scanning speech and oculomotor dysfunction. Within three months, symptoms were progressive, he could only walk with a rollator. Whereas initial cerebral magnetic resonance imaging (MRI) in 06/20 was normal, follow-up imaging in 10/21 revealed a marked cerebellar atrophy. Cerebrospinal fluid (CSF) analysis showed a mild lymphocytic pleocytosis of 11 M/L (normal range 0-4), and oligoclonal bands type II. Anti-neurochondrin antibodies (IgG) were detected in serum (1:10'000) and CSF (1:320, by cell-based indirect immunofluorescence assay (IFA) and immunoblot, analysed by EUROIMMUN laboratory). After ruling out alternative causes and neoplasia (tumour screening by blood analysis, whole body computer tomography, abdominal MRI, testicular ultrasound, gastro-/coloscopy, FDG-PET scan), a diagnosis of PACA was established and immunotherapy (steroids and cyclophosphamide) was started in 01/22. In 05/22, except for a slight progression in oculomotor disorders, a stabilization of disease was observed.

Conclusions: Cerebellar ataxia associated with anti-neurochondrin antibodies has only been described in 14 cases; however, the number of unrecognised cases with PACA may be higher. As anti-neurochondrin antibodies target an intracellular antigen and exhibit a mainly cytotoxic T cell mediated pathogenesis, important therapeutic implications may result. Because of the severity and rapid clinical progression of the presented case, an aggressive and prompt immunotherapy was warranted. This case highlights the need for rapid diagnosis and therapy in PACA, as stabilization and even improvement of symptoms is attainable.

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- **Schwarzwald A** has no conflicts of interest to disclose.
- **Chan A**has served on advisory boards for, and received funding for travel or speaker honoraria from, Actelion-Janssen, Almirall, Bayer, Biogen, Celgene, Sanofi-Genzyme, Merck, Novartis, Roche, and Teva, all for hospital research funds; and research support from Biogen, Genzyme and UCB. Chan A is associate editor of the European Journal of Neurology and serves on the editorial board for Clinical and Translational Neuroscience and as topic editor for the Journal of International Medical Research. He reports no conflicts of interest related to this manuscript.
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EP0806

Validation of McDonald 2017 multiple sclerosis diagnostic criteria in patients with a first demyelinating event in Argentina

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Introduction: In the absence of a specific diagnostic test for Multiple Sclerosis (MS), diagnostic criteria have been developed. They have been through several modifications, the last one in 2017, to reach a more accurate and early diagnosis. Unfortunately, evidence about their applicability in Latin America is scarce.
Objectives: To validate the 2017 McDonald diagnostic criteria in patients with a first demyelinating event (FDE) in Argentina and compare the diagnostic precision with the criteria developed in 2010, in the same cohort.
Methods: Retrospective cohort of patients who consulted in a neurological center of reference in Buenos Aires from 2003 to 2019. Adult patients with a FDE under 55 years of age were randomly selected, and evaluated clinically and radiologically 3 months after the onset of symptoms, with a time minimum follow-up of 2 years. Demographic and clinical variables, oligoclonal band status, and MRI characteristics were recorded. Clinically defined MS (CDMS) was defined as the gold standard for subsequent calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the 2017 and 2010 diagnostic criteria in this cohort.
To compare global precision of 2010 vs. 2017 criteria, patients diagnosed by criteria 2017 were assumed as cases to build the models and were explored through a logistics regression analysis, its comparison through Akaike information criterion (AIC) and the calculation of area under the curve (AUC) with their respective CI95%.
Results: We included 120 patients with a median follow-up time of 4,8 years (IQR 1-3: 2,5-8,5), 66,7% were women, and median age at consultation was 31 years-old. Conversion to CDMS was reached in 39% of cases. The prevalence of MS according 2017 and 2010 diagnostic criteria was 74% and 45%. Performances of diagnostic criteria were: sensitivity 76,6 vs 41%, specificity 26,4% vs 41%, PPV 40,4 vs 50% and NPV 63.3 vs 32% for 2017 and 2010 criteria, respectively. In addition AUC for 2017 and 2010 diagnostic criteria were 95.9% (CI95% 91.3-100%, AIC=38.7) and 88% (CI95% 81%-94%, AIC=84.5).
Conclusions: The use of 2017 diagnostic criteria increases the possibility of diagnosing MS in our cohort with significantly better performance than the 2010 criteria. The effect of early treatment could have biased the reduced specificity.

Disclosure

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EP0807

Persistent central and peripheral nervous system inflammation following Johnson & Johnson vaccine: a case series

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Introduction: Transverse myelitis has previously been reported following administration of the Johnson and Johnson (J&J) vaccine against SARS-CoV-2. Brain and peripheral nervous system involvement is less well described.
Aims/Methods: We report on a case series of 3 patients who developed neuro-inflammation following administration of the J&J vaccine (Ad26.COV2.S). Spinal cord was involved in all 3 patients, brain – in 2, and peripheral nervous system involvement (facial nerve enhancement, radiculitis) in 2.
Results: Case 1: A 43F developed progressive gait difficulty and ascending paresthesias in bilateral lower extremities ~4 weeks after J&J COVID-19 vaccination. MRI revealed multiple enhancing cervical and thoracic cord lesions and 1 small enhancing subcortical brain lesion. Workup included extensive serum and CSF testing that was unremarkable, except for matching bands in CSF and serum. 3 months later she developed symptom recurrence with persistent enhancement and enlargement of one cord lesion.
Case 2: A 39M developed bilateral ascending numbness, tingling, gait instability, urinary hesitancy/urgency and bilateral peripheral facial weakness 10 days after J&J COVID-19 vaccination. MRI revealed bilateral facial nerve enhancement, patchy cervical and thoracic cord and cauda equina enhancement. CSF revealed lymphocytic pleocytosis and elevated protein, with no oligoclonal bands. Extensive serum/CSF testing was otherwise unremarkable. Patient developed recurrent symptoms during steroid taper 3 months later; MRIs showed persistent enhancement and enlarging lesions.
Case 3: A 34F developed blurred vision, body aches, paresthesias and urinary retention 2 weeks after J&J COVID-19 vaccination. MRI revealed large, mostly enhancing fluffy occipital/parietal lesions, cervical lesion, longitudinally extensive thoracic lesion and lumbar nerve root enhancement. CSF revealed neutrophilic pleocytosis and elevated protein. 3 months later she developed new enhancing brain lesions with persistent enhancement in the spine.
Conclusion: Our case series highlights that central and peripheral nervous system inflammatory involvement without clear alternative explanation can rarely be seen in close temporal relationship to administration of the J&J COVID-19 vaccine. Unusual feature of our cases was clinical/radiographic worsening and persistent enhancement several months after initial presentation.Two patients required second-line immunotherapy for disease control.
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EP0808

The prospective acute optic neuritis network

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Introduction: The visual outcomes following multiple sclerosis (MS)-, neuromyelitis optica spectrum disorder (NMOSD)- and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)-optic neuritis (ON) differ significantly. In contrast to MS-ON, patients with NMOSD- and MOGAD-ON present with more severe vision loss and can carry a high rate of permanent visual loss. While many NMOSD and MOGAD studies reported to date have focused on relapse reduction, overlooking the aim to improve the immediate outcome following an acute ON attack, prior retrospective studies suggest that early steroid treatment may improve visual outcomes following the first presentation of NMOSD- and MOGAD-ON.

Objectives: To identify diagnostic markers for early disease stratification and to improve treatment of acute ON.

Aim: To set up an international multicenter network to longitudinally study patients with acute ON with the aim to investigate factors associated with favorable visual outcome in acute ON secondary to distinct demyelinating disorders.

Methods: Inclusion of patients with a first episode of acute ON. Each participant will receive acute in-person visits and annually thereafter with multimodal standardized assessments of medical history, disability staging, visual outcome measures, structural imaging of the neuroaxis and retina and extensive sampling of biological specimens.

The following centers will participate in the Acute Optic Neuritis Network:

- Charité University Hospital, Berlin, Germany
- Rabin Medical Center, Tel Aviv, Israel
- University of Southern Denmark, Odense, Denmark
- Lyon University Hospital, Lyon, France
- University of Oxford, UK
- University of Verona, Italy
- Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
- Mayo Clinic, Rochester, Minnesota, USA
- Concord Hospital, Sydney, Australia

Results: The Acute Optic Neuritis Network will investigate multiple key aspects of acute ON outcomes, including the distinct immunophenotypes and clinical profiles of each disorder, correlations between functional impairment and structural change, trajectories of change for different biomarkers over time and, importantly, treatment effects and determinants of long-term disease course.

Conclusions: The Acute Optic Neuritis Network has the potential to contribute to a better understanding of MS-, NMOSD- and MOGAD-ON with a substantial improvement in treatment strategies and final visual outcomes.

Disclosure

COIs

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Alon Tiosanoreports no COIs.
Adi Wilf-Yarkoni reports no COIs.
Nasrin Asgari reports no COIs.
Caroline Froment Tilikete reports no COIs.
Romain Marignier serves on scientific advisory boards for Alexion, Horizon Therapeutics, Roche, and UCB and has received speaker honoraria from Alexion, Biogen, Horizon Therapeutics, Novartis, Roche and Sanofi Genzyme.
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John Chen, MD, PhD is a consultant to UCB, Roche, and Horizon, unrelated to this submitted work.
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EP0809

Alternative diagnosis in first-line referral for suspected MS

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Background: Multiple sclerosis (MS) misdiagnosis is common, more so with the regular use of MRI for various symptoms and the subsequent identification of white matter lesions. Misdiagnosis leads to serious consequences for patients, such as anxiety, insurance issues, adverse events from investigation and treatment, as well as an increased burden on health care systems with unnecessary visits and exams, higher costs and decreased MRI availability.
Objectives: To assess the frequency and predictors of early misdiagnosis and identify alternative diagnosis in patients with suspected MS evaluated by neurologists.
Methods: We reviewed all MS referrals from January 1st to December 31st 2018. A unique regional referral system, catching all first-line referrals, allows the inclusion of all eligible patients during this period. We extracted patients' clinical characteristics, referral symptoms, prior brain MRI, subsequent investigations and final diagnosis.
Results: 121 patients were referred by their general practitioner over 12 months. Of these, 103 (85%) were referred for diagnosis confirmation, 15 (12%) for follow-up of a previously diagnosed MS patient and 1 (1%) referred for a relapse in a previously diagnosed MS patient. MS diagnosis was confirmed in 12/103 patients (12%) with MS suspicion and 13/15 patients (81%) in previously diagnosed MS. Overall, 94/121 (78%) had an alternate diagnosis. Only 2% were diagnosed with radiologically isolated syndrome. The most common alternative diagnosis were non-specific sensory symptoms (38%), musculoskeletal injuries (13%), peripheral nerve lesions (7%) and headaches (7%). 98 patients (81%) had a MRI prior to neurology consultation. Of those, 51 (52%) had non specific cerebral white matter lesions and 19 (19%) had normal MRI. Interpretation by a neuroradiologist yielded higher probability of MS diagnosis (32%) compared to interpretation by a general radiologist (9%) ($p=0.01$). Lumbar puncture was performed in 20 patients (17%). Oligoclonal bands (OCB) were present in 8 patients, all diagnosed with MS, except one. The 12 OCB-negative patients did not have a MS diagnosis at follow-up.
Conclusions: Our study shows that 78% of patients referred by their general practitioner for suspected MS had a different diagnosis after neurological evaluation. Specific findings on MRI and CSF help making the diagnosis. Strict application of diagnostic criteria, especially in the context of typical MS syndromes, is paramount.

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EP0810

Onset of various CNS inflammatory demyelination diseases following COVID-19 vaccinations

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Introduction: Since the start of COVID-19 vaccination worldwide, there have been several reports of inflammatory demyelinating disease in CNS (CNS-IDDs) following vaccination. However, case studies of CNS-IDDs following COVID-19 vaccination are still lacking, especially in the Asian population, and the proportion of CNS-IDDs cases having a temporal relationship with COVID-19 vaccination has not been provided.
Objectives & Aim: Report cases of new-onset CNS-IDD following COVID-19 vaccination and investigate the frequency of post-vaccinal CNS-IDDs among newly registered cases of CNS-IDDs in National Cancer Center (NCC) registry.

Methods: We prospectively collected new-onset CNS-IDDs cases with a temporal relationship between the disease onset and COVID-19 vaccination, and investigated its proportion among newly registered patients with CNS-IDD from March 2021 to March 2022.
Results: During the study period, 117 patients were newly registered in the CNS-IDD cohort. Of these patients, ten (8.5%) were diagnosed as having CNS-IDDs with a temporal relationship with COVID-19 vaccination, and all of them were new-onset patients: two with MS, two with AQP4-IgG-positive NMOSD, three with MOGAD, and three unclassified CNS-IDDs (two with seronegative isolated optic neuritis, and one with seronegative myelitis). They developed neurological symptoms after the first (n = 4), second (n = 5), or third (n = 1) dose of COVID-19 vaccination (BNT162b2, n = 4; mRNA-1273, n = 4; ChAdOx1 nCoV-19, n = 2) with a median interval of 6.5 (range, 3–28) days after vaccination. At onset, the mean age was 36.5 years (range, 22–67 years), and the male-to-female ratio was 4:6.
The most common phenotype in patients with CNS-IDD after COVID-19 vaccination was optic neuritis (n=6, 60%), and the remaining four presented with encephalomyelitis, longitudinal extensive transverse myelitis, multifocal short-segment myelitis, and single demyelinating CNS lesion (medulla).
Conclusions: We report ten cases of new-onset CNS-IDD following COVID-19 vaccination in the past year. Among the newly registered patients with CNS-IDDs in the NCC cohort, 8.5% of them showed a temporal relationship between the disease onset and COVID-19 vaccination, and they manifested with diverse types of CNS-IDDs, regardless of the vaccine type or order. This observation suggests that COVID-19 vaccination may trigger the onset of various CNS-IDDs in susceptible individuals.

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Clinical aspects of MS - Pregnancy in MS

EP0811

Motherhoodmotherhood choice in multiple sclerosis (MoMS) – feasibility and pilot study of two decision support programmes choice in multiple sclerosis (MoMS) – feasibility and pilot study of two decision support programmes

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Introduction: Motherhood is an important topic for many women with multiple sclerosis (wwMS). Thus, a decision support tool (DST) and a Decision Coaching Programme (DCP) for wwMS considering pregnancy were developed to support their decision-making. Both programmes consist of a decision aid on motherhood choice in multiple sclerosis (MS).
The DCP includes a nurse-led coaching session as a key component. We evaluated the feasibility of the DST and DCP.
Methods: We assessed prototypes of the programmes for feasibility with wwMS, an expert patient, MS experts and researchers. For the following pilot study, we recruited wwMS considering pregnancy via social media and newsletters and trained 2 nurses for the DCP. We used qualitative (interviews) and quantitative methods (questionnaires) during feasibility testing. All interviews were recorded, transcribed and analysed using qualitative thematic analysis. Questionnaires were analysed descriptively. Decisional conflict was measured as an explorative primary outcome in the pilot study using the Decisional Conflict Scale (DCS; 0-100). High values indicate a high decisional conflict. We analysed involvement in decision making in the DCP group using the Multifocal Approach to the Sharing in Shared Decision Making (MAPPIN'SDM) via questionnaires and audios.
Results: In the feasibility study, we conducted 2 focus groups (n=7), 1 individual interview with wwMS, and 5 expert interviews. Results indicated the feasibility of both programmes and provided information for optimizing the DST and DCP. 36 wwMS were recruited and randomised unequally (DST n=23; DCP n=13). Follow-up data was available for 30 wwMS (DST n=19; DCP n=11). In the DST group, the mean DCS score was 56 at baseline and 34 at follow-up. In the DCP group, the mean DCS score was 49 at baseline and 20 at follow-up. MAPPIN'SDM assessment showed good levels of involvement in the DCP group. We interviewed 11 wwMS (DST n=5; DCP n=6), who described the programmes as user-friendly. Results suggest that the DCP group was more satisfied and that the coaching session was helpful. Nurses stated that they appreciated their role and received positive feedback.
Conclusions: Both programmes are feasible and acceptable. The DCP needs more resources, but might provide more confidence in the decision-making process than the DST alone and might offer an attractive role for MS nurses. The effectiveness of both programmes should be evaluated in a randomised controlled trial.

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EP0812

Anxiety and serum cortisol levels during pregnancy in multiple sclerosis: a prospective cohort study

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Introduction: Existing literature indicates that anxiety is more prevalent in people with multiple sclerosis (pwMS). Furthermore, anxiety is more prevalent during pregnancy in healthy women.
Objective and Aims: To explore if there was any difference in the prevalence of anxiety in pwMS and healthy women (HCW)during pregnancy.
Methods: We consecutively included 25 pregnant pwMS and 30 HCW, followed at Hospital Universitario Gregorio Marañon between 2018 and 2022. To asses anxiety, twoSpanish-validated tests were used ((State-Trait Anxiety Inventory (STAI) and PregnancyRelated Anxiety Questionnaire Revised(PRAQ-R2)). Additionally, serum cortisol levels were measured during the first trimester of pregnancy in the pwMS cohort in order to asses its correlation with the anxiety profile. Statistical analysis was performed by non-parametrical Mann–Whitney Utest and theSpearman correlation coefficient.
Results: No statistically significant differences in age and educational level were observed between pwMS and HCW.
The trait scores were found normal in both groups (median score in pwMS 26, IQR [21-30] and HCW 24 (IQR [20-26]).In the state scores, both groups showed high levels of anxiety (median score in pwMS 50 (IQR [43-52] and HCW 50, IQR [40-56]. In PRAQ-R2, pwMS scored a median of 20, IQR [14-24] and HCW median of 21,5 IQR [15-26], both groups within normal range. Serum cortisol levels did not show any correlation with none of the anxiety scores.
Conclusions: The profile of anxiety was similar in HCW and pwMS. Both groups showed high levels of perceived anxiety during the first trimester of pregnancy, suggesting that pregnancy itself could be a trigger for anxiety, independently of MS. Cortisol serum levels did not correlate with self-reported anxiety levels in our study. Therefore, the use of patient reported outcomes related to emotional state could be helpful.

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EP0813

Situation of breastfeeding in multiple sclerosis – a questionnaire survey in Germany

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Introduction: According to the World Health Organization recommendation, breastfeeding should be intensively promoted due to its various health benefits. Many female patients with multiple sclerosis (MS) are in childbearing age, so family planning, delivery and breastfeeding are important issues for them. Few data exist on the attitude towards breastfeeding in MS patients.
Objectives and aims: The aim of this study was to analyze breastfeeding rate, duration of breastfeeding, reasons for weaning and the impact of disease severity on successful breastfeeding in MS. Furthermore, the extent of education about breastfeeding and multiple sclerosis was assessed.
Methods: Data were collected between 02/2019 and 11/2021 by questionnaire. The study included patients with multiple sclerosis who gave birth within three years before study participation. Fisher´s exact test and descriptive analysis were used for evaluation.
Results: In our study, 62 patients giving birth to 64 children were included. Compared to published data, we found a significant difference (p = 0,0007) between the nursing rate in the general population (96,6 %; Kersting et al., 2020,http://www.dge.de/14-dge-eb/vvoe/kap3) and women with MS (85,9 %). However, a higher rate of exclusive breastfeeding could be observed in our study population with exclusive breastfeeding for 5-6 months in 40,6% of MS patients vs. 8.3 % in the general population. Reasons for weaning were predominantly (68,7 %) related to breastfeeding barriers based on multiple sclerosis. Unexpectedly, no significant impact of pre- or postpartum education and breastfeeding rate could be observed. Prepartum relapse rate and prepartum disease modifying drugs (DMDs) had no effect on breastfeeding success.
Conclusions: Our survey provides an insight of the situation of breastfeeding in MS patients demonstrating a lower nursing rate, but higher rate of exclusive breastfeeding than in the general population. Currently, an increasing number of DMDs may be used while breastfeeding according to their approval.This in conjunction with patient education, especially regarding frequent and avoidable reasons for weaning, may result in higher breastfeeding rates, making more children and mothers benefit from the health-related advantages of breastfeeding.

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EP0814

Perspectives of health care providers concerning current practice in supporting women with multiple sclerosis in reproduction and treatment decisions

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Introduction: MS more commonly affects females than males, and often first causes symptoms in women of childbearing age. This makes treatment decisions even more complicated for both women with MS and their health care providers (HCPs).
Objectives: Explore the role HCPs play in supporting women in their decisions about treatment and family plans, and the challenges they face when providing this service.
Aim: Improve the experience of the decision making process for both women and HCPs by exploring the current practice.
Methods: Semi-structured, online interviews with key HCPs supporting women with MS, (1 pharmacist, 2 nurses and 5 Neurology Consultants) from different hospital services across the UK. Interviews were conducted using Microsoft Teams. Transcripts were autogenerated by Microsoft Stream and thematically analysed.Four fundamental areas were discussed with HCPs which are, (current practice, resources, decision making approach and challenges).
Results: Only one hospital service have a formalised dedicated service to support women in decisions about disease modifying drugs (DMD) choice related to family plans. It showed clearly how standardisation created a clear pathway and specific role for each healthcare provider to follow and more time to educate and discuss details with women compared to other practices. HCPs also talked about the scarcity of lay language resources for patients, as well as accessible resources for HCPs. When talking about challenges, managing clinically active patients, unplanned pregnancies, DMDs off-label use and its level of acceptance by women, and lack of resources such as time, staff and information were reported.
Conclusion: DMD choice and family planning is a very important aspect of MS care. However, my findings indicated that it is usually delivered in a non-standardised manner which creates variability in care. Formalization of a service run by multidisciplinary team to support women with these decisions, is lacking due to shortage in different resources.

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EP0815

The UK MS pregnancy register: baseline data from the first 83 enrolled participants

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Background: The UK MS Pregnancy Register is a patient-facing pregnancy register collecting information directly from women

with MS during pregnancy, with follow-up data on pregnancy outcomes. Recruitment opened in Autumn 2021. We present baseline data on the first 83 participants enrolled.
Methods: Data collected via online questionnaires from consenting participants until 6th May 2022 were included.
Results: 83 participants (82 relapsing remitting, 1 secondary progressive MS; mean age of symptom onset 26.4 years; mean age at diagnosis 28.3 years; mean current age 30 years) were included. Median webEDSS on the most recently completed questionnaire was 3.0 (n=27). Gestation at recruitment ranged from 2 to 40 weeks. 79.5% reported discussing their pregnancy in advance with their MS team. This discussion occurred most frequently when considering pregnancy (51.8%), followed by when starting DMT (34.9%) and at the time of diagnosis (26.5%). 65% and 61.4% of participants had this discussion with their Neurologist and MS Nurse respectively.
90.3% of patients had ever taken DMT. Of the patients that had stopped DMT (n=39), 41% stopped prior to (n=16) and 30.8% following conception (n=12). 23 women are continuing DMT during their current pregnancy: Glatiramer acetate (8), Natalizumab (9), Peginterferon beta-1a therapy (3), not reported (3). Eleven women plan on stopping their DMT at some point during their pregnancy and two were undecided at the time of completing the questionnaire.
In prior pregnancies, 50.7% (32/63) reported pregnancy loss (ectopic, miscarriage, stillbirth or termination for medical reasons). In addition, two participants reported problems with their baby including one case of a rare genetic condition in the baby and one case of laryngomalacia and two septal defects that closed spontaneously. Four participants reported maternal health problems in previous pregnancies including previous postpartum haemorrhage and fetal macrosomia (n=1), acute fatty liver in pregnancy (n=1), pre-eclampsia (n=1) and gestational diabetes (n=1).
Conclusions: Our results show that a patient-facing pregnancy MS registry is feasible and can collect adverse previous pregnancy outcomes. The high rate of previous adverse pregnancy outcomes may represent ascertainment bias, and deserves further study. Future results will inform clinicians and women about the safety of DMT and adjunctive medications during pregnancy and postpartum.

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EP0816
Sexual dysfunction in MS brazilian patients

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Introduction: People with Multiple Sclerosis (PwMS) show an increased risk of Sexual Dysfunction (SD) in both women and men.
Objectives: To evaluate SD in Brazilian PwMS
Aims: It was to apply the Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19) and evaluate our results by comparing them with those in the literature, applicability, and engagement of PwMS to talk about SD in Brazil.
Methods: We have developed a questionnaire in Google Forms, for the assessment of demographic data and sexual function. Baseline characteristics were reported as proportions and mean ± standard deviation or median ± Interquartile Range (IQR), according to data distribution. Categorical variables were stratified by sex and compared with Chi-Squared tests. Statistical analyses were performed using STATA v. 16 (StataCorp., College Station, TX).
Results: Of the 621 respondents, 541 were included in the analysis. Among the patients with MS, a total 347 (64,14%) exhibited of SD. When stratified by gender, the frequencies of SD were not significantly different.
Conclusion: There is a high incidence of sexual dysfunction among PwMS and we need to identify the reasons for this and implement strategies to treat and counsel our patients. The MSISQ-19 can be used to help clinicians to assess sexual functioning in a quick and easy way and give patients the possibility to address this topic and receive appropriate help and support.

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Clinical aspects of MS - MS symptoms

EP0817

MoCA test and SDMT to detect cognitive impairment in MS patients

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Introduction: Cognitive impairment (CI) occurs in up to 40-65% of multiple sclerosis patients (PwMS). Cognitive processing speed, learning, and memory are most frequently involved. In recent years, the study of CI has increased but the best screening tool remains unknown.
Objectives: To study the value of Symbol Digit Modalities Test (SDMT) and Montreal Cognitive Assessment (MoCA) test as a cognitive tool in PwMS and to evaluate different factors that can influence these two test results.
Methods: 50 healthy controls (HC) and 50 PwMS matched for age, education and gender completed SDMT and MoCA and also Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A) and Fatigue Severity Scale (FSS). EDSS, age of onset and disease duration education were described. CI was diagnosed with Z-score ⩽-1.
Results: There were no statistically significant differences between HC and PwMS in age (mean 40 years), education (mean 16 years), gender (72% women vs 74%) and employment (78% vs 80%).
There were statistically significant differences in SDMT between HC and PwMS (z-score: median 0 vs 0,7; p 0,001), BDI (median 3 vs median 8; p 0,000), HAM-A (median 7 vs 15; p 0,003) and FSS (median 22 vs 44; p 0,000).
Surprisingly there were no statistically significant differences in MoCA (median 28,5 vs 28 (p 0,062)) between both groups.
Subanalysing PwMS, 48% had CI according to SDMT results. A statistically significant association was found between higher scores in BDI (14 vs 6; p 0,001) and HAM-A (20 vs 13; p 0,027) in patients with and without CI. There were no statistically significant differences in age, age of onset, disease duration, EDSS, MoCA and FSS in patient with and without CI.
There were no statistically significant differences between PwMS with CI complains and PwMS with no complains in SDMT (z-score -0,85 vs -0,56; p0,237) and in MoCA. However, there were statistically significant differences in EDSS (2.7 SD 1.6 1 vs 1.59 SD 1.6; p 0,025), patients with higher EDSS complained more about memory problems.
Conclusions: SDMT seems to be a valid and sensitive tool to screen for cognitive impairment in MS patients. In our cohort the MoCA study do not differ between healthy and patients and between patients with and without CI. Almost 50% of patient with no cognitive complains may have CI and only 50% of patients with cognitive complains present normal results in cognitive test. So CI cognitive tool should be applied in all MS patients at least yearly.

Disclosure
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EP0818

Modified fatigue impact scale criteria may not serve as a reliable predictor of neurogenic fatigue in patients with MS

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Introduction: Multiple Sclerosis-related fatigue (MSF) is associated with brain damage and clusters together with depression and anxiety. Our previous results showed that one third of those Multiple Sclerosis (MS) patients who never had clinically significant fatigue per Modified Fatigue Impact Scale (MFIS) criteria were actually treated with medications that lower fatigue, depression and/or anxiety.
Objective: To investigate the association of anti-fatigue, antidepressant and anxiolytic treatments with brain diffusion abnormalities in never fatigued MS patients.
Methods: The following groups of patients were selected from the CLIMB (Comprehensive Longitudinal Investigations of MS at the Brigham and Women`s Hospital) study: (1) Never fatigued under treatment (NFT, n=16): biennial MFIS score was always ＜38 (5 assessments minimum) and was treated with anti-fatigue and/or antidepressant and/or anxiolytic medication(s) at the most recent clinical visit. Of note, 8 out of the 16 NFT patients were on anti-fatigue medication. (2) Treatment-Naïve Never Fatigued (TNNF, n=26): biennial MFIS was always ＜38 (5 assessments minimum) and received none of the above-mentioned medications. 3T brain MRI was used to perform voxel-wise comparison of fractional anisotropy (FA) between the groups controlling for age, sex, disease duration, physical disability, white matter lesion load (T2LV) and depression (family-wise error corrected p-value=0.05). In secondary analysis, we re-run these statistical models to contrast the 8 NFT patients on anti-fatigue medication with the TNNF patients.
Results: We found reduced FA in bilateral frontal and striatal areas in NFT versus TNNF patients, controlling for age＋sex＋disease duration＋physical disability＋T2LV. When controlling also for depression, the signal (ie, lower FA) showed similar distribution in the aforementioned regions, but FA became significantly lower in the left parieto-occipital and cerebellar areas.

Patients who were on anti-fatigue medications showed significantly lower FA in bilateral frontal, parietal, temporal, occipital, striatal, thalamic and cerebellar areas compared to the TNNF patients, independent of age+sex+disease duration+physical dis ability+T2LV+depression.
Conclusion: A subset of MS patients who are not considered "fatigued' per MFIS criteria, but are treated with anti-fatigue medications has diffuse degenerative brain damage. MFIS criteria may need revision to define clinically significant fatigue.

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Dr. Guttmann has nothing to disclose that could constitute a conflict of interest for this work. Dr. Guttmann has received research funding from Sanofi, the National Multiple Sclerosis Society, and the International Progressive Multiple Sclerosis Alliance as well as travel support from Roche Pharmaceuticals.

EP0819

Characterization of prodromal symptoms in multiple sclerosis - a single-centre observational study

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Introduction: The prodromal phase of multiple sclerosis (MS) has been recently identified and might span for 5-10 years prior to MS diagnosis. Previous studies reported MS prodromal profiles according to gender and MS-type. Socio-demographic and lifestyle factors have not been studied, although their impact in MS outcomes is recognised.
Aims: We aimed to identify the prodromal symptoms in recently diagnosed MS patients in our centre.
Methods: All patients in our centre are submitted to an extensive questionnaire at the time of diagnosis, which includes socio-demographic, lifestyle and education data and subjective complaints in cognition, sleep, fatigue, sphincter and sexual domains. We evaluated the prevalence of MS prodromal symptoms and its relation with socio-demographic, lifestyle data and MS-type at the time of diagnosis in adult patients admitted between January 2019 and December 2021.
Results: We identified 138 patients, with a mean age of 38.6 (standard deviation 11.7) years and 65.9% of the female gender. The most common MS-type was the relapsing form of MS (RRMS) in 84.8% (n=117) with the progressive form (PPMS) occurring in 15.2% (n=21).
Most patients presented at least one prodrome 79.7% (n=110): subjective cognitive complaints in 39.1%, sleep disorders in 37.7%, urinary (32.6%) or bowel (23.2%) complaints, fatigue in 18.1% and sexual dysfunction in 13.0%.
There was no difference in the prevalence and in the type of prodromes between age, gender, MS-type, education and lifestyle factors ($p>0.05$), except for a higher prevalence of urinary complaints in patients over 30-years-old (38% compared to 18.9%, p=0.035) and in PPMS (52.4% compared to 29.3%, p=0.038); bowel complaints were also more prevalent in the female gender (29.6% compared to 13.6%, p=0.044) and physical exercise was associated with fewer cognitive complaints (35.9% compared to 58.2%, p=0.027).
Conclusion: In our sample, the prevalence of prodromes was mostly not influenced by age, gender, MS-type, socio-demographic or lifestyle factors, with a few exceptions previously described. The better characterisation of a MS prodromal phase might have implications in earlier recognition of MS, contribute to its prevention and influence prognosis.

Disclosure
The authors have nothing to disclose.

EP0820

A single center, open, non-controlled pilot investigation to evaluate the effects of intermittent negative pressure on spasticity and concomitant pain in patients with multiple sclerosis

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Introduction: A novel non-invasive medical device applying intermittent negative pressure (INP) to the lower leg have shown promising effects on spasticity and pain in single patients with multiple sclerosis (MS).
Aims: To assess the safety and potential clinical benefit of INP treatment on spasticity, pain, and quality of life in patients with MS.
Methods: This was a prospective, non-controlled clinical pilot investigation of patients diagnosed with MS with spasticity and concomitant pain. Patients with a numeric rating scale (NRS) reported spasticity ≥ 4, combined with pain in the lower extremities were included. Self-reported spasticity, pain, and sleep (NRS) over the last 24 hours and 7 days, multiple sclerosis impact scale (MSIS 29), hospital anxiety and depression scale (HADS), fatigue scale for motor and cognitive function (FSMC), modified Ashworth scale, expanded disability status scale (EDSS), two-minute walk test, and 25-foot walk test were assessed at baseline and after 4 weeks of INP treatment.

Results: In total 43 patients were assessed for eligibility, 10 patients were enrolled, and 8 patients completed the 4-week treatment period. After four weeks of treatment, median change (range) in in spasticity was -2 (-5, 3) NRS points reported over the preceding 24 hours, and 7 days. Pain was reduced by -1.5 (-4, 0) points reported over the preceding 24 hours, and -1.5 (-5, 1) points over the preceding 7 days. Sleep remained unchanged. There was a change in MSIS 29 total score of -3.5 (-36, 19), and a change in HADS of -3 (-6. 3) after 4 weeks of treatment. No change in FSMC was observed. There was an improvement in two-minute walk test of 8.5 m (-20, 75), and a change in the timed 25-foot walk of -0.4 s (-2.0, 1.2) after 4 weeks of treatment. No changes in Ashworth Scale and EDSS was observed after 4 weeks of treatment. No serious adverse events were reported during the study.
Conclusion: The results from this pilot investigation indicate that INP treatment may improve spasticity, pain, quality of life and walking ability in patients with MS. INP treatment seems to be safe and well tolerated in this patient group.

Disclosure
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EP0821

Physical and cognitive profile of elderly persons with multiple sclerosis and comparison with healthy controls

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Introduction: Multiple Sclerosis (MS) is an inflammatory demyelinating disease that has a peak at ages 20-40. Most of the clinical trials are mainly included patients younger than 50-55 years of age. Even the 2017 McDonald criteria for the MS diagnosis should be applied with caution to the patients 50 years and older. On the other hand, because of the growing effectiveness of disease-modifying drugs, the likelihood of survival of MS patients increases, which faces us with another population of elderly MS patients.
Aims: Our study aimed to describe the physical and cognitive profile of elderly persons with MS (pwMS) and compare them with healthy controls.
Methods: Fifty-six pwMS (mean age: 63.57±3.56) and 20 healthy controls (mean age: 65.35±4.85) were enrolled in this study. Physical [Timed 25 Foot Walk (T25FW), 9-Hole Peg Test (9HPT)] and cognitive [Brief International Cognitive Assessment for MS (BICAMS) consists of Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMTR)] assessments were performed.
Results: The mean Expanded Disability Status Scale (EDSS) was 4.22±2.01 (range between 0-6.5), the mean disease duration was 20.88±11.07 (range between 1-44), and 69.6% of the participants had a relapsing form of MS. The initial symptom of 37.7% of the patients was the spinal cord, 9.4% was the optic pathway, 24.5% was supratentorial, and 28.4% was the brainstem involvement. There were no significant differences between groups regarding age, gender, and education level ($p>0.05$). The elderly pwMS have longer T25FW (21.29±42.4 vs. 4.68±0.78) and 9HPT (43.99±92.1 vs. 23.45±4.2) performance and decreased SDMT (29.5±14.67 vs. 38.68±11.64) and BVMTR (17.78±7.35 vs. 21.74±5.79) scores than healthy controls ($p<0.05$). There was no significant difference between thegroups in CVLT-II (7.78±2.66 vs. 8.75±2.05) score ($p>0.05$).
Conclusions: Our study provides demographic and clinical data of elderly pwMS followed by Dokuz Eylül University. The elderly pwMS showed significantly less performance in gait speed, manual dexterity, information processing, and visuospatial memory. Our results pointed out verbal learning and memory preserved in elderly pwMS compared to healthy controls.

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EP0822

Relationship between fatigue, disability, and reserve in patients with MS: a cross-sectional and longitudinal analysis

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Background and Aims: Fatigue is among most debilitating and common symptoms in multiple sclerosis (MS). Here, we hypothesized that individual resilience could affect motor and cognitive

fatigue in MS patients, as already described for cognitive and motor disability, and explored the impact of clinico-demographic features and brain structural damage on fatigue.
Methods: Fifty-four MS patients were prospectively enrolled and underwent clinical examination (including Expanded Disability Status Scale-EDSS, Symbol Digit Modalities Test-SDMT and Beck Depression Inventory II-BDI) and MRI acquisition at baseline and after a mean follow-up of 14 months. Physical and cognitive MS-related fatigue was evaluated with the respective Modified Fatigue Impact (MFIS) subscales (MFIS-P and MFIS-C). Structural brain damage was estimated as white matter (WM) lesion load (JIM 6.0) and brain volume (SIENAX and SIENA). Percent change over time ($\%_c$) for clinical and MRI variables were also computed. A cognitive reserve index (CRI) was estimated by combining educational level, premorbid IQ and the participation in cognitive leisure activities. Brain reserve was expressed as sex adjusted intracranial volume (ICV). The association between putative risk factors (age, gender, phenotype, EDSS, SDMT-z, BDI, log transformed WM lesion load and normalized brain volume-NBV, brain reserve, cognitive reserve) and fatigue scores was assessed using bivariate correlations (preliminary screening) and hierarchical linear regressions. To explore the impact of risk factors on fatigue changes over time, partial correlations were tested between baseline features, their $\%_c$and fatigue scores $\%_c$, accounting for follow-up interval.
Results: At the cross-sectional analysis, MFIS-P was correlated with age, EDSS, BDI, NBV (r ranging from 0.01 to 0.001), but only marginally with brain reserve ($p=0.06$). The full regression model accounted for 32% of the variance in MFIS-P ($p=0.001$). The only variable accounting for significant variance was BDI ($p<0.001$). MFIS-C was correlated with BDI ($p<0.001$). As per the longitudinal analysis, none of the baseline features was associated to MFIS-P and MFIS-C $\%_c$. BDI $\%_c$was associated to MFIS-P and MFIS-C $\%_c$($r=0.55$, $p<0.001$; $r=0.57$, $p<0.001$).
Conclusions: Among the explored features, only depression was strongly associated to both physical and cognitive fatigue. Brain and cognitive reserve did not affect fatigue symptoms in MS patients.

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EP0823
Cognitive outcomes in MS: predictors at diagnosis

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Introduction: Cognitive impairment is a relevant and debilitating deficit in Multiple Sclerosis (MS), affecting 40-70% of patients. The identification of factors predicting cognitive outcome is still incipient but would help to increase mechanistic knowledge and optimize the approach to MS patients.
Aims: To evaluate the patterns of cognitive impairment of our sample and identify predictors at the time of diagnosis.
Methods: In this retrospective cohort study, we included all consecutive MS patients followed at a Portuguese tertiary center between 2016-2021 who were subjected to formal neuropsychological testing (NPT) due to suspected cognitive decline.
All patients in our center are submitted to a questionnaire at diagnosis on sociodemographic, reproductive, lifestyle and cardiovascular (CV) data. We analyzed the relationship between these factors and the outcomes of NPT.
Results: We included 140 patients, 77.1% women. At diagnosis, 35.9% had completed higher education, 64.3% were actively employed; 53.4% were previous/current smokers, 10.7% had other CV risk factors; 10.2% of women were post-menopausal. Sleep disturbances occurred in 50%; 34.0% practiced regular physical exercise. At the time of NPT, 80.4% of patients had a Relapsing Remitting MS diagnosis, 12.3% Secondary Progressive MS and 5.8% Primary Progressive MS; mean age was 49.1 ± 12.3 and mean disease duration 15.7 ± 11.4 years. NPT showed most often some cognitive deficit (54.3%): mostly memory (30.7%), followed by frontal (17.1%) and multidomain dysfunction (5.7%). In 35.7% of patients, it revealed psychiatric symptoms, largely mood changes. Having completed higher education reduced the risk of cognitive decline approximately by half in the first 16 years after symptom onset (HR 0.549 [CI 95% 0.309-0.973], $p=0.040$). The remaining factors did not predict cognitive decline during follow-up ($p\geqslant0.05$).
Conclusion: In our study, having completed higher education at the time of diagnosis reduced the risk of cognitive decline, reinforcing the relevance of the patients' baseline cognitive reserve. Other factors linked to cognitive outcome in general population (employment status, sleep disturbances, CV factors) did not influence the cognitive outcome. We suggest stricter cognitive monitoring of patients with lower education levels and that measures aimed at minimizing cognitive risk should prioritize accessible

therapeutic interventions directed at optimizing cognitive reserve early in the disease course.
Disclosure: The authors have nothing to disclose.

EP0824

Factors related to cognitive fatigability in persons with multiple sclerosis and differences between healthy controls

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Introduction: Cognitive fatigability has been defined as a decline in cognitive performance during a sustained cognitive task. Although correlates of subjective fatigue are well-studied in multiple sclerosis (MS), related factors of cognitive fatigability (CF) are less described. Therefore, we aimed to investigate determinants of CF in persons with MS (pwMS).
Methods: We administered the Paced Auditory Serial Addition Test (PASAT) and calculated the percentage change between the first 1/3 part of the test and the last 1/3 part of the test to determine the cognitive fatigability index (CFI). Brief Repeatable Battery of Neuropsychological Test (BRB-N), including the Selective Reminding Test (SRT), 10/36 Spatial Recall Test (SPART), Symbol Digit Modalities Test (SDMT), the Paced Auditory Serial Addition Task 3 s (PASAT 3), and the Word List Generation (WLG) was applied to 83 pwMS (mean age:35.97±9.55, mean EDSS:1.76±1.18) and 35 age-gender matched healthy controls (HC). Subjective fatigue, sleepiness, and depression were also assessed.
Results: SPART (r=0.241), SDMT (r=0.327), and Stroop (r=0.233) scores were correlated with CFI. SDMT, SPART, Stroop, and WLG were significantly associated with CF in the multivariate regression analyses and explained 12.5% of the variance. Age, neurological disability level according to the EDSS, disease duration, sleepiness, depression, and subjective were not associated with the CF.There was a non-significant difference between pwMS and HC on CFI.
Conclusions: Our findings show that cognitive processing speed, visual memory, and verbal fluency are weakly associated with CF in pwMS. Future work extending the present findings with more detailed cognitive batteries, especially to the pwMS with higher disability levels, to determine predictors of CF might be more informative.

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The bladder control scale correlates more robustly with ambulatory disability than the bladder functional system score

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Introduction: Bladder dysfunction is a prevalent and disabling symptom of multiple sclerosis (MS) yet is only partially characterized by the Expanded Disability Status Scale (EDSS) due to the insensitivity of the Bowel/Bladder Functional System (BBFS). The bladder control scale (BLCS) is a patient reported assessment of the impact of bladder control problems on daily activities.
Objectives: To compare associations between BBFS vs BLCS on in-clinic (Timed-Up and Go [TUG]; Timed 25 Foot Walk [T25FW])) and remote (i.e., average daily step count) measures of ambulatory function.
Methods: Data on adults with relapsing or progressive MS, without recent relapse, who were able to walk (with or without an assistive device), and who were prospectively recruited into remote monitoring studies at UCSF were pooled. Daily mobility was monitored remotely using Fitbits (average daily step count, over 30 days: STEPS). In-clinic evaluations of disability included: EDSS (FS), TUG, T25FW. Patient reported outcomes (PROs) were completed online via secure REDCap surveys (12-item MS walking scale: MSWS-12 and BLCS).
Results: The 155 participants had mean age 50 years (SD:13), 67% were women, 62% had relapsing MS and disability was moderate (median EDSS 4.0. IQR: 2.5-6.0). In univariate models, BLCS showed strong correlations with TUG (ρ =0.49, $p<0.001$), T25FW (ρ =0.53, $p<0.001$), MSWS-12 (ρ =0.58, $p<0.001$), EDSS (rho=0.59, $p<0.001$), and STEPS (ρ =-0.22, p=0.011). BBFS showed similar, although less robust, correlations with all measures, bar STEPS (p=0.051) which showed a trend towards correlation. Adding covariates (age, sex, disease duration) did not alter results. Linear mixed effects models - including both bladder outcomes, covariates, and either TUG, T25FW or MSWS-12 as dependent variables - consistently showed BLCS the strongest and significant independent predictor of these MS disability measures.
Conclusions: Impairments of walking and bladder function may be linked through pathologic processes involving the spinal cord. BLCS correlates more strongly than the BBFS with both in-clinic and ecologically valid assessments of ambulatory function; therefore it likely more accurately assesses bladder dysfunction. The BLCS is simple, easy to use, and these findings support its use in assessment of MS-related bladder dysfunction and exploration of its longitudinal relationship with overall MS-related function in the real world.

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Clinical aspects of MS - Clinical assessment tools

EP0826
Analysis of color perception in multiple sclerosis patients

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Background: Optic neuritis is a very frequent manifestation in the course of the disease and can lead to changes in visual function.
Objective: To analyze color perception and contrast sensitivity (CS) in patients with and without optic neuritis.
Methods: MS patients with more than six months of follow-up and clinically stable in the last six months were analyzed. We performed a complete ophthalmologic study. Chromatic perception was assessed with the Ishihara test and the Farnsworth-Munsell D28 test, low contrast VA was assessed with the ETDRS Bailey-Lovie test at 2.50% and 1.25% and contrast sensitivity with the Pelli-Robson test. We compared patients with and without previous optic neuritis (ON).
Results: 18 females (mean age: 42) and 7 males (mean age :44) were recruited. Of the 50 eyes that were evaluated, 16 were with previous ON and 34 without previous ON. The Ishihara test were normal in 92% of patients with a reading of 17 lamellae or more, however in the Farnsworth Munsell D28 test only 12 patients were normal trichromats in both eyes, 2 patients clearly showed colour defects in the blue-yellow axis (tritan) in both eyes, 2 patients showed an undefined pattern in both eyes and the rest of the patients presented different patterns in each eye. 56% of patients with previous ON presentedan altered chromatic pattern versus 26% without previous ON (p: 0.05) in the Farnsworth Munsell D28 test.
Patients who had past optic neuritis showed a slight decrease in low contrast VA (greater reduction in the 1.25% test than in the 2.50% test) both monocularly and binocularly, with respect to those who have never had an optic neuritis. In the contrast sensitivity test, reduced values were also observed in those who had previous optic neuritis.
Conclusions: To discriminate chromatic alterations in MS patients, it seems that the Farnsworth Munsell D28 test is much more sensitive than the Ishihara test. MS may affect color perception more slowly resulting in clearly defined patterns, such as blue-yellow axis defects in the long term.
Patients with optic neuritis have worse low-contrast VA and worse contrast sensitivity.

Disclosure
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EP0827
Can the dual-task paradigm predict disability in persons with multiple sclerosis? Four-year follow-up study

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Introduction: Dual-task (DT) assessment is a holistic method that contains both motor and cognitive components. Therefore, it is considered a valid marker of daily life restriction. Therefore, it might be used as a disability predictor.
Objective: This present study aimed to investigate whether DT performance could predict disability level, walking, and cognitive function after four years among persons with MS (pwMS).
Methods: Timed Up and Go (TUG) test was performed as a single motor and as a DT (with a concurrent cognitive task of serial subtraction backward). Walking was assessed with Timed-25 Foot Walk (T25FW) and 6-Minute Walk Test (6MWT). Cognitive processing speed was evaluated with Symbol Digit Modalities Test (SDMT). The Expanded Disability Status Scale (EDSS) was applied to assess disability levels. Participants were tested at two time points (T1 and T2), approximately four years apart. DT performance was examined as a predictor of walking, cognition, and disability level at T2.
Results: Fifty pwMS (mean age: 41.36±11.58, mean EDSS: 1.64±1.94) were enrolled in this longitudinal study. Baseline single-task performance was not correlated with change in any variable ($p>0.05$). However, baseline DT performance was significantly correlated with the change in EDSS score at four years ($r=-0.323$, $p<0.05$), and it explained 31.4% of the variance of EDSS at T2.
Conclusion: Our findings have demonstrated the possibility of predicting 4-year disability progression by using DT performance. However, DT performance was not associated with 4-year walking and cognition performance. As this result could be related to the difficulty and type of given tasks, our findings should be confirmed with tasks of different complexity in future studies.

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EP0828

The isometric rate of force development of knee extensors is highly sensitive in the evaluation of lower extremity motor function in individuals with multiple sclerosis who do not have any associated clinical symptoms

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Introduction: Despite the prevalence of motor symptoms in individuals with multiple sclerosis (IwMS), current clinical assessments of the lower extremity are mainly limited to Expanded Disability Status Scale (EDSS) and 25-ft walk test (T25FW), which are commonly criticized due to their subjective nature and limited sensitivity to detect mild disability.
Objectives: To develop objective and sensitive assessment tools to evaluate neuromuscular functioning in IwMS.
Aims: To evaluate the sensitivity of the isometric testing (maximum force; MaxF and maximum rate of force development; MaxRFD) of the knee extensors in the assessment of neuromuscular functioning in IwMS who don't have any associated clinical symptoms.
Methods: Thirteen IwMS with no clinical motor symptoms (pyramidal and cerebellar functional scores:0; gender: 5 males and 8 females; age: 47.7±7.1 yrs; weight: 93.4±28.9 kg; EDSS: 1.3±1.0) and thirteen age- and gender-matched controls (age: 47.1±9.1 yrs; weight: 83.1±22.1 kg) participated in this study. In isometric testing, participants sat on a custom designed force measuring chair and their knee and hip joints were secured at approximately 70° and 90° of flexion, respectively. Individuals completed three trials for each of MaxF and MaxRFD under the instruction to kick "as hard as possible" and "as fast and as hard as possible", respectively. The order of isometric testing is counterbalanced and thereafter participants completed three trials of T25FW. The highest values of each test were used for further analysis.
Results: Independent sample t-tests revealed that while T25FW performance between IwMS and controls were not different (IwMS=4.0±0.8 s and controls=3.6±0.3 s; p=0.1), both the normalized MaxF (IwMS=5.0±2.3 N/kg vs controls=6.7±1.6 N/kg; p=0.03) and MaxRFD (IwMS=34.6±13.9 N/s/kg vs controls=48.0±9.5 N/s/kg; p=0.009) were lower in IwMS.
Conclusions: Our findings indicated that the isometric testing, especially the MaxRFD, is highly sensitive to detect the motor deficiencies in IwMS even when the current standard clinical assessments lack to detect those differences.

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EP0829

Multiple sclerosis, cognitive function and graph literacy in people with multiple sclerosis

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Introduction: Multiple Sclerosis (MS) is a disease characterized by relapses, progression and EDSS defined disability. There are currently multiple available disease modifying therapies (DMT) with varied efficacy for treatment of people with MS (PwMS). DMT choice is typically completed by a shared decision making process. Cognitive impairment (CI) in PwMS is common and can vary in degree and type. The clinician does not easily recognize these varying degrees/types of CI. Screening for CI in PwMS is not common in routine care, SDMT might not be sufficient to recognize CI across multiple cognitive domains. Information discussed or provided as part of the SDM process might include graphic images or discussion of risk/benefit odds. Unrecognized CI in PwMS might adversely influence interpretation of this information and the SDM process. The relationship of Graph/Numeracy Literacy and CI in PwMS has not been extensively explored.
Objectives: To enhance insight into the relationship of CI in PwMS and Graph-Numeracy Literacy.
Methods: A retrospective review of information collected in routine care of PwMS registry collected prospectively including demographics (age, gender, DMT prescribed), patient reported outcome (PRO): Brief Graph Literacy (BGL), a validated questionnaire consisting of 4 questions relating to mathematical topics with different levels of difficulty, and multiple cognitive domains of a validated computerized cognitive testing battery (CAB, NeuroTrax), a Global Cognitive Summary Score (GCS) is calculated from the average score across 7 Cognitive Domains (CD). ANOVA: Single Factor and Two-Sample t-test Assuming Unequal Variances was performed across all groups.
Results: PwMS cohort, (N= 203), gender 72.8% female, average age 52 +/-12 years. ANOVA: Single Factor and Two-Sample t-test Assuming Unequal Variances identified the following significant differences in the GCS across total BGL score groupings ($p<0.05$): statistically significant difference in PwMS mean GCS who correctly score 0% vs 75%; 25% vs 75%; 25% vs 100%; and 50% vs 75%.
Conclusions: Cognitive impairment in PwMS negatively impacts graph/numeracy literacy ability. Impaired ability to interpret such information reflecting risk/benefit odds, relative relapse rate

reduction (therapy efficacy) is associated with CI in PwMS. Unrecognized CI in PwMS in varying degrees and combinations could greatly adversely influence the SDM process for appropriate DMT choice and change.

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EP0830

The rapid disability assessment for patients with relapsing forms of MS: a pilot study

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Introduction: Numerous tools exist to assess for physical and cognitive disability in patients living with relapsing forms of multiple sclerosis (MS). Many of these assessment tools have shortcomings, including, but not limited to: provider/clinical support staff time constraints, cost, learning effect, noncompliance with smartphone applications for remote monitoring, and lack of validation from Phase 3 regulatory trials. Since lower extremity dysfunction and cognitive impairment have the potential to lead to long-term disability, routine longitudinal assessments of lower extremity dysfunction and cognitive impairment are paramount during routine clinic visits.
Objectives: We sought to determine if the use of the timed 25-foot walk (T25FW) and Processing Speed Test (PST, a validated digital analogue of Symbol Digit Modalities Test (SDMT)) could be used to stratify patient clinical outcomes on ocrelizumab therapy as a composite measurement. We termed this composite measure the rapid disability assessment (RDA).
Aims: To assess whether the use of the RDA as a rapid screening tool could objectively inform clinicians about patient clinical status, thus stratifying patients as clinically stable, worsened, or improved.
Methods: From January 2019 to March 2022, we used the RDA to assess 25 patients with relapsing forms of MS on ocrelizumab immunotherapy measuring T25FW and PST during routine clinic follow-up visits as a composite outcome measure. Patients were required to have a minimum of three measurements for T25FW and PST in order to qualify for this retrospective analysis.
Results: Twenty (80%) patients had stable or improved PST scores and five (20%) worsened. Twenty-three (92%) patients had stable or improved T25FW and two (8%) worsened. Combining both patient scores (PST and T25FW) into the RDA composite measure, nineteen (76%) patients were stable or improved in both scores and six (24%) patients worsened in one or both scores.
Conclusions: The RDA is an efficient, rapid, and easily repeatable tool to assess for lower extremity/cognitive dysfunction in MS patients longitudinally. Importantly, the RDA is performed by clinical support staff in the office just prior to the patient's clinician visit, with no disruption in clinician workflow. The RDA is agnostic to immunotherapy treatment. Routine administration of the RDA could serve as an important screening tool for monitoring disability longitudinally to help inform treatment decisions.

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EP0831

Sensor-based gait analysis using mobile phones is useful for the assessment of fatigue in patients with multiple sclerosis – a proof of concept study

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Background: Gait disturbances are common symptoms in patients with multiple sclerosis (MS). Several studies investigated altered gait parameters, and few studies demonstrated an association with fatigue. Sensor-based gait analysis can help to assess gait in real world situations, but the sensors often are additional wearables placed at the hip, thigh or ankle.
Aim: We used the sensors in common mobile phones to assess gait disturbances and the association with fatigue in patients with multiple sclerosis and healthy controls.
Methods: 25 patients with MS (median EDSS 2.0, range 1-7) and 24 healthy controls performed a 6-Minute Walk Test (6MWT) in which they walked back and forth for 6 min on a straight 15 m path at their own speed. Steps were assessed during the straights, not during the turns. Overall number of steps and steps per path were video-recorded and counted, as well as analyzed with an algorithm based on the extracted data from a common mobile phone mounted at the mid position of a belt. Subjective fatigue of each participant after the 6MWT was assessed with a 10-point

VAS.Patients with MS additionally were assessed with the 12-item MS walking scale (MSWS) and the fatigue scale for motor and cognition (FSMC).
Results: Number of overall steps and steps per path counted using the videotapes did not differ from accelerometer-determined step counts (each $p>0.27$). Patients with MS had significantly fewer overall steps (mean 508.12, SD 77.79) yet more steps per path (mean 23.22, SD 7.82) compared to healthy controls (steps: mean 569.63, SD 30.69; steps per path: mean 18.00, SD 1.61; each $p<0.005$). Both overall number of steps and steps per path correlated with VAS for all participants (each $p<0.001$), and with MSWS ($p<0.001$) and FSMC ($p<0.05$) for patients with MS.
Conclusion: Gait analysis in patients with MS can be performed with sensors integrated in common mobile phones mounted on a belt. As expected, patients with MS have an impaired gait even in case of mild overall disability. Gait parameters are associated with both subjective fatigue rating after the motor performance and the commonly used FSMC. Mobile phone-based gait analyses might therefore help to objectively assess motor fatigue in MS.

Disclosure
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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

EP0832
What do you need to complete the nine hole peg test?

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Introduction: The nine hole peg test (PEG) as being part of the Multiple Sclerosis Functional Composite is a common measure of upper-limb function in persons with multiple sclerosis (pwMS). The trial duration is used as the main outcome, however, trial durations can be prolonged due to a multitude of different factors, for instance, muscle weakness, ataxia, spasticity, or numbness. Other assessments, like tapping or grip strength tests, could be used to identify driving factors that impede PEG performance in pwMS and could therefore add valuable information concerning therapeutic measures.
Objectives: The objective was to identify factors that impact the PEG performance.
Methods: We assessed the nine hole peg test trial durations, finger tapping frequencies, distances to a randomly moving target in a pursuit task, and grip strengths in 90 pwMS (67% female, age 50.2a ±10.6a (25-73a), 64% relapsing remitting MS, EDSS 4.0 ±1.9 (1.0-8.0)). Grip strength was expressed as sex-specific z-scores and the reciprocal (i.e., 1/duration) of the PEG duration was used to acquire a normal distribution. A model of multiple linear regression was computed to predict PEG performance.
Results: The resulting model had an adjusted R^2 of 0.53 ($p<.001$). Impacting factors were the tapping performance ($\beta=0.50$, $p<.001$), pursuit performance ($\beta=-0.22$, $p<.001$), and a sex:tapping interaction (sex was used as binaries with female being 1 and male 0) (0.33, $p<.001$).
Conclusions: Although we were only able to explain 53% of the variance, included assessments already indicated driving factors of the PEG performance. Tapping, as reported as a reliable and valid marker of disease severity and with a meaningful association with neural conduction, showed a strong impact, with an emphasis on female pwMS (although the EDSS did not differ between sexes, sensorimotor performances did). Interestingly, there was no significant addition of grip strength, indicating that tapping already covers muscular strength to a sufficient degree. Additional to this, the pursuit performance pointed towards the relevance of accuracy under time pressure. Further investigations should include metrics of spasticity and sensory discrimination tasks to cover hypesthesia.

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EP0833
Multiple sclerosis and ambulation: the relationships of the timed up and go (TUG) to quantitative gait parameters during preferred walking speed and dual task walking

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Introduction: People with Multiple Sclerosis (PwMS) experience disease courses characterized as having relapses and/or progression of disease impact. Some features of accumulative disability in PwMS are currently measured by EDSS and/or a Timed Up and Go (TUG) and the changes in these parameters. The TUG has been utilized to assess ambulation as well as fall risk in PwMS. Ambulation is a complex function and one ordinal outcome measure does not likely provide sufficient information to assess and quantify such impact or change. Quantified gait analysis includes multiple unique and critical parameters that underlie

walking performance and can be quantitatively captured along a continuum. These gait parameters also significantly vary along the EDSS and within homologous EDSS disability groups. Current approaches to identify "no evidence of disease activity" (NEDA) as a measure of disease stability or change are likely insufficiently granular and quantitative to identify early changes with ordinal outcome measures.

Objectives: To enhance insight into the relationship of the one measure of TUG to several critical measures underlying the gait cycle.

Methods: A retrospective review of data that was collected in routine care of PwMS including: demographics (age, gender), digital gait analysis (GA), and the TUG on the same day. GA captured the following gait parameters: Velocity (V), Double Support (DST), Cadence (C), Functional Ambulation Profile (FAP), Gait Variability Index (eGVI), and Walk Ratio (WR) averaged across 3 trials during preferred walking speed and then dual task walking. Regression analysis was completed.

Results: PwMS (N=105), gender 69% female, average age 53.7 +/- 11 years. Along a continuum the TUG values related to the following gait parameters during preferred walking speed: V R^2=0.38, DST R^2=0.58, C R^2=0.52, FAP R^2=0.7, eGVI R^2=0.35, WR R^2=0.12; dual tasking walking: V R^2=0.31, DST R^2=0.67, C R^2=0.37, FAP R^2=0.55, eGVI R^2=0.21, WR R^2=0.19.

Conclusions: Walking ability reflects a complex integration of multiple factors. Although the TUG represents one of the traditional outcome measures utilized to gauge MS impact and disease progression, the complex relationship of the one TUG value obtained to the many underlying aspects of ambulation ability that can be easily quantified raises the question as to whether our current measures of disease impact, disease change and NEDA sufficient and whether they are sufficiently recognize important change.

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EP0834

Modified fatigue impact scale as proxy of motor disability changes over time

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Background and Aims: Patient reported outcomes (PROs) are gaining increasing interest as efficient tools for patients monitoring in Multiple Sclerosis (MS). Among these, the 21-item Modified Fatigue Impact Scale
(MFIS) has been recommended by the MS Council for Clinical Practice Guidelines for use in clinical practice and research. However, although high levels of fatigue have been associated with impairment in functional mobility and disability progression, the relationship between changes in fatigue and objective disability scores over time remains largely unexplored.

Methods: Fifty-four MS patients were prospectively enrolled and underwent clinical examination (Expanded Disability Status Scale-EDSS, Timed 25-Foot Walk Test-T25FWT, 9-Hole Peg Test-9HPT and
Beck Depression Inventory II-BDI) and MRI acquisition at baseline and after a mean follow-up of 14 months. Physical MS related fatigue was evaluated with the relative Modified Fatigue Impact (MFIS) subscale (MFIS-P). Structural brain damage was estimated as white matter (WM) lesion load (JIM 6.0) and brain volume (SIENA and SIENAX). Longitudinal changes in clinical variables
were explored with paired t-tests. Percent change over time (% c) for clinical scores and MRI variables were also computed. The association between MFIS-P % c and baseline clinico-demographic features (age, gender, phenotype, disease duration, follow-up interval), brain structural damage, percent changes in motor disability scores and depression was screened using bivariate correlations. Significant relationships between MFIS-P % c and objective disability measures % c was further tested using partial correlation analysis, accounting for possible confounders emerged from bivariate analyses.

Results: No significant changes were detected in clinical scores over time. Mean percent changes in MFIS-P, EDSS, T25FWT, 9HPT, and BDI were 0.24, -0.05, 0.59, -3.77, and 1.39, respectively. When
applying cut-offs to assess meaningful worsening, 18 patients showed worsening in one or more motor scales. Among explored features, MFIS-P % c was correlated to T25FWT % c (r=0.52, p=0.001) and BDI % c (r=0.49, p<0.001). Even accounting for BDI % c, MFIS-P % c was correlated to T25FWT % c (r=0.46, p=0.006).

Conclusions: MFIS-P could represent an efficient tool to assess subtle changes in walking performance in MS patients remotely or in settings where the execution of walking tests is limited by time and logistic constraints.

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EP0835

Wireless sensor-based movement analysis is useful in detection of gait impairment within early stages of people with multiple sclerosis

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Introduction: In the Expanded Disability Status Scale (EDSS), criteria for impaired ambulation in multiple sclerosis (MS) is defined as the inability to walk for 500 meters, although previous studies showed that gait impairment starts earlier in disease course. However, it is not known if gait impairment can be present in the earliest stage, and which gait-related parameters are affected first.
Objectives: Multiparametric assessment of gait related parameters in a cohort of pwMS and healthy controls (HCs) by clinical scales, patient-reported outcome measures and a wireless sensor system.
Methods: People with MS with an EDSS score below 6.5 were included in this study. Patients were grouped into three groups (0-2, 2-4, and 4-6) according to their EDSS scores. Timed 25-Foot Walk (T25FW), Twelve Item MS Walking Scale (MSW-12), and Modified Fatigue Impact Scale – 5-item version (MFIS-5) were used for clinical measurement. Two Minutes Walk Test (2-MWT) was performed at a normal walking pace and objectively assessed by APDM Opal Sensors (Portland, USA) and 18 gait-related parameters were recorded.
Results: 53 pwMS (41.1±12.8, F:M = 40:13) and 21 HCs (31.9 ± 8.06, F:M= 12:9) were analyzed. EDSS 0-2 group was matched for age and gender with HCs. Gait parameters such as cadence, gait speed, stride length, step time, stance phase, swing phase, double support phase, circumduction, foot strike angle, toe off angle, toe out angle, lumbar range of motion (ROM), turn velocity and angle were significantly different in patients in the EDSS 4-6 group compared to EDSS 0-2, 2-4 and HCs. Gait phases especially stance, swing and double support phases were changed in the EDSS 2-4 group. Lateral step variability increased in the EDSS 0-2 and 2-4 groups and lumbar sagittal ROM was increased within all MS groups compared to the HCs.
Conclusions: Sensor-based gait assessment is a promising tool for detection of gait impairments within early stages and follow-up the disease progression. Besides, lumbar sagittal ROM could be a potential biomarker for the gait assessment in the early stages of MS.

Disclosure
no conflict of interest

EP0836

Trail making test could predict impairment in cognitive domains in patients with multiple sclerosis: a study of diagnostic accuracy

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Objective: Cognitive impairment (CI) and executive dysfunction (ED) are prevalent in patients with multiple sclerosis (PwMS). MACFIMS is the gold standard neuropsychological battery (NPB) for detecting CI. DKEFS is an NPB comprehensively evaluating ED. We aimed to find test(s) from DKEFS with acceptable diagnostic utility and practical considerations for early detection of impairment in the most affected cognitive and executive domains in PwMS.
Methods: Cognitive and executive tasks, physical disability, and depression scores of 30 PwMS were assessed (13 males and 17 females, age: 38.1, age of disease onset: 30.1). SDMT, PASAT, and COWAT from MACFIMS and TMT, DFT, and VFT from DKEFS were selected. The association between patients' characteristics and their performance in tests and the diagnostic accuracy of selected DKEFS tests in detecting impairment in cognitive

tasks were evaluated, using Pearson correlation analysis and ROC analysis, respectively.
Results: No significant association was observed between test scores and the disease onset age or the number of relapses. A significant correlation was found between the disease duration and SDMT and TMT subtests. EDSS was significantly related to SDMT, VFT-switching, and TMT subtests. BDI was significantly related to DFT. TMT-switching detected abnormalities in SDMT and PASAT with 100% sensitivity, 93.3% (for SDMT), and 85.7% specificity (for PASAT). The TMT-letter showed 100% sensitivity and 90% specificity in identifying abnormalities in COWAT.
Conclusions: TMT, particularly the switching condition, is a practical paper-based test that could predict impairment in cognitive tasks. Clinicians may use TMT as a screening tool among PwMS.
Keywords: Multiple Sclerosis; Neuropsychological Tests; Delis-Kaplan Executive Function System; Trail Making Test; Minimal Assessment of Cognitive Function in Multiple Sclerosis; Symbol Digit.

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nothing to disclose

EP0837
Cognitive impairment and its trajectory in MS patients with different phenotypes: a 1-year longitudinal observational study

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Introduction: Cognitive impairment is common in patients with multiple sclerosis (MS). The connection between cognitive impairment and the occurence of relapses (or a progressive course) has not been sufficiently investigated.
Aims: Our study aims to fill this gap by investigating a wide range of cognitive impairment symptoms and their course over a 1-year period within different types of MS.
Methods: The study included 88 participants (22 healthy controls [HC], and 22 patients each with relapsing-remitting MS [RRMS], primary progressive MS [PPMS], and secondary progressive MS [SPMS]). BICAMS and 3 additional cognitive tests (Paced Auditory Serial Addition Test, Block Design Test, Controlled Oral Word Association Test) were administered at baseline and at 1 year.
Results: Episodic memory remained constant in HC und RRMS patients over 1 year. However, in comparison with the RRMS group, episodic memory deteriorated for the SPMS (0.589 SD, 95% CI 0.17 to 1.00, p Holm adjusted = 0.019) and PPMS groups (0.471 SD, 95% CI 0.04 to 0.90, p unadjusted = 0.034). Global cognition also deteriorated in the SPMS group in comparison with the RRMS group. (0.375 SD, p unadjusted = 0.034)
Conclusions: SPMS and PPMS patients display more severe cognitive impairment than RRMS. Our results showed that the RRMS group performed better than the PPMS group in terms of executive functions and visual cognition. It is known that patients with PPMS have greater cognitive deficits than RRMS patients. PPMS patients have pronounced deficits in verbal learning, processing speed, immediate and delayed verbal memory.Clinicians should be aware that these patients require close monitoring of cognitive status.

Disclosure
No disclosures.

EP0838
Moving MS: activity profiles are linked with disability scores, a cross-sectional study

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Introduction: Therapeutic breakthroughs in the treatment of multiple sclerosis (MS) during the past decade have significantly improved the burden of disease and reduced the risk for disability accumulation. At the same time disability changes in patients have become more subtle, requiring new, sensitive measures for patient follow-up. This is particularly true in the assessment of walking disability, which is a key determinant of disability in MS.
Objectives: The goal of this study is to assess the clinical utility of wearable devices to continuously assess motion and gait in MS patients and use it as a predictor of disability.
Aims: Finding objective measures quantifying gait and movement in patients with multiple sclerosis (pwMS).
Methods: Participants were equipped with a wearable sensor and asked to continuously wear the sensor for two consecutive weeks. For each day, the following measures are calculated: total steps per day, maximum cadence, longest consecutive activity duration, and longest consecutive activity steps. These day-based measures are averaged for the duration of the study participation. The 6-minute walking test, FSMC, recent routine MRI white matter lesion volume, and EDSS have been used as comparators.
Results: We have recruited 56 pwMS and 25 healthy age and gender-matched controls. The majority (47) of patients had a relapsing-remitting disease course, while only 9 had a predominantly progressive (primary or secondary) clinical form. When using seven days of data, maximum cadence significantly differentiates healthy participants and high-EDSS patients (>=4) and additionally low- and high-EDSS patients. Within patients, the function score for cerebellar function can be differentiated best by the average steps per day, and the pyramidal score by the longest continuous steps. The six-minute walking test showed a correlation with maximum cadence, and so did fatigue measured by the FSMC.
Discussion: The sensor-derived parameters show a strong association with the EDSS. Furthermore, the combination of walking parameters is predictive of cerebellar or pyramidal disabilities, and even motor fatigue. Our data suggests that a continuous measurement of seven days is sufficient to establish a baseline for further assessment of gait disability. The ubiquity of these measures

and potential insight into symptom-specific changes support their clinical utility.

Disclosure
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EP0839

The effect of the presence of cervical cord lesion on upper extremity function in newly diagnosed persons with multiple sclerosis

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Introduction: In people with multiple sclerosis (MS, pwMS), upper extremity functions assessed using the Nine-Hole Peg Test (9HPT) have been shown to be a risk indicator for activity and participation restrictions, such as the ability to perform activities of daily living. Even in the early stage of MS, mild upper extremity dysfunction may be present that will affect the performance of manipulation tasks.
Aims: This study aimed to determine the effects of cervical cord lesion on upper extremity function in newly diagnosed pwMS.
Methods: We collected data from 378 patients who followed Dokuz Eylul University Hospital, Izmir. PwMS who was diagnosed in six months were included. Upper extremity function was assessed with 9HPT. The Expanded Disability Status Scale (EDSS), disease duration, number of relapses, time from the diagnoses to treatment, disease modified treatments (DMT), age, and gender were obtained from medical records. A neurologist examined the MRI in terms of the presence of a cervical cord lesion.
Results: Female to male ratio was 2.4:1. The mean age was 33.37±10.48 (range 18-78 years), disease duration was 2.62±4.64 (range 0-38 years), and time from the diagnosis to treatment was 33.37±10.48 (range 18-78 years). The mean EDSS score was 1.0±1.06, and the number of relapses was 1.63±0.92. The number of cervical cord lesion-positive patients was 236 (62.4%). Glatiramer Asetat was the most common DMT (33.1%, n=125). Other treatments were, Interferon Beta 1b (5.8%, n=22), Interferon Beta 1a (32.0%, n=121), Teriflunomide (4.5%, n=17), Dimetil Fumarate (24.3%, n=92). The pwMS with cervical cord lesion have a longer 9HPT (21.04±4.26 vs. 20.47±4.87). Also, there was a weak positive correlation between the 9HPT score and disease duration (rho=0.159, p=0.002), time from the diagnosis to treatment (rho:0.196, $p<0.001$), and EDSS score (rho:0.214, $p<0.001$).
Conclusions: This study showed that the presence of cervical cord lesion has a negative effect on upper extremity function. Moreover, upper extremity function is related to the time to initiation of DMT. Our results suggest that 9HPT could be used as a prognostic factor for follow-up studies.

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EP0840

Age related multiple sclerosis severity score in a Colombian population: data from clinical practice

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Introduction: Multiple sclerosis (MS) is a disease with a heterogeneous course. It is important to assess the current status of each patient as well as determine possible future severity (1,2). Due to the limitations of the cross-sectional nature of the EDSS score, the MS Severity Score (MSSS) and the Age-Related MS Severity Score (ARMSS) were developed to allow a patient's EDSS to be classified by years from disease onset or by age. Normalized ARMSS (nARMSS) represents an outcome measure that offers stability over time and is capable of capturing an effect that contributes to a change in disability scores by years.
Objective: To estimate nARMSS in a Colombian EM population
Methods: Retrospective cohort in a specialized institution, in 15 cities of Colombia, between 2015 and February 2022. To estimate nARMSS, the integral corresponding to the area under the curve between the ARMSS scores was used, with respect to the age at time of estimation in relation to the expected median (1). Quartiles were estimated according to nARMSS scores. Absolute and relative frequencies and 95%CI were calculated for qualitative variables, and median with interquartile range (IR) for quantitatives, according to each quartile and for the total population studied.
Results: The cohort included 554 patients with MS, with a median age of 47 years (IR 38 to 57). The overall nARMSS was -0.27 (RI -1.9 to 1.8), with a higher EDSS value at the end of follow-up 2.5 (RI 1.0 to 6.0), compared to baseline 2.0 (RI 1.0 to 5.0). In the nARMSS score, an increase was found in the median to higher quartiles, with estimates higher than those expected for age in patients from Q4: 3.2 (RI 2.5 to 4.1), compared to those from Q1: -2.7 (RI -3.0 to -2.5). Additionally, in the MS classification, the percentage of patients with secondary progressive disease was higher in Q4 with 25.3% (95%CI 18.3 to 33.1) compared to Q1 with 1.5% (95%CI 0.2 to 5.3). The time of evolution of the pathology had a higher median in the last quartile, of 12.3 years, while in the first it was 8.8.

Conclusion: Results are consistent with the report of cohorts in populations in which nARMSS was initially standardized, with the similarity that higher nARMSS median would be related to greater severity of MS. According to the tools of the MS care model, the disease in the population has been appropriately intervened, according to global nARMSS, with a progression to severity below that expected for the age of the patients studied.

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EP0841

Six-spot step test with cognitive tasks: a proposed method to assess dual-task ability in people with multiple sclerosis

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Introduction: The Six-Spot Step Test (SSST) is a valid measure to assess the ability of people with multiple sclerosis (pwMS) to maintain balance whilst challenging stability during walking. It assesses many essential components of walking such as postural stability during one-leg stance, limb dexterity, dual tasking, and cognitive capacity during walking. We hypothesized that adding cognitive tasks to SSST can increase its discriminative ability by creating more cognitive load.
Objective: This study aimed to compare the performance of SSST plus two different cognitive tasks in pwMS and healthy controls (HC).
Methods: Fifty-two pwMS (mean EDSS=2.21±1.84) and 19 HC were recruited. Participants performed the SSST under three different task conditions: conventional SSST, SSST with word list generation (WLG), and SSST with the serial-7 backward task. The dual-task cost (DTC) was calculated for two cognitive task conditions.
Results: There was a significant difference across different SSST conditions in both groups. There was also significant condition*group interaction. PwMS completed all SSST conditions in a longer duration compared to HC. The DTC of SSST with backward and WLG tasks was greater in the MS group than in HC. However, non-significant differences were found in the number of correct answers during the dual-task conditions between pwMS and HC. Furthermore, we did not find a significant difference in SSST performance between the backward and WLG tasks in pwMS, but the difference was significant in HC.
Conclusion: The SSST had the ability to discriminate between pwMS and HC in terms of dual-task performance. Adding cognitive tasks to SSST increases its discriminative ability.

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EP0842

Assessment of the relation between physical disability and trunk control, balance and pedobarographic parameters in persons with multiple sclerosis

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Introduction: The most common problem associated with physical disability in persons with Multiple Sclerosis (pwMS); is the deterioration in gait parameters with imbalance.
Aims: This study examined the relations between physical disability and trunk control, balance, pedobarographic parameters.
Methods: Twenty-three patients with relapsing-progressive MS (13 female, 10 male) who were in remission were included in the study. The functional status of the patients was assessed with Expanded Disability Status Scale (EDSS), 9-Hole Peg Test (9DPT). Trunk control was assessed with the Trunk Impairment Scale (TIS), gait analysis was assessed with pedobarography device (Zebris Medical GmbH, Germany), and balance parameters were assessed with Biodex (Biodex Medical Systems, NY, USA).
Results: The mean age of the patients was 35.52±7.51 and the mean EDSS score was 2.34±0.47. A statistically significant correlation was found between TIS static and dynamic score and 9HPT duration of the dominant and nondominant extremities (respectively; r:-0.665, r: -0.645, r: -0.685, r:-0.636) ($p<0.05$). A statistically significant correlation was found between TIS static (r: 0.464) and dynamic scores (r: 0.458) and the mean pressure of the left forefoot ($p<0.05$). In balance parameters, a statistically significant correlation was found between anterior-posterior index (API)(eyes open-dynamic foam surface-EODFS) (r-0.42) and medial-lateral index (EODFS) (r:-0.483) and TIS static score ($p<0.05$). A statistically significant correlation was found between the API (eyes closed-dynamic foam surface)(r:-0.423) and TIS static score ($p<0.05$). A statistically significant correlation was found between stride width and TIS static score (r:-0.495) ($p<0.05$). A statistically significant correlation was found between API (EODFS) and right forefoot maximum power average (r: 0.442) ($p<0.05$).
Conclusions: As a result, it was seen that many factors are associated with physical disability in pwMS, especially trunk control affects upper extremity performance, balance and gait parameters.

These results suggest that trunk control should be focused on in MS rehabilitation.

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Clinical aspects of MS - Patient reported outcomes

EP0843

The COVID MS patients satisfaction survey (COVIMPSAT): COVID-19 outcomes in people with multiple sclerosis and the role of multiple sclerosis centers during the pandemic

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Introduction, objectives and aims: COVID-19 pandemic caused a significant disruption of clinical activities at Multiple Sclerosis (MS) Centers. As part of a national multicenter survey (COVId Ms Patients SATisfaction survey – COVIMPSAT) aimed at collecting patients' opinion regarding the quality of care and information received from MS Centers (MSC) during the pandemic, we report data about COVID-19 infections and vaccination cycle and how they were managed by the MSC.
Materials and methods: In April-May 2021, 16 Italian MSC developed and sent a digital (35-item) survey by email to their patients. Statistical analyses were performed with SPSS, version 25.
Results: 1670 people with MS (pwMS; 67.3% women) completed the survey. 169 (10.1%) reported a diagnosis of COVID-19 infection: 63% were symptomatic, while 37% were not. As regards treatment for COVID-19, only 3% of the patients were hospitalized. The impact of COVID-19 infection on MS-related neurological symptoms was as follow: 69.3% of pwMS stated that the severity of their MS-related symptoms remained stable, 21.5% reported a worsening of pre-existing symptoms, 7.4% affirmed that new neurological symptoms emerged, while only 1.8% reported an improvement of MS-related symptomatology. At the time of the survey, 60.6% of pwMS were inoculated at least one dose of COVID-19 vaccine. Vaccination appointments were scheduled by: MSC staff alone (44.9%), MSC staff together with the general practitioner (17.5%), the general practitioner alone (16.1%), other Institutions (12.1%), and by the patients themselves (9.3%). At the moment of the survey 39.4% of pwMS were not vaccinated yet. The three major reasons for not being vaccinated yet were: being already on a vaccination list (40.8%), willing to be vaccinated but without an appointment (17.6%), still undecided or not willing to be vaccinated (19.3%).
Conclusions: The results of this multicentre survey revealed a low hospitalization rate of pwMS, in line with previous studies (Moghadasi et al, 2021). In the majority of the sample, COVID-19 symptomatology did not have a significant impact on MS-related neurological symptoms. MSC promoted and facilitated vaccination procedures and scheduling, alone or in combination with the general practitioner, in more than half of pwMS.

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EP0844

Identifying hopelessness and associated factors in early-stage relapsing remitting multiple sclerosis

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Introduction: Patients with early-stage relapsing remitting multiple sclerosis (RRMS) might experience intense emotions as diagnosis is disclosed. Hopelessness is defined as a negative emotional state characterized by the sense that one lacks control over desired events in the future and has clinical utility for suicide risk assessment.

Objectives and aims: The aim of this study was to assess the presence of hopelessness and associated factors in early-stage RRMS patients.

Methods: A multicentre, non-interventional study was conducted. Adult patients with RRMS diagnosis, disease duration ⩽3 years, and Expanded Disability Status Scale (EDSS) score between 0-5.5 were included. The State-Trait Hopelessness Scale (STHS) was used to assess patients' hopelessness. Patient-reported measures were administered to gather information on different outcomes.

A multivariate logistic regression analysis was performed to assess the association between STHS-state and demographic, clinical characteristics, and patients' perspectives.

Results: A total of 189 patients were included (mean age: 36.1±9.4 years, 71.4% female, mean disease duration: 1.2±0.8 years). Median EDSS score was 1.0 (IQR=0.0-2.0).

A proportion of 65.5% (n=124/189) patients had a moderate to severe hopelessness.

Bivariate analyses suggested that patients were significantly more likely to have hopelessness if they were older, had a higher perception of pain, fatigue, symptom severity and a worse perception of their quality of life, disease, and their hand dexterity and gait function. Also patients with higher depression score, probable cases of anxiety, stigma cases, those with cognitive complaints and workplace barriers were more likely to have state-hopelessness.

Older age, higher depression score, worse illness perception, and psychological barriers at workplace were predictors of moderate

to severe hopelessness (OR=1.050, 95%CI:1.005-1.101; OR=0.963, 95%CI:0.932-0.994; OR=1.773, 95%CI:1.388-2.375; OR=1.095, 95%CI:1.039-1.161; OR=1.057, 95%CI:1.007-1.114, respectively, all $p<0.05$).

Conclusions: Hopelessness is a common phenomenon among patients with early RRMS. Identifying state-hopelessness and its associated factors and establishing individualized interventions may help patients deal with their condition in the long-term.

Disclosure

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EP0845

Self-reported physical activity behavior in a MS cohort from the Saskatchewan MS drugs research program, Saskatchewan, Canada

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Introduction: Data on physical activity (PA) in individuals living with MS may provide important context for survival and disability outcomes. The objective of this study is to report PA behavior according to the Godin Leisure-Time Exercise Questionnaire (GLTEQ) from an observational sample of people with MS applying for Ministry of Health funding for disease-modifying drug therapy (DMT) in Saskatchewan (SK), Canada.

Methods: All individuals applying for DMT funding between September 2014 and March 1, 2021, were invited to complete a paper GLTEQ. Demographics included sex and age, disease duration from MS symptom onset, and duration of treatment on any DMT at survey completion. Linear regression analyses examined relationships between GLTEQ scores and demographics. Post hoc Kruskal Wallis Test was used to analyze GLTEQ scores grouped according to established categories: sufficiently active, moderately active or insufficiently active for health benefits.

Results: 1693 participants were invited to participate. 849 (50%) [RMS1]returned completed questionnaires (75% female, mean age 46 (SD 12) years; mean duration from MS symptom onset 12 (SD 10) years and a mean of 5.8 (SD 6) years on DMT; 247 (28%) participants never started DMT treatment. 494 (58%) of responders were insufficiently active and 224 (27%) moderately active and 131 (15%) sufficiently active for health benefits. Female sex; B=-3.83, p=0.012) and increasing age (B= -0.37, p= <0.001) were significant predictors of total physical activity score, accounting for 7.4% of the variance in the GLTEQ scores. Post hoc analysis revealed having never started a DMT was associated with being sufficiently active for health benefits (χ^2 (2) =19.51, $p<0.001$).

Conclusion: Increasing age and female sex accounts for a small amount of variance in GLTEQ scores. Over half of this MS cohort were insufficiently active for health benefits. A quarter of the sample who never started DMT treatment reported higher levels of physical activity.

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Disclosure

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EP0846

Influence of cognition and fatigue on the correlation between objective and subjective upper limb measures in people with multiple sclerosis

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Background: A small correlation between 9-Hole Peg Test (9HPT), Box and Block test (BBT),Hand Grip Strength (HGS) and Manual Ability Measure 36 (MAM-36) has been reported.
Objectives: Influence of cognition and fatigue on the correlation between objective and subjective upper limb measures.
Aims: The study aimed at evaluate the influence of cognition and fatigue on these correlations.
Methods: The multicentre study included 5 Italian neurological centres. Subjects were assessed trough 9HPT,BBT,HGS,MAM-36, Modified Fatigue Impact Scale (MFIS) and Symbol Digit Modalities Test(SDMT). Spearman correlation was used to assess correlation in the whole sample and stratifying based on MFIS and SDMT cut-off.
Results: Sample consisted of 200 PwMS: 132 females; mean age of 51.66(13.60) years; mean disease duration of 14.75(10.91) years; 105 relapsing-remitting, 39 primary progressive, 56 secondary progressive disease course, mean EDSS of 4.89 (1.92).
Scores obtained at the test were: 9HPT-R 36.41(30.24) s, 9HPT-L 40.86(37.35) s, BBT-R 45.48(15.87) blocks, BBT-L 44.70(15.39) blocks, HGS-R 20.01(9.91), HGS-L 18.11(8.94), SDMT 38.02(14.07), MFIS 33.01(18.43).
Fatigue showed correlations with left-9HPT (L:r=0.167, $p<0.05$), with BBT (R: r=-0.208, $p<0.01$; L:r=-0.216, $p<0.01$) and HGS (R:r=-0.178, $p<0.05$; L:r=-0.228, $p<0.01$) on both arms, and with MAM36 (r=-0.490, $p<0.01$). SDMT correlated with MAM-36 (r=0.170, $p<0.05$), BBT for both arms(R:r=0.214, $p<0.01$; L:r=0.261, $p<0.01$), and 9HPT on both arms (R: r=-0.235, $p<0.01$; L: r=-0.307, $p<0.01$). No correlations emerged between HGS and SDMT.
Correlation between the MAM-36 and objective upper limb (UL) measures showed minor variations based on the level of cognitive impairment and fatigue. On both arms, correlations between 9HPT and MAM36 were significantly stronger among patients without cognitive impairment (SMDT>48) (i: R: r=-0.310, p=0.000; L:r=-0.271, p=0.01; n-i: R: r=-0.592, p=0.000; L:r=-0.531, p=0.000; p-value<0.001). There were no significant differences across the groups in the correlation between the MAM-36, HGS and BBT. Stratifying the sample based on MFIS cut-off (MFIS>38) no significant differences across the groups in the correlation between MAM-36 and objective UL measures were observed.
Conclusion: Although cognitive function were evaluated only using SDMT, cognition, but not fatigue, may influence correlation between objective and subjective UL measure.

Disclosure

All authors have nothing to disclose

EP0847

Disability progression: can doctor and patient agree?

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Introduction: The favoured outcome to assess disability progression in MS is change in a clinically assessed EDSS score over time. This requires regular assessments by ideally the same trained neurologist which is not practical for the majority of people with MS (pwMS). The UK MS Register (UKMSR) has collected patient reported outcomes (PROs) on a bi-annual basis for 11 years. PROs are completed at home, at low cost and low impact for pwMS thus could offer a long-term method of disability assessment. Among the PROs measured, the motor section of the Multiple Sclerosis Impact Scale (MSIS-29) and the webEDSS questionnaires capture a measure of physical disability.

Objectives/Aims: To compare the rates of worsening during longitudinal assessment between the clinical EDSS, MSIS-29 motor and webEDSS scores.
Methods: To evaluate a confirmed disability change a minimum of 3 longitudinal data points were required per patient, per outcome measure. The PRO cohort includes participants who answered both outcomes with answers spaced ~6 monthly. The clinical cohort was distinct from the online respondent cohort. A disability progression was considered to have occurred for the webEDSS and clinical EDSS when +1 point change occurred when baseline score was^{3}5.5 and a +0.5 change if baseline >5.5. For the normalised MSIS motor score (range 0-100) a 10-point increase was considered a progression event.
Results: 559 pwMS on the UKMSR answering the MSIS-29 and webEDSS, and 293 UK Clinical patients, fulfilled the inclusion criteria. Median time to progression was
1.54yrs MSIS motor score, 1.32yrs webEDSS, and 1.46yrs using clinical EDSS. There was no significant difference in the survival curves for all three curves (p=0.23).
Conclusion: The median time to survival for a defined progression event in a clinical EDSS score, web EDSS and MSIS motor were similar. This implies that online self-reported PROs could be used to monitor disease progression in pwMS more closely than was previously possible using clinically assessed EDSS alone.

Disclosure
JR,RM, and TKD have no pecuniary interests to declare, all are contracted to Swansea University for the UK MS Register, which is funded by the UK MS Society
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EP0848

Relapse activity and disability progression in COVID-vaccinated patients with multiple sclerosis: homologous vs. heterologous vaccination scheme

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Background: Vaccination reduces the likelihood of a severe COVID-19 disease course. Therefore, vaccination against COVID-19 is generally recommended, even for people with autoimmune diseases such as multiple sclerosis (MS). Nevertheless, some people with MS (PwMS) have concerns about the vaccinations due to fear of disease worsening after the vaccinations.
Objectives: We aimed to analyse relapse activity and disability progression of PwMS stratified by COVID-19 vaccination scheme (homologous [HOM] vs. heterologous [HET]).
Methods: This study is based on a longitudinal observational study regarding the safety and tolerability of COVID-19 vaccines in PwMS. Acquisition of socio-demographic, clinical and vaccination data was conducted via several pseudonymised online surveys. PwMS with a minimum age of 18 years, a diagnosis of MS and a basic immunisation (usually two vaccinations) as well as ⩾1 booster vaccination against COVID-19 were included (N=2062). Patients with HOM (same vaccines) and HET vaccination schemes (different vaccines) were compared regarding relapse activity following vaccination and disability status (patient-determined disease steps [PDDS]).
Results: The 2062 PwMS analysed showed a mean age of 47.1±11.0 years and a female proportion of 78.5%. The most common MS course was relapsing-remitting MS (74.8%). Most PwMS were currently treated with a disease-modifying drug (73.9%). Relapses after any COVID-19 vaccination occurred in 5.8% of PwMS. Comparing the disability level following the first vaccination with the period after the booster vaccination, a PDDS decrease was reported by 16.4% of PwMS, an increase by 13.6% and no change by 70.0%. The majority of patients reported a HOM vaccination scheme (59.4%), while 40.6% received HET vaccination (28.0%: different mRNA vaccines [HET1], 12.6%: mRNA + vector vaccines [HET2]). The only significant difference (p=0.012) between patients stratified by vaccination scheme was related to the mean age: PwMS receiving HOM vaccination (46.5±11.2 years) were younger than patients with HET vaccination (HET1: 48.4 years, HET2: 48.1 years). These patient subgroups revealed no considerable difference regarding the frequency of relapses following vaccination (HOM: 4.7%, HET1: 5.2%, HET2: 6.9%; p=0.3).
Conclusions: The frequency of relapses and disability progression following COVID vaccinations do not appear to be associated with the type of vaccination regimen administered.

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David Ellenberger, Firas Fneish, Sarah Schilling and Melanie Peters had no personal financial interests to disclose other than being employees of the German MS Registry.
Judith Haas has no personal pecuniary interests to disclose, other than being the President of the German MS Society, federal association, which receives funding from a range of public and corporate sponsors, recently including BMG, G-BA, The German MS Trust, Biogen, (Bristol Myers Squibb, Merck Serono, Novartis, Roche, Sanofi, Viatris (former Mylan).

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EP0849

Caring for the carer of people with multiple sclerosis

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Introduction: Family caregivers are essential assets in the health and rehabilitation process, and their psychophysical health should represent a concern for healthcare services. Considering caregivers' quality of life (QoL) is critical to adequately design health and rehabilitation programs. The aim of the study was to assess the QoL of family caregivers and its associated variables.
Methods: A cross-sectional study carried out with 200 family caregivers during 2021 evaluated the QoL using Adult Carer Quality of Life scale (AC-QoL), and psychological variables such as mood through Hospital Anxiety and Depression Scale and cope strategies using the Coping Orientation to Problems Experienced 25-items. In addition, a questionnaire about caregiver socio-demographic information and disease specific questions related to their care recipient was completed. Simple linear regressions analyzed the relationship between each independent variables and the dependent variable (AC-QoL total score). Multiple regression analyses were performed using a hierarchical approach (a block-wise analysis). Independent variables, with $p < 0.10$ in univariate analysis, were entered into the models in three steps: 1: caregiver's socio-demographic variables; 2: caregiver's psychological variables and 3: patient's clinical variables. The goodness of fit of the models were examined using R^2, Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).
Results: Of the 200 participants, almost half (49%) were female, mean age was 58.7 ($\pm$12.7) years, over 60% had a moderate-high educational level and 40.5% currently employed. Among the eight subscales of AC-QoL, support for caring and personal growth resulted the more compromised areas. In hierarchical regression analysis, incorporating additional covariates improved the fit of the models to the QoL data. A significant increase was observed when caregiver's psychological variables were included in the model (R^2=0.45, BIC=1565.9, AIC=1542.9) respect to caregiver's socio-demographic only (R^2=0.11, BIC=1657.7, AIC=1644.5), while the inclusion of patient's clinical variables had not effect on the model goodness-of-fit.
Conclusion: Family healthcare represents a primary policy issue. Caring the psychological component could improve the QoL of both caregiver and MS patient with consequent better adherence to health and rehabilitation programs.

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EP0850

Long-term unmet needs in multiple sclerosis

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Introduction: Needs are "the requirements of individuals to enable them to achieve, maintain or restore an acceptable level of social independence or quality of life, as defined by the particular care agency or authority". Unmet needs are those which are not satisfied by current service provisions. People with MS (pwMS)

have long-term unmet needs which adversely affect their quality of life.
Objectives: To understand the long-term unmet needs experienced by pwMS.
Aims: To measure the prevalence and impact of long-term unmet needs in pwMS.
Methods: Long-term unmet needs were measured using the LUN-MS questionnaire. It covers 29 long-term unmet needs in multiple sclerosis and is split into four categories: informational, physical, psychological and social. Descriptive statistics were used to explore the prevalence and severity of the long-term unmet needs measured. Spearman's Rho was used to assess the correlation between unmet needs, and EDSS and MSIS scores.
Results: Data from 123 participants (mean age=44 years, SD=13, mean duration since diagnosis=130.55 months, SD=115.20 (10.88 years, SD=9.6)) was used. EDSS ranged from 0 to 7.5 (median=5.5). 87% reported at least one long-term unmet need. The number of unmet needs varied from 0 to 21 (Median=5) Fatigue was the most problematic long-term unmet need with 41.5% reporting it, followed by memory (39%) and information on self-care (36.6%). 68.5% had at least one long-term unmet informational need, 71% had at least one long-term unmet physical need, 47.6% had at least one long-term unmet psychological need and 39.5% had at least one long-term unmet social need. The number of long-term unmet needs did not correlate with EDSS (Spearman's Rho (R_s(115)=-0.049, p=0.604). The number of long-term unmet needs showed significant correlation with MSIS physical (R_s(109)=0.607, P<0.001) and, MSIS psychological (R_s(115)=0.773, P<0.001) domains.
Conclusions: A significant proportion of long-term needs experienced by pwMS are not met by current services. Physical needs were highest, followed by informational, psychological and social needs. Long-term unmet needs were not related to disease severity. MS had a greater physical and psychological impact on people with higher number of unmet needs. These findings can be used to inform future service provisions to optimise the quality of life for pwMS.

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EP0851

Natalizumab-treated RRMS patients with prior DMT use report better outcomes, treatment satisfaction and unique benefits than similar patients treated with ocrelizumab

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Introduction: Natalizumab and ocrelizumab are both highly efficacious disease modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS). Currently, there is limited comparative patient-reported data on these two therapies. Although a recent real-world survey showed that natalizumab-treated RRMS patients reported better outcomes on key physical, emotional, and cognitive domains than those treated with other DMTs, the percentage of ocrelizumab patients was small.
Objective: To describe survey results including RRMS patients' self-reported assessments and any unique benefits since starting natalizumab or ocrelizumab.
Methods: RRMS patients aged ⩾21 years completed a voluntary anonymous survey. Questions included demographics, disease and DMT history; self-assessments of disease activity, symptoms, social roles/activities; and treatment satisfaction and unique benefits seen with their current DMT. This analysis focused on respondents who had taken ⩾1 prior DMT. The proportion of patients with different responses were compared between those taking either natalizumab or ocrelizumab using a chi-squared or Fisher's exact test.
Results: The survey was conducted from 6 Dec 2021 to 24 Jan 2022.The analysis included 52 natalizumab-treated patients and 92 ocrelizumab-treated patients.Baseline characteristics were similar between groups, except for age and time since RRMS diagnosis. More natalizumab- than ocrelizumab-treated patients reported improvements in disease activity (84.6% vs 59.8%; P=0.0015), emotional health (73.1% vs 35.9%; P<0.0001), physical symptoms (69.2% vs 43.5%; P=0.0084), cognitive symptoms (61.5% vs 32.6%; P=0.0023), and social roles/activities (71.2% vs 35.9%; P=0.0003). Unique benefits related to disease activity, emotional health, physical symptoms, and/or cognitive symptoms were reported more frequently in natalizumab- than ocrelizumab-treated patients (76.9% vs 59.8%;P=0.0371). More natalizumab- than ocrelizumab-treated patients reported their DMT met/exceeded treatment expectations (96.2% vs 72.8%).
Conclusions: RRMS patients with prior DMT use who were taking natalizumab more frequently reported improvements in disease activity, symptoms, social roles/activities plus unique benefits and treatment satisfaction than those taking ocrelizumab. These results support the comparative patient-reported data for natalizumab and ocrelizumab and may be useful to healthcare providers and their patients with RRMS.

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EP0852

Multiple sclerosis, graph literacy and perception of disease impact: performance versus patient perception of illness impact in people with multiple sclerosis

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Introduction: Multiple Sclerosis (MS), a disease characterized by relapses, progression and EDSS measured disability. There are currently multiple available disease modifying therapies (DMT) with varied risk/benefit ratios to treat people with MS (PwMS). DMT choice is typically completed by a shared decision making (SDM) process. Cognitive impairment (CI) in PwMS is common and can vary in degree and type. The treating clinician does not easily recognize these varying degrees/types of CI. "Objective" screening for CI in PwMS is not common in routine care. Information provided to review during the SDM process includes graphic/numeracy information. Unrecognized CI in PwMS could impact this SDM process. The relationship of Graph/Numeracy Literacy in PwMS as it relates to a patient centric perception of disease impact has not been extensively explored. The Graph Literacy portion of the questionnaire consists of 4 questions relating to mathematical topics and ranging from different levels of difficulty. The Brief Illness Perception Questionnaire reflects patient centric impression of disease impact.
Objectives: To enhance insight into the relationship of patient centric perception of disease impact and graph/numeracy literacy.
Methods: A retrospective review of prospectively collected information in routine care of PwMS including: demographic information (age, gender, DMT prescribed), and patient reported outcomes (PRO) for Short Graph Literacy (SGL) and The Brief Illness Perception Questionnaire (BIP) which reflects a patient centric measure of their disease impact.
Results: PwMS (N= 207), gender 72.5% female, age 52.5 ±12 year. A t-test analysis was completed between SGL groups and their BIP scores. Subjects who scored 0-50% on SGL have an increased threatening view of their MS than those who scored 51-100% correct on SGL. Those who scored 0% vs 75% had significantly different scores on BIP. The average BIP score for PwMS who scored 0%-100% on the Graph Literacy respectively, was 45, 42.1, 39, 36, and 36 respectively.
Conclusions: Patient centric illness self-perception of disease impact in PwMS is not related to the degree of graph literacy. Objective examiner independent cognitive screening across multiple cognitive domains and not just relying on patient reported perception of disease impact is warranted in routine care of PwMS to evaluate patient centric cognitive ability to effectively participate in the shared decision-making.

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EP0853

COVID-19 influence on the progression of post-traumatic growth in multiple sclerosis

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Introduction: The experience of suffering multiple sclerosis (MS) can generate patient personal benefit gain and self-improvement. The global pandemic might play a role in the development of post-trauma growth, as patients can perceive the 2019 coronavirus (Covid-19) as a higher threat than the average due to MS condition.
Objectives/Aims: To study possible changes in post-traumatic growth in people with MS and Covid-19 influence.
Methods: The sample comprised 260 participants (179 women and 81 men), receiving health care at Virgen Macarena University Hospital. Mean age was 45.05 years (SD= 10.61), from 19 to 78 years old. The MS type were Relapsing-Remitting (n=228) and Progressive (n=32), the Expanded Disability Status Scale (EDSS) mean score was 3.21 (SD=1.93), and mean MS duration was 144.77 months since diagnosis (SD=89.33). Post-traumatic growth inventory (PGI-21) was applied to evaluate patient perception of personal benefit on two different occasions: (T1) 2018-2019 and, 18 months later, (T2) 2020-2021. At T2, Covid-19 influence was appraised asking patients if they felt affected or not about the Covid situation. Paired t-test examine changes in Post-Traumatic Growth between T1 and T2. Unpaired t-test tested

differences in patients affected (n=123) and not affected (n=137) by Covid-19 at T2.
Results: From T1 to T2 every subscale: relating to others, new possibilities, personal strength, spiritual change, appreciation of life, and PGI-21 total score significantly increased ($p<0.0001$ for all). Patients affected by Covid-19 reported significant higher scores of PGI-21 subscales and total scores than patients stated not to be affected by Covid-19.
Conclusions: Patients showed an increase in post-traumatic growth over an 18 months follow-up period, this suggest that elaborating a post-trauma growth is a process that might require time. Additionally, patients who felt affected by Covid-19 presented higher scores in post-traumatic growth. Feeling in an adverse situation, as a global pandemic, might promote the personal benefit gain process in MS.

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EP0854

How people benefit from doing patient and public involvement: a scoping review

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Introduction: Current literature identifies the impact that patient and public involvement (PPI) has on research, while less is known about how it benefits participants. A focus group with the Barts MS Advisory Group in June 2021 highlighted the importance of understanding motivations for and challenges faced by people when taking part in PPI.
Aims: To synthesise benefits and challenges associated with participating in PPI.
Objectives: 1) Conduct a systematic search of published and grey literature, 2) Examine reported benefits and challenges, and 3) Propose recommendations to improving PPI practice
Methods: We searched five online databases for studies published in English from 1996. Grey literature sources were also included.
Results: From 2077 unique records, 57 papers progressed to data extraction. NVivo 12 qualitative software and Braun and Clarke's framework for thematic analysis were used to identify common concepts and themes. All included articles were published after 2007 and 33 of the original studies were from the UK.
People reported benefitting from PPI personally and professionally. Personally, PPI helped them to dealwith their diagnosis, illness and build confidence. They appreciated meeting others in similar circumstances and engaging with researchers outside a clinical setting. Professionally, people developed skills such as presenting at conferences, writing papers and conducting research. This helped a small number to return to paid work or start a university degree.
However, participants and researchers identified there was often a lack of organisational structures and commitment to PPI, for example not always involving people from the beginning of the research project. Additionally, some people experienced a "burden of involvement," being overwhelmed from the emotional stress of participating, time commitment and navigating through an academic environment. Finally, researchers did not always value people's "experiential" knowledge, which meant their feedback and input was not always considered to inform research.
Conclusions: Participating in PPI can offer people a wide range of benefits. Researchers should consider 1) informing people of potential benefits of PPI when recruiting, 2) how they manage any "burdens" people experience and 3) how they use people's feedback to inform research or communicate why it has not been used.

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EP0855

Communicating the relevance of neurodegeneration and brain atrophy to multiple sclerosis patients: patient, provider and researcher perspectives

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Background: Central nervous system (CNS) atrophy provides valuable additional evidence of an ongoing neurodegeneration

process in persons with multiple sclerosis (PwMS), independent of lesion accrual. However, there are limitations for interpretation of CNS volume changes at individual patient-level. Whether or not the topic of CNS atrophy should be proactively discussed with PwMS, during office appointments, is currently controversial.

Objectives: To develop educational guide for patients and providers with recommendations for minimizing confusion and anxiety, and facilitating proactive discussion about brain atrophy.

Methods: During years 2020/2021, three subcommittees (patient's, provider's and researcher's) were formed among 6 academic and non-academic MS centers in the USA, and several workshops were held to discuss relevant topics. The providers' and patients' surveys were developed to better understand practices for discussing MRI findings with focus on brain atrophy in PwMS

Results/Conclusions: The following recommendations were created: 1) PwMS should receive basic information on understanding of brain functional anatomy, and explanation of inflammation and neurodegeneration; 2) the expertise for atrophy measurements should be characterized as evolving, 3) quality patient education materials on these topics should be provided, 4) the need for standardization of MRI exams has to be explained and communicated, 5) providers should discuss background on volumetric changes, including references to normal aging, 6) the limitations of brain volume assessments at an individual-level should be explained, 7) the timing and language used to convey this information should be individualized based on the patient's background and disease status, 8) a discussion guide may be a very helpful resource for use by providers/staff to support these discussions, 9) understanding the role of brain atrophy and other MRI metrics may elicit greater patient satisfaction and acceptance of the value of therapies that have proven efficacy around these outcomes, 10) the areas that represent possibilities for positive self-management of MS symptoms that foster hope for improvement should be emphasized, and in particular regarding use of physical and mental exercise that build brain reserve through increased network efficiency, and 11) an additional time during clinical visits should be allotted to discuss these topics, including creation of specific educational programs.

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EP0856

Patient-reported outcome measures as indicators of Progressive disease in multiple sclerosis: a "must" in the elaboration of a set of minimum relevant data in multiple sclerosis patient-centered healthcare

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Introduction: The information provided by the person with multiple sclerosis (pwMS) through patient-reported outcomes measures (PROMs) may allow to anticipate changes in disease evolution and to design personalized strategies in a model of patient-centred healthcare.
Objective: To determine the value of standardized PROMs in MS in addition to clinical variables and biochemical markers in terms of detecting progressive disease in a relapsing MS cohort.
Methods: Atrasversal analysis in two cohorts of patients with relapsing (n=79) and progressive MS (n=30) was performed. Clinical variables and biomarker assessment were contemporary to self-administration of the questionnaires: EuroQol-5D (EQ-5D), MusiQol, Modified Fatigue Impact Scale (MFIS) and Beck's Depression Inventory II (BDI-II), through an electronic platform. The RMS cohort was prospectively followed for 2-years. Non-parametric tests were used to compare groups or variables.
Results: The information retrieved from all PROMs correlated between them in both RMS and PMS groups ($P<0.001$), except for EuroQoL that did not correlate with the other PROMs in the PMS group. PROMs in RMS and PMS were different, with lower EuroQol and MusiQol and higher MFIS and BDI-II scores in the PMS cohort (Kruskal-Wallis $p<0.01$). Correlation analysis of PROMs and other variables (clinical and biochemical) was performed. All PROMs correlated with the Expanded Disability Status Scale (EDSS) at the time of filling out the questionnaire (Kruskal Wallis $P < 0.01$). MFIS questionnaires provided the better tool to distinguish between patients with distinct clinical data in the RMS cohort. MFIS scores over 29 correlated with longer disease duration (Rho= 0.498, p=0.000), older patients (Rho=0.415, p=0.001), longer performing times in 9HPT for dominant hand (Rho=0.818, p=0.000) and T25FW test (Rho=0.239, p=0.036), and with biochemical biomarkers as baseline CSF CHI3L1 (Rho=0.227, p=0.043), a known biomarker of progressive disease. Contemporary sNFL did not correlate with the information retrieved from the PROMs.
Conclusion: In our analysis PROMs differed between RMS and PMS patients. MFIS scores in the RMS cohort, in particular, correlated with clinical and biochemical variables that are usually elevated in progressive disease. PROMs could be a potential tool for early detection of disability progression, along with other biomarkers, and should be included in the minimum set of relevant data to be gathered in the clinical visit.

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EP0857

Impact of the coronavirus SARS COV-2 (COVID19) pandemic on the quality of life and mood of patients with multiple sclerosis

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Introduction: Multiple Sclerosis (MS) is a disabling chronic disease with clinical heterogeneity and uncertain prognosis. Evaluating the health-related quality of life (HRQoL) of patients is important for the multidisciplinary therapeutic approach including physical, psychic and social aspects that influence the well-being of people with consequences in the course of the disease. As of March 2020 due to the Coronavirus 2019 (COVID-19) pandemic and quarantine measures, habits and access to the health system have been substantially modified.
Objective: Our aim was to evaluate depression level and HRQoL of MS patients and compare this results with pre-pandemic assessment (2019).
Patients and methods: A cross-sectional study was conducted between March and July 2021. Measuring instruments: Clinical, HRQoL: Multiple Sclerosis International Quality of Life questionnaire" (MusiQol), Depression: Beck Depression Inventory II (BDI-II), and pandemic-related aspects using a ad-hoc questionnaire. The results of MusiQol and BDI-II were compared with those obtained from the 2019 evaluations. Parametric and non-parametric statistics were used, to define significance a value of $p < 0.05$ was accepted.
Results: We evaluated 62 patients. In the comparative analysis with 2019, a significant decrease in HRQoL was observed ($z=-2.21$, $p=0.03$). The affected domains were activities of daily living, psychological well-being, and sexual and sentimental life. In contrast, no significant changes were observed in the assessment of depression using BDI-II ($z=-0.39$, $p=0.69$).
Conclusions: HrQoL of MS patients is decreased compared to 2019. The pandemic itself, health and quarantine measures have negatively impacted on HRQoL, substantially impairing patients' performance in activities of daily living, psychological well-being, and sexual and sentimental life.
Disclosure: nothing to disclose

EP0858

Resilience and perceived stress in recently diagnosed people with MS: relations with quality of life and psychosocial outcomes

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Introduction: Multiple Sclerosis (MS) may lead to high levels of stress, either due to the disorder itself or due to uncertainty about the future. Higher resilience and lower perceived stress have been associated with higher quality of life (QoL) and less severe psychosocial symptoms (i.e. anxiety, depression) in MS. However, as their relationship has mostly been studied in patients with longer disease durations, effects in the earliest stage of MS are currently unknown.
Aim: To investigate whether levels of resilience and perceived stress differ between early RRMS patients and healthy controls (HC) and to explore relations with psychosocial and QoL outcomes.
Methods: In this preliminary analysis, data of 41 recently diagnosed RRMS patients (i.e. 6-12 months after diagnosis, 34 women, 37±10 years old, Expanded Disability Status Scale (EDSS): 3, range 2–4) and 16 matched HCs (9 women, 38±10 years old) were included. Data collection is currently ongoing. Disability was assessed with the EDSS, resilience with the Connor-Davidson Resilience Scale and stress with the Perceived Stress Scale. Questionnaires on depression, anxiety (HADS), fatigue (CIS-20r), QoL (MSIS-29) and cognitive complaints (MSNQ) were also administered. Independent t-tests were used to explore group differences and Pearson's or Spearman's correlation to investigate relations. Relations were corrected for multiple testing.
Results: MS patients reported more stress compared to HCs (15.3±5.4 vs. 12.0±6.0, p=0.05, d=0.58). A moderate to high stress level (PSS>14) was seen in 68.3% of the patients versus 37.6% of HCs. Resilience levels were comparable between patients and HCs (p=0.48). In patients, stress levels were not related to disability (p=0.14) but they were associated with more psychological symptoms (anxiety r=0.723, depression ρ=0.415), fatigue (r=0.432), cognitive complaints (r=0.465) and lower QoL (ρ=0.518, all p<0.01). In HCs, stress was associated with anxiety (r=0.596), depression (ρ=0.624), fatigue (r=0.696) and cognitive complaints (r=0.741, all p<0.05).
Conclusion: Compared to HCs, early RRMS patients report higher stress levels even though resilience was comparable between patients and HCs. More perceived stress was related to lower QoL and more severe psychosocial symptoms, but not disability. Longitudinal studies are needed to investigate how stress and resilience evolve over time and if these are potential targets for improving QoL of early RRMS patients.

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EP0859

Functional outcomes in highly-active multiple sclerosis after diagnosis

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Introduction: Highly-active multiple sclerosis (HAMS) during the first years of diagnosis, could lead to higher disability and brain atrophy, with subsequent poor medication response.
Aims: The objective of this study is to analyze functional and imaging evolution of HAMS patients during the first 5 years after index diagnosis.
Methods: We performed a retrospective analysis of subsequent MS patients from a tertiary neurological center in Republica Dominicana; HAMS was defined as the presence of at least >2 relapses per year, during the first 5-years after diagnosis. Univariate and multivariate analysis was done to evaluate association with bad functional status (EDSS ⩾5), in all types of MS.
Results: A total of 167 cases were recruited (71.3% female, with median age of 38 years [IQR 30-46]), accounting for 77.8% remitent-recurrent (RR), 12.0% secondary progressive (SP) and 10.2% primary progressive (PP). Median time of disease evolution was 6 years (IQR 3-10), with HAMS in 23.8% of RR (OR 0.2 [95%CI 0.1-0.5], p<0.001), 57.1% of SP (OR 3.5 [95%CI 1.4-9.0], p=0.006), and 56.3% of PP (OR 3.2 [95%CI 1.1-9.2], p=0.02); EDSS ⩾5 accounted for 13 (25.0%) HAMS cases (OR 3.5 [95%CI 1.4-8.6], p=0.005), and brain atrophy for 31 (60.8%) HAMS cases(OR 2.0 [95%CI 1.0-4.1], p=0.04) after age and sex adjustment, in all three MS variants. Number of lesions (>7) increased the risk for HAMS (OR 2.2, p=0.04), but after covariate adjustment was non-significant.
Conclusion: HAMS increase the risk of bad functional status and brain atrophy during the first 5-years of the index MS diagnosis; this could be an useful measurement to guide disease modifying therapies in early MS stages.

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No conflict of interest to be reported by the authors

EP0860

Towards a self-assessment of autonomy for patients with multiple sclerosis

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Introduction: Independently of disease activity, many patients report impacts of multiple sclerosis (MS) on their autonomy. The literature reports neither a stable definition nor a specific measurement tool for autonomy in MS.
Objectives: To propose a definition of autonomy in MS, to develop an innovative tool to assess patient's autonomy.
Methods: A qualitative study was conducted by a sociologist using semi-structured interview guides with 20 MS patients and 12 HCPs. Patients were asked about their MS history and consequences in their daily lives. HCPs were asked about their assessment of patients' autonomy. Interviews were analyzed using a validated sociological theoretical model. From patients' verbatim, items were identified and grouped into dimensions of autonomy (taxonomy). A questionnaire was then created using these items. Its understanding and relevance were tested with 12 patients in 4 focus groups.
Results: The evaluation of patient's autonomy by HCPs is not standardized and depends on what patients report spontaneously. Beyond functional impairment, patients reported difficulties in maintaining their social roles (professional, parental, etc.) as the main impairment to their autonomy. The preservation of their autonomy depends on maintaining these roles. A new definition of autonomy is proposed: "being able to perform one's most important roles, with or without any assistance".
130 questions were generated and grouped into 13 domains covering 12 social roles and 1 domain covering the reconciliation of these roles. Patients associated this questionnaire to the notion of autonomy and judged that it addressed valid items that were rarely mentioned with HCPs. They found it readable and understandable and suggested improvements.
Discussion: This study shows the importance of social roles in patient's autonomy. It opens a new perspective on its evaluation while underlining the importance of multidisciplinary support (medical, medico-social, psychological and family). It has concrete implications for improving patients' lives: prioritizing what is important to patients will help structure the discussion between patients and HCPs around management goals.
Conclusion: An instrument for assessing patient's autonomy in MS was developed based on patients' experiences and adjusted with them in focus groups. This questionnaire allows to objectify the repercussions of MS on patient's autonomy. A short form will be available after psychometric validation.

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EP0861

Improving health literacy in MS through a multidisciplinary brain health program

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Background: Providing a comprehensive multidisciplinary approach to Brain Health in MS care is an unmet need. Health literacy in particular has been known to play a role in patient outcomes, but there are few standardized interventions aimed at improving it. Our Brain Health Program is designed to provide a multidisciplinary approach that is customized via participant interviews to meet the individual needs of our patients. The purpose of this study was to determine if participation in our brain health program would improve health literacy for patients with MS.
Methods: 24 patients with MS and their caregivers completed a total of 14 1-hour sessions including topics such as MS epidemiology, pathogenesis, natural history and clinical presentation, disease-modifying therapies, the role of exercise, sleep, music therapy and nutrition on brain health, symptom management, and cognition in MS. 78% of participants were females. The mean age at participation was 51 years old, with a mean disease duration of 10 years (ranging from 1 to 33 years). The distribution of MS type was: 55% Relapsing Remitting MS, 25% Secondary Progressive MS and 20% Primary Progressive MS[JF1]. A 5-question Likert scale questionnaire assessing health literacy was administered before beginning the program and again two months after completion.
Results: At the end of our program, all participants (100%) rated a statistically significant improvement on their understanding of MS in order to make educated decisions on their MS therapies. In addition, all participants (100%) felt more confident in their overall knowledge of MS, and more familiar with the concepts of Brain Reserve and Brain Health in MS. Most patients (83%) understood the difference between MS progression and deconditioning. The number of participants who improved their scores on all 5 questions was significant ($p < 0.001$). There was also a significant improvement between patients with the highest level of health literacy pre-intervention versus post-intervention for each question ($p < 0.01$).
Discussion: Our program is unique in the sense that it applies well-established techniques used in medical education to develop patient education programs. We measured the impact of our intervention by utilizing a health care literacy questionnaire. At the end

of our program, all patients improved their knowledge on critical principles necessary to make educated decisions in their MS care.

Disclosure
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EP0862

Association between resilience and total T2 lesion volume on brain MRI in young patients with multiple sclerosis

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Introduction: The links between disease-specific variables at diagnosis, resilience, and psychological adjustment of MS patients remain unknown.
Aims: The study aim is to explore the hypothesis that resilience in MS might be driven not only from psychological, social and cultural factors but also from mechanisms that are intrinsic to the disease process.
Methods: Fifty-one patients with newly diagnosed MS (i.e. no more than two years) and age between 18 and 45 years were recruited in an observational study at University of Verona MS Centre, Italy, in which a predefined set of clinical, psychological, MRI and laboratory measures were collected cross - sectionally at inclusion. The primary endpoint of the study was the correlation between resilience and total T2 lesion volume (TLV) on brain MRI.
Results: The analysed sample currently consists of 41 consecutive patients (27 females) with a mean age of 33.9 years. 87.6% of patients have relapsing-remitting MS and 73.2% an EDSS score $\leqslant 2$. There was no correlation between TLV and resilience. Despite none of the performed correlation analyses showed statistically significant results, a moderate correlation between resilience and age (Pearson coefficient 0.25) and between resilience and time from symptoms onset (0.28) was numerically observed; a weak inverse correlation was found between EDSS score and resilience (- 0.19). In addition, there was a numerical correlation between resilience and the physical health subscore of the MS quality of life-54 questionnaire (0.30).
Conclusion: Resilience of young patients with MS, although not associated with TLV on brain MRI, might be potentially connected to demographic variables, physical wellbeing, disease duration and neurological disability in the early stages of disease.

Disclosure
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All of the authors have nothing to disclose

EP0863

VEP score of the left eye had predictive value for reaching better outcome of treating patients with multiple sclerosis over ten years

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Introduction: In recent years, progress has been made in the treatment of MS with the use of therapy that modifies the course of the disease. A new strategy has emerged in recent years- "treating to target", which aims to achieve the absence of disease activity.
Objectives: To determine the predictive value of VEP in patients with RRMS in achieving better outcome during ten years of first-line immunomodulatory therapy.
Aims: To determine whether lateralization of optic nerve damage may have prognostic significance in clinical disability and good response to therapy.
Methods: In a retrospective study, patients were followed for 2, 5 or 10 years. Visual evoked potentials (VEPs) were performed at the beginning of the follow-up and also after many years of follow-up. Data on optical neuritis (ON) were obtained, the degree of disability was estimated, and magnetic resonance imaging (MR) of the endocranium was performed. Achieving complete remission is a favorable outcome of treatment.
Results: 83 patients with RRMS participated. Favorable outcome reached 19 (22.9%) and did not reach 64 (77.1%) treated with RRMS. Findings of EP score ($r = 0.008$, OR = 0.344 (0.156–0.757)) and latency ($r = 0.042$, OR = 0.966 (0.934–0.999)) at the onset of the disease are predictive factors in achieving favorable outcome.
Conclusion: A regular VEP at the beginning of the disease increases the chance of reaching better outcome about 6 times.

Disclosure
The authors declare no conflict of interest.

EP0864

Caregiver burden and associated factors among caregivers of persons with multiple sclerosis: application of a specific instrument

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Background: Caring for persons with MS (PwMS) may negatively impact several aspects of a caregiver's life.
Objectives: To describe the caregiver burden; to analyze the association between clinical and cognitive variables and caregiver burden and to study the internal consistency of Caregiver Health-related quality of life(CAREQOL-MS).
Aim: to study caregiver burden.
Methods: 50 PwMS and their respective 50 caregivers were included. PwMS=Relapse-Remitting: 41;Secondary-Primary Progressive:6/3; Age:47.08±14.43; Education:14.38±2.91; Disability:4.09±2.65; Evolution:19.18±10.87. Depression: 14.30±10.33 Fatigue:4.01±1.81. Caregivers:Age:53.58±14.05;

Education:14.88±3.08. Measures: Expanded Disability Status Scale, Fatigue severity scale, Beck Depression Inventory, Information processing speed=Symbol Digit Modalities Test and CAREQOL-MS. Statistical analysis: for objective 2, a probit regression was performed and the results are shown in predicted probabilities format, to allow testing of a more comprehensible result and for objective 3, the Item-total correlation test (SPSS) was used.

Results: Considering the median (47) as the cut-off point, 48% of caregivers show burden. For the regression model, physical disability, fatigue, depression, information processing speed and burden (dependent variable) were initially analyzed, as they are considered, from the theoretical framework, to be interrelated. Depression was not significant in the univariate analysis and fatigue largely lost significance when included in the model (p=0.54). Finally, the model had as independent variables: information processing speed (Coefficient:-.05;p=0.0001) and physical disability (Coefficient:-.16; p=0.07). $R^2$43.5%. Prob. chi2=0.22. For the predicted probabilities, the burden level was divided into 6 groups (from lowest to highest) and it was shown that the probability of having a information processing speed is very high in the 1st and 2nd groups (.98 and .87 respectively, lowest confidence interval 0.72) and very low in the 5th and 6th groups (0.07 and 0.01 highest confidence interval 0.22), with no overlapping confidence intervals. Physical disability remained in the model as an adjustment variable. Correctly classified 82.61%. The total corrected item-total correlations of the 24 CAREQOL-MS items ranged from 0.5 to 0.8.

Conclusion: Information processing speed were associated with caregiver burden, adjusting for physical disability. The CAREQOL-MS show adequate internal consistency.

Disclosure

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EP0865

Assessing the impact of US patient support programmes on relapsing-remitting MS patients on dimethyl fumarate

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Introduction: Biogen Patient Support Programmes (PSP) are designed to address unmet medical needs (education, compliance to therapy, disease management) of patients on Multiple Sclerosis (MS) treatments. These programmes may be valuable in improving health related outcomes for MS patients.

Objectives: To compare health outcomes of RRMS patients receiving dimethyl fumarate (DMF) and enrolled on a PSP vs patients receiving DMF and not on a PSP.

Methods: Analysis was conducted using data from the Adelphi MS Disease Specific Programme (DSP), a cross-sectional survey of US neurologists and their MS patients between 2019 and 2021. Data was analysed from PSP and non-PSP patients receiving DMF for at least 12 months. Outcomes for patients enrolled on a PSP were compared to those not on a PSP using propensity score matching (with replacement and allowing for ties). Patients were matched on age, sex, EDSS and disease activity at treatment initiation, lines of therapy, current treatment duration and nurse involvement.

Results: Of 267 DMF Patients, 134 were enrolled on a PSP and 133 were not. A higher proportion of DMF patients on the PSP had improvement in MS disease activity (n=134 74% vs n=133 63%, p=0.043). Patients on a PSP had more consults with a physiotherapist in the last 12 months (n=134 0.36 vs n=133 0.05, p=0.019) and a higher proportion of DMF patients on the PSP reported a moderate or high risk of future progression (n=134 31% vs n=133 18%, p=0.024). Patient outcome measures revealed that DMF patients on the PSP reported higher levels of current treatment satisfaction (scored 1-5) (n=58 4.50 vs n=75 4.17, p=0.007), and a higher proportion were completely satisfied (scored 5) with their current treatment (n=58 53% vs n=75 26%, p=0.001). Patient reported needs revealed that mental and physical fatigue were reported as areas of improvement required by DMF patients not on the PSP but were mentioned less by DMF patients on a PSP (n=58 0% vs n=75 22% p<0.001).

Conclusions: Enrolment on a PSP appears to be associated with improved outcomes in relation to disease activity, greater treatment satisfaction, and less problems with mental and physical fatigue. A higher number of consultations with a physiotherapist suggests that patients on a PSP could be more engaged in their treatment and access more services. Initiating treatments with access to a PSP for patients may have some additional benefits and value beyond the effects of the drug alone.

Study support: Biogen.

Disclosure

DCDLF is an employee of and holds stock/stock options in Biogen. YI is a former employee of and held stock/stock options in Biogen. EJ, MB, JP, ET, and LL are employees of Adelphi Real World.

EP0866

One year with siponimod: a case series with unexpected improvement of spastic bladder

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Introduction: Twenty-one patients (8 males and 13 females) with Secondary Progressive Multiple Sclerosis (SPMS) treated at 251Hellenic Air Force General Hospital with siponimod were assessed in terms of several MS parameters. These data are from patients who have been provided treatment via the siponimod Managed Access Program and patient's signed consent have been obtained.
Methods: All patients at baseline had normal blood and heart tests (ECG and heart U/S), normal eye examination and OCT. Eight of them showed spastic bladder, for at least 2 years before baseline examination, proven with urodynamic test. The follow up included neurological examination and extended blood examination every 3 months. ECG, heart U/S and OCT also were performed every 6 months.
Results: After 1 year, blood tests, heart tests, eye examination and OCT remained normal. There were no signs of clinical or MRI worsening. Most notable was the improvement of spastic bladder in most patients. Five patients stopped all treatment for spastic bladder, including catheterization, one stopped the medical treatment with a 40% reduction of daily catheterizations and the remaining 2 had no improvement.
Conclusion: Siponimod is a S1PR modulator, especially of type 1 and 5 receptors. The follow up results support that siponimod, as an S1P modulator, appears to have benefits on bladder function over above what has been previously reported with other S1P modulators. Indeed, it is unusual for 5 out of 8 patients to stop not only medical treatment but also catheterization. Experimental models, suggest that S1P signalling pathway was significantly up-regulated in association with overexpression of Rho kinases and they hypothesised that S1P-induced bladder overactivity. These findings may suggest that S1P modulates detrusor contraction through a Rho-kinase signalling pathway in overactive bladder. Further studies are needed to elucidate the reasons for such an improvement in bladder symptoms.

Disclosure
Dimitrios Naoumis: Nothing to disclose

EP0867
Social media use and its impact on stigma, coping, and quality of life in patients with multiple sclerosis

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Introduction: Many patients with multiple sclerosis (MS) have already had experiences with stigmatization due to their disease and often report a reduced quality of life. Influences on both stigma experience and quality of life are perceived social support and effective coping.
Aims: This study hypothesizes that social support may also occur online in social media, affecting the patients' coping, perceived social support, stigma experience, and quality of life.
Methods: Using questionnaires, patients with MS were asked about their social media use behaviour, perceived social support, coping, stigma experience, and quality of life.The data were adjusted for age, sex, disease disability, cognition, depression and fatigue. Linear regression models were performed to determine whether the use of social media had an effect on perceived social support, coping, stigma experiences and quality of life.
Results: 90.1 % of the total 88 participants reported having used social media with regard to their MS before. The main reasons were the search for information (84.1 %) and the exchange of advice among the patients themselves (53.4 %).Social media use showed an influence on stigma experience ($\beta = .27$, $p < .02$), social support on quality of life ($\beta = .22$, $p < .01$), and coping on stigma experience ($\beta = .24$, $p < .04$).
Conclusions: To address stigma experiences and quality of life, it is important to increase patients' social support and coping skills with the help of supportive social media use.

Disclosure
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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Clinical aspects of MS - Economic burden

EP0868
Socioeconomic influence on DMT prescribing strategies

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Introduction: Recent studies have shown differing outcomes for patients with MS based on socioeconomic status. As MS providers have gained an increasing number of DMT options there has become a delineation between those drugs that are considered high vs moderate efficacy. Given this evolving treatment paradigm, we were interested in whether socioeconomic status influences prescribing of high vs moderate efficacy DMTs.
Objectives/Aims: To determine whether socioeconomic status, using U.S. Census social vulnerability index (SVI), impacts prescribing strategies for high vs moderate efficacy DMTs for MS.
Methods: SlicerDicer (Epic) was used to identify patients with MS seen at our center in the past 5 years (1/1/2017 to 12/31/2021) on an FDA-approved DMT for MS. This population was divided

by U.S. Census Social Vulnerability Index (SVI) into quartiles (<24%, 24-49%, 49-74%, >74%). SVI data included poverty level, unemployment, income, and attainment of a high-school diploma. High efficacy DMTs included natalizumab, ocrelizumab, alemtuzumab, mitoxantrone, fingolimod, siponimod, ozanimod, ponesimod, and ofatumumab. Moderate efficacy DMTs were considered dimethyl fumarate, monomethyl fumarate, diroximel fumarate, glatiramer acetate, teriflunomide, interferon beta 1a, and peginterferon beta 1a. Distribution of high vs moderate efficacy DMT prescribing within SVI quartiles was evaluated using two-factor ANOVA. Post-hoc analysis was performed by Bonferroni correction.

Results: An average of 1451 patients per year from 2017 to 2021 on a DMT for MS were identified. There was a trend toward increasing rates of high efficacy prescribing for all groups (43.3% on high efficacy in 2017 vs 60.9% on high efficacy in 2021). A significant difference in prescribing between quartiles was seen (p-value 0.00023). Post-hoc analysis revealed a difference in prescribing for the second quartile (24-49%) for whom high efficacy drugs were less frequently prescribed early in the study.

Conclusions: DMT prescribing strategies differed for patients in the second quartile (24-49%) of socioeconomic status by SVI at our center over the past 5 years. This difference was seen early in the study with all levels of socioeconomic status trending toward similar rates of high efficacy prescribing by the end. The cause for this lower rate of high-efficacy prescribing will require further evaluation; one theory is that patient assistance programs may distort the economics of DMT affordability for this quartile of patients.

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EP0869

Clinical and economic burden of comorbidities in multiple sclerosis

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Introduction: Comorbid conditions are common in persons with multiple sclerosis (pwMS), and can lead to poorer outcomes negatively impacting on MS course, delay of diagnosis, progression of disability, treatment management and adherence. Existing literature has examined the economic cost of MS (1), however, evidence is lacking on the specific contribution of comorbidities to this burden. The aim of the study was to quantify the clinical and economic burden of comorbidities in pwMS, providing estimates based on a bottom-up approach related to main component of costs (health, non-health care cost and productivity loss).

Methods: The study is a retrospective study carried out in two Northern Italian areas (Pavia and Genoa). The presence of main comorbidities was investigated through an anonymous self-assessment questionnaires. Costs were compared between pwMS with at least one comorbidity vs. pwMS without comorbidity. Adjusted incremental costs associated with comorbidities were reported using general linear models with log-link and gamma distributions or two-part models (for cost components > 5% zero values). Models were controlled for age, sex, educational and disability levels; robust sandwich-type variance estimator was used to account for clustering within MS Centers.

Results: Six hundred pwMS were included in the analysis. 51.0% had ⩾1 comorbidity. Hypertension (21.0%), depression (15.7%) and anxiety (11.7%) were the most prevalent comorbidities. The average annual total cost per patient was 18,500€ and 14,533 € for those with ⩾1 comorbidity and without comorbidity, respectively. The total cost remained significantly greater when at least one comorbidity was present, with an incremental cost amounted to 3,311 € after controlling for age, sex, educational and disability levels (<0.001). The main components of costs resulted increased in comorbidity group, being incremental costs significant for health care costs and productivity loss (1,077€, p<0.001 and 333€, p=0.046, respectively) after controlling for potential confounders.

Conclusion: Presence of comorbidities increases the complexity of patient management and have health, social, and economic consequences for pwMS. These data can provide a more complete picture for the economic implications in MS to health and non-health care providers and policy makers.

Disclosure

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Bergamaschi R. has served on scientific advisory boards for Biogen, Merck-Serono, Novartis, Roche, Sanofi-Genzyme; received research support from Almirall, Bayer, Biogen, Merck-Serono, Novartis, Sanofi-Genzyme; received support for travel and congress from Biogen, Roche, Merck-Serono, Roche, Sanofi-Genzyme, Teva; received honoraria for speaking engagement from Biogen, Celgene, Merck-Serono, Novartis, Roche, Sanofi-Genzyme.

EP0870

The impact of cognitive impairment on disease burden in Chinese patients with multiple sclerosis: a model simulation study

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Introduction: The prevalence of cognitive impairment (CI) is above 40% in Chinese patients with multiple sclerosis.
Objectives: To assess the potential impact of CI on the disease burden in Chinese patients with newly diagnosed relapsing-remitting multiple sclerosis (RRMS) .
Methods: A Markov model was designed to simulate the risk of CI, risk of developing secondary progressive MS (SPMS), and mortality risk in Chinese patients with newly diagnosed RRMS (mean age: 36.6 years; female: 63.8%). Another Markov model was constructed to simulate the age and gender-matched Chinese general population as the control. Both English and Chinese bibliographic databases were searched for appropriate evidence to estimate model inputs. Base case analysis compared the disease burden outcome measures, which included cumulative risk of CI, life years, quality-adjusted life years (QALY), and lifetime costs, between the two model cohorts. One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) assessed the uncertainty of the estimated disease burden.
Results: Model simulations estimated that the lifetime cumulative risk of developing CI in Chinese patients with newly diagnosed RRMS was 85.2%. Relative to the matched Chinese general population, newly diagnosed RRMS patients were associated with reduced life expectancy (33.2 years vs. 41.7 years, difference: -8.5 years), reduced QALY (18.4 QALY vs. 38.4 QALY, difference: -19.9 QALY), increased lifetime medical costs (¥613,883 vs. ¥202,726, difference: ¥411,157), and increased lifetime indirect costs (¥1,099,021 vs. ¥94,612, difference: ¥1,004,410). The patients with developed CI alone the simulation process accounted for 99.9% of reduced life years, 76.0% of the reduced QALY, 55.8% of the increased lifetime medical costs, and 79.2% of the increased lifetime indirect costs, respectively. The disease burden outcome measures were mainly driven by the risk of developing CI, progression risk from RRMS to SPMS, hazard ratios of mortality associated with CI relative to no CI, utility of patients with RRMS, annual relapse risk, and annual costs of personal care. PSA confirmed the robustness of the base case analysis.
Conclusions: Most Chinese patients with newly diagnosed RRMS would develop CI in their lifetime and patients with developed CI could make a major contribution to the disease burden of RRMS by driving mortality risk, reducing the quality of life, and increasing both direct and indirect costs.

Disclosure
Qian Jiang: No conflicts of interest to declare.
Wenjun Wang: No conflicts of interest to declare.
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Yan Xu: No conflicts of interest to declare.

EP0871

Determination of the main reason for work difficulties in persons with multiple sclerosis: physical disability or social cognitive function

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Background: Although it is not expected that multiple sclerosis (MS) has a significant limiting effect on life expectancy, it causes disability that develops over the years, leading to substantial psychological and socio-economic consequences in addition to its biological effects. Appropriate and effective interaction with the social environment is fundamental in being a biopsychosocial healthy person in society. Deficits of social cognitive abilities and an increasing physical disability can cause significant job losses.
Aim: The study aims to define the relationship between physical disability, social cognitive function, and work difficulties in persons with MS (pwMS).
Methods: This cross-sectional study was conducted at the Outpatient MS Unit of Dokuz Eylül University Hospital, Izmir, Turkey. Reading the Mind in the Eyes Test (RMET), Facial Affect Recognition (FAR) test and Empathy Quotient (EQ) was used to evaluate social cognition. Physical disabilities were assessed with 2 Minute Walk Test (2MWT), the Multiple Sclerosis Walking Scale-12 (MSWS-12), and the Expanded Disability Status Scale (EDSS). Also, The Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ) was used to assess the level of perceived workplace difficulties.
Results: The mean EDSS score was 1.61±1.57 (range between 0-5.5), the mean age was 36.65±9.9 (range between 19-53), and the mean disease duration was 6.65±6.0 (range between 0-23). There was no relationship between social cognitive assessment and MSWDQ. On the other hand, there was a moderate positive correlation between EDSS and MSWS-12 and MSWDQ (rho=418; p=0.047 and rho=566; p=0.005, respectively). Also, 2MWT and MSWDQ have a moderate negative correlation (rho=-0.487) (p=0.022).
Conclusion: This study showed that physical disabilities could be the major reason for perceived workplace difficulties for pwMS. Also, it is important the highlight that our participants had low EDSS scores. These results indicated that pwMS with low disability level experience work-related difficulties welded lower extremity performance.

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Emre Bora: Nothing to disclose
Serkan Ozakbas: Nothing to disclose

Clinical aspects of MS - Neuro-ophthalmology

EP0872

The evolution of internuclear ophthalmoparesis in multiple sclerosis: a one year follow-up study

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Introduction: Internuclear ophthalmoparesis (INO) affects about 25% of individuals with multiple sclerosis (MS) if assessed by infrared oculography. The assessment of INO by infrared oculography is more sensitive than bedside assessment. The evolution over time of an INO detected by infrared oculography is not known.
Objectives: We aimed to describe the evolution of INO over time as assessed by infrared oculography and to investigate the relation of the course of INO to clinical characteristics of MS.
Methods: In a prospective, longitudinal, cohort study from the MS Center Amsterdam, horizontal pro-saccades were measured and analysed using a validated standardized infrared oculography protocol (DeMonS) at baseline and one year follow-up. Presence of an INO was defined by previously published cut-off levels of the versional dysconjugacy index (VDI). All subjects were also assessed for clinical function, including Expanded Disability Status Scale (EDSS), Nine Hole Peg Test (NHPT), High and Low Contrast Visual Acuities (HCVA and LCVA).
Results: There were 80 individuals (74% female, age 47 ± 10 years) with eye-tracking data at baseline and after one year follow-up. The median disease duration was 11 years (IQR 11). The median EDSS was 3.5 (IQR 1.5). At baseline an INO was present in 21/80 (26%) participants, which was bilateral in 6/21 (29%). At one year follow-up the INO persisted in 14/21 (67%) participants and resolved in 7/21 (33%) participants. Among participants without an INO at baseline 3/59 (5%) developed a de novo INO. Overall INO wasmore prevalent among males (52%) than females (22%) (p=0.002). MS subtype or EDSS had no statistically significant relation with the course of INO. Compared to participants in which INO resolved after one year, participants with a persistent INO performed worse on the NHPT at both baseline (median 26 vs. 21 sec, p=0.012) and follow-up (median 24 vs. 20, p=0.031) and LCVA (median 13 vs. 24, p=0.040) at follow-up. Participants with a novel INO performed worse on LCVA at follow-up compared to individuals without INO (median 14 vs. 29, p=0.028).
Conclusions: Consistent with clinical experience spontaneous resolution of an INO was observed in a proportion of patients using infrared oculography.For the majority of subjects the INO persisted independent of the MS disease course. Both persistent and de novo INO were related, statistically, to loss of function on other clinical scales.

Disclosure
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EP0873

Clinical and paraclinical characteristics of optic neuritis in the context of the McDonald criteria 2017

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Introduction: Optic neuritis is often the first manifestation of multiple sclerosis (MS). The symptom triad of visual reduction, color desaturation, and retrobulbar pain is considered characteristic. Since the diagnosis of optic neuritis is primarily clinical and based on subjective information provided by patients, there is a risk of possible misdiagnosis. The 2017 revision of the McDonald criteria emphasizes the need for objectifiable clinical or paraclinical criteria for the diagnosis of clinically isolated syndrome (CIS). Detailed studies on subjective complaints of optic neuritis as the initial manifestation of MS using the 2017 McDonald criteria are lacking.
Objectives: Data were analysed to determine whether the constellation of symptoms and the presence of objectifiable findings in the setting of optic neuritis can point to the possible diagnosis of CIS or MS.
Aims: The aim of this work was to find out which symptom constellations and objective findings in the clinical diagnosis of optic neuritis may indicate the presence of CIS or MS.
Methods: Data were collected retrospectively from all patients who were hospitalized for the first time at the Department of

Neurology, Hannover Medical School, between 2010 and 2018 for a clinical diagnosis of optic neuritis.
Results: A total of 252 patients with optic neuritis were included. 110 of these patients had MS, 101 patients had CIS, and 41 patients were diagnosed with isolated optic neuritis without objective findings (ON). Visual disturbance was the most commonly reported symptom (95.1% of ON patients, 97% of CIS patients, and 96.4% of MS patients). Colour desaturation was the second most common (ON: 43.9%; CIS: 66.3%; MS 69.1%). The least frequently reported symptom was retrobulbar pain (ON :43.9%; CIS: 62.4%; MS: 62.7%). The combination of all three symptoms was present in 24.4% of all ON patients, in 40.6% of all CIS patients, and in 47.3% of all MS patients.Comparison between groups of visual acuity (using the decimal visual acuity scale) of the affected eye showed a significant difference between the ON and MS groups with a mean of 0.64 for ON and 0.28 for MS.
Conclusions: Analysis of the data shows that the typical symptom triad is most common in patients diagnosed with MS. It also shows that visual acuity is lower in patients with optic neuritis in MS than in patients with isolated optic neuritis.

Disclosure
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Clinical aspects of MS - Comorbidity

EP0874
Comorbidities in colombian patients with multiple sclerosis

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Introduction: Comorbidities have become an area of growing interest due to their high frequency in people with Multiple Sclerosis (pwMS) and their negative impact on the overall course of the disease. Comorbidities are present in up to 35% of pwMS at the time of diagnosis and have been associated with a progressive course and also have implications for treatment choice, rate of health care use and quality of life. Several studies have characterized the pattern of comorbidities in high prevalence regions of Multiple Sclerosis (MS), but less is known about comorbidities in low prevalence MS countries such as Colombia.
Objectives: Describe the frequency of comorbid conditions and their impact on MS clinical outcomes in two cohorts of Colombian pwMS.
Methods: This is a cross-sectional observational study. A validated, digital, self-reported questionnaire covering over 30 comorbidities was sent to consecutive pwMS in reference centers from the two major cities in Colombia. The overall frequency and that of selected comorbidities was calculated in the whole sample and according to the center studied, and selected clinical variables were analyzed according to the comorbidity status.
Results: We surveyed a total of 249 pwMS, 182 in Bogotá and 67 in Medellín. 70.7% were women, with a mean (SD) age of 38 (12.4) years, 92.8% had relapsing MS, and a median (IQR) EDSS of 1.0 (0.0 to 2.0). Mean (SD) disease duration was 9.3 (7.2) years. A total of 117 (53.7%) pwMS reported comorbid conditions, 19.7% at least one comorbidity, 14.2% two and 19.7% of them had 3 or more comorbidities. 51.2% pwMS from Bogotá and 60.7% from Medellín had at least one comorbidity (p=0.284). The most common comorbidities were Psychiatric (22.9%), Autoimmune (20.6%) and Vascular (19.7%). Patients with comorbidities were found to be older (39.7 vs 35.3, p 0.005) and comorbidities were more frequent in patients with progressive compared to relapsing MS (90.9% vs. 50%, p=0.021). There was a trend for higher disease duration in patients with comorbidities (9.6 years vs. 7.8, p=0.093).
Conclusions: Comorbidities patterns in pwMS in our equatorial country appear to be similar to other regions studied. There seems to be no difference in the frequency of comorbidities between pwMS from the two cities studied. As in other studies, comorbidities are likely related to progressive MS and older age. We still have a knowledge gap about the prevalence of comorbidities in other Latin American countries.

Disclosure:
C.G.-S is an ECTRIMS clinical fellowship awardee 2022-2023, has received consulting fees from Novartis, Biogen-Idec, Sanofi-Genzyme, Merck, Bristol Myers Squibb and Roche, and travel expenses for scientific meetings from Sanofi-Genzyme,

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S.C.-R. was an ECTRIMS clinical fellowship awardee 2019-2020; has received travel expenses for scientific meetings from Genzyme; compensation for consulting services or participation on advisory boards from Merck, Roche, Biogen-Idec and Novartis; speaking honoraria from Novartis; and research support from Biogen-Idec.
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EP0875

Exploring COVID-19 vaccine uptake, hesitancy, and disease-related beliefs in people with multiple sclerosis

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Introduction: People with multiple sclerosis (MS) are vulnerable to severe outcomes from COVID-19 infection and were prioritised for COVID-19 vaccination in Australia from March 2021. Despite this, vaccine hesitancy may hinder optimal vaccination uptake.
Aims: This study explored COVID-19 vaccine uptake, beliefs, and hesitancy in people with MS.
Methods: People with MS receiving MS healthcare management at two Australian health services were invited to participate in an online survey, between September and October 2021. The survey collected sociodemographic and disease-specific characteristics, as well as vaccine status, vaccine hesitancy and beliefs towards COVID-19 vaccination using validated scales: the Oxford COVID-19 Vaccine Hesitancy Scale, the Oxford COVID-19 Vaccine Confidence and Complacency Scale, and the Disease Influenced Vaccine Acceptance Scale-Six. Regression analyses were used.
Results: Of the 281 people with MS (mean age 47.7 [SD 12.8] years; 75.8% females) who participated, 82.9% had received ⩾1 COVID-19 vaccine dose. There were 17.1% who were unvaccinated, of which 51.2% reported they were likely to accept vaccination in future. Younger participants were less likely to be vaccinated (B[SE] 0.05[0.01]), as were those within 1-5 years disease duration (B[SE] -1.17[0.39]), all $p<0.05$. Compared to vaccinated participants, unvaccinated participants reported higher vaccine hesitancy (B[SE] 9.66 [0.72]), greater negative attitudes around vaccine complacency and confidence (B[SE] 13.36[1.40]), greater complacency toward COVID-19 in the context of MS (B[SE] 1.80[0.50]), and higher MS interaction concerns (B[SE] 3.38[0.52]), all $p<0.001$. Participants who reported no impact of MS on their daily life had lower concerns about the impact of COVID-19 vaccination on MS treatments or disease progression, compared with those reporting MS impacted their daily life all of the time (B[SE] -2.00[0.66], $p=0.002$).
Conclusions: General and disease-specific COVID-19 vaccine concerns may influence uptake for people with MS. Understanding the reasons for hesitancy and how they correlate with MS disease and treatment interaction concerns may inform tailored education messages at individual and population levels that addresses these concerns, particularly for ongoing booster doses.

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EP0876

Blood pressure variability is altered in secondary progressive multiple sclerosis but not in patients with clinically isolated syndrome

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Objectives: To investigate differences in beat-to-beat systolic blood pressure variability (SBPV) in people with secondary

progressive MS (pwSPMS), clinically isolated syndrome (pwCIS) and healthy controls (HC).
Methods: *This retrospective study, case-control study included 46 pwSPMS, 46 pwCIS and 44 HC were included in this study. A semi-automated software made with MATLAB R2019b (The MathWorks, Inc.) was used for evaluation of SBPV. The frequency domain characteristics observed were the power spectrum in the LF and HF bands and the LF/HF ratio. Data is expressed in absolute power (mmHg²) of LF and HF and ratio (LF/HF) during both supine and tilt-up phases of testing.*

Results: There were no significant differences in mean systolic (sBP) or diastolic blood pressure (dBP) values during supine and tilt-up phases of testing between groups. During the supine phase of testing LF and LF/HF were significantly lower in SPMS group (4.17±5.38 and 3.52±2.34, respectively) compared to CIS (5.42±3.59, p=0.015 and 5.92±4.63, p=0.029, respectively) and HC group (6.03±4.55, p=0.011 and 6.52 ±5.09, p=0.010, respectively), while during tilt-up phase LF was significantly lower compared to both CIS and HC group, and HF was significantly lower only compared to CIS group.
Conclusion: SBPV is altered in pwSPMS compared to pwCIS and normal controls. Further research in the field of MS related dysautonomia is warranted not only because of its relevance to comorbidities and MS symptoms, but also because of its likely involvement in the pathophysiology of MS.

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EP0877
Assessment of prevalence of diabetes mellitus according to the serum level of hemoglobin A1C in patients with multiple sclerosis; a case-control study

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Introduction: Diabetes mellitus, especially type-1 and multiple sclerosis (MS) are both autoimmune diseases that are differed in clinical manifestations and pathogenesis. The causes of type-1 diabetes and MS remain largely unknown, but genetic and environmental factors, including infectious agents, are believed to be considerable.
Objectives: Reports of familial and intrapersonal co-occurrence of type 1 diabetes and MS have suggested a possible etiological relationship. However, most previous observations have been reported based on case reports, patient collections, or small epidemiological studies reported by a few number of MS patients and self-reported information about family relationships and family histories. Therefore, the concurrent reporting of type 1 diabetes and MS needs further confirmation.
Aims: Due to the importance of diabetes prevention in improving the course of disease, health and quality of life in patients with MS and due to the lack of a study on chronic diabetes-related blood factors (Hb-A1C) in these patients, we decided to conduct this study for the first time in Iran.
Materials and Methods: In this cross-sectional study done in 2019, 80 patients with multiple sclerosis referred to an MS clinic were selected by the available sampling method. 80 healthy individuals were also included as a control group. Participants' information was collected through a checklist. After obtaining informed consent, about 5 ml of venous blood was taken from each participant and sent to the laboratory to measure serum levels of FBS and Hb-A1c. Statistical significant point was set at $>$ 0.05.
Results: In the group of MS patients, 58 were female (72.5%) and 22 were male (27.5%). Based on the results, no significant difference was observed between the serum level of Hb-A1C in the two groups of patients and controls (p 0.07). In logistic regression analysis, after adjustment of confounders (age, sex, smoking, alcohol consumption, history of hypertension, body mass index, and duration of disease), no significant result was obtained for serum level of Hb-A1C in MS population.
Conclusion: The results of our study showed that after adjustment of the confounding factors, no significant difference was seen in the serum level of Hb-A1C between patients and healthy controls.

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Maryam Poursadeghfard: nothing to disclose
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EP0878
COVID-19 and its outcomes in multiple sclerosis patients

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Background: Coronavirus Disease 2019 (COVID-19) is a highly contagious disease that resulted in 4533645 deaths until September first, 2021. Multiple Sclerosis (MS) patients receive immunosuppressive drugs. Thus, there is a concern that these drugs will reduce the patient's immune system resistance against COVID19.
Objectives: This study aimed to evaluate the epidemiology of COVID19 and its impact on MS patients in our university hospital in Tehran City, Iran.
Materials & Methods: A cross-sectional study was conducted based on hospital-based registry data from May 2020 to March 2021. Among more than 500 registered MS patients in Imam Khomeini Hospital in Tehran City, Iran, referring within our study period, 84 patients reported SARS-COV2 infection. The diagnosis of MS was confirmed by the McDonald criteria. Moreover, the diagnosis of COVID-19 in MS patients was established by the real-time-PCR technique and chest computed tomography.
Results: Out of 84 MS patients with SARS-COV2 infection, 55(65.5%) were women, and their mean age was 37.48 years. The most commonly used medications by MS patients were Rituximab 20 (26.3%) and Dimethyl Fumarate 14(18.4%). Totally, 9(10.8%) of the patients needed to be hospitalized due to COVID-19, with a mean hospitalization duration of 5.88 days. A total of 1 (1.2%) death was reported.
Conclusion: Compared to the healthy population, COVID-19 is not more serious in MS patients. Most MS patients with COVID-19 infection were not hospitalized and continued their medication during the infection.
Keywords: Multiple Sclerosis (MS), Coronavirus Disease 2019 (COVID-19), Epidemiology

Disclosure
nothing to disclose

EP0879

Older patients with multiple sclerosis have greater enlargement of the brain ventricles following COVID-19

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Introduction: The effect of COVID-19 on brain pathology in multiple sclerosis patients is currently unknown.
Objectives: To describe changes in brain lesion activity as well as brain and spinal cord volumes following COVID-19.
Methods: We included 181 MS patients (McDonald 2017 criteria) with available MRI scans (N=650) before (#scans>=2) and after (>=1) COVID-19. All patients were clinically stable (no relapsing activity or disability progression), did not received high-dose steroids, and did not change treatment status. All patients were scanned on a single 3T scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). Brain MRI activity was assessed manually by neuroradiologist using automatic subtraction. Global and regional brain volumes were evaluated using the MorphoBox prototype software, and the mean upper cervical cord area (MUCCA) was assessed using ScanView software. Linear mixed models (with random intercept for patient) adjusted for sex age, disease duration, Expanded Disability Status Scale (EDSS), treatment status at infection, severity of COVID-19, and use of anti-covid treatment were used to analyze the difference in MRI measures before and after COVID-19.
Results: The sample consisted of 75.7% of women, the mean duration of the age was 45.5 years, the mean disease was 15.1 years, and median EDSS was 2.0 (range 0-6.5). A total of 7.2% patients had not immunomodulatory treatment, 39.8% were on platform, 37.0% were on oral, and 16.0% were on high-efficiency monoclonal antibody immunomodulatory therapy. Together, 3.3% of the patients were asymptomatic, 82.3% had a mild infection, 14.4% had suspected or confirmed pneumonia. Patients with a higher age had a greater enlargement of the total ventricle volume (interaction age vs. COVID-19: b=0.0029; p=0.0027), right and left lateral ventricles (b=0.0012-0.0013; p=0.0069-0.0015), third ventricle (b=0.0002; p=0.027) and a greater reduction of mesencephalon volume (b=-0.0004; p=0.013) following the infection. In eleven patients on anti-CD20 treatment we found reduction of normalized white matter (b=-0.58; p=0.044) and hippocampal white matter volume (b=-1.73; p=0.0063). The brain lesion activity (occurrence of new and enlarging T2 lesions) was not influenced by the infection.
Conclusions: Older MS patients had greater enlargement of brain ventricles after COVID-19. We did not find clear changes in lesion activity or brain tissue volumes following the infection.

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EP0880

Combined implications of ageing and multiple sclerosis on bone health: a systematic review

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Introduction: The existing literature regarding bone health (the bone mass and the architectural structure of the bones) and bone mineral density (BMD), has largely focused on young and middle-aged persons with multiple sclerosis (pwMS) while there is a lack of knowledge regarding bone health in older pwMS. Due to the combined effects of aging (having deleterious impact on bone health) and MS, older pwMS thus likely possess greater risk of osteopenia and osteoporosis.
Objectives/Aim: To systematic review current evidence on bone health among older pwMS and to compare this to bone health data from the general populations and health registers.
Methods: A systematic literature review regarding bone health among older pwMS was conducted in February 2021 on Pubmed, Embase and Scopus.
Results: The results of the literature research showed no studies, that had examined bone health in pwMS aged ⩾60 years, meanwhile 3 studies on middle-aged pwMS (mean age range 51-56 years) were found. Data from these studies did however reveal high prevalence of osteoporosis (16-44%) on lumber spine and head of femur level. These numbers are substantially greater than the prevalence in age-matched healthy controls (men 16-44-fold greater; women 5-15-fold greater). If focusing on the lowest reported prevalence of osteoporosis (16%) in middle-aged pwMS, this corresponds to the prevalence observed in healthy 70-74-year-old women and almost two times greater than the prevalence observed in healthy very old men (⩾90 years). The largest frequency of osteoporosis in the general population is women in the age group 85-89 years (29.4%), which is approx. 1.5 times smaller than the upper range of osteoporosis in middle-aged pwMS (44%).
Conclusion: No studies reporting on bone health in older pwMS could be identified. However, we can conclude that 1) BMD decreases progressively with ageing; 2) bone health in pwMS is reduced compared to the general healthy population; and 3) middle-aged (51-56 years) pwMS have similar or larger prevalence of osteoporosis compared to that of healthy women aged ⩾ 70 years and larger prevalence of osteoporosis compared that of healthy men aged ⩾ 90 years. Based on our findings, we speculate that bone health of older pwMS is substantially affected producing very high prevalence of osteoporosis.

Disclosure
Nothing to disclose

EP0881

Occipital neuralgia in multiple sclerosis patients: a tertiary center experience in Turkey

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Introduction: Multiple sclerosis (MS) is a demyelinating, neurodegenerative and inflammatory disease of central nervous system (CNS). Unclear nature of MS may manifest itself in various clinical presentations. Headache is well known issue which exists not rarely in MS patients and it adversely affects quality of life. Neuralgias have high prevalence and incidence in MS patients compared to general population. Even though occipital neuralgia (ON) may be an initial complaint, the lack of unquestionable frequency data is an open question.
Objectives: Our goal was to determine the relation between localization of cervical lesion and occipital neuralgia.
Aims: We aimed to investigate the frequency of occipital neuralgia in our MS patients.
Method: Between January 2019 and March 2022, we collected data of 296 patients diagnosed with MS by MS consultant neurologists according to McDonald 2017 criteria in our tertiary center. Demographic data, medical history, MS subtype and duration of disease, treatment, expanded disability status scale (EDSS) score and magnetic resonance imaging (MRI) assessment were recorded. International classification of headache disorders (ICHD) 3rd edition (beta version) was used to diagnose ON. Diagnose of ON was made independently by two neurologists.
Results: One hundred fifty three patients out of 296 have cervical lesion on MRI and 103 of them accepted to be included in the study. Mean age was 35.67±11.4 and 61.2% (n=63) were female. The most frequent MS subtype was RRMS (72.8%, n=75). Mean duration of disease was 6.81±6.58 years; mean EDSS score was 1.91±1.78. Our 13 patients (12,7%, n=13) diagnosed with ON and 8 (7.8%) of them were female. The mean pain duration was 5.1±1.6 minutes and pain localization was dominantly on the right side. All patients had episodic type of ON. C2-3 localization was detected in 38.5%(n=5) of ON patients and determined in 6.7%(n=6) non-ON patients. That difference pointed statistical significance (p=0.004) between ON and C2-3 localization. There was no significant relation between age, sex, MS subtype, duration of disease and EDSS with ON (p>0.05).
Conclusion: Contrary to what is believed, ON is not rare in MS patients. It can be the initial manifestation of an attack. Early diagnosis and relief of pain with effective treatment may help to raise quality of life. This study was designed to increase the awareness of ON.
Disclosure: The authors declare no conflict of interest.

Clinical aspects of MS - Digital health and global networks

EP0882

Addressing the MS care paradox: practical solutions

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Introduction: At ECTRIMS 2021, we presented the 70 centre UK MS Service and DMT prescribing audit [1]. This uncovered an MS care paradox: an increasing ability to affect MS patient outcomes, but adiminishingability to deliver MS outcomes. This is due to; shortages of resources and alignment, inability to influence change, suboptimal utilisation of available data and lack of accountability and responsibility failures at all levels.

Objectives: Here we describe actions taken post audit to address the paradox.

Methods: The audit results were discussed with NHS organisations, third sector (patient charities) and others.Potential projects were proposed, discussed and refined. A set of deliverable projects actionable by the UK MS community were identified.

Funding models that maximise the benefits of funding were considered.

Results:

The projects, for which funding has been sought, are:

Clarifying roles and responsibilities of MS team members

Website, to facilitate communication and good practice repository

Where's the care? – UK MS care map development

Recording care – MS team documentation

Measuring outcomes – MS expectation frameworks (for Patients and teams)

Maximising core activities – making blueteq (England web-based drug reimbursement forms) and prescribing databases indispensable

Advancing data value – improving Hospital Episode Statistics (HES) data quality and routine use

Ensuring the future – making MS an attractive career option

A ring-fenced entity (Transforming MS 4 All) was established within an existing not-for-profit community interest company (CiC).

Conclusions: We believe that the challenges faced by UK MS services are not unique and that the proposed solutions are transferrable worldwide. These deliverable, impactful projects should improve UK MS care. Managing governance and finances under a not for profit organisation, enables transparency, accountability and reinvestment of funding, to sustain services. Nevertheless, much more is needed.

Reference

1 UK MS services in crisis? An audit of 70 Centres exposes the MS care paradox. J Hobart, J Mathews D Rog and the Raising the Bar MS study group. ECTRIMS 2021 E poster

Disclosure

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MSGo, a digital support program for multiple sclerosis patients in Australia using novartis disease modifying therapies

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Introduction: The MSGo Programme is a patient support platform (PSP) designed for patients commencing on multiple sclerosis disease modifying therapies (DMTs) provided by Novartis. The PSP is delivered through RxMx, a digital health company. The technology aims to connect patients and doctors, improve patient safety and create real-time insights with the support of nurses to assist patient navigation. The patient apps feature tailored functions, including medication reminders, appointment scheduling and educational materials. The nurses work directly with patients to address DMT issues and questions, in order to promote engagement and adherence. The patient app also includes a care partner function, to enable a caretaker to monitor from their own device.

Objective: The rapidly changing landscape of DMTs, pharmacovigilance and COVID-19 has added challenges to DMT prescreening, onboarding and ongoing support of patients, with many clinics being restricted on physical attendance. The patient app, paired with the HCP and care partner function, aims to keep patients on track with their DMTs and appointments whilst maintaining active communication with their healthcare team.

Aim: A recent study of MS Nurse care in Australia found that for 5% of participants the PSP services offered across all DMTs was their sole source of support. The aim is to explore the effectiveness of MSGo, a PSP which has evolved since the COVID-19 pandemic as a resource of support, information and communication for both the patient and treating MS team.

Method: Patients utilising the MSGo app were sent voluntary surveys every 3 months, to ascertain effectiveness of the programme (phone, app or email) since enrolling.

Results: There are 1200+ patients actively enrolled within the programme. An average patient satisfaction score of 9/10 was recorded for all questions, which covered various aspects of the PSP including DMT initiation, virtual support, at home support and nursing support. The full results of the survey will be presented.

Conclusion: Patient survey responses indicate that MSGo has been an effective PSP and demonstrates an ongoing need for patients to be supported during their DMT journey, particularly in situations where the PSP nurses are the sole source of support.

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Gina Saad is an employee of Novartis Pharmaceuticals Australia
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EP0884

Demographic patterns of MS patients using BRISA–an MS specific app in Germany

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Introduction: Multiple Sclerosis (MS) is one of the most common neurological disorders with a high incidence rate in Germany. It is a chronic and progressive neurological autoimmune disease affecting the central nervous system to varying extents. This severely impacts the quality of life of patients impairing their day-to-day activities over a course of time. BRISA is a digital app specifically designed to help MS patients in Germany track their disease course by regularly monitoring symptoms. In this study, we aimed to comprehensively understand the demographic and health-related characteristics of BRISA users.
Methods: Demographic and health-related data provided by 2095 patients/users during onboarding were analyzed to describe patient characteristics such as gender, age, type of MS and medication. Using the symptoms tracked during the course, their distribution based on age, and time since diagnosis were studied. Additionally, the probability of symptom pairs tracked together were also analyzed, based on the type of MS. Significant differences in proportions across different study groups were statistically evaluated using a pairwise chi-square test.
Results: Users of the BRISA app are predominantly females between the age of 26–55 years. Relapsing-remitting MS (RRMS) was the most prevalent form of MS observed within this cohort. The time since MS diagnosis commonly varied between 0–30 years. The standard first-line category 1 drugs were most frequently used followed by the high-efficacy category 3 drugs (such as monoclonal antibodies). The relative frequencies of use of category 1 and category 2 drugs (such as spingosine-1-phosphate receptor modulators) significantly altered with time since diagnosis, whereas the relative frequency of use of category 3 drugs remained unchanged. Fatigue, concentration disorders, tingling, forgetfulness, and pain were the top 5 symptoms that mainly affected users. While the relative frequency of these symptoms did not depend on age, it seemed to depend on the time since diagnosis. Novel symptom pairs such as concentration disorders-tingling and fatigue-tingling were frequently tracked by RRMS patients in comparison to primary progressive MS patients.
Conclusion: The results from this descriptive study highlight the diversity among MS patients and the need for extensive cohort characterization in a real-world scenario. In-depth analysis could also help in identifying novel insights that could aid in disease management.

Disclosure
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EP0885

Exploring the utility of ActiGraph in measuring gait impairment and physical activity in patients with MS using digital biomarkers

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Introduction: Gait impairment is a common, clinically relevant issue for patients with multiple sclerosis (MS). Traditional disability assessments (eg, Expanded Disability Status Scale [EDSS], Timed 25-Foot Walk [T25FW]) are widely used, but more sensitive, objective, and clinically meaningful real-world gait impairment measures are needed. Wearable sensors measure multiple gait parameters, but data on their potential to detect gait deficits in patients with MS and correlation to traditional disability parameters are limited.
Objective/Aim: To report findings from a pilot sub-study of the Phase 2b tolebrutinib long-term safety (LTS) study (NCT03889639) that assessed compliance with a wearable actigraphy device and describe the design of a validation sub-study of the Phase 3 tolebrutinib studies to assess the use of actigraphy in measuring gait changes in patients with progressive MS (PwPMS).
Methods: The Actigraphy LTS pilot sub-study assessed compliance with the ActiGraph device (defined as 8/14 compliant days with ⩾11 hours/day of device wear/monitoring period) that monitored gait and activity over 4 one-month monitoring periods. The Phase 3 validation sub-study will recruit approximately 250 PwPMS from the PERSEUS (NCT04458051) and HERCULES (NCT04411641) tolebrutinib trials. Patients will receive instructions for using the device and will be monitored 14 days/month

for ⩾12 months. The primary endpoint is correlation of gait measures with standard disability progression assessments (EDSS, T25FW). Key gait measures include gait speed, step duration, and step length. Physical activity measures include number of steps and number of walking episodes. The secondary endpoints are to establish normative values for velocity, stride length, and step duration for subsets of EDSS in PwPMS.

Results: Compliance in the Actigraphy LTS pilot sub-study was 61%–90% over 4 monitoring periods, with a mean daily wear time ranging from 5.9–14.9 hours. The mean daily wear time for 79% of patients was >10 hours. As reported in the literature, actigraphy gait measures were correlated with EDSS. Findings from the Actigraphy LTS pilot sub-study supported the design of the Phase 3 validation sub-study.

Conclusions: The Actigraphy LTS pilot sub-study showed that patients can use the ActiGraph device with relatively good compliance. This Phase 3 validation sub-study will provide further clinical data on actigraphy as a more sensitive measure to track disability progression in PwPMS.

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EP0886

A prospective study of the feasibility of smartphone-based self-monitoring to characterise cognitive and neurological impairment in people with multiple sclerosis: Floodlight MS moreactive

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Introduction: Floodlight™ MS (FL MS) is a smartphone app-based solution comprising five Software-as-a-Medical-Device-regulated, self-administered assessments that measure hand function, gait and cognition in people with multiple sclerosis (PwMS), in addition to patient-reported outcome measures (PROMs).

Objectives: To describe the FL MS MoreActive study, which evaluates the feasibility of FL MS assessments for characterising cognitive and neurological impairment and trajectories in PwMS.

Methods: FL MS MoreActive is a multicentre, prospective, non-interventional, primary data collection study in PwMS (ISRCTN62225263). Eligibility criteria include: Age ⩾18 years; verified diagnosis of MS; Expanded Disability Status Scale (EDSS) score of 2.0–7.0 inclusive; not experienced a clinical relapse in the 30 days prior to enrolment and owns a FL MS compatible smartphone. Three digital tools will be used: FL MS, MSReactor and Redenlab. Study endpoints include cross-sectional and longitudinal correlations between digital outcome measures and cognitive and clinical outcome assessments, MRI and PROMs.

Results: 600 participants will be enrolled across seven sites in Australia. After familiarization and baseline (BL) periods (~8 weeks), patients will be allocated into three cohorts according to the frequency (1-, 2- or 4-weekly) of FL MS Cognitive Test performance (information processing speed) to investigate practice effects. All other FL MS tests will be performed remotely every 2 weeks. MSReactor (cognitive impairment) and Redenlab (speech impairment) apps will be used remotely every 4 weeks. Clinic visits are at BL and Months (M) 6, 12, 18 and 24. A self-administered neuropsychological brief battery (Audio Recorded Cognitive Screen) will be measured in clinic (BL, M12 and M24) in addition to EDSS score, information on relapses and treatment (all visits). In-clinic FL MS (BL, M6), Redenlab (BL) and MSReactor (tests and PROMs; BL, M12, M24) assessments will also be performed. MRI scans (lesion and brain volume metrics) will be obtained at BL and then performed annually. For participants with an initial disability progression/improvement at M24, EDSS data up to M36 will be collected.

Conclusions: This novel study will provide evidence for the feasibility of smartphone-based test scores to characterise cognitive and neurological impairment, providing insight into the potential of digital outcome measures to monitor disease trajectories for PwMS.

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EP0887

Satisfaction with remote visits for people with multiple sclerosis: The TELE MS randomized controlled trial

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Introduction: Continuous monitoring is the hallmark of managing chronic disease. Multiple sclerosis, in particular, requires patients to visit their treating neurologists typically twice a year, at least.
Objectives: To determine satisfaction with remote visits for people with multiple sclerosis (MS) and investigate non-inferiority compared to conventional visits.
Aims: To investigate feasibility of singular remote visits.
Methods: TELE MS was a randomized controlled trial that was open to any person with MS. We randomized a volunteer sample of 45 patients. We compared satisfaction with remote visits (via phone or via videochat) with conventional outpatient visits. The primary endpoint was patient satisfaction determined by the Telemedicine Perception Questionnaire (TMPQ, min: 17 and max: 85 points) with the assumption of non-inferiority of televisits compared to conventional visits. Physician satisfaction measured on the PPSM score (Patient and Physician Satisfaction with Monitoring, min: 5 and max: 25 points) was the secondary endpoint.
Results: The trial met both endpoints. Mean (SD) TMPQ scores in the individual groups were 58 (6.7) points for conventional visits, 65 (7.5) points for phone visits, and 62 (5.5) points for video visits. Physician satisfaction over the whole cohort was similarly high. Median (range) PPSM scores were 23 (16-25) for the whole cohort, 19 (16-25) for conventional visits, 25 (17-25) for phone visits, and 25 (16-25) for video visits.
Conclusions: Televisits in multiple sclerosis yield a high level of satisfaction for both patients and treating physicians. The concept or remote patient monitoring may be communicable to other chronic diseases as well.

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Nothing to disclose

EP0888

Digital symbol-digit modalities test with modified protocols in patients with CNS demyelinating diseases: feasibility and patient preference

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Introduction: Cognitive impairment (CI) is prevalent in patients with multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD), and its monitoring is important. The paper-based Symbol Digit Modalities Test (SDMT) is the most widely used clinical assessment tool, however traditional methods may be time-consuming in routine practice and have unwanted learning effects. We hypothesized that modifying the SDMT protocol to prevent learning effects may reliably evaluate CI with a shorter test time and improve the patient satisfaction.
Objectives: Recently, we developed novel tablet-based modified digital SDMT (MD-SDMT), of which symbol-digit combination changes with every trial, and devised two protocols according to test time (MD-SDMT_1-min and MD-SDMT_2-min). We aimed to explore their feasibility and patient preference, as compared to the paper-based SDMT.
Methods: Between July 2021 and February 2022, patients with MS and NMOSD who visited a tertiary hospital were prospectively enrolled. Participants were assessed with MD-SDMT_1-min and MD-SDMT_2-min, along with paper-based SDMT. During the MD-SDMT trials, participants were given a randomly changed key ofnine symbol-digit pairs with each test trial. Pearson correlations (r) between MD-SDMT and paper-based SDMT scores were evaluated. Participants who provided additional consents responded to a questionnaire about preference for the assessment tools.
Results: A total of 144 patients (99 [70%] with MS, 45 [30%] with NMOSD) were enrolled and assessed (mean age: 49 years, mean Expanded Disabilty Status Scale: 3.0). Both MD-SDMT scores were well correlated with paper-based SDMT scores (2-min, $r = 0.88$; 1-min, $r = 0.85$, all $p<0.0001$) in all participants. These close correlations were comparable between MS (2-min, $r = 0.89$, 1-min, $r = 0.83$, all $p<0.001$)and NMOSD patients (2-min, $r = 0.85$, 1-min, $r = 0.88$, all $p<0.001$). A total of 92 participants answered the questionnaire, and they preferred the tools in order of MD-SDMT_2-min (59%), MD-SDMT_1-min (33%), and paper-based SDMT (8%). Remarkably, the lowest tercile age group (<41 years) tended to prefer the MD-SDMT_1-min tool.
Conclusions: MD-SDMT protocols reliably evaluated CI even with a short test time in patients with MS and NMOSD. Most (>90%) patients preferred MD-SDMT over paper-based SDMT, while the preferred test time may vary depending on patient characteristics.

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Pathology and pathogenesis of MS - Pathology

EP0889

Characterization of the transcriptional response of human brain derived endothelial cells to pro-inflammatory cytokines IFNγ and TNFα in vitro

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Background: Multiple sclerosis (MS) is an auto-immune disease of the central nervous system (CNS), characterized by a disruption of the blood-brain barrier (BBB) and the meningeal brain barrier (BMB). The mechanisms leading to barrier degradation in MS involve effects of secreted cytokines/chemokines on the endothelial cells (ECs), thereby leading to CNS immune infiltration. Exposure of the endothelium to pro-inflammatory cytokines interrupts the homeostasis of the barriers by disrupting tight and adherent junctions, consequently increasing the permeability of the barrier. Cytokines secreted by different effectors of the immune system induce various functional responses in ECs, quantifiable through measurement of the transcriptome.
Objectives: Compare the transcriptomes of BBB and BMB-associated ECs in steady-state.
Identify the transcriptional response of ECs to cytokine stimulation.
Methods: ECs from human brain tissue removed at surgery were put in culture and inflamed with cytokines (TNFα and IFNγ). Bulk RNA-Seq was performed on treated and untreated EC with paired-end fragments on an Illumina NextSeq500 machine, at a targeted depth of 50M reads per sample. Reads were aligned to the human reference genome with STAR. Differential expression analysis was performed with R packageslimma. Biological insights from sets of differentially expressed genes were obtained through gene-set enrichment analysis.
Results: Preliminary analysis on three samples per group showed significant transcriptomic differences between the ECs forming the BBB and the BMB. We found that BMB and BBB differed in their immunological profiles for the expression of cell adhesion molecules, chemokines and cytokines such as IL11 and CCL26. Moreover, cytokine stimulation induced significant transcriptional changes in the BBB/BMB-associated ECs. These changes included genes such as SOD2, IL32 and IRF1. Overall, ECs' response to cytokine stimulation involved both immune pathways (e.g. defense response, inflammatory response) and house-keeping functions (e.g. chromosome segregation, tissue development).
Conclusion: The results demonstrate that there are differences in the molecular properties of ECs depending on the structure they are forming. Gene expression changes induced by cytokine stimulation showed that ECs are highly responsive to cytokine stimulation, suggesting they play an important role in the processes that lead to immune infiltration.

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nothing to disclose

EP0890

Early signs of myelin degeneration in the diffusely abnormal white matter in MS

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Introduction: The diffusely abnormal white matter (DAWM) in MS brains is characterized by ill-defined borders, myelin thinning and signs of axo-myelinic degeneration in absence of frank inflammation. Moreover, recent imaging studies have reported that this region might evolve into a white matter focal lesion over time, supporting the possibility that the DAWM represents an early phase of demyelination in MS.
Objectives and methods: To further explore this possibility we performed an in-depth (immuno)histochemistry characterization of the DAWM to investigate the level of post-translational modification (PTM, citrullination) of the myelin basic protein, a process recently shown to represent a primary sign of cytodegeneration in MS NAWM able to trigger a secondary immunological attack against myelin constituent.
Results: As expected the DAWM in MS brains revealed a subtle reduction in myelin lipid content ($P<0.001$). DAWM regions with lower myelin percentage were also accompanied by higher degree of inflammatory markers (major histocompatibility complex type-II + cells, $p<0.05$). Assessment of axonal integrity by virtue of axonal neurofilament markers showed neither significant axonal loss nor increase in axonal swellings in comparison with the NAWM ($P>0.05$) suggesting that the DAWM less likely represents an area of Wallerian degeneration than previously hypothesized.
Analysis of the content of citrullinated (citMBP) and degraded MBP (dMBP) in the DAWM showed overall enhanced proportion of both markers in comparison with the NAWM ($p<0.05$). Intriguingly, analysis of the ratio normal MBP/dMBP or citMBP per myelinated axon in the DAWM showed a significant difference for the latter protein only ($p<0.05$), suggesting that the observed overall increase in dMBP is mostly due to fragmented myelin content.

Conclusions: In light of these findings, the DAWM may represent an early lesion region of MS brains that holds biochemical signs of myelin degeneration in absence of overt inflammation. The release of cit/dMBP content may secondarily trigger the well-described immunological attack against myelin in MS.

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EP0891

Profiling MS with MS: utilization of mass spectrometry imaging to profile molecular expression during MS progression

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Introduction: Multiple sclerosis (MS) is a neuroinflammatory and demyelinating disease of the central nervous system (CNS) that affects millions of people worldwide, predominantly young adults. A pathological hallmark of MS is the presence of focal inflammatory-mediated demyelination within the brain and spinal cord white matter. However, the molecular profile and mapping of the demyelination process remain unresolved. Additionally, myelin's high lipid content and unique lipid profile have been relatively under-studied mechanistically and as molecular targets for immunotherapy treatments. Myelin contains high levels of 3-O-sulfogalactocylceramides (sulfatides), associated with oligodendrocyte maturation and myelin formation, and its accumulation has been associated with neurodegenerative diseases, including MS.
Objective: The recent development of more sensitive molecular imaging applications utilizing mass spectrometry imaging (MSI) allows for further elucidation of immunopathological features of MS and their impact on disease outcomes. Our objective was to use MSI to define the spatial dynamics of MS lesions.
Aim: We have developed a sample preparation method for molecular imaging and chemical characterization of in situ neuronal sulfatides utilizing matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry imaging. MSI provides information onin situ spatial distribution, colocalization, and relative abundance of sulfatides within tissue samples, reducing the amount of precious sample required for molecular profiling.
Results: We have combined modified histology staining methods with MSI to visualize lipid expression and examine lipid expression at particular disease stages, with the spatial resolution capable of replicating tissue morphology. We observed an apparent decrease in sulfatide expression during disease progression.
Conclusions: We posit that MSI lipid profiling of MS progression will aid understanding mechanisms of demyelination and provide the foundation for alternative drug targets in immunotherapy treatments. Our results serve as a stepping stone to other mass spectrometry applications, such as guided proteomic expression in MS. In time, the continued evolution of MSI will reveal complete lipidomic and proteomic profiles from CNS tissue sections.

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EP0892

Association between brain volume and blood lipids changes in multiple sclerosis patients: a large sample size real-world study

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Introduction: Association between altered cholesterol metabolism and multiple sclerosis (MS) disease activity has been suggested. However, there are still a lot of unanswered questions essential for establishing the causal relationship.
Objectives: To investigate association between brain MRI imaging and blood lipid measures in MS patients.
Methods: In this large longitudinal study we included 1505 MS patients (all MS phenotypes) with available pairs of MRI scans and blood lipid levels (n=4966 pairs; time difference <3 months). All patients were scanned on a single 1.5-T MRI (Gyroscan, Phillips). Whole brain volumes and T2 lesion volumes were evaluated using ScanView software. Lipid profiles consisting of total cholesterol, low density-lipoprotein cholesterol (LDL-C), high density-lipoprotein cholesterol (HDL-C), and triacylglycerol (TAG) were obtained in routine clinical practice. Cross-sectional analysis at baseline was performed using adjusted linear regression model. The linear mixed models (with random intercept for patient) adjusted for sex age, disease duration, Expanded Disability Status Scale (EDSS), treatment status at visit and time between MRI scans were used to analyze the association between imaging and lipid measures.

Results: The sample consisted 70% of women, the mean duration age was 35.9 (SD = 9.77) years, the mean disease duration was 8.02 (SD = 7.20) years, median EDSS 2.0 (IQR = 2.0,3.0), mean follow-up duration was 7.7 years. A total of 17.1% patients were not on immunomodulatory treatment, 72.3% were on first-line and 10.6% were on second-line immunomodulatory therapies. In longitudinal mixed model analysis, we found an association between brain parenchymal fraction (BPF) and HDL-C (b=-0.5; 95% CI: -0.51, -0.27; p=<0.001). At baseline, BPF was associated with LDL-C (b=0.25; p=0.001) and HDL-C (b=-0.52; p=0.0012). We also found associations between (log+1) EDSS and TAG (b=0.027; p=0.011) and HDL-C (b=-0.07; p=0.008).
Conclusions: This large longitudinal real-word cohort shows association between whole brain volume and blood lipids changes in MS patients. Whether this association is causal, or only epiphenomenon requires further investigations.

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EP0893
Ultrastructural analysis of myelinated axons in normal appearing white matter in multiple sclerosis reveals reduced axon density without alterations in axon area and g-ratio

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Introduction: The underlying pathophysiology of multiple sclerosis (MS) include inflammation, demyelination and neurodegeneration, but the exact mechanisms of disease initiation and progression are still unknown. While demyelination is evident in MS lesions, subtle macroscopically visible changes in the myelin content and morphology are observed in non-demyelinated areas of people with MS. Additional ultrastructural characterisation of (sub)cellular features of myelinated axons in non-lesional areas may provide novel insight and a more complete understanding of (local) pathological mechanisms involved in MS.
Aim: Identify early pathological features in MS by revealing hidden abnormalities of myelinated axons and their mitochondria at the nanoscale.
Methods: Post-mortem white matter brain tissues of people with MS (normal appearing white matter, NAWM) and control subjects (control white matter, CWM) were subjected to large scale scanning transmission electron microscopy. Typically, sub-millimetre areas were studied at nm-range resolution. Myelinated axons were analysed for the following parameters: radius, myelin thickness, g-ratio, myelin degeneration, density and cross-sectional area. In addition, the number, size and shape of mitochondria in myelinated axons were examined.
Results: Our findings showed a significant, 1.5-fold reduction in the density of myelinated axons in NAWM compared to CWM, which was not paralleled by a decrease in cross-sectional axon area and an increase in myelin deterioration. Accordingly, in NAWM the number of small myelinated axons (<0.25um) was reduced and the average axon radius tended to be slightly higher (10%), while the g-ratio and myelin thickness were similar as in CWM. Furthermore, the extracellular space was increased. The number and morphological parameters of mitochondria in myelinated axons marginally differed between NAWM and CWM.
Conclusions: Our results suggest a selective loss of smaller myelinated axons in NAWM of people with MS versus control subjects. This may than be compensated by swelling of the remaining axons and subsequent adjustment of myelin thickness to maintain the g-ratio. These subtle ultrastructural changes in NAWM point to early pathological alterations in MS.

Disclosure
The authors declare no conflict of interest.

Pathology and pathogenesis of MS - Experimental models

EP0894
In vitro model for investigating the effect of patient-derived multiple sclerosis monocytes on cellular-scale cortical network function

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Introduction: Studies suggest that progressive multiple sclerosis (MS) results from local central nervous system (CNS) inflammation driven by CNS-resident cells following the infiltration of cells such as monocytes from the periphery. Yet little is known about whether monocytes in MS directly disrupt neuronal function and if that effect differs in different stages of the disease.
Objectives: To establish an in vitro humanized model for mechanistic evaluation of the effect of monocytes on cortical function in MS.
Methods: We compared network activity in healthy human cortical neurons with and without the presence of MS derived and healthy monocytes using microelectrode array (MEA) recordings. Monocytes from relapsing remitting MS, secondary progressive MS and healthy controls were co-cultured with cortical neurons–differentiated from healthy human derived induced pluripotent stem cells–and human primary astrocytes. Another control consisted of cortical neurons in culture with astrocytes without monocytes. The cortical cultures and primary astrocytes were plated on MEA plates (6 wells, 64 electrodes per well, Axion Biosystems) that allowed repeated recordings of spontaneous network activity from each developing culture network. Ten-minute-long recordings were performed weekly for 2.5 weeks at baseline before adding monocytes and immediately following the addition of monocytes to culture and then every 3 days for 3.5 weeks after co-culturing with monocytes. The neuronal synaptic activity was analyzed using our unique semi-automated network analysis pipeline in the MATrix LABoratory (MATLAB) platform.
Results: The cortical cultures (n=75000 cells/well) and primary astrocytes (n=12000 cells/well) were plated on MEA plates. In our pilot experiments, addition of monocytes collected from MS patients and healthy controls at days-in-vitro (DIV) 19 was not toxic to the cortical neurons and we were able to record network activity until DIV 45. We had 40 percent increase in action potential after each feeding suggesting robust activity in the culture. Our next step is to test different concentrations of monocytes and compare cell-autonomous and non-cell-autonomous effects on the cortical networks.
Conclusion: Our study aims to establish an in vitro humanized platform for testing the effect of monocytes, or other immune cells, on cortical function at the cellular scale. This model may provide both mechanistic insight and be utilized for screening potential therapeutics.

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EP0895

Chronology of chitinase 3-like-1 (CHI3L1) expression in early and late lesions in a marmoset EAE model

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Introduction: Chitinase 3-like 1 is a protein secreted by endogenous glia in the central nervous system with prognostic implications in multiple sclerosis (MS) and a predictive role in progression of disability. Experimental autoimmune encephalomyelitis (EAE) in the common marmoset recapitulates many radiological and pathological features of focal MS lesions in the cerebral white matter.
Objective: Our aim was to analyze the chronology of CHI3L1 expression by astrocytes and/or microglia in correlation with the age of acute MS lesions in the marmoset EAE model.
Methods: Three marmosets (three females, aged 2–5 years) received intradermal injections of 600 ul white matter homogenate emulsified in complete Freund's adjuvant, in four dorsal sites around the inguinal and axillary lymph nodes. Eight lesions were detected in the MRI, dated, and processed for histology. Serial in vivo proton density-weighted (PDw) magnetic resonance imaging (MRI) was used to track lesions and to determine age, stage of development, and location. Immunohistochemistry was performed for CHI3L1 and Iba1 in consecutive sections from histopathological specimens, and percentage area of staining in lesions was quantified. Immunofluorescence was performed with CHI3L1, GFAP, Iba1, and APP antibodies. Pictures were acquired with optical and confocal microscopes, respectively.
Results: In the marmoset EAE model, CHI3L1+ was expressed by astrocytes. CHI3L1+ astrocytes and Iba1+ microglia were found within active lesions, and their expression did not overlap. Iba1 expression varied depending on lesion age with a peak in lesions aged 2 to 6 weeks (< 2 weeks: 11.9% area; 2-6 weeks: 25.2% area; > 6 weeks: 12.8% area). On the contrary, CHI3L1+ astrocytes were increased in late-stage lesions (< 2 weeks: 6.3% area; 2-6 weeks: 6.2% area; > 6 weeks: 13% area). Thus, late-stage lesions had a similar proportion of Iba1+ microglia and CHI3L1+ astrocytes. APP+ transected axons were associated with CHI3L1+expansions in late-stage lesions.
Conclusions: In summary, our data support the notion that Iba1+ microglia could be the main cell type in early-stage lesions in the marmoset EAE model, and CHI3L1+ astrocytes more characteristic of late-stage lesions. This fact could be potentially explained as a recruitment and activation of CHI3L1+ astrocytes by microglial cells upon lesion infiltration. This neuroinflammatory feedback might account for the axonal damage in late lesions.

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EP0896

Remibrutinib, a novel Bruton tyrosine kinase inhibitor, exhibits improved target selectivity and potency in vitro

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Introduction: Bruton's tyrosine kinase (BTK) is a key signaling node in B cell receptor and Fc receptor signaling. BTK inhibitors (BTKi) are an emerging oral treatment option for patients suffering from multiple sclerosis (MS). Several covalent and reversible BTKi are in clinical development for MS. For covalent enzyme inhibitors, in vitro assays are influenced by experimental conditions and are time dependent.
Objectives: To assess the potency and selectivity of BTKi under comparable experimental conditions.
Methods: In human blood, in vitro binding of covalent inhibitors to BTK was assessed over time and concentration. The in vitro inhibition of human blood B cells and basophils for the covalent and the reversible BTKi was assessed, as well as the impact of drug washout on in vitro B cell inhibition of the reversible compared to a covalent BTKi. Kinase selectivity of BTKi was assessed in a binding assay to allow direct comparison of covalent and reversible BTKi. Selectivity was first screened kinome-wide, followed by Kd (dissociation constant) determinations on selected kinases.
Results: Covalent inhibitors showed time- and concentration-dependent BTK binding in vitro in human blood with IC_{50} at 1 hour of 21 nM for remibrutinib, 508 nM for evobrutinib, 165 nM for tolebrutinib and 427 nM for orelabrutinib. These values correlated well with the in vitro B cell inhibition with IC_{50} of 18 nM for remibrutinib, 320 nM for evobrutinib, 74 nM for tolebrutinib, 185 nM for orelabrutinib, and 15 nM for the reversible fenebrutinib. Comparable potency was found for basophil inhibition. B cell inhibition in vitro by the covalent BTKi remibrutinib was not sensitive to washout in contrast to the reversible BTKi fenebrutinib. Kinome selectivity screening at 1 μM showed the following ranking: remibrutinib, fenebrutinib, evobrutinib, orelabrutinib and tolebrutinib (from least to most off-target kinase binding). The same pattern was confirmed in a quantitative assessment of binding constants to a subset of kinases.
Conclusions: BTKi currently in clinical development for MS exhibit a varying degree of selectivity across the human kinome with the highest selectivity seen for remibrutinib. Such a distinction may translate into differences in safety and clinical efficacy.

Disclosure
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EP0897

Inducible nitric oxide synthase deficiency leads to early and severe demyelination in a murine coronavirus induced disease model of multiple sclerosis

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Introduction: Inducible nitric oxide synthase (iNOS) catalyses production of nitric oxide during an inflammatory stimuli and is a signature marker of M1-like microglia/macrophages. iNOS mRNA and protein were found in brain lesions of MS patients however its role in demyelination remains unclear. We employed RSA59, a mild hepatoneurotropic strain of Mouse hepatitis virus (MHV) which in 4-weeks-old C57BL/6 mice causes biphasic CNS disease characterised by acute neuroinflammation (day5 p.i.) and chronic demyelination and axonal loss (day30 p.i.). Microglia/macrophages are central to the disease pathology and require assistance from infiltrating CD4+ T cells to mount protective host immune response. The CNS immune interactions during the acute-adaptive transition stage thus determine disease trajectory.
Objectives: To understand the role of iNOS in microglia/macrophage and peripheral T cell communication and assess its effect on demyelination.
Aims: To study the role of iNOS in demyelination.
Methods: 4–5-weeks-old MHV-free wildtype C57BL/6 (WT) and iNOS knockout (iNOS-/-) mice were infected intracranially with 20000 or 10000 pfus of RSA59 and assessed daily for weight loss and disease score. Mice were sacrificed at day9/10 and day30 p.i. CNS viral titers were detected by plaque assay. Transcript levels of anti-inflammatory and phagocytic M2-like phenotype markers were analysed by qRT PCR. Differential CNS immune cell infiltration was assessed by flow cytometry. LFB and Iba1 staining was used to study demyelination and microglia/macrophage activation in the CNS.
Results: iNOS-/- mice infected with RSA59 at 20000 pfus exhibited aggravated disease and high mortality at the acute-adaptive transition stage i.e., day9/10 p.i. as compared to wildtype controls despite being no differences in virus clearance by the CNS. Histopathology at this stage showed early demyelination in the spinal cords accompanied by presence of amoeboid microglia macrophages; high CNS mRNA expression of M2-like phenotype markers, TGFβ, Arg1, CD206 and TREM2; and more infiltration of T regulatory cells. iNOS-/- mice infected at low pfus of virus i.e., 10000 also showed significantly more chronic demyelination at day30 p.i.
Conclusion: Our studies reveal a protective role of iNOS against RSA59 induced demyelination by regulating the CNS

inflammatory phenotype specifically the phenotypic transition of microglia/macrophages and thereby their interaction with peripheral immune cells.

Disclosure
The authors declare no conflict of interest.
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B. Saha has nothing to disclose.

Clinical aspects of MS - NMOSD

EP0898
Neuromyelitis optica spectrum disorders in an argentinian cohort: a hospital-based study

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Introduction: Neuromyelitis optica spectrum disorders (MOSD) is a severe autoimmune inflammatory disorder of the central nervous system with a prevalence of 0·5–4·4 cases per 100000 people.
Objective: Diagnosis awareness has increased in recent times; however, information on NMOSD characteristics in Latin America is little known. To our knowledge this is the largest study of NMOSD in Argentina.
Aim: The aim of this study is to describe a cohort of Neuromyelitis Optica Spectrum Disorders (NMOSD) patients in a Public Hospital of Buenos Aires City, Argentina.
Methods: This is a descriptive study in which we assessed the medical records of NMOSD patients followed up at Neurology Department, Ramos Mejia General Hospital. The 2015 diagnostic criteria of the International Panel for NMO diagnosis were used. Data was analyzed using SPSS version 25.0 and a (p) value <0.05 was considered significant.
Results: 96 patientswere diagnosed.80,2%% were females with a male / female ratio of 1:4. Mean age at onset and disease duration was 30 (range 2-68) years and 9 (6-15) years respectively. 9,3% had an onset of the disease at an age greater than 50 years,18,7% debuted before 18 years of age.
At the debut, 42 (43,7%) had optic neuritis (ON), 31 (32,2%) transverse myelitis (TM),10 (10,41%), simultaneous TM&ON and 7 (7,3%) area postrema syndrome. Association with other autoimmune diseases occurred in 27% patients. Out of 88 / 96 patients tested, 65 (73,8%) were positive for antibodies against aquaporin-4. 19% of the patients showed abnormal brain magnetic resonance imaging (MRI) with nonspecific lesions. Spinal cord MRI showed that 74% of the cases had longitudinally extensive transverse myelitis and 26% had short transverse myelitis. All patients were on treatment with immunosuppressants (47,7% with rituximab, 33,2% with azathioprine,10% with azathioprine plus corticosteroids
(CTC), 4% with CTC only and 6% others.
Conclusions: This is the largest descriptive study in an Argentinian cohort of patients with NMOSD. We show a wide epidemiological, clinical, radiologic and treatment spectrum of NMOSD.

Disclosure
All the authors: nothing to disclose

EP0899
Drawing the road map for the future pandemic with what we learned from the COVID-19 in neuromyelitis optica spectrum disorder: a large cohort study

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Introduction: There is concern that people with neuromyelitis optica spectrum disorder (NMOSD, pwNMOSD) may be defenseless to developing coronavirus disease 2019 (Covid-19) due to immunosuppressive therapy. Moreover, there is limited information prognosis of Covid-19 in NMOSD.
Aims: The study aims to investigate the relationship between the demographic, clinical, and therapeutic characteristics of the NMOSD cohort and the outcome of Covid-19 infection and compare it with the general population.
Methods: The whole NMOSD cohort, consisting of 90 people followed up at the Dokuz Eylul University Hospital, was interviewed at least once, face-to-face, via text message, or by phone, and the participants were questioned whether they were infected with Covid-19. The Covid-19 infection was detected in 19 pwNMOSD. A semi-structured phone interview consisting of 34 questions was done with all patients infected with Covid-19 infection, and detailed information about the Covid-19 infection course was obtained. Clinical information was obtained from the patient's medical records.
Results: We identified 16 confirmed and three suspected (not confirmed with real-time PCR) pwNMOSD who had experienced Covid-19 infections. Three pwNMOSD have reinfection with Covid-19. The mean (SD) age, body mass index, disease duration, and Expanded Disability Status Scale score were 43.5 (13.9), 26.3 (5.3), 6 (6.6), and 2.5 (2), respectively. Of pwNMOSD, 17 (89.5%) were female, 12 (63.2%) were working. None of the participants reported smoking. Covid-19 cases (21.1%) were 1.4 times more common in our NMOSD population than in the general

population (16.6%). The rate of Covid-19 infection course was the following: 3 (15.8%) people experienced severe, 1 (5.3%) people reported pneumonia which was treated in hospital, 16 (84.2%) people experienced mild, and no pwNMOSD died due to Covid-19 infection. The most common reported symptoms were fever, cough, weakness, and musculoskeletal pain. The major differences were observed for rituximab between pwNMOSD with and without Covid-19 infection.

Conclusions: Our results indicated that pwNMOSD appear to be at higher risk of contracting Covid-19 than the general population. However, most people with pwNMOSD recover mildly from the Covid-19 infection. Available data show that there is no need for additional concern for people with pwNMOSD in a similar pandemic that may develop in the future.

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EP0900

IL-6 as a Blood Biomarker in NMOSD patients: a positive correlation between clinical status and imaging to IL-6 serum levels

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Background: Neuromyelitis Optica spectrum disorder is a rare demyelinating disorder that preferentially affects the spinal cord and optic nerve. There are no valid clinical or laboratory methods to predict disease progression, disability outcome, and relapse rate. Interleukin 6 (IL-6) is a proinflammatory cytokine elevated in the serum and CSF of NMOSD patients.In our study, we aimed to determine if serum levels of IL-6 could serve as a biomarker for NMOSD disease activity.

Methods: We evaluated the serum levels of IL-6 in 26 NMOSD patients at various disease pivot points, using enzyme-linked immunosorbent assay (ELISA). We correlated serum IL-6 levels to brain MRI volumetric measures using volBrain software, as well as to Expanded Disability Status Scale (EDSS), NMO preventing treatments, and clinical subtypes (relapse and remission states).

Results: NMOSD patients at relapse had higher levels of IL-6 than at remission. No differences in the serum levels of IL-6 was found between NMOSD patients at remission and HCs. IL-6 levels at relapse positively correlate with CSF total protein levels during relapses. Furthermore, IL-6 Levels at relapse negatively correlate with the volume of total grey matter, whole Brain, cerebellum, brain stem, thalamus, and putamen.

Conclusion: Our finding suggests that serum levels of IL-6 might serve as a biomarker for disease activity (e.g., relapse vs. remission). The association between increased levels of IL-6 and reduced brain volume suggests that IL-6 signaling pathway may play a role in mediating disability.

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EP0901

Understanding the symptoms of patients with neuromyelitis optica spectrum disorder and their impact on patients' lives: a qualitative interview study

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a rare complement-mediated, autoimmune disease characterised by unpredictable attacks targeting the spinal cord and optic nerve. To date, there has been limited research evaluating the symptoms of NMOSD from the patient perspective.

Objectives: This study aimed to systematically assess NMOSD-related symptoms and impacts most important to patients, both during and between relapses.

Methods: This was an observational, noninterventional, qualitative study where adults (aged ⩾ 18 years) with NMOSD engaged in one-on-one, semistructured, qualitative interviews. Patients were required to have received treatment with an immunosuppressant therapy or an approved treatment for NMOSD prior to the study. Patients completed a sociodemographic form, the EuroQol (EQ)-5D-3L, and participated in a ~60-minute telephone/teleconference interview with trained personnel, which was recorded and transcribed. Transcripts were coded in ATLAS.ti and symptom code frequency counts were exported for analysis.

Results: From July 28 to October 29, 2021, 34 patients with NMOSD participated in the study. The mean age was 48.4 years; 28/34 (82.4%) patients were female. Patients experienced a median of 7 (range 3–14) symptoms during their most recent attack, and 16/34 (41.7%) patients reported between 6–10 NMOSD-related symptoms.Patients mostly reported motor/sensory symptoms (muscle numbness/tingling, muscle weakness, paralysis, limbs stiffness, tremor, and balance issues; 32/34, 94.1%), generalised pain/spasms (22/34, 64.7%), and ophthalmologic concerns (vision impairment, blindness, and eye pain; 19/34, 55.9%). Patients also reported that these symptoms had the most bothersome impact on their lives. Between attacks, 28/34 (82.4%) patients reported that NMOSD-related symptoms remained stable, including motor/sensory symptoms (14/28,

50.0%), generalised pain/spasms (13/28, 46.4%), and ophthalmologic concerns (9/28, 32.1%).
Conclusions: The most common symptoms experienced by patients with NMOSD during their most recent attack were motor/sensory-related, generalised pain/spasms, and ophthalmologic concerns, which all remained stable following the attack. Due to the nature of the disease the focus of treatment for NMOSD is on symptom management and attack prevention with available therapies. Additional analyses are needed to examine the impact of these symptoms on patient and caregiver quality of life.

Disclosure
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EP0902
Atypical polyphasic presentation of autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy

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Introduction: Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a newly identified immunotherapy-responsive inflammatory central nervous system disorder.
Objectives/case report: A 50-year-old previously fit man presented with Miller Fisher Syndrome (MFS) like syndrome with ophthalmoplegia and ataxia post prostatitis. His initial CSF and MRI showed changes were supportive of MFS. After intravenous immunoglobulin (IVIG) he improved. Gradually, he deteriorated again with progressive paraparesis, urinary sphincter dysfunction and optic neuropathy. His repeat MRI showed longitudinal extended transverse myelitis (LETM) with leptomeningeal enhancement at the brainstem, cervical spine and conus medullaris. His repeat CSF showed raised protein and lymphocytosis with matched CSF oligoclonal bands. His 1st and 2nd line neuro-inflammatory and infective screen came back negative. He was treated with pulsed IV methylprednisolone (IVMP) and his condition stabilized before deterioration again after few weeks with limbic encephalopathy and could not recognize his wife. Further MRI neural axis showed T2 changes at bilateral temporal lobes with LETM extended from cervical to the whole cord. His positron emission tomography/computed tomography (PET/CT) body scan revealed no malignancy. His neuroradiology differential diagnoses were primary Central Nervous System (CNS) vasculitis, primary intravascular lymphoma, primacy CNS sarcoidosis. He was given more IVIG, steroid and had plasma exchange (PLEX). Further extended blood and CSF autoantibodies screen were sent with provisional plan for brain biopsy if his 3rd line screening blood tests failed to yield any positive results. His CSF for GFAP-IgG antibody came back positive eventually. In total, he received 2 cycles of pulsed IVMP, 2 cycles IVIG, 1 cycle of PLEX and has been on slow tapering prednisolone since last relapse 9 months ago. He is now on 10mg prednisolone, started walking unaided and returning to work.
Conclusion: We presented an atypical polyphasic stepwise presentation of GFAP astrocytopathy which responded well with immunotherapy. Further research into pathophysiology of this rare but treatable autoimmune meningoencephalomyelitis is needed and hopefully will come up with an international consensus in management protocol one day.

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K Mohamed: Nothing to disclose
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YK Lee: Nothing to disclose

EP0903
Neuromyelitis optica spectrum disorders with and without associated autoimmune diseases

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Background: The relationship between neuromyelitis optica spectrum disorders (NMOSD) and autoimmune diseases (AD) has

been reported, but no studies from Latin American (LATAM) cohorts had been done to describe the association. We aimed to assess and compare the features of NMOSD with and without AD in a LATAM population.
Methods: We retrospectively reviewed the medical records of patients with NMOSD according to the 2015 diagnostic criteria. Patients from Argentina (n=77), Brazil (n=46) and Venezuela (n=17) were enrolled, and they were divided into two groups as follows: with AD or without AD. Aquaporin-4 antibodies (AQP4-ab) status was measured using indirect immunofluorescence (23%) and cell-based assay (77%). Clinical, paraclinical, magnetic resonance imaging (MRI) and prognosis data were compared.
Results: A total 140 patients with NMOSD were included. Of these, 33 (23.5%) patients had associated an AD during follow-up of 58.3 (±44.6) months. Positive AQP4-ab were observed in 67%. This cohort had 41.5% of non-Caucasian population. The most frequently associated AD was Hashimoto disease (n=10) followed by lupus (n=7) and Sjogren (n=6). There were no statistically significant differences in age, clinical course, ethnicity, frequency of relapses, AQP4-ab and oligoclonal bands positivity, spinal cord MRI findings, disability (at the last follow-up) and acute treatment schemes between groups. However, Rituximab use (42.4% vs. 21.5%, p=0.02), female gender (82.2% vs. 100%, p=0.006), corticospinal lesions on MRI (0% vs. 12.5%, p=0.01) at onset and positivity for antinuclear antibodies (21.2% vs. 48.4%, p=0.03) were significantly associated with NMOSD patients with AD vs. NMOSD patients without AD.
Conclusion: One-quarter of NMOSD patients had associated AD. In addition, NMOSD patients with and without associated AD were similar in most features evaluated. Treatment strategies (azathioprine and mycophenolate) were also similar. However, rituximab was more frequently used in patients with AD

Disclosure
None of the authors has any potential financial conflict of interest relating to this poster.

EP0904
Two years follow up study of the psychological effect of COVID19 pandemic on neuromyelitis optica spectrum disorder patients, the dramatic effect of vaccination

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Background: Coronavirus 2019 (COVID19) created a pandemic since early 2020. NMOSD patients are more affected by psychological effects of the pandemic such as anxiety and fear because they may be worried about suffering COVID19 infection. They often concern about their treatment protocol and disease relapses during the pandemic too.
Aims: In this study we tried to show some psychological complications epidemic on NMOSD patients in Isfahan province, Iran. the first aim of the study was to evaluate the presence and the prevalence of anxiety among NMOSD patients during the first year from epidemic beginning and also in post vaccination phase after 24 months. The second goal was to see the level of respecting preventive measures among the same group. The follow up period is 2 year after declaring COVID19 epidemic in our country Iran, since late February 2020.
Methods: The objective of the study was to evaluate the anxiety due to COVID19 infection, 3, 12 and 24 months after beginning of epidemic. The study was done in NMOSD Clinic of Isfahan Kashani hospital. We first asked patients if they were anxious or afraid of the pandemic subjectively.To investigate the objective level of anxiety,we benefited Hospital Anxiety and Depression Scale(HADS-A) questionnaire. We asked them about respecting general health cautions to prevent infection.
Results: Study included 120 patients(96 female) with mean age of 36.37±9.69 and mean duration of disease 8.49±5.35 years. 96 cases(80%) experienced anxiety during the first 3 months of pandemic and 66 patients(55%) were anxious after a year. The point is that their level of anxiety decreased significantly in post vaccination phase after 24 months and just 35 patients (29.16%) showed anxiety subjectively on the third survey. Based on HADS-A score, 92 patients (76.66%) were anxious on the third month while after one year of epidemic 70 cases(58.33%) and in post vaccination survey just 53(44.16%) were anxious. Respecting preventive measures increased in the first year but decreased after vaccination.
Conclusion: Results showed that prevalence of anxiety was almost high in the first months of epidemic but it decreased gradually during a year and had a dramatic decline after vaccination. The level of alertness and attention seems to remain high and they respected the sanitary rules. We concluded that vaccination against COVID19 have positive impact on peoples mental health and reduced psychological distress.

Disclosure
The corresponding author, On behalf of others, declares that there is no conflict of interest.
All aspects of human researches considered by the researchers. This work was supported by the Isfahan University Of Medical Sciences and Isfahan Neuroscience Research Center.
Dr Mehdipour : nothing to disclose.
Dr Ashtari : nothing to disclose.

EP0905
Therapeutic strategies of rituximab in NMOSD and MOGAD patients: multicenter cohort study in Latin America

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Although rituximab (RTX) has been increasingly used in NMOSD and MOGAD, considerable heterogeneity exists, mainly concerning the number and dosage of infusions and the frequency of treatment cycles. The objective of the study was to describe the RTX regimen strategies most frequently used in NMOSD and MOGAD patients from Latin America (LATAM), according to patients' disease.

Methods: observational retrospective multicenter study including patients with NMOSD and MOGAD treated with RTX from 8 countries and 14 referral centers of LATAM (Argentina, Chile, Ecuador, Brazil, Venezuela, Mexico, Colombia and Paraguay). Demographics and clinical aspects were collected and RTX strategies on naïve patients are summarized as follows: scheme A: Two 1000 mg infusions 15 days apart and repeated every 6 months; scheme B: four 375 mg/m2 infusions every week for 4 weeks and repeated every 6 months; scheme C: one 1000 mg infusions and repeated every 6 months; scheme D: Other scheme used (free text and described).

Results: a total of 217 patients were included, 197 NMOSD (164, 83.2% AQP4-ab seropositive and 16.7% AQP4-ab seronegative) and 20 MOGAD. All MOG-ab tests were done by cell-based assay, while in NMOSD 134 (68%) tests were done by this method. In 95 (50.8%) NMOSD patients, the first treatment received was RTX vs. 13 (68.4%) in MOGAD (p=0.12). In those NMOSD and MOGAD naïve patients on RTX, the most common scheme used was two 1000 mg infusions 15 days apart and repeated every 6 months in 79 (83.1%) and 11 (84.6%) (p=0.55) respectively, followed by the scheme B: four 375 mg/m2 infusions every week for 4 weeks and repeated every 6 months in 6 (6.3%) and 2 (15.4%) (p=0.17) for NMOSD and MOGAD, respectively. In 50 (52.6%) NMOSD patients' reinfusions of RTX were dependent on CD19 cells reappearance vs. 8 (61%) in MOGAD patients (p=0.23). Adverse events (AE) were reported in 12 (12.6%) of NMOSD vs. 2 (15.3%) of MOGAD. They were more frequent in patients receiving the scheme B.

Conclusions: induction and maintenance protocols to treat NMOSD and MOGAD are warranted. This study helps to understand how patients are treated in LATAM and how much should be done to optimize patients' care.

Disclosure

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EP0906

The effect of health-related hardiness education program in patients with neuromyelitis optica

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Introduction: Health-related hardiness is a psychological characteristic of individuals, which could regulate the mental health problems caused by chronic disease. Neuromyelitis optica (NMOSD) is a chronic disease which causes high morbidity and recurrence. Many studies have shown that disability caused by neuromyelitis optica could increase perceived stress. The increased perceived stress could lead to fatigue, anxiety, and depression, and then reduce the quality of life. The health-related hardiness education program is a comprehensive psychological intervention to change the patient's perception and enhance the ability to cope with stress.

Aims/objectives: The aim of this study is to investigate the role of health-related hardiness between disability and perceived stress in patients with NMOSD and conduct health-related hardiness education for patients to observe the effect of health-related hardiness on perceived stress.

Methods: 109 patients were recruited. The perceived stress scale (PSS) and Health-related hardiness scale (HRHS) were used to investigate the perceived stress and health-related hardiness, and the hierarchical multiple regression method was used to examine the mediating effect of health-related hardiness between disability and perceived stress. The experimental group received health-related

hardiness education and routine follow-up, and the control group was given routine follow-up. The independent-sample t-test was used to evaluate the effect of the intervention.
Results: The results indicated the correlation between health-related hardiness, disability and perceived stress. EDSS was negatively correlated with HRHS, and it also positively correlated with PSS, HRHS was negatively correlated with PSS. Health-related hardiness played a partial mediating role between disability and perceived stress, and the mediating effect accounted for 18.3% of the total effect. Compared with the control group, the HRHS score of patients in the experimental group significantly increased after receiving health-related hardiness education, and the score of PSS was reduced.
Conclusions: This study showed a relationship between health-related hardiness, disability, and perceived stress in NMOSD patients. Health-related hardiness plays a partial mediating role between disability and perceived stress. The implementation of health-related hardiness education for patients could improve health-related hardiness, and reduce the perceived stress.

Disclosure
Yafang Xu: nothing to disclose

EP0907
Rheumatological comorbidities and autoantibodies in NMOSD and MOGAD

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Introduction:AQP4-IgG seropositive neuromyelitis optica spectrum disorder (AQP4+ NMOSD) is associated with comorbid autoimmune diseases. The impact of autoimmune disease on NMOSD and myelin oligodendrocyte glycoprotein associated disease (MOGAD) outcomes is unclear.
Objective: To characterize the frequency of rheumatological and other autoimmune co-morbidities and autoantibodies in a large, single-center, cohort of AQP4+ NMOSD and MOGAD patients and explore associations with relapse rate and disability.
Methods: Retrospective chart review of AQP4+ NMOSD and MOGAD patients followed at an academic center from 2010-2021. Rheumatological and other autoimmune comorbidities, autoantibodies and their associations with baseline annualized relapse rate (ARR) and gait, bladder (Aminoff & Logue scale) and visual (EDSS) disability were assessed.
Results: 149 AQP4+ NMOSD and 57 MOGAD patients were included. 27 (18%) AQP4+ NMOSD patients had an autoimmune co-morbidity compared with 5 (9%) MOGAD patients. Diagnoses included, in the AQP4+ NMOSD group, 8 (5.3%) Sjogren's, 7 (4.6%) systemic lupus erythematosus (SLE), 3 psoriasis, 3 autoimmune thyroid disease, 2 rheumatoid arthritis, 2 myasthenia gravis, 1 ulcerative colitis, and 1 immune thrombocytopenia. In the MOGAD group, 2 (3.5%) patients had SLE, 2 (3.5%) had Sjogren's, 1 had psoriasis and 1 had Graves' disease.
Out of 109 AQP4+ NMOSD patients tested, 57 (38%) had positive anti-nuclear antibodies compared to 6/42 (14%) MOGAD patients. Double-stranded DNA antibodies were positive in 6/94 (6%) AQP4+ NMOSD patients versus none in the MOGAD group. Anti-Ro antibodies were positive in 16/101 (16%) AQP4+ NMOSD and 4/42 (9.5%) MOGAD patients. Anti-La antibodies were positive in 9/102 (9%) AQP4+ NMOSD patients but no MOGAD patients. One AQP4+ NMOSD patient had antineutrophil cytoplasmic antibodies. The median annualized relapse rate (ARR) before immunotherapy was 2.7 [0.8-4.3] for MOGAD and 1.5 [0.5-5.1] for AQP4+ NMOSD. In preliminary analyses, no differences in the ARR or disability at last follow-up was found in patients with versus without markers for rheumatologic disease in AQP4+ NMOSD or MOGAD.
Conclusions Rheumatological and other autoimmune co-morbidities are common in AQP4+ NMOSD, but less so in MOGAD, and their presence does not appear to be associated with relapse rate or disability.

Disclosure
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Eleni Vasileiou has nothing to disclose.
Elias Sotirchos has consulted for Alexion, Viela Bio, Horizon Therapeutics, Genentech and Ad Scientiam and has received speaking honoraria from Alexion, Viela Bio and Biogen.

EP0908
Cognitive and physical profile of the persons with neuromyelitis optica spectrum disorder

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) may result in neurological deficits involving paresthesia, visual and walking impairment, and cognitive dysfunction.
Aims: Our study aimed to assess and compare the cognitive functions and physical disability between pwNMOSD and age- and gender-matched healthy controls (HC).
Methods: Twenty pwNMOSD (15 female; mean age=37.85±12.15) and 10 HC (7 female; mean age=37.30±11.19) were enrolled in the study. Brief Repeatable Battery of Neuropsychological Tests (BRBN-T) battery which included the Selective Reminding Test (SRT), the 10/36 Spatial Recall Test (SPART), the Symbol Digit Modalities Test (SDMT), the Paced Auditory Serial Addition Test (PASAT) and the Word List Generation test (WLG) were used to assess cognition. Timed 25 Foot Walk (T25FW) and 9-Hole Peg Test (9-HPT) were used for physical assessment. The clinic and demographic characteristics of the participants were recorded.
Results: There was a significant difference between pwNMOSD and HC in terms of cognitive tests scores such as SRT-delayed recall, SDMT score, and verbal fluency (6.50±2.28 vs. 8.4±1.71; 43.94±14.07 vs. 54.2±8.40; 49.73±16.42 vs. 69.90±7.87;

27.31±11.85, respectively) ($p<0.05$). The T25FW was higher in pwNMOSD (5.26±1.19) compared to HC (4.17±0.49) ($p<0.05$). There was a statistically significant difference between pwNMOSD (19.82±2.85) and HC (17.19±2.15) regarding 9-HPT. Besides, there were no significant differences between groups in SPART, SRT, PASAT, and categorical fluency performance ($p>0.05$). A moderate negative correlation was found between the T25FW and cognitive test scores as SRT- immediate recall, SRT-delayed recall and SDMT (rho= -.596, p=0.019; rho= -.577, p=0.024; rho= -.534; p=0.040; rho= -.579,p=0.030, respectively) There was a strong negative correlation between the T25FW and verbal fluency (rho= -.779; p=0.001). Also, moderate negative correlation was found between the 9-HPT and SRT-delayed recall and SDMT (rho= -.628, p=0.012; rho= -.547, p=0.035)

Conclusion: Our results showed that pwNMOSD has worse performance on physical and most cognitive assessments. However, we found that compared to age- and gender-matched HC, visual memory, working memory, complex attention, and verbal fluency were preserved in pwNMOSD. These results pointed out that pwNMOSD should comprehensively assess cognitive functions. Also, it should be emphasized that cognitive and physical disability levels go about with each other.

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EP0909

Access to NMOSD care in an Argentinean cohort: real world patient experiences

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Introduction: Neuromyelitis optica spectrum disorders (NMOSD) is an emergent disease in Latin America (LATAM),which raises substantial socioeconomic challenges.NMOSD has a high burden of disease, which comprises frequent neurological visits, magnetic resonance imaging (MRI) use, long-term medication, and utilization of NMOSD care services during follow-up, with a high impact on healthcare system. We aimed to evaluate barriers in the access to healthcare of NMOSD patients in an Argentinean cohort stratified by health coverage.

Methods: Cross-sectional study based on a self-reported survey conducted in Argentina. NMOSD patients were divided into three groups regarding coverage: prepaid health insurance (PHI), social health insurance (SHI) and state-run health insurance (SRHI, Public Health Ministry)in order to detect differences in access and barriers (neurological visit, MRI use and long-term medication).

Results: We surveyed100 NMOSD patients (74% female, mean age at diagnosis 38.7 years, mean EDSS 2.8 and a mean of follow-up time of 5.2 years), 40% were employed (full-time: 57.5%), 11% were currently unemployed and 13% were retired due to NMOSD. More than half (55%) of patients visited between 2-3 specialists before NMOSD diagnosis was performed, and Aquaporin-4-antibody and/or MOG-Ab tests were requested in 91% (healthcoverage paid partially in 15.3% and in 32.9% they were paid by the patient). NMOSD patients receiving care from the private sector(PHI and SHI) reported greater accessto MRI (80% and 85% vs.68%), neurological visits (91% and 80% vs.68%,p=0.79)and fewer problems obtaining NMOSD medications compared to those treated at public institutions (95% and 85% vs 50%, p=0.005), respectively. We also observed a longer mean time to access to MRI(9.3 ±13.4 vs 4.5±10.7 and 5.3±9.1 p=0.005) and neurological visits (7±5.4 vs 3.7±2.9 and 3.8 ±3.2, p=0.008) in the SRHI group when compared with PHI and SHI, respectively. Regression analysis showed that having private insurance(PHI and SHI)(OR=3.84, p=0.01) was the only factor associated with appropriate delivery of NMOSD medications.

Conclusion: These findings suggest that barriers to access and utilization of NMOSD care services in Argentina are common. NMOSD patients experienced problems to receive NMOSD medication properly, especially those from the public sector (SRHI).

Disclosure

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EP0910

Breakthrough COVID-19 infection after vaccination in patients with NMOSD in Latin America: data from RELACOEM registry

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Objective: The objective of the study was to evaluate the incidence of COVID-19 infections after vaccination in NMOSD patients included in RELACOEM, a LATAM registry of MS and NMOSD patients infected and vaccinated for COVID-19.
Methods: Retrospective cohort study developed between May 2021 to December 2021. The primary outcome was the appearance of infection during the follow up time (at least three months after complete vaccination (second dose)). Data was collected through the contact between the treating physician and the patient. Specific information was requested (vaccine received, dose, date, symptoms, COVID-19 infection, need for hospitalization, ventilatory assistance, treatment, and evolution). The primary objective of the analysis was to compare the incidence of breakthrough SARS-CoV-2 19 infections among the vaccinated pwMS in each DMT group. These conditions entail a PCR-confirmed test, and a time lag of at least 14 days from a full vaccination cycle (after the second vaccination dose). Cumulative incidence was reported by Kaplan Meier survival curves as well as incidence density.
Results: A total of 49 NMOSD patients from eight countries in LATAM were included. Mean age was 43.8 ±13 years. The most frequent treatment use was rituximab in 29 (59.2%). The mean follow up after the second dose was 149 ± 32 days. Most frequent first and second dose received was Pfizer (28.6%), followed by Sinopharm (24.5%). During follow up a total of 2 COVID-19 cases were observed for a total exposure time of 8627 days. Cumulative incidence was 4.1% (SE 0.87%) with an overall incidence density of 2.31 x 10.000 patients/day (95%CI 1.13-3.71). Both cases occurred in patients under rituximab (2/29, exposure time 4208, IR 4.7 x 10,000 patients/day 95%CI 3.5-5.1). No hospitalizations were reported for both cases.
Conclusion: We observed an ID of COVID-19 infection after vaccination of 2.31 x 10.000 patients/day in NMOSD patients.

Disclosure
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EP0911

Development and validation of a claims-based algorithm to identify patients with neuromyelitis optica spectrum disorder

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Introduction: There is no validated algorithm to identify patients with neuromyelitis optica spectrum disorder (NMOSD) in healthcare claims data. ICD-10 diagnosis codes exist for NMO, transverse myelitis (TM) and optic neuritis (ON), which may be found in patients with NMOSD. Whether these codes can be used to identify patients with NMOSD and distinguish them from patients with NMOSD mimics (e.g. multiple sclerosis [MS] and myelin oligodendrocyte glycoprotein antibody–associated disease [MOGAD]) is unknown.
Objectives: Develop and test the performance of a healthcare claims-based algorithm to identify patients with NMOSD.
Methods: We developed algorithms of ICD-10 codes and medications through structured cognitive interviews with neurologists. We tested their sensitivity and specificity in the billing and medication data of a purposive sample of 101 adults with NMOSD, MS, or MOGAD from 5 neurology clinics to identify the best-performing algorithm. We then tested this algorithm's face validity using 2016–2019 data from the IBM MarketScan Commercial and Medicare Supplemental Databases. Algorithm-identified adult patients with NMOSD were required to have ⩾1 year of continuous enrolment after a qualifying diagnosis code during the study period. Demographics and clinical characteristics were reported.
Results: Best-performing algorithm inclusion criteria were ⩾18 years AND (⩾1 NMO diagnosis [or ⩾1 TM and ⩾1 ON diagnosis] AND ⩾1 NMOSD drug) OR (⩾2 NMO diagnoses ⩾90 days apart). Exclusion criteria were MS diagnosis or MS-specific drug after the last NMO diagnosis or NMOSD drug; sarcoidosis diagnosis after the last NMO diagnosis; ⩾1 immune checkpoint inhibitor. In billing and medication data of 50 patients with NMOSD, 30 with MS, and 21 with MOGAD, the algorithm had 82.0% sensitivity and 70.6% specificity. Mean (SD) age of NMOSD patients

was 50.1 (16.5) years and 78.0% were female. In claims data, the algorithm identified 382 patients with NMOSD. Mean (SD) age was 46.2 (13.3) years, 83.0% were female and 99.2% had ⩾1 claim for NMO, 28.0% for ON and 17.0% for TM.
Conclusions: This clinically derived algorithm performed reasonably well in identifying true positive and negative patients in clinic billing and medication records. When tested in healthcare claims data, demographics and clinical characteristics were consistent with previous clinical findings. This algorithm will enable a more accurate estimation of NMOSD disease burden using insurance claims data sets.

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Pathology and pathogenesis of MS - Genetics/ Epigenetics

EP0912

β-interferon treatment is a potent and targeted epigenetic modifier in multiple sclerosis

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Background: Interferon Beta (IFN-β) remains an important injectable treatment for multiple sclerosis (MS). The biological mechanism of action of IFN-β is only partially understood and is important for personalising treatment regimens to reduce adverse reactions and maximise efficacy. DNA Methylation is a reversible epigenetic mechanism that may modulate gene expression via exposure to IFN-β. IFN-β is known to have a global effect on DNA methylation levels, but the specific target genes and effect sizes are not known.
Objective / Aim: Here we examine the specific effects of IFN-β treatment on immune-cell DNA methylation by performing an epigenome-wide scan in people with MS (pwMS).
Methods: We included 349 pwMS. A discovery group (IFN-β = 31, Untreated = 83) and a replication group (IFN-β = 33, Untreated = 202). DNA was extracted from whole blood samples representing the circulating mixture of immune cells. Illumina Infinium methylationepic (EPIC) arrays were used to test for differential methylation between IFN-β treated and untreated pwMS.
Results: We found and replicated 22 differentially methylated CpGs mapping to 11 genes ($P<9.8e10^{-8}$) that were associated with IFN-β treatment. All CpGs map to well-known IFN-related genes and are known to influence gene expression levels. The strongest effect was for IF144L (Db =23%, $P=4.3e10^{-23}$), a gene coding for the Interferon Induced Protein 44 Like protein, involved in response to virus infections. We then combined datasets and constructed a multi-CpG methylation risk score (MRS), which clearly differentiates IFN-β treated from untreated patients (AUC = 0.83, $p = 1.01e10^{-25}$). The MRS was correlated with decreasing B cell proportion (r=-0.15, P=0.006) and increasing monocytes (r=0.14, P=0.01), but was not correlated with age-related MSSS (r=0.1, P=0.3). Interestingly, several novel genes were differentially methylated in the combined dataset ($P<9.8e10^{-8}$) eg. the tyrosine non-receptor kinase gene (TNK2), which has been implicated in CNS inflammation via cytokine signalling.
Conclusion: Our results show that IFN-β has a potent and target-specific effect on DNA methylation that is linked to gene expression levels. These findings will help clarify the specific mechanism

of action of IFN-β treatment. Our MRS score could also be used as a biomarker of IFN-β activity and to investigate IFN-β response in MS patients.

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EP0913

Exploring the role of expanded tandem repeat sequences in multiple sclerosis progression

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Introduction: Tandem repeat (TR) sequences are common in the human genome and are frequently polymorphic in regards to the number of sequence motif repeats. Several of these TRs result in Mendelian forms of neurodegeneration when the number of repeats is markedly expanded beyond that typically seen. Given that the recently completed genome-wide association study (GWAS) of progression in multiple sclerosis (MS) has suggested that central nervous system (CNS) resilience is an important determinant of the rate at which neurodegeneration develops, we hypothesised that perhaps repeat lengths might be correlated with rate of progression in MS.

Traditional methods for genotyping TRs are prohibitively expensive and time consuming. However, computational methods have recently emerged that make it possible to complete this genotyping for multiple TRs in parallel using paired-end whole genome sequencing (WGS) data.

Objectives: This pilot analysis sought to genotype TR loci, known to be pathogenic in monogenic diseases, in samples from MS patients. Our goal was to explore and develop methods for conducting association studies between TR length and MS progression.

Aims: We hope to lay the foundations for a large-scale study of TRs in MS progression. This may help to further elucidate the pathogenesis of the disease and suggest therapeutic targets.

Methods: TRs were genotyped by 'ExpansionHunter' software using paired-end, PCR-free WGS data from 8 MS patients. MS progression was measured by age related multiple sclerosis severity (ARMSS) score.

Results: We characterised the genotyping of TR length at 59 loci and evaluated ExpansionHunter as a tool for TR-based association studies. We showed that repeat lengths at individual TRs are rarely normal and we employed regression methods suitable for performing association analysis in data with long-tailed distributions, both at individual loci and collectively.

Conclusions: Our results demonstrate an analysis pipeline for conducting association studies between TR length and MS progression. Having optimised this pipeline, we are now extending the analysis to include WGS data from 6,000 additional MS patient.

Disclosure

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EP0914

Epigenetic profiling of blood in multiple sclerosis: a closer look at lipid mediator machinery gene regulation

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Introduction: Impaired resolution of inflammation can lead to chronic inflammation, which is an underlying pathogenic event in a variety of diseases, such as multiple sclerosis (MS). Resolution is orchestrated certain autocoids called specialized pro-resolving lipid mediators (SPMs), which are derived from omega-3 and -6 fatty acids. However, when there is an imbalance in the pro-resolving and pro-inflammatory lipid mediator profiles, the resolution process is disturbed.
Objective: In this project, we aim to explore the underlying (epigenetic) mechanisms of disruptions in lipid mediator profiles in MS patients.
Methods: Epigenetics allows for the understanding of the regulation of the resolution machinery and how this is altered during disease. One of the most important epigenetic marks is DNA methylation. For this reason, an Illumina EPIC 850K array was performed on control and MS blood samples. Differentially methylated genes were analyzed in MS patients (total n=66) vs. healthy controls (n=20), which contained the following MS group subtypes: relapsing remitting MS (RRMS)-remission (n=23), RRMS-relapse (n=19), secondary progressive MS (SPMS) (n=11), and primary progressive MS (PPMS) (n=13).
Results: In this study we provide a large dataset containing information on the epigenetic profile of MS patient groups and healthy controls. This allowed for the discovery of differentially methylated genes in MS and pathways associated with MS patients groups in the genome-wide screen. Additionally, when focusing on the lipid mediator-associated gene methylation sites, we were able to detect changes in the lipid mediator machinery, possibly contributing to failed resolution in MS.
Conclusions: By using epigenetic profiling of human blood, we here provide an extensive dataset of DNA methylation in MS and a possible explanation for failed resolution trough altered regulation of lipid mediator machinery genes. This might be of interest for novel diagnostic or therapeutic purposes and provides new insights in MS pathogenesis.

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EP0915

CD4$^+$ T cell gene expression profile of relapsing-remitting multiple sclerosis patients reveals a dysregulated nuclear receptor signalling

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Introduction: Altered cholesterol, oxysterol, sphingolipid, and fatty acid concentrations have been reported in the blood, cerebrospinal fluid, and brain tissue of people with multiple sclerosis (MS), and blood lipid profiles have been linked to disease progression and responses to treatment.
Objectives: Here, CD4+ T cell gene expression was assessed in patients with relapsing remitting MS (RRMS) focussing on differentially regulated lipid metabolism pathways for better understanding of disease pathogenesis.
Methods: RNA sequencing was performed on CD4$^+$ T cells from 10 RRMS patients and 10 matched heathy controls (HCs). Expression of lipids on CD4 T cells was assessed by flow cytometry.
Results: 3940 differentially expressed genes were identified in CD4+ T cells in HCs vs RRMS.Upregulated genes were enriched in pathways involving cytokine signalling, autophagy and lipid metabolism. Downregulated pathways were predominantly related to immunity and metabolism, including signalling of nuclear receptors. The most significantly altered nuclear receptor was NR1H2, or liver X receptor β (LXRβ), that regulates lipid homeostasis and immunity. LXRβ was upregulated in RRMS and LXR-target genes were both up (n=26) and down (n=40) regulated, including genes involved with cellular lipid metabolism (IDOL), the rate-limiting enzyme for glycosphingolipid biosynthesis (UGCG) and EEPD1which positively regulates ABCA1-medated cholesterol efflux. Correspondingly, glycosphingolipid and cholesterol levels (known to influence immune function) were reduced and increased respectively in CD4$^+$ T cells from RRMS vs HCs. Notably the expression of LXR-regulated genes (UGCG, IDOL, EEPD1) were normalised towards HC levels after 3 months IFNβ treatment.
Conclusion: LXR-mediated pathways are dysregulated in RRMS and could contribute to MS pathogenesis by modifying pro/anti-inflammatory immune phenotypes. Correcting lipid metabolism defects may contribute to the therapeutic effect of IFNβ on T cells in this context.

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EP0916

Non-coding circular RNA genomowide profiling in MS reveals a pathogenic circuit disrupting B cells

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Introduction: Multiple sclerosis (MS) is highly heterogenic disorder with respect to clinical course, diagnosis and treatment response. There is an urgent need to search for simple and reliable fluid body biomarker which would assist the diagnosis and prediction of clinical and treatment prognosis. So far a major interest has been dedicated to the search of protein biomarkers but circular non- coding RNA (cirRNA) emerge as a promising candidates for a molecules signifying the MS status.
Objective and aims: To assess the genome-wide expression changes of the circRNA in relapsing-remitting MS patients.
Methods: A genome-wide expression profiling of circRNA in peripheral blood mononuclear cells (PBMC) from 20 untreated patients with relapsing-remitting MS (RRMS: 10 in relapse, 10 in remission) and 10 healthy controls (HC) was performed. We analyzed close to 14000 individual circRNA per sample. The discovery set data were validated using quantitative reverse transcription polymerase chain reaction (qRT-PCR) with an independent cohort of RRMS patients and HC. The power of the validation study has been calculated according to the number of the samples and determined as a parameter alpha=0.9.
Results: analysis revealed 246 circRNA differentially downregulated ($P < 0.05$) in RRMS patients versus HC. We positively validated three circRNA showing highest levels (hsa_circRNA_101348, hsa_circRNA_102611 and hsa_circRNA_104361) and two circRNA showing lowest levels (hsa_circRNA_101145 and hsa_circRNA_001896) of differential expression in the RRMS remission versus HC group: hsa_circRNA_101145 and hsa_circRNA_001896. The expression of these molecules was found to be a marker of the disease clinical status (relapse, p= p=0.0002 or remission p=0.0000332) as well as showed a correlation with a presence of the gadolinium-enhancing lesions in brain MRI (p=0.0039) We have also provided in silico analysis of the miRNA interacting with these circRNA and positively validated 3 protein-coding mRNA likely to be affected by the expression these circRNAs. Intriguingly a changes of the MS marker circRNA were most likely to lead to a disturbed B cell activity.
Conclusions: We have described a previously unknown changes of the circRNA during RRMS and implicated a circRNA-miRNA pathways operating in the MS pathogenesis.

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EP0917

Establishing the CNS distribution of genes implicated in multiple sclerosis progression

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Introduction: The majority of people with multiple sclerosis (pwMS) ultimately develop inexorably worsening disability. Unfortunately, as little is known about the key mechanisms responsible for the neurodegeneration underlying this progressive aspect of the disease, it is unsurprising that currently available disease modifying treatments have little or no effect on this progression. The recently completed genomewide association study (GWAS) of disease severity undertaken by the International Multiple Sclerosis Genetics Consortium (IMSGC) has, for the first time, identified a genetic variant confidently associated with MS progression. This success offers real hope for the identification of rational targets for drug discovery, but this translation first requires an understanding of how this variant exerts its biological effect.
Objectives: Across the genome, the MS progression GWAS correlates with gene expression in the central nervous system (CNS). Therefore, to begin the process of understanding the biological effects of the associated variant, our objective was to establish the CNS distribution of the genes flanking this variant.
Aims: We aimed to characterise the cell-type specific expression of the genes mapping close to the associated variant and explore the expression of the proteins that these genes encode in MS post-mortem brain tissue.
Methods: We have explored the expression of the implicated genes in bulk and single-cell RNA sequencing data from human brain tissue and cerebral organoids. We have also undertaken immunohistochemical (IHC) analysis of pathological tissue from unaffected control individuals and MS post-mortem brain tissue.
Results: The genes flanking the associated variant are enriched in oligodendrocytes and neurons at the RNA level but are predominantly expressed in neurons at the protein level. IHC analysis of pathological tissue revealed neuronal upregulation of one of the implicated genes in MS demyelinated lesions.
Conclusions: Our work suggests that either of the two genes mapping nearest to the SNP associated with progression are potential candidates. This work points toward future SNP-based studies in human induced pluripotent stem cell-based models to unravel the functional consequences of the SNP. We believe that illuminating the pathological mechanisms through which this SNP affects MS severity is likely to reveal novel targets for rationally designed drugs to slow, stop, or prevent MS progression.

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EP0918

Micro-RNA-22 secreted from microglial exosomes is a major regulator of oligodendrocyte differentiation

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Introduction: Multiple Sclerosis (MS) is an inflammatory, demyelinating disorder of the central nervous system, characterized by myelin loss in the brain and/or spinal cord. Current research into the treatment of multiple sclerosis is directed towards promoting repair of demyelinating lesions that occur through a process called remyelination, which requires differentiation of oligodendrocyte progenitor cells (OPCs) to mature oligodendrocytes (OLs). While the OPCs are present in MS lesions, they do not differentiate to mature OLs for reasons unknown. Maturation of OPC's are controlled by modulation of factors both intrinsic and extrinsic to OPCs. We previously identified microRNAs (miR) intrinsic to OPCs affecting remyelination. In this study, we focus on functional implications of microglial microRNAs in controlling OPC differentiation.
Methods and Results: Investigating extrinsic effects on OPC differentiation, we screened for microRNAs in MS lesions. We identified miR-22, expressed by microglia, as an inhibitor of OL differentiation. Immunofluorescence analysis showed miR-22 expressed in microglial cells was increased in MS lesions and animal models of demyelination. Interestingly, decrease in levels of miR-22 was a requisite for effective remyelination to occur. Addition of miR-22 mimic in primary OPC cultures led to inhibition while miR-22 inhibitor led to increased expression of mature OL marker MBP (myelin basic protein). Strikingly, inhibitory effects of miR-22 was significantly greater than the positive regulatory effects of the myelinogenic miRNA, miR-219. Exosomes have been identified as one of the mechanisms of cell-cell signaling. Upon investigation we found that microglial exosomes secrete miR-22 when co-cultured with OPCs leading to its inhibitory effects. Moreover, we also found that miR-22 regulates exosome release from microglial cells forming a positive feedback loop. Finally, increasing miR-22 levels using lentiviral transfection caused impaired remyelination in acute organotypic slice cultures as well as in vivo injections.
Conclusion: We conclude that microglial miR-22, increased in MS lesions is an inhibitor of remyelination. This inhibitory effect on remyelination is possibly mediated by release of miR-22 from microglial exosomes and acting on target genes in OPCs. Our results therefore provides rationale for targeting microglial miRNAs as a possible option to augment the process of remyelination.

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Adya Sapra: Nothing to disclose

EP0919
The CXCL8 rs2227306 polymorphism influences central inflammation and cortical thickness in early multiple sclerosis

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Introduction: Multiple sclerosis (MS) represents a model of chronic disease of the central nervous system (CNS) characterized by a complex interplay between neuroinflammation and neurodegeneration. Among the various soluble mediators and proinflammatory cytokines involved in MS, IL-8 represents one of the targets that seems to be associated with worse clinical outcomes and disease progression. The C-X-C Motif Chemokine Ligand 8 (CXCL8 or IL-8) C>T rs2227306 polymorphism, which regulates molecular response of IL-8, influences the severity of some inflammatory and neuropsychiatric diseases, but its role in MS has never been investigated.
Aims: The aim of this work is to explore the role of CXCL8 rs2227306 in the early phases of MS.
Methods: In 154 relapsing-remitting (RR)-MS patients, we explored at the time of diagnosis the associations between rs2227306 polymorphism, clinical and demographic characteristics (age, sex, EDSS, disease duration, clinical activity, presence or not of oligoclonal bands (OCB)), and the cerebrospinal fluid (CSF) levels of a large set of pro-inflammatory and anti-inflammatory molecules. In addition, in 54 patients, correlations between rs2227306 haplotypes and structural MRI measures were assessed.
Results: We identified an association between the presence of the rs2227306 polymorphism of CXCL8 and CSF levels of IL-8 (C-allele carriers: median [IQR]: = 18.08 [13.18-26.78] pg/ml vs T-allele carriers: median [IQR] = 21.52 [16.02-28.27] pg/ml, p=0.049), in the absence of significant associations with clinical and demographic characteristics (age at LP, p=0.796; sex F/M, p=0.721; EDSS at LP, p=0.211; disease duration in months, p=0.702; clinical activity, p=0.591; OCB at diagnosis, p=0.576). We also performed an analysis between levels of IL-8 and MRI measures at the time of diagnosis, evidencing a negative linear correlation between levels of IL-8 and cortical thickness only in patients carrying T-allele for rs2227306 (T-allele carriers, Spearman's Rho, coefficient of correlation -0.420, p=0.011).
Conclusions: We describe for the first time an association between rs2227306 polymorphism of IL-8 and inflammatory neurodegeneration in MS brains, emphasizing the influence of inter-individual genetic variability in inflammatory response and neuronal damage in this disorder.

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EP0920

Initiation of ocrelizumab in patients with relapsing multiple sclerosis is associated with a broad immunomodulatory response implicating proinflammatory T-cells: a multi-omics study

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Introduction: It is generally acknowledged that depletion of B cells expressing CD20 accounts for the therapeutic effects of ocrelizumab; yet, little is known about the downstream effects other than reduction in antigen presentation and immune globulin synthesis. Thus, we have conducted a multi-omic study to further our understanding of ocrelizumab's mechanism of action and its effects on a diverse set of -omic biomarkers, including plasma proteome and metabolome and gut microbiome.
Objectives: To demonstrate that multi-omic analyses of patients treated with ocrelizumab will deepen and expand our insights into potential therapeutic mechanisms of action that go beyond the effects of B-cell lymphocyte destruction in the periphery.
Methods: The prospective study enrolled 7 patients so far, 6 women and 1 man (age M=35 years) with relapsing MS; EDSS scores ranged from 1 to 3.5 (M=2.29); disease duration since symptom onset $<$ 12 months; two patients were naïve to MS DMTs. All provided a baseline peripheral blood sample prior to their first dose of ocrelizumab, and prior to their 24 and 48 week doses. Extracted plasma was assayed using Olink's qPCR-based proteomic platform (274 proteins) and Metabolon's Global platform quantifying $>$1,000 human metabolites.
Results: Longitudinal analyses using paired nonparametric t-tests revealed statistically significant (permutation P's$<$0.05) reductions in plasma abundance of proteins indexing B and T cell activation and a range of cytokines, including TNF-related proteins, from baseline to 24 weeks. Furthermore, metabolomics profiling revealed a reduction in peripheral abundance of sphingolipids and increases in plasma antioxidants as well as a possible shift away from glycolysis and towards beta-chain oxidation following the administration of ocrelizumab.
Conclusions: Our preliminary findings suggest potential roles of ocrelizumab treatment beyond B-cell depletion via effects on proinflammatory T-cell populations and T-cell activation, decreased cytokine production and other biochemical pathways. These results warrant further investigation into the potential relationship between observed -omic perturbations and clinical variations in treatment efficacy, their long-term prognostic implications, and extent of mapping onto disease activity in patients. Targeted proteomics is a valuable avenue for the development of cost-effective minimally invasive assays for the assessment of treatment efficacy, and possibly determination of long-term prognosis.

Disclosure
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JA is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd.
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EP0921

Genetic variation in GLA elucidates a link between Fabry Disease and Multiple Sclerosis in Sweden

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Introduction: Previous studies have observed a potential overlap between Multiple Sclerosis (MS) and Fabry Disease (FD), an X-linked lysosomal storage disorder caused by deficient alpha-galactosidase A. Shared symptoms include fatigue, neuropathic pain, cerebellar gait ataxia, and white matter lesions (WML). Radiological MS criteria are also met by a proportion of FD patients, and initial misdiagnosis as MS has been described, particularly in women, resulting in an eight year delay of proper FD diagnosis and subsequent treatment. Furthermore, mutations in theGLA gene associated with FD were observed in nearly 5% of MS cases in a small Italian cohort.
Objectives: The objective of this study was to identify variations in theGLA gene among Swedish MS cases.
Aims: We hypothesized that those with progressive onset (PPMS) and without oligoclonal bands (OCB) in the cerebrospinal fluid represents atypical forms of MS, and could therefore be particularly vulnerable to misclassification. Therefore, we aimed to identify OCB- PPMS-specificGLA variants and describe their functional effect.
Methods: Swedish PPMS cases (N=497) were matched to relapsing onset MS (ROMS) cases based on gender and ethnicity (N=569) and to controls based on age, gender and ethnicity (N=579). DNA fragements were captured using Nimblegen's SeqCap V2 Exome kits with library prep optimized for generating ~150 bp DNA molecules. Whole exome sequencing was performed on Illumina's HiSeq 2500, using paired-end 2x76 sequencing. Genomic variants were identified using GATK v3.6 pipeline and extracted forGLA.
Results: We identified 10 variants in theGLA gene among Swedish MS cases. Eight of these are associated with FD, including missense variants and a splice region variant, and range in effect on alpha-galactosidase A enzyme activity from severe to mild. There was no single variant that segregated to the OCB- PPMS group, and combinations of functional variants need to be investigated. OCB-PPMS cases (N=24) had higher Age Related Multiple Sclerosis Severity Scores (p=0.0002) and less improvement on Symbol Digits Modalities Test (p=0.003) than OCB+ PPMS cases (N=176).
Conclusions: Based on global prevalence, 207 FD cases are estimated to exist in Sweden, while merely 70 cases have been identified. We found eight FD-associated variants in GLA, warranting clinical investigation of FD in persons who carry these mutations to elucidate if there are Swedish MS cases with FD.

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Pathology and pathogenesis of MS - Immunology

EP0922
COVID-19 antibody response after two doses of SARS-CoV-2 vaccines in multiple sclerosis patients; an update to the previous study

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Introduction: Disease-modifying therapy (DMT) may decrease the immune response to COVID-19 vaccines, and the antibody response against SARS- CoV-2 is still not fully explored in people with multiple sclerosis(pwMS).
Aims: To evaluate the immune response after messenger RNA (mRNA) BNT162b2 (Pfizer/BioNTech) and inactivated Coronavac vaccines in pwMS treated with a DMT compared to healthy controls(HC).
Methods: Patients who came to our MS unit for treatment or routine control were included in the study. Serum samples were collected at least two weeks after the second dose of the vaccine. The cutoff level or seropositivity is ⩾ 50 antibody units (AU)/ml. The antibody titers were compared between HC and each treatment group.
Results: 815 pwMS treated with DMT, 90 untreated MS patients and 92 healthy controls were enrolled in this single-center cross-sectional study. In total, 500 (50.2%) participants received two doses of inactivated Coronavac, and 497(49.8%) received two doses of BNT162b2. In HC group, only one patient who had mRNA vaccine was seronegative. All patients on cladribine (n =14, 100%)and azathioprine (n=5) treatment have seropositive results in both vaccine types. Among treatment groups, fingolimod and ocrelizumab were associated with lower antibody titers ($p<0.005$). Only in fingolimod group, seropositivity rate was higher for mRNA vaccine compared to inactivated vaccine. The SARS CoV-2 antibody titer was significantly associated with mRNA vaccine [β= 0.739 (0.067) 95%CI= 0.607; - 0.870 $p<0.001$], EDSS [β= -0.061 (0.024) 95%CI= -0.108; - 0.013 $p<0.012$], time between second vaccine dose and sample collection dates [β=-0.002 (0.001) 95%CI= -0.003; - 0.001 $p<0.001$] and relapsing MS type [β= -0.395 (0.136) 95%CI= -0.662; - 0.127 $p<0.004$]
Conclusions: Fingolimod and ocrelizumab therapy are associated with decreased immunity after SARS CoV2 vaccines. mRNA type of vaccine is the preferable choice in pwMS.

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EP0923

Comparative single-cell meta-analysis of leukocytes in the CSF and parenchyma of MS patients

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Introduction: Given the recent advances in single-cell transcriptomics, researchers have been given the opportunity to phenotype leukocytes present within the cerebrospinal fluid (CSF) of MS patients. However, it is still unclear whether the sample of cells collected within the CSF is an unbiased representation of the cells within the parenchyma, or if there is preferential clearance of certain cellular populations.
Objectives: We integrated two publicly available single-cell RNA sequencing datasets (from CSF or cells within brain lesions) to interrogate this. We sought to compare the transcriptional states of similar cell populations across either biological compartment.
Aims: To demonstrate that cells that are within the CSF are a biased population of cells from the CNS.
Methods: Data integration was performed as described by Stuart et al. Common cellular states are identified across both data sets and expression values are then scaled. Variation due to technical differences across each study was minimized.
Results: Firstly, we identified an enrichment of CD8+ T cells within the brain tissue. This result replicates previous literature and confirms the data integration was successful. Interestingly, we also identified a second cluster of CD8T cells that contains cells only from the CSF. Utilizing lists of the differentially expressed gene between the CD8T cell clusters, we found that common biological pathways involved in the immune response were enriched within both populations. However, the cluster that contains parenchymal and CSF CD8T cells had a larger enrichment of pathways relating to metabolism. Secondly, when comparing myeloid cells from the CSF and the parenchyma, we observed that certain clusters contained cells entirely from the parenchyma (microglia populations), as well as clusters that contained cells from both compartments. The cluster that had the largest overlap between the two compartments was enriched for genes involved in classical complement pathway activation.
Conclusions: Together, these data suggest that the cells found within the CSF may be a biased sample of cells present within the CNS tissue. Consequently, this supports the idea that there exists a mechanism in which populations of cells that are involved in processes that promote neurodegeneration (metabolically active CD8T cells or complement releasing myeloid cells, for example) are being preferentially removed from the parenchyma in an attempt to inhibit CNS damage.

Disclosure
Nothing to disclose for all authors

EP0924

Humoral immune response to SARS-CoV-2 booster vaccination in patients with multiple sclerosis and healthy controls: a prospective multicenter study

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Introduction: Booster vaccination against SARS-CoV-2 is recommended for patients with multiple sclerosis (pwMS), usually six months after the last vaccination.
Objectives and aims: To investigate humoral response after SARS-CoV-2 booster vaccination in pwMS compared to healthy controls (HC), as well as the role of the third vaccination in the primarily seronegative and therefore more vulnerable group of treated pwMS (S1PMs, anti-CD20 mAbs).
Methods: In this prospective multicenter study on 292 pwMS and 46 HC, who had all received two vaccinations, SARS-CoV-2 IgG response was measured in the month before and 2–4 months after booster vaccination. PwMS were categorized as follows: untreated (N-DMT, n=32), receiving disease-modifying therapy (DMT) with expected humoral response (er-DMT: interferon-beta preparations, glatiramer acetate, dimethyl fumarate, teriflunomide, natalizumab, cladribine, alemtuzumab; n=120) or no expected humoral response (nr-DMT: S1PMs, CD20mAb; n=140).
Results: PwMS on nr-DMT had significantly lower median antibody levels before (12.1 U/ml [0.4–2500]) and after booster vaccination (305 U/ml [0.4–2500]) in comparison to other groups ($p<0.001$). We did not find differences in antibody levels after homologous (n=281; 2500 [0.4–2500]) and heterologous (n=57; 2500 [0.4–2500]) vaccination regime regardless of the DMT group. The DMT group (= –0.16; 95% CI –34.88, –5.08;p=0.009) were associated with antibody levels after booster vaccination, while time to revaccination(6 months [1–13]) was not. After booster vaccination, seropositivity was reached in 75.8% and 82.2% of pwMS on anti-CD20 mAbs and S1PMs, respectively.

Complete B-cell depletion significantly decreased the probability of seroconversion even after the third vaccination (OR 0.14;p=0.021), whereas time interval to last DMT intake and time to revaccination did not. Twenty-three patients reported a SARS-CoV-2 infection (3 N-DMT, 10 er-DMT, 10 nr-DMT), one being asymptomatic and the rest having a mild course.
Conclusion: Humoral response to SARS-CoV-2 booster vaccination in pwMS is excellent. While reduced by S1PMs and CD20mAb, protective response is still expected in the majority of patients.

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EP0925

Immunophenotyping human cerebrospinal fluid: CXCL10 and neurofilament light chain levels correlate with CSF immune cell subsets and provide pathophysiological relevance in multiple sclerosis

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Introduction: In multiple sclerosis (MS), the cerebrospinal fluid (CSF) contains immune cells and represents an important biological fluid for assessing ongoing disease-related processes. CXCL10 is a chemokine that is highly expressed within the injured central nervous system (CNS) of MS patients and recruits CXCR3+ immune cells towards sites of injury. Neurofilament light chain (NfL) is a widely investigated biomarker of axonal injury that is also elevated in MS and can be measured in both CSF and blood plasma.
Objectives: Within the CSF compartment, perform a comprehensive evaluation to determine a potential relationship between NfL, CXCL10, and various immune cell subsets.
Aims: The aims of this study were: 1) In the CSF of MS and non-inflammatory neurological disease (NIND) controls, measure NfL and CXCL10 levels, and examine associations with numbers of various immune cell subsets, and 2) To elucidate function, measure mRNA and protein expression of glutamate transporters in astrocytes treated with CSF and/or recombinant CXCL10.

Methods: CXCL10 and NfL were measured in CSF by ELISA (BD Biosciences & UMAN Diagnostics, respectively). Immune cells within CSF (2.5mL) were stained using DURAclone IM Phenotyping BASIC tubes (Beckman Coulter) and quantified by flow cytometry. In peripheral blood, expression of CXCR3 was also assessed by flow cytometry. In vitro, human fetal astrocytes were treated with CSF and/or recombinant human CXCL10 and glutamate transporter expression (glt-1, glast) was measured by qPCR and Western blotting.
Results: Compared to NIND controls, CSF from MS cases had higher CXCL10 levels (p=0.021) and was correlated with numbers of immune cells (p=0.04) and T cell infiltrates (CD3+, p=0.01; CD4+, p=0.01; CD8+, p=0.02). In the CSF, NfL levels were positively correlated with numbers of CD8+ T cells (p=0.02) and NK cells (p=0.03). In peripheral blood, expression of CXCR3 on T cells, B cells, and monocytes was not associated with CXCL10 levels in the CSF. In vitro, human fetal astrocytes treated with MS patient-derived CSF and/or recombinant human CXCL10 alone resulted in a downregulation of glutamate transporter expression;glt-1 ($p<0.001$) and glast (p=0.024).
Conclusions: In the CSF of MS patients, elevated CXCL10 levels are associated with increased T cells and appears independent of peripheral CXCR3 expression. Increased CXCL10 may also be partly responsible for dysregulated glutamate handling by astrocytes within the injured CNS.

Disclosure
The authors have nothing to disclose

EP0926

Glucocorticoid treatment increases A20 expression and decreases NF-κB pathway activation in MOGAD and healthy control CD4+ T cells in vitro

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Introduction: There is increasing evidence that T cells play a key role in MOGAD (myelin oligodendrocyte glycoprotein antibody-associated disease) pathophysiology. Recently, we found that A20, a negative regulator of NF-κB (nuclear factor kappa B) pathway, was decreased in central memory T cells and in the serum during relapses in MOGAD. Antigen stimulation, glucocorticoids, and sex hormones have been reported to modulate the expression of A20.
Objective: To investigate the in vitro differential expression of A20 and IκBα (inhibitor kappa B-alpha) levels and NF-κB activation in central memory CD4+ T (CD45RA- CCR7+, Tcm) cells of MOGAD patients after antigen stimulation, sex hormone and glucocorticoid treatment in MOGAD patients compared to age-matched healthy controls (HC).
Methods: 4 pediatric MOGAD remission samples (untreated) and 4 sex and age matched HC were studied. Depending on the experiment, 1.5×10^5 or 2×10^5 PBMCs were plated per well in a 96-well plate. As in vitro stimulant, we used MOG peptide pool, anti-CD3/CD28 or PMA/Ionomycin. To evaluate the effects of steroid hormone treatment, we added prednisolone, estradiol, and testosterone in vitro. A20, IκBα, and phospho-p65 (p-p65) expression levels (MFI, mean fluorescence intensity) were determined by flow cytometry. NF-κB activation was determined by increased p-p65 MFI levels and decreased A20 and IκBα MFI levels in Tcm.
Results: Ex vivo expression levels of A20, IκBα, and p-p65 levels were not significantly different in MOGAD compared to HC in Tcm. Upon short PMA/Ionomycin (0-15-50 minutes) stimulation, we observed similar NF-κB activation in the Tcm from both groups. MOG peptide and anti-CD3/CD28 stimulation for 8 and 24 hours decreased A20 and IκBα levels in both MOGAD and HC. When PBMCs were incubated with anti-CD3/CD28 and steroid hormones simultaneously for 24 hours, we observed increased A20 and IκBα levels and decreased p-p65 levels in the prednisolone+anti-CD3/CD28 condition, in the Tcm cells both in MOGAD and HC. However, we did not observe a change in A20 and IκBα levels or p-p65 after the addition of estradiol or testosterone in vitro.
Conclusions: Prednisolone treatment increases A20 levels and inhibits activation of NF-κB in CD4+ Tcm cells from both MOGAD and HC, while MOG antigen stimulation had the opposite effect. Sex hormones did not appear to affect A20 expression. Modulation of the NF-κB-A20 pathway in T cells may have therapeutic potential in MOGAD.

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EP0927

Characterization of accelerated immunosenescence in multiple sclerosis through the analysis of immunological cell populations

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Introduction: The **immunosenescence** is an age-related process that leads to a progressive reduction in the ability of the immune system (IS) to trigger effective immunological responses, a multifactorial phenomenon that affects both, natural and acquired immunity.
However, the continuous activation of the IS could lead to premature aging of the IS. **Premature immunosenescence** has been linked to immune-mediated diseases like HIV infection, Alzheimer disease or **multiple sclerosis (MS)**.
Objectives/Aims: Despite several studies related MS with an accelerated aging of the IS, much remains to be discovered. We analyzed the principal immunological cell populations, their function (immunological response) and senescence marks, to check if MS patients show premature immunosenescence.
Methods: This study was carried out using 3 different multicolor flow cytometry panels. Blood samples of 42 healthy controls (HC) and 68 MS patients from different ages (20-82) were obtained. Cell surface markers were used to analyze immunosenescence and immunological response (after an in vitro stimulation with PHA):CD3, CD19, CD56, CD14, CD16, CD4, CD8, CD28, CD57, CD69, CD25, CD127 and CD196. The correlation analysis with age was done with the percentage data in IBM SPSS Statistics and R studio.
Results: The analysis of the main immunological populations reveals that CD19+ cells increase with age in HC while they remain stable in MS patients. On the contrary, CD14+ CD16- cells tend to fall with age in HC and raise in MS patients.
Regarding T cells, CD4+ cells decrease with age in MS patients, while they remain stable in HC. The CD8+ cells of the MS patients present an increase in the CD57 and CD28 antigens with age, while, in the case of the HC, this only occurs with CD57. The CD8+CD28+CD57- cells increase with age in MS patients, while they fall in HC. The CD8+CD28+CD57+ cells show an age-related increase in MS patients. In the case of the CD8+CD28-CD57+ cells, a raise with age was observed in both groups, while it only reached statistical significance for MS patients.
Conclusions: Our results show age-related differences in some immune cells, including some monocyte, B cell and T cell populations, although we cannot confirm an overall accelerated immunosenescence in MS. MS patients show an increase of CD28 with age, an antigen that provides co-stimulatory signals for T cell activation and survival. Further research is needed to understand the mechanism behind these promising results.

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EP0928

Cerebrospinal fluid of Progressive multiple sclerosis patients reduces differentiation and immune functions of oligodendrocyte progenitor cells

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Introduction: Oligodendrocyte progenitor cells (OPCs) are responsible for remyelination in the central nervous system (CNS) in health and disease. For patients with multiple sclerosis (MS), remyelination is not always successful, and the mechanisms differentiating successful from failed remyelination are not well-known. Growing evidence suggests an immune role for OPCs, in addition to their regenerative role; however, it is not clear if this helps or hinders the regenerative process.
Objectives: We hypothesized that CSF from rMS patients would have a different effect on OPC differentiation and immunomodulatory properties as compared with exposure to CSF from pMS patients.
Methods: We studied the effect of cerebrospinal fluid (CSF) from relapsing MS (rMS) and progressive MS (pMS) patients on primary OPC differentiation and immune gene expression and function.
Results: We observed that CSF from either rMS or pMS patients has a differential effect on the ability of mice OPCs to differentiate into mature oligodendrocytes and to express immune functions. CSF of pMS patients impaired differentiation into mature oligodendrocytes. In addition, it led to decreased major histocompatibility complex class (MHC)-II expression, tumor necrosis factor (TNF)-αsecretion, nuclear factor kappa-B (NFκB) activation, and less activation and proliferation of T cells.
Conclusions: Our findings suggest that OPCs are not only responsible for remyelination, but they may also play an active role as innate immune cells in the CNS. Our data enhanced the current understanding of the roles of OPCs, highlighting their specific role in inflammation in different clinical manifestations of MS. These findings may provide new avenues for therapeutic intervention as well as furnishing a better understanding of disease pathogenesis.

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EP0929

Safety and efficacy of a third booster dose of BNT162b2 mRNA Covid-19 vaccine in patients with multiple sclerosis treated with ocrelizumab or fingolimod

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Introduction: Patients with Multiple Sclerosis (pwMS) treated with Ocrelizumab (OCR) and Fingolimod (FNG) have shown a blunted humoral response to the first two doses of the BNT162b2 mRNA Covid-19 vaccine. The assessment of the safety and the humoral response to a third booster dose of the same vaccine is therefore relevant within this population.
Aim: To investigate the safety and the humoral response to a third booster dose of the BNT162b2 mRNA Covid-19 vaccine in pwMS on OCR/FNG, comparing it with age- and sex-matched healthy controls (HCs).
Methods: Serum samples were collected from HCs and pwMS treated with OCR or FNG at the following scheduled time points: before the first of two vaccine doses (T0); 8 (T1), 16 (T2), 24 (T3) weeks after the first dose; within 8 weeks before (T0b) and after (T1b) the booster dose. IgG antibodies to SARS-CoV-2 trimeric spike protein (Anti-TSP IgG) were quantified and expressed as binding antibody units (BAU)/mL.
Results: 40 HCs and 47 pwMS (28 on OCR and 19 on FNG) were included in the study. All (100%) HCs mounted a positive (>33.8 BAU/mL) humoral response at T1 and preserved it until (T2-T3-T0b) and after (T1b) the third booster dose. At T0b only 12 (42.9%) pwMS on OCR and 6 (31.6%) on FNG were positive while, at T1b 16 (57.14%) pwMS on OCR and 16 (84.2%) on FNG, passed the threshold of positivity.
Anti-TSP IgG titers in HCs were significantly higher than those of pwMS on OCR and on FNG at all time points, while no differences were found at all time points between pwMS on OCR and those on FNG. HCs showed a significant higher (relative) increase of Anti-TSP IgG levels at T1b with respect to OCR ($p<.001$) and FNG ($p=.032$) groups. The increase of Anti-TSP IgG levels in the pwMS on FNG was significantly higher than those in the OCR group ($p<.001$). No socio-demographic, clinical, or laboratory variables were able to predict the increase of anti-TSP IgG levels between T0b and T1b.
Neither clinical relapses nor severe adverse events were reported in pwMS after each of the three doses of vaccine during the follow-up period.
Conclusions: The administration of a third booster dose of BNT162b2 mRNA Covid-19 vaccine to OCR- and FNG-treated pwMS is able to revive the humoral response, independently of any demographic, clinical or laboratory variable, and confirms a good safety and tolerability profile, not only in terms of adverse events but also in terms of MS relapses.

Disclosure
R. Capuano, M. Altieri, M. Conte, A. Bisecco, A. d'Ambrosio, G. Donnarumma, E. Grimaldi, N. Coppola, M. Galdiero, C. Abbondanza, G. Tedeschi, A. Gallo report no disclosure

EP0930

CLADRIPLAS: Does cladribine Target CNS plasma cells and reduce neuro-axonal damage in people with MS?

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Introduction: Cladribine is a CNS penetrant disease-modifying treatment, which – in an oral preparation (Mavenclad®) – was licensed for people with highly active relapsing MS in August 2017. Our experience with cladribine dates back to 2014 when we started using subcutaneously injected cladribine as a compassionate immunotherapy in people with MS (pwMS) off-label. This programme enabled us to embed CLADRIPLAS, a mechanistic study of the effect on intrathecal B cell and plasma cell function and axonal damage focussing on progressive MS (PMS) (IRAS # 240360).
Objectives: To study the effect of cladribine on peripheral and intrathecal B and plasma cells.
Aims: To study the effect of cladribine on oligo-clonal bands (OCB) and the level of neurofilament light (NfL) chain.
Methods: Observational study involving two lumbar punctures and phlebotomies, 6-12 months apart, to collect B cell subsets, and intrathecal plasma cell as well as neurofilament light chain (NfL) level in pwMS eligible and not eligible for cladribine treatment based on cerebro-spinal fluid (CSF) NfL, clinical and/or MRI evidence of inflammatory disease activity. Here, we report baseline cohort characteristics.
Results: Thirty-eight pwMS were recruited (19 women, 19 men) and had their first sample collections. Eight pwMS were eligible for cladribine treatment (7 based on elevated NfL, 1 due to MRI

activity). Follow-up samples have been collected in 21. Mean age at baseline was 55 years (40-76). Fourteen had primary, 24 secondary PMS. Median EDSS=6.5 (3.5-8). Twenty-one pwMS had been treated with DMT before consideration of cladribine, 17 were immunotherapy-naïve. Mean CSF-NfL level was 552 (176-2072) pg/ml.
Conclusions: Despite restrictions due to COVID-19, 38 of 40 planned pwMS were enrolled. 7/8 were eligible based on CSF-NfL level indicating the importance of using biomarkers other than MRI to establish disease activity in PMS. We expect our cohort to enable meaningful comparison between groups. CLADRIPLAS will finish in early 2023.

Disclosure
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EP0931
Divergent complement system activation in two clinically distinct murine models of multiple sclerosis

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Background: There is evidence of significant activation of the complement system (CS) in MS lesions, likely contributing to its pathogenesis. However, the components/pathways of the CS implicated in disease mechanisms remain unidentified.
Objectives: To determine which complement pathway is active in two clinically distinct murine models of MS, relapsing-experimental autoimmune encephalomyelitis (rEAE) and Theiler's Murine Encephalomyelitis Virus-Induced Demyelinating Disease (TMEV-IDD).
Aims: (1) I will use gene expression of complement factors and clinical outcomes to determine which complement pathway is active. (2) I will utilize immunofluorescent microscopy to locate complement factors in the spinal cords of affected mice to determine if they are associated with disease mechanisms.
Methods: Analyses were performed in SJL/J mice with chronic progressive TMEV-IDD and acute $PLP_{139-151}$-induced rEAE. In spinal cords, we assessed complement activation (C1q, CFb, MBL, C3, and IgG1) and central nervous system (CNS) inflammation and tissue damage (IBA1, NeuN, Fluoromyelin, and APP) by real-time PCR and immunofluorescent image analysis, respectively. Intrathecal production of immunoglobulins (Igs) was determined via rt-PCR and by protein analysis (ELISA and Luminex). Motor function was quantified in both models throughout their respective disease courses.
Results: Upregulation of C3 indicates activation of the CS in both models. To determine which pathway activates the CS in each model, we analyzed C1q, MBL, and CFb. C1q and CFb expression was increased in both models (p£0.0003). In TMEV-IDD, C1q expression was associated with worse disease outcomes (r^2=0.1568; p=0.0168). Conversely, in rEAE, C1q expression correlated with improved disease outcomes (r^2=0.243; p=0.0307), and CFb expression associated with worse clinical outcomes (r^2=0.5062; p=0.0006). We analyzed intrathecal Ig production, and only in TMEV-IDD increased expression of IgG1 was associated with worse disease outcomes (r^2=0.143, p=0.0268) and increased C1q (r^2=0.219; p=0.0079). Accordingly, C1q deposition was localized in regions of inflammation, neuroaxonal damage, and demyelination in TMEV-IDD only.
Conclusions: Overall, these results indicate potential divergent roles for the CS in MS. Chronic-progressive forms seem reliant on activating the classic complement pathway while protecting from relapses. Conversely, relapsing forms appear more likely affected by the alternative pathway.

Disclosure
All authors have nothing to disclose.

EP0932
The role of the mannose receptor C type 2 in migration of peripheral blood mononuclear cells across brain endothelial cells

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Introduction: Multiple sclerosis (MS) is characterized by a disturbance of the blood-brain barrier (BBB), and infiltration of

immune cells attacking the host's own central nervous system (CNS) tissue. To reach inflamed CNS sites, peripheral immune cells degrade extracellular matrix (ECM) components at the BBB.
Objectives: Evaluating the relevance of the mannose receptor C type (MRC)-2, responsible for the internalization and degradation of the ECM component collagen IV, in immune cell transmigration in the context of MS pathology.
Methods: Flow cytometry analysis of untreated peripheral blood mononuclear cells (PBMCs) and in vitro polarized T cells to determine surface MRC2 levels. Immunohistochemistry of active MS lesions on postmortem tissue to evaluate the relevance of MRC2 in MS pathology. Assessment of collagen IV expression of ex vivo human brain endothelial cells using immunofluorescence microscopy.In vitro trans endothelial migration of human PBMCs from MS and healthy donors treated with MRC2-specific blocking antibody or isotype control, followed by flow cytometry analysis to assess MRC2-mediated migration.
Results / Discussion: First flow cytometry analysis of PBMCs showed that CD14+ monocytes express high levels of MRC2 under steady-state conditions, whereas upon in vitro polarization pro-inflammatory T helper (Th1, Th17) and T cytotoxic subpopulations (Tc1, Tc17) upregulate MRC2. Indeed, MRC2 expression was significantly co-localized with perivascular accumulating $CD8^+$ Tc cells entering pre-active and active CNS lesions on post-mortem brain tissue from 5 MS patients evidenced by confocal microscopy. Expression of collagen IV on in vitro cultured human brain endothelial cells was detected by immunofluorescence microscopy. In vitro trans-endothelial migration of PBMCs from healthy donors and MS patients followed by flow cytometry analysis indicates that treatment with MRC2-specific blocking antibody might interfere with migration of CD14+ monocytes.
Conclusion: Our first results indicate a role for MRC2 in monocytes and pro-inflammatory activated T cells. Further confirmation of migration assays and ongoing analysis including in vivo studies using the experimental autoimmune encephalomyelitis mouse model will elucidate whether MRC2 indeed represents a novel therapeutic target to interfere with MS disease development and progression.

Disclosure
C.L. has served on scientific advisory boards and/or as speaker for EMD-Serono, Alexion, Biogen, Bristol-Myers Squibb, Roche, Novartis, Teva, Celgene, Actelion and Sanofi-Genzyme and has received travel support from Sanofi-Genzyme.
All other authors declare that there is no conflict of interest.

EP0933

Targeting myeloid-derived suppressor cells via miR-223, in alternative to glucocorticoids, in multiple sclerosis

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Introduction: Multiple sclerosis (MS) drugs specifically targeting the innate immune system are still under investigation. Myeloid-derived suppressor cells (MDSCs) are arising during chronic inflammation, and are defined by their T cell immunosuppressive functions. Glucocorticoids (GCs) are effective drugs in treating neuroinflammatory diseases, such as MS, and among other mechanisms, they can also influence the function of MDSCs. The prolonged use of GCs in clinical practice is limited by the multiple side effects associated with chronic administration.
Aims: Study MDSC suppressive activities in people with MS (pwMS) and find new MDSC makers.
Methods: MDSCs isolated from healthy controls (HC), and pwMS were co-cultured with CD4+ T cells to evaluate their immunosuppressive activities. qPCR was used to evaluate the expression of microRNAs, STAT3, and cytokines, such as IL-10. Anti-miR-223 or scramble control transfection was induced on MDSCs. Cytokines and chemokines were evaluated by Luminex assay on the serum of HC, pwMS, and other neuroinflammatory diseases.
Results: Here we report impaired MDSC suppressive activities in pwMS, reverted by GC treatment. Mechanistically, in vitro steroid treatment decreased the expression of miR-223, an important myeloid-specific microRNA, in MDSCs but not T cells. Both miR-223 and GCs enhanced MDSC suppressive activities, and this effect was mediated by STAT3, an important transcription factor involved in regulating MDSCs, for miR-223, but not GC. MDSC phosphorylated STAT3 levels were correlated with GM-CSF serum levels from HC and pwMS.
Conclusions: These results suggest that miR-223 could be used as a specific therapeutic target for implementing MDSC suppressive activities in alternative to GCs.

Disclosure
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EP0934

Perturbed mitochondrial respiratory activity in the different clinical forms of multiple sclerosis

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Background: Multiple sclerosis (MS) results from the interaction of genetic and environmental factors. Recently, a Mendelian randomization study demonstrated a genetically-predicted increased basal metabolic rate (BMR) as an independent causal risk factor for MS. BMR relates to the energy balance and mitochondria are the cell energy engine. In addition, the relevance of metabolic processes in activation, expansion, and effector functions of immune cells has been described.
Aim: To evaluate the mitochondrial function and glycolytic activity of immune cells isolated from healthy controls and patients with the different clinical forms of MS.
Methods: Oxygen consumption and extracellular acidification rates were measured with a Seahorse XFp Extracellular Flux Analyzer (Agilent Technologies) in unstimulated or PHA-stimulated cells. Mitochondrial mass and membrane potential were also ascertained by flow cytometry with MitoTracker™ Green and JC-1 dye.
Results: In resting conditions, MS progressive clinical forms showed significantly higher basal and maximal respiration and ATP production ($p<0.05$), while relapsing remitting patients behaved similarly to controls. After PHA activation, all patients showed lower responses than controls in the mitochondrial parameters studied, reaching statistical significance for the progressive forms ($p<0.04$). Fold increases in mitochondrial mass after PHA-activation correlated with respiratory activity, being significantly lower for progressive patients in both overall and CD3+ lymphocytes ($p<0.02$). Altered mitochondrial membrane potential, an indicator of mitochondrial stress, was also observed in both populations ($p<0.001$).
Upon activation, lymphocytes face major metabolic changes to meet the increased bioenergetics and biosynthetic demands, and shift to aerobic glycolysis. In this regard, prior to activation, we observed statistically significant increments for every clinical form compared to controls, both in basal and in maximal glycolysis ($p<0.03$). After PHA activation, significantly decreased fold changes were detected in patients compared to controls.
Conclusion: Leveraging the direct analyses of patients' cells, substantial perturbations in mitochondrial respiratory activity and glycolytic rates have been detected, which underlines the relevance of metabolic processes in immune cells in MS pathology.

Disclosure
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EP0935

In-depth analysis of cerebro-spinal fluid CD4+ t cells in multiple sclerosis and controls reveals disease-associated subpopulations

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Introduction: The pathogenesis of early Multiple Sclerosis (MS) is still incompletely understood. Current treatments are broadly immunomodulatory or even immunosuppressive, which impedes also beneficial immune functions. A deeper understanding of pathogenic immune cell subsets is needed to design personalized treatment approaches instead of broad cell ablation.
Objectives: Using the animal model of experimental autoimmune encephalomyelitis (EAE), we characterized CD4+ T cells in the acute phase and compared these with T cells surviving in the CNS lesions long after onset of the disease with an unbiased, explorative approach by single cell transcriptome analysis. To translate these findings in the human disease, we designed a marker panel for multi-dimensional flow cytometry to identify CD4+ T cell subpopulations. The current study compares the relevance of those markers in human MS at the onset of disease.
Methods: Patients with first diagnosed MS (n=10) and as a control group (n=5) patients with suspected idiopathic intracranial hypertension (IIH) were recruited. Cerebro-spinal fluid (CSF) samples were obtained during routine diagnostics. Cells were fixated and stained with the previously defined marker panel (26 markers in total). Multi-dimensional flow cytometry was performed using Cytek Aurora.
Results: In our animal model EAE, we identified 5 distinct central nervous system (CNS) subpopulations of CD4+ T cells, of which 3 are novel (innate-like, tissue resident memory- and lymphoid tissue like) and have not been characterized in EAE. As hypothesized, we found distinct changes in those subsets between acute and chronic phase of EAE. Interestingly, the analysis of human CSF data shows a mix of elevated markers between MS and IIH, which were either upregulated in acute or chronic phase of EAE. Furthermore markers of the T cell populations we defined as innate-like and memory T cells were more abundant in MS vs. IIH.
Conclusions: The in-depth analysis of CSF by multi-dimensional flow cytometry identifies novel CD4+ T cell subpopulations in MS patients. In particular markers of chronic persistence might be of relevance for more targeted treatment approaches.

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EP0936

Immune-mediated CNS injury in a young woman - a case report from Uzbekistan

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Introduction: Myelopathy is a syndrome that occurs in demyelinating, infectious, neoplastic, vascular, and rheumatic diseases. Their structure does not
more than 3% of cases of spinal cord injury for systemic lupus erythematosus (SLE). The clinical picture of SLE in most cases precedes the onset of
neurological symptoms. However, the spinal syndrome may be the first manifestation of the disease. Objectives: We aimed to give a clinical example of myelopathy in a young woman, who is the first and leading manifestation of lupus.
Methods: Patient I., 41 y. MRI of the CNS revealed changes in the subcortical regions of the brain and multiple foci in the spinal cord at the level of the cervical and thoracic regions. Multiple sclerosis was diagnosed. When taking interferon beta-1b, tonic convulsions appeared in the lower extremities, regarded as a side effect. Appointment of axoglatiran - no effect.
Results: 06.17 - stopped moving without anybody's help, hospitalized in the scientific center of neurology. MRI revealed foci of active accumulation of the contrast agent at the cervical level of the spinal cord. A systemic connective tissue disease is suspected. To suppress myelitis, therapy with mitoxantrone IV N 3 was carried out from 2019 to January 2021, and MP pulse therapy has noted a reduction of paresis, zones of hypesthesia, decrease in titers ANF 2 times. Appeared dizzy pain, intense pain, and cramps in the upper and lower extremities, violation of the act of urination, fever 37 ºC, arthralgia of small joints of the hands, and morning stiffness ness, arthritis of the left ankle joint, skin erythema right leg 9 cm.
Conclusions: Given the presence of clinical, hematological, and immunological clinical markers of the disease and lesions of the central nervous system, the diagnosis of SLE became reliable. The peculiarity of this case is that the primary and only clinical syndrome for 3 years was a syndrome of progressive myelitis with the late addition of other manifestations of lupus, including immunological. It came to the cause of the difficulty in diagnosing and interpreting encephalomyelitis in SLE. Activity control diseases against the background of the use of cytostatics are based on the assessment of myelitis activity in MRI contrast of the spinal cord.

Disclosure
No disclosure

EP0937

The role of 5-HT_{2B}-receptor in the fluoxetine mediated macrophages-induced Th17-immune response in multiple sclerosis

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Introduction: Fluoxetine is a selective serotonin reuptake inhibitor, which also has an immunomodulatory effect.
Objectives: To clarify the influence of fluoxetine on macrophages-induced Th17-immune response, which plays a crucial role in multiple sclerosis (MS) pathogenesis.
Aims: To study the effect of fluoxetine on the production by macrophages Th17-differentiation cytokines as well as the ability of macrophages to induce interleukin-17 (IL-17) and interferon-gamma (IFN-γ) by autologous $CD4^+$ T-cells in relapsing-remitting MS patients.
Methods: Twenty MS patients and twenty healthy subjects were examined. Monocyte were obtained from peripheral blood mononuclear cells (PBMCs) by magnetic cells sorting and were cultured with granulocyte-macrophage colony stimulating factor for 6 days. On day 7, monocyte-derived macrophages were pre-incubated in the presence of fluoxetine (10^{-5} M), whereafter were pulsed with IFN-γ for two hours and activated with lipopolysaccharide (LPS) for 24 hours. To induce IL-1β production, adenosine triphosphate was added to the culture for 30 minutes at the end of incubation. To study the effect of fluoxetine on the ability of macrophages to induce IL-17 and IFN-γ production by T-cells, macrophages were pre-incubated in the presence of fluoxetine (10^{-5} M) or agonist/antagonist of 5-HT_{2B}-receptor (10^{-6} M) and fluoxetine, whereafter were pulsed with IFN-γ for two hours. Thereafter, the cells were washed and activated with LPS for four hours. Then, LPS-activated macrophages were co-cultured with autologous $CD4^+$ T cells (obtained from PBMCs by magnetic cell sorting). The levels of IL-6, IL-1β, IL-17, and IFN-γ in culture supernatants were assessed by ELISA.
Results: Fluoxetine reduced IL-6 and IFN-γ production by LPS-activated macrophages in both groups without affecting cell viability ($p<0.01$). Fluoxetine also reduced the ability of LPS-activated macrophages to induce IL-17 and IFN-γ

production by $CD4^+$ T-cells in both groups ($p<0.01$). Blockade of 5-HT_{2B}-receptor decreased the inhibitory effect of fluoxetine on macrophages-induced cytokine production by $CD4^+$ T-cells in both groups ($p<0.05$).
Conclusions: These data suggest an anti-inflammatory role for fluoxetine in MS, which could be mediated by the influence on the macrophages-induced Th17-immune response. The anti-inflammatory effect of fluoxetine on macrophages-induced Th17-immune response could be mediated by the 5-HT_{2B}-receptor activation.

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EP0938

Methionine intake modulates neuroinflammatory and neurodegenerative processes in murine models of multiple sclerosis

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Introduction: Multiple Sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system (CNS). Dietary methionine restriction (MR) displays anti-inflammatory properties and improves metabolic health through sexually dimorphic mechanisms. We found that methionine pathway is induced upon T cell activation in vitro and that MR affects the effector function and proliferation of TH17 cells, considered pathogenic in MS and its animal model, experimental autoimmune encephalomyelitis (EAE).
Objective: To study the manipulation of T cell methionine metabolism as a new therapeutic avenue for controlling neuroinflammatory diseases such as MS in both sexes.
Methods: We immunized C57BL/6 mice exposed to low methionine (MR) vs. control diet with $MOG_{35-55}$and used transgenic TCR1640 mice developing spontaneous EAE and exposed to MR vs. control or methionine supplemented (M+) diet to test the impact of methionine intake on clinical course and immune cell distribution and activation (flow cytometry and RNAseq). We assessed the impact of methionine intake on the composition of gut microbiome with 16S rRNA-sequencing. Finally, serum neurofilament light chain (sNfL) levels were measured to evaluate neuroaxonal injury.
Results: We found that MR delays onset of neurological deficits in MOG-induced active EAE and this is paralleled by lower numbers of pro-inflammatory immune cells in the spleen at day 7 post-induction (presymptomatic), in the spleen and CNS at day 10 (pre-onset) and in the CNS at day 15 (peak). Moreover, MR delays onset of spontaneous EAE in TCR1640 mice of both sexes, with a near complete abrogation in males. This is associated with lower numbers of pro-inflammatory immune cells in the spleen and CNS at the presymptomatic and chronic stages of spontaneous EAE. In addition, the elevation of sNfL observed at peak of active EAE is reduced in both males and females exposed to MR, with a more pronounced impact on females. Similarly, we found reduced levels of sNfL as well in males and females exposed to MR during the chronic phase of spontaneous EAE, while M+ diet is associated with increased sNfL levels in females. Finally, T cell transcriptomic and gut microbiome composition reveal differences according to sex and diet that could mediate the beneficial impact of MR on neuroinflammatory processes.
Conclusion: MR ameliorates EAE clinical course and limits neuroinflammatory processes and neuroaxonal injury in two preclinical models of MS.

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EP0939

Investigating the relationship between Siponimod efficacy in secondary progressive multiple sclerosis and pathogenic Th cell populations

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Introduction: Secondary progressive multiple sclerosis (SPMS) is a chronic neuroinflammatory disease that can develop in relapsing/remitting MS (RRMS) patients. Active immune processes are indicated in RRMS and treatments targeting lymphocytes can be clinically effective.
In contrast, the pathogenesis of SPMS is poorly understood, with recent evidence now associating SPMS with active immune responses with unknown pathogenic immune cell components. Our recent data also support this concept, showing an association between a cytotoxic-like T helper cell (Th cell) subset and active disease in SPMS (Raveney et al., PNAS 2021).
Siponimod (Drug name Mayzent) is a modulator of S1P receptors that targets lymphocyte trafficking and has recently been approved for SPMS treatment. However, it is unclear which immune cell populations may be targeted by this drug or why this treatment succeeds where other lymphocyte tracking modulators have failed.
Aim: To examine the role of populations of immune cells in SPMS pathogenesis that may be targeted by Siponimod treatment
Methods: Peripheral blood mononuclear cells were prepared from patients before Siponimod treatment and at 3, 6 and 12 months after Siponimod initiation. Immune cell subsets were examined by multiparameter flow cytometry and compared with treatment efficacy.
Results: Preliminary data indicated that targeting lymphocyte trafficking in our novel SPMS mouse model ameliorated chronic neuroinflammatory disease symptoms, supporting a potential mechanism for Siponimod treatment in targeting T cells in SPMS. In SPMS patients, clinical improvement was observed in 12 out of 48 subjects that were switched to Siponimod treatment. Effective Siponimod treatment was linked to a reduction in proportions of peripheral Th cells with an activated/effector phenotype ($p<0.01$). These data suggest this treatment may be effective in SPMS by limiting active pathogenic Th cells. Retrospective analysis indicated that measurement of these effector T cells could act as a specific biomarker (ROC AUC=0.886) that could inform clinical decisions in treatment choice.
Conclusions: Different efficacy of drugs in RRMS versus SPMS and between SPMS individuals may relate to different pathogenic mechanisms in play. Detailed examination of T cell subsets could pave the way for personalized medicine in targeting the correct treatments against the particular populations of pathogenic Th cells extant in particular SPMS cases.

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EP0940

Gene expression and immune repertoire: intraindividual stability throughout the cryopreservation process

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Background: Biobanking of patient material has become instrumental in both fundamental and clinical research. The availability of cryopreserved peripheral blood mononuclear cells (PBMC) greatly simplifies experimental design and effectively reduces intraexperimental batch effects as all samples can be processed in a short lapse of time. The use of cryopreserved PBMCs holds great potential for the identification of disease predictors in multiple sclerosis (MS), but it is essential to confirm the intraindividual stability of gene expression, immunophenotype, and immune repertoire throughout the cryopreservation process.
Objectives: Our goal is to assess the stability of gene expression and T cell repertoire of fresh versus frozen PBMC samples from MS patients and healthy control.
Methods: Single-cell RNA Sequencing (scRNA-Seq) using 10X Genomics technologies was used to perform an in-depth characterization of the transcriptome and the T cell repertoire of PBMCs from 2 untreated relapsing-remitting MS patients and 2 healthy controls. For each subject, a fraction of the PBMC sample was processed immediately and the rest was frozen in liquid nitrogen for processing after two timepoints of cryopreservation; 2 days and 10 months.
Results: Our correlation analysis showed that the gene expression is highly preserved through cryopreservation with a R of 0.99 and a p value of $< 0{,}0001$ in each paired comparison for each donor.

Moreover, clustering of the samples based on the most variable genes showed perfect segregation of samples belonging to the same individual. Clonality and diversity of the T cell repertoire, as well as the proportion of clusters based on the sequence of the T cell receptor sequence, were also highly preserved.
Conclusions: Our data demonstrates a highly preserved PBMC profile at the transcriptome level over cryopreservation time, confirming that biobanked PBMCs are suitable for projects using scRNA-seq on large cohorts.

Disclosure
The authors have nothing to disclose.

EP0941
Immune response against SARS-CoV-2 vaccines in treatment-naive multiple sclerosis patients

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Introduciton: Multiple Sclerosis (MS) is an autoimmune disease with B-cell dysregulation playing an essential role in pathogenesis. As B-cells are also responsible for antibody production, their disfunction could also affect the humoral immune response against SARS-CoV-2 vaccines.
Aims: To compare the immune response after messenger RNA (mRNA) BNT162b2 (Pfizer/BioNTech) and inactivated Coronavac vaccines in newly diagnosed treatment-naive MS (tnMS) patients and healthy controls (HC).
Methods: A single-center cross-sectional study evaluating antibody response against SARS-CoV-2 vaccines (inactivated vs mRNA) in HC and newly diagnosed and treatment-naive MS patients. Serum samples were collected at least two weeks after the second dose of the vaccine. The cutoff level of seropositivity is $\geqslant$ 50 antibody unit (AU)/ml.
Results: 46 participants had two doses of inactivated Coronavac (35 HC and 11 tnMS), and 103 (57 HC and 46 tnMS) had two doses of mRNA. There was no significant difference in antibody response between HC and tnMS in the inactivated vaccine group. In the mRNA group, the antibody titers were significantly higher in HC (p=0.009), though no difference in the seropositivity rates was observed.
Conclusions: Although MS is an autoimmune inflammatory disease, it does not affect immunity against the SARS-CoV-2 vaccine in treatment-naive patients.

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Covid-19 vaccination can induce multiple sclerosis via cross-reactive CD4+ T cells recognizing SARS-CoV-2 spike protein and myelin peptides

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Introduction: Infection with the SARS-CoV-2 coronavirus can lead to a wide range of acute and also chronic disease manifestations. The rapidly developed vaccinations are highly effective in preventing severe disease courses and have been proven safe. Both natural infection and, to a much lower extent, the mRNA-based vaccinations can be accompanied by transient autoimmune phenomena or onset of autoimmune diseases.
Objectives: We report here two cases of multiple sclerosis (MS) with clinical and new radiological signs beginning in close temporal relation to spike (S) protein mRNA-based vaccinations.
Aims: To establish that the onset of MS in these two cases is very likely caused by CD4+ T cell clones that cross-recognize SARS-CoV-2 S protein-derived peptides and peptides derived from myelin proteins, which have previously been implicated in MS.
Methods: Spike specific CD4+ T cells from peripheral blood and CD4+ T cells from CSF sample were isolated and expanded for autoantigen screening test. A list of well-known MS-related autoantigens including immunodominant peptides and isoforms from MBP, MOG, PLP, RASGRP2, TSTA3 peptides were included to assess T cell reactivity. CD4+ CFSElow fraction were sorted after stimulate with positive autoantigen pools or SARS-Cov-2 Spike protein, followed by expansion and testing with autoantigen peptides and Spike protein. Supernatant from cell culture were further analyzed for IFN-gamma secretion.
Results: Self-reactive T cells were detected from Spike specific T cell population in both patients. CD4+ T from CSF also showed reactivity to MBP, MOG, PLP peptide pools. Finally, we found proinflammatory T cell clones that recognize both Spike protein and immunodominant MBP peptides and MOG peptides, which have previously been implicated in MS.
Conclusions: Detailed studies of both peripheral blood- and CSF-derived CD4+ T cells show that the onset of MS in these two cases is very likely caused by CD4+ T cell clones that cross-recognize SARS-CoV-2 S protein-derived peptides and peptides derived from myelin proteins, which have previously been implicated in MS.

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Neuway, CellProtect, Third Rock; patent holder and co-holder on patents of: daclizumab in MS, JCV VP1 for vaccination against PML; JCV-specific neutralizing antibodies to treat PML; antigen-specific tolerization with peptide-coupled cells and novel autoantigens in MS; co-founder of Abata, co-founder and co-owner of Cellerys®

Pathology and pathogenesis of MS - Microbiology and virology

EP0943

Serum antiviral antibody titers in multiple sclerosis patients after six months under teriflunomide treatment and their clinical implications: a longitudinal study

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Introduction: Epstein-Barr virus (EBV) and Human herpesvirus 6 (HHV-6) have been associated with multiple sclerosis (MS). Teriflunomide is an oral disease modifying therapy approved for treatment of relapsing forms of MS. In the preclinical Theiler's Murine Encephalitis Virus model of MS, the drug demonstrated an increased rate of viral clearance versus the vehicle placebo. Furthermore, teriflunomide inhibits lytic EBV infection in vitro.

Objectives: 1. To evaluate the variation of IgG antibody titers against EBNA-1 and VCA of EBV and IgG and IgM against HHV-6 in serum between baseline visit (no treatment) and after 6 months of teriflunomide treatment, as part of their regular clinical follow-up. 2. To correlate this variation with the clinical response (relapses and progression) and radiological response (variation in the lesion load in T2 and number of Gadolinium-enhancing lesions) after 12 months and 24 months of treatment with teriflunomide.

Methods: A total of 101 MS patients (62 females; mean age: 43.4 years) with one serum sample at baseline visit (prior teriflunomide onset) and another serum sample after 6 months of teriflunomide treatment were recruited: 80 had been treated at least 24 months, 13 had stopped teriflunomide before 24 months and 8 were currently under teriflunomide therapy but with less than 24 months of follow-up. We analyzed the levels of the viral antibodies titers above mentioned in serum samples with ELISA commercial kits, following manufacturer instructions.

Results: 1. After 6 months of teriflunomide treatment antiviral antibodies titers decreased in: 60/100 (60%) MS patients for HHV-6 IgG, 74/100 (74%) for HHV-6 IgM, 74/101 (73.3%) for EBNA-1 IgG and 69/100 (69%) for VCA IgG. 2. Among the 80 MS patients that fulfilled 24 months under teriflunomide therapy: 13/21 (61.9%) of MS patients with EBNA-1 IgG titers increased after 6 months treatment experienced EDSS increase and/or relapses vs. 22/59 (37.3%) of MS patients without EBNA-1 IgG increased ($p=0.05$; O.R.=2.7). No associations were found for HHV-6 or VCA of EBV.

Conclusions: Teriflunomide significantly reduced the levels of IgG antibody titers against EBNA-1 and VCA of EBV and IgG and IgM against HHV-6 after 6 months of treatment in a real-life cohort of Spanish MS patients. Increased in EBNA-1 IgG titers after 6 months of treatment was associated with a higher probability of experiencing EDSS increase and/or relapses after 2-years under teriflunomide therapy.

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EP0944

Serum 3-phenyllactic acid level is reduced in benign multiple sclerosis and is associated with effector B cell ratios

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Introduction: 3-phenyllactic acid (PLA) is actively generated by the host and the gut microbiota and exists in its D- and L- chiral forms. It modulates human immune functions, thereby acting as a mediator of bacterial-host interactions.PLA can modulate the immune system through activation of the hHCAR family. Dimethyl fumarate (DMF), an immunomodulatory treatment for MS, has been shown to ameliorate MS by dampening these hHCAR-mediated pathogenic factors.
Objectives: It is possible that PLA might be modulating the immune response in MS via its action on HCAR-expressing immune cells. Although MS pathogenesis is mostly associated with antigen specific acquired immunity, PLA could be exerting influence on the MS phenotype.
Aims: Our aims were to determine the amount and potential influence of PLA on clinical and immunological features of MS.
Methods: We measured serum D- and L-PLA levels in 60 MS patients and 25 healthy controls and in bacterial supernatants.We investigated potential associations between PLA levels, clinical features of MS, serum cytokine levels and ratios of peripheral blood lymphocyte subsets.
Results: Genome analysis andin vitroculturing showed multiple gut commensal bacteria possessed the capacity to generate PLA, varied by bacterial species. MS patients with benign phenotype showed markedly lower D-, L- and total PLA (T-PLA) levels than healthy controls. Fingolimod-treated MS patients showed significant reduction of serum D-PLA. Fingolimod resistant patients had higher D-, L- and T-PLA levels at baseline. Furthermore, MS patients with higher D- and L-PLA levels displayed increased memory B and plasma cell ratios, elevated IL-4 levels and increased ratios of IL-4 and IL-10 producing T cell subsets.
Conclusions: Our work indicates that serum levels of bacterial-derived D-PLA could be associated with the benign MS phenotype and possibly be used as a biomarker.

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Extracellular vesicles isolated from probiotics activate human T cells and modulate immune response on multiple sclerosis patients and controls

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Introduction: Multiple sclerosis (MS) has been related to an alteration in intestinal microbiota. Therefore, the study of the recovery of the microbiota and its function may play a key role in the pathogenesis of MS. However, the mechanisms by which bacteria interact with the host and its immune system are still poorly understood. Our hypothesis is that extracellular vesicles (EVs) secreted by both bacteria and host cells could be involved in the regulation of the immune system.

Objetives/ Aims: This investigation aims to analyze how both isolated strains of commercial probiotics and EVs secreted by these bacteria, may regulate the cultured immune cells from MS patients and controls.
Methods: To assess the effect produced by both the strains and the EVs, PBMCs from MS patients and controls were cultured and treated with different isolated strains of commercial probiotics (Lactibiane iki and Vivomixx) and EVs derived from them. A flow cytometry method combining antibodies for specific cell surfer markers (CD4, CD25, CD127 and CD196) and viability assessment was performed then to determine the activation of regulatory T-lymphocytes (T reg) and T helper 17 lymphocytes (Th17). These cell populations were characterized with the expression of CD4+CD25+CD127- and CD4+CD196+ antigens respectively.
Results: Both bacteria and isolated EVs had strain dependent capacity in immune modulation. Surprisingly, EVs elicited different immune responses than the bacteria from which they originated. Moreover, different responses between MS patients and controls were found. All strains and EVs proved an immunomodulatory capacity, but among them,Bifidobacterium lactis derived EVs showed promising results as they promoted greater activation of Treg against Th17.
Conclusions: The current work provides evidence on bacterial and bacterial derived EVs immunomodulatory capacity and takes a further step in the knowledge of the mechanisms involved in the relationship between microorganisms and the host own cells. It may also open a new field in the development of new MS therapies.

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EP0946

Effectiveness of BBIBP-CorV vaccine in preventing SARS-CoV2 infection and severe outcomes in patients with multiple sclerosis

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Introduction: Although clinical trial studies examined the efficacy of SARS-CoV-2 vaccines, evaluation of vaccine effectiveness in real-world is critical to understand whether these vaccines protect MS patients against the infection and poor outcome.
Objectives: To compare change in the hazard ratio of being positive for SARS-CoV-2, COVID-19-related hospitalization and death among confirmed cases in MS patients who received one or two doses of BBIBP-CorV (Sinopharm) vaccine.
Aims: To estimate the effectiveness of BBIBP-CorV in preventing SARS-CoV-2 infection, hospitalization, and mortality in MS patients in Isfahan, Iran.
Method: This retrospective observational population-based study was conducted from February 09, 2021 through November 04, 2021. We extracted individual-level data on all confirmed COVID-19 patients from Isfahan COVID-19 registry and linked to data on date and type of SARS-CoV-2 vaccine administration and information of 10639 MS patients in Isfahan. To estimate the hazard ratio between vaccinated and non-vaccinated groups, we applied the extension of the Cox proportional-hazards model, which the time-varying vaccination status was accounted. We estimated the change in the hazard ratio associated with partial immunization (⩾14 days after receipt of the first dose) and full immunization (⩾14 days after receipt of the second dose). Vaccine effectiveness (%) was calculated as 100 * (1 - adjusted hazard ratio). The model was adjusted for age, sex, course of MS, and duration of MS.
Results: The real-world vaccine effectiveness of preventing SARS-CoV-2 infection and hospitalization were 39.3% (95% confidence interval [CI]: 16.1%, 56%) and 64.9% (95%CI: 1.3%, 87.5%) in partially immunized MS patients. Among 4107 MS patients who were fully immunized, the adjusted vaccine effectiveness against COVID-19 infection was 63.9% (95%CI: 56%, 70.3%). The adjusted vaccine effectiveness in fully vaccinated patients with confirmed COVID-19 was 75.7% (95%CI: 57.5%, 86.1%) in preventing COVID-19-related hospital admissions. During follow-up, 6 and one deaths occurred among non- and partially-vaccinated groups, respectively.
Conclusion: Our study shows that BBIBP-CorV vaccine can effectively prevent SARS-CoV-2 infection and hospitalization among the MS population.

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EP0947

SPMS patients-derived gut bacterial strain accelerates neuronal inflammation via intestinal Th17 cells

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Introduction: Recent advancements have established a bidirectional causality between gut commensal bacteria and MS. We

revealed the characteristics of gut microbiomes associated with RRMS and SPMS, respectively based on the metagenomic sequencing and metabolome analyses (Takewaki et al., PNAS. 2020). However, the causal relationship between MS progression and dysbiosis in the gut microbiome remains elusive.
Objectives: To identify the specific gut bacterial taxa associated with MS progression from RRMS to SPMS and reveal the mechanism which exacerbates neuronal inflammation.
Methods/Result: We comparatively analyzed the composition of fecal microbiome between 62 RRMS patients and 15 SPMS patients based on the 16S rRNA gene and metagenomic sequencing data. We identified the single bacterial species (bacteria X) whose abundance was significantly enriched in SPMS and positively correlated with EDSS score of the patients. The significant increase of bacteria X in SPMS (vs RRMS) was confirmed by publicly available metagenomic data provided by international joint research in western countries.
We then isolated this bacterial strain from the fecal samples of SPMS patients and conducted the in vivo analysis to verify the functional significance of this strain. Mono-colonization of germ-free mice with SPMS-derived bacteria X strain caused exaggerated neurological disability ($p=0.0007$) after immunization with significantly increased Th17 cells in central nervous system ($p<0.0001$) and large intestine lamina propria ($p<0.0001$) compared with controls.
In the bacterial genome comparison among various strains belonging to bacteria X, the genome of SPMS-derived bacteria X strain specifically included an almost full set of flagella-related genes, which was confirmed by electron microscopic analysis.
Discussion: Flagella is closely associated with bacterial motility and has an important role in the interaction between gut epithelial cells and microbiome. Moreover, a specific bacteria-derived flagellin is a selective agonist of toll-like receptor 5 and potentially induces Th17 cells in the gut.
Conclusions: Bacteria X enriched in the gut of SPMS patients exacerbates neuronal inflammation via intestinal Th17 cells.

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EP0948
Antibody response after a booster dose of SARS-CoV2 vaccines in multiple sclerosis

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Introduction/Objectives: Immunity after two doses of inactivated and messenger RNA(mRNA) SARS-CoV 2 vaccines in Multiple Sclerosis (MS) is influenced by the Disease-Modifying Therapy (DMT) and vaccine type used. Being lower in fingolimod, ocrelizumab, and inactivated vaccine groups. A booster dose could change this discrepancy.
Aims: To compare the immunogenicity of a booster dose of mRNA BNT162b2 (Pfizer/BioNTech) versus inactivated vaccine, performed after completing two doses of inactivated Coronavac in people with MS (pwMS).
Methods: pwMS and Healthy Controls (HC) who received a booster dose of SARS-CoV 2 mRNA or inactivated vaccine after completing two doses of inactivated Coronovac were enrolled in this single-center cross-sectional study. Serum samples were collected at least two weeks after the third dose of the vaccine. The antibody titers were compared between HC, MS, and each treatment group.
Results: Each of 339 pwMS and 52 HC received three doses of SARS-CoV-2 vaccines. 283 (72,3%) participants received a booster dose of mRNA, and 108 (27,7%) participants received a booster dose of inactivated Coronavac. In all comparisons, patients treated with ocrelizumab had the lowest antibody titer ($p<0.005$). In the fingolimod group, booster mRNA caused a higher antibody titer than the inactivated vaccine. In total, pwMS had a lower antibody titer than HC regardless of the vaccine type. In regression analyses having a booster mRNA [β= -0.671 (0.133) 95%CI= -0.933 – -0.409, $p<0.001$] and lower disease duration [β−0.019 (0.010)95%CI= −0.038 – 0.000, $p=0.44$] were two markers which significantly associated with higher antibody titer in pwMS.
Conclusions: The study shows that a third dose vaccine is an effective strategy to boost antibody response in the MS population, and the mRNA SARS CoV-2 vaccine's booster is preferable to inactivated ones.

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Pathology and pathogenesis of MS - Environmental factors

EP0949
Socioeconomic status is associated with amygdala microstructure in early onset multiple sclerosis

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Introduction: Early-onset MS (EOMS) and low socioeconomic status (SES) are associated with changes in brain maturation and lower volumes. While EOMS is associated with increased brain mean diffusivity (MD), low SES is associated with decreased MD in the amygdala and structures involved in emotional regulation.
Aims: To assess: 1) the longitudinal MRI correlates of amygdala tissue microstructure and 2) the relationship between baseline SES and amygdala microstructure in EOMS compared to healthy controls (HC). We hypothesized: 1) decreased amygdala volume and increased amygdala MD in EOMS compared to HC; 2) accelerated volume loss and decelerated MD increase in EOMS with lower baseline SES.
Methods: MRI scans were acquired on a 3T scanner using a standardized protocol in youth with EOMS (onset < 18y) and matched HC. Only EOMS were scanned longitudinally. At baseline most participants' caregivers completed the Barratt Simplified Measure of Social Status (BSMSS). Amygdala subnuclei (lateral, central, basal) were segmented using FreeSurfer and manually quality checked. Normalized amygdala volume and average MD were computed using in-house software. BSMSS was compared between groups using a linear regression accounting for age and-sex. The relationship between SES and MRI metrics in the two groups was assessed using multivariable generalized linear models accounting for age, disease duration, amygdala side, BSMSS, and a subject-specific random intercept.
Results: We included 32 EOMS [mean (SD) age at onset: 14y(2.02); baseline age 18y(3.1); baseline disease duration 3.9y(3.2); baseline BSMSS recorded in 23/32, median (IQR) 30.5(26-57); median (IQR) n of scans 1(1-2)] and 44 HC [age 18.4y(4.9); BSMSS recorded in 36/44, median (IQR) 44(39-57)]. EOMS had lower BSMSS (-7.4 points, p 0.042). Amygdala volume or MD were not statistically different between EOMS and HC and did not change significantly over time in either group. The right amygdala showed higher MD compared to the left (+0.018, p 0.0008). In EOMS, lower baseline BSMSS was associated with slower increase of amygdala MD over time (+0.00023,p 0.044). This association was not significant in HC.
Conclusions: Even though amygdala volume or MD were similar between EOMS and HC, we detected a relationship between SES and amygdala MD in EOMS, where lower SES was associated with a "pseudo-normalization" of MD trajectory. This may suggest that disease processes affecting the amygdala in EOMS are sensitive to SES.

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EP0950

Visual function influence on non-visual manifestations in EAE

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Introduction: Among environmental factors in MS, light has been associated with seasonal variations in relapse susceptibility and in disease severity. However, the role of the eye has not directly been investigated, although ~70% of patients experience visual symptoms in the course of the disease. Here, we focused on a particular subset of retinal neurons, intrinsically photosensitive retinal ganglion cells (ipRGCs), whose function is altered in MS. In the brain, these cells have non-image-forming functions; they control biological rhythms, such as the circadian cycles of wake-sleep and hormone secretion.
Objective: We hypothesize that ipRGC functional properties influence non-visual manifestations of EAE.
Material and methods: For all groups, EAE was induced in C57BL/6J male mice using $bMOG_{1-125}$. Effect of ipRGC depletion on EAE was studied by intravitreally injecting an immunotoxin constituted by anti-melanopsin/OPN4 IgG conjugated to Saporin (anti-OPN4-SAP, 0.8 µg/eye), a ribosome-inactivating toxin. Two weeks after the injection of immunotoxin or control IgG-SAP, clinical scores, using the five-point scoring system, and body weights were followed for 30 days. To automatically record EAE-induced changes in locomotor activity, mice were placed in Digital Ventilated Cages (DVC, Tecniplast). After tissue fixation, neuronal survival was analysed on retinal flat-mounts stained for ipRGC using melanopsin or all RGCs usingRNA-binding protein with multiple splicing(RBPMS), and spinal cords demyelination was investigated on paraffin sections.
Results: In EAE, longitudinal monitoring of locomotion in DVC revealed a marked delay and decreased level in the nocturnal activity, correlated to clinical scores. EAE reduced the density specifically of ipRGCs by ~8% (n=5 per group, unpaired t-test, $P<0.05$) after 30 days, but did not affect other RGCs labelled with RBPMS. Anti-OPN4-SAP caused the loss of ~70% of ipRGCs and was associated with lower clinical score incidence (~50% vs 100%) and severity of clinical scores (on average ~1 out of 5 vs ~2 out of 5) for anti-OPN4-SAP (n=9) and control IgG-SAP (n=6), respectively. However, we did not observe a difference in spinal cord demyelination.
Conclusion: ipRGC functional impairment may contribute to circadian activity changes and motor deficits in mouse EAE.

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We have no conflict of interest to disclose

EP0951

Sun exposure and the risk of progressive-onset multiple sclerosis

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Introduction: There is a well-established latitudinal gradient with multiple sclerosis (MS) prevalence, and sun exposure has been associated with the risk of MS. However, the gradient is less obvious in progressive-onset MS (POMS), which could suggest that sun exposure is less important in POMS.
Objectives: To examine whether high sun exposure prior to MS onset is associated with a decreased risk of POMS and to compare the magnitude of association with relapse-onset MS (ROMS).
Methods: The case-control study included 153 POMS cases, 204 incident ROMS cases, and 555 community controls. A telephone interview collected information on skin type and sun exposure. A lifetime calendar measured leisure time outside in summer and winter for each year from age 6 years until the age of the first MS symptoms, which was converted to a cumulative UV dose for each 5-year age period. Logistic regression was used to examine associations, adjusted for age of the first symptom, sex, latitude band, birth period, smoking, and infectious mononucleosis history.
Results: Compared with controls, POMS cases were less likely to have high leisure-time sun exposure (⩾4 hours/day) in summer (age 6-10 years, aOR 0.28 (0.15-0.51); age 11-15 years, aOR 0.32 (0.16-0.63); age 16-20 years, aOR 0.41 (0.23-0.73)), while there was no association with ROMS. Associations were also present for leisure-time sun exposure in winter. Cumulative leisure-time sun exposure was also associated with POMS, for example age 6-20 years (aOR 0.85 (0.80-0.90) per 100 kJ/m² UV dose increment), and age 6 to symptom onset (aOR 0.93 (0.91-0.96)), while for ROMS an association was only found at age 16-20 years (aOR 0.85 (0.74-0.97)).
Conclusions: High sun exposure was associated with a reduced risk of developing POMS. The effect sizes were stronger than for ROMS. These results indicate sun exposure throughout the life course, from childhood to MS symptom onset, is potentially predictive of MS risk.

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EP0952

Exploring the association between diet and the human gut microbiome diversity in patients with multiple sclerosis

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Objective: Comparedietary intake and identify differences of gut microbiome diversity (GMD) between patients with multiple sclerosis (MS) and healthy controls (HCs). Explore the association between diet and the GMD in MS-patients and HCs. Investigate if markers of a healthy diet and/or a high GMD are associated with MS disease severity.
Methods: Cross-sectional case-control study including 125 participants (78 MS-patients, 47 HCs). Dietary intake-assessment by myfood24® and a FFQ. GMD-assessment by 16S rRNA gene amplicon sequencing, α-diversity (Shannon-Wiener diversity index, Observed features), and β-diversity (Bray-Curtis, weighted UniFrac distance (UniFrac)). Disease severity-assessment by MS Severity Score (MSSS), Fatigue Severity Scale (FSS), and SymptoMScreen.
Results: Based on the total study population, 17% had a fruit and vegetable (FV) -intake ⩾ 600 g/10 MJ/day, 34% had a fiber-intake ⩾ 30g/10 MJ/day, and 40% had a saturated fatty acid (SFA) -intake ⩽ 10 E%. MSSS correlated with SFA-intake in both g/day and g/MJ/day. UniFrac and Bray-Curtis metrics showed differences between MS-patients and HCs. Bray-Curtis showed GMD differences between high and low SymptoMScreen scores and UniFrac showed differences in FV-intakes for MS-patients and the total study population, as well as in fiber-intakes for HCs.
Conclusion: The MS-patients and HCs have different GMDs despite having similar dietary intakes. Most study participants did not comply with the current Danish official dietary guidelines and Nordic nutritional recommendations. A high disease severity is correlated with a high SFA-intake and might be associated with an altered GMD.

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EP0953

Epstein Barr virus infection and the risk of multiple sclerosis in Argentina

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Introduction: Multiple Sclerosis (MS) is a demyelinating, chronic, autoimmune disease that affects the central nervous system. MS is the leading cause of non-traumatic neurological disability among young adults yet its etiology is not absolutely clear. A combination of genetic and environmental factors such as infections are considered to play a role in its development and progression. Herpes virus infection, Epstein Barr virus (EBV) in particular,has been suggested as an environmental factor associated with MS risk and severity.
Aim: To study herpes virus' role in MS development and progression.
Objectives:
To assess antibody (Ab) titers against EBV, Cytomegalovirus (CMV) and Varicella Zoster virus (VZV) between MS patients and healthy controls (HC) from Argentina.
To characterize EBV polymorphisms in EBNA-2 gene and assess their presence with disease risk.
Methods: 146 patients with MS (134 relapsing remitting MS, 1 secondary progressive MS, 5 primary progressive MS and 6 clinically isolated syndrome) and 129 HC were included in this study. Serum samples were analyzed for IgG Ab titers against EBV viral capsid antigen (VCA), nuclear antigen-1 (EBNA-1), CMV and VZV.
In a subset of MS cases and HC, a portion of the viral gene EBV nuclear antigen-2 (EBNA-2) were amplified and Sanger sequenced.
Results: All MS patient and HC were IgG positive for EBV and VZV, while 60.4% of the HC and 71.8% of the MS patient were seropositive for CMV (P=0.013). Significantly higher levels of IgG Ab against EBV-VCA (P=0.006) and CMV (P=0.017) were found in MS patients as compared to HCs. Sequencing of EBNA-2 revealed a CTC insertion at nucleotide position 633-635 in 8/26 (31%) of MS patient as compared to 1/16 (6%) of HC.
Conclusions: MS is a complex disease with a strong interaction between genetic and environmental factors, and different herpes viruses may have an effect on MS pathology, as suggested by differences in titers for EBV-VCA and CMV Ab, and the existence of EBV EBNA2 gene variant potentially linked to MS patients. Further research is needed to better understand the significance of EBV variants and differential antibody levels in MS patients.

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EP0954

Drug substance and alcohol consumption and the risk of primary progressive multiple sclerosis: a population-based case-control study

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Background: The onset of primary progressive multiple sclerosis (PPMS) like any other autoimmune diseases can be triggered by environmental risk factors such as drug substances and alcohol consumption which require to be assessed in order to minimize our exposure to such events as much as possible.
Objective: We examined the association of drug substances and alcohol consumption with PPMS.
Methods: The present population-based case–control study recruited PPMS cases and healthy controls from the general population during 2019–2020 in Tehran, Iran. 146 PPMS cases and 294 controls were enrolled. Clinical diagnosis of PPMS was based on the 2017 McDonald criteria and confirmed by a neurologist. The standard random digit dialing (RDD) was used to select sex-matched control participants. Logistic regression analysis was used to estimate unadjusted and adjusted odds ratio (OR) (odds ratio) using Stata software 13.
Result: Totally 440 participants were assessed in the study. Mean ages (SD) for cases and controls were 47.0 (9.4) and 37.7 (6.1), respectively (P =0.001).We did not find any significant association of PPMS risk with drug substances abuse and alcohol consumption including opioids (OR= 0.90, CI=0.35-2.29), cannabis (OR= 1.58, CI=0.47-5.24), stimulants (OR=0.85, CI=0.14-4.87), beer intake (OR=0.61, CI=0.29-1.26), whisky/vodka intake (OR= 0.71, CI=0.34-1.49), wine intake (OR= 0.73, CI=0.35-1.53).
Conclusion: This study was the first study which examined associations between alcohol consumption and drug substances and PPMS. However we didn't find any significant association between alcohol and drug substances, efforts should be made to reduce alcohol consumption and drug substances use due to their other side effects and their increasing prevalence in the world.
Key word: primary progressive multiple sclerosis (PPMS), alcohol, drug substances, risk factor.

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Pathology and pathogenesis of MS - Neurobiology

EP0955

XCL1 a serum biomarker in neurological diseases; HTLV-1-associated myelopathy/tropical spastic paraparesis and multiple sclerosis

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Introduction: Multiple sclerosis (MS) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) are chronic inflammatory diseases that chemokines and chemokine receptors play a critical role in the leukocyte infiltration into the CNS and induction of the inflammatory immune response. The XCL1-XCR axis has a potential role in the recruitment of immune cells to the site of inflammation.
Objectives: This study included 45 patients with HAM/TSP, 43 HTLV-1 asymptomatic carriers (ACs), 45 newly diagnosed MS patients, and 46 healthy controls (HCs).
Aims: The aim of this study was evaluation of the relation of serum levels of XCL1 with the outcome of HTLV-1 infection and MS.
Methods: The serum levels of XCL1 were evaluated in all mentioned groups, and proviral load (PVL) was also quantified in HAM/TSP patients and ACs.
Results: The serum levels of XCL1 were significantly higher in patients with HAM/TSP (97.37+/- 41.40) than ACs (50.20 +/- 23.04) and HCs (29.8+/-14.87) ($p<0.001$ and $p<0.0001$, respectively). The serum levels of XCL1 was also significantly higher in MS group (66.89+/- 20.85) compared to HCs ($p<0.0001$). The serum levels of XCL1 was significantly different between the ACs and HCs group ($p<0.0001$). The median HTLV1 PVL (44.26) in HAM/TSP patients was higher than those of ACs (1.39) ($p<0.0001$).
Conclusions: In conclusion, increased expression of XCL1 might contribute to the migration of auto reactive T cells to the central nervous system and plays a critical role in the development and pathogenesis of inflammatory neurological diseases including HAM/TSP and MS.

Disclosure
Nothing to disclose

EP0956

Oxygen concentrations impact reactive astrogliosis, this is evidenced by a decrease in the expression of inflammatory astrocyte markers and differential secretion of chemokines and cytokines by reactive astrocytes

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Introduction: MS is a neurodegenerative disorder characterized by inflammation in the central nervous system (CNS), which results in the demyelination, and injury of axons in the CNS. Astrocytes (AC), a resident cell of the CNS, are understood to be heterogeneous and play a defensive role in the CNS. Their defensive functions manifest as reactive astrogliosis, in which many components of AC are remodeled in response to lesions in the CNS. Reactive AC, which have been detected in active demyelinating MS lesions and surrounding areas, are known to be induced in vitroby LPS and a cytokine cocktail that contains Il-1a, TNF-a, and C1q. In conventional cell culture conditions, the amount of oxygen (O_2) the cells encounter is almost four times higher (21%) than what they encounter in the brain (1-6%). Furthermore, hypoxia can be found in demyelinating lesions in the brains of mice. AC are known to be sensitive to changes in O_2 levels and our study aims to uncover any changes they undergo when cultured in physiologically relevant conditions.
Objective: We aim to determine the impact of various O_2 levels, such as physiological, atmospheric, and hypoxic levels, on reactive astrogliosis in MS.
Aims: Our study seeks to understand how AC may adapt to different oxygenation levels in culture.
Methods: Using a trigas incubator, in which we can regulate O_2 concentrations, we are able to analyze how astrocyte function and behaviour changes under different O_2 conditions. We utilize LPS to stimulate astrogliosis and induce the pro-inflammatory astrocyte phenotype through a cytokine cocktail.
Results: We show that culturing AC at various O_2 concentrations results in changes in astrocyte morphology and proliferation. Using a scratch assay, we observe that AC cultured at physiological oxygen levels (~3%) are less reactive and repopulate the scratch at a lower rate compared to those cultured at atmospheric O_2 levels (~21%). Using flow cytometry, we show that physiological O_2 levels decrease the expression of the markers CD44 and H-2 by reactive AC. Furthermore, O_2 levels differentially affect the secretion of LIX, IL-6, MIP-2, and VEGF by cultured astrocytes.
Conclusions: Together, our results indicate that O_2 concentrations impact in vitroastrogliosis, as well as astrocyte immune functions. Therefore, we should take O_2 concentration into account when studying reactive astrogliosis and its role in MS; thereby allowing for a more accurate understanding of the pathophysiology of MS.

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Pathology and pathogenesis of MS - Neurodegeneration

EP0957

Investigating the role of astrocytes for the survival of axons in chronic inflammatory lesions

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Introduction: Neuronal damage in autoimmune neuroinflammation is the correlate for long-term disability in patients suffering from Multiple Sclerosis. Glutamate-mediated excitotoxicity plays an important role in the development of various neurodegenerative diseases glutamate transporters are increasingly becoming a focus of MS research.
Objectives/Aims: We investigated two astrocytic amino acid transporters: the excitatory amino acid transporter 1 (EAAT-1) and the excitatory amino acid transporter 2 (EAAT-2). These largely astrocyte-specific glutamate transporters play an important role in eliminating extracellular glutamate from the synaptic cleft.
Methods/Results: First, we performed immunofluorescence staining on spinal cord sections of acute and chronic EAE mice and compared the expression levels of EAAT-1 and EAAT-2 in inflammation areas with their expression levels in respective control areas. We investigated naïve animals and compared these with acute EAE and chronic EAE (at least 14 days after onset of clinical signs). We measured a significant upregulation of EAAT-2 in inflammation areas in acute and chronic EAE. EAAT-1 was increased in acute EAE, whereas we could not find significant alterations in chronic EAE lesions. Second, we induced EAE in transgenic mice expressing a genetically encoded Ca2+ indicator in neurons and their processes (thy1-CertnL15) or a genetically encoded glutamate indicator in neurons (NEX-Cre x iGlusnfr) and performed intravital microscopy of EAE lesions in the brainstem of these mice. We used fluorescence lifetime imaging microscopy (FLIM), which identifies the fluorescent decay rate as highly sensitive read-out of Foerster resonance energy transfer (FRET) to analyze the intracellular Ca2+ or glutamate dynamics in axons and neurons. During imaging we locally applied inhibitors of the astrocytic excitatory amino acid transporters EAAT1 and EAAT2. We monitored the effect of these substances on axonal damage for several hours and showed the predominant role of EAAT-2 for the prevention of excitotoxicity in inflammatory lesions in chronic EAE.
Conclusion: These findings highlight the role of glutamate transporters on astrocytes in the protection of axons in inflammatory demyelination and identify new therapeutic targets to stop progressive disability in MS patients.

Disclosure
no conflict of interest in context of this project

EP0958

Familial and sporadic multiple sclerosis: axonal and neuronal changes of the retina

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Introduction: The familial multiple sclerosis (fMS) accounts for a significant proportion of MS patients. There is still ongoing discussion on the distinction between familial and sporadic MS (sMS) with respect to pathologic mechanisms. Opticalcoherence tomography(OCT) offers non-invasive and relatively simple method to assess axonal and neuronal changes of the retina which correspond to the CNS pathology.
Objectives: This study was aimed to assess axonal and neuronal pathology of the retina in fMS versus sMS.
Methods: We included 45 patients with fMS, 58 patients with sMS and 35 healthy controls. OCT was performed with the spectral domain optical coherence tomography (SD-OCT, Heidelberg Engineering). The retinal nerve fiber layer (RNFL) thickness and macular volume (MV) were measured as markers of axonal and neuronal component of the retina, respectively.
Results: A significant thinning of the global RNFL thickness was detected in both forms of MS compared to control group (86,61 (+/- 14,74) μm in sMS, 85,8 (+/- 12,7) μm in fMS, 97,96 (+/- 7,6) μm in control group; p <0,001).A significant reduction of the MV was also shown in sMS and fMS compared to control group (8,12 (+/- 1,14) mm³ in sMS, 8,1 (+/- 1,12) mm³ in fMS, and 8,81 (+/- 0,31) mm³ in control group; p = 0,003). Most importantly, in eyes with history of optic neuritis MV was significantly reduced in sMS versus fMS (8,12 (+/- 2,87) mm³ vs. 8,42 (+/- 0,54) mm³; p=0,05).
Conclusions: These data suggest more pronounced neuronal damage in sMS versus fMS in response to optic nerve inflammatory disease. Thus, these results might support hypothesis ondiscrete differences in pathologic mechanisms between sporadic and familial MS.

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EP0959

Preferential degeneration of the peripheral nervous system in lower versus upper limb of persons with multiple sclerosis – implications for neuromuscular function and physical function

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Introduction: Multiple sclerosis (MS) is a disease of the central nervous system, yet the peripheral nervous system (PNS) also undergoes deleterious changes. Peripheral nerve stimulation has shown reduced compound muscle action potential (CMAP) amplitude and number of functional motor units (MUs) in pwMS.
Objective/aim: To investigate how changes in CMAP amplitude and MUs (i.e. PNS changes) might have consequences on neuromuscular function (e.g. muscle strength) and physical function (e.g. walking capacity, hand dexterity) in the upper and lower limb (UL and LL, respectively) across the disease spectrum of MS.
Methods: A total of n=29 participants were enrolled: MS_{mild}(patient determined disease steps (PDDS) score 0-2; n=14 (9 females), age 44±12 years), $MS_{moderate}$(PDDS score 3-7, n=7 (5 females), age 55±8 years), and healthy controls (HC; n=8 (5 females), age 49±11 years). Using the MScanFit MUNE technique, CMAP amplitude and MUs were determined in m. tibialis anterior (TA; representing LL) and m. abductor pollicis brevis (APB; representing UL). Neuromuscular function was assessed by strength tests in which TA and APB are prominent contributors, thus maximal dorsiflexion force (TA_{mvc}) and maximal thumb abduction force (APB_{mvc}) were assessed along with force steadiness measurements ($TA_{fs}$and APB_{fs}). Physical function was assessed by six-spot step test (SSST) and nine-hole peg test (NHPT). Data are shown as mean±sd.
Results: Disease status (i.e. HC vs MS_{mild} vs $MS_{moderate}$) was accompanied by marked reductions ($p<0.05$) in TA MUs (125±37 vs95±52 vs 55±51) and TA CMAP (7.2±1.7 vs 6.4±1 vs 5.7±1.9 mV). A parallel pattern of changes was observed for TA_{mvc}(1.37±0.27 vs 1.25±0.25 vs 0.94±0.27 Nm/kg), TA_{fs}(HC 1.67±1.18 vs 1.96±1.56 vs 3.85±3.92 CV%), and SSST (5.2±0.3 vs 5.8±1.7 vs 11.8±5.1 s). In the UL only NHPT (17.4±1.8 vs 18.3±2.6 vs 25±9.7 s) differed between groups. In contrast, no differences were observed for APB MUs (76±32 vs 71.8±38 vs 64.3±18), APB CMAP (6.9±3.4 vs 8.6±3.5 vs 8.6±2.2 mV), APB_{mvc}(0.31±0.06 vs 0.34±0.19 vs 0.23±0,19 Nm/kg) and APB_{fs}(1.52±1.5 vs 3.14±5.23 vs 1.03±0.77 CV%).
Conclusions: Our data revealed that PNS degeneration along with neuromuscular and physical function is most pronounced in LL, and furthermore that it follows disability progression of MS, with greater deleterious changes in $MS_{moderate}$> MS_{mild}> HC. These findings might have implications for future rehabilitation of pwMS.

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EP0960

Neurodegeneration quantitative systems pharmacology modelling for analysis of multiple sclerosis therapy

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Introduction: The major determinant of neurological impairment during multiple sclerosis (MS) is axonal degeneration, represented as MS lesions and brain atrophy. One of commonly used biomarkers

of axonal degeneration is neurofilament light protein (Nfl) elevation in cerebrospinal fluid (CSF) and plasma [1]. Modulation of lymphocyte dynamics demonstrated efficacy on several biomarkers.
Objectives: Mechanistic description of lymphocyte dynamics and neurodegeneration is warranted. Quantitative Systems Pharmacology (QSP) model of MS biomarkers would allow for therapy optimization.
Aims: To develop and verify QSP model describing Nfl dynamics and neurodegeneration in MS progression and during lymphocyte targeting therapy.
Methods: The model includes cell apoptosis, proliferation, migration and B-T cells interaction with subsequent T-cell activation, based on the data for self-reactive brain-homing effector-memory CD4+ T cells proliferation upon interaction with memory B cells [2]. Cytoskeletal processes are represented by synthesis of neurofilaments and their degradation, phosphorylation, formation of pathological aggregates, and the release of Nfl from degenerating axons into the extracellular space with distribution to the CSF. Proinflammatory cytokines, expressed by activated lymphocytes influence on neuronal cytoskeletal dynamics through intracellular signals (Ca, kinases) activation. For calibration we used literature data on the concentration of Nfl in brain, CSF and plasma, phosphorylation level, numbers of lymphocyte subtypes in blood and CSF in healthy and MS patients and cell proliferation assay.
Results: The model describes the difference between CNS T-cell accumulation in healthy and MS subjects. It correctly captures the increase of the Nfl concentration in CSF and plasma, as well as brain and T2 lesions volume change due to MS progression. It describes natalizumab, rituximab, alemtuzumab and fingolimod treatment effects on lymphocytes and Nfl. Thus, natalizumab treatment leads to reduction of Nfl in CSF by 35%. Model also captures the dynamics of recovery of Nfl after treatment discontinuation [3].
Conclusions: The model describes major contributors to MS progression and couldbe applied for analysis of therapeutic interventions.
Citations:
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[2] Jelcic, I. et al. Cell 175, 85-100.e23 (2018).
[3] Proschmann, U. et al. Front. immunol. Vol.12 715195. (2021).

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Pathology and pathogenesis of MS - Repair mechanisms

EP0961

Secondary progressive multiple sclerosis: *in vitro* effect of cerebrospinal fluid on human neural stem cells behavior and immunomodulatory molecules production

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Multiple sclerosis (MS) is an inflammatory disease of the central nervous system characterized by demyelination. Several studies have attempted to identify soluble factors present in the cerebrospinal fluid (CSF) of MS patients related to course of the pathology. Human neural stem cells (hNSCs) obtained from foetal tissue following spontaneous abortion or in utero death, were injected into cerebral lateral ventricle of 15 patients affected by secondary progressive MS (SPMS) recruited in phase I clinical trial (EudraCT 2015-004855-37 NCT03282760). CSF was collected from these patients before and six months after being treated with hNSCs. The aim of this project is to measure the expression of inflammatory factors released in the CSF of MS patients, verify their variation after hNCS therapy and evaluate the effect of CSF on hNSCs behaviour. We cultured hNSC in standard differentiation condition, in presence of 5% CSF. Supernates were collected during the culture while cells were prepared for RNA extraction once completely differentiated. We used ELISA assays to measure the content of serum, CSF and culture supernates of B lymphocyte chemoattractant (CXCL13) and Aquaporin-4 (AQP4). mRNA from cultures was analysed with real time PCR to evaluate the expression of osteopontin (OPN), neurotrophin 3 (NT3), Brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and CXCL13; CSF of healthy patients and supernates from standard differentiation and undifferentiated cells were used as controls. The quantitative analysis of AQP-4 and CXCL-13 showed that they decrease in CSF and serum six months after treatment compared to pre-treatment and to control and, in the same way there was a reduction of their production in cell cultures treated with CSF. Regarding the gene expression analysis, the NT3 and CXCL13 genes appear to be poorly expressed in all the samples analysed, while VEGF shows greater expression in the undifferentiated control compared to the other controls and patients. Our preliminary results suggest that there may be a slightly decrease in brain inflammation due to the high expression of VEGF, that modulates the production of CXCL13 and AQP-4. We will present complete results of the study also comparing those with the data obtained by the clinical team in order to evaluate the differences between diverse time points, if any, and the potential role of the biomarkers involved in neuroinflammation.

Disclosure
the authors declare no conflict of interest.

Imaging and non-imaging biomarkers - MRI & PET

EP0962

Percentage Brain volume change primarily reflects white matter and cortical atrophy

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Introduction: Global brain atrophy in multiple sclerosis (MS), as measured by percentage brain volume change (PBVC), has been established as an outcome parameter in clinical trials. However, it is unknown to what extent atrophy rates in different brain tissue compartments contribute to PBVC.

Objectives:

- Longitudinal measurements of global and compartmental brain atrophy
- Assessment of compartmental contributions to PBVC through multiple regression analysis

Aims: To evaluate the contributions of deep gray matter (GM), white matter (WM), and cortical atrophy as well as WM lesion changes to PBVC.

Methods: We analyzed pairs of MRI scans with a minimum interval of six months in 600 patients with relapsing-remitting MS. Structural image evaluation of normalized atrophy (SIENA) software was used for PBVC calculation, statistical parametric mapping (SPM12) with the computational analysis toolbox (CAT12) and the lesion segmentation toolbox (LST) was used for calculation of compartmental volumes. The contributions of atrophy in different brain tissue compartments to PBVC were assessed through general linear models with PBVC as outcome variable.

Results: Deep GM atrophy was significantly greater than PBVC ($p < 0.001$), while WM and cortical GM tissue loss were both lower than PBVC ($p = 0.013$ and $p < 0.001$, respectively). All compartmental volume change measures correlated significantly with PBVC, yet multiple regression revealed varying contributions to PBVC. WM and cortical GM change were the main drivers of PBVC. This observation was confirmed via a stepwise regression approach; WM together with cortical GM atrophy accounted for 62.6% (R^2) of the total variance in PBVC, whereas adding deep GM and WM lesion volume change improved the fit of the model to only 65.5% (R^2).

Conclusions: PBVC mainly reflects WM and cortical atrophy, while deep GM atrophy is less well represented. Changes in WM lesion volume are unlikely to considerably interfere with PBVC.

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EP0963

Exploring the association between iron rims in MS lesions, mood disorders, fatigue and cognition

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Introduction: The paramagnetic iron-rim is being proposed as a biomarker of active inflammation in multiple sclerosis' (MS) chronic lesions and might be associated with neurodegenerative processes. However, the association between iron-rims, neuropsychological and mood disorders, as well as fatigue, still need to be investigated.

Objectives: To study the association between the iron-rim lesion (IRL) count, cognitive performance, anxiety, depression and fatigue.

Methods: 3T-brain exams were acquired from 25 MS patients (9 men; mean age 43.3 years ± 9.2; mean years of education: 13.2 ± 4.4), including susceptibility-weighted images (SWI). Two experienced radiologists had scored the MS-lesion with visible low

intense rim in SWI. Cognitive performance was assessed using the Symbol Digit Modality Test (SDMT) and Paced Auditory Serial Addition Test (PASAT); anxiety and depression using Hospital Anxiety and Depression Scale (HAD); fatigue using Fatigue Severity Scale (FSS), and upper limb function using the 9-Hole Peg Test (9-HPT). Two-tailed Bivariate Pearsons' correlation was used to explore associations between IRL count and the tests performances and subjective scales. Multivariate General Linear Model (GLM) analysis, using IRL count as fixed factor and years of education as a co-variate was used to confirm the effects.
Results: IRL were present in 18/25 (72%) of the MS-patients (median= 3; mean= 4.2 ± 1.1). The number of IRL had a significant correlation with PASAT (r= -0.468; p= 0.32) and FSS (r= -0.761; p< 0.001). In the multivariate GLM analysis, after adjusting for education, IRL had only a significant interaction with FSS (p= 0.16) and a tendency to be associated with HAD (depression form) (p=0.052).
Conclusions: IRL lesions might be a marker of chronic or silent inflammation in MS patients and possible ongoing neurodegenerative processes. Our results show an association between the IRL burden information processing speed, attention and fatigue. However, after adjusting for multiple comparisons and education, IRL has a main effect on fatigue.

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EP0964

Quantitative multi-parameter mapping in myelin oligodendrocyte glycoprotein IgG-associated disease and neuromyelitis optica spectrum disorders

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Introduction: Multi-parameter mapping (MPM) is a novel MRI sequence that provides quantitative maps of magnetization transfer (MT) saturation, proton density (PD), longitudinal relaxation rate (R1), and transverse relaxation rate (R2*) after reconstruction. Knowledge of the cerebral microstructural changes in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and aquaporin-4-immunoglobulin G positive (AQP4-IgG+) neuromyelitis optica spectrum disorders (NMOSD) is still sparse.
Objectives: This study aimed to investigate MPM in MOGAD and AQP4-IgG+ NMOSD.
Aims: The aim of this study was to evaluate and compare the cerebral microstructural tissue differences between the diseases using MPM.
Methods: From October 2019 to October 2021, 22 AQP4-IgG+ NMOSD (22 female), 11 MOG-IgG+ MOGAD (6 female and 5 male) patients and 14 healthy controls (HC) were prospectively included in the ongoing observational study. All participants underwent 3D MPM (1.6mm isotropic voxel resolution) and fluid-attenuated inversion recovery (FLAIR) MRI (0.8mm isotropic resolution) on a 3.0T scanner. White matter lesions were manually segmented by experienced graders on FLAIR images. Mean metrics from normal appearing cortical gray matter (NACGM), normal appearing deep gray matter (NADGM), and normal appearing white matter (NAWM) were extracted from reconstructed MPM maps. Group differences in each tissue class were analyzed using linear regression models and analysis of variance.
Results: In NACGM, both NMOSD and MOGAD patients showed a decreasing trend in MT (F=14.5, p<.001) and R1 (F=3.4, p=.016) compared to HC. In NADGM, MOGAD patients showed an increase in R2* maps compared to HC (F=16.9, p<.001). From PD maps, NMOSD and MOGAD patients were characterized by a decrease in NADGM (F=11.3, p<.001) and NAWM (F=40.0,p<.001) compared to HC. There were no significant differences between NMOSD and MOGAD patients on each tissue class from all MPM metrics.

Conclusions: NMOSD and MOGAD patients display comparable microstructural differences from HC as shown by MPM metrics. Despite their different cellular pathology, both diseases display abnormal MPM maps in tissues not considered to be immediately involved in their pathology, suggesting unspecific changes that may nonetheless be disease relevant.

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Claudia Chien: has received speaker honoraria from Bayer and research funding from Novartis, unrelated to this study.
Alexander Ulrich Brandt: Dr. Brandt is cofounder and holds shares of medical technology companies Motognosis GmbH and Nocturne GmbH. He is named as inventor on several patents and patent applications describing methods for retinal image analyses, motor function analysis, multiple sclerosis serum biomarkers and myelination therapies utilizing N-glycosylation modification. He is cofounder, member of the board and currently elected Secretary/Treasurer of IMSVISUAL.

EP0965

A novel clinical diffusion magnetic resonance imaging protocol to simultaneously dissect brain grey and white matter microstructure

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Introduction: The chronic inflammatory process in MS involves not only the white matter (WM) but also the cortical and deep grey matter (GM). Diffusion MRI (dMRI) is a powerful technique that, thanks to advanced signal modeling like the Soma And Neurite Density Image (SANDI) can probe microstructural information from both GM and WM. However, this model requires multishell acquisitions including b-values that are 6 times higher than those used in clinical practice.
Aims: Propose a 10-minute acquisition protocol that enables to acquire such images on a clinical 3T scanner and show feasibility and utility on subjects affected by MS.
Methods: We enrolled 5 healthy subjects (HS) and 5 relapsing-remitting patients. We implemented an acquisition protocol based on a spin-echo multishell dMRI sequence on a 3T Siemens Prisma scanner (whole brain, resolution 2x2x2mm^3, b-values up to 6000s/mm^{2}split in 213 directions). We also acquired FLAIR and MPRAGE images for lesion and regions of interest (ROIs) segmentation. We used 84 GM ROIs of Desikan-Killiany atlas and corresponding WM ROIs. We compared microstructural maps coming from state-of-the-art diffusion tensor imaging (DTI) and neurites orientation dispersion and density image (NODDI) with neurite, soma, and extracellular densities (fneurite, fsoma, fextra), apparent soma radius and intra and extra neurites diffusivities from SANDI. We evaluated the repeatability and reliability of each metric using the intraclass correlation coefficient (ICC) and coefficient of determination R^2. We also compared mean values of all the metrics in HS WM, MS NAWM, MS FLAIR hyperintense lesions, HS GM, MS NAGM, and MS GM lesions using a t-test without the assumption of equal variances and paired t-test as appropriate.
Results: Statistical indices showed that the repeatability and reproducibility of SANDI are comparable with those of DTI and NODDI (ICC$>$ 0.7, $R^2>0.7$). Looking at WM lesions that appeared similar in FLAIR and MPRAGE images, SANDI showed an increase of fextra in almost all of them, but different fsoma behaviors within lesions and in comparison to NAWM. Finally, SANDI allowed an accurate separation in mean values between HS WM/GM and MS patients NAWM/NAGM as well as NAWM and FLAIR hyperintense WM lesions and NAGM and GM lesions within patients.
Conclusions: Our results suggest that SANDI is a repeatable, reproducible, feasible, and practical method to characterize WM and GM tissues in both healthy subjects and MS patients.

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EP0966

Reducing acquisition time in diffusion MRI sequences: a DTI and NODDI white matter tract study

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Introduction: Multi-shell diffusion Magnetic Resonance Imaging (MRI) data has been widely used to characterise white matter microstructure in Multiple Sclerosis (MS). The lack of a consensus on acquisition protocol often leads to the acquisition of more measurements than required, implying long acquisition time.
Aims: Investigate the reduction of number of directions in multi-shell diffusion MRI using Diffusion Tensor Imaging (DTI) and Neurite Orientation Dispersion and Density Imaging (NODDI) model.
Methods: We included 3 healthy controls datasets: 93 subjects from ADNI3 (mean age 75.64±8.42; 64 females; directions: 6 b=500, 48 b=1000, 60 b=2000; 3 timepoints of 7 min 20 sec acquisition time; TE=71ms), 12 from University of Basel (6 females; 6 b=700, 20 b=1000, 45 b=2000 e 60 b=3000; 3 timepoints of 15 min 18 sec; TE=75ms) and 24 from University of Sherbrooke (mean age of 36.15±4.8; 19 females; 8 b=300, 32 b=1000, 60 b=2000; 5 timepoints of 9 min 19 sec; TE=92ms). For each dataset the number of directions collected in each shell was reduced by 10%, 30% and 50% using an in-house algorithm to select optimal directions to uniformly cover a unit sphere and each separate shell at once.
Then, we estimated DTI and NODDI measures on a set of 6 bundles clinically relevant for MS: Corpus Callosum, Corticospinal Tract, Inferior Fronto-Occipital and Inferior Longitudinal Fasciculi, Optic Radiation (OR) and Superior Longitudinal Fasciculus (SLF). White matter bundles were reconstructed using TractSeg. Relative absolute differences between downsampled and reference data were estimated for DTI and NODDI measures in each bundle.
Results: A sampling rate of 30% induced a mean signal loss in Fractional Anisotropy (FA) up to ~3% and in Mean Diffusivity (MD) up to ~4%. In Radial Diffusivity (RD) mean loss is below 5.5%. Sampling at a 50% rate we obtained a mean loss of ~4% in FA, less than 5% in MD and up to ~7% in RD. For the isotropic volume fraction of NODDI signal loss was less than 15% when sampling at 10% rate. The Intra-Cellular Volume Fraction (ICVF) presents a mean signal loss up to ~3% at 30% sampling rate, and ~4% at 50%.
Conclusions: DTI metrics and ICVF are still sound while saving up to 30% of the acquisition time. SLF and OR obtain the best overall results in terms of relative signal loss. Reliable diffusion metrics for DTI and NODDI model can be estimated with a reduction in acquisition time using 14 directions at b value of 1000 and 32 at 2000.

Disclosure
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Manon Edde: nothing to disclose.
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Stefano Magon is an employee and shareholder of F. Hoffmann-La Roche Ltd.
Muhamed Barakovic is an employee of Hays plc and consultant for F. Hoffmann-La Roche Ltd.
Susanna Gobbi is a consultant for F. Hoffmann-La Roche Ltd.
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EP0967

Prevalence of whole and regional brain atrophy in newly diagnosed relapsing-remitting MS patients

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Introduction: Multiple Sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system (CNS). In MS, brain atrophy is thought to be the result of demyelination and axonal loss in the CNS, and its measurement has been proposed as a marker of MS severity and progression. Indeed, brain atrophy is significantly correlated with worse prognosis and clinical outcomes. Despite its clinical importance, there is scarce information regarding the prevalence of whole and regional brain atrophy in recently diagnosed MS patients.
Objective: To establish brain atrophy prevalence in a cohort of Argentinian patients recently diagnosed with relapsing-remitting MS.
Methods: All new patients consulting at our Neuroimmunology Department from January 2018 until January 2022 who were diagnosed with relapsing-remitting MS according to the 2017 McDonald criteria were included. 3D T1-weighted images were collected from those patients. MRI-based measurements included: whole-brain parenchymal fraction (BPF), white matter (WM), grey matter (GM), cortical and subcortical areas (77 brain areas). Atrophy was defined as any brain area below percentile 5 of a normative database of healthy controls. Brain volumetric analysis was performed using Entelai Neuro version 4.0 (Entelai LLC, USA).
Results: We recruited 166 newly diagnosed relapsing-remitting MS patients, with a mean age of 39±11 SD years old. One hundred eleven were females (67%). Median time from the first symptom until diagnosis was 3.6 months (range 0-74). Five patients (3%) showed global brain atrophy as measured by BPF, 6% (10 patients) presented WM atrophy and 3.6% (6 patients) presented decreased GM volume. Thirty-seven patients (22%) showed thalamic atrophy and 4 (2%) displayed hippocampal

atrophy. 22.89% of patients with thalamic atrophy also had global or regional atrophy in other areas.
Conclusions: Thalamic atrophy affected approximately one out of five relapsing-remitting MS patients at the time of diagnosis. Global and other regional atrophies were less prevalent. Since brain and thalamic atrophy is linked to poorer prognosis, our work highlights the relevance of measuring brain atrophy in clinical practice due to its prevalence, even in newly diagnosed MS patients.

Disclosure
Sofía Rodríguez Murúa: Nothing to disclose
Hernán Chaves: is CTO & Co-Founder of Entelai LLC.
Jorge Correale: is an advisory board member of Biogen, Genzyme, Merck, Novartis, and Roche.
Diego Fernández Slezak: is CTO & Co-Founder of Entelai LLC.
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EP0968

Depression and prefrontal metabolism explain unique variability in processing speed ability in multiple sclerosis: a calibrated fMRI study

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Background: Cognitive processing speed deficits are common in multiple sclerosis (MS). Previous work has shown that cerebral metabolism in dorso-lateral prefrontal cortex (dlPFC) is known to be related to the slowed processing speed observed in MS. Depression is also common in MS and is associated with processing speed decline. In this study, we sought to assess the extent to which depression contributes to these metabolism-processing speed relationships.
Objective: Assess whether depression and metabolism account for unique proportions of variability in MS-related processing speed decline.
Methods: MS and healthy control (HC) participants who met inclusion criteria were scanned using a 3T MRI scanner with a dual-echo calibrated fMRI (cfMRI) sequence which provided near-simultaneous measures for both cerebral blood flow (CBF) and BOLD signal. During imaging, participants performed a block-design digit-symbol substitution task (DSST) that required the viewing of a digit-symbol pairing key and responding as to whether a probe digit-symbol pair matched the key as fast as they could using button boxes. A hypercapnia gas challenge involving periodic inhalation of room air (4 min) and 5% CO_2 (6 min) permitted measures of cerebral metabolic rate of oxygen ($CMRO_2$). Data were pre-processed and average percent signal change from baseline was calculated in each voxel providing BOLD and CBF time series. The anatomical region of interest (ROI) was defined as dlPFC after Freesurfer cortical parcellation. Regression analyses were performed controlling for ROI size to assess whether BOLD, CBF, or $CMRO_2$ could explain variability in processing speed ability. Prior to imaging, participants were administered a cognitive assessment battery that included the Beck Depression Inventory (BDI).
Results: An independent-samples t-test showed that the MS group had a significantly higher response time (RT) for the DSST ($t[42]=2.77$, $p=.008$) and higher BDI scores ($t[42]=3.02$, $p=.004$) compared to HCs. Within the MS group, regression analyses using RT for correct trials as the dependent factor were not significant for BOLD and CBF PSC but was significant for BDI ($R^2=.115$, $p=.045$) and $CMRO_2$ ($R^2=.124$,$p=.024$). No regression analyses were significant within the HC group.
Conclusion: Results suggest that depression and prefrontal metabolism account for unique proportions of variance in MS-related processing speed declines.

Disclosure
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EP0969

Predictors of long-term disability in MS patients using routine MRI data: a 15-year retrospective study

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Introduction: Studies have shown that more than half of MS patients are likely to develop a severe disability after 15 – 30 years. Thus, the early identification of patients at risk of greater disability is crucial and it would be effective for initiating/ determining a personalised treatment strategy. MRI findings, such as white matter lesion (WML) number, volume, and regional brain atrophy have been proposed to predict disability. To our knowledge, these predictors have not yet been validated against findings of long-term clinical follow-up has not yet been tested.
Aim: Assess whether there is a role for baseline and yearly change in lesion number and volume, in predicting disability. Also, investigate the relationship between regional brain atrophy and clinical outcomes using four linear brain atrophy measurements.
Methods: 82 MS patients (female/male ratio 53:29; 12 converted to secondary progressive MS) were selected with more than10 years of clinical follow-up and had two MRI scans at baseline (first disease onset) and a follow-up scan (after 4 – 6 years). Clinical data were obtained at three times,at baseline, follow-up

(4-6 years interval) and last visit (⩾10 years). The Expanded Disability Status Scale (EDSS) was calculated for all patients at three time points to assess the clinical progression. WML counts and volumes, linear brain measurements of corpus callosum index (CCI) and medulla width (MEDW), all of which were measured on T2/FLAIR. Third ventricle width (TVW) and inter-caudate distance (ICD) were measured on axial T1-weighted image.
Results: Linear brain measurements, at baseline and follow-up, showed significant, positive, correlations with EDSS at the last visit, including ICD, and TVW. Lesion counts and volumes showed a greater median in the follow-up scan than baseline, with an annual rate of new lesions (1.11 lesion/year), and lesion growth rate (0.16 lesion/year). Out of the 82 patients, 79 patients had new lesions with a mean (SD) of 10.8 (11.8). Patients who developed SPMS at 10 years had a lower median number of T2 lesions compared with patients who remained RRMS (13 versus 16 respectively). However, a steeper rate of lesion volume increase was observed in SPMS compared to RRMS (0.23 versus 0.155).
Conclusion: In this study, linear brain atrophy, specifically ICD and TVW, have a significant impact in predicting disability after 10 years, whereas WML counts and volumes seem to be weak predictors of disability

Disclosure
Nothing to disclose

EP0970
Tracking longitudinal change in Brain volumes through conditional quantiles

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Background: Changes in brain structure in people living with multiple sclerosis (MS) can be attributed to natural aging processes or to disease-related atrophy. Differences in baseline brain volumes make it challenging to interpret changes over time in many cases due to regression to the mean. The field of growth chart modeling has recognized that personalized charts that consider prior measurements yield markedly more informative representations and are less susceptible to misinterpretation. However, no such conditional brain charts are available for the study of brain volume changes.
Objective: To develop and implement statistical models that incorporate heterogeneously and longitudinally acquired magnetic resonance imaging (MRI) measurements to establish personalized and informative brain charts.
Methods: 273 people with MS were imaged between 2 and 4 times over a period of up to 6 years using 1.5T and 3T MRI scanners from 2 manufacturers. FDA-cleared software was employed to measure the volume of ventricles as well as the intracranial space (ICV). Conditional generalized additive models for location, scale, and shape were fit for ventricle volume at each time point, based on contrast-to-noise measured from T1-weighted imaging, previously observed volume, and time interval. Model fit was assessed by visual inspection of worm plots across scanners, age ranges, and image quality. Raw volumes were modeled, and results were compared with normalization and adjustment for intracranial volume.
Results: Predictors of ventricle volume distribution included patient age ($p<0.001$), previous ventricle volume ($p<0.001$), and the time interval of observation ($p<0.01$). Higher image quality was associated with less variance in volumes ($p<0.02$). Visual inspection of worm plots indicated good model fit across all variables of interest. Assessment of fitted conditional centiles indicated that they provide intuitive visualizations of longitudinal changes in ventricle volume. ICV-adjusted and ICV-normalized modeling resulted in similar conclusions.
Conclusion: Brain growth changes in people with MS can be challenging to interpret due to statistical biases and age-related normal changes. Longitudinal, personalized brain charts promise to revolutionize physician decision support systems for the management of MS patients.

Disclosure
All authors are employees of Octave Bioscience

EP0971
QSM in MS shows large regional susceptibility differences but is constant over time

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Introduction: Quantitative susceptibility mapping (QSM) values in magnetic resonance imaging may be a measure for biomarkers such as myelin and iron, and thus could serve to characterize lesions, deep grey matter (DGM), white matter (WM) and normal-appearing WM (NAWM) in multiple sclerosis (MS).
Aim: In the current study, subjects with early relapsing-remitting MS (RRMS) and healthy controls (HC) were scanned longitudinally, with the aim to identify regional differences, and to compare RRMS and HC, both cross-sectionally and longitudinally. Furthermore, we looked at the variability of lesion susceptibility.
Method: A total of 28 RRMS subjects and 13 age- and sex-matched HC were scanned three times, at intervals of one year at 3T (GE Discovery), using 3D T1-weighted, 3D FLAIR and 3D QSM. Susceptibility values in DGM, NAWM lobes and lesions were analysed using a repeated measure ANOVA with time and hemisphere as within-subject factors and subject group as between-subject factor. When appropriate, post-hoc testing was performed. Susceptibility values between RRMS and HC were compared with an unpaired two sided t-test.
Results: Large regional variation was observed between the various DGM structures (range: -0.03 to +0.09 ppm). The susceptibility of NAWM was within a smaller range (-0.016 to -0.001 ppm), but large differences were observed between the lobes and was generally lower for RRMS compared to HC. The average susceptibility of lesions in RRMS was higher than for overall NAWM ($p<0.05$), but a large variation between lesions was observed

within and between subjects, both cross-sectionally and longitudinally. Longitudinally, DGM and (NA)WM susceptibility was stable, in both groups.
Conclusion: Our results show large regional variability in susceptibility sources both in HC and RRMS subjects. The myelin content of DGM is generally low, suggesting that the observed high susceptibility is likely an effect of high iron concentration. Large variation in lesion susceptibility suggests an interplay of pathological processes leading to both highly negative and highly positive susceptibility, and could potentially distinguish lesion types, such as chronic black holes or active lesions. The decreased susceptibility in NAWM in RRMS is compatible with chronic microglia activation, resulting in a reduction of iron-containing oligodendrocytes, whereas demyelination effects are expected to have less influence on susceptibility values.

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PJWP has nothing to disclose

EP0972
brain white matter tractography in MS tremor patients

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Introduction: Current models fail to fully explain the connectivity impairment responsible for tremor in multiple sclerosis (MS). Tremor is a common manifestation of MS affecting 26–58% of the patients sometimes with disabling impact on their quality of life and resistance to treatment.
Objectives: Devising an agnostic tractography approach to study putative tracts involved in MS tremor.
Methods: Patients with MS tremor (n=36) had 3.0 T MRI scans with T1-weighted, FLAIR, and diffusion-weighted (DWI) sequences. Subjects, aged 24-67 years, were gender and age-matched with a control MS group (n = 36) without tremor. DTI Studio was used to decode and extract tensor data from DWI sequences. Atlas-based DTI segmentation using MRICloud software was performed to obtain mean diffusivity and fractional anisotropy from 168 well-identified brain regions. Group comparisons were performed to show the areas with significant differences between the two groups adjusting the results for multiple comparisons. Using multiple linear regression adjusting for other variables, we were able to find the white matter regions that correlated most with tremor severity.
The second step was conducted in DSI Studio software. Diffusion connectometry was used to derive the correlational tractography that has quantitative anisotropy correlated with tremor severity in the tremor group. A nonparametric Spearman partial correlation was used to derive the correlation, and the effects of age and gender were removed using a multiple regression model and utilizing a deterministic fiber tracking algorithm. To estimate the false discovery rate, a total of 10000 randomized permutations were applied to the group to obtain the null distribution of the track length.
Results: Using this method, we were able to identify 18 white matter regions that showed group differences and correlated with tremor severity as well as 14 fiber tracts that correlated with tremor severity. Subsequently, we were able to synthesize a list of tracts agnostically to investigate.
Conclusions: This method shows promise in investigating the structural connectivity correlates behind some neurological disorders.

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EP0973
The Central Vein Sign to differentiate multiple sclerosis from migraine

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Background: The Central Vein Sign (CVS) has been demonstrated its potential in differentiating multiple sclerosis (MS) from its comorbidities. Migraine represents the most common MS mimic.
Aims: The aims of this study were to investigate, in two cohorts including MS and migraine patients (i) the prevalence of CVS, (ii) the spatial distribution of CVS+ lesions, (iii) the best CVS threshold able to differentiate them.
Methods: Sixty MS patients and 50 age and gender-matched migraine patients underwent a 3T MRI scan. A ROC-curve analysis was performed to identify the best threshold in terms of

proportion of CVS+ lesions and the absolute number of CVS+ lesions able to differentiate MS from migraine.
Results: Lesion volume (LV) was different between CVS+ and CVS− lesions (median = 1273 mm³ vs 181.5 mm³ for MS cohort; median = 35.1 mm³ vs 52.2 mm³ for migraine cohort; $p<0.001$ for all). CVS+ LV and number were higher in MS with respect to migraine both considering whole brain and its subregions ($p<0.001$). The proportion of CVS+ lesions in juxtacortical and infratentorial areas was higher in MS than migraine (p=0.016 and p=0.034 respectively). The best CVS proportion-based threshold able to differentiate MS from migraine was 23% (sensitivity 90%, specificity 90.5%). The "pick 6" rule seemed to be preferable in terms of specificity with respect to the "pick 3" rule.
Conclusions: A CVS proportion-based threshold of 23% is capable to distinguish MS from migraine with high sensitivity and specificity. The "pick 6" algorithm may be useful in the clinical setting.

Disclosure
All Authors declare nothing to disclose

EP0974
The brain-age paradigm and clinical outcomes in multiple sclerosis

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Introduction: The brain-age paradigm has been used to investigate neurological disease progression, including multiple sclerosis (MS).
Objectives: To investigate the factors affecting the difference between the predicted brain-age and chronological age (brain-PAD) in patients with MS.
Methods: Among 192 relapsing remitting MS patients from Imperial College Healthcare NHS trust, we used 401 T2 MRIs to calculate Brain-PAD. Using linear regression and non-parametric tests we evaluated how the Brain-PAD is affected by clinical and demographic factors. Patients had received as last treatment highly active therapies (Alemtuzumab (25.373%), Ocrelizumab (16.417%) or Natalizumab (55.224%) or haematopoietic stem cell transplantation (2.985%)).
Results: Following treatment initiation patients were followed up for 5.8 mean years; whilst on treatment, 51 (26.5%) and 56 (29.2%) progressed or improved on the EDSS, respectively, 46 (24.0%) had a relapse and 38 (19.8%) experienced progression independent of relapses (PIRA). Overall, the brain predicted age (median: 48.344, IQR: 39.449-58.021) was significantly higher than the chronological age (median: 46.000; IQR: 37.000-54.000; $p<0.01$). On univariate analysis, longer disease duration (B=0.104; p=0.012), older age at symptom onset (B=-0.100; p=0.002) higher EDSS at therapy initiation (B=0.333; p=0.004) and within 6-months of the reference MRI, (B=0.545; p=0.046) significantly predicted higher brain-PAD. Gender (B=-0.464; p=0.387), presence of relapses on treatment (B=1.148; p=0.088), progression (B=0.782; p=0.064) or improvement (B=0.997; p=0.09) of EDSS whilst on therapy, and PIRA (B=0.915; p=0.163) did not affect the brain-PAD. On multi-variate analysis, only young age at symptom onset (B=-0.169, 0.033) and EDSS atther-apy initiation (B=0.732; p=0.043) remained significant predictors of the brain-PAD. Among 128 patients who had consecutive scans the annual brain-PAD change was calculated (median: 0.239; IQR: -1.713-2.043); on univariate analysis, only shorter disease duration (B=-0.282; p=0.042) significantly predicted greater changesbrain-PAD/year.
Conclusions: Results indicate that MS patients exhibit accelerated brain aging; greater brain-PAD was observed among those diagnosed atyounger age and with higher EDSS. More severe longitudinal changes in brain-PAD are observed in the early stage of the disease, among patients with a shorter disease duration, and could be used as biomarker to monitor treatment response.

Disclosure
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EP0975
The role of RIM lesions in predicting longitudinal brain and retinal atrophy

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Introduction: In multiple sclerosis (MS), paramagnetic rim lesions (PRLs) are thought to reflect chronic active inflammation which may lead to a progressive neuronal damage. Loss of brain volume has been reported to be higher in patients with PRLs. However, the role of PRLs in predicting retinal atrophy has not been explored.
Objectives: To assess whether PRLs are associated with patients' brain and retinal atrophy over follow-up (FU).
Methods: In this ongoing study, we included MS patients who underwent 3T MRI and spectral domain optical coherence tomography (SD-OCT) at baseline and during the subsequent FU [median (range) FU: 16 (12-24) months]. At baseline, white matter lesions were stratified as PRLs and no-PRLsby visual inspection on GRE-phase images and QSM maps. Baseline and FU values of brain volumes and ganglion cell-inner plexiform layer (GCIPL) thickness were also collected. After adjusting for sex,

age, disease duration and MS phenotype, the association between number of PRLs at baseline and changes in terms of percentage-brain-volume-change (PBVC) or rates of GCIPL atrophy (difference between baseline and FU GCIPL thickness) was explored with linear regression models, while ANCOVA was used to investigate differences in term of PBVC and retinal atrophy between patients in patients with < 4 PRLs and those with ⩾4 PRLs.

Results: A total of 25 MS patients were included [female: 64%; RRMS phenotype: 84%; mean (SD) age and disease duration: 38 (11.8) and 6.8 (6.3); median (range) EDSS: 2 (0-6.5)]. At baseline MRI, median (range) number of PRLs was 1 (0-7); 17/25 patients had at least one PRLs, 6/25 had>4 PRLs. Mean (SD) PBVC and GCIPL atrophy over FU were -0,48 (1.05)% and 0.72 (1.2) μm, respectively.The baseline number of PRLs was able to significantly predict PBVC (B=-0.202, 95% CI: -0.396 - -0.008; p=0.042) and GCIPL thickness reduction (B=0.225, 95% CI: 0.001-0.448; p=0.049). We observed higher rates of PBVC (-0.89+0.92 vs -0.35±1.08) and more pronounced GCIPL atrophy (1.56±1.66 vs 0.4±1.01) in patients with>4 PRLs as compared to those with < 4 PRLs (p=0.05 and p=0.028, respectively).

Conclusions: We observed an association between higher number of PRLs and more pronounced brain volume or retinal thickness loss over FU. Our findings confirm and strengthen the role of PRLs as a marker of disease severity in MS.

Disclosure

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EP0976

Automatic estimation of brain parenchymal fraction in patients with multiple sclerosis: comparison between Synthetic MRI and FSL

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Background: Automatic quantification of brain volume in multiple sclerosis (MS) is of crucial importance for the assessment of neurodegeneration as a biomarker for disease progression and disability status.

Aims: We aimed to validate the estimation of brain parenchymal fraction (BPF) in MS patients using synthetic magnetic resonance imaging (SyMRI) in comparison with FSL. In addition to a cross-sectional method comparison, a longitudinal assessment of volume changes was conducted to further elucidate the suitability of SyMRI for quantification of disease specific changes.

Methods: MRI scans from 217 MS patients, 18 Neuromyelitis optica (NMO) patients, and 28 healthy controls (HC) were included for volume estimation by SyMRI and FSL Software. All MS-Subtypes (SPMS, PPMS, RRMS) were represented. In order to calculate BPF from FSL-SIENAX, which by default estimates brain tissue volumes normalized by head size, CSF, gray and white matter masks were saved for manual computation of BPF. Moreover, longitudinal data from 41 MS patients was used to estimate two-timepoint, registration-based percentage brain volume change with SIENA, part of FSL, which was compared to difference-based calculation of percentage volume changes based on SyMRI.

Results: Strong correlations of estimated brain volumes between the two methods were observed (Pearson correlation coefficient: 0.95, $p < 0.0001$). While SyMRI overestimated BPF compared to SIENAX (BPF mean ± standard deviation across all participants: 0.80 ± 0.07 vs. 0.74 ± 0.04), indicating a systematic bias, there was good agreement for BPF (intraclass correlation coefficient (ICC): 0.651). Bland-Altman plots suggested that the inter-method difference was smaller in patients with brain atrophy. Overall, higher variability was obtained for SyMRI than for SIENAX. Group comparisons between HC, NMO, and MS subtypes yielded consistent BPF results for SyMRI and SIENAX, respectively (RRMS > PMS and PMS < HC). Longitudinal analyses revealed a tendency for higher atrophy rates for SyMRI (-1.07 ± 1.35) than for SIENA (-0.42 ± 0.78), but a robust pearson correlation coefficient of 0.596 ($p < 0.001$), and a good agreement (ICC: 0.6).

Conclusion: In summary, BPF from SyMRI and SIENAX is not transferable one to one since an overestimation and higher variability of SyMRI values were observed. However, the consistency and correlations between the two methods were satisfactory and our results showed that SyMRI is suitable to quantify disease specific atrophy in MS.

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EP0977

Spinal Cord Reserve: Validation of cervical cord canal estimations using brain and spinal cord volumetric MRI in a prospective cohort of multiple sclerosis patients

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Background: The spinal cord is an area of preferential damage in multiple sclerosis (MS). Obtaining estimations of the spinal canal area (SCaA) would allow testing the existence of a spinal cord reserve, in homology to the brain reserve concept. We have recently developed an algorithm based on the Spinal Cord Toolbox to obtain semi-automatic estimations of the SCaA (SCaA-SCT). The objectives of the present work are: i) to compare SCaA-SCT and manual ground truth (GT) segmentations of SCaA, in healthy controls (HC) and patients with MS (pwMS) ; ii) to estimate changes of SCaA over a one-year period using SCaA-SCT; iii) to compare SCaA-SCT measurements obtained with 3DT1 whole-brain and spine MRIs.
Methods: The cohort included HC and pwMS who underwent baseline and follow-up brain and spine MRIs. SCaA was measured in all acquisitions using SCaA-SCT and, at baseline, manually outlined by two experienced operators (GT). SCaA-SCT estimations of SCaA were compared to GT (operator 1) with dice coefficients (DC). Variation between baseline and follow up / brain vs spine acquisitions SCaA estimations were assessed with the Intraclass Correlation Coefficient (ICC).
Results: We included 19 pwMS (12 women, 63.2%), matched by age and sex with 10 HC (5 women, 50%). Agreement between operators was high -DC (range)=0.95(0.88-1)-, as well as between the SCaA-SCT and GT -DC=0.90(0.82-0.98)-. No significant differences in SCaA were observed between HC and pwMS (218.1mm2 vs 218.2 mm2, p=0.99). Agreement between SCaA obtained with brain and spine acquisitions was ICC(95%CI)=0.77(0.47-0.91), and between baseline and follow-up spine MRI acquisitions was 0.76(0.53-0.88).
Conclusions: Measurement of SCaA-SCT shows a very good agreement with manual outlining and is a stable measure over a one-year period. Estimations obtained from brain and spinal cord MRI acquisitions are rather similar. SCaA-SCT is a valid, robust and reproducible semi-automatic algorithm to calculate SCaA.

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AR: serves/ed on scientific advisory boards forNovartis,Sanofi-Genzyme, Synthetic
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JS-G: serves as co-Editor for Europe on the editorial board of Multiple Sclerosis Journal and as
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EP0978

Unsupervised clustering of acute multiple sclerosis lesions across spatial, geometric and textural domains

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Introduction: Multiple sclerosis (MS) lesions exhibit substantial pathophysiological heterogeneity. This heterogeneity may be observable macroscopically using conventional MRI, as geometric and/or textural patterns detected within MS lesions. Unsupervised clustering approaches leveraging radiomic features may identify prototypical groups of MS lesions that are pathologically distinct and offer clinical value for prognosis and/or predicting treatment response.
Objectives: To identify populations of focal acute MS lesions using machine learning approaches and radiomic features that exhibit consistent positional, textural and/or geometric patterns, as observed on conventional non-contrast cross-sectional T1- and T2-weighted brain MRI.
Methods: Brain T1- and T2-weighted MRIs from the ADVANCE (1,512 patients with relapsing-remitting [RR]MS, NCT00906399)

and ASCEND (886 patients with secondary progressive [SP]MS, NCT01416181) trials were retrospectively analysed. In total, 7481 focal acute (T1 gadolinium-enhancing and/or new or enlarging) white matter T2 lesions were identified across all scans. Each lesion was represented via its center of mass, a set of shape properties and a set of texture properties, as measured via radiomics. Similar lesions were grouped together according to an unsupervised clustering algorithm based on LP-stability, applied separately across the spatial, textural, and shape domains. The optimal combination of a similarity metric and a sub-populations count was identified via an extensive search, optimizing for a cluster quality metric defined as a weighted average of the silhouette score and Davies-Bouldin index.

Results: We observed optimal clustering quality when we stratified acute lesion samples into 9 prototypical spatial locations in the supratentorial white matter, 14 prototypical textures and 3 prototypical shapes. In each domain, the proportion of lesions assigned to each cluster was evenly balanced.

Conclusions: Clusters of acute MS lesions were identified with specific spatial, geometric, and textural patterns, the clinical relevance of which will be further characterized against, clinico-radiological endpoints of disease progression. Future efforts will also target the clustering analysis of multi-focal chronic lesion conglomerates, which may allow to discover heterogeneity patterns associated with chronic active inflammatory and neurodegenerative pathology.

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CE is an employee of NeuroRx.

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EP0979

Cerebellar atrophy and cognitive function in multiple sclerosis: does it matter?

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Introduction: In detriment of its classic association with motor function, the cerebellum has been disregarded in cognitive functioning. Nevertheless, it is involved in emotion and cognition, and increasing evidence indicates that cerebellar damage plays an important role in a range of cognitive disorders.

Objectives & Aims: To investigate the association of cerebellar atrophy with cognitive impairment in multiple sclerosis (MS) patients.

Methods: Sixty MS patients and 60 healthy controls (HC) demographically matched were enrolled. All participants underwent cognitive testing (MACFIMS) and 3Tesla brain MRI. Using Freesurfer software, white-matter (WM), cortical and subcortical grey matter volumes were calculated, including cerebellum-WM and cerebellum-cortex volumes.

Results: Compared to HC, MS patients had lower scores on all cognitive domains and decreased volumes of cerebellum-WM and cerebellum-cortex ($p<0.05$). Moreover, cerebellum WM and cortex volumes were significantly reduced in patients with cognitive impairment compared to those with normal cognitive performance($p<0.05$). In MS group, cerebellum-WM volume correlated positively and was the main predictor of information-processing speed (SDMT and PASAT) while cerebellum-cortex volume correlated positively and was the main predictor of visual-learning (BVMT-R).

Conclusions: This study suggests that cerebellar atrophy contributes to cognitive impairment in MS patients, particularly affecting information-processing speed and visual learning domains, which may reflect disruption of the cortico-cerebellar pathways.

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EP0980

A 5-year longitudinal study identifies multi-modal brain MRI signatures that predict cognitive decline in an Australian multiple sclerosis cohort

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Background: Cognitive impairment is a clinical hallmark of multiple sclerosis. Identifying the predictive signatures of cognitive decline in MS patients over time is important to customise preventative treatment strategies. Structural and functional brain characteristics as measured by various MRI methods have been correlated with variation in cognitive function in MS, but typically these studies are limited to single MRI modalities and/or are cross-sectional designs.
Objective: We assess the predictive value of multiple different MRI modalities in relation to cognitive decline in a patient cohort followed for 5 years.
Methods: A cohort of 43 people with MS (pwMS) were assessed at baseline and 5 years follow-up. Baseline (input) data consisted of 76 multi-modal MRI metrics (volumetric, diffusion tensor imaging and MR spectroscopic) for different brain regions and tissues. Age, sex, disease duration and treatment were also included as inputs. Cognitive function was assessed using the Audio Recorded Cognitive Screen (ARCS) and the Symbol Digit Modalities Test (SDMT). Cognitive decline (outcome) was change in scores over the 5-year period. Multi-factor prediction modelling was performed using the machine learning package - GLMNet. This fits penalised regression models to select informative features when there are many, including correlated, variables.
Results: *The best performing model for change in ARCS selected 16 predictive features from across the various MRI modalities and explained 50% of the variation in change over time (R^2=0.5, 95% CI = 0.48-0.51). The features included 9 metabolites (top = GLX and NAA), 4 volumetric (top = CSF, lesion vol.), and 2 DTI (top = FA white matter and lesion). Importantly, the model also selected disease duration as a predictive feature. By comparison, the best model for SDMT selected many of the same features and explained 39% of the change over time (R^2=0.39, 95% CI = 0.48-0.51).*

Conclusion: We identified multi-modal brain MRI signatures for predicting change in cognitive function over 5 years in a cohort of Australian MS patients. These findings highlight the importance of using several MRI measures analysed in combination when assessing cognitive decline. Future studies will benefit from the inclusion of even more MRI modalities eg. functional MRI as well as other potential predictors eg. genetic, environmental, clinical.

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EP0981

Cross-sectional and longitudinal comparative analyses of Brain volumes in MOGAD, NMOSD, and MS

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Background: Little is known about trajectories of global and regional brain volume changes in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) relative to other neuroinflammatory disorders, such as Multiple Sclerosis (MS) and Neuromyelitis optica spectrum disorder (NMOSD), and healthy controls (HC).
Objective: To describe the brain volumetric changes over time in MOGAD in comparison to MS, NMOSD, and HC.
Methods: We retrospectively reviewed the NYU Multiple Sclerosis Care Center database to identify all adult NMOSD and MOGAD patients with available brain MRI performed in stable remission and compared them with MS patients and HC. Cross-sectional and longitudinal volumetric parameters were analyzed using the FDA-approved ico**brain**software. One-way analysis of variance (ANOVA) and Generalized Linear Model (GLM) were used for cross-sectional (patients and controls) and longitudinal (patients only), respectively, correcting for patient age and sex. Post-hoc testing was calculated with Tukey adjustment for multiple comparisons.
Results: 24 MOGAD, 47 NMOSD, 40 MS patients and 37 controls were included. In cross-sectional comparison, the whole brain (WB) volume in MOGAD, NMOSD and MS was significantly lower than controls (p=0.0002, p=0.042, and p=0.01, respectively). In regional brain comparisons, parietal gray matter (GM) volume was lower in all patient groups compared to controls (MOGAD: p=0.02, NMOSD: p=0.0051, and MS: p=0.0062); The global cortical GM (CGM) volume and the occipital GM volume were significantly lower only in MOGAD compared to controls (p=0.012 and p=0.0016, respectively), while thalamic volume was significantly lower in both MOGAD (p=0.00042) and MS (p=0.000042) compared to controls. In the longitudinal analysis, a trend toward reduction in the WB volume, CGM volume and thalamus volume was observed in all three disease groups. The MOGAD group differed significantly from the MS and NMOSD groups in terms of the evolution of their thalamic (MS: p=0.019, NMOSD: p=0.018) and hippocampal volumes (MS: p=0.003, NMOSD: p=0.020), with a more substantial decrease over time for MOGAD patients.
Conclusions: Our study demonstrates that whole brain volume loss is more evident in all neuroinflammatory conditions compared

to controls, and MOGAD patients have a faster loss of thalamic and hippocampal volumes than MS and NMOSD. Further studies are warranted to validate our findings and investigate their clinical implications.

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EP0982

Structural brain topology differences in African-American and Caucasian patients with MS: bridging the inclusivity gap in advanced neuroimaging studies

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Introduction: Several studies have reported differences in disease burden, assessed as grey matter atrophy and white matter lesion load in African-American (AA) and Caucasian (CA) multiple sclerosis (MS) patients.
Objective and aims: We aimed to investigate, for the first time, changes in brain network topology sustained by such damage.
Methods: 169 subjects, part of an ongoing longitudinal study, were included in the analysis (AA MS n=47, age 37.7±10.5, 36F vs AA HC n=40, 36±11.8, 28F; $p>0.05$ for both; CA MS n=49, age 36.8±8.4, 31F vs CA HC n=33, 33.9±9.9, 21F; $p>0.05$ for both). Structural networks were constructed from dMRI data using probabilistic tractography and assigning the strength to each connection using the COMMIT framework. Between-group comparisons of network properties were performed with ANCOVA analysis accounting for age, sex (and race in the comparison of MS vs HC). Results were considered significant at $p<0.01$ (Bonferroni corrected for multiple comparisons [0.05/5 as the number of network properties considered]). To test the impact of structural abnormalities and race on disability a stepwise regression model was run (1st block: demographics, 2nd block: network properties).
Results: AA MS patients presented more severe motor disability than CA MS (median EDSS 2 vs 1.5, p=0.006). Analyzing the impact of MS on brain connectivity (comparing MS patients and HC accounting for age, sex and race) we identified widespread abnormalities in network topology, involving clustering coefficient, modularity and mean strength ($p<0.01$). As per the impact of MS in different races, comparing AA and CA MS patients with race-matched HC, the two groups showed similar changes in modularity ($p<0.001$), but AA also showed significant reduction in mean strength (p=0.01) and clustering coefficient ($p<0.001$). These findings were confirmed by the direct comparison of AA and CA patients, which showed lower mean strength and clustering coefficient in AA than CA patients (not reaching the statistical significance). The regression model identified age, race and modularity as independent predictors of EDSS ($R^2=0.22$, p=0.002; F changes 9.2, 7.9 and 9.7 with p=0.003, p=0.006 and p= 0.002 respectively).
Conclusion: AA MS patients presented a more profound disruption of brain structural connectivity than CA MS patients. Both race and structural disconnection significantly contributed to motor disability, suggesting that MS might exert a differential impact across races.

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EP0983

Wave-CAIPI is an efficient and sensitive method for paramagnetic rim lesion detection

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Introduction: Paramagnetic rim lesions (PRL) appear to be highly specific to MS and may function as a marker of disease activity and severity, resulting in potential diagnostic and prognostic value. However, conventional 3D FLAIR and SWI sequences used to depict these lesions are time consuming to obtain. Wave-controlled aliasing in parallel imaging (Wave-CAIPI) is a highly accelerated acquisition and reconstruction approach for Wave-FLAIR and Wave-SWI that provides maximal efficiency for parallel imaging.
Objectives: To assess the utility of detecting PRLs using clinical grade Wave-CAIPI sequences and to explore the relation between disability and PRLs, to better understand the prognostic value of PRLs.
Aims: The first aim of this study was to demonstrate utility of Wave-CAIPI for evaluating PRLs in MS, the second aim was to evaluate the relationship between PRLs and disability in MS.
Methods: Brain MRI with Wave-CAIPI sequences were acquired at the Massachusetts General Hospital between September 2020 and March 2022 on 3T Siemens MRI systems (MAGNETOM Prisma and Vida, Siemens Healthcare, Erlangen, Germany) in 111 people with MS. Using the Wave-CAIPI protocol, the acquisition time for Wave-SWI was 1:58 minutes and 3D Wave FLAIR sequences was 2:30 minutes. The total number of white matter lesions (WML) was calculated using an automated Lesion Segmentation Tool. Two neuroradiologists and a research assistant assessed PRLs. Discrepancies between raters were discussed, and a consensus was reached. Expanded Disability Status Scale (EDSS) was derived from the most recent clinical neurological exam.
Results: A total of 42 PRLs were identified in 111 cases. There was a strong agreement between raters (Cohen k= 0.833, $p < 0.001$). Using Wave-CAIPI it was determined that 7.74% of WMLs were PRLs and that the patient-level prevalence was 36.4%. Patients with a PRL were on average 8.5 years younger than patients without a PRL (p= .003). There was no significant relation between the lesion-level prevalence of PRLs and the EDSS (p=.357).
Conclusions: The Wave-CAIPI sequence was a time efficient method of obtaining relevant information on PRLs in MS. The sensitivity of PRL detection was similar to other gold standard sequences with longer acquisition times. In contrast to existing literature, no significant relation between PRLs and EDSS was found in this study.

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EP0984

Advanced track-profiling diffusion- & myelin-based MRI detects anomalies in MS patients from a normative control reference

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Introduction: Most multiple sclerosis (MS) clinical trials focus on lesion count and volume change. Diffusion magnetic resonance imaging (dMRI) and quantitative myelin-based MRI can generate promising endpoints to characterize drug effects on the white matter (WM) microstructure.
Objective/Aim: Assess the potential of whole-bundles (WB), normal appearing white matter (NAWM), lesion load and track-profiling endpoints to detect anomalies in MS patients, when compared to healthy controls (HC) normative references.
Methods: 19 MS patients and 24 HC multi-shell dMRI (processed using Tractoflow to generate apparent fiber density [AFD-fixel] and tissue-specific radial diffusivity [RDt]) and inhomogeneous magnetization transfer (processed to generate ihMTsat) were acquired. Major WM bundles (n=33) were extracted using RecoBundleX and subdivided in 20 track-sections (track-profiling). High (HLL-TS) and low (LLL-TS) lesion load track-sections were identified in MS patients. HLL-TS had lesions in more than 10% of the total section volume, whereas LLL-TS had less than 10%. Since reporting the results from all bundles of all patients is outside the scope of this abstract, only results from one MS patient for the left inferior fronto-occipital fasciculus (IFOF-L) are compared to HC using Z-scores (considered anomalies when $> \pm 2$). Our patient's metrics averaged in WB, NAWM and lesion masks were compared to HC metrics averaged in WB. Then, HLL-TS (n=5) and LLL-TS (n=15) averaged measures of our patient were compared to the analogous track-sections of HC.
Results: AFD-fixel was similar to HC in WB, NAWM, lesion masks and in HLL-TS and LLL-TS, suggesting that IFOF-L axonal structure was preserved. Concerning myelin measures, WB ihMTsat and RDt were different when compared to HC (Z= -3.17, 1.99, respectively). IhMTsat was smaller in the NAWM ($Z = -3.19$), whereas RDt was higher in lesion masks ($Z = 2.62$). Myelin measures were similar to HC in LLL-TS (all Z-scores $< \pm 1$), whereas IhMTsat and RDt were respectively lower and higher to HC in HLL-TS, suggesting that demyelination occurs specifically in these track-sections.

Conclusion: Looking specifically at HLL-TS of bundles of interest appears to be the most promising and robust method to localize anomalies in MS patients. Using only WB measures lacks location specificity, whereas a lesion mask approach does not account for the WM penumbra, which holds important information that might be more sensitive to drug interventions.

Disclosure
FH is a PhD student at USherbrooke and an employee at Imeka Solutions Inc. MDumont is an employee at Imeka Solutions Inc. ME is a MITACS postdoctoral researcher at USherbrooke and Imeka. MDescoteaux is co-owner and chief science officer at Imeka and Pr. at Usherbrooke. SM is an employee and shareholder of F. Hoffmann-La Roche Ltd. MB is an employee of Hays plc and a consultant for F. Hoffmann-La Roche Ltd.

EP0985

Development of an unsupervised, automated segmentation algorithm for enlarged perivascular spaces on 7 tesla magnetic resonance imaging

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Introduction: Enlarged perivascular spaces (EPVS), which are detectable on magnetic resonance imaging (MRI), have been proposed as an imaging biomarker for multiple sclerosis (MS). However, manual quantification of EPVS is time-prohibitive, particularly for longitudinal assessment of EPVS.
Objective: Adapt an unsupervised EPVS segmentation method developed on 3T MRI by Ballerini et al. (2017) to 7T MRI, optimize specificity while maintaining reasonable sensitivity, and provide open-source code.
Methods: 64 adults with MS (45 relapsing remitting, 19 progressive) were imaged using 7T T1w and 3T FLAIR MRI at baseline. A single annual follow-up scan was available for 14 patients, and two annual follow-up scans were available for 43 patients, resulting in 164 total scans. Manual segmentation of T1w baseline scans for three patients was performed by a neuroradiologist for gold-standard evaluation.
For these three scans, we performed a grid search on T1w MRIs of three parameters – two 3D Frangi filter settings and a threshold for labeling a voxel as EPVS. This resulted in candidate EPVS segmentations for each parameter set, with varying sensitivity and specificity for EPVS.
For all EPVS segmentations, we removed candidate EPVS under 0.75mm^3 and then analyzed sensitivity and specificity within normal-appearing white matter and basal ganglia to choose the optimal parameter set.
Results: For the three scans with manual segmentations, the automated method had a specificity of 0.998, sensitivity of 0.233, and accuracy of 0.995. The low sensitivity of the method was due largely to misclassification of EPVS presenting as higher T1w intensities.
For the 161 other scans, automated segmentation was internally consistent within patients. For EPVS segmentations of the normal-appearing white matter, basal ganglia, or both, intraclass correlations were 0.877, 0.901, and 0.883, respectively. This internal consistency was not seen in data generated under the null, where patients were shuffled within years.
Conclusions: We extend an unsupervised EPVS segmentation method to 7T MRI and show it is highly specific, accurate, and internally consistent. The method had low sensitivity, reflecting challenges in identifying small, low-prevalence structures in an unsupervised manner when prioritizing specificity. Partial volume averaging with nearby hyper-intense tissue may also play a role. Supervised approaches or higher-resolution imaging could be explored to address this limitation.

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EP0986

Lack of functional reorganization in the early stages of multiple sclerosis may result in cognitive impairment

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Functional upregulation may be one path through which the brain reorganizes or compensates for structural damage to minimize clinical symptoms in multiple sclerosis (MS) patients. Identification of the mechanism or biomarker of functional reorganization is crucial to better understand the brain's resiliency mechanisms. Brain connectivity analysis provides a promising tool with which to map the effect of MS-related pathology and potentially capture reorganization mechanisms in response to pathology. Our recent study showed that brain's structural disconnectivity (i.e., white matter pathways damaged by MS lesions) and functional connectivity (FC) (i.e., flow of electrical signals) can be successfully estimated from lesion masks using the Network Modification Tool (Tozlu et al., 2021). However, how well this estimated FC (eFC) can reflect functional reorganization and corresponding cognitive resilience is unknown. Therefore, the principal aims of this work are to 1) cluster MS patients using regional eFC and structural disconnectivity and compare the different groups' levels of functional upregulation and structural disconnectivity and 2) identify the regions where

functional upregulation occurs. Four hundred seventy-six MS patients (female: 72%, mean age: 42.33 years) were included in the study. K-means clustering was applied to the regional structural disconnectivity and eFC networks. EDSS, which measures disability, cognitive scores (Symbol Digit Modalities Test [SDMT], California Verbal Learning Test [CVLT], and Brief Visuospatial Memory Test [BVMT]), and demographics were compared between the three optimal clusters. Patients in cluster 2 showed higher structural disconnectivity but lower eFC compared to cluster 1. EDSS scores were similar in clusters 1 and 2, however, the patients in cluster 2 were younger and had shorter disease duration and lower cognitive scores. The patients in cluster 3 had higher eFC and better cognitive scores compared to cluster 2. Specifically, eFC in cerebellum, frontal and occipital lobes was lower in cluster 2 compared to the other clusters. Our approach suggests that the lack of functional upregulation, in particular in the cerebellum, frontal, and occipital lobes, may result in lower cognition. Overall, our study demonstrates that functional upregulation may play a critical role in cognitive resilience to disease pathology.

Disclosure
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EP0987
Brain charts for people living with multiple sclerosis

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Background: Multiple sclerosis (MS) is associated with brain volume loss through the disease course. Ventricular volume has been advocated for as a robust measurement of brain volume based on clinically acquired magnetic resonance imaging (MRI), and can be measured using FDA-cleared automated segmentation methods. However, ventricle volume changes naturally with age and may be susceptible to biases associated with acquisition hardware, imaging protocol, and image quality.
Objective: To establish brain charts for ventricle volume based on MRI for people living with MS that account for demographics and differences in acquisition and image quality.
Methods: 1.5T (n=259) and 3T (n=486) imaging was acquired in 374 people aged 23 to 76 with MS at 5 centers. 13 scanner models from 2 scanner manufacturers used a variety of protocols that included T1-weighted and T2-weighted FLAIR imaging. Quality control metrics were automatically extracted and ventricle volume was measured using FDA-cleared software. World Health Organization-recommended generalized additive modeling for location, scale, and shape was employed to chart expected quantiles of ventricle volume through the age span. Raw volumes were modeled, and results were compared with normalization by and adjustment for intracranial volume (ICV).
Results: Average ventricle volume evolved through the age span in MS ($p<0.001$) and differed across scanner manufacturers ($p<0.01$). Variance in ventricular volume was also associated with contrast-to-noise ratio on T1-weighted imaging ($p<0.03$). Upon visual inspection, plots revealed expected nonlinear increases in ventricular volume with age. Model diagnostics indicated good fit of the model across sites, scanners, manufacturers, and age ranges. Results for ICV-adjusted and ICV-normalized modeling were similar.
Conclusion: Brain charts for people living with MS are a promising method for turning quantitative volumetrics into interpretable knowledge about a patient's disease. Growing databases of heterogeneously acquired MRI in MS will facilitate increasingly precise assessments of brain structure in clinical practice settings.

Disclosure
All authors are employees of Octave Bioscience

EP0988
Differences in N-acetylaspartate concentration in the spinal cord confirm heterogeneity of the double antibody-negative cohort of patients with NMOSD features

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Introduction: Using unsupervised clustering based on MS/NMOSD clinical and imaging discriminators we previously identified four subgroups (termed "MS-like", "spinal MS-like", classic NMO-like" and "NMOSD-like with brain involvement") in the cohort of double antibody-negative patients with NMOSD features
Aim: In this study we examined whether identified subgroups differ in the cervical spinal cord metabolite concentration.
Methods: 25 antibody-negative patients with at least one NMOSD feature underwent MR single-voxel spectroscopy of the cervical spinal cord.
Results: Spectra from 16 patients fulfilled quality criteria and were included in the analysis. The concentration of N-acetylaspartate (NAA), but not inositol or choline, differed significantly between the four subgroups ($p<0.05$). In particular patients in the "MS-like" group had 47.8% lower NAA when compared with patients in the "classic NMOSD-like" group ($p<0.05$). While NAA correlated with disability score in the whole cohort ($r = -0.5$, $p<0.05$), the disability score did not differ significantly between the subgroups to explain subgroup differences in NAA concentration.
Conclusion: Differences in NAA concentration between identified subgroups suggest that the identified subgroups contain patients with distinct disease processes.

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EP0989

Exploring pathological processes in RRMS with synthetic magnetic resonance imaging

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Introduction: Conventional magnetic resonance imaging (MRI) has a high sensitivity for detecting inflammatory disease activity of the brain, but is time-consuming, only semi-quantitative and rely on subjective assessments. On the contrary, the technique called 'synthetic MRI' (SyMRI) use a single pulse sequence, can create contrast-weighted images from quantitative maps based on relaxometry which simultaneously provides automatic brain volume and myelin measurements. All this information is delivered after a single 5-minute scan and the software post-processing time is less than 1 minute. SyMRI enables the measurement of brain volume and myelin content in vivo, which could provide new insights into the relationship between two dominant pathological processes in multiple sclerosis (MS), demyelination and neurodegeneration and the impact of disease modifying treatments (DMTs) on these processes.
Objectives: The aim was to assess brain volume and myelin content over time in patients with relapsing-remitting MS (RRMS) and in healthy control persons.
Methods: We prospectively included 118 patients newly diagnosed with RRMS, one patient with clinically isolated syndrome (CIS), and 51 healthy control subjects (HC). The diagnostic MRI and SyMRI were performed at baseline and at 6, 12, 24 and 36 months. All patients were treated with DMTs. The HC cohort had SyMRI at baseline and at 24 months. Brain parenchymal fraction (BPF) and myelin content (MyC) of the brain were calculated via SyMRI software.
Results: At baseline, there was no significant difference in BPF between newly diagnosed RRMS/CIS and HC (89% and 89.1%, respectively, p=0.87) or in MyC (184 ml and 184.7 ml, respectively, p=0.87). At month 24, BPF and MyC were unchanged in HC compared to baseline. At month 36, the mean change of BPF and MyC in patients was -1% (±1.3) $p<0.001$ and -1.82 ml (±12.46) p=0.052, respectively. While patients with disease activity (clinical and/or contrast enhancing lesion) showed reduced MyC (n=74), the MyC increased in patients who were stable (n=42); -4.56 ml and 2.52 ml, respectively, p=0.028. No significant difference was found in BPF between these groups.
Conclusions: SyMRI showed significant brain atrophy in RRMS/CIS after 3 years of follow up and signs of increased demyelination was found in patients with disease activity. MyC unexpectedly increased in stable RRMS at follow up suggesting remyelination.

Disclosure
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JL has received travel support and/or lecture honoraria and has served on scientific advisory boards for Biogen, Novartis, and Sanofi Genzyme; and has received unconditional research grants from Biogen and Novartis.

EP0990

brain predicted age difference in myelin oligodendrocyte glycoprotein and aquaporin-4 disease

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Introduction: Magnetic resonance imaging (MRI) techniques have been increasingly used to classify patients based on alterations in brain structure. It has been found that Multiple Sclerosis (MS) patients have older appearing brains, resulting in a higher brain predicted age difference (BPAD). It is unknown how this metric is affected in other demyelinating diseases such as myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP4) diseases.
Objectives: To investigate the differences in BPAD in MOG and AQP4 disease in comparison to a MS cohort
Methods: Our cohort consists of 18 patients with MOG antibodies (age±SD: 32±12.9), 16 with AQP4 antibodies (age±SD: 40.7±14.0), and 1913 control MS (age±SD: 44.5±10.5). Structural MRI brain MRI data were collected at multiple timepoints for every patient. We used a trained machine learning model to predict the patient's chronological age using their T1 and T2 MRI scans and explored the differences between predicted brain age and chronological age for all 3 groups.
Results: Using the T1 scans, patients from the MOG group had a significantly higher mean predicted brain age difference of 11.0±17.8 years using their T1 scans, while the mean predicted brain age was 1.4±15.3 years and 2.2±14.5 years for AQP4 and the control MS group respectively. A one-way ANOVA with post-hoc Tukey HSD showed a significant difference in T1-brain predicted age between the MOG and MS control groups (p=0.036).
Conclusions: These findings imply a significant impact on the brain in MOG versus AQP4 disease that warrant further investigation.

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EP0991

Digit Span tests are more sensitive than SDMT to measure cognitive dysfunction and correlate with metabolic dearrangement of deep gray matter nuclei in multiple sclerosis – in vivo MR-spectroscopic study

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Background: The Single Digit Modality Test (SDMT) has been claimed to be one of the most sensitive test to measure attention and information processing speed in multiple sclerosis (MS). However, other brief, easily performed tests may also be as sensitive as SDMT, such as Forward Digit (FD) and Backward Digit (BD) Span tests. Furthermore, advanced MRI methods could help reveal pathological metabolic dearrangement occurring in the cognitively-disabled MS- brains, e.g. the special-edited (Mescher–Garwood technique) proton magnetic resonance spectroscopy (MEGA-^{1}HMRS). This method enables to evaluate metabolites such as N-acetyl-aspartate (tNAA), myoinositol (mIns), choline, and creatine compounds (tCho, tCr), together with neurotransmitters: γ-aminobutyric acid (GABA) and glutamate-glutamine (Glx).
Objectives: In the present study, we used FD, BD, and SDMT tests to measure cognitive dysfunctions in patients with relapsing-remitting MS (RRMS). Moreover, we are supposed to find an association between the results of the cognitive tests and subcortical gray and white matter (G-WM) metabolites using the MEGA-^{1}HMRS.
Methods: The study enrolled 22 patients with RRMS and 23 healthy controls (CON). The MEGA-^{1}HMRS was performed at 3 Tesla MR-scanner Siemens Magnetom PrismaFit. Spectra were evaluated across G-WM (i.e., putamen, caudate nucleus, corpus callosum, thalamus, hypothalamus, and hippocampus).
Results: CON was superior over RRMS patients in all cognitive tests (SDMT: $p<0.001$; FD: $p=0.001$; BD: $p<0.001$). The random Forest statistical method identified the BD as the most sensitive to identifying RRMS patients over CON. FD was also more sensitive than SDMT. Furthemore, FD correlated with GABA/Glx rearrangement in the thalamus and corpus callosum, and SDMT was associated with tCho/tNAA and mIns/tNAA in the thalamus, hypothalamus, and corpus callosum. BD results did not correlate with^{1}H MRS metabolite ratios in any of the brain structures.
Conclusions: FD, BD, and SDMT measure short-term memory and attention. FD memory span has amore substantial attentional component than BD recall measures; however, the BD test is more likely correlated with episodic immediate recall memory attributed to frontal lobe connections and functioning. BD memory span seems superior to SDMT in the detection of MS-specific cognitive dysfunction.

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EP0992

Baseline MRI characteristics of multiple sclerosis patients enrolled in two phase 2 studies of elezanumab

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Introduction: Magnetic Resonance Imaging (MRI) is essential in the diagnosis, prognosis and monitoring of multiple sclerosis (MS) progression and treatment. MRI was collected in two Phase 2 studies of elezanumab (NCT03737851and NCT03737812), an investigational monoclonal antibody neutralizing repulsive guidance molecule A (RGMa) in patients with relapsing (RMS) and progressive (PMS) forms of MS.
Objectives: This work compares the MRI characteristics in RMS and PMS, assesses correlations within MRI characteristics and with clinical measures at baseline.
Methods: MRI from 208 RMS and 123 PMS patients were collected at baseline from 1.5T or 3T scanners, using a standardized protocol including 3DT1, Fluid-Attenuated Inversion Recovery, Magnetization Transfer, PD/T2, Diffusion Tensor Imaging and T1 post-contrast in the brain, and T1, STIR and T2* in the spine. Gadolinium-enhanced lesion, T2 lesion (T2L) and cervical spinal cord lesion (CSCL) counts were collected. Volume of T2L, predefined brain regions and cervical spinal cord area (CSCA) were measured. Magnetization Transfer Ratio (MTR), Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) were estimated in T2L, Normal Appearing White Matter (NAWM) and Whole Brain (WB).
Results: ADC was significantly higher in the PMS group than RMS in NAWM (0.000784 vs 0.000775, $p=0.027$ after adjusting for age and sex). Combining all patients, significant moderate correlations ($|\rho|\sim0.4$-0.6, $p<10^{-5}$) were found between T2L ADC and T2L volume, T2L MTR and volumetric measures, and between WB ADC and T2L counts, T2L volumes and volumetric measures. Weaker correlation was found between gray matter volume and MTR in T2L, NAWM and WB ($|\rho|\sim0.2$-0.3, $p<10^{-5}$). CSCL count and CSCA showed the strongest relationship with the Expanded Disability Status Scale (EDSS) ($R^2\sim0.25$-0.32,$p<10^{-5}$) while correlation with brain results was weaker ($R^2=0.22$, $p<0.001$ with T2L ADC and $R^2=0.18$, $p<0.05$ with T2L MTR). Moderate but significant correlation ($p<10^{-4}$) was found between the Symbol Digit Modalities Test (SDMT) and volumetric measures ($R^2=0.21$ in NAWM) as well as microstructural properties (WB ADC: $R^2=0.15$; T2L ADC: $R^2=0.13$; T2L MTR: $R^2=0.12$) adjusted for age, sex and MS subtype.
Conclusions: Baseline MRI data from the two studies provided a standardized dataset to assess the MRI characteristics of the brain

and cervical spinal cord in MS patients with different underlying pathologies and their relationship with clinical measures.

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Scott Gladstein is an employee of AbbVie Inc., and is receiving stock and/or stock options.
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AbbVie Inc. participated in the study design; study conduct and financial support for this research; collection, analysis, and interpretation of data; and writing, reviewing, and approving of this abstract for submission.
All authors had access to the data; participated in the development, review, and approval of the abstract; and agreed to submit this abstract to ECTRIMS 2022 for consideration as an oral presentation or poster.
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EP0993

Longitudinal assessment of changes in cerebral white matter integrity in MOGAD patients

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Introduction: Myelin oligodendrocyte antibody-associated disease (MOGAD) patients may have abnormal cerebral MRI and white matter (WM) lesions. Further understanding of lesion development and WM changes over time is of high clinical interest.
Objectives: To examine changes in WM lesions and quantify the extent of damage in specific WM bundles of interest over time.
Aims: Utilizing a custom lesion classification system, disconnectome mapping, and diffusion MRI analysis, WM damage in MOGAD patients is assessed in a longitudinal setting.
Methods: 3D T2-weighted and diffusion-weighted MRI were acquired. Lesions were classified into nine location- and neuromyelitis optica spectrum disorder-based categories. Non-zero lesion load was calculated for lateral ventricle, juxtacortical, brainstem and non-specific WM (NSWM) categories. WM disconnectome maps were created and longitudinal changes were evaluated with voxel-based morphometry (VBM) using a multiple regression model with family-wise error correction. Additionally, WM integrity of cortical and thalamus/brainstem edge regions of left and right optic radiation (OR) and corticospinal tract (CST) were examined.
Results: Twelve MOGAD (m:f=4:8) patients (mean age ± standard deviation (SD)=44.48±17.69 years) with a baseline mean disease duration±SD of 5.8±5.33 years were included. Follow-up examinations were carried out at a mean time interval±SD of 1.04±0.1 years. At baseline, patients had a median number of 1 myelitis attacks and 3 optic neuritis attacks.In subsegmentations some patients showed changes in lateral ventricle and NSWM lesion count due toeither lesion conversion or resolution. Total lesion volume remained stable. VBM revealed no significant longitudinal difference in disconnectomes. Paired t-tests of longitudinal differences in mean fractional anisotropy in OR (left:t=-2.19,p=0.051, right:t=-1.41,p=0.186) and CST (left:t=1.12,p=0.289, right:t=-0.87,p=0.403) cortical edge regions and OR (left:t=-0.37,p=0.715, right:t=-1.28,p=0.227) and CST (left:t=0.1,p=0.923, right:t=-1.03,p=0.326) thalamus/brainstem edge regions revealed no significant changes.
Conclusions: Conventional MRI suggested some patients had lesion conversion over time, however disconnectome comparison and simple diffusion MRI-extracted measures did not detect changes in WM integrity. More sophisticated MRI methods such as whole WM-bundle analysis of diffusion metrics could be a promising tool to quantify damage in a personalised manner.

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EP0994

Quantitative susceptibility mapping in multiple sclerosis: a systematic review

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Introduction: The diamagnetic properties of myelin and the paramagnetic properties of iron make quantitative susceptibility mapping (QSM) an attractive candidate for multiple sclerosis (MS) research especially with regard to the characterisation of white matter lesions (WML) (beyond the existence of a central vein) and accumulation of iron in deep grey matter (DGM).
Objective: Systematic review on studies using QSM in MS research.
Methods: A systematic literature search from inception to March 2022 generated 664 publications, of which 41 studies used QSM in MS. The search terms included 'multiple sclerosis', 'clinically isolated syndrome', 'radiologically isolated syndrome', and 'quantitative susceptibility mapping'. The main quantitative findings were different characterisations of WML, the average susceptibility values in DGM subregions, and correlations of QSM findings and MS clinical outcomes. Studies on histological correlates of QSM measures were also systematically reviewed.
Results: Of the five histological studies, four reported significant positive correlation between iron content and the susceptibility values of WML and DGM regions. On WML characteristics, 11 studies reported an average of 14.66 WML per subject visible on QSM, of which 10 recorded an average of 1.70 rim+ lesions, and eight studies reported a mean of 8.64 non-rim lesions. Of the 10 studies, which investigated the association between QSM characteristics in WML and the Expanded Disability Status Scale (EDSS), only five reported significant findings. Only these five studies searched for an association of rim+ lesion frequency with disability (EDSS) and all demonstrated that rim+ lesions are associated with more severe disability. As for DGM, findings of putamen were most consistent. Seven out of 10 studies included age-matched healthy controls (HC) (n = 710); they reported a significant increase of susceptibility in the putamen in MS (n = 1511). Five out of six studies, relating QSM and EDSS, showed that higher susceptibility value in the putamen is associated with higher EDSS; however, we did not find a report of this association controlled for age.
Conclusions: Histological studies indicate that QSM represents a valid method to detect iron in WML and DGM. We found convergent evidence on an association of QSM rim+ lesions with disability and on higher susceptibility value in the putamen in MS than HC.

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EP0995

Clinical and MRI outcomes in pediatric-onset MS patients on ocrelizumab and fingolimod

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Introduction: Fingolimod is approved for pediatric-onset MS (POMS). However, there is limited data on the efficacy of other disease-modifying treatments (DMTs) approved for adult MS, including ocrelizumab, in patients under 18 years. Observational

studies looking at clinical and MRI outcomes of various off-label treatments in children could help inform the design of future clinical trials.

Objective/Aims: To describe clinical and MRI outcomes in POMS patients treated with ocrelizumab and fingolimod.

Methods: This is an analysis of prospectively collected clinical and MRI data from 12 regional clinics participating in the US Network of Pediatric MS Centers. MS patients included in the study started treatment with either ocrelizumab or fingolimod prior to age of 18. New T2 lesions analyses required a minimum of two brain MRIs while on treatment. For gadolinium-enhancing lesions, MRIs performed within the first two months of treatment start were excluded.

Results: Patient characteristics at the time of treatment initiation (fingolimod n=57, ocrelizumab n=25, 41% untreated in the previous 6 months) were similar (mean age: 15.9; 66% females; mean disease duration 1.9 years; median EDSS 1.0; mean years on treatment: 2.3). Mean relapse rate in the year prior to treatment initiation was 0.4 and 0.7 for the fingolimod and ocrelizumab groups, respectively. New T2 lesions during the year prior to treatment initiation occurred in 79% and 77% of the patients on fingolimod and ocrelizumab, respectively. On treatment, 52% on fingolimod vs none on ocrelizumab developed new T2 lesions (mean treatment duration 25.8 and 18.6 months, respectively) and 32.7% on fingolimod vs 8.3% on ocrelizumab developed gadolinium-enhancing lesions. Data on clinical relapses and B cell counts will be presented.

Conclusions: These data will help design future trials to confirm effectiveness of ocrelizumab.

Disclosure

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EP0996

Probing brain microstructural connectivity in patients with early multiple sclerosis using diffusion weighted MRI

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Introduction: Diffusion-weighted imaging (DWI) allows to measure microstructural changes in Multiple Sclerosis (MS), uncovering brain structural connectivity and axonal/myelin injury. Methods such as Diffusion-Tensor Imaging (DTI), and Neurite Orientation Dispersion and Density Imaging (NODDI) show promising results in modelling DWI data, rendering them good candidates for the development of meaningful structural biomarkers of MS.

Objectives: To use NODDI and DTI to model diffusion data and study differences between groups, in tissues such as the Normal Appearing White Matter (NAWM) and lesions in the brain of patients, and the white matter (WM) of the brain in matched healthy controls, and in the whole brain of both groups.

Methods: Diffusion data from 18 patients with Relapsing-Remitting MS (RRMS, mean age 31.92 ± 8.33 years, 10 females, mean Expanded Disability Status Scale – EDSS 2.08 ± 0.88) and 18 healthy controls (CNT, mean age 31.89 ± 8.38 years, 10 females) were acquired on a 3T MRI system with a multi-shell protocol (TR/TE = 3230/89.20ms, voxel size = 1.5mm isotropic, b-value = 1000, 2000 and 3000s/m^2) and modelled using DTI with MRtrix3 and NODDI with the NODDI Matlab toolbox. MS lesions were segmented automatically with Lesion Segmentation Toolbox. Maps of DTI and NODDI parameters were analysed voxel-wise and compared between groups using SPM12 (significance level at $p<0.05$, corrected for false discovery rate), in the whole brain, in the NAWM (RRMS)/WM CNT) and in MS lesions (RRMS)/WM (CNT), using global masks from the combination of the individual lesion maps and from WM segmentation images. Means of Fractional Anisotropy (FA), Apparent Diffusion Coefficient (ADC), Neurite Density Index (NDI) and Orientation Dispersion Index (ODI) were also computed within these tissues to assess differences between groups (with t-test), using masks at the individual level.

Results: Voxel-wise analysis shows decreased FA and NDI in patients in the whole brain, the NAWM and lesions, increased ADC in the whole brain, the NAWM and lesions, and increased ODI in the NAWM. Statistical analysis of the means shows decreased FA and increased ADC in the NAWM and lesions; decreased ODI in lesions; decreased NDI in the NAWM but increased NDI in lesions.

Conclusions: NODDI was able to uncover changes not seen in DTI, such as increased average NDI in lesions, which could be an indicator of the presence of remyelination in early MS patients.

Disclosure

The authors have no conflicts of interest to report.

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EP0997

AI-based characterisation of multiple sclerosis clinical symptomatology using lesion parenchymal fraction: consistency with the topographical model of MS

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Introduction: The clinical-radiological paradox remains a challenge in MS management, as brain lesion burden does not always match symptoms and disability. Two factors help resolve this paradox: lesion location and neurological reserve. The topographical model of MS integrates these factors by depicting localised lesion burden in a pool of variable reserve, with the cervical cord at the shallow end.

Objective: To evaluate the relationship between lesion location, functional systems, and disability using an artificial intelligence (AI) model.

Methods: 57 people with MS (28 RRMS, 29 SPMS, 46 female, baseline age 45±10 yrs) were longitudinally evaluated with MRI and clinical metrics (EDSS and Kurtzke functional system scores [FSS]) with median 2 timepoints, max. 6, follow-up 2.2±2.5 years. Imaging: icobrain was used to measure volume and location of T2-FLAIR lesions on brain MRI, and was adapted to measure T2 lesion volumes on cervical cord MRI. To create a lesion/reserve ratio, localised lesion volumes were divided by whole brain volume, yielding a novel metric, lesion parenchymal fraction (LPF). Modeling: in 500 iterations, patients were split 50/50 into training/testing subsets keeping data from same patients in same tier. Random Forest (RF) regression models were trained to estimate cross-sectional EDSS and FSS. Estimated values from the testing data were Spearman correlated with actual scores and median correlation across iterations was assessed. To evaluate the role of LPF in RF models, two estimator sets were used: 1) simple model: age and sex, and 2) full model: age, sex, and topographical LPF (cerebral, infratentorial and cervical cord).

Results: Spearman correlations between fitted and true clinical scores were highest for pyramidal (R=0.42), bowel/bladder (R=0.35) and overall EDSS (R=0.32). Models including LPF outperformed the simple model in 96%, 94% and 82% of iterations, respectively. For the pyramidal FSS, infratentorial and cerebral LPF were most strongly associated. EDSS was most strongly associated with cervical cord LPF.

Conclusion: Lesion localisation can be mapped to specific functional systems to explicate disease heterogeneity. Lesion parenchymal fraction, an assessment of lesion load/brain volume ratio, is a quantified expression of the topographical model of MS and may be a useful MRI correlate of MS clinical symptomatology. Using this metric, AI techniques can be refined to identify specific thresholds with prognostic implications.

Disclosure

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EP0998

Diffuse white matter pathology in multiple sclerosis and effect of treatment with dimethyl fumarate – a three year longitudinal study of normal appearing white matter using magnetic resonance spectroscopy

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Introduction: Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) with neurodegenerative features and risk for long-term disability progression

in affected individuals. The pathologic mechanisms driving disability progression and to what extent intervention with disease-modifying treatments (DMT) could mitigate such progression needs further investigation.

Objectives: *To investigate diffuse white matter pathology in MS using proton magnetic resonance spectroscopy (^{1}H MRS) in patients treated with dimethyl fumarate (DMF) for three years.*

Methods: In total 26 patients with DMF-treated MS were followed longitudinally for up to 3 years with assessment of absolute quantification of metabolites in normal appearing white matter (NAWM) at baseline and after one and three years. Metabolite concentrations were analyzed both cross-sectionally and in relation to disease course during follow-up. 10 controls without inflammatory CNS disease were used for baseline comparisons.

Results: MS patients had higher concentrations of astroglial marker myo-inositol (mIns) in NAWM compared with controls at baseline ($p<0.01$). The disease duration was negatively correlated with baseline NAWM concentrations of neuroaxnal marker total N-acetylaspartate (tNA) ($r= -0.62$, $p<0.01$) but positively correlated with the baseline ratio of mIns and tNA, mIns/tNA ($r=0.51$, $p=0.03$), reflecting astrogliosis. Except for increasing levels of lactate (Lac), all ^{1}H-MRS metabolites were stable during the three year follow-up treatment with DMF. At all time points, there was a negative correlation between levels of tNA and mIns ($r= -0.44$ to -0.65, $p=0.04$ to 0.004). Disease activity during follow-up was not reflected in changes of metabolite concentrations.

Conclusions: During the three year follow-up period, ^{1}H-MRS metabolite concentrations in NAWM were overall stable. The findings of a consistent inverse relation between levels of neuronal marker tNA and glial marker mIns, as well as the negative correlation between levels of tNA and disease duration, indicate the presence of diffuse white matter pathology associated with long-term progression in this MS cohort.

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EP0999

Detection of MS lesions helps to predict MS disease using artificial intelligence

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Introduction: AI, especially deep-learning methods using CNNs, are much more efficient at detecting and segmenting white-matter lesions automatically. Manual segmentation with tracing of the region-of-interest, lacks in accuracy and is time consuming. Highly sensitive lesion-detection can help identify demyelinating diseases at an earlier stage allowing developing treatments increased likelihood in helping to prevent worsening disability.

Methods: A novel fully-automated algorithm has been developed that can detect and segment both active and non-active lesions from MRI images. Pre-processing, such as skull-stripping, denoising and intensity normalisation, was performed on the original MRI images to improve the results. Datasets consisting of 171 scans from 3 different scanners have been used. For training with validation, 61 scans and testing 110 scans were used. The training data consisted of MRI imaging, had been manually segmented by expert radiologists. Results were instead compared against state-of-the-art algorithms approved for clinical use.

The fully automated method was developed using CNN that consists of two pathways. These pathways have 6 convolutional layers each with decreasing filters size from 256 to 8, such that first CNN layer has 256 filters, second has 128 and so on. Each filter has 3x3 windowing size. The size was selected by comparing results using different filter sizes. Results showed that small windowing size gives better results as the lesions are only 1% of total volume of brain. It also helps to detect the lesions near the cortex. The first pathway is for first prediction, while the second pathway is to reduce false positives. Instead of FC layers, again CNN layers are used for the prediction, as FC layers are complex and computationally expensive making them unsuitable for real time applications.

Results: Evaluations were performed with different evaluation metrics such as sensitivity, precision, and dice-similarity-coefficient (DSC). Overall accuracy of the developed algorithm was 91%. This result is better than most of the state-of-the-art methods report.

Conclusion: A fully-automated algorithm using a novel two pathway technique was developed. The algorithm has successfully detected and segmented white matter lesions with an accuracy of 91%. The developed algorithm is not only fast and accurate but also robust in nature. The robustness was checked by testing with MRI scans from different scanners with different manufacturers.

Disclosure

nothing to disclose

EP1000

Tumefactive demyelinating lesion with MOG antibodies preceding late-infantile metachromatic leukodystrophy

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Introduction/Objective: The development of acute neurological dysfunction associated with tumefactive demyelinating lesions

(TDL) and mild diffuse involvement of the corpus callosum has been described in children as a sentinel event that may allow diagnosis of juvenile metachromatic leukodystrophy (MLD) at an early and potentially treatable stage. We report a child in which this clinico-radiological pattern associated with myelin oligodendrocyte glycoprotein (MOG) antibodies that preceded by several months the onset of progressive symptoms of late infantile MLD.
Methods: Review of symptoms, neuroradiological features, and response to treatment. MOG antibodies were determined in serum and CSF using live cell-based assays.
Results: Symptoms were subacute, focal motor signs and encephalopathy. The patient showed inflammatory TDL on brain MRI associated with high titer of MOG antibodies in serum. After corticosteroid therapy there was an early clinical improvement, resolution of TDL, and negativization of MOG antibodies. Eight months later, neurological regression together with progression of an incipient splenium corpus callossum lesion already present at onset and development of deep white matter tigroid pattern on the MRI lead to the diagnosis of late-infantile metachromatic leukodystrophy (MLD).
Conclusions: Some patients may develop acute steroid-responsive inflammatory demyelinating episodes preceding the onset of the progressive symptoms typical of MLD. Subtle involvement of the splenium of the corpus callosum in association with tumefactive demyelinating lesions (TDL) with or without myelin oligodendrocyte glycoprotein (MOG) antibodies in a child may be a clue for early diagnosis of late infantile MLD. Clinical and radiological improvement of TLD lesions with immunotherapy along with persistence or progression of the splenium involvement should lead to genetic and/or biochemical testing for MLD. The knowledge of this links has important diagnostic and therapeutic implications.

Disclosure
No disclosure of interest

EP1001

Study design: the impact of quantitative structured MRI reports on clinical decision making in MS

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Introduction: There is a lack of objective data measuring the effect of quantitative brain measures such as lesion counts, volumes, and longitudinal regional brain volumes on clinical decisions made by Multiple Sclerosis (MS) Specialist Neurologists (MSNs). This delays the uptake of MS-specific MRI metrics into routine clinical care, ultimately depriving patients with MS the ability to make fully informed treatment decisions.
Objective: This study aims to understand the impact of structured quantitative magnetic resonance imaging (MRI) reports of patients with multiple sclerosis (MS) on MSNs' understanding, reporting, satisfaction, and clinical decision making relative to qualitative standard reports.
Methods: 90 de-identified MS subjects with 2 (median 1 year apart) MRI exams from the University of Basel from 2012 to 2019 were retrospectively enrolled. Three board-certified neuroradiologists (NRs) will interpret raw images to provide a standard or care report (Round 1) and raw images + post-processed data derived from FDA-cleared algorithms to provide a quantitative structured report (Round 2) with a one-month washout period between rounds. 270 sets of reports prepared by the NRs will be randomized 1:1:1 to 3 groups of 2 MSNs. The 6 MSNs will independently review their assigned 90 reports in a similar 2 round format. For each report, MSNs will complete a survey rating the clarity, completeness, usefulness, overall quality, confidence, and satisfaction of the report. The 2nd section of the survey addresses clinically impactful treatment decisions, such as the MSNs impression of disease activity, level of concern for the patient, potential treatment changes, test orders, time to next visit, & follow-up communication.
Results: Statistical analyses will be conducted to compare the MSN-reported ratings, quality, satisfaction, and level of concern for the patient for the standard of care report to the quantitative structured report. These analyses will use the Wilcoxon signed rank test for paired nominal data and McNamar's test for binomial paired data. Inter- and intra-rater agreement analysis will evaluate the degree of agreement between different neurologists and the self-consistency of each neurologist, respectively.
Conclusions: Understanding the effect of standard-of-care vs. quantitative structured MRI reports on clinical decision making is crucial to transitioning quantitative imaging metrics from the research bench to routine clinical practice.

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Lynden Bajus is an employee of Octave.
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EP1002

The evolving pattern of cerebellum atrophy in multiple sclerosis patients treated with natalizumab and its impact on cognition and physical disability

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Introduction: The cerebellum represents a target of neuroinflammation and neurodegeneration in multiple sclerosis (MS). It is a

source of physical and cognitive impairment as it is tightly imbricated into cortico-cerebellar loops with highly cognitive functions.
Objectives: To assess the effect of one specific MS treatment, Natalizumab (NTZ), on cerebellum atrophy evolution and its correlation with the cognitive profile and the progression of physical disability.
Aims: To investigate the cerebellum grey matter (GM) and white matter (WM) atrophy evolution as a potential biomarker of the disease progression and of treatment efficacy.
Methods: We recruited twenty patients diagnosed with relapsing-remitting MS (RR-MS) and treated with NTZ. Over a 4-year-period of time following the initiation of NTZ, we tracked the cerebellum atrophy including both cortical and deep GM and WM using MRI scans processed with an automated image segmentation technique (Freesurfer; version 5.3.0) and we calculated their annual atrophy rates (AAR). We also assessed the progression of physical disability based of the expanded disability status scale (EDSS) annual assessment over the 4 years and the cognitive function evaluated during the fourth year of treatment using a fast battery of tests: the symbol digit modalities Test (SDMT), verbal fluency tests, and 10/36 Spatial recall test (SPART).
Results: During the first two years of treatment, we noted a significant volume loss of the total cerebellum GM (p=0.047). The AAR of the cerebellum GM correlated with greater impairment of SPART delayed recall score assessing memory impairment (p=0.032, r= -0,849). The annual progression rate of the cerebellar function of the EDSS score (0.25 point/year) was correlated with the AAR of the GM of the cerebellum (p= 0.033, r= −0.909). As for the third and fourth years of treatment, a significant atrophy revolved around GM too, mainly the cortical one (p= 0.003).
Conclusion: Cerebellum atrophy in MS patients treated with NTZ is regional and dynamic targeting mainly the grey matter. Pseudo-atrophy phenomenon was commonly described in previous studies and was restrictive to white matter. According to our study, it may include cortical cerebellum GM since meningeal inflammation in the deep folia accommodates a persistent inflammation in direct contact with cerebellum cortex. Thus, cerebellum atrophy specifically could be a marker of physical disability progression and cognitive impairment.

Disclosure
None to declare.

EP1003

Infratentorial lesions as predictors of Long-term disability in clinically isolated syndrome

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Introduction: Abnormalities on baseline brain magnetic resonance imaging(MRI) in patients with initial findings suggestive of multiple sclerosis(MS) are known to predict clinical outcome in terms of disability.
Objectives: To assess the long-term predictive value of baseline MRI infratentorial lesions in patients with initial diagnosis of Clinically Isolated Syndrome(CIS) for the occurrence of clinically relevant disability as defined by an Expanded Disability Status Scale(EDSS) score worsening of 1point or EDSS score of 3.
Methods: Patients enrolled fulfilled these inclusion criteria: 1) Age 15-60years; 2)Diagnosis of CIS after first episode of neurologic dysfunction suggestive of MS; 3)Baseline MRI performed in first 6 months with only one relapse; 4)Minimum follow-up 24 months or progression to clinically definite MS(CDMS).
Results: 316 patients were enrolled, 220(69.6%) women. At initial examination, mean age was 34.22±9.89years. Mean duration follow-up was 70.97±41.3months. Conversion to CDMS occurred in 162(51.3%) patients and 233(73.8%) were diagnosed MS according to 2017-McDonald criteria. Baseline MRI showed infratentorial lesions in 136(43%) patients, asymptomatic infratentorial lesions in 84(26.6**%).**Grouped by number of lesions, 89(28.2%) patients had 1 and 47(14.9%) had ⩾2 infratentorial lesions.Progression in EDSS score of 1point was not significantly related to presence of infratentorial lesions(hazard-ratio:1.47,p=0.15), asymptomatic infratentorial lesions(hazard-ratio:1.17,p=0.6) or existence of⩾2 infratentoral lesions(hazard-ratio:1.81,p=0.11).No significant relationship was found between EDSS score 3 and infratentorial lesions(hazard-ratio:1.37,p=0.16) orasymptomatic infratentorial lesions(hazard-ratio:1.74,p=0.19), but⩾2 infratentorial lesions showed significant relationship with EDSS score 3(hazard-ratio:1.94,p=0.02).
Conclusions: Infratentorial lesions can predict development of clinically relevant and early disability as measured by EDSS score, mostly when having at least 2 infratentorial lesions in baseline MRI.

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EP1004

Evaluation of the relationship of social cognition with structural magnetic resonance imaging measurements in persons with multiple sclerosis

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Background: Social cognitive impairment is an overlooked but essential aspect of disability. Social cognitive skills dramatically affect the lives of pwMS. Identification of underlying structural and functional pathologies is of great importance.
Objective: This study aims to assess the relationship between social cognition and neuroimaging data in multiple sclerosis

(MS). Additionally, the relationship between social cognitive impairment and physical disability was evaluated.
Methods: Thirty-eight persons with MS (pwMS) and 28 healthy controls (HC) were enrolled in this study. Participants underwent the Reading the Mind in the Eyes Test (RMET), Faux Pas Test (FPT), Facial Affect Recognition (FAR) test, Empathy Quotient (EQ), and 2 Minute Walk Test (2MWT), Nine-Hole Peg Test (9-HPT) for outcome measures. All participants underwent 3 T, 3D T1 magnetic resonance imaging (MRI).
Results: No statistically significant differences were observed between MS and HC groups regarding age, gender, education level, and estimated total intracranial volume (ICV) ($p > 0.005$). PwMS performed worse in EQ, upper and lower extremity functions ($p < 0.005$). Impairment was found in 36.8% of pwMS in EQ and RMET and 21.1% of pwMS in FAR and Faux Pas Test. On the other hand, only 17.9% of the HC was impaired in EQ, RME, and FAR Tests, and 14.3% of HC in FPT. Impaired and non-impaired pwMS in each test were compared in terms of cortical and subcortical brain volumes, and there were no significant differences observed in the FPT ($p > 0.005$). There were positive correlations between RMET performance and volume of the left posterior cingulate cortex and right lingual cortex; FAR test performance and the left pericalcarine cortex thickness; EQ test performance and the volume of the left amygdala and left entorhinal cortex ($p < 0.005$). In regression analysis, left amygdala volume was the predictor of EQ performance, contributing to the differences observed between MS and HC.
Conclusion: Social cognition impairment may occur in pwMS, and social cognition is not directly related to depression and physical disability. Social cognitive performance in MS is correlated with the atrophy of areas associated with social cognitive connectivity.

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EP1005
Imaging glial activation and oxidative stress in Progressive MS

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Introduction: There are no FDA-approved treatments that directly address the neurodegeneration characteristic of progressive MS. The activation of microglia and oxidative stress are two processes that have been implicated in neurodegeneration in multiple disease processes, however because of our limited ability to assess these processesin vivo this relationship is not firmly established. Our fundamental hypothesis is that increasing microglial activation correlates with increased oxidative stress and that this may be assessed with cutting edge imaging techniques, utilizing PET and MRS.bPET using the translocator protein (TSPO) radioligand PBR28 is sensitive to alterations in microglial activation, though it is expensive to synthesize and scans may be technically challenging. MR spectroscopy to assess cerebral glutathione is also challenging, but can be reliably performed with modern spectral editing techniques.
Objectives: This goal is to assess the feasibility of using positron emission tomography (PET) and MR spectroscopy (MRS) as markers of glial activation and oxidative stress respectively. We also aim to assess the relationship between microglial activation and cerebral glutathione concentration using these imaging techniques.
Design/Methods: We are currently undertaking a cross-sectional study of 10 subjects with progressive MS and 10 healthy controls. Each subject will have a TSPO PET scan alongside MRS to assess glutathione using a hybrid PET-MR scanner. Our first scan is scheduled for April 26, 2022.
Results: We plan to present the limited results from our initial scans. We will also present the results of our preliminary investigations assessing TSPO binding affinity in our progressive MS cohort based on a previously described single nucleotide polymorphism.
Conclusions: Our proposed project is a vital step toward filling a major gap in our understanding of the links between inflammation and neurodegeneration in PMS. While we will not be able to assess causality, such an association would support the growing body of evidence that link these processes.

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Rebecca Spain: nothing to disclose

EP1006
Accelerated brain volume loss in patients with multiple sclerosis: do real-world observations align with standardized research findings?

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Introduction: Accelerated global and regional brain volume loss (BVL), has recently emerged as an interesting magnetic resonance imaging (MRI) marker of neurodegeneration in patients with multiple sclerosis (MS), correlating with concurrent and future clinical disability. However, validation of these findings in real-world MS populations is still lacking, mainly due to the confounding impact of technical and biological variability.

Objectives/aims: To explore, in a dataset obtained during routine medical follow-up, whether BVL in patients with MS differs from that of healthy controls and/or correlates with measures of clinical disability.
Methods: All MS patients with two brain MRI exams that were suitable for brain volumetry, performed minimum 48 and maximum 60 months apart, were selected from the database of the Belgian National MS Center in Melsbroek. Demographics and clinical outcome measures collected at the same timepoints of the scans (+/- 6 months) were extracted as well and included Expanded Disability Status Scale, Timed 25-Foot Walk Test, 9-Hole Peg Test (9HPT) and Symbol Digit Modalities Test. Brain MRI pairs from a group of healthy volunteers were available from a previous study; both exams were performed under the same methodological circumstances in this cohort, scan interval ranging from 21 to 49 months. Whole brain (WB), white matter (WM), total grey matter (TGM), cortical grey matter (CGM) and deep grey matter (DGM) volumes were measured using icobrain ms software, only retaining MRI pairs with a sufficiently high similarity index in the MS patients, as previously described in the literature.
Results: No differences were observed for annualized WB, WM, TGM, CGM and/or DGM volume percentage change between 72 patients with MS and 27 HCs. Age and gender were similar between both groups. Annualized TGM and CGM volume loss was more pronounced in the MS patients demonstrating a 9HPT score worsening of 20% or more, as compared with those who did not (-1.10 versus -0.37%, $p = 0.005$ and -1.07 versus -0.30%, $p = 0.004$). Deterioration in 9HPT negatively correlated with brain volume changes in TGM and CGM ($\rho = -0.301$, $p = 0.017$ and $\rho = -0.307$, $p = 0.015$, respectively).
Conclusions: This study based on real-world measurements was not able to demonstrate increased BVL in patients with MS. Nonetheless, our results highlight the clinical relevance of grey matter pathology in this disorder and may help to select endpoints for similar projects in the future.

Disclosure
JT has no potential conflicts of interest relevant to this study.
AVR has no potential conflicts of interest relevant to this study.
MMJW is a part-time employee of icometrix.
MB has no potential conflicts of interest relevant to this study.
MBD has no potential conflicts of interest relevant to this study.
GN is a shareholder of icometrix.
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JVS has no potential conflicts of interest relevant to this study.
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EP1007

Thalamic radiomics to predict symbol digit modalities test performance in multiple sclerosis

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Introduction: Thalamic atrophy is correlated with cognitive impairment in Multiple Sclerosis (MS). However, other thalamic features derived from magnetic resonance imaging (MRI) data may also be associated and could help to predict cognitive dysfunction.
Objectives: To predict Symbol Digit Modalities Test (SDMT) performance using high-dimensional "radiomic" features of the thalamus extracted from clinical MRI data.
Methods: Forty-nine MS participants with remitting-relapsing MS from the MS Snapshot study who had both an SDMT measure and a clinical MRI were included (36 Female, mean age=46). In each participant, both thalami were segmented using normalized 3D-T1 weighted images acquired in a 3T MRI scanner and the FreeSurfer 6.0 thalamic subnuclei segmentation tool. Using these thalamic masks, 1158 data features per patient were extracted using the Columbia Image Feature Extractor. These "radiomic" data capture the size, shape, density and density heterogeneity from the right and left thalamus. Multivariate regression analyses (controlling for age, sex, intelligence quotient-IQ and years of education) were performed to identify associations with SDMT, and we attempted to predict SDMT with radiomic features using the Least Absolute Shrinkage and Selection Operator (LASSO) algorithm with 20-fold cross-validation. The cross-validation process was repeated 20 times.
Results: After correcting for multiple hypothesis testing, only one radiomic feature was significantly associated with SDMT: gt_Uni_3Dgt_Para_1 (R^2=0.24, p=0.000035). This radiomic feature captures the volume of the thalamus. The LASSO analysis returned a model with 10 radiomic features predicting SDMT. Among them, LoG_Mean_Gray_Intensity showed the highest LASSO weighting and had a significant positive correlation with the SDMT (R^2=0.309, $p<0.001$).
Conclusions: Despite our modest sample size, we demonstrted that a radiomics approach has the potential to leverage conventional clinical MRI data and uncover thalamus-cognition relationships in MS. This pilot is being extended to a set of 300 MS participants to identify more radiomic features.

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EP1008

Machine learning parcellation of multiple sclerosis lesions into texturally consistent super-voxels for lesion classification

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Introduction: Multiple sclerosis (MS) lesions, which are detectable as white matter hyperintensities (WMHs) on T2-weighted (T2-w) MRI, can form large conglomerates as they accumulate over time. In these conglomerates, lesions can be difficult to isolate into discrete lesion types. Voxel-level supervised machine learning approaches for lesion classification are time-consuming and very noisy; it is challenging to assign a ground truth label to voxels located at the interface between confluent lesion types.
Objectives: To develop an algorithm to parcellate WMHs into super-voxel sub-regions, grouping texturally consistent voxels in terms of spatial proximity and signal intensities.
Methods: Brain T1-w and T2-w MRIs from the ADVANCE (NCT01416181; n = 1,512, patients with relapsing-remitting [RR]MS), ASCEND (NCT01416181; n = 886, patients with secondary progressive MS), DECIDE (NCT01064401; n = 1841, patients with RRMS,) and EXTEND (NCT01797965; long-term extension from DECIDE, n = 1,501) trials were retrospectively analysed. In each T2-w scan, WMHs were delineated by NeuroRX via a semi-automatic method and were further segmented into acute and chronic MS lesion masks, based on the presence of gadolinium enhancement or concurrence with new or enlarging T2 lesions. The mean-shift algorithm was applied to each WMH, using Gaussian kernels of standard deviations 1.5 and 0.3, as well as Euclidean and Mahalanobis distances, for the spatial and intensity domains, respectively. In each super-voxel, the volumetric proportion of acute versus chronic MS lesion activity was measured to evaluate the homogeneity of the resulting super-voxels.
Results: Patients' WMHs were typically parcellated into 500 super-voxels, which had on average a size of 17.1 mm^3, with a median at 7.2 mm^3, and a first and third quartile at 2.5 mm^3 and 19.8 mm^3, respectively. Each super-voxel generally contained a strong volumetric dominance of one lesion class (e.g., acute or chronic) over the other.
Conclusions: Super-voxels were dominantly partitioned within a specific lesion type. This suggests that mean-shift could be used as a pre-processing step enabling voxel-level classification of MS lesion types (e.g., acute versus chronic) from a super-voxel level processing, allowing for faster predictions and improved accuracy for MS lesion classification, resulting from the expected reduction in label noise.
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Disclosure
QS, DI and AC are employees of Therapanacea.
BC, AG, XJ, DB, EF, and SB are employees of and hold stock/stock options in Biogen.
RP was a previous employee of and held stock/stock options in Biogen.
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CE is an employee of NeuroRx.
NP is an employee of Therapanacea, employee of CentraleSupélec, Université Paris-Saclay, French Ministry of Higher Education and Research; holds stock options in Arterdrone and TheraPanacea; receives compensation for editorial services from Elsevier.

EP1009

Magnetization transfer imaging of the whole spinal cord in multiple sclerosis patients

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Context: Magnetization transfer ratio (MTR) has shown promise to assess tissue microstructure modification in MS patients. To date, such exploration has been limited to the brain and the cervical spinal cord (SC) portions of the central nervous system (CNS). Studying the MTR abnormalities in the whole SC could provide a better association with ambulatory disability in MS patients.
Objectives: i) to compare mean MTR values in MS patients and healthy controls (HC) according to the SC level; ii) to describe the link between MTR measurements at the cervical and thoracic SC levels; iii) to evaluate the link between MTR measures and disability according to the spinal cord level.
Methods: 21 relapsing remitting MS (RRMS; median EDSS=2.5), 10 progressive MS patients (PMS; median EDSS=5.25) and 13 HC were scanned on a 3T Siemens MRI scanner. The imaging protocol included 3 MT imaging acquisition slabs to cover the whole SC. For each subject, MTR maps and vertebra labeling were computed using the SCT toolbox. MTR means were computed in semi-automatic delineated SC for the following vertebral levels: C4 to C6, T4 to T6, T9 to T10. Group differences as well as correlations with lesions in the whole SC and EDSS were assessed controlling for age.
Results: Evidence of group difference was only found in the cervical SC (C4C6; mean MTR=41.7pu, 39.4pu, 35.4pu for HC, RRMS and PMS resp.; $p<.001$). No evidence for group difference was found in the thoracic SC. A positive association was found between the mean MTR in the cervical SC and in the thoracic SC (r=.45, p=.01 for T4T6 and r=.54, p=.002 for T9T10) in MS patients. We observed negative associations between mean MTR in the cervical SC and the EDSS score (r=-.51, p=.004) and between mean MTR in the cervical SC and the SC lesion load (r=-.6, $p<.001$), while no clear evidence of correlation was found between SC lesion load and EDSS score (r=.35; p=.084). No evidence of correlation was found between mean MTR in the thoracic cord and EDSS score.
Conclusions: The microstructural damage in the SC of MS patients seems to be predominant in the cervical SC and is linked

to the lesion load and the disability. In our sample data, the added value of exploring thoracic SC in addition to cervical SC using MTR to explain disability in MS patients seems limited. Potential explanations could be the presence of higher variabilities in MTR measurement in the thoracic SC or the preferential location of MS lesions in the cervical SC.

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EP1010
Improving automated lesion segmentation using intensity constraints: the cleaning step

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Introduction: Although a variety of tools for multiple sclerosis (MS) automated lesion segmentation were developed, their performance is still suboptimal. Further, tools relying on manual editing usually do not account for the impact of rater variability (i.e., on manual masks provided by several raters).
Aim: To validate a cleaning step designed to reduce the impact of the inter-rater variability on tools' performance and to refine automated lesion segmentation.
Methods: The cleaning step refines lesion segmentation using sequence dependent intensity constraints obtained from pure tissues at both 3D/2D levels. It was tested on database 0 (DB0, 25 MS patients: 5 with 3D FLAIR/T1W; 10 with 2D FLAIR/PD/T1W; 10 with 2D PD/T2W/T1W); DB1: 100 MS patients with 2D FLAIR/T1W; DB2: 40 MS patients with 3D FLAIR/T1W. On DB0, the DICE spatial similarity index (SI) among the manual masks provided by 2 raters was assessed with and without the cleaning. On DB1/2, the cleaning step was applied to BIANCA, nicMS and lesion growth/prediction algorithms (LGA/LPA) outputs. We then assessed the SI and the number of false positive/negative clusters (nFPC/nFNC) obtained by the tools, in comparison to manual segmentation, with and without the cleaning step.
Results: The cleaning step increased the SI between the two raters (no clean vs with clean: 0.75 ± 0.05 vs 0.87 ± 0.04; $p<0.01$). On DB1/2, the cleaning step i) increased tools' SI (no clean vs with clean, DB1: BIANCA 0.63 ± 0.19 vs 0.72 ± 0.2, nicMS 0.67 ± 0.22 vs 0.8 ± 0.22, LGA 0.33 ± 0.2 vs 0.44 ± 0.25, LPA 0.52 ± 0.19 vs 0.72 ± 0.21; DB2: BIANCA 0.66 ± 0.23 vs 0.75 ± 0.23, nicMS 0.71 ± 0.31 vs 0.83 ± 0.31, LGA 0.6 ± 0.24 vs 0.73 ± 0.24, LPA 0.6 ± 0.21 vs 0.7 ± 0.22; $p<0.01$); ii) reduced the tools' nFPC (no clean vs with clean, DB1: BIANCA 24 ± 21 vs 12 ± 12, nicMS $9+7$ vs 6 ± 6, LGA 1 ± 3 vs 1 ± 3, LPA 7 ± 10 vs 4 ± 6; DB2: BIANCA 18 ± 9 vs 15 ± 8, nicMS 6 ± 9 vs 6 ± 8, LGA 6 ± 5 vs 5 ± 5, LPA 18 ± 22 vs 14 ± 13; $p<0.01$); iii) did not alter the tools' nFNC (no clean vs with clean, DB1: BIANCA 3 ± 6 vs 3 ± 6, nicMS 4 ± 5 vs 4 ± 6, LGA 16 ± 13 vs 16 ± 13, LPA 8 ± 9 vs 8 ± 9; DB2: BIANCA 3 ± 8 vs 3 ± 8, nicMS 5 ± 3 vs 5 ± 3, LGA 13 ± 20 vs 13 ± 20, LPA 6 ± 9 vs 6 ± 10).
Conclusion: The cleaning step increased the inter-rater agreement, thus reducing the source of variability when evaluating tools' results. Its use improved automated segmentation accuracy, irrespective of the tool used, without decreasing sensitivity.

Disclosure
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Imaging and non-imaging biomarkers - OCT

EP1011
Hyperreflective foci in the outer nuclear layer of the retina in relapsing remitting multiple sclerosis

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Introduction: Optical coherence tomography (OCT) enables non-invasive and high- resolution imaging of the retina with the potential to identify small highly reflective dots called hyperreflective foci. Hyperreflective foci may represent aggregates of

activated microglia and has been investigated as a clinically accessible in vivo biomarker in a broad spectrum of retinal disorders. However the pathogenic role of hyperreflective foci in several autoimmune diseases of the central nervous system such as multiple sclerosis are currently unknown.
Objective: To investigate the presence of hyperreflective foci in the outer nuclear layer of the retina in patients with relapsing remitting multiple sclerosis (RRMS)
Methods: This is a cross-sectional exploratory study investigating 88 eyes of 44 RRMS patients and 86 eyes of 43 age- and sex-matched healthy controls (HCs). All participants underwent spectral domain OCT imaging with Heidelberg Spectralis machines. In total 20,880 OCT B-scans were obtained and analysed according to distinct morphological features of hyperreflective foci. Statistical analysis was performed by the use of SPSS Statistics. For evaluating between group differences of quantitative variables, a Mann– Whitney U test was performed according to distribution.The significance level was set at 0.05.
Results: We identified well- circumscribed hyperreflective foci in the retina of patients with RRMS and found that these patients showed a significantly higher number of hyperreflective foci in the outer nuclear layer of the retina compared with HCs ($p < 0.001$). Hyperreflective foci tended to be located toward the centre of the macula (i.e. 64.1% of all hyperreflective foci were located within a 1400 μm distance from the fovea). No association was found between the number of hyperreflective foci and structural OCT parameters (i.e. the mean retinal nerve fiber layer or ganglion cell layer thickness ($p = 0.37$, $p = 0.52$).
Conclusions: This study provides supportive evidence of a potential new pathological finding in RRMS patients. Hyperreflective foci may represent retinal microglia and further prospective studies with larger sample sizes are needed to explore the pathogenic role of hyperreflective foci in multiple sclerosis.

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EP1012
Could be related the RFNL thinning as a predictive for multiple sclerosis severity?

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Introduction: There is an actual need to develop a useful tool to predict a worse prognosis at an initial stage of MS, we suggest the use of optical coherence tomography (OCT) as a prognostic marker related to the severity of MS in a third world country with limited resources.
Aims: The aim of this study was to determine the factors associated with retinal nerve fiber layer (RFNL) thinning in the population with MS and to determine if RFNL thinning is predictive of disease severity at 10 years of evolution.
Methods: We conducted a retrospective, longitudinal study of RFNL analysis by OCT, it was carried out in patients with relapsing remitting MS at the beginning of their recruitment in a tertiary hospital in Mexico as part of their early stratification with a 10-year follow-up.
Results: We enrolled 75 patients with baseline characteristics of which only 54 met the 10-year follow-up criteria of which 55% were female,19 (35%) had low efficacy disease modifying therapy (DMT) and 35 (65%) had high efficacy therapy in the last year, smokers at study entry were 57 (13.9%), 19 (35%) with past medical history of optic neuritis (ON), with mean age of 37.9+- 11.8, mean body mass index of 25.8 +- 3.8, mean RFNL nm of 86.27 +- 10.6, median progression index of 0.22(0.13-0.42), with median disease evolution at study entry of 5.5 years (2-11). In the bivariate analysis, we found a difference in the mean RFNL thickness in overweight and obese patients. (8.36±1.70 vs 10.65±1.97 μm, considering that being overweight increases an OR 2 for risk of thickness less than 85um (95% CI 1.2-3.2,$p = 0.001$). There was no statistically significant difference when comparing the mean RFNL between men and women (83.61±1.51 vs 85.95±2.65 p= 0.42), in patients with EDSS >3.5 vs EDSS ⩽ 3.5 (83.5±1.8 vs 87.27±2.25, p= 0.24), between smokers and non-smokers (83.89±1.72 vs 87.64±2.0, p= 0.3), in patients with and without a history of ON (86.8±2.23 vs 83.48±1.85, p=0.027), in patients with overweight and obesity vs normal weight (8.36±1.70 vs 10.65±1.97 μm, $p = 0.001$), in patients with less than 5 years of evolution vs more than 5 years (84.03±2.4 vs 85.27±1.56, p=0.67) and in patients using high efficacy therapy vs low efficacy (85.96±1.03 vs 84.57 ±1.52, p=0.82).
Conclusions: OCT as a measure of initial stratification by itself is not a useful tool to predict the severity and future behavior of multiple sclerosis.

Disclosure
Nothing to disclose.

EP1013
Association of retinal nerve fiber layer thickness, corpus callosum index and EDSS in multiple sclerosis

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Introduction: Neuroaxonal degeneration is considered the basis of MS disability and is present since the early stages of the disease. Different biomarkers are used both in research and clinical practice.
Objective: To evaluate the association of the peripapillary nerve fibre layer thickness (RNFL) measured by spectral-domain optical coherence tomography (OCT), the corpus callosum atrophy by means of the corpus callosum index (CCI) and the Expanded Disability Status Scale (EDSS) in patients with MS.
Methods: Cross-sectional and longitudinal analysis. RNFL thickness was recorded with a mean estimate of OCT-derived measurements for the two eyes in case of not having a history of optic neuritis (ON) or the value of the unaffected eye in the case of prior history of ON. A cut-off <=88um was used for categorical analysis. Global and regional (anterior, middle, posterior) CCI was calculated on sagittal T1-weighted MRI performed within 3 months of OCT. The last EDSS recorded has been included as an outcome of interest.
Results: 57 patients with MS, median age 35(16-73)years, women 40(70.2%), relapsing/progressive phenotype 47(82.4%)/10(17.6%), median baseline EDSS 2.5(1-7), median disease duration 7(0-40)years, median follow-up since OCT 2(0-4)years. History of ON was present in 23(40.3%), (9 at the onset of the disease and 14 during follow-up). 49(86%) patients were on disease-modifying therapies (DMT), 19(39%) on platform DMT (interferon beta 1a or glatiramer acetate) and 30(61%) on high-efficacy DMT (fingolimod or anti-CD20). The median of RNFL was 90um (54-119.5), 26(45.6%) patients had RNFL ⩽ 88 um, and the mean global CCI was 0.38+0.05. A partial correlation was observed between RNFL and posterior CCI(Rho 0.33, p=0.025), and between RNFL and last EDSS (Rho -2.93, p=0.03), adjusted for age and disease duration. In the univariate analysis, a baseline RNFL ⩽88 μm was associated with a worse EDSS (median EDSS 3.5 vs 2.0, p=0.05) with a median follow-up of 2 years. No statistically significant differences were observed in baseline EDSS or follow-up between both groups. In the linear regression, age (B 0.64, p<0.001) and global CCI (B-0.39, p=0.001) were independent predictors of worse last EDSS.
Conclusion: RNFL thinning was correlated with posterior corpus callosum atrophy and worse EDSS by the end of follow-up in the univariate analysis. In this small cohort with a short time of observation, age and global CCI were the main independent predictors of worse EDSS.

Disclosure
nothing to disclose

EP1014
Optical coherence tomography angiography in MS patients

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Introduction: Optical coherence tomography angiography (OCT-A) is a new imaging method that allows quantification of retinal vascular density in neurodegenerative and inflammatory diseases. It is a non-invasive technique without dye. OCT-A has been reported to be useful in the diagnosis and understanding of many retinal diseaes, however there are very few reports using OCT-A in patients with multiple sclerosis.
Objective: To investigate vascular changes and vessel density in macular and peripapillary regions detected by OCT-A in multiple sclerosis (MS) patients with and without neuritis.
Methods: Twenty-eight MS patients clinically stable within the last six months and with a follow-up of more than six months were examined. A complete ophthalmological study was carried out, assessing both visual function and retinal microvasculature using the OCT-A Heidelberg Spectralis device. We compared patients with and without optic neuritis.
Results: 56 eyes were analysed. 18 eyes suffered from a previous optic neuritis and 38 had no s episodes of optic neuritis in the past. The mean vessel thickness in macula in patients with previous optic neuritis was clearly lower (230.33μ±22.29μ) than in patients without previous optic neuritis (250.47μ±25.18μ) (p-value=0.007). All sector showed significant differences between eyes with or without previous optic neuritis with the exception of the external lower sector (p-value=0.072).
Otherwise, the macular vessel volume showed differences in patients with previous optic neuritis (2.16μ ± 0.17μ) and without previous optic neuritis (2.27μ ± 0.18μ) (p-value=0.015).All sectors are significantly reduced except the lower outer sector (p-value=0.012).
Conclusions: MS patients with ON have a significant retinal vascular loss compared to patients without previous neuritis. Retinal vessel density could represent a novel early biomarker to monitor the MS pathological burden.

Disclosure
C Oreja-Guevara has received honoraria for speaking and serving on advisory boards from Biogen Idec., F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck, Janssen, BMS, Novartis and Teva. J Quezada-Sánchez, J Díaz-Díaz, I Gómez-Estévez and E Alba-Suárez report no relevant disclosures.

EP1015
Optical coherence tomography angiography as a measure of dynamic retinal vascular changes in early demyelinating disease: 6 month follow up

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Introduction: Vascular disease plays an important role in MS disability, and may provide an early clue to disease progression. Our working model is that early vasculopathy damages blood-brain

barrier (BBB) integrity, facilitating infiltration of leukocytes and driving focal inflammation. We propose that antecedent vasculopathy due to presence of microvascular disease predisposes pwMS to increased BBB permeability and thus leaves them susceptible to more active, inflammatory disease. Optical Coherence Tomography Angiography (OCTA) is a novel, non-invasive measure of microvasculopathy in MS and other diseases. This technique builds on optical coherence tomography (OCT), which has shown retinal nerve fiber layer thinning is common in MS and serves as a correlate to brain atrophy and overall patient disability. OCTA combines the structural data from OCT with microvascular data in the retina and thus provides an in vivo assessment of both structural and microvascular changes in MS. We hypothesize that microvascular changes in the retina in patients with early demyelination will correlate with visual and neurological disability.

Objectives: Characterize microvascular changes in the retina in early demyelinating disease to identify baseline vasculopathy in people with multiple sclerosis (pwMS).

Methods: Fifteen participants with early demyelination were enrolled in a 6-month, prospective, observational study evaluating OCTA and visual measures, including visual acuity, low contrast acuity, and visual quality of life.

Results: Fifteen participants with early demyelination were enrolled in a 6-month, prospective, observational study. Mean age was 32.1 years and average disease duration was 2 years. 20% (n=3) report history of unilateral optic neuritis and 20% (n=3) report history of bilateral optic neuritis. Cross-sectional OCTA data showed no significant difference in vascular density in macular SVC (MS M = 0.60, SD = 0.075) and HC M = 0.62, SD = 0.59; t(df) = 67, p = 0.10; peripapillary NFLP (MS M = 0.68, SD=0.074) and HC M=0.67, SD=0.008; t(df) = 71, p = 0.61; or peripapillary SVC (MS M = 0.81 SD = 0.01) and HC M= 0.80, SD = 0.007) t(df) = 71, p=0.18 at baseline using paired t-tests. Pending analysis will evaluate longitudinal changes in microvascular density.

Conclusions: This pilot study evaluates longitudinal, microvascular changes in the retina in early demyelinating disease as a method to identify baseline vasculopathy in pwMS.

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EP1016
Retinal degeneration in multiple sclerosis and myelin oligodendrocyte glycoprotein-associated disease: a comparative longitudinal Italian OCT study

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Background and aim: Data about Optical Coherence Tomography (OCT) in patients with Myelin Oligodendrocyte Glycoprotein-antibody associated disease (MOG-AD) compared with relapsing remitting multiple sclerosis (RRMS) patients are lacking. We investigated OCT features in a cohort of MOG-AD and RRMS patients.

Methods: We obtained OCT scans from MOG-AD and RRMS patients referred to IRCCS Mondino Foundation (Pavia). We compared retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thicknesses among MOG-AD and RRMS groups.

Results: Our cohort included 34 patients (13 MOG-AD and 21 RR-MS; male/female ratio: 6/28). Mean age was 35 years (SD 9.6). At disease onset, 20 patients experienced optic neuritis (ON; 10 RRMS and 10 MOG-AD), 4 had myelitis with motor symptoms,10 sensory symptoms. OCT scans were obtained in remission phase at mean 2.9 years (SD 3.4) from disease onset.

Considering 20 eyes with ON, mean GCL thickness was lower in RRMS (65 μm, SD 9) than in MOG-AD (70 μm, SD 9). In unaffected eyes mean GCL thickness was similar between groups (79 μm in RRMS and 81 μm in MOG-AD). Considering 14 patients without history of ON, mean GCL and RFNL were similar between RRMS (82 and 98 μm, respectively) and MOG-AD (82 and 100 μm).

In 8 patients with ON (4 RRMS and 4 MOG-AD) we obtained a follow-up (FU) OCT at 1 (SD 1,8) mean year since the first one; no ON relapses occurred in FU period. Mean percentage of GCL reduction in affected eyes at FU was similar among groups (0,025% in RRMS-0,017% in MOG-AD).

Conclusions: According to our data,GCL thickness in RRMS patients with ON is lower than MOG-AD, suggesting that ON in RRMS could be more severe. Thinning rates over time seem to be quite overlapping among groups, indicating that the entity of neurodegeneration after ON could be similar in the two groups.

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Imaging and non-imaging biomarkers - Fluid Biomarkers

EP1017
Do overweight and obesity fuel kynurenine pathway overactivation in persons with MS? A cross-sectional study

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Introduction: Multiple sclerosis (MS) is characterized by a pathologic overactivation of the kynurenine pathway (KP), as indicated by an elevated kynurenine-to-tryptophan ratio (K/T ratio). The K/T ratio correlates positively with disease severity. A high BMI is a critical metric for MS, as it is a causal factor to MS susceptibility and may also promote MS pathophysiology by fuelling inflammation-mediated KP overactivation. A positive relation between BMI and K/P ratio has already been shown in healthy humans.
Objective: To investigate KP metabolite concentration differences between normal weight and overweight/obese persons with MS (pwMS), classified by BMI.
Aims: Evaluating the impact of overweight/obesity on KP activity, considering (I) K/T ratio and (II) concentrations of KP downstream metabolites in pwMS.
Methods: For this cross-sectional study, we used baseline data of 98 pwMS with an Expanded Disability Status Scale (EDSS) score $\leqslant$ 6.5 that participated in a larger randomized controlled trial (NCT04356248). Participants were retrospectively classified as normal weight if BMI was 18.5–24.9, or as overweight/obese if BMI was $\geqslant$ 25. Targeted metabolomics (high-performance liquid chromatography coupled with tandem mass spectrometry) was used to determine resting serum concentrations of KP metabolites. K/T ratio was calculated as serum concentration of kynurenine (µmol/L) divided by serum concentration of tryptophan (µmol/L). Independent samples t-test was performed to assess between-group differences, with $p \leqslant .05$ indicating statistical significance. The effect size was calculated using Cohen's d.
Results: According to BMI, 54 pwMS have been classified as normal weight and 44 pwMS as overweight/obese. Age and EDSS score did not differ between groups. Overweight/obese pwMS (26.69 $\pm$ 7.45) revealed significantly higher K/T ratio than normal weight pwMS (22.96 $\pm$ 7.59) (p=.018, d= 0.5). Moreover, overweight/obese pwMS presented with significantly higher concentrations of KP downstream metabolites, such as quinolinic acid.
Conclusion: High BMI indicative of overweight/obesity seems to promote KP overactivation in pwMS. However, replication of results and considerations on clinical relevance require future prospective studies.

Disclosure
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EP1018

Could high sensitivity ELISA method be an option to determinate serum neurofilaments in patients with multiple sclerosis?

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Introduction: Neurofilaments are the most promising biomarker in patients with multiple sclerosis (MS). One of the possible methods for detection of serum neurofilament light chain (NfL) is the single molecule array (SIMOA). Recently, a new high sensitivity enzyme-linked immune sorbent assay (hs-ELISA) was introduced too.
Objectives: This study objective was to compare the serum NfL and neurofilament heavy chains (NfH) concentrations by using the SIMOA versus hs-ELISA in patients with known MS.
Methods: Serum samples were collected from MS patients attending our MS centre, University Hospital Ostrava (Czech Republic). The concentrations of NfL and NfH were determined by SIMOA (NF-light™ Advantage Kit HD-1/HD-X, REF 103186; pNF-heavy Discovery Kit HD-1/HD-X, REF 102669; Quanterix Corporation) and hs-ELISA assays (Nf-light serum ELISA, REF 30210101, UmanDiagnostics AB; Neurofilament (pNf-H)-high sensitive ELISA, REF Q6562-9601, Euroimmun AG). To compare both these methods, we used a nonparametric Spearman correlation and Passing-Bablok regression analysis. For comparison of systematic difference, Bland-Altman plot was performed. All analyses were conducted with the Stata Statistical software version 17.
Results: The medians of NfL (n = 31) for SIMOA vs. hs-ELISA were: 11.7 (interquartile range [IQR] 9.5 – 17.3) pg/mL vs. 8.6 (IQR 6.0 – 13.0) ng/L. The medians of NfH (n = 32) for SIMOA vs. hs-ELISA were: 34.8 (IQR 9.3 – 53.4) vs 6.0 (IQR 1.7 – 27.3) ng/L. The Spearman´s correlation coefficient between the NfL SIMOA and NfL hs-ELISA and between the NfH SIMOA and NfH hs-ELISA was moderate r_s= 0.553 (p = 0.001) and r_s= 0.583 (p = 0.001), respectively. A significant bias between these methods was demonstrated by the Passing-Bablok analysis. The equally significant bias between the methods was confirmed by a Bland-Altman plot, where a significant dependence of the differences on concentration was found. The differences between the methods were greater than the clinically allowed errors (25%).
Conclusions: The methods do not give identical results in patients, as follows from the statistically significant bias, and the individual differences between the methods provide greater differences than the clinically acceptable error. At the same time, due

to the low coefficient of variation, the results cannot be recalculated among patients.
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Disclosure:
The authors declare no conflicts of interest regarding this study.

EP1019

Glial fibrillary acidic protein and multiple sclerosis progression independent of acute inflammation

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Introduction: Cross-sectional associations between glial fibrillary acidic protein (GFAP) and multiple sclerosis (MS) subtypes, disease severity, relapses, and MRI inflammatory activity have been documented. The clinical relevance of serum GFAP (sGFAP) as a dynamic biomarker of MS disability progression independent of acute inflammation has yet to be quantified.
Objectives: To test whether longitudinal changes in sGFAP concentrations are associated with disability progression in the absence of relapse and MRI signs of inflammatory activity.
Methods: We retrospectively analysed longitudinal sGFAP and clinical outcome data from the Phase 3 ASCEND study, which assessed the efficacy and safety of natalizumab in participants with secondary progressive MS. Clinical outcomes included Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), and the Confirmed Disability Progression (CDP) based on the composite of all three outcomes. sGFAP concentration was measured in samples collected at baseline, week 48, and week 96 by Single Molecule Array (Simoa®) technology on an HD-1 instrument using the NF-light™ Advantage Kit, as described by the manufacturer (Quanterix, Billerica, MA, USA). Analyses were performed on the intention-to-treat population with available sGFAP samples across all 3 timepoints and no detectable relapse or MRI signs of inflammatory activity at baseline or through the course of the study (n =303). Associations between sGFAP concentration changes and clinical outcomes (EDSS, T25FW, and 9HPT) measured at baseline, week 48, and week 96 were assessed using generalized estimating equations; associations between CDP and sGFAP changes were analyzed using logistic regression. The main outcomes were the correlations, 95% confidence intervals, and odds ratios for sGFAP as a biomarker and/or predictor of current disability status or future disability progression.
Results: In the absence of clinical and MRI signs of acute inflammation no or only weak correlations between changes in sGFAP concentration and changes in EDSS, T25FW, and 9HPT were observed in either the treatment or placebo arms. Similarly, changes in sGFAP concentrations over time were not associated with short or longer-term composite CDP.
Conclusions: In this study of participants with progressive MS without inflammatory activity, changes in sGFAP concentration were neither associated with nor predictive of disability progression.

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Disclosure
ARG, XJ, CS, CMS, BC, EF, CdM, and SB are employees of and hold stock/stock options in Biogen.

EP1020

NFL as a predictor of GdE lesions in patients with relapsing multiple sclerosis treated with ozanimod in the phase 2 RADIANCE trial

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Introduction: In patients with multiple sclerosis (MS), neurofilament light chain concentration (NfL) is increased in blood and cerebrospinal fluid, and may serve as a biomarker for neurologic damage and disease activity. In phase 3 trials of ozanimod in patients with relapsing MS (RMS), higher baseline plasma NfL (pNfL) was associated with higher brain MRI lesion counts, lower baseline brain volume, and greater likelihood of on-treatment relapse. Ozanimod treatment reduced pNfL; greater pNfL reduction was associated with fewer new brain MRI lesions, less brain atrophy, and fewer relapses.
Objectives: To evaluate pNfL as a predictor of gadolinium-enhancing (GdE) lesion count and vice versa in patients with RMS treated with ozanimod 0.92 mg in the phase 2 RADIANCE trial (NCT01628393).
Methods: pNfL was measured at baseline and weeks 4, 12, and 24 using Simoa Nf-light digital immunoassay (Quanterix, Lexington, MA). GdE lesion counts were assessed from available MRI scans at baseline and weeks 8, 12, 16, 20, and 24. Predictive modelling was performed using penalized logistic regression on 100 bootstrap samples.
Results: In patients treated with ozanimod 0.92 mg, a decrease in pNfL was observed at week 4 (median [Q1, Q3] % change from baseline: −7.891 [−18.933, 14.486]), with further decreases

through week 24 (−15.883 [−32.039, 1.759],P<0.0001). GdE lesion counts were lower in patients treated with ozanimod vs placebo at week 8 (mean [SD] 1.096 [2.346] vs 2.267 [5.660]) and at week 24 (0.193 [0.594] vs 3.153 [9.984]). Patients who relapsed had higher baseline pNfL and week 24 GdE lesion counts than non-relapsers (median [Q1, Q3] pNfL pg/mL: 11.597 [8.107, 14.474] vs 10.939 [7.541, 15.123]; mean [SD] GdE lesion count: 0.333 [0.707] vs 0.176 [0.582]). pNfL decreased from baseline more at week 4 in patients without vs with on-study relapses (median [Q1, Q3] % change from baseline: -7.891 [-19.475, 12.030] vs 0.389 [-17.513, 31.415]). Week 12 and week 24 pNfL were the best predictors of week 24 GdE lesion count. Week 12 GdE lesion count was the best predictor of week 24 pNfL.

Conclusions: In phase 2 RADIANCE, ozanimod 0.92 mg reduced pNfL from baseline and was associated with fewer GdE lesions than placebo in patients with RMS. pNfL at week 12 and week 24 predicted GdE lesion count at week 24; GdE lesion count at week 12 predicted pNfL at week 24. This analysis is unique in that few randomised clinical trials have such frequent plasma sampling and MRI scans.

Disclosure

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Disclosures

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XM: Speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past 3 years with Actelion, Alexion, Bayer, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, EXCEMED, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, Merck, Mylan, MSIF, Nervgen, NMSS, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceuticals, and TG Therapeutics.

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EP1021

Evobrutinib, a Bruton's tyrosine kinase inhibitor, decreases neurofilament light chain levels over 2.5 years of treatment in patients with relapsing multiple sclerosis

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Introduction: Evobrutinib (EVO) is a highly selective Bruton's tyrosine kinase (BTK) inhibitor. A prior post hoc analysis of a Phase 2 trial of EVO in patients with relapsing multiple sclerosis (pwRMS; NCT02975349) showed that EVO 75mg twice-daily (BID) significantly lowered neurofilament light chain (NfL) levels from baseline (BL) at Weeks (W) 12 and 24.

Objectives: To assess the long-term treatment effect of EVO on blood NfL levels in patients with relapsing multiple sclerosis (pwRMS).

Methods: Levels of NfL were measured (Simoa NF-light™) in the double-blind (DB) arms of the intent-to-treat (ITT) population. During the 48W DB period (DBP), pwRMS received placebo (PBO; switched to EVO 25mg once-daily [QD] at W24), EVO 25mg QD, 75mg QD or 75mg BID. Patients participating in the open-label extension (OLE) after the DBP received EVO 75mg QD and then, after a mean of 49.8W, switched to EVO 75mg BID. NfL levels were reported as age and BMI adjusted median (interquartile range [IQR]) percentiles based on healthy controls (Benkert et al., Lancet Neurol. 2022) to OLE W96 (144W of treatment). Treatment effects versus PBO/EVO 25mg QD, up to DBP W48 were reported as estimated mean differences, based on a mixed effects model using Z-scores as dependent variable, in the modified ITT and patients with BL and ⩾1 post-BL NfL value.

Results: The median BL NfL level was 11.4 pg/mL. BL, W48 (DBP) and OLE W96 median (IQR) percentiles, respectively, were: PBO/EVO 25mg QD/75mg BID: 90.5 (51.0, 99.1), 81.0 (31.0, 92.0), 54.5 (29.0, 83.0); EVO 25mg QD/75mg BID: 87.0 (32.0, 98.4), 70.5 (38.0, 90.0), 51.0 (36.0, 75.0); EVO 75mg

QD/75mg BID: 91.5 (55.0, 98.0), 59.0 (34.0, 91.0), 49.0 (19.0, 76.0); EVO 75mg BID: 87.0 (56.0, 99.0), 55.5 (24.0, 78.0), 45.0 (30.0, 79.0). Estimated mean NfL Z-scores dose-responses were observed at DBP W12, 24 and 48; with EVO 75mg BID these NfL Z-scores were significantly reduced from W12 (W12: -0.46, p=0.01; W24: -0.41, p=0.03; W48: -0.53, p=0.01).

Conclusion: At the group level, EVO reduced and normalised NfL levels up to 144W of treatment. EVO 75mg BID (fasted dose – equivalent to 45mg BID fed dose in Phase 3) significantly reduced NfL levels from W12 (DBP), compared with PBO/EVO 25mg QD, showing an early dose-response, W12–48. This reduction in NfL provides evidence that EVO markedly reduces neuroaxonal damage in pwRMS.

Disclosure

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EP1022

Myeloid-derived suppressor cells are good biomarkers of fingolimod efficacy in multiple sclerosis

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Introduction: The increasing number of available treatments for multiple sclerosis (MS) highlights the need for biomarkers for individualized medicine. Fingolimod (FTY720), an oral disease modifying treatment approved for relapsing-remitting MS, acts as a sphingosine-1-phosphate receptor modulator preventing lymphocyte egress from lymphoid tissues. However, it has been described that it promotes the immunosuppressive activity of Myeloid-Derived Suppressor Cells (MDSCs), a cell type which can be used as biomarker of disease severity in MS and of the degree of demyelination and axonal damage extent in its animal model, experimental autoimmune encephalomyelitis (EAE).

Objective/aim: We interrogate whether the abundance of MDSCs at the onset of EAE or prior to start treatment in MS patients can be related to a better response and higher efficacy to fingolimod.

Methods: In EAE, treatment with vehicle or FTY720 was orally administered for 14 days in an individualized manner, i.e. the day wheneach mouse began to develop clinical signs. Peripheral blood from EAE mice was collected previous to treatment and human peripheral blood mononuclear cells (PBMCs) were collected from MS patients at baseline, 6 and 12 months after fingolimod treatment. In both cases, different immune cell populations were analyzed by flow cytometry. According to the clinical response, a patient was considered as responder when met two or more criteria of NEDA-3 12 months after treatment.

Results: MDSC content in the peripheral blood of FTY720 treated animals was associated with a milder EAE disease course

with a less demyelination and axonal damage. However, a small proportion of the FTY720 treated mice showed a clinical course similar to vehicles (non-responders), which was invariably associated to a very low abundance of MDSCs prior to treatment initiation. Remarkably, higher MDSC abundance also revealed to be an important parameter to distinguish EAE mice prone to respond to FTY720 with a higher efficacy. Cox regression analysis showed that FTY720 effectiveness was related to MDSC abundance and independent of other clinical or immunological variables. Lastly, a higher MDSC abundance in MS patients at baseline allows the identification of responders to fingolimod treatment after 12 months of follow-up.

Conclusion: In sum, our data indicate that MDSCs may be good biomarkers for fingolimod responsiveness and treatment efficacy in MS.

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EP1023

Monitoring of treatment with dimethylfumarate using microRNAs as biomarkers in people with multiple sclerosis

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Introduction: Dimethylfumarate (DMF) is one of the most frequently used oral drugs for the treatment of people with multiple sclerosis (pwMS). However, about 61% of DMF-treated pwMS develop lymphopenia during treatment, leading to an increased risk of progressive multifocal leukencephalopathy (PML) and consequentially a discontinuation of DMF. Therefore, biomarkers to monitor treatment response and lymphopenia would be highly useful.

Objective: We aimed to investigate microRNAs (miRs) as biomarkers for predicting the development of lymphopenia and treatment response in DMF-treated pwMS as miRs are stable, highly conserved and easily obtained biomarkers as has been proven already in other clinical contexts.

Methods: 16 microRNA candidates were identified in isolated T cell populations of a screening cohort of 6 DMF-treated index patients using TaqMan Expression Array Cards. These candidates were then validated in serum samples from 48 DMF-treated pwMS at baseline, month 6 and month 12 using quantitative real-time PCR (qRT-PCR).

Results: Of the 48 enrolled pwMS, 80% responded to DMF therapy (defined by NEDA-3 criteria) and 30% developed lymphopenia within the first year of treatment (64,3 % grade 1 ($<1*10^9$ lymphocytes/L), 35,7 % grade 2 ($<0.8*10^9$ lymphocytes/L)). Descriptively significant changes in miRNA expression from serum samples of pwMS were most evident at 12 months: during DMF therapy, miR-15b-5p (p=0.0102) and miR-339-5p (p=0.0039) showed increased expression levels in our cohort. Subgroup analysis showed that the following miRs were upregulated only in non-lymphopenic pwMS, but not in lymphopenic patients: miR15-5p (p=0.0204) and miR-339-5p (p=0.0071). miR-629-3b (p=0.0371) was increased only in lymphopenic patients. Responders to DMF-treatment showed an upregulation of miR-339-5p (p=0.0307), while non-responders showed an upregulation of miR-15b-5p (p=0.0312) and miR-28-5p (p=0.0312).

Conclusion: This study identifies miR-15-5p, miR339-5p, miR-623-3b and miR-28-5p as potential biomarkers for DMF-treatment response monitoring in pwMS. Further studies are needed to confirm these effects in larger cohorts. In addition, the relevance of these miRs candidates for the molecular mode-of-action of DMF should be investigated in more detail.

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EP1024

Impact of 2015 neuromyelitis optic spectrum disorders consensus diagnostic criteria and neurofilament light chain levels as biomarker of severity according to the presence of anti-AQP-4 and anti-MOG

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Introduction: Neuromyelitis Optic Spectrum Disorder (NMOSD) is a severe Central Nervous System (CNS) inflammatory and autoimmune disease, preferentially affecting the spinal cord and optic nerves. Advances in diagnostic criteria have allowed greater diagnostic sensitivity and specificity, and also the inclusion of patients without antiaquaporin-4 antibody (AQP-4 ab).
Objectives: To assess the impact of the 2015 consensus diagnostic criteria for NMOSD in patients from HUCFF Neurology Clinic, followed up for 20 years, discussing the demographic characteristics, and correlate AQP4-ab status with Nuerofilament (NfL) levels.
Methods: Bidirectional, descriptive study, lasting 48 months. Of the 720 patients at the HUCFF Demyelinating Diseases outpatient clinic, 59 consecutive patients who met the 2015 diagnostic criteria for NMOSD were included, after consensus and signing of the informed consent. Patients underwent anamnesis, laboratory tests and neuroimaging. Part of the aliquots were separated for immunological investigation. The immunological investigation included the measurement of anti-AQP4 and anti-MOG antibodies, using the cell-based assay (CBA) method. Among these patients with NMOSD, 36 patients were analyzed for NfL analysis. NfL concentration was measured in duplicate by ultra-sensitive single molecule array (Simoa).
Results: 59 cases were included in this work. The application of the 2015 criteria impacted the diagnosis, increasing the classification of patients as NMOSD by 45%. The proportion of patients with positive AQP4+ (50.8%) was higher than for negative patients (30.5%). Patients with unknown serology represented 16.9% and those with positive anti-MOG, 1.7%. Patients during relapse NMOSD had an increase in NfL compared to non-relapse patients and healthy controls ($p<0{,}001$). Patients with non-relapse NMOSD had also significant NfL concentrations ($p< 0.001$) relative to healthy controls. Independently of relapse moment, AQP-4 ab (+) patients present significant higher level of NfL compared with AQP-4 ab (-) ($p<0.01$).
Discuccion/Conclusions: The application of the 2015 diagnostic criteria impacted the classification of patients, allowing the inclusion of AQP-4 ab (-) patients, which increased the diagnosis rate by almost 45%, compared to 2006 criteria. Otherwise, the NfL high level may represent not only a biomarker of active disease, but also suggest a more severe and neurodegenerative course in AQP-4 ab (+) group of patients.

Disclosure
nothing to disclose

EP1025

Plasma neurofilament light chain and glial fibrillary acidic protein levels correlate and are elevated in people with progressive multiple sclerosis

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Introduction: Blood biomarkers to aid in sensitive monitoring remain a critical unmet need for people with progressive and relapsing remitting multiple sclerosis (PwPMS; PwRRMS). While blood neurofilament light chain (NfL) is elevated in PwMS, some PwPMS have comparably low NfL levels despite clinical progression. Additionally, the interpretation of elevated plasma NfL without evidence of disease progression remains unclear. Glial fibrillary acidic protein (GFAP), an astrocyte cytoskeleton protein, is an emerging biomarker that may add clinical prognostic value.
Objectives: To define the relationship between blood NFL and GFAP levels in PwRRMS, PwPMS, and healthy controls (HC).
Aims: To characterize novel prognostic biomarkers for PwPMS.
Methods: GFAP and NfL were measured in cryopreserved plasma samples using a sensitive single molecule array (Simoa®, Quanterix, Lexington, MA) 2-plex assay kit. Patient data were collected by survey for HC and by retrospective chart review for PwMS, and were analyzed using generalized linear models adjusted for relevant potential confounders.
Results: This interim analysis included 73 HC, 79 PwPMS, and 92 PwRRMS in analysis (mean age PwMS 45.3 ± 11.6 years, 72% female). Median EDSS in PwPMS was 5.0 (IQR 3.5-6.0) and in PwRRMS 2.0 (IQR 1-3); <5% in either group had a relapse within the year prior to study entry. In HC, age was strongly associated with both NfL and GFAP. The effect size between age and NfL was larger than the effect size for age and GFAP (standardized b[age,

NfL]: 0.05; standardized b[age, GFAP]: 0.006). In PwMS, age-adjusted NfL and GFAP levels were significantly positively correlated (r=0.50; p<0.001). Both NfL and GFAP were higher in PwPMS than in HC in multivariable models (NfL: 20.9%; 95: CI: 5.97-38.1%; p=0.005; GFAP: 28.0%; 95% CI: 8.8-50.8%; p=0.003). PwPMS had higher levels of GFAP than HC even after accounting for NfL (17.9%; 95: CI: 0.9-37.8%; p=0.02). The relationship between NfL and GFAP was stronger in PwRRMS than in PwPMS (difference in NfL per 1SD increase in GFAP: RRMS: 30.4%; 95% CI: 20.0-41.7%; PMS: 19.2%; 95% CI: 0.6-23.9%; p for interaction=0.02).

Conclusions: Adjusted plasma NfL and GFAP levels are elevated in PwPMS versus HC, with GFAP less affected by age than NfL in HC. Future analyses will assess associations of NfL and GFAP to clinical disease progression and whether GFAP provides additional prognostic information in PwPMS.

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EP1026

Matched plasma modification for calculating a disease activity score in a serum-validated multivariate proteomic multiple sclerosis disease activity test

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Introduction: A Multiple Sclerosis Disease Activity (MSDA) Test that measures the concentrations of 18 proteins in serum, and utilizes an algorithm to determine 4 disease pathways scores (immunomodulation, neuroinflammation, myelin biology and neuroaxonal integrity) and an overall Disease Activity (DA) score was analytically and clinically validated. Whether the MSDA test also works in plasma samples remains to be established.

Objective: Validate the MSDA test in plasma by devising a process for modifying measured protein concentrations of plasma prior to calculating disease activity and pathway scores.

Methods: 336 matched serum and EDTA plasma samples (CIS, MS, healthy and inflammatory controls) were assayed across 17 plates. Correlations and median % differences were calculated between plasma and serum prior to any adjustments. Scores (DA and 4 pathways) were calculated for 245 paired serum and plasma samples (CIS and MS) for reference. 2 methods were tested to adjust plasma values. The 1st was applying a factor on plasma concentrations based on the median % difference of samples between serum and plasma. The 2nd method adjusted plasma based on the linear regression from the matched serum and plasma. Scores were calculated from both methods of modified plasma values and compared to the serum scores to evaluate equivalency.

Results: The DA and pathway scores range from 1.0-10.0 (with 0.5 increments). DA scores are grouped into 3 categories: Low (1.0-4.0), Moderate (4.5-7.0), and High (7.5-10.0) Disease Activity. 17/18 proteins correlated well between plasma and serum with R2>0.81. The median % differences ranged from -19 to 75 with 17/18 proteins within ±20. Between serum and plasma the mean DA score difference=0.6 and mean pathway scores differences between 0.2 to 1.0. Using the factor adjustment, the mean DA Score difference=-0.1 and mean pathway score differences between -0.5 to -0.1. Using the regression adjustment, the mean DA Score difference=0.0 and mean pathway score differences=0.0. For the CIS and MS samples, DA score category changes (eg. H, M, L) were observed as follows: unadjusted (50), factor adjusted (33), and regression adjusted (30).

Conclusions: Adjusting values of plasma concentrations using the linear regression model provided the closest approximation of

serum values for calculating DA and pathway scores for the MSDA Test. This model can be applied to future studies involving plasma to calculate equivalent DA and pathway scores.

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EP1027

Exploring the relationship between serum GDF-15 and disease stability in patients with a first clinical demyelinating event treated with subcutaneous interferon β-1A or placebo in the REFLEX study

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Introduction: Subcutaneous interferon beta-1a (sc IFN β-1a) is an established disease-modifying therapy (DMT) for multiple sclerosis (MS), with an estimated cumulative exposure of 1,889,156 patient-years (to 30-Apr-22). In the REFLEX study of patients with a first clinical demyelinating event (NCT00404352), stable disease activity – based on MS conversion/lesion counts/relapse-free rates – was observed in those receiving sc IFN β-1a 44μg three times weekly (tiw) vs placebo recipients.

Objectives: Longitudinal studies show higher serum levels of growth differentiation factor 15 (GDF-15; an anti-inflammatory cytokine) in clinically stable MS patients during DMT. We sought to explore findings for serum GDF-15 in patients from the REFLEX study.

Aims: To study GDF-15, based on whether patients were treated or not with sc IFN β-1a in the REFLEX study, by use of mixed models repeated measures to account for repeated GDF-15 measures over time.

Methods: Adults from REFLEX (mean age=30.7 years; first clinical event suggestive of MS within the last 60 days and ⩾2 clinically silent lesions on T2-weighted MRI scan with Expanded Disability Status Scale score of 0–5) were randomised to sc IFN β-1a 44 μg once weekly, 44μg tiw, or placebo, for up to 24 months. For thispost hoc exploratory analysis, serum GDF-15 was measured in serial samples from patients treated with sc IFN β-1a tiw or placebo. All randomised patients with ⩾1 non-missing GDF-15 value at baseline (start of REFLEX) and post-baseline were included. The impact of multiple covariates or factors on serum GDF-15 were assessed using a multivariate approach.

Results: Blood samples from 157 sc IFN β-1a tiw-treated and 161 placebo recipients were analysed. After 6 months, least squares (LS)-mean serum GDF-15 was 15% higher in treated vs placebo patients (396.87 pg/mL and 337.78 pg/mL, respectively; p=0.0002). Higher LS-mean serum GDF-15 for treated vs placebo patients was also seen at Months 12 (390.45 pg/mL vs 317.73 pg/mL; p<0.0001) and 24 (366.61 pg/mL vs 321.37pg/mL; p=0.0213). Such differences were more pronounced in patients with higher serum GDF-15 at baseline. Age also had a significant impact on serum GDF-15 (p=0.0006).

Conclusions: This exploratory analysis is compatible with a relationship between higher serum GDF-15 and disease activity in early MS. Further analyses will assess GDF-15 as a marker for treatment response.

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EP1028

Cerebrospinal fluid biomarkers of early worsening in primary progressive multiple sclerosis

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Background: Available therapy for active primary progressive multiple sclerosis (PPMS) warrants early diagnosis and recognition of unfavorable disease outcomes. Since rapid clinical deterioration is possible without MRI activity, more sensitive biomarkers of ongoing pathology are needed. Cerebrospinal fluid (CSF) chemokine CXCL-13, chitinase-3-like protein 1 (CHI3L1), and neurofilament light chains (NFL) were shown to predict disability progression in relapsing-remitting MS, but have not been studied extensively in PPMS.
Objective: We aimed to evaluate the prognostic potential of CSF biomarkers reflecting central nervous system B cell recruitment (CXCL-13), microglial activation (CHI3L1), and neuroaxonal damage (NFL) in our PPMS cohort.
Methods: Forty-five PPMS patients (29 women) with a median age of 53 years (range 34,5 – 72,9 years) were admitted to our department between 2013-2021. They presented with a median 3-year (range 0.5-30-year) history of spastic paraparesis and had basic CSF analysis with oligoclonal bands (OCB) and quantitative IgG synthesis done at the time of diagnosis. At least one follow-up EDSS score was available for 43 patients (median follow-up 1.1, range 0.3-6.6 years). Immunoassays were used for CXCL-13, CHI3L1 (Quantikine ELISA, R&D), and NFL (UmanDiagnostics AB) quantification. The Spearman's rho test was used to test for associations between CSF biomarkers and disability progression.
Results: All patients had typical brain MRI lesions (80% more than 10), including spinal cord lesions (26/32), whereas Gd enhancement was only rarely seen (4/25). CSF OCB were detected in 93% of patients and 19 patients showed EDSS progression at follow-up. Intrathecally produced CXCL-13 correlated with CSF cell count ($\rho = 0.615$, $p < 0.001$) and IgG index ($\rho = 0.557$, $p < 0.001$) but only fairly with ARMSS score at follow-up ($\rho = 0.366$, $p = 0.04$). Despite the correlation between CSF CHI3L1 and NFL levels ($\rho = 0.510$, $p = 0.016$), CHI3L1, but not NFL, was significantly higher in patients with EDSS progression (173 ng/ml vs. 229 ng/ml, $p = 0.005$) and correlated fairly with one-year EDSS change ($\rho = 0.325$, $p = 0.04$). NFL correlated negatively with disease duration ($\rho = -0.426$, $p < 0.01$) and was not related with the number of MRI lesions at the time of diagnosis.
Conclusion: CHI3L1 seems to be a better predictor of early disability progression in PPMS patients than NFL and CXCL-13. Its prognostic potential should be further studied in a larger, prospective cohort.

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EP1029

Circulating myeloid-derived suppressor cells as a potential biomarker of an anti-inflammatory T-cell balance associated with improved relapse recovery in multiple sclerosis

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Introduction: One of the main characteristics of MS is the great variability of symptoms and the unpredictability of its disease course. For this reason, it is very important to find biomarkers that help the clinicians to make decisions about relapse management from early stages of the disease. Myeloid-derived suppressor cells (MDSCs) represent a heterogeneous group of myeloid cells with a regulatory role in MS. Our group has data indicating that monocytic-MDSCs (M-MDSCs) are good biomarkers for relapse recovery in untreated MS patients. However, nothing is known about the predictive value of this cell population and the T cell balance at relapse or after recovery.
Objective: We aim to establish the relationship between the proportion of M-MDSCs, different effector and regulatory T-cell subsets at baseline and after relapse recovery in RRMS patients.
Material and Methods: Peripheral blood mononuclear cells of untreated RRMS patients were collected at baseline and after 12 months of follow-up. MS patients were separated into those whose blood was collected $\leqslant$30 days (relapse) or $>$30 days (remission) after relapse. In both cases, different immune cells populations were analyzed by flow cytometry.
Results: Patients at relapse showed the level of M-MDSCs directly related to a higher effector T cell frequencies, i.e. Th17, CCR2+CCR5+ Teff, including those highly resistant to immunosuppression ($CD161^{+}$). In contrast, elevated frequencies of M-MDSCs at baseline were indicative of lower levels of $CD4^{+}$ T cells, particularly on Th1.17 cells, together with an increase of Th2 cells after 12 months of follow up. Interestingly, our data showed that the higher abundance of M-MDSCs at baseline was directly associated with higher frequencies of $CD25^{hi}CD127^{lo}FoxP3^{+}$ T cells (Treg) at baseline and after 12 months of follow-up, including $CCR6^{+}$ Treg prone to migrate to inflammatory areas. In contrast, no important associations were detected at any experimental time in remission patients. Lastly, a lower Teff/M-MDSCs balance might not only be a hallmark of a higher patients' affectation at relapse, but also emerged as a useful predictor of relapse recovery.
Conclusion: In sum, our data indicate that circulating M-MDSCs at MS relapse is associated with a more regulatory T cell compartment after 12 months of follow-up. Moreover, a lower Teff/M-MDSCs balance at baseline is a prognostic factor for a better relapse recovery.

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EP1030

High neurofilament level in neuromyelitis optica spectrum disorder AQP4 (+) Patient associated to chronic hepatitis c

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Introduction: There is a wide neuromyelitis spectrum disorders (NMOSD) associated to AQP-4 antibody identified after different viral trigger, suggesting a probable relationship between viral infections and neurological manifestations. Hepatitis-related viruses usually stimulate extra hepatic manifestations in most of the cases. An important representant of these viruses is the hepatitis C virus (HCV), which is also associated to chronic silent infections that can last several years before a diagnosis, leading to cirrhosis and hepatocellular carcinoma.

Objective: To demonstrate a rare phenotype of extra hepatic manifestation involving nervous system, the NMOSD, and the correlation with plasma biomarker level of neurodegeneration.
Results: We identified a 68-years-old female patient who has been diagnosed for the hepatitis C in 2014, with a sustained high viral load along the years (~10^6UI/mL). In 2021, she received the diagnosis of NMOSD, with anti-AQP4 detection. Neuroimaging showed extensive lesion involving brainstem and extensive central spinal cord lesion until dorsal level. During the onset of NMOSD, she was also presented urinary infection, hemorrhagic gastritis and high HCV viral load, followed by several hospitalization events, with active disease since then. For a better understanding of this case, we evaluated neurofilament light chain (NfL) levels using SIMOA (Single Molecule Array).
Result/Discussion: The plasma NfL level in 2022 was 365.51 pg/mL (SD=48.39) that compared with matched age control group was very high (~11.73 pg/mL). This result corroborates the severity findings for patients in neuroinflammatory and neurodegenerative processes associated to viral trigger and can contribute to better understanding the large spectrum of NMOSD. The NfL levels can contribute as biomarker for neuroinflammatory and neurodegenerative disease, including those associated to viral trigger.

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Andreza Salvio Lemos: nothing to declare

EP1031

A stable cohort of relapsing remitting multiple sclerosis (RRMS) has reduced tetrahydrobiopterin (BH4) In plasma

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Introduction: Reliable biomarkers of disease activity in multiple sclerosis [MS] are lacking.Tetrahydrobiopterin (BH4) is an endogenous metabolite with a crucial role in regulating inflammatory homeostasis through nitric oxide synthase coupling (NOS). Inflammatory events lead to BH4 depletion, causing NOS uncoupling with further oxidative stress induced cellular insults. Although BH4 is known to impact inflammatory pathways, little is known about its role in MS.
Objectives: To measure differences in BH4 plasma levels between a cohort of clinically and radiographically stable relapsing remitting MS (RRMS) on natalizumab and a matched healthy control cohort.
Aims: To investigate BH4 metabolic pathways as potential biomarker in MS.
Methods: The present study was a prospective observational study comparing levels of plasma BH4 in a sample of stable RRMS (MS group, n=20) and age and sex-matched healthy controls (control group, n=20). Inclusion criteria for the MS groups were: $\geqslant$ 6 months of natalizumab treatment, $\geqslant$ 6 months of MS stability, Expanded Disability Status Scale (EDSS) $\leqslant$ 3. Exclusion criteria were ages $<$1 8 and $>$ 40, body mass index (BMI) $<$ 18.5 and $>$ 29.9, presence of comorbidities, and use of alcohol and cigarettes. An additional exclusion was a history of fumaric acid esters usage, due their direct effect on BH4 de novo synthesis. Blood was processed immediately after venipunctures to preserve BH4 stability. Preanalytical and metabolite extraction methods validation were performed. Targeted Liquid Chromatography Mass Spectrometry (LC-MS) were performed to quantify plasma BH4. Independent samples t- test was performed to measure group differences.
Results: Participants were 65% female; age 34$\pm$5 and BMI 25$\pm$2.3. Measurement of plasma BH4 was highly reliable between two blind LC-MS assays (α=0.94). Plasma BH4 peak area was significantly reduced in MS group ($p<0.01$,Cohen's $d>0.8$), indicating a lower abundance of BH4 ions compared to controls. Following absolute quantification of BH4 metabolite in plasma using an internal standard, BH4 concentration was 7.7$\pm$2 in control and 6$\pm$2 ng/mL and in MS groups, suggesting reduced BH4 in the plasma of MS group ($p<0.01$,Cohen's $d>0.8$).
Conclusions: BH4 plasma level is reduced in people with MS with young age, low disability and over 6 months of clinical and radiographic disease stability. Our findings provide a novel insight of BH4 level alteration and its potential contributions to MS pathogenesis.

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EP1032

Oligoclonal M bands is a risk factor to early secondary progressive multiple sclerosis from a clinically isolated syndrome. A 12 years follow-up study

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Objective: To determine baseline cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) variables at onset of clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS) that predicts evolution to secondary progressive MS (SPMS).
Methods: 276 CIS patients with a minimum follow-up of 10 years were studied. Baseline presence of oligoclonal IgG and IgM bands (OCGB and OCMB respectively); number of brain T2 lesions (B-T2L), brain gadolinium enhancement lesions (brain-GEL), spinal cord T2 lesions (SC-T2L); and fulfillment of 2017 McDonald criteria, among other variables, were collected.
Results: 14 patients ended up with a non-MS condition. 138/276 CIS patients fulfilled 2017 McDonald criteria. Mean age was 32.4 years, 185 female. 227 received treatment, 95 as CIS. After a mean follow-up of 12 years, 36 patients developed SPMS. Conversion to SPMS was associated with OCGB (p=0.02), OCMB (p=0.0001); ⩾ 9 B-T2L (p=0.03), brain-GEL (p=0.03), and SC-T2L (p=0.03). However, after adjusting for sex, age, BT2L, brain-GEL, SC-T2, and OCMB status, only OCMB (HR 4.4, 1.9-10.6) and SC-T2L (HR 2.2, 1.0-6.2) suggested an independent association with risk of conversion to SPMS.
Conclusion: OCMB and SC-T2 lesions are potential independent predictors of conversion to SPMS.

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EP1033

Dimethyl fumarate's transcriptional signature in peripheral blood mononuclear cells of multiple sclerosis-treated patients and its association with clinical response in a 2-year follow-up study

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Background: Dimethyl fumarate (DMF) is a first-line therapy for relapsing-remitting multiple sclerosis (RRMS). DMF exerts immunomodulatory properties through mechanisms that are not fully understood. A variable number of patients exhibit a suboptimal response to DMF, highlighting the need to search for treatment response biomarkers.
Objectives: To study the effects of DMF on gene expression. To identify differential gene expression regulation according to clinical response.
Methods: RNA was extracted from peripheral blood mononuclear cells (PBMCs) from 10 healthy donors (HD) and 10 RRMS patients (at baseline and at 12 months of DMF therapy). Patients were clinically followed for 2 years to assess no evidence of disease activity (NEDA3) or evidence of disease activity (EDA3). Five patients were classified as NEDA3 and five as EDA3. RNA-sequencing was used for transcriptome profiling.
Results: Principal component analysis showed that HD tend to situate in a differentiated region of space compared to RRMS. Patients grouped together independently of the time of treatment, indicating a mild transcriptional effect of DMF. No aggrupation was obtained either between NEDA3 and EDA3. Interestingly, female and male samples separated into two clearly discernible groups. After 1 year of DMF treatment, the number of differentially expressed genes (DEGs) was 328. DMF produced a down-regulation of chemokine (CXCL10, CCR6, CXCR6, CCR9, CXCR5, CXCR3) and pro-inflammatory (CD8A, CD8B, IL2RG, IL12A, CD70, CD79A, CD79B, FCRL4) genes. Other downregulated transcripts included the immune checkpoint LAG3 and activators of the NF-kB pathway (TNFRSF13B, TIFA, TRAF4, NUAK2, PRKCZ, TRIM13). At baseline, no DEGs were found between NEDA3 and EDA3 patients. However, during DMF treatment a differential transcriptomic response was observed, with NEDA3 presenting a higher number of DEGs (902 genes) compared to EDA3 (189 genes).
Conclusions: DMF induces a mild transcriptional effect, overall producing the down-regulation of pro-inflammatory genes. NEDA3 and EDA3 patients present a differential gene expression regulation that could be further investigated in the search for response biomarkers in a larger cohort.

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EP1034

Longitudinal testing with a multivariate blood serum biomarker panel for multiple sclerosis disease activity: patterns of results in a real-world clinical setting

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Background: A proteomic Multiple Sclerosis Disease Activity (MSDA) test which utilizes an algorithm consisting of 18 biomarkers to produce a disease activity (DA) score has been analytically and clinically validated to correlate with gadolinium-enhancing lesions on MRI. The MSDA test score is scaled from 1.0-10.0 with 0.5 intervals and defines low, moderate, and high DA categories as having ranges of 1.0-4.0, 4.5-7.0, and 7.5-10.0, respectively.
Objectives: To characterize intra-patient variability of MSDA scores upon longitudinal testing in a real-world patient population.
Methods: A total of 749 patient samples from Rocky Mountain Multiple Sclerosis Clinic were assayed using the MSDA test to generate DA scores. Of these, 11 patients had at least four MSDA tests performed over approximately a 20 month period, with the average length between the first and second test of 12 months, 2 months between the second and third tests, and 1 month average for subsequent tests thereafter. Simple descriptive statistics were used to characterize the relative stability of MSDA scores with longitudinal sampling.
Results: Each of the 11 patients with at least 4 timepoints maintained treatment with natalizumab throughout the 20 month period. The mean MSDA score at baseline was 3.7 ± 1.42 (range 1.5-6.5) with a mean difference of 1.1 ± 0.45 between the min and max score observed across the 4 timepoints (range 0.5-2.0). A total of 4 patients had scores after baseline which resulted in a category change (2 from low to moderate, 2 moderate to low).
Conclusions: MS patients in a real-world clinical setting, all on a high efficacy disease modifying therapy, showed some minor fluctuations in MSDA score with repeated longitudinal testing. Although we observed a range of baseline MSDA scores between patients, intra-patient changes were on average within the reported analytical precision for the DA score (3 SD = 1.5 score units). These results complement the extensive clinical validation of the MSDA test with real world examples of repeated testing. Moreover, they may provide additional context for clinical interpretability of the MSDA test by helping to establishthe minimally important score difference for use in longitudinal clinical monitoring.

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EP1035

The intrathecal levels of osteopontin associate with cortical damage accumulation and disease activity in early multiple sclerosis

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Objectives: Preliminary data suggested that the intratechal inflammatory profile and especially the osteopontin levelsrepresent key prognostic factor of multiple sclerosis (MS)-related long-term cortical damage and disability accumulation.
Aims: To evaluate possible cerebrospinal fluid (CSF) inflammatory markers of accumulation of cortical damage as well as disease activity in early relapsing remitting MS (RRMS).
Methods: CSF levels of OPN and other 68 inflammatory markers were assessed using immune-assay multiplex technique in 133 RRMS patients (36M/97F, mean age 38.7±12.5 years). All patients underwent regular clinical assessment and yearly 3T MRI scans for a median of 3 (2-5). White matter (WM) lesion number and volume, cortical lesions (CLs) and volume (CLv) and global cortical thickness (CTh) were evaluated together with the 'no evidence of disease activity' (NEDA-3) status, defined by no relapses, no disability worsening and no MRI activity, including CLs.
Results: After applying a random forest approach using minimal depth and times to root measures to all markers, 10 molecules were significantly associated with changes in global CTh, being Osteopontin (OPN) and CXCL13 the best related. Linear regression model on CSF markers confirmed CXCL13 ($p<0.001$), sTNFR1 ($p=0.01$), and OPN ($p=0.013$) as associated with accumulation of cortical atrophy. The 10 selected molecules wereadded in a multivariable regression model with demographical, clinical and MRI measures of WM damage. Increased CXCL13 (Beta -4.15×10^{-15}, $p<0.001$) and OPN (Beta -1.56×10^{-8}, $p<0.001$) associated with CTh changes. Notably, when adding also variables associated to GM damage (CLs and CLv), increased levels of OPN (Beta-1.38×10^{-8}, $p=0.014$) and sTNFR1 (Beta-2.692×10^{-7}, $p<0.047$) provided additional value in predicting CTh changes (adjusted R-squared 0.62) when compared to the same model without CSF markers (adjusted R-squared 0.20). Among 69 markers,OPN and CXCL13 revealed also significantly and best associated to the NEDA-3 status (65/133 patients at 2 years).
Conclusions: These data confirm and extend published data on the prognostic role ofCSF inflammatory profile in predicting changes in cortical pathology and disease activity in early MS. Particularly we underline a crucial role of OPN, a molecule involved in many intrathecal proinflammatory processes, in addition to clinical, demographic and MRI variables.

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EP1036

K index utility as quantitative biomarker in multiple sclerosis: determination of diagnostic and prognostic cut-offs

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Introduction: Identification of early biomarkers in Multiple Sclerosis (MS) is crucial for providing more individualized treatments.
Objectives and aims: The aim of the study is to evaluate the role of cerebrospinal fluid (CSF) immunoglobulin free light chains (FLCs) as quantitative biomarker in the initial assessment of patients with suspected MS and to explore diagnostic and prognostic cut-offs useful in clinical practice.
Methods: We designed a cross-sectional and longitudinal study. We included 126 consecutive patients admitted to the neurological department of San Grarardo Hospital who underwent lumbar puncture for routine investigations (59 Clinical Isolated Syndrome/MS subjects and 81 no CIS/MS subjects) and 14 consecutive patients without any neurological disease who underwent lumbar puncture for locoregional anesthesia. For each patient CSF oligoclonal bands (OCB), serum and CSF FLC and κ index (κFLCs-ratio/albumin-ratio) were determined. A subgroup of patients with CIS or MS was followed-up for a median of 7 (4-10) years, registering radiological available data, relapses, annual Expanded Disability Status Scale (EDSS) and disease modifying therapies (DMT) introduction.
Results: K index resulted more sensible and specific (optimal cut-off 6.04) for MS diagnosis than OCB (AUC 0.98 versus AUC 0.92) and other FLC indicators. Moreover, κ index differentiated MS patients with higher basal lesion load on the first MRI ($p<0.05$) and directly correlated with MS Severity Score (MSSS) at the end of follow-up (rho=0.33; p=0.041). MS patients with κ index $\geqslant$ 106 showed a four-fold greater risk of relapse over time (HR=0.24; p=0.003) and a three-fold greater risk of DMT introduction (HR=0.39; p=0.023).
Conclusions: This study provides Class III evidence that k index $\geqslant$6.04 has elevated discriminatory ability for MS diagnosis and k index $\geqslant$106 individuates MS patients at higher risk of future relapse and potentially eligible to early treatment with highly effective DMT.
Our initial evidence promotes further investigations to confirm the full potentiality of k index and to validate prognostic cut-offs in large multicentric cohorts. In our opinion, the definition of diagnostic and prognostic quantitative cut-offs should facilitate the diffusion of k index into the routine assessment of patients with suspected MS, to improve diagnosis, prognosis and therapeutic decisions.

Disclosure
All the Authors declare that there is nothing to disclose. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

EP1037

Evaluating large scale proteomic changes in cerebrospinal fluid of multiple sclerosis patients

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Introduction: Molecular biomarkers are needed to measure multiple sclerosis (MS) disease activity and to evaluate therapeutic efficacy. Proteins measured in the cerebrospinal fluid may serve as a window into neuroinflammation and may be prognostic of disease course, as well as help provide evidence of treatment response following therapy. O-link proteomics is a high-throughput, multiplex immunoassay technology that enables the measurement of over 1000 proteins from small sample volumes. This approach allowed us to monitor protein changes in the context of CNS disease.
Objectives: Characterize the proteomic landscape in the cerebrospinal fluid (CSF) of MS patients in the context of therapeutic intervention.
Methods: O-link proteomics was performed on the CSF of MS patients. This cohort included treatment naïve MS patients as well as those treated with a B-cell depleting agent (anti-CD20 antibody).Additionally, this cohort also included clinically isolated syndrome (CIS) patients, radiologically isolated syndrome (RIS) patients, HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients, and healthy controls.
Results: Over 1,400 unique proteins were measured in the CSF samples using O-link proteomic technology. Differential abundance analyses were performed to identify proteins with altered abundances in MS, CIS, RIS, and HAM/TSP patients compared to healthy controls. We confirmed that soluble CD27 levels are elevated in MS patients as well as in the HAM/TSP cohorts.
Conclusions: Protein levels exhibit altered abundances in MS, CIS, RIS, and HAM/TSP patients compared to healthy controls.

Our work contributes to an improved understanding of protein alterations in the CSF of MS patients and proposes molecular biomarkers for evaluating therapeutic efficacy.

Disclosure
ASB is an employee of Sanofi and may hold shares and/or stock options in the company.
DO is an employee of Sanofi and may hold shares and/or stock options in the company
TJT is an employee of Sanofi and may hold shares and/or stock options in the company
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EP1038

Distinguishing disease activity in multiple sclerosis by analysis of intrathecally produced inflammatory and CNS injury targets

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Background: Multiple sclerosis (MS) is very heterogeneous in its clinical phenotype and the course of the disease is difficult to predict. Intrathecally synthetized proteins involved in inflammation and central nervous system (CNS) injury may be used in the development of accurate prediction models for MS disease activity
Objectives: To investigate the molecular patterns and network of intrathecally synthetized inflammatory and CNS damage mediators in MS patients and determine how they relate to the short-term disease activity in relapsing remitting MS (RRMS).
Aims: To 1) identify patterns of differentially produced intrathecally proteins in MS patients with "active" and "non-active" disease. And 2) use bioinformatics approaches to create a predictive models for acute disease activity.
Methods: 46 inflammatory mediators and 11 markers of CNS injury and glial activation were evaluated using either Luminex or ELISA assays in matched serum and CSF samples from 26 RRMS and 25 clinically isolated syndrome (CIS) patients at their primary diagnosis. All patients were followed for ⩾12 months in a retrospective follow-up study and ultimately classified into "active" (having disease activity, n=21) or "non-active" (not having disease activity, n=30). 27 patients with non-inflammatory neurological diseases (NIND) were included as positive and negative controls. Data were subjected to differential expression analysis of positive and negative controls and then to a unique set of statistical and data-driven modeling techniques that allowed for clear segregation of "active" and "non-active".
Results: Intrathecal expression CXCL13 and IL1B were differentially expressed in "active" versus "non-active" patients. Network analysis in patient subgroups revealed unique negative correlations between sTREM2 (soluble TREM2) and inflammatory cytokines in "non-active" patients, indicating a possible modulatory effect that is lost during activity. AUROC and Kaplan-Meier analysis reveals predictive value of intrathecally produced proteins correlation between CCL11 and sTREM2 for disease activity.
Conclusions: Our data suggest a neuroimmunological distinction between patients with higher and lower risk of developing disease activity within the next 12 months. Thus, present findings can be used to develop a predictive model for MS activity.

Disclosure
All authors have nothing to disclose

EP1039

Positive MRZ reaction differentiates multiple sclerosis from MOG antibody-associated autoimmune disease

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Introduction: Myelin oligodendrocyte glycoprotein antibody-associated autoimmune disease (MOGAD) is a rare inflammatory demyelinating disease of the central nervous system (CNS) and causes several atypical, but multiple sclerosis(MS)-like syndromes, i.e. optic neuritis (often recurrent), myelitis, (brainstem) encephalitis and other. It is considered a disease entity separate from MS and neuromyelitis optica spectrum disorder. Recently, a large multi-center study characterizing cerebrospinal fluid (CSF) findings in MOGAD patients found no cases with a positive measles/rubella/zoster (MRZ) reaction and only in 10% of cases an intrathecal IgG production, two features specifically respectively frequently found in MS.
Aim: To analyze CSF parameters of MOGAD and relapsing-remitting MS (RRMS) patients.
Objective: To distinguish between RRMS and MOGAD patients based on CSF findings.
Material and Methods: We retrospectively assessed demographic, clinical and CSF findings from clinical routine in 28 patients with MOGAD and 293 patients with RRMS, who were punctured at our center. A positive MRZ reaction was defined as polyclonal intrathecal production of IgG against ⩾2 of 3 virus antigens. Furthermore, patients were compared for CSF white cell count, CSF/serum albumin ratio, Reibergram parameters and CSF-specific oligoclonal bands.
Results: MOGAD patients were significantly older than RRMS patients, and had in 42.9% of cases a monophasic- and in 57.1% a relapsing-remitting disease course. There was no significant difference between both groups in terms of mean CSF white cell count or frequency of intrathecal synthesis of IgA and IgM

according to Reibergram. Increased CSF/serum albumin ratio was significantly more frequent in MOGAD patients. Furthermore, MOGAD patients showed a significantly lower frequency of intrathecal IgG synthesis (14.3% in MOGAD vs. 92.1% in RRMS) and positive MRZ reaction. A positive MRZ reaction was found in 36.5% of MS patients, but in none of the MOGAD patients.
Conclusion: We corroborate previous findings showing absence of MRZ reaction and low prevalence of intrathecal IgG production in MOGAD patients. Furthermore, CSF white cell count and frequency of intrathecal synthesis of IgA and IgM according to Reibergram are not helpful to distinguish between MOGAD and RRMS. These findings highlight the diagnostic usefulness of a positive MRZ reaction as a rule-out parameter for MOGAD and rule-in parameter for MS.

Disclosure
None

Clinical aspects of MS - MOGAD

EP1040
Meteoroid: a randomised, double-blind, placebo-controlled, multicentre phase 3 study of satralizumab in patients with myelin oligodendrocyte glycoprotein antibody-associated disease

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Introduction: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a rare, demyelinating, autoimmune disease of the central nervous system that can cause severe, persistent neurological deficits and disability. There is a need for approved, long-term relapse prevention therapies that are efficacious and safe. Like aquaporin-4-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD), evidence suggests a key role of interleukin-6 (IL-6) in MOGAD pathogenesis. Satralizumab, an IgG2 recycling antibody targeting the IL-6 receptor, reduced relapse risk vs placebo with a favourable safety profile in two phase 3 trials in NMOSD (SAkuraSky/SAkuraStar [NCT02028884/NCT02073279]).
Objectives: METEOROID (NCT05271409) is a randomised, double-blind (DB), placebo-controlled study to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of satralizumab as monotherapy or in addition to background immunosuppressive therapy (IST) in patients with MOGAD.
Methods: METEOROID will enrol patients (⩾12 years) with relapsing MOGAD (⩾2 attacks in the last 24 months, consistent with optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, or other brain, brainstem, or cerebellar syndrome compatible with demyelination) confirmed by MOG-IgG cell-based assay.
The study comprises an event-driven DB period, followed by an open-label extension (OLE) period. Patients will be randomized 1:1 to satralizumab or placebo, administered subcutaneously at Weeks 0, 2, 4 and Q4W thereafter. Patients refractory to azathioprine (AZA) or mycophenolate mofetil (MMF) may maintain a stable dose of AZA or MMF throughout. Oral steroids must be discontinued by Week 16. Patients can enter the OLE and receive satralizumab after completing the DB period or after an adjudicated relapse in the DB period.
Results: The primary endpoint is time to first MOGAD relapse in the DB period, adjudicated by an independent committee. Disease activity (relapse rate, active neuroaxis lesions, hospitalisation, and proportion of patients receiving rescue therapy), disability progression, patient-reported outcomes, MRI/optical coherence tomography outcomes, PK/PD data and longitudinal biomarker assessments will be evaluated. Safety outcomes include the frequency, seriousness and severity of adverse events.
Conclusions: METEOROID is the first study of satralizumab in MOGAD, providing efficacy, safety, and PK/PD data for satralizumab ± IST in patients with MOGAD.

Disclosure
F. Paul has served on advisory boards for Novartis, MedImmune and Viela Bio, has speaker honoraria and travel grants from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis / Genzyme, Janssen, Merck Serono, Alexion, Chugai, MedImmune, Shire, Roche, Actelion, and Celgene; serves as the academic editor for PLoS ONE and associate editor for Neurology, Neuroimmunology and Neuroinflammation; has consultancies for SanofiGenzyme, BiogenIdec, MedImmune, Shire,and Alexion; has research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis / Genzyme, Alexion, Merck Serono, German Research Council (DFG Exc 257), Werth Stiftung of the City of Cologne, German Ministry of Education and Research (BMBF Competence Network Multiple Sclerosis), Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program (combims.eu) and Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis Society of the USA. **E.P. Flanagan** has served on advisory boards for Alexion, Genetech, UCB and Horizon Therapeutics, has a speaker honoraria from Pharmacy Times, is an Editorial Board Member for the Journal of the Neurological Sciences 2021 onward; Editorial board member of

Neuroimmunology Reports, is an author of a chapter on MOG antibody associated disease in UpToDate and will receive Royalties for this from 2021 onwards; was a site primary investigator in a randomized clinical trial on Medi551 in NMOSD run by Medimmune, from which he received compensation; has received funding from the NIH (R01NS113828).**T. Kümpfel** has served on advisory boards for Roche and Alexion; has received personal compensations/speaker honoraria from Bayer Healthcare, Merck, Novartis, Sanofi-Aventis/Genzyme, Roche, and Biogen, as well as research support from Novartis and Chugai. **R. Marignier** serves on scientific advisory boards for Viela Bio/Horizon Therapeutics, Roche, Alexion, UCB; and has received funding for travel and fees from Alexion, Biogen, Merck, Novartis, Roche, and Viela Bio/Horizon Therapeutics. **K. Fujihara** received grants from Ministry of Education of Japan, Ministry of Health, Welfare and Labor of Japan; received personal fees from Roche/Chugai, Alexion, Viela Bio, Biogen, Eisai, Mitsubishi Tanabe, Novartis, Astellas, Takeda, UCB, Merck Biopharma, Abbvie and Asahi Kasei. **C. Hemingway** has received honoraria from Novartis and consulting fees from UCB, Novartis, Biogen, Roche and VielaBio. **I. Vodopivec**, **D. Stokmaier** and **K. Weber**are employees of F. Hoffmann-La Roche Ltd. **M. Levy** receives research support from National Institutes of Health and has previously received research support from Genzyme, Alexion, Alnylam, and Shire; received personal compensation for consultation with Alexion, Acorda, Genentech/Roche, Horizon, Quest Diagnostics, UCB and Sanofi; and he serves on the scientific advisory boards for Alexion, Horizon, Genentech/Roche.

EP1041

Myelin oligodendrocyte glycoprotein antibody disease associated with intracranial hypertension: an algerian series

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Introduction: Recent immunological progress has made it possible to describe a rare inflammatory autoimmune pathology: Myelin-Oligodendrocyte Glycoprotein antibody disease (MOGAD).
MOG antibodies are found in a wide clinical spectrum (which continues to expand) of acquired demyelinating diseases of the central nervous system.
We describe 4 cases of MOGAD revealed by intracranial hypertension (ICH).
Aims: Highlighting intracranial hypertension as an atypical manifestation of MOGAD, to illustrate the importance of looking for this pathology even when faced with an isolated intracranial hypertension syndrome and a normal MRI.
Objectives:
-Describe the clinical symptoms and evolution of each patient
-Confirm association of intracranial hypertension syndrome with sero-positive Mogopathy.
-Prove the effectiveness of usual treatments against intracranial hypertension and MOGAD.
Methods: Retrospective study of 4 cases of MOGAD revealed by a table of ICH; collected in the neurology department of the CHU Mustapha in Algiers, Algeria. We performed a neurological exam, a lumbar punction, a cerebral and spinal MRI, and a complete biological assessments with notably MOG antibodies
Results:
-The clinical description of ICH syndrome is most often typical and generally precedes a significant drop in visual acuity. This hypertension is confirmed by a manometric measure of the cerebrospinal fluid pressure.
-The ophthalmological examination confirms the visual impairment by the fundus examination and must be completed by the Optical coherence tomography (OCT) which will define the grade.
- The cytochemical and immunological study of the cerebrospinal fluid was normal in the 4 cases studied.

- The cerebrospinal MRI does not show any lesions that could explain the clinical symptoms.

-Therapeutically, the response to the treatment of ICH with Acetazolamide and subtractive lumbar punctures is complete.
-2 patients of 4 received plasma exchanges as an attack treatment for optic MOGAD, the 2 others benefited from plasma exchange with improvement in visual acuity, then we proposed a long-term therapy in order to avoid relapses (2 patients with Rituximab /2 others on Azathrioprine)
Conclusions: The ICH syndrome is a clinical manifestation broadening the spectrum of MOG antibody disease and worsening the visual prognosis. This is an atypical manifestation of Mogopathies but it should be considered because a specific treatment could be proposed.

Disclosure
Mouhouche Imed: Nothing to disclose

Imaging and non-imaging biomarkers - Other Biomarkers

EP1042

Association of kappa and lambda free light chain indices with disease activity determined by No Evident Disease Activity (NEDA) in multiple sclerosis

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Introduction: Free light chain indices of kappa (KFLC) and lambda (LFLC) isotypes are promising diagnostic biomarkers in

multiple sclerosis (MS). Studies have also demonstrated their prognostic role, thus suggesting a potentially useful tool for early therapeutic stratification. The concept of No Evidence of Disease Activity (NEDA) has become the cornerstone outcome measure, combining a minimum three-parameter evaluation of relapses, disability worsening, and magnetic resonance imaging (MRI) lesions.

Aims: To assess the relationship between baseline FLC indices and follow-up disease activity as defined by NEDA.

Methods: FLC indices were calculated at the time of initial diagnosis. Neurological disability as measured by the Expanded Disability Status Scale (EDSS) and MRI lesion load (the number of T2 and contrast-enhancing lesions) were determined at baseline and at the end of observation. During this period, the occurrence of relapses was also ascertained. Logistic regression was used to evaluate the relationship between baseline FLC indices and the progression of disability and MRI lesion load upon follow-up. Linear regression was used to establish the role of FLC indices in predicting relapses.

Results: Of the 41 patients, 83% were treated with immunomodulatory therapy, and 46% fulfilled the NEDA criteria at a median follow-up time of 3.6 years. The linear regression models combining either of the indices and elapsed time did not predict the presence of relapses (KFLC p=0.607, LFLC p=0.383). This was also true for the logistic regression models comprised of either of the indices and elapsed time in predicting the progression of EDSS (KFLC p=0.358, LFLC p=0.892), as well as the number of T2 (KFLC p=0.978, LFLC p=0.930) and contrast-enhancing lesions (KFLC p= 0.670, LFLC p=0.984).

Conclusions: FLC indices do not predict clinical and radiological disease activity in early MS.

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EP1043

Cognitive function, MRI Brain volume and optical coherence tomography in young and elderly patients with multiple sclerosis

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Introduction: During the last two decades life expectancy of people with MS (pwMS) has been rising. It is essential to gather information on cognitive function and
biomarkers in elderly multiple sclerosis (MS) patients.

Objective: To explore association between cognitive scores, brain volume and retinal nerve fiber layer (RNFL) thickness in a group of young and elderly MS patients.

Methods: Patients with MS according to McDonald Criteria 2017 were divided into younger (between 18 and 35 years) and older (over 50 years) age groups. Complete
cognitive assessment, 3T brain MRI post-processed with a Deep Learning Software (Entelai Pic v2) and retinal nerve fiber layer (RNFL) measurement by spectral domain
optical coherence tomography (OCT) were obtained in all cases. The Stata program version 15 (Statacorp) was used for the analysis. Independent t-tests were used to compare groups for continuous variables, chi-squared test for categorical data, Pearson's correlation coefficient to compare continuous variables and linear regression to predict disability progression and brain atrophy rates.

Results: 92 pwMS were included, 56 young (52% female) and 36 elderly (69% female). In young patients, significant correlations were found between cognitive function
(immediate recall/ delayed recall and executive-attentional functions) and thalamic volume (rho: 0.41, 0.34, 0.29, respectively). Total brain lesion volume correlated with
immediate and delayed recall (rho: -0.38, -0.31). Conversely, in older patients we found a significant association with whole brain volume (rho: -0.47) but no correlation with brain lesion volume. No significant association was observed between whole brain volume, thalamic volume, or total lesion volume and RNFL measurement.

Conclusions: Cognitive function in young pwMS is related to thalamic and total lesion volume. Meanwhile, in older patients it appears to be more related to global atrophy. These findings suggest additional mechanisms of neurodegeneration may be involved in aging patients with MS.

Disclosure:

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Dr Jorge Correale In recent years has received financial compensation for academic presentations, and attended advisory boards from: Biogen, Merck, Novartis, Roche, Bayer, Sanofi-Genzyme, Gador, Raffo, Bristol Myers Squibb, and Janssen
Dr Celica Ysrraelit has received reimbursement for developing educational presentations, attendance to advisory boards and travel/accommodations stipends from Merck-Serono Argentina, Biogen, Genzyme Argentina, Bayer Inc, Novartis Argentina, TEVA and Roche Argentina.
Dr Mariano Marrodan has received fees for educational presentations and/or conference attendance from Merck-Serono Argentina, Biogen-Idec Argentina, Novartis Argentina, Gador and Roche Argentina.
Dr Mauricio Farez has received travel acommodations from Teva, Merck-Serono, Biogen-Idec and Novartis. He also received research funds from Biogen-Idec and Novartis Argentina. He is CEO & Co-Founder of Entelai LLC.
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EP1044

Anti-CD20 therapies decrease humoral immune response to SARS-CoV-2 vaccine in a cohort of patients with multiple sclerosis

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Background: B cells are responsible for the synthesis of antibodies in people who receive SARS-CoV-2 vaccines. In multiple sclerosis (MS), the seroconversion rate after SARS-CoV-2 vaccine may be influenced by disease-modifying therapies (DMTs) specially by anti-CD20 therapies.
Objective: To investigate the seroprevalence and the quantity of SARS-CoV-2 antibodies in a cohort of patients with MS.
Methods: It is a retrospective study in which we included MS patients treated with DMTs who were vaccinated against SARS-CoV-2 between February 18 – August 4, 2021.A blood collection at 4 weeks after the second dose was planned. Statistical analysis was performed using SPSS version 24. Significant statistical differences between variables were determined using the U Mann Whitney and chi squared tests.
Results: A total of 43 MS patients were included in the study, the age range was 23-68. Sixty-nine percent (31/43) of the patients demonstrated a humoral response. Stratified by DMT type, patients treated with interferon yielded 100% measurable antibodies; 62% of the MS patients developed antibodies following vaccination with fingolimod. Finally, only 43% of MS patients with anti-CD20 therapies developed a humoral response (p=0.03). The mean of SARS-CoV-2 antibodies in MS patients with anti-CD20 therapies were lower in comparison with patients treated with interferons and fingolimod (61,9 UI/ml vs 546,5 Ul/ml vs 263,4 Ul/ml) $p<0.001$.
Conclusions: MS patients are able to mount a humoral vaccine response to SARS-CoV-2, irrespective of the vaccine type administered; patients treated with fingolimod and anti-CD20 agents are least likely to mount such a response in comparison with MS patients treated with interferon.

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EP1045

Objective speech metrics in MS: a longitudinal study

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Background and Goal: A swift and reliable detection of disease progression would inform treatment decisions and better safeguard the neurological reserve of people with Multiple Sclerosis (pwMS). Previous cross-sectional work pointed to the objective acoustic analysis of speech as a potential tool to monitor overall disease progression. Here, we tested if those speech metrics changed over time in a cohort of pwMS.
methods: We recorded speech from pwMS at baseline and after one to three years. At both timepoints, the speech sample included one trial per visit of telling a personal story from memory, and two trials of reading a phonetically balanced paragraph, saying a long "ah", and repeating the syllables "pa-ta-ka" as fast as possible. The acoustic metrics of interest included three composite scores related to speech intelligibility, speech naturalness, and overall neurological disability, which were compared between baseline and follow up.
Results: Fifty pwMS completed the study protocol (70.6% female; age mean=47.2, SD=10.6; median EDSS=4, interquartile range=3.5). We observed a negligible mean change for the intelligibility score (from 0.329 to 0.328, p=0.97), the naturalness score (from 4.30 to 4.20, $p = 0.12$), and the overall neurological score (from 4.62 to 4.41, p=0.32). Only five pwMS had worsening of their Expanded Disability Status Scale (EDSS) scores of at least one point over the course of the study. Those five pwMS presented mixed acoustic speech results (i.e., some worsened, some improved speech scores).
Conclusion: This cohort of pwMS did not present with significant changes in objective speech scores over one to three years of disease. Experimental factors such as disease-unrelated variation in speech (e.g., circadian, seasonal, mood) may have impacted performance. The stability of these speech measurements in a cohort with relatively stable disease prompt further exploration of this domain in MS where disability status varies.

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EP1046
Using MEG to probe effects of pediatric ADS and MOG-Ab disease on functional networks and subsequent cognitive outcomes

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Introduction: Acquired demyelinating syndromes (ADS) disrupt extensive brain networks, especially in paediatrics where disease effects are superimposed upon typical neurodevelopment. It is unclear whether disruptions are functionally relevant to neurodevelopmental outcomes, and whether autoantibodies such as those to myelin oligodendrocyte glycoprotein (MOG-ab) differentially effect network disruption.
Aims: To investigate neurophysiological responses as an indicator of cognitive outcome, using magnetoencephalography (MEG), in paediatric ADS patients with and without MOG-ab.
Methods: To date, n=10 children with ADS have been recruited, of which n=3 had MOG-ab positivity. Neurophysiological responses were assessed using a child-adapted visuomotor MEG task. Participants executed a button press in response to a visual grating. This characterised post-movement beta rebound (PMBR), a motor response following movement cessation, with an observable power increase in beta oscillations (14–30 Hz). Using beamformers, we performed source localisation of greatest difference in beta-band oscillations during the active epochs (500-1000ms relative to button-press) contrasted against baseline (2700-3200ms) and extracted virtual electrode time-series. Time-frequency spectrograms of beta-band oscillatory power at this location, were used to estimate PMBR neurophysiology (e.g. peak power, latency of peak power).
Participants also completed neuropsychological assessment (Wechsler Intelligence Scale for Children (WISC-V)).
Results: In preliminary analyses, no differences were found between participants with and without MOG-ab in behavioural or neurophysiology. However, groups did differ on IQ, with greater scores in the MOG group ($t(5.05) = -2.7302$, p-value $= 0.041$). Controlling for age, we found significant negative correlations between latency of the maximum beta power increase and WISC-V IQ ($r = -0.90$, $p=0.006$) across all participants.
Conclusions: We echo previous relationships between neurophysiology of PMBR and cognition in MS, and expand these findings to paediatric ADS. This could reflect the role of PMBR in long range integrative processes over distributed brain networks, relying heavily on structural connection integrity, which are more likely to be damaged with increased ADS severity and cognitive difficulties. Further work should establish the feasibility and pathogenic relevance that neurophysiological measures produced using MEG have.

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Therapy - Immunomodulation/ Immunosuppression

EP1047
Nasal anti-CD3 monoclonal antibody (Foralumab) reduces PET microglial activation and blood inflammatory biomarkers in two patients with non-active secondary progressive MS

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Introduction: There are no effective treatments for non-active secondary progressive MS (SPMS), which is mediated by compartmentalized CNS inflammation, including activated microglia. We found that fully human anti-CD3 intranasal monoclonal antibody (Foralumab) suppressed disease in a chronic EAE model by dampening microglia and astrocyte inflammation. Nasal Foralumab does not enter the bloodstream or brain. A dose-finding study of nasal Foralumab in controls dosed at 10ug, 50ug and 250ug for 5 days found the drug to be safe with immune effects seen at 50ug. COVID patients dosed with 100ug of nasal Foralumab for 10 days was well-tolerated and exhibited positive effects on blood markers and lung inflammation.
Objective: To determine if nasal Foralumab has a therapeutic effect on patients with non-active SPMS.
Methods: Two patients were identified with non-active SPMS and sustained clinical progression, despite use of approved DMT. EA1 is a 61-year-old male diagnosed for over 20 years and EA2 is a 42-year-old male diagnosed for 8 years, both last treated with ocrelizumab for 3 years. Treatment occurs in 3-week cycles with intranasal Foralumab 50ug/day administered 3x/week for 2 weeks with 1 week rest. Each cycle, clinical and neurological assessments are repeated, and imaging is repeated every 3 months.

Results: EA1 has completed 6 months and EA2 has completed 3 months of treatment. To date, there have been no adverse reactions, local irritation, or laboratory abnormalities, and symptom progression has subsided. EA1 is feeling more stable, subjectively, and has noted improvement in lower extremity strength. EDSS, pyramidal motor score and T25FW have stabilized or improved. SDMT and 9HPT were stable during treatment. Microglial activation as measured by [F-18]PBR06 PET scan was significantly reduced 3 months after the start of nasal Foralumab, and this reduction was sustained after 7-week washout and at 6 months. Serum protein measurements of cytokines showed reduction of IFN-γ, IL-18, IL-1ß and IL-6 levels (Olink assay). Cellular immune studies showed increase in CD8 naïve cells and decrease in CD8 effector cells, and alteration in gene expression as measured by single cell RNA sequencing. EA2 3-month laboratory and imaging results are pending and will be presented.
Conclusions: Nasal Foralumab in non-active SPMS patients treated for at least 3 months reduced microglial activation, decreased levels of proinflammatory cytokines, and had positive clinical effects.

Disclosure
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EP1048

Effects of anti-CD20 monoclonal antibody therapy on cerebrospinal fluid B cell subsets in relapsing-remitting multiple sclerosis

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Introduction: B cells are implicated in the immunopathogenesis of multiple sclerosis, underlined by the effectiveness of treatment with anti-CD20 monoclonal antibodies (mAb). CSF B cells are reduced in number following treatment with anti-CD20 mAb, but the effects on B cell subsets remains unclear.
Objectives: To assess the effects of anti-CD20 mAb therapy on frequencies and phenotypes of B cell subsets in CSF.
Aims: To investigate the impact of anti-CD20 mAb therapy on intrathecal B cell subsets in relapsing remitting multiple sclerosis (RRMS).
Methods: We used flow cytometry to analyze CD19+ B cell subsets in the CSF from treatment naïve patients with RRMS (n=9) and anti-CD20 mAb treated patients with RRMS (n=9) 6 months after their first infusion series of rituximab or ocrelizumab.
Results: CSF white cell count was higher in treatment naïve patients than in patients treated with anti-CD20 mAb (median 8 vs 2 cells/µl, $p<0.01$), with no difference in percentage of CD19+ B cells of total CSF cells (median 4% for both groups). However, we observed a differential composition of B cell subsets in the CSF after anti-CD20 mAb therapy: median frequency of $CD27^{hi}CD38^{hi}$ plasmablasts was 14% in treatment naïve patients vs 3% after anti-CD20 mAb therapy (p=0.03), median frequency of $CD27^{+}CD38^{-}$ memory B cells was 27% in treatment naïve patients vs 13% after anti-CD20 mAb therapy (p=0.01), and median frequency of $CD27^{+}CD38^{+}$ memory B cells was 27% in treatment naïve patients vs 64% after anti-CD20 mAb therapy (p=0.02). Remarkably, B cells remaining in the CSF after anti-CD20 mAb therapy were predominantly positive for both CD11cand membrane-bound lymphotoxin alpha (memLTa), which was not the case for treatment naïve patients (median frequency 22% in treatment naïve patients vs 92% after anti-CD20 mAb therapy, $p<0.01$).
Conclusions: Our study demonstrates that anti-CD20 mAb therapy changes the frequencies of B cell subsets in the CSF of patients with RRMS with a reduced frequency of plasmablasts and $CD27^{+}CD38^{-}$ memory B cells, and a higher percentage of $CD27^{+}CD38^{+}$ memory B cells. Furthermore, the study suggests that CSF $CD11c^{+}memLTa^{+}$ B cells are relatively resistant to anti-CD20 mAb therapy.

Disclosure
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EP1049

Demographics and baseline disease characteristics of patients with relapsing multiple sclerosis from Kenya participating in the CHIMES trial

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Introduction: Black people from Africa have lower incidence and prevalence of multiple sclerosis (MS) vs Black American or White individuals; however, this population is historically underrepresented in MS clinical trials. Inclusion of Black African patients (BApts) offers an opportunity to expand our understanding of MS. The ongoing CHIMES trial (NCT04377555) is designed to assess disease activity and response to ocrelizumab in underrepresented populations.

Aim: To present demographics and baseline MS characteristics of a subpopulation of BApts from Kenya enrolled in the CHIMES trial.

Methods: The CHIMES trial is a North American trial with one site in Kenya. To promote inclusive recruitment in Kenya, study-related patient materials were available in English and Kiswahili, flexible scheduling options were based on specific needs of the recruitment catchment area for recruitment from rural areas and to comply with local healthcare ecosystems. Baseline characteristics for BApts from Kenya were summarized, and the comparability with the intent-to-treat (ITT) population was assessed.

Results: Of 182 enrolled patients, 10 (5.5%) are in Kenya. Mean (SD) age was similar (35.5 [10.5] y and 37.8 [9.6] y, respectively) and ≈70% of the ITT and BApts were female. ITT had a higher mean (SD) body weight (86.8 [22.2] kg) vs BApts (69.7 [13.5] kg). Mean (SD) time since RMS diagnosis was longer for ITT vs BApts (2.9 [4.5] and 1.5 [1.9] y, respectively); however, ITT had lower mean (SD) expanded disability status scale score (2.4 [1.4] vs 3.5 [1.9]), number of relapses in the past 24 months (0.7 [0.6] vs 1.2 [0.4]), gadolinium (Gd)-enhancing T1 lesions (1.9 [4.3] vs 2.2 [3.7]) and volume of T2 lesions (18.9 [18.1] vs 27.4 [21.3] cm^3) vs BApts. Mean time since first MS symptoms, since onset of last MS relapse before enrolment and normalised brain and thalamic volume were similar among both groups.

Conclusions: Differences seen in demographic and disease characteristics between patients enrolled in Kenya and North America in CHIMES could reflect unique geographical and racial differences. Enrolment of diverse populations in clinical studies has the capacity to lead to more equitable inclusion and improved generalisability of MS pathophysiology, safety and efficacy data. Study design methodologies that consider specific population needs can enhance the enrolment of underrepresented populations without compromising on-study deliverables and operational considerations.

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EP1050

Evaluation of the use of High Efficacy Treatments (HETs) in patients with relapsing remitting multiple sclerosis in Argentina

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Background: Disease-modifying therapies (DMTs) in multiple sclerosis (MS) can be broadly classified according to the efficacy with which they prevent MS relapses. To date, there are scarce data regarding the use of high-efficacy treatments (HETs) in LATAM.
Objectives: The aim of this study was to analyze the use of HETs in Argentina, focusing on the clinical and sociodemographic characteristics of the patients and the trend use of HET over the last years
Methods: A retrospective cohort study was done based on the Argentinian Multiple Sclerosis (MS) patient registry, RelevarEM. Patients diagnosed with Relapsing Remitting MS (RRMS) according to validated diagnosis criteria and under HETs (natalizumab, alemtuzumab, cladribine, rituximab or ocrelizumab) were included.
Results: Out of 2450 RRMS patients under a disease-modifying therapies (DMTs), 462 (19%) were currently on HETs. One-third of those patients (35%) received HETs as the first treatment. The most frequent reason for switching to a HETs was treatment failure to previous DMT (77%). The time from MS diagnosis to the first HET in treatment-naive patients was less than one year (IQR: 0-1 year) and in treatment-experienced patients it was 5 years (IQR: 3-9 years). Between 2015 and 2017 (P1), 729 patients included in RelevarEM started a new treatment, of which 85 (11.65%) were HETs. Between 2018 and 2020 (P2), 961 patients included in RelevarEM started a new treatment, of which 284 (29.55%) were HETs. When comparing P2 vs P1, a significant increase in the use of HETs is observed ($p < 0.01$).
Conclusion: Our study showed a significant trend towards and a rapid increase in the use of HET in clinical practice.

Disclosure
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EP1051
Effectiveness of cladribine in a Portuguese real-word population

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Introduction: Based on the CLARITY study, cladribine tablets have been approved for relapsing-remitting multiple sclerosis (MS). Nevertheless, the placement of cladribine in the therapeutic spectrum has been a discussion topic. Although data from the phase 3 study CLARITY and its extension is available, long-term data from real life studies on patient disease activity is still coming to light.
Objectives: To report outcomes of MS patients treated with cladribine tablets in a real-life setting.
Methods: We collected clinical, laboratory and MRI data from all MS patients that were prescribed cladribine tablets, and analyzed relapse rate, disease progression measured as expanded disability status scale (EDSS), no evidence of disease activity (NEDA-3), and progression independent of relapses (PIRA).
Results: Cladribine was prescribed for 52 MS patients, 67% feminine, with mean age of 36,42 ± 11,04 years and mean disease duration 6,327 ± 5,12 years. After a mean follow-up time of 22,50 ± 10,68 months, there were no significant changes in median EDSS (baseline EDSS 2.0 (1.5) vs present date EDSS 2.0 (2.0). NEDA-3 was achieved in 53,85% patients but PIRA occurred in 11,54%. Patients with baseline EDSS below 3.0 achieved NEDA-3 more frequently than those with higher scores (64,1 % vs 23,08%, p=0,01). Patients switching from treatments associated with known rebound activity association (fingolimod or natalizumab) did not show an increased risk of relapses in the first year.
Conclusions: Our data suggests that starting cladribine in patients with EDSS below 3 is associated with higher probability of attaining disease remission (NEDA-3) and therefore may be an effective option as an immune reconstitution therapy.

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Emanuel Martins has nothing to disclose.
Inês Correia has nothing to disclose.
Sónia Batista has nothing to disclose.
Carla Nunes has nothing to disclose.
Carmo Macário has nothing to disclose.
Lívia Sousa has nothing to disclose.

EP1052
Longitudinal study of humoral and cellular responses to COVID-19 mRNA vaccines with and without 3rd ("booster") dose in MS patients on ocrelizumab: 24-week results from VIOLA (NCT04843774)

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Background: Patients on OCR have attenuated antibody, but largely intact T-cell responses to COVID-19 vaccination. Little is known about durability of post-vaccine responses in OCR-treated patients.
Objective: To examine antibody and cellular responses to mRNA COVID-19 vaccines (Pfizer,BioNTech/Moderna) in Ocrelizumab (OCR)-treated MS patients over 24-week period.

Methods: MS patients on OCR were recruited from NYU (New York City) and Rocky Mountain at CU (Denver) MS Centers. Antibody responses to SARS-CoV-2 spike proteins were assessed with multiplex bead-based (MBI) immunoassays, and cellular responses to SARS-CoV-2 Spike protein with ELISpot and activation induced marker (AIM) panel in a Cytek Aurora full-spectrum flow cytometry platform. Data on samples collected pre-vaccine and 4-, 12-, 24-weeks post 2-doses and 4-, 12-weeks post-third dose will be presented.
Results: 40/61 enrollees (age 38.3±10.9; 77.5% female; 57.5% non-white) had 24-week post-vaccination data and 9 patients had 4-week post 3rd dose data. Antibody response increased from pre-vaccine level of 972.0 U/mL to 6307.4 U/mL at week-4 (p=0.0002), then decreased to 4633.8 u/mL at week-12 (26% decrease from week-4, p=0.1377), and further to 2878.4 u/mL at week-24 (37% decrease from week-12, p value=0.109). Spike-specific IFNγ T-cell responses by ELIspot were 125.7 SFU/106 cells pre-vaccine, increased to 362.9 SFU/106 cells at week-4 (p=0.009), then to 511.5 SFU/106 cells at week-12 (40.9% increase relative to 4-week time-point, p=0.8474), and remained elevated at 501.7 SFU/106 cells at week-24 (p=0.7393, 1.9% compared to week 12). 4-week post 3rd dose, Ab level increased to 5094.8 U/mL (189.9% compared to pre-3rd dose, p =0.076) and IFNγ responses to 1253.3 SFU/106 cells (484.5% increase, p=0.037).
Conclusions: Antibody responses to 2-series vaccine peaked at 4 weeks and trended downward thereafter, while cellular responses were sustained at 24 weeks. Third-dose resulted in marked increases in both antibody and T-cell responses 4-weeks. Expanded analyses, including in-depth immunophenotyping and 12-week post 3rd vaccination responses will be presented.

Disclosure
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EP1053

A changing target - adapting ongoing autologous haematopoietic stem cell transplantation clinical trials to evolving clinical practice in the treatment of highly active relapsing remitting multiple sclerosis

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Background: Autologous hematopoietic stem cell transplantation (aHSCT) is an effective and safe treatment resulting in suppression of disease activity and delay of disease progression in patients with highly active relapsing remitting multiple sclerosis (RRMS) who failed first line disease modifying treatments (DMT) (Burt et al. 2019). However, its safety and effectiveness compared to high efficacy DMTs remains undetermined.
Around 4-14% RRMS patients present with an aggressive clinical course (Lacobaeus et al. 2020). There is no unanimous definition of aggressive MS but rapidly evolving severe MS (RES-MS) is defined as patients with ⩾2 disabling relapses in 1 year, and ⩾1 gadolinium-enhancing lesions or a significant increase in T2 lesion load on brain magnetic resonance imaging (MRI). High efficacy DMTs are usually a first line treatment to prevent long term disability (Laffaldano et al. 2021). In a retrospective study Das et al. (2021) demonstrated no evidence of disease activity in 100% of patients with treatment naïve aggressive RRMS treated with aHSCT.
Method: Star-MS, ISRCTN88667898, is a multicentre parallel-group rater-blinded randomised controlled trial of aHSCT versus high efficacy DMT (alemtuzumab, cladribine, ocrelizumab and ofatumumab) of 198 RRMS patients in the United Kingdom. aHSCT is delivered using non-myeloablative conditioning with a cyclophosphamide/anti-thymocyte globulin regimen followed by an unselected autologous graft.
Eligibility was based on clinical practice at the time the trial was conceived in 2019 and included patients with ⩾2 relapses, or 1 relapse and evidence of MRI disease activity >3 months before or after its onset, in the last 12 months despite use of a DMT (but not a comparator DMT).
Star-MS opened recruitment in September 2021 following an 18 month delay due to COVID. Changes to clinical practice, namely early use of high efficacy treatment, no longer aligned with trial design, reducing the pool of eligible patients, resulting in slower than expected recruitment.
Trial protocol was revised to include active RRMS, defined as ⩾1 relapse or evidence of MRI disease activity in last 12 months use of a DMT, or RES-MS in treatment naïve patients. Here we describe the positive impact of utilising adaptations to study design to keep clinical trials aligned with clinical practice.
Conclusion: Clinical trials must be responsive to changing clinical practice to ensure success and relevance to the target patient population.

Disclosure
The authors declare that they have no relevant financial or non-financial competing interests.

EP1054

Wearing off fenomenon in MS patients in treatment with monoclonal antibodies: clinical and biological implications

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Introduction: Patients with multiple sclerosis (MS) treating with monoclonal antibodies report occasionally MS-related symptoms prior to the next dose of treatment. This situation is called "wearing-off phenomenon", and his existence is controversial.
Objectives: Our objective is to analyze the prevalence of the wearing-off phenomenon in our patients with MS using natalizumab and ocrelizumab, describe the clinical phenomenon in our patients, and investigate potential causes or predicting factors.
Methods: We present a retrospective study. We review patients treated with natalizumab and Ocrelizumab. We collect data from clinical history about the presence or not of wearing-off phenomenon in order stablish the prevalence, and correlate this phenomenon according different factors: age, EDSS pre and post treatment, time from last dose,efficacy (relapses and progression) in both treatments. For Natalizumab we study the alfa4-integrin receptor ocupation (RO), for Ocrelizumab CD19+ count.
Results: We review 48 patients treated with Natalizumab and 83 patients treated with Ocrelizumab (Relapsing Multiple Sclerosis). We analyze the prevalence of "wearing off" in our Natalizumab and Ocrelizumab patients. The majority of the symptoms were psicological. We didn,t find worsering in EDSS in "wearing off" patients. The prevalence of "wearing off" in natalizumab patient was stable during the treatment but in Ocrelizumab patients decrease along the time. We study the association between "wearing off" with RO in Natalizumab patients and association between "wearing off" and CD19+ count and levels or NfLs.
Conclusions: In our study we try find a rationale explanation of wearing off phenomenon, and a possible way of optimize the treatments and avoid suboptimal response.

Disclosure
Nothing to disclosure

EP1055
Real-world experience switching from high-efficacy infusions to cladribine tablets

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Background: Cladribine tablets are a short-course oral disease-modifying therapy (DMT) administered in four four-to-five-day courses over two years. Cladribine tablets are indicated for the treatment of adults with relapsing forms of MS (RMS) based on data from pivotal clinical trials, including the phase 3 study, CLARITY, and its extension. Switching DMT in patients with relapsing forms of multiple sclerosis (RMS) is quite common.
Objectives: Our study aims to assess the real-world safety and efficacy of switching a subgroup of patients with RMS from high-efficacy infusions to oral cladribine tablets. Infusion DMTs include ocrelizumab, natalizumab and alemtuzumab.
Methods: Prospective and retrospective chart review. Patients 18 to 74 years old (n=84) with RMS who received care from the MS Center of Sarasota and were treated with ⩾1 course of cladribine tablets from May 2019 to March 2022 were included in this analysis. A subgroup analysis was also performed for patients who were previously on an infusion DMT prior to treatment with cladribine tablets. Patient monitoring was performed in accordance with the US prescribing information.
Results: We report on a subgroup of 33 patients (39.3% of an 84 total patient cohort) switched from infusions to oral cladribine tablets. 14 patients (16.7%) switched from ocrelizumab, 13 patients (15.5%) from natalizumab, and 6 patients (7.1%) from alemtuzumab. The mean washout period was 75 weeks in the complete subgroup; 45 weeks in the ocrelizumab group, 20 weeks in the natalizumab group, and 160 weeks in the alemtuzumab group.
The percentage of patients with grade 0, 1, 2, 3, 4 lymphopenia were 9%, 9%, 42%, 39% and 0% respectively. The most common side effects (>5%) were fatigue, headache, upper respiratory and urinary tract infection.
The 2 year annualized relapse rate (ARR) prior to switching to cladribine was 0.7. The 1 year ARR prior to switching to cladribine was 0.58. The post-switch ARR in patients with at least 1 year of follow-up (n=23) was 0.17.
Conclusions: In this subgroup of patients switching from high-efficacy infusions to oral cladribine tablets in a real-world setting, the treatment was well-tolerated. There were no new safety signals. ARR was decreased. Owing to short follow-up time, it was not possible to assess long-term outcomes. Ongoing follow-up will further expand on these results as more patients complete their full treatment course.

Disclosure
Donald Negroski received fees as a speaker/consultant for: Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Inc., Genentech, Janssen, Novartis, Sanofi-Genzyme, and TG Therapeutics.
Daniel Sellers received fees as a speaker/consultant from Biogen, Bristol Myers Squibb, EMD Serono, Inc., and Sanofi-Genzyme.
Amir Khiabani and Devon Khiabani have nothing to disclose.

EP1056
Intrathecal methotrexate treatment for progressive forms of multiple sclerosis

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Introduction: In progressive forms of MS (PMS), the immune response is trapped behind a partially closed blood-brain barrier (BBB), thus less amenable to systemic anti-inflammatory disease-modifying therapy. Methotrexate (MTX) is an anti-metabolite preparation used in many autoimmune diseases. Intrathecal

methotrexate (ITMTX) administration bypasses the closed BBB and thus may be better suited for treating compartmentalized chronic inflammation. The potential benefit of ITMTX therapy for unresponsive progressive MS has been previously reported, but prospective data is needed to establish safety and efficacy.
Objective: Assessing the safety, tolerability, and efficacy of ITMTX therapy in patients with progressive forms of MS.
Methods: Prospective, open-label single arm, single center phase 1 study (ClinicalTrials.gov Identifier: NCT02644044) to assess the safety and effectiveness of intrathecal methotrexate (ITMTX) in the treatment of PMS. All patients were evaluated Clinically, and their expanded disability status scale (EDSS), 25-foot walk test (25FW), and symbol digit modalities test (SDMT) were performed at every treatment. In addition, we performed CSF analysis and volumetric measurements of total lesion volume and brain volumes.
Results: Twenty-three patients with PMS were recruited for the study, of which 16 completed 12 months of ITMTX treatment. The mean ±SD age was 56.56 ± 9.97, the overall female-to-male ratio was 9:14, and the median EDSS was 6.5 (IQR=2).No serious adverse events related to ITMTX were noted. There was no significant change from baseline to 12 months in clinical or CSFmeasurements. The median annual brain volume percentage change was -0.54%, (IQR=3.01%). Normalized gray matter, white matter, CSF, and lesion volume were stable, with no significant change during the study period.
Conclusions: ITMTX therapy was well tolerated in PPMS and SPMS patients with no serious adverse events. All patients remained clinically and radiologically stable over a year of treatment. This study, therefore, provides a basis for further investigation of ITMTX treatment for PMS and emphasizes the need for a longer follow-up after a larger cohort.

Disclosure
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EP1057

A Norwegian prospective randomized open-label blinded endpoint multicentre non-inferiority study of oral cladribine and rituximab in multiple sclerosis (NOR-MS) - baseline patient data

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Introduction: Cladribine and rituximab are considered highly effective disease modifying therapies (DMTs) in relapsing multiple sclerosis (MS). High economic costs of available DMTs limit access to treatment. Oral cladribine is approved for treatment of MS, while rituximab is used off-label in Norway.
Objectives: We present demographic and clinical characteristics of the participants at baseline, as we approach completion of recruitment.
Aim: Our goal is to compare the efficacy and safety of these two DMTs in patients with relapsing MS. To our knowledge, no phase III studies have compared rituximab with any established high-efficacy DMTs. Formal safety data are also lacking for rituximab treatment in MS. NOR-MS is a phase III prospective randomized open-label blinded endpoint multicentre non-inferiority study.
Methods: Study participants were randomized 1:1 to cladribine or rituximab. Inclusion criteria are: a diagnosis of relapsing MS, age 18-65 years, contraceptive compliance, one or more clinical relapses and/or new T2-lesion activity on magnetic resonance imaging (MRI) within the last 12 months. Exclusion criteria are any current contraindication or prior use of anti-CD20 therapy or cladribine, natalizumab (<6 months), fingolimod (<6 months), or pregnancy. The primary endpoint is the number of new or enlarging T2-lesions between 12 and 96 weeks.
Results: As of May 15th 2022, we have recruited 249 patients with relapsing MS (94% of the planned 264 patients) from 10 sites in Norway. Most patients were treatment naïve (66.3%) and 63.4% are female. Mean age was 38.0 (SD 10.0) years and mean disease duration from first onset 4.7 years (SD 6.8, range 0-40.4). At baseline, no significant (2-tailed p-value threshold of 0.05) inter-site differences were found for age, gender or Expanded Disability Status Scale (EDSS), nor any significant variation between prior use of DMTs and treatment naïve patients. Median EDSS at baseline was 1.5 (IQR: 1.25, range 0–4.5).
Conclusions: The results of this study will provide valuable knowledge concerning treatment strategies and may potentially have great economic impact on MS treatment worldwide. We report baseline patient data showing a homogenous national study population across ten Norwegian sites, as well as a representative MS population comparable to other international phase III studies. The NOR-MS study is on track to complete recruitment by the

summer of 2022, with expected final results by the summer of 2024.

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TB has nothing to disclose.
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PS has nothing to disclose.
HFH has nothing to disclose.
GON has nothing to disclose.

EP1058

Defining post-translational modifications of deoxycytidine kinase to predict lymphocyte response to caldribine treatment using mass spectrometry

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Introduction: Activation of cladribine (2CdA), a drug approved for multiple sclerosis, is driven by a high deoxycytidine kinase (dCK)/5'nucleotidase ratio. Due to their high dCK content, lymphocytes are a preferential target for 2CdA. We demonstrated that 2CdA-induced apoptosis in stimulated T and B cells is correlated with enhanced dCK expression and activity. Up to 14 phosphorylation sites have been described to date for dCK but little is known about how such post-translational modifications affect its activity, apart for phosphorylation at serine 74 which has been associated to an enhanced dCK activity.
Objectives: Assess the different composition of post-translational dCK isoforms in healthy donor peripheral blood mononuclear cells and T cells to understand their possible impact on dCK activity in the context of cladribine treatment.
Aims: Devise a routinely applicable assay to measure dCK activity in lymphocytes from MS patients to monitor the response to 2CdA treatment.
Methods: We used Phos-tag™ electrophoresis, which traps phosphorylated proteins according to their phosphorylation status, thereby reducing their migration. Subsequent immunoblotting on polyvinylidene difluoride (PVDF) membrane with an anti-dCK monoclonal antibody could identify the bands containing phosphorylated dCK isoforms. Cell lysates treated with alkaline phosphatase were used to define the control band corresponding to non-phosphorylated dCK.
Results: We observed different intensity of specific bands in activated cells with or without cladribine treatment, indicating differential phosphorylation status linked to treatment. We have developed an in-house method to extract phosphorylated dCK isoforms and total dCK from the bands cut out from the membrane. To optimize mass spectrometry data acquisition, we first analyse total phosphorylated dCK run on conventional SDS-PAGE. Protein digestion with trypsin was performed on the cut-out band and the digest was analyzed using Q Exactive™ Plus Hybrid Quadrupole-Orbitrap™ mass spectrometer. Of the three different dCK peptides identified so far, two contained the ATP binding site (Glycine 28-Threonine 36), whereas only one contained a phosphorylation site (at serine 35).
Conclusions: Experiments are ongoing to identify further post-translational sites including serine 74 that might be relevant to the response to 2CdA treatment in multiple sclerosis.

Disclosure
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EP1059

Ocrelizumab extended interval dosing in multiple sclerosis during SARS-CoV-2 pandemic: a real-world experience

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Background: During COVID-19 pandemic second line disease modifying therapies (DMTs) for multiple sclerosis (MS), have been frequently postponed because of the epidemiological situation and the lack of safety information.
Objectives: To evaluate clinical implications of delaying ocrelizumab dosing in MS.
Aims: To assess the occurrence of clinical relapses, disability worsening and neuroradiological disease activity in MS patients receiving extended interval dosing ocrelizumab in a real-world setting.
Methods: Data from 90 MS patients (65 RRMS, 25 PPMS) who underwent ocrelizumab dose delay have been retrospectively obtained: in particular MS history, neurological examinations, white blood cells count (particularly lymphocyte subsets) and neuroradiological data have been collected.
Results: Enrolled patients have been followed up for a mean of 9.5±2.8 months after ocrelizumab dose delay (mean dosing interval 7.67±0.79 months). None of our 65 RRMS patients had clinical relapses, nor rapid disability worsening has been experienced by the PPMS cohort. Pre-infusion CD19+/CD20+ lymphocyte subset was available in 75/90 patients, with 18/75 patients showing significant B cells repopulation (defined as CD19+/CD20+ ⩾ 1.0%). MRI data were available in 47/90 patients, with 5/47 patients showing evidence of neuroradiological disease activity (mild in all reported cases and in the absence of any correlation with B cells repopulation).
Conclusions: Our data suggest ocrelizumab dose delay is generally safe in MS patients. Experiences during COVID-19 pandemic could be a starting point towards a more personalized scheduling of ocrelizumab therapy.

Disclosure
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EP1060

CLADCOMS - CLADribine tablets long-term Control Of MS – a post-marketing investigator driven study

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Background: Cladribine is a deoxyadenosine analogue prodrug that selectively induces immune reconstitution by targeting B- and T-lymphocytes. Cladribine tablets (CladT) are administered in two courses, 12 months apart, for patients with relapsing multiple sclerosis (RMS). Post-marketing surveillance is important for evaluation of long-term safety and effectiveness in a real-world setting. CLADCOMS (CLADribine tablets long-term Control Of MS) is a post-marketing investigator driven study. Here we report one year follow-up data on the first 100 patients included in the study in April 2021.
Objective: 1) To investigate for how long a full dose treatment with Cladribine 10 mg tablets (3.5 mg/kg over two years) offers freedom of disease activity in relapsing MS patients.
2) To collect complete data on safety and effectiveness with the help of the Swedish Neuroregistry to enable future assessment on effectiveness and safety in comparison with other in Sweden commonly used disease modifying treatments.
Methods: CLADCOMS includes patients with relapsing MS from the eight academic clinics starting Cladribine treatment after 23rd of March 2018. Data is collected in the Swedish Neuroregistry using highly structured yearly follow-up routines. Descriptive data on relapses, MRI activity, Patient Reported Outcome Measures and Serious Adverse events (SAEs) from the first 100 patient included in the study are obtained from the registry.
Results: Up to April 2022 1XX patients were included in the study. In April 2021 the first 100 patient entered the study. 40% of patients included were treatment naïve, 29% switched from natalizumab and 13% from rituximab. By April 2022, 5 patients experienced a relapse during the treatment initiation and showed MRT activity with contrast enhancing (CEL)
lesions more than six months after initiation of treatment, of which 2 patients showed CEL more than six months after the second treatment course year two. 20% of the patients showed new lesions on the first MRI performed up to 18 months after treatment initiation. Two patients reported SEAs. Analysis of CD19 and CD27- B-cells counts over time will be performed.
Conclusions: Cladribine treatment demonstrates clinical stability in patients treated ⩾ 12 months. However, continued follow-up is needed to assess the effectiveness and safety of treatment with Cladribine over a longer time to investigate time to disease reactivation after the second treatment course year two has been administered.

Disclosure
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FP, PN, LA, AS, MG, NL, AA, MV, JB have nothing to declare.

EP1061

Longitudinal quantification of neutralising antibodies after two doses of SARS-CoV-2 mRNA vaccine in MS, NMOSD and other neuroimmunological diseases

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Introduction: Several studies have reported attenuated humoral responses following SARS-CoV-2 mRNA vaccination in Multiple Sclerosis (MS) patients on anti-CD20 therapies and fingolimod. However, neutralising antibodies (NAbs) against the receptor-binding domain of the SARS-CoV-2 spike protein were quantified in only a few reports and there is limited data in neuromyelitis optica spectrum disorder (NMOSD) patients.
Objectives and Aims: To measure serum NAbs levels prior to, and, at several time points after the first (V1) and second (V2) SARS-CoV-2 mRNA vaccination in patients with neuroimmunological conditions on various immunotherapies, and, to identify the factors associated with poor humoral responses.
Methods: This was a prospective observational study performed at the National Neuroscience Institute, Singapore. Patients with MS (n=77), NMOSD (n=33), myelin oligodendrocyte glycoprotein-antibody associated disease (n=6), autoimmune encephalitis (n=3), other CNS inflammatory diseases (n=5), myasthenia gravis (n=9) and healthy controls (HCs, n=42) were recruited. No subjects had COVID-19 infection prior to V1, V2 and the sampling time points. NAbs were measured using the Genscript® cPass™ surrogate virus neutralisation test.
Results: No patients or HCs had detectable NAbs prior to V1. Two to 4 weeks after V1, patients on anti-CD20 therapies had lower NAbs levels ($p=0.010$) compared to HCs and untreated patients. Two to 6 weeks post V2, patients on disease-modifying anti-rheumatic drugs (DMARDs) ($p=0.010$), fingolimod ($p<0.0001$) and anti-CD20 therapies ($p<0.0001$) showed decreased NAbs levels compared to HCs and untreated patients. This was also observed 8 to 16 weeks post V2 – DMARDs ($p=0.046$), fingolimod ($p<0.0001$) and anti-CD20 therapies ($p<0.0001$). NAbs levels decreased in both HCs and patients with increasing time interval following V2. There was no correlation between NAbs levels and the time interval from last anti-CD20 treatment to V1 ($p=0.508$). A multivariable logistic regression model adjusted for age, expanded disability status scale, gender, mRNA vaccine type, ethnicity and body mass index, revealed that fingolimod ($p=0.026$) and anti-CD20 therapies ($p=0.003$) were independent predictors of undetectable NAbs following V2.
Conclusions: Fingolimod and anti-CD20 therapies are associated with attenuated NAbs levels post-vaccination. Future studies are needed to determine whether this translates to an increased risk of COVID-19 infection.

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EP1062

Tumefactive demyelinating lesions in multiple sclerosis 24 months after the 2nd cycle of alemtuzumab: changes in immune cell populations and candidate biomarkers

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Introduction: Paradoxical multiple sclerosis (MS) activation has been reported after alemtuzumab treatment.
Objective: To expand knowledge of alemtuzumab side effects.
Aim: To report our experience with a patient who developed multiple Tumefactive Demyelinating Lesions (TDLs) 24 months after the 2nd cycle of alemtuzumab, a very long period of time which hasn't previously been described.
Methods: Clinical and MRI description of thepatient's case. Longitudinal analysis of the peripheral blood lymphocyte T and B subpopulations using flow cytometry.
Results: A 24-year-old woman with relapsing MS discontinued fingolimod (Gilenya®) after 2 years due to gestational desire. Two months later, she experienced severe disease activation requiring methylprednisolone and plasma exchange. Alemtuzumab was initiated. Nine months after the 1st cycle, she experienced a relapse. The brain MRI demonstrated 12 T1Gd+ lesions. An increase in total B-cell and a decrease in T-cell subpopulations were observed with no changes in minor B- and T- subsets.
Twenty-four months after the 2nd cycle, she developed cognitive impairment. The brain MRI showed multiple T1Gd+ lesions, including TDLs. We found again an increase of B-cells, but also of CD4+ Th1 central memory. B-cell dysregulation has been associated with the pathogenic mechanism of paradoxical disease activation being the re-population a possible trigger of disease

activity and, in addition, CD19+CD24hiCD38hi cells have been proposed as putative biomarker of disease activation. Transitional B cells were analyzed but no differences were found. In contrast, an increase in Th1/Th17 cells was detected 3 months before the LTDs detection.
Conclusion: TDLs can appear after 24 months of the 2nd cycle of alemtuzumab in MS. These results suggest that the increase of Th1/Th17 cells could be a candidate biomarker of TDLs in MS patients treated with alemtuzumab.

Disclosure
None.

EP1063

Rapid onset of effect on various immune cell subpopulations after treatment initiation with cladribine and ocrelizumab

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Introduction: Ocrelizumab and cladribine are frequently used as highly effective disease modifying therapies in the treatment of people with multiple sclerosis (MS). Rapid onset of efficacy of MS therapeutics is critical especially in cases of highly active disease.
Aims: The aim of this study was to investigate the early impact of cladribine and ocrelizumab on various immune cell subpopulations.
Methods: Peripheral blood was collected from 33 patients who were either treated with ocrelizumab (n=21) or cladribine (n=12) immediately before and two weeks after initial treatment. Lymphocyte subpopulations were analyzed using multicolor flow cytometry. CD3, CD4, CD8, CD19, CD20, CD56, T cell receptor 1 and T cell receptor 2 were analyzed.
Results: Ocrelizumab as well as cladribine resulted in significant reduction of different lymphocyte subpopulations already two weeks after first treatment. The application of ocrelizumab resulted in a nearly complete depletion of $CD19^+$ and $CD20^+$ B cells as well as CD20-expressing $CD3^+$ T cells. Cladribine led to a significant decrease of various lymphocyte populations with $CD19^+$ and $CD20^+$ B cells being the most profound depleted subpopulations. Also $CD3^+CD4^+$and $CD3^+CD8^+$T cell subsets were significantly reduced 2 weeks after first cladribine application. $CD56^+CD3^-$ natural killer cells, $CD56^+CD3^+$ natural killer T cells and $CD20^+CD3^+$ T cells were not significantly reduced two weeks after first cladribine treatment.
Conclusions: Ocrelizumab as well as cladribine result in rapid and profound depletion of different lymphocyte subpopulations after treatment initiation with a particular impact on B cells.

Disclosure
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EP1064

A Long term post-marketing observational monocentric study of a population of patients treated with dimethyl fumarate

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Introduction: To date, long-term data of efficacy and safety of Dimethyl Fumarate(DMF) in relapsing-remitting multiple sclerosis patients (RR-MS) in real-world practice are poor.
Objective: to assess the long term use ofDMF in patients with mild moderate MS.
Aim: to analyze long-term effectiveness and safety of DMF in RR-MS and to identifying predictive factors of efficacy
Methods: 838patients, who started DMF between January 2014 and July 2020 at San Raffaele Hospital MS Center, were included. The mean follow-up was of 39.5 months (±25.2) with a maximum of 90 months. We analyzed the results for protocol.
Results: Basal characteristics of this population: mean age of 36,6 years, predominantly females (66,5%), the mean disease duration 7,4 years. Considering previous treatments: 40% were naïve, 37%

switched from first-line treatment for intolerance and 16% for inefficacy, 7% switched from second-lines treatment. Globally the patients presented mild/moderate disease activity before starting DMF treatment. Annualized relapse rate (ARR) decreased from 0.63 at baseline to 0.12 and 0.05 at first and second year respectively ($p < 0.0001$) and then remained low for over 5 years. 72% and 84% of patients were relapse free and progression free at 5 years respectively. T1-gadolinium-enhancing lesions decreased from 0.39 at baseline to 0.25 and to 0.10 at first and second year respectively ($p < 0.0001$) and then remained low. Of total, 30% discontinued DMF: 14% stopped DMF due to inefficacy, 13,4% for intolerance/adverse events and 2,6% for patients' choice. Predictive factors of discontinuation for inefficacy were age, ARR in the previous year, MRI activity at baseline, disease activity at rebaseline. 2017 was considered a watershed for a better patient's selection with a decrease of discontinuation rate for inefficacy from 19.2% to 8%. The incidence/type of adverse events were in line with the known safety profile of DMF with no serious adverse events.

Conclusion: our data confirm the favourable long-term effectiveness and safety profile of DMF in patients with RR MS. DMF can be considered as initial treatment for naive patients with low/moderate activity and without negative predictive factors and as switching for patients with intolerance/adverse events during other lower efficacy treatments. However we strongly suggest a close monitoring in order to make a vertical switch in patients with subresponse to DMF.

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EP1065

The effect of cladribine versus fingolimod on clinical and MRI measures in relapsing remitting multiple sclerosis

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Background: Data regarding the comparison between the effect of cladribine (CLAD) and fingolimod (FINGO) in relapsing remitting (RR) multiple sclerosis (MS) in terms of clinical and MRI measures in the real-life setting are still sparse.

Aims: To compare the impact of CLAD (I course) and FINGO on clinical outcome measures, new T2/gadolinium enhancing lesions, brain volumes, white-matter microstructure and cortical lesions in a cohort of RRMS patients.

Methods: In this ongoing study, RRMS patients underwent 3T-MRI at the time of treatment start and at 12-months follow-up (FU). Changes in percentage-brain-volume-change (PBVC) and multi-compartment spherical-mean-technique (SMT) diffusion metrics of the normal-appearing-white-matter (NAWM) were evaluated with repeated measures ANCOVA.

Results: A total of 31 patients were included in the analysis, [16 CLAD and 15 FINGO; females: 67.6%; mean age, disease duration, ARR previous year: 41.3+2.8, 12.5+1.8 years, 0.5+0.2; median (range) EDSS: 1.5 (0-4.5); no differences in terms of age, gender, disease duration, ARR and baseline EDSS were found between the two groups]. At 1-year FU, 1 patient in CLAD group and 1 patient in FINGO group showed a clinical relapse; 4/16 (25%) in CLAD group had new T2/gadolinium-enhancing lesions vs and 5/18 (27.8%) in FINGO group. No differences were noted in terms of PBVC (-1%CLAD vs -0.8% FINGO) and SMT metrics of the NAWM between the two groups. Cortical lesions number did not differ between baseline and 1-year FU both in CLAD and FINGO group.

Conclusions: We did not observe a superiority of FINGO vs CLAD (I course) in terms of clinical and MRI measures at 1-year FU in our cohort of RRMS patients. Our findings have to be confirmed in further analysis that should also consider the impact of the second course of CLAD treatment.

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EP1066

Preliminary data of a multicenter observational study on real-life experience with cladribine in naïve patients

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Introduction: Cladribine is a deoxyadenosine (purine) analog that induces selective and transient reductions of CD19+ B cells and T cells, followed by reconstitution of adaptive immune function. Nadir of lymphopenia is nine weeks with up to 12 weeks to recover. It is a semi-selective IRT with high efficacy.
Aim: To evaluate the efficacy and safety of cladribine in a population of MS naïve patients.
Methods: A multicenter observational study in a cohort of naïve MS patients treated with cladribine. 10 Italian MS Centers participated, integrating clinical and neuroradiological parameters collected from patient's clinical records.
Results: 52 patients were included in this study. 71,2% were females, mean age of 29,9 years (±8.1), mean disease duration of 16.8 months (±28.4). Basal median EDSS 1.5 (range 1-6), mean number of relapses in the previous year 1,19 (±0.72). The majority of patients presented more than nine but less than 20 T2 brain lesions at basal MRI, mean Gd-enhancing lesions 2.75 (±3.52), mean T2 spinal lesions 2.74 (±2.17), mean Gd-enhancing lesions 0.50 (±0.74). 32/52 patients received the second year of therapy, and 23 patients had a 24-month follow-up. Improvement of the EDSS at 24 months 0.54 points (±0.89). 92,1% of patients were relapse-free at 12 months, and 87,5% at 24 months. New T2 lesions were present on 13/37 at 6, 4/30 at 12, and 2/17 at 24 months MRI. No patients presented new Gd-enhancing lesions at 24 months MRI. NEDA-3 was 60.9%. Two patients interrupted therapy after the first year, one for lack of efficacy and one for side effects (hepatitis), and five interrupted after the second year for lack of efficacy. No severe adverse events were reported.
Conclusions: These preliminary data in active MS patients confirm cladribine's efficacy and safety. Promising data on NEDA-3, relapse rate reduction and MRI activity were observed. We think that a naïve patient is an ideal candidate for a treatment with a semi-selective IRT with high efficacy. Our cohort disclosed low disability, young age, and short disease duration. Furthermore, a more extended observation and a larger number of patients are needed to confirm this data.

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EP1067

Secondary bile acids taurodeoxycholic acid and glycodeoxycholic acid dampen primary murine microglia activation

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Introduction: With time the relapsing remitting multiple sclerosis (RR-MS), marked by acute demyelinating lesions with extensive peripheral immune infiltrates, can develop into progressive disease (P-MS), characterized by chronic glial activation and neurodegeneration. To date most available treatments target the acute leukocyte driven inflammation, while therapeutic options for progressive MS remain limited.
Using metabolomic profiling our group has previously shown that the circulating levels of bile acids are altered in MS and, in particular, in P-MS compared to RR-MS. Oral administration of one of these acids, tauroursodeoxycholic acid (TUDCA), ameliorated experimental autoimmune encephalitis (EAE), leading to a phase 1/2a clinical trial on TUDCA supplementation in progressive MS.
Objectives/ Aims: In this study we investigate the effect of an array of bile acids, that are also altered in PMS, on glial cell activation: two primary bile acids – cholic acid (CA) and taurocholic

acid (TCA) – and two secondary bile acids – taurodeoxycholic acid (TDCA) and glycodeoxycholic acid (GDCA). Further, we aim to identify the receptor mediating these effects. Of particular interest are the bile acid receptors G protein-coupled bile acid receptor 1 (GPBAR1) and farnesoid X receptor (FXR), which are both expressed on glial cells in white matter lesions.
Methods: Microglial cells and astrocytes were derived from murine mixed glial cultures and polarized with LPS/ IFNγ and TNFα/ IL-1α/ C1q respectively. Inflammatory activation was accessed using flowcytometry and confirmed with qPCR. To determine the mechanism by which TDCA and GDCA mediate their effects, we are performing experiments using bile acid receptor inhibitors and glia from GPBAR1 knockout mice.
Results: TDCA and GDCA reduce the microglial expression of iNOS, IL-6 and pro IL-1β in response to LPS/ IFNγ stimulation. The primary bile acids CA and TCA, on the other hand, had no effect on microglial activation. Experiments with GPBAR1 knockout mice and receptor inhibitors are ongoing.
Conclusions: Secondary bile acids, GDCA and TDCA, reduce microglial pro-inflammatory activation, while the primary bile acids, CA and TCA, have no effect on microglial polarization. These findings suggest that further investigation of GDCA and TDCA as potential therapeutics in MS is warranted. The results also provide insight into how alterations in bile acid metabolism by the gut microbiota may shape microglial activation.

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EP1068

Safety and efficacy of cladribine therapy following a treatment with anti-CD20 compounds in relapsing multiple sclerosis patients: a pilot study

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Background: Prolonged therapy with ocrelizumab and rituximab, two anti-CD20 monoclonal antibodies used in multiple sclerosis (MS), can lead to hypogammaglobulinemia and increased risk of infections. Cladribine, an MS immune reconstitution therapy, has not be associated with hypogammaglobulinemia so far.
Objective: To investigate IgG and IgM serum concentration changes up 12 months after switching to cladribine in patients previously treated with anti-CD20 compared to continued anti-CD20. Secondary aims were measures of effectiveness (EDSS, clinical relapses, new T2 lesions) and safety.
Methods: This is a prospective observational monocenter study including MS patients treated with anti-CD20 antibodies for ⩾18 months. Patients with a ⩾10% reduction of IgG and/or IgM or recurrent infections were switched to cladribine (CLAD-group). IgG and IgM concentrations, effectiveness and safety measures in CLAD-group were compared with those of patients continuing on anti-CD20 (CD20-group).
Results: Forty-five patients were included (median age=46.5 [36-54.5]; females=27 [60%]). Fifteen (33%) patients were switched to cladribine, 30 (67%) continued on anti-CD20. At baseline, IgG concentrations were similar between CLAD-group and CD20-group (8.2 [6.3-10.3] vs 8.7 [7.6-10.2] g/L, p=0.455). IgG (β=-0.03, p=0.048) and IgM (β=-0.004, p=0.030) concentration decreased over 1 year-follow-up, with no difference between groups (interaction p=0.850 and p=0.153 respectively). No patients in each groups experienced relapses or MRI progression. One patient in each group had worsening EDSS over follow-up. The number of severe adverse events was 2 in the CD20-group (both cases of inflammatory-bowel disease) and 1 in the CLAD-group (pelvic infection).
Conclusions: Rate of IgG and IgM decline following a switch to cladribine after anti CD20 treatment is similar to that observed in patients continuing anti CD20. Both treatment approaches are associated with low disease activity and similarly benign adverse event profile.

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EP1069

Natalizumab extended-interval dosing in a real-life context: efficacy study

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Introduction: Natalizumab (NTZ) is a widely used second-line treatment for multiple sclerosis (MS), administered with a four-weeks infusion interval. Extending the interval between two infusions could reduce the economic costs of this therapy, the incidence of rare side effects such as progressive multifocal leukoencephalopathy and improve the patients' quality of life with less frequent day-hospitalizations.
Aims: At the Fondation Rothschild Hospital in Paris, for sanitary reasons during COVID-19 lockdown, patients were systematically switched to a 6-weeks NTZ extended-interval dosing (EID)

from April 2020 to the present day. In this monocentric retrospective study, we aimed at evaluating the clinical and radiological efficacy of NTZ EID compared to the 4 weeks standard-interval dosing (SID) in adult patients with active MS.
Methods: We screened the local pharmacy database for NTZ administration and included all adult patients diagnosed with MS and treated with NTZ for at least 6 months with a SID, before being treated with an EID for at least 12 months. Data about disease activity, treatments received, MRI and clinical data were retrospectively collected from the local French MS observatory (OFSEP) database. The primary outcomes were the incidence of MS attacks, new MRI lesions or the presence of gadolinium-enhancing lesions during NTZ SID or EID.
Results: A total of 49 patients were included for final analysis. 21 (42.9%) were male, with a median MS duration from the first symptom to NTZ introduction of 60 [30, 110] months. Patients were treated for a median time of 34.6 [15.1, 72.4] months by a SID, followed by a median time of 18.6 [14.7, 20.6] months by an EID. The mean EDSS before EID was 2.0 [1.5, 3.0] and 1.5 [0.0, 2.8] during EID. During natalizumab SID, one patient (2%) presented a new MS attack, 5/45 patients (11%) had new MRI lesions, with gadolinium enhanced lesions in 1/45 (2%) patient. This did not differ significantly during natalizumab EID where no MS attack were observed ($p = 1$), new MRI lesions were present in 1/41 (2%) patient and no gadolinium-enhancing lesion was found. Patients were followed for a median time of 130 [78, 205] months in total.
Conclusion: We did not observe more clinical attacks or MRI activity signs when extending the interval between NTZ infusions from 4 to 6 weeks. Data from randomized controlled trials are needed to allow better consideration of side-effects and safety.

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EP1070

Unmet need of current disease-modifying treatments reported by physicians in patients with nonactive secondary progressive multiple sclerosis in the United States

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Introduction: Information is limited about the rationale for physicians' disease-modifying therapy (DMT) choices and current unmet need in patients with nonactive secondary progressive multiple sclerosis (SPMS).
Objectives/Aims: To understand physicians' reasons for selecting current DMTs and unmet need in patients with nonactive SPMS in the United States (US).
Methods: The Adelphi Disease Specific Programme was used to identify patients with nonactive SPMS in the US from 2016 to 2021. The physician-reported annual cross-sectional survey was used to determine current DMT, reasons for selecting current DMT, issues with current DMT, and areas for DMT improvement for these patients.
Results: A total of 324 patients with nonactive SPMS were evaluated and 24% were not currently on a DMT. Of the patients who were on a DMT (n=245), 20% reported only the current therapy. Current treatment consisted of 41% on infusions, 35% on orals, and 22% on injectables.
Physicians selected the current DMT mainly for effectiveness (94–100%), driven by slowing disease progression (67–90%), followed by administration (57% infusions; 67% orals; 44% injectables), safety and tolerability (46%), and quality of life (45% infusions; 31% orals; 26% injectables). Patient requests were higher in orals (24% vs 10%), while patient support programs were higher in infusions (18% vs 5%). Insurance coverage was considered in 15% of patients on infusions or orals and 10% on injectables.
Safety and side effects were the largest issues for current DMTs (18% infusions, 20% orals, 17% injectables). Physicians reported lack of efficacy/compliance with the current DMT in 12% of patients on infusions, 12% on orals, and 32% on injectables. Insurance or cost were issues for 9% of patients currently on infusions, 5% on orals, and 6% on injectables.
Physicians reported the following areas of improvement needed for DMT in nonactive SPMS: 1) effectiveness (73–83%), with disease progression being a key driver (37% infusions, 51% orals, 59% injectables); 2) safety and tolerability, including less monitoring required (32% infusions, 40% orals, 26% injectables); 3) administration (17% infusions, 8% orals, 36% injectables); 4) cost effectiveness (13% infusions, 10% orals, 3% injectables); and 5) quality of life and insurance (<10% across all DMTs).
Conclusion: There continues to be a high unmet need for effective and safe treatments for patients with nonactive SPMS, where there are no approved treatments.

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EP1071

Impact of ozanimod on absolute lymphocyte count and recovery in patients with relapsing multiple sclerosis

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Introduction: Ozanimod is a sphingosine 1-phosphate (S1P) receptor 1 and 5 modulator approved in multiple countries for treatment of adults with relapsing MS. S1P receptor modulators decrease absolute lymphocyte count (ALC) by reducing lymphocyte egress from secondary lymphoid organs.
Objectives: To describe ALC in ozanimod-treated patients in phase 3 "parent" trials (SUNBEAM−NCT02294058; RADIANCE−NCT02047734) and an open-label extension (OLE) trial (DAYBREAK−NCT02576717), shifts in ALC over time, and ALC recovery in patients with ALC $<0.2\times10^9$/L.
Methods: ALC was measured in patients treated with oral ozanimod 0.92 mg/d or intramuscular interferon β-1a (IFN) 30 μg/wk in the parent trials and with ozanimod 0.92 mg/d in the OLE. Patients were divided into 5 ALC groups: ⩾lower limit of normal (LLN), 0.8×10^9/L−<LLN, 0.5−$<0.8\times10^9$/L, 0.2−$<0.5\times10^9$/L, and $<0.2\times10^9$/L. The percentage of patients in each ALC group was assessed every 3 months from parent baseline through OLE month 48. Time to ALC recovery (⩾0.2 and $\geqslant0.5\times10^9$/L) was assessed in patients with confirmed ALC $<0.2\times10^9$/L (<18-day retest) during the OLE.
Results: A total of 762 and 737 patients were treated with ozanimod 0.92 mg or IFN, respectively, in the parent trials. Decreases in mean ALC from parent baseline (1.82×10^9/L) were observed at month 3 (0.77×10^9/L) in the ozanimod 0.92 mg group. Mean ALC remained stable through OLE month 48 in patients continuously treated with ozanimod 0.92 mg. In patients who switched from IFN to ozanimod in the OLE, mean ALC decreased from 1.82×10^9/L (OLE baseline) to 0.76×10^9/L (OLE month 3) and remained stable through OLE month 48. ALC was $\geqslant0.5\times10^9$/L in ~71%−77% of patients 3 months after initiation of ozanimod 0.92 mg. The percentage of patients in each ALC group remained stable from 3 months after initiation of ozanimod through OLE month 48. A total of 215/2251 patients had an ALC $<0.2\times10^9$/L at any time during the OLE; 24 (1.1%) had confirmed ALC $<0.2\times10^9$/L. After discontinuing ozanimod, 22/23 (>95%) patients recovered to $\geqslant0.2\times10^9$/L and to $\geqslant0.5\times10^9$/L within 1 month and 3 months, respectively; the remaining patient recovered to $\geqslant0.2\times10^9$/L by month 3 and to $\geqslant0.5\times10^9$/L by month 6.
Conclusion: ALC decreased within 3 months in patients treated with ozanimod 0.92 mg and remained stable through OLE month 48. ALC was generally stable during the observation period. Less than 2% of patients had confirmed ALC $<0.2\times10^9$/L during the OLE; all recovered off-drug to $\geqslant0.2\times10^9$/L within 3 months.

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EP1072

Treatment patterns and therapy selection drivers comparison between S1P agents among multiple sclerosis patients who recently switched disease-modifying therapies

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Introduction: The number of disease-modifying therapies (DMTs) within the S1P receptor modulator class has expanded since siponimod (SIP)'s approval in 2019.

Objective: To compare treatment patterns and therapy selection decisions between S1P receptor modulator agents for multiple sclerosis (MS) patients recently switching DMT treatment.
Aim: To identify treatment patterns and therapy selection decisions for S1P receptor modulator agents.
Methods: 216 US neurologists completed a survey and provided cross-sectional chart data from Feb 10-Mar 13, 2022, on MS patients who switched to a new DMT within the prior 3 months. Analyzed data include patients switched to fingolimod (FIN; n=57), SIP (n=26), ozanimod (OZA; n=63), and ponesimod (PON; n=24).
Results: The majority of patients switched to an S1P agent were diagnosed with relapsing-remitting MS (FIN: 91%; SIP: 69%; OZA: 83%; PON: 88%). However, more patients switched to SIP vs. FIN were diagnosed with active secondary-progressive MS (SPMS; 23% vs. 2%).
Switch line of therapy did not differ significantly between the S1P DMTs. Patients switched to SIP (50%), OZA (54%), and PON (67%) most often switched from oral DMTs. More patients switched to PON vs. FIN were previously treated with dimethyl fumarate (DMF; 42% vs. 9%).
The desire for a high efficacy agent (FIN: 57%; SIP: 62%; OZA: 51%; PON: 48%), belief that it was the best option (FIN: 46%; SIP: 42%; OZA: 43%; PON: 52%), and preference for oral dosing (FIN: 59%; SIP: 46%; OZA: 37%; PON: 35%) were influential reasons for switching to each brand.
Mechanism of action (MOA) was more influential in switches to SIP than FIN (62% vs. 26%) and comfort/familiarity in switches to FIN and SIP vs. newer S1Ps (FIN: 35%; SIP: 39%; OZA: 13%; PON: 4%). Being studied in SPMS clinical trials was also influential for SIP (19%).
If the current DMT had not been available at the time of prescribing, SIP (64%), OZA (64%), and PON (62%) patients would most likely have been switched to another S1P DMT. OZA was the most common alternative for PON (52% vs. 4% for FIN); PON for OZA (37% vs. 4% for FIN and 4% for SIP); FIN (27%) or PON (31%) for SIP; and a platform oral DMT (41%) for FIN.
Conclusions: While recent switch patterns among S1P receptor modulators were similar, SIP's MOA and evaluation in SPMS trials is influential in driving its use among MS patients. Its more established position on the market relative to OZA and PON are also drivers of use over these agents.

Disclosure
EM is an employee of Spherix Global Insights, an independent market intelligence firm, and have received no industry funding to conduct and report on this study.

EP1073

A real world multi centre study on efficacy and safety of natalizumab in indian patients with multiple sclerosis

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Introduction: Natalizumab (NTZ) is increasingly being used in Indian multiple sclerosis (MS) patients after its availability in 2012. There are no reports on the efficacy and safety of NTZ in Indian patients.
Objectives: To describe the patient characteristics, treatment outcomes, and adverse events, especially the occurrence of PML in NTZ treated MS patients.
Methods: A multicentre ambispective study was conducted across 18 centers, in India, from Jan 2012 to Dec 2021. All MS patients above the age of 18 years treated with NTZ were included. Data were obtained from case records with respect to the type of MS, duration of MS, duration of NTZ treatment, relapse rate and EDSS score at baseline and follow-up, treatment administered before and after NTZ, and adverse effects especially occurrence of PML. Descriptive and comparative statistics were applied to analyze data using SPSS version 25(IBM).
Results: During the study period of 9 years, 116 MS patients, 92(79.3%) RRMS, and 24 (20.7%) SPMS received NTZ. The mean age of the cohort was 35.6 ± 9.7 years; 83/116 (71.6%) were females. 91% of patients were on first-line disease-modifying drugs (DMDs) while 8.6% (10/116) were given NTZ directly. The relapse rate for the entire cohort in the year before NTZ was 3.1±1.51 while after NTZ, at the last, follow-up, it was 0.20±0.57 (p=0.001; CI 2.45 -3.35). EDSS of the entire cohort before NTZ was 4.5±1.94 and after NTZ was 3.8±2.7 (p=0.013; CI 0.16-1.36). The duration of NTZ treatment was 22±19.3 months (range 5-127 months). Post-NTZ 65.5% (76/116) were on rituximab treatment. During the last follow-up (38.3 ± 22.78 months, range 6-96 months) there were no cases of PML identified.
Conclusions: Natalizumab appears highly effective and safe in Indian MS patients, with no cases of PML identified during the last follow-up.

Disclosure
Nothing to disclose

EP1074

Impact of COVID-19 infection and COVID vaccinations on the management of MS and related disorders in a low middle income country - real world experience from a demyelinating disease registry

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Background and objective: The impact of COVID-19 infection and the effect of vaccinations on patients with demyelinating central nervous system disease in low middle income countries (LMIC's) have not been reported in detail earlier. We sought to identify risk factors associated with COVID-19 infection and the role of vaccinations in patients with MS and related disorders in order to develop management guidelines relevant to our patients.
Methods: A total of 621 patients (297 MS and 324 non MS disorders) from our registry were contacted. COVID-19 infection and vaccination status were queried. Patients who had infection were compared with noninfected patients to identify factors associated with susceptibility for COVID-19 infection. Univariate and multivariate analysis of potential risk factors included demographic and clinical features, body mass index (BMI), presence of comorbidities, absolute lymphocyte count, treatment types and vaccination status.
Results: Sixty seven patients with MS and 27 with non MS disorders developed COVID-19 infection. Among them 13 patients were hospitalized, all of whom recovered. Vaccination status was known in 582 patients among whom 69.8% had completed or taken one dose of vaccine at the time of inquiry. Majority of treated patients (61.3%) were on nonspecific immunosuppressants. Multivariate analysis of all patients with MS and related disorders showed that higher mean body mass index(BMI [p – 0.002,OR- 0.86,95% CI – 0.78-0.94]),presence of ⩾ 1 comorbidity (p-0.005,OR- 3.57,95% CI- 1.46- 8.7) and concurrent treatment with disease modifying therapy(p- 0.004, OR- 2.80, 95% CI- 1.39- 5.6)were significantly associated with risk of COVID-19 infection. Vaccination against COVID-19 infection was strongly protective (p- 0.0001, OR- 0.10, 95% CI- 0.05-0.20). In the unvaccinated group, patients on treatment (61% were on nonspecific immunosuppressants) were significantly at risk of Covid-19 infection (p- 0.001, OR- 10.1, 95% CI- 4.59-22.22) when compared to untreated patients.
Conclusion: Frequency and severity of COVID-19 infection was low among our patient cohort.Higher rate of infection in the treated group was significant among unvaccinated
patients. Our preliminary results suggests that in LMIC's, where "off label therapies" with inexpensive immunosuppressives are the main disease modifying drugs, mRNA
vaccinations appear safe and protective against severe COVID-19 infection.

Disclosure
No conflict of interest to disclose. This study recieved no funding.

Therapy - Neuroprotection and Repair

EP1075

***Centella asiatica* increases cortical mitochondrial oxidative respiration and antioxidant gene expression, and reduces spinal cord inflammation in experimental autoimmune encephalomyelitis**

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Introduction: Centella asiatica is a botanical with antioxidant and anti-inflammatory properties used in ayurvedic medicine to promote healthy aging. Preliminary studies of a water extract ofCentella asiatica (CAW) in animal models of aging and dementia demonstrate improved cortical mitochondrial oxidative respiration and increased antioxidant gene expression.
Objectives: Because of common pathophysiology, we hypothesized that CAW would have antioxidant and anti-inflammatory benefits in an animal model of multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE).
Aims: To determine the effects of CAW on cortical oxidative respiration, antioxidant gene expression, and spinal cord inflammation in EAE. Secondary aims evaluated changes in EAE disability.
Methods: Thirty female C57Bl/6J mice were divided equally into sham induction (saline) with placebo treatment (CTR), EAE plus placebo (PBO), and EAE plus CAW (CAW). EAE induction was by myelin peptides and pertussis toxin with booster at 2 days post-inoculation. Treatment starting day 6 continued up to and including day 20 with CAW (500 mg/kg/d CAW orally in vehicle of 5% sucrose in phosphate buffered saline) versus vehicle for placebo. Disability was using the EAE disability scale. Post-mortem studies included SEAHORSE for cortical respiratory oxygen consumption, cortical NRF2 and target antioxidant protein gene expression, and immunohistochemistry of spinal cords for immune cells, myelin, axons, and markers of microglial activation. ANOVA and t-tests determined treatment effects.
Results: CAW treatment attenuated the significant EAE deficits in basal and maximal mitochondrial oxidative respiration returning bioenergetics to CTR values. CAW increased antioxidant gene expression of NRF2, GCLC, NQ01, and HMOX1 significantly above the increases caused by EAE alone. CAW significantly reduced CD3 infiltration into spinal cords. There were no differences in EAE scores between CAW and PBO. Significance set at $p<0.05$.
Conclusion: Centella asiatica demonstrates mitochondrial, antioxidant, and anti-inflammatory benefits in EAE. Development of MS therapies may benefit from advances in other neurodegenerative diseases that share common pathological processes.

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EP1076

Preventive effects of ponesimod on cingulum demyelination

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Introduction: Fatigue is a prominent symptom in multiple sclerosis (MS) and limits daily performance. Abnormalities in the limbic pathway, such as cingulum, have been clinically associated with MS fatigue and cognitive decline.The cuprizone model, that serves as an animal model of MS, is commonly used to assess demyelination and remyelination mainly in corpus collosum (CC). We recently identified that cuprizone induced robust demyelination in not only CC, but also in cingulum. Moreover, preventative treatment of ponesimod, a U.S. Food and Drug Administration (FDA)-approved MS drug that is a sphingosine 1-phosphate receptor 1 ($S1P_1$) selective modulator, protected mice from demyelination selectively in cingulum. Moreover, therapeutic treatment of ponesimod enhanced remyelination in cingulum.
Objectives: Determine gene expression alterations in cortex, CC, and cingulum of ponesimod-treated cuprizone mice.
Methods: C57BL/6 male mice were fed a 0.2% cuprizone diet for 5 weeks with concomitant preventative treatment with vehicle or ponesimod (30 mg/kg) for 5 weeks. Histological assessment was conducted to validate demyelination and cellular profiles. Moreover, single nucleus RNA-sequencing (snRNA-seq) were conducted in cortex, CC, and cingulum of cuprizone-fed mice treated with or without ponesimod.
Results: Ponesimod increased $Olg2^+$ oligodendrocyte progenitor cells in both CC and cingulum, and suppressed $Iba1^+$ microglial accumulation in the cingulum. The snRNA-seq analyses identified neuronal cell types (neurons, astrocytes, and oligodendrocytes) and accumulation of myeloid cells in CC and cingulum. Moreover, a considerable number of differentially expressed genes (DEGs) and their associated gene ontologies were identified in each cell type.
Conclusion: Ponesimod prevented demyelination and accelerated remyelination in cingulum, which may partly explain ponesimod's efficacy in fatigue reported in a completed phase 3 clinical trial (OPTIMUM).

Disclosure
J.C. has received consulting fees or research support from Johnson & Johnson. The other authors declare that they have no competing financial interests.

EP1077

Combining remyelination and immunosuppression for multiple sclerosis therapy

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Introduction: Multiple sclerosis (MS) is characterized by white as well as grey matter inflammation, consisting of loss of axons, myelin and oligodendrocytes. Inflammatory demyelination disrupts nerve signals and contributes to irreversible axonal degeneration and neuronal loss.
Objectives: Remyelination represents a promising therapeutical target with the potential to restore motor functions and axonal integrity in MS patients. Several studies suggest a potential role of the κ-opioid receptor (KOR) in MS. For instance, KOR ligands have been identified by high-throughput screening as remyelination-inducing compounds. Activating KOR alleviates disease symptoms in the experimental autoimmune encephalomyelitis (EAE) model, by promoting oligodendrocyte differentiation and remyelination. Thus, targeting the KOR represents an intriguing strategy to develop novel therapeutics for the treatment of MS.
Aims and Methods: Preclinical exploration of combined immunosuppressive and remyelination efficacy using the EAE mouse model, receptor pharmacology, immune cell signalling and histology.
Results: The circular peptide [T20K]-kalata B1 (T20K), exerts potent immunosuppressive effects, ameliorating the onset and symptoms severity of EAE. Specifically, T20K inhibits human T-cell proliferation by an IL-2-dependent mechanism. Preclinical studies have confirmed the lack of significant infiltration of mononuclear cells and an intact myelin sheath of the spinal cord following T20K treatment in vivo. This led to a significant reduction of inflammation and lower grade of demyelination in the central nervous system. Extensive efforts in identifying the molecular target of T20K led to KOR. T20K bound to and activated KOR with moderate potency and is a positive allosteric modulator by stimulating the efficacy and/or potency of known KOR ligands. We present our efforts in preclinical development of T20K, and to further understand details of the mechanism of action of a novel combination therapy (T20K and established opioid drugs), specifically addressing pharmacology at KOR and preclinical assessment of neuroinflammation and neurodegeneration associated with MS.
Conclusion: Therapeutics such as the T20K/opioids that control overreactive immune cells and promote remyelination and nervous tissue repair would represent an ideal combination for maximum benefit in MS therapy.

Disclosure
CWG is shareholder and scientific consultant of Cyxone AB.

Therapy - Long-term treatment monitoring

EP1078

Clinical effectiveness and safety of dimethyl fumarate for patients treated at least 6 years in the swedish post-market surveillance study "immunomodulation and multiple sclerosis epidemiology 5" (IMSE 5)

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Introduction: Dimethyl fumarate (DMF) is an oral therapy for relapsing-remitting multiple sclerosis (RRMS). DMF is included in the Swedish post-market surveillance study "Immunomodulation and Multiple Sclerosis Epidemiology" (IMSE).
Objectives/Aims: To assess the effectiveness and safety of DMF with focus on patients treated at least 72 months.
Methods: Descriptive data of Extended Disability Status Scale (EDSS), Multiple Sclerosis Severity Scale (MSSS), Symbol Digit Modalities Test (SDMT), Multiple Sclerosis Impact Scale (MSIS-29), European Quality of Life - 5 Dimensions Test (EQ-5D), Visual Analog Scale (VAS), Adverse Events (AEs) and Serious AEs (SAEs) is obtained from the nationwide Swedish Neuro Registry (NeuroReg). Effectiveness measures were assessed using the Wilcoxon Signed Rank Test and drug survival using the Kaplan-Meier curve.
Results: 2565 DMF-treated patients were included between March 2014 and March 2022 with an overall drug survival rate of 38.7% and a mean treatment duration of 37 months. The main reasons for discontinuation were AEs (47%) and lack of effect (30%). 199 AEs were reported of which 63 were serious. For both serious and non-serious AEs reported, gastrointestinal disorders were the most common (19% and 27%, respectively).
509 patients had continuous treatment for at least 72 months. This cohort had a mean age of 42 years and a mean treatment duration of 84 months. The majority (51%) had switched from interferon or glatiramer acetate and 24% were treatment naïve.
Significant improvements in mean values at 72 months of treatment compared to baseline were noted for MSSS, MSIS-29 Psychological, and EQ-5D ($p<0.05$). All other tests remained stable after 6 years of treatment. Number of relapses per 1000 patient years were improved from 199.6 before DMF treatment start to 23.0 during treatment with DMF.
49 patients (10%) have discontinued DMF treatment in the 72 month cohort with a mean treatment duration of 84 months (range 70-97 months). The main reasons for discontinuation were other reasons (33%), lack of effect (29%), stable condition (14%), and AEs (12%).
Conclusions: DMF demonstrates partly clinical improvements in patients treated 72 months. However; due to the high discontinuation rate there is an unavoidable selection bias. Continued follow up is needed to assess the effectiveness and safety of DMF over longer time periods in a real world setting.

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EP1079

Evolution of the RebiSmart®autoinjector device in support of adherence to subcutaneous interferon beta-1a therapy for relapsing multiple sclerosis

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Introduction: The RebiSmart® autoinjector device helps people with relapsing multiple sclerosis (MS) to adhere to treatment with subcutaneous interferon beta-1a (sc IFN β-1a).
Objectives: Evolution of the device is designed to meet the changing needs of people with relapsing MS.
Aims: Report on adherence to/persistence with the existing RebiSmart® autoinjector device among people receiving sc IFN β-1a for relapsing MS, and describe the results of a formative study designed to evaluate evolution of the device.
Methods: Adherence/persistence data were derived from the anonymised MSdialog database (database closure, November 2019). Adherence (%) = no. of injections recorded/no. of injections prescribed, and calculated on a monthly basis. Persistence (in terms of device usage) = duration (in months) between first and last recorded use. Descriptive and multivariate analyses were performed on data concerning the first 3 years of use (device lifetime). In parallel, a formative study of adolescent proxy subjects, adults with MS, and MS nurses evaluated an updated version of the device in order to inform future summative studies.
Results: A total of 2644 device users were evaluated (median age, 38.3 years; females, 69.1%). Over 3 years, monthly adherence averaged ~85% for males and females alike. There was a trend for higher adherence with increasing age of users and first recorded depth of injection. Mean persistence (standard deviation) was 1.35 (1.06) years. A trend for higher persistence with increasing age of users was also apparent, but persistence tended to be lower for females and those who received titrated dosing to the full therapeutic dose from initiation. There was no relevant impact of injection depth on device persistence.
In the formative study, participants (n=9) identified several strengths of an updated device, including ease of use (such as on-screen prompts/audible reminders), favourable size/safety, and personalisation options. Opportunities for improvement included consideration of dexterity among people with relapsing MS and modification of on-screen functionality.
Conclusions: The existing RebiSmart® autoinjector device is associated with high rates of adherence/persistence. The formative study of an updated version of the device identified several strengths and opportunities for improvement, which have been implemented as part of a commitment to improving the care of people with relapsing MS.

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LA, **MK**, and **FP** are employees of Ares Trading S.A. Eysins, Switzerland (an affiliate of Merck KGaA).
EH is an employee of Evi-Science, Geneva, Switzerland and provides statistical consultancy to Merck.
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EP1080

Reconstitution of lymphocytes following discontinuation of dimethyl fumarate (DMF) due to lymphopenia in the swedish post-market surveillance study "immunomodulation and multiple sclerosis epidemiology 5" (IMSE 5)

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Introduction: Dimethyl fumarate (DMF) is an oral therapy approved for patients with relapsing-remitting multiple sclerosis (RRMS) where a decline of the lymphocytes is a known pharmacodynamic effect. Currently, research has suggested meaningful lymphocyte reconstitution may occur within 2-4 months after discontinuation of DMF. To date, the only factor shown to be associated with a slower rate of recovery is the duration of lymphopenia.
Objectives/Aims: To describe lymphocyte count profiles following discontinuation of Dimethyl fumarate (DMF) due to lymphopenia in a nationwide Swedish population-based setting.
Methods: The IMSE 5 study obtains demographics, clinical and safety data, including absolute lymphocyte count (ALC), from the Swedish population-based Neuro Registry. Key inclusion criteria were RRMS patients, treatment with DMF for at least 12 months, age >18 years at initiation, and discontinuation of DMF due to lymphopenia or with a lymphocyte count of $\leq 0.80 \times 10^9$/L at time of discontinuation. The least square mean estimation of ALC values at different time points was calculated using Linear Mixed Models.
Results: A total of 102 DMF patients were included, 70% were female and the mean age at treatment start was 44.8 years. The mean treatment duration was 2.5 (SD 1.3) years. 30% of the patients were treatment naïve, 46% had switched from interferons or glatiramer acetate (GA), 4% from natalizumab and 3% from

fingolimod. ALC values following discontinuation of DMF significantly increased during follow up; at drug discontinuation the mean ALC was 0.54x10^9/L (95% CI 0.48-0.61), at 13-16 weeks following discontinuation 0.79 x10^9/L (95% CI 0.61-0.96; p=0.0109) and at 29-32 weeks 0.85 x10^9/L (95% CI 0.68-1.02; p=0.001). The mean time from discontinuation to start of a new treatment following DMF discontinuation was 2.7 (SD 4.5) months, where 35% switched to rituximab, 9% to teriflunomide, 5% to Natalizumab, and 3% to GA.

Conclusions: Data from the Swedish IMSE 5 study suggest that a lymphocyte reconstitution occurs within 13 to 16 weeks following the discontinuation of DMF. However, larger datasets will be needed to verify this finding and also to determine the possible impact of any newly started therapy.

Disclosure

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EP1081

Real-world data of ocrelizumab effects on disability progression; A 2-year follow-up study

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Introduction: Ocrelizumab is an effective treatment in reducing relapse rate and slowing disability progression in the short term.

Aims: To evaluate disability progression in people with multiple sclerosis (pwMS) treated with ocrelizumab.

Methods: pwMS candidates for ocrelizumab treatment were enrolled in this prospective single-center observational study and followed up for two years. Disability was evaluated with Expanded Disability Status Scale (EDSS), Timed 25 Feet Walk (T25F) test, 9 Hole Peg Test (9HPT), Timed up and Go (TUG) test, and Twelve Item MSWalking Scale (MSWS) survey. First assessments were done before the ocrelizumab initiation and every six months afterward. Patients with secondary progressive and primary progressive MS were analyzed as progressive MS (PMS). A change of %20 in test performance time was considered clinically significant.

Results: 107 PMS patients were enrolled. When analyzed separately, there was no significant difference between baseline and two-year follow-up scores in total EDSS and functional subscores ($p>0.05$). PMS showed significant worsening in the TUG test ($p=0.043$) in the first, T25FW ($p=0.03$) in the second, and MSWS-12 scores in the first (N:99, p:0,006) and the second (N:43 p:0.002) years of evaluation in comparison to baseline results. Of 53 PMS evaluated in the second year, 39 had not shown significant change on 9HPT results, two had improved performance, and 12 had a %20 increase in the test time compared to baseline. Overall 9HPT results did not show a significant change in two-year follow-up ($p>0.05$).

Conclusions: Although ocrelizumab does not show favorable results in the lower extremity functions in the progressive form, it could halt the disability accumulation in the upper extremity in the long term.

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Serkan Ozakbas: nothing to disclose

EP1082

Proportion of relapsing MS patients with low vs high annualised whole brain volume atrophy rates after 5–6 years of ozanimod and relationship to cognitive processing speed

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Introduction: Ozanimod 0.92 mg/d for ⩽24 months was superior to interferon β-1a (IFN) 30 μg/wk on clinically meaningful measures of disease activity (relapses, MRI brain lesion counts, brain

volume, and cognition) in phase 3 trials of ozanimod in relapsing MS (RMS).
Objectives: To identify the proportion of patients (pts) with RMS with low (⩽0.4%) vs high (>0.4%) annualised rate of brain volume loss (ARBVL) during long-term ozanimod treatment in phase 3 and open-label extension (OLE) trials and assess relationships between ARBVL and cognitive processing speed on the Symbol Digit Modalities Test (SDMT).
Methods: Patients with RMS were treated with oral ozanimod 0.46 or 0.92 mg/d or intramuscular IFN 30 μg/wk for ⩾12 months (SUNBEAM–NCT02294058) or 24 months (RADIANCE–NCT02047734). Completers were eligible to enrol in an OLE trial (DAYBREAK–NCT02576717), in which they received ozanimod 0.92 mg/d. Whole brain atrophy rates were calculated from MRI scans obtained at baseline, months 6 and 12 in SUNBEAM, months 12 and 24 in RADIANCE, and months 12, 24, 36, and 48 in the OLE. Proportions of pts with ARBVL ⩽0.4% and >0.4% were assessed. SDMT scores were assessed every 6 months in SUNBEAM and annually in DAYBREAK and reported by ARBVL category (⩽0.4% vs >0.4%).
Results: During phase 3 trials, significantly greater proportions of pts in the ozanimod 0.92 mg group had low ARBVL vs the IFN group (SUNBEAM month 12: 50.9% vs 37.5% [nominal P<0.001]; RADIANCE month 24: 63.1% vs 50.0% [nominalP<0.01]). In pts continuously treated with ozanimod 0.92 mg, the proportion of pts with low ARBVL increased over time (SUNBEAM into OLE, month 48: 66.4%; RADIANCE into OLE, month 48: 79.2%). In pts continuously treated with ozanimod 0.92 mg, those with low ARBVL had significantly higher mean SDMT scores than those with high ARBVL (SUNBEAM into OLE, month 48: 52.7 vs 45.4, difference 7.2 [95% CI, 3.3–11.2]; RADIANCE into OLE, month 48: 50.5 vs 40.5, difference 10.1 [95% CI, 3.5–16.7]). The same was true in pts who switched from IFN to ozanimod in the OLE (SUNBEAM into OLE, month 48: 50.9 vs 45.8, difference 5.1 [95% CI, 1.4–8.9]; RADIANCE into OLE, month 48: 48.5 vs 42.0, difference 6.5 [95% CI, 0.2–12.7]).
Conclusion: In phase 3 trials, a nominally significantly greater proportion of pts treated with ozanimod 0.92 mg vs IFN had lower ARBVL. Patients with low ARBVL exhibited significantly higher cognitive processing speed performance (measured by SDMT) than those with high ARBVL.

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JVR, CC, and CP: Employees and shareholders of Bristol Myers Squibb
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EP1083

Two years of high-efficacy therapy reduces disease activity and brain volume loss in Japanese patients with relapse-onset multiple sclerosis

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Introduction: High-efficacy therapy (HET) can favourably affect disability progression and brain volume loss in patients with multiple sclerosis (MS). However, whether HET also affects regional brain volume loss remains unclear. Additionally, there is limited evidence regarding the effectiveness of HET in Asian individuals with MS.
Objectives: The aims of this study were to compare the clinical disease activity as well as the cortical and subcortical grey matter regional volumes in Japanese patients with MS receiving HET or low-efficacy therapy (LET).
Methods: This prospective study included 44 patients with relapse-onset MS who underwent HET (n = 19) or LET (n = 25). First, we observed neurological status of study patients and measured the regional brain volume change using three-dimensional T1-weighted magnetic resonance imaging and FreeSurfer software. Then, we developed generalised linear mixed models

(GLMMs) to evaluate associations between changes in volume and the treatment type.
Results: The average observation period was 2.0 ± 0.16 years. During which, HET was associated with a significantly higher rate of a "no evidence of disease activity-3" status than LET ($p = 0.012$). HET also positively correlated with volume changes in the left cortex ($\beta = 0.65$, $p = 0.048$), left ($\beta = 0.98$, $p = 0.0033$) and right ($\beta = 0.77$, $p = 0.019$) caudates, and right putamen ($\beta = 0.87$, $p = 0.0077$) after adjusting for age, sex, and MS severity scores in the GLMMs.
Conclusions: HET improves the two-year prognosis of Japanese patients with relapse-onset MS by reducing disease activity and regional brain volume loss.

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EP1084

Effects of ocrelizumab on disability progression and inflammatory activity in multiple sclerosis patients during the two-year follow-up

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Background: Progression is still not adequately managed in multiple sclerosis.Ocrelizumab was shown to halt the disability progression for a short period in the phase 3 clinical trial.
Aims: To prospectively evaluate the silent progression and incomplete recovery from a relapse in patients treated with ocrelizumab.
Methods: This isa prospective cohort study of multiple sclerosis patients on ocrelizumab treatment.Expanded Disability Status Scale (EDSS), Timed 25 Foot Walk (T25FW) test, 9 Hole Peg Test (9HPT), and MRI was done before the ocrelizumab infusion and yearly afterward. No evidence of disease activity (NEDA-3) was defined as no evidence of clinical relapse, disease progression measured by EDSS, new T2 lesions, or contrast-enhancing lesion on MRI throughout the observation period. Progression independent of relapse activity (PIRA) was defined as having at least one of these components in the absence of relapse activity in the last 30 days before and after the initial increase in disability; a)increase in EDSS score, b)an increase of %20 in T25FWT result or c)an increase of %20 in 9PHT time compared to baseline and which sustained for at least three months. Relapse-associated worsening (RAW) is at least a 1.0 point increase in EDSS score within 180 days of relapse.
Results: In the first year of ocrelizumab treatment, NEDA-3 was achieved in 244(88.4%, N:276), RAW occurred in 3(42,8%, Number of relapses: 7), and PIRA was seen in 21 patients (23,6%, N:89). The results for the second year of follow-up are NEDA-3: 167 (78,4 %, N:213), RAW: 1(12,5%, Number of relapses: 8) and PIRA: 15 patients (41,7%, N:36).
Conclusions: Protective effect of ocrelizumab on disability progression lessens during the second year of treatment, while relapse-associated worsening improves due to a decrease in inflammatory activity.

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EP1085

Real world experience with cladribine treatment in Slovakia

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Background: Data from registration studies indicate that cladribine is effective for the treatment of MS and has a promising safety and tolerability profile. However, careful long-term monitoring is needed. Real world data could provide valuable information about cladribin in routine clinical practice.
Objectives: This paper present a retrospective analysis of the effectiveness and safety of cladribine treatment in two MS Centers in Slovakia.
Methods: We performed a retrospective cohort study of 93 patients with relapsing MS, receiving cladribine treatment since December 2018 to May 2022. One patient was excluded, follow-up was lost. We collected information about relapses, disability

(using EDSS), and MRI activity before and during cladribine treatment. Data about previous immunomodulatory medicaments (IMT) and adverse events associated with cladribine treatment were also found.

Results: Mean age of group was 44years, 71% were women. Before starting cladribine mean EDSS was 4.4 (+/- 3.1), disease duration was 11.6 (+/- 8.3), 97.8% patients experienced relapses and 25.8% had MRI activity. Before starting cladribine treatment, 33% received 1 IMT, 27% were on 2 IMT, and 33% were on ⩾ 3 IMT. 7 patients were IMT-naiive. Patients were most frequently switched to cladribine from dimetylfumarate and teriflunomide. In Year I cladribine treatment,86% (n = 78) of patients did not experience a relapse, and 79% of patients had no radiological activity, 96% of patients had no increase in EDSS following cladribine treatment. In Year II, 83% (n = 53) of patients did not experience a relapse, 92% of patients had no radiological activity, and 80% of patients had no increase in EDSS following cladribine tablets treatment. In Year III, 93% (n = 30) of patients did not experience a relapse, 88% of patients had no radiological activity, and 96% of patients had no increase in EDSS. None of the patient had grade 4 lymphopenia. Lymphopenia grade 2 was the most frequent (41%). We detected one case of mammal carcinoma and 2 precancerosis (dysplasio cervicis uteri) after Year I. The patients did not continue in treatment. Upper respiratory tract infections, Covid-19, fatigue, back pain and artralgy were most common adverse effects in the group.

Conclusions: Our study confirmed high long-term efficacy of cladribine in MS patients. Considering relative risk of cancer we strictly require patients to have a periodic preventive medical evaluation

Disclosure

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EP1086

Assessment of treatment satisfaction across oral DMTs for multiple sclerosis: a preliminary baseline analysis from the STATURE study

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Introduction: Medication adherence is crucial to maximise disease modifying therapy (DMT) efficacy. Understanding treatment satisfaction, side-effects and perceived efficacy across different DMT administration schedules is important for clinical decision-making that maximises DMT adherence in people with multiple sclerosis (MS).

Objective: STATURE is a multi-site prospective longitudinal trial to assess the real-world relationship between treatment burden, medication adherence and quality of life in people newly prescribed oral DMTs: cladribine, dimethyl fumarate, fingolimod, teriflunomide and ozanimod, within routine care.

Aim: The current preliminary baseline data analysis aims identify differences in DMT satisfaction at time of initiation.

Methods: Participants include 91 people with MS (80.2% female; age M=43.3, SD=13.9) recruited across 10 Australian healthcare sites between September 2020 and 15 May 2022. Of these, 65 (71.4%) had commenced cladribine, 16 (17.6%), dimethyl fumarate, 6 (6.6%) fingolimod and 4 (4.4%) teriflunomide. The Treatment Satisfaction Questionnaire for Medication (TSQM) was administered at baseline. The TSQM measures four treatment domains: global satisfaction, effectiveness, side-effects and convenience. T-tests were used to identify between DMT differences.

Results: Participants prescribed fingolimod and cladribine reported significantly higher perceived convenience when compared to participants prescribed dimethyl fumarate (mean difference [MD] =22.8, t=2.7, p=.007; MD=11.2, t=2.7, p=.009, respectively). Fingolimod was also significantly higher for perceived convenience when compared to cladribine (MD=11.6, t=2.1, p=.04) and for global satisfaction when compared with teriflunomide (MD=25.0, t=2.7, p=.02). There were no other significant between group differences (all p>.05).

Conclusions: Understanding perceived satisfaction related to DMTs prescribed for people with MS is important. While results of this preliminary analysis require cautious interpretation because of the small sample sizes for fingolimod and teriflunomide, identification of baseline differences in medication satisfaction highlights the need for this current research that assesses the relationship between treatment burden, such as administration schedule and side-effects, with medication adherence and quality of life across oral DMT options for people with MS.

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Mardan, Joshua has nothing to declare
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Savickas, Sharryn has nothing to declare
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EP1087

Quantitation of bivalent and monovalent natalizumab: providing a tool to study effects of IgG4 arm exchange

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Background: Natalizumab, a therapeutic antibody that targets the α4 chain of integrins, is indicated for treatment of relapsing–remitting multiple sclerosis. While highly efficacious, the immunosuppressive activity of natalizumab has been associated with JC polyomavirus driven progressive multifocal leukoencephalopathy (PML). Natalizumab can undergoin vivo arm exchange, where a heavy chain and associated light chain from one antibody is swapped with that from another, to form a monovalent, bispecific antibody that has a reduced target binding affinity compared to the original bivalent form. The clinical significance of a PK/PD relationship with this monovalent to bivalent ratio or a relevance to the risk of PML has not been thoroughly investigated. Simple assays that can quantitate the different forms are thus needed.

Method and Results: Natalizumab was treated in vitro to generate a monovalent form that contains one arm from natalizumab (with kappa light chains) and the other from an irrelevant antibody with lambda light chains. Use of an anti-lambda antibody for detection allows monitoring of monovalent natalizumab generated in thein vitro reaction. Two ELISA capture reagents, an anti-idiotype antibody and a peptide mimetic (Veritope™), were compared in their ability to bind total, monovalent, and bivalent forms of natalizumab. The anti-idiotype antibody captured all species of natalizumab enabling quantitation of the total level. However, Veritope™ exclusively captured bivalent natalizumab, allowing a simple subtraction of bivalent from total to calculate the quantity of monovalent. Clinical samples, collected at nadir, were tested with the assays. It was expected that most natalizumab would be monovalent, but some samples contained bivalent natalizumab at a significant level (3-9ug/ml).

Conclusion: A complete understanding of the PK/PD relationship for natalizumab must include the function differences of monovalent and bivalent natalizumab resulting from in vivo arm exchange. Tools and assays that can distinguish the biologically relevant forms are an important step towards this goal. We have leveraged the difference in binding affinities of a peptide mimetic and an anti-idiotype antibody to create a pair of assays that measure total and bivalent natalizumab and can be used towards this goal in clinical studies.

Disclosure

Lesley Page: Employment by Aegirbio
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EP1088

Efficacy and safety profiles of cladribine in highly active multiple sclerosis: a tertiary MS center experience in Turkey

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Introduction: The patients who manifest rapid accumulation of physical and cognitive decline despite treatment with one or more disease-modifying drugs (DMTs) are accepted as highly active multiple sclerosis (HA-MS). Cladribine is an effective treatment option for HA-MS. We aimed to evaluate the efficacy and safety profiles of cladribine HA-MS patients.

Methods: HA-MS patients under cladribine from July 2020-May 2022 were included in the study. Demographic data, disease duration and progression parameters, and Covid-19 infection data were evaluated.

Results: The study included 82 patients (64 female,18 male). The mean ages were 38.17±8.7 years. According to the Lublin classification, 18 (22%) patients had non-active/non-progressive, 35 (42.7%) had active/nonprogressive, 21 (25.6%) had non-active/progressive and 8 (%9.7) patients had active/progressive MS. The mean disease durations were 9.75±6.42 years. The mean follow-up duration under cladribine was 8.32±5.4 months. The median EDSS score both before and after treatment was 2.5 (0-7) (p=0.086). Fifty (61%) of the patients were switched from first-line DMT, 27 (32.9%) from second-line DMT, and cladribine was the first drug in 4 patients. Most of the patients were switched from interferon/glatiramer acetate (24.4%), teriflunomide (20.7%), and fingolimod (19.5%). 12 (14.6%) of the patients had grade 1, 14 (17.1%) had grade 2, 2 (2.4%) had grade 3 lymphopenia. None of the patients observed had grade 4 lymphopenia. Overall, 24 (29.2%) patients had mild complaints under cladribine. Most common side effects were hair loss (n=8; 9,75%), mild ALT/AST elevation (n=5; 6.1%); headaches (n=3; 3.7%), mild skin reactions (n=5; 6.1%). One patient had a zona zoster infection, while 2 complained of frequent urinary infections. No serious infection, allergic reactions, and malignancy were observed. 8 (9.75%) patients developed attacks under cladribine while under cladribine for at least one month, and the symptoms resolved after intravenous methylprednisolone. 18 (21.95%) patients had Covid-19 infection, and all but 1 had mild symptoms. One patient had a mild MS attack one month after the Covid-19 infection. None of the patients experienced any attacks or severe side effects after the Covid-19 vaccination.

Conclusion: Cladribine therapy is a well-tolerated and so far effective treatment option for HA-MS patients. Long-term efficacy and safety studies are still needed.

Disclosure

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Dr. Asli Tuncer has nothing to disclose.
Dr. Rana Karabudak has nothing to disclose.

Therapy - Risk management for disease modifying treatments

EP1089

DISCOntinuation of disease-modifying therapies in MS (DISCOMS) extension – study design and baseline demographics to date

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Introduction: Whether and when it is safe to discontinue disease-modifying therapy (DMT) in older multiple sclerosis (MS) patients remains unclear. Prior surveys show many are hesitant to consider stopping DMT, and studies with longer post-discontinuation data are needed. We performed the DISCOMS study, a randomized, controlled, rater-blinded non-inferiority study of 259 patients continuously taking DMT who were 55+ years old, and without relapse for ⩾5 years and new magnetic resonance imaging (MRI) lesions for ⩾3 years. Over a mean 22 months follow-up, we did not show that discontinuation was non-inferior to continuing DMT when looking at a combination outcome of relapse and/or new brain MRI lesions (the primary outcome). Disease activity was most commonly 1-2 new MRI lesions, but without relapse. Relapses alone were rare in both groups and discontinuation was not inferior. There was no difference in rate of disability progression.
Objective: Complete a controlled, blinded extension of DISCOMS by performing a single visit 30-54 months post-enrollment in 100 prior participants in DISCOMS.
Aims: Compare risk of new relapses or brain MRI lesions, disability progression (by the Extended Disability Status Scale - EDSS), and changes in cognition, quality of life and other patient-reported outcomes (PROs) between those continuing and discontinuing DMT.
Methods: From 10 participating sites, we will enroll 100 patients who have completed DISCOMS; did not reach the primary endpoint of a relapse or brain MRI lesion during the original trial; and retained original randomized assignment throughout. Participants will be included regardless of whether they have developed new disease activity after completion of the primary study. All will undergo one study visit and brain MRI at approximately 30-54 months after original enrollment in DISCOMS. Primary endpoint will remain time to relapse or new brain MRI activity due to MS. Secondary endpoints include time to EDSS change, mean change in SDMT, and mean changes in PROs over time.
Results: We have enrolled 47/100 planned participants, 40.4% continuers and 59.6% discontinuers. Overall, 80.8% are women, 91.5% White, and 95.7% have relapsing MS. Mean EDSS 3.0 (range 0-6). At DISCOMS baseline, 66.0% were using either an interferon or glatiramer acetate as their DMT.
Conclusions: These trials will provide valuable data on durability of disease inactivity, and potential risks, after discontinuing MS DMTs.

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Ilya Kister: IK served on the scientific advisory board for Biogen Idec, Genentech, Alexion, EMDSerono; received consulting fees from Roche; and received research support from Guthy-Jackson Charitable Foundation, National Multiple Sclerosis Society, Biogen Idec, Serono, Genzyme, and Genentech/Roche
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Speakers' Bureau Biogen Idec (unbranded disease awareness programs only); EMD Serono (unbranded journal club); Alexion (unbranded disease awareness programs only); Genentech (unbranded disease awareness programs only
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EP1090

SARS-CoV-2 specific T cell immunity in spike protein antibody negative MS patients after vaccination

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Introduction: MS patients on highly-active disease-modifying treatment develop no or insufficient amounts of protective antibodies after vaccination against SARS-CoV-2, a matter of general concern. Besides the humoral response, the development of cellular vaccine response has not been reported.
Aims: To assess SARS-CoV-2 spike protein-specific cellular immunity in those multiple sclerosis (MS) patients who remain seronegative in response to vaccination.
Methods: In our centre, patients with no antibodies against the Spike-protein after two oder three doses of a SARS-CoV-2 vaccine were offered additional testing with a commercially available SARS-CoV-2 Elispot assay.
Results: All patients had been vaccinated using two or three doses of mRNA vaccines, according to national and international recommendations. To date, 10 patients on sphingosin-1 phosphate receptor modulators (S1PRM) were seronegative; none of these had SARS-CoV-2 specific T-cell reactivity. 12 patients on B cell depleting therapy were seronegative; in contrast to S1PRM treated patients, seronegative patients on B-cell depleting therapy showed a measurable T-cell based vaccine response.
Conclusion: In patients on S1PRM, absence of mRNA-vaccine induced SARS-CoV-2 antibodies corresponds to a lack of cellular response, while on B cell depletion, seronegativity provides only partial assessment of vaccine response. Analyses in patients who decide to get a booster vaccination are ongoing. The differential cellular response in MS patients on DMT targeting trafficking of all lymphocytes (S1PRM) vs depleting select lymphocyte populations might be expected.

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CG, ABa, US, ABo and FTB have nothing to disclose related to this project. The funding was provided by the University of Leipzig.

EP1091

Humoral and T-cell response to SARS-CoV-2 mRNA vaccine in multiple sclerosis patients treated with disease modifying therapies

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Introduction: The vaccination against SARS-CoV-2 is the main strategy to contain the pandemic and minimize hospitalizations principally in people with chronic diseases such multiple sclerosis (MS). Disease-modifyng therapies (DMTs) may impact on vaccine responses in MS people.
Objective and Aims: To evaluate humoral and T-cell response after SARS-CoV-2 mRNA vaccine in MS people treated with different DMTs.
Methods: 130 MS patients treated with different DMTs were recruited, blood samples for detection of SARS-CoV-2 antibodies were collected at T0, before the first dose of vaccine, at T1, before the second dose, and T2 one month after. In a subgroup of 51 patients and 20 controls, samples were collected at T0 and T2 to test T-cell immune response to Spike antigen of SARS-CoV-2 by ELISPOT-IFNγ.
Results: All 130 patients had negative SARS-CoV-2 antibodies before vaccination, 66% showed IgG response to the first dose of vaccine (mean [SD],757[852] AU/mL), and 88,5% after the second dose (7259,06[7251]).The IgG response rate to vaccine was 100% (20/20) in healthy controls and MS patients treated with teriflunomide (5/5), dimethyl-fumarate (5/5) and natalizumab (9/9), while it was significantly lower in patients treated with fingolimod (76.2%, 16/21) and ocrelizumab (36.4%, 4/11). The IgG levels in fingolimod (552.3 [957.9]) and ocrelizumab (159.1 [301.2]) were also significantly lower than healthy controls ($P<0.0001$). We detected positive Spike–specific T-cell responses in 100% of vaccinated healthy controls and patients treated with teriflunomide, dimethyl-fumarate and natalizumab, in 90.5% (19/21) of patients treated with fingolimod, and 63.8% (7/11) of patients treated with ocrelizumab.
Conclusions: The study confirm that the mRNA vaccine induce humoral specific responses in the majority of DMT-treated SM patients. It is noticeable the development of a T- cell–specific response to SARS-CoV-2 in patients treated with fingolimod and ocrelizumab, even with lower rates of humoral response. These findings encourage SARS-CoV-2 vaccination in all MS patients treated with DMTs.

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EP1092

Infections in patients with multiple sclerosis treating with disease-modifying therapies: a risk assessment cohort study

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Introduction: Multiple sclerosis (MS) is an ongoing challenge in 21 century. Disease-Modifying Therapies(DMTs) are the most common treatment regimens for MS patients. Several infections may occur during these treatments. Viral, bacterial, and fungal agents can cause these infections, and all should be considered to prevent the risk of the disease relapse or exacerbation.
Objectives: To assess the effects of DMTs on infection rates.
Aims: Outlook of common complications of DMTs on patients with MS.
Methods: This paper is a cohort study conducted from June 2020 to January 2022 using prospectively collected data from every registered patient at Tehran's Multiple Sclerosis referral research center. This study's inclusion criteria consisted of patients diagnosed with MS based on McDonald criteria and exposed to DMTs for at least six months. The exclusion criteria were under 18 years of age, diagnosis change during the study and mortality.
Results: We inducted a total of 979 patients into this study. We attempted 1:6 nearest neighbor propensity score matching without replacement with a propensity score estimated using logistic regression of the group on age and sex. 41 cases and 210 controls were discarded due to missing values for age and sex. Following matching, 18 more participants from the control group were discarded. Finally, data from 938 cases and 5628 control participants were analyzed. Urinary tract infection rate increased when patients were under treatment with Rituximab, Interferon beta1b,Fingolimod, Glatiramer Acetate, Azathioprine, or Teriflunomide. Bacterial vaginitis incidence was increased when patients were exposed to Fingolimod or Glatiramer Acetate. Moreover, Dimethyl Fumarate and Rituximab increased the rate of herpes (HSV) infection.
Conclusions: The use of DMTs can result in an increased rate of certain infections based on the type of drug usage. The population of healthcare providers and patients with multiple sclerosis should be enlightened about the consequences of DMTs.

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EP1093

Safety assessment of a natalizumab home administration procedure: results from a real-life cohort at the Lille university hospital

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Introduction: Natalizumab (NTZ) is a well-established disease modifying therapy used in active multiple sclerosis (MS). The most serious adverse event (AE) is progressive multifocal leukoencephalopathy. For safety reasons, hospital implementation is mandatory. Risk management strategy consists in monitoring exposition index to the JC virus (JCV) and regular MRI evaluation depending on the JCV exposition. The SARS-CoV-2 pandemic has deeply affected hospital practices leading French authorities to temporarily authorize to administer the treatment at home. The safety of NTZ home administration should be assessed.
Objectives: To describe the procedure and assess the safety in a home infusion NTZ model.
Methods: Patients presenting remitting-MS treated by NTZ for over two years, non-exposed to JCV and living in the area covered by the home care department were included from July 2020 to February 2021 to receive NTZ infusion at home every four weeks for 12 months. We did not include patients with inconsistent adherence to proper clinical and MRI monitoring or who had significant cognitive impairment. Each infusion was necessarily preceded by a teleconsultation (TC) with a neurologist to allow or cancel infusion the day before the scheduled date. A home care physician then received the information and notified the nursing team intervening at home. JCV serologies and clinical examination were organized and performed every 6 months for each patient at the hospital. Patients could ask for a visit in hospital at any time if neurological status was suspected to have changed. TC occurrence, JCV risk management, annual MRI completion were analyzed.
Results: From 198 NTZ-treated patients in Lille MS center,35 were eligible and included in the analysis. Seven of them did not complete the one-year home infusion follow-up. Preliminary results show that 369 TC allowing infusion were performed, 100% (369/369) of the home infusion were preceded by a TC. Two TC canceled the scheduled infusion, two TC led to a hospital visit to assess a potential relapse. No AE related to the home infusion process was reported. All 28 patients who have completed the follow-up benefited from hospital examination and JCV serologies two times and one annual MRI.
Conclusion: Preliminary results suggest that the established home NTZ procedure was safe. However, multicenter, prospective and comparative cohorts with large numbers are needed to confirm the safety of a home infusion NTZ model.

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EP1094

Longitudinal humoral immune response against COVID-19 adenovirus-based vaccines in patients with multiple sclerosis from Argentina undergoing immunosuppressive treatment

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Introduction: Most reports related to humoral immune response to COVID 19 vaccines in people with Multiple Sclerosis (pwMS) were performed on mRNA-based vaccines.
Objective: to analyze the longitudinal humoral immune responses to adenovirus-based vaccines (Sputnik V and AZD1222) in pwMS under different diseases modifying therapies (DMTs)
Methods: IgG anti- SARS-COV-2 spike titers in a cohort of 101 pwMS and 28 healthy controls (HC) were measured 6 weeks after vaccination using the COVID-AR kit according to the manufacture instructions. Both patients and controls received two or three doses of Sputnik, AZD1222 or a mixed schedule (MS) of both vaccines. The neutralizing capacity was evaluated by measuring antibody neutralizing titers using SARS COV-2 pseudotyped particles.
Results: 60.5% of pwMS were female, mean EDSS: 2.49 ±1.5, age: 36.6 ±10.7, disease duration 7.6 ± 5.1 years. DMTs: 45 pwMS were under fingolimod, 23 under dimethyl fumarate, 14 under cladribine and 19 under antiCD20 monoclonal antibodies. Vaccines: 35.7% Sputnik V, 51.9% AZD1222 and 12.4 % MS.
No antibody response to a 2nd dose was found in 41.3% of pwMS under fingolimod and 73.6% under antiCD20. We found a correlation between lower lymphocyte count and lower antibody titers in pwMS under fingolimod (r: 0.67, 95% CI: 0.46-0.81, p=⩽0.0001). A correlation was also found between the antibody titer and the last dose of antiCD20 (r: 0.49, 95% CI: 0.03-0.7, p=0.03). In March 2022, 57 pwMS received their 3nddose, 6 patients under fingolimod and 7 under antiCD20 remained without any antibody response. We did not find differences in the neutralization capacity with different DMT and or vaccines. Multivariate regression analysis showed antiCD20 (β= -,349, 95% CI: -3655.6 - -369.01, p=0.017) and fingolimod (β=-,399, 95% CI: -3363.8 - -250.9, p=0.023) treatments as independent factor associated with low antibody response (r^2 adjusted=0.157).

Conclusion: This is the first report of longitudinal humoral immune response of patients under adenovirus-based vaccines, specially Sputnik V, that demonstrate that these vaccines have similar results to those obtained with mRNA-based vaccines.

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EP1095

Tixagevimab and cilgavimab (Evusheld) boosts antibody levels to SARS-CoV-2 in patients with multiple sclerosis on b-cell depleters

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Introduction: B-cell-depleting therapies may affect the development of a protective immune response following vaccination against SARS-CoV-2. It is important to have a different strategy for creating immunity. Evusheld (tixagevimab co-packaged with cilgavimab) is currently approved by the FDA under an emergency use authorization (EUA) for use in patients who are not able to mount an immune response to the COVID-19 vaccines. No study has been undertaken to evaluate its efficacy in people with MS.
Objectives/aims: To evaluate whether Evusheld (tixagevimab co-packaged with cilgavimab) affects the antibody response to SARS-CoV-2 following an existing attenuated response to the vaccines against SARS-CoV-2.
Methods: This was a single-center cohort study performed at Methodist Hospitals in Merrillville, IN, USA. It included patients with multiple sclerosis treated with ocrelizumab and ofatumumab. Patients had already received the mRNA vaccinations against SARS-CoV-2 and had demonstrated an attenuated response on antibody testing. All participants received 150mg of Evusheld (tixagevimab co-packaged with cilgavimab). Antibody levels were measured at least two weeks following Evusheld injections.

Results: All patients (100%) developed the highest level of antibodies possible at least two weeks following Evusheld injections.
Conclusions: In this study, patients with MS who had an attenuated antibody response to the COVID-19 vaccines due to exposure to b-cell depleters now had the highest antibody response possible after receiving Evusheld. This is important as it provides a different strategy for protection against COVID-19.

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EP1096

Exploring the reasons behind Ocrelizumab infusions delay during the first wave of COVID-19 pandemic in Italy: results of a survey among MS centers

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Introduction: MS centers (MSc) activities related to OCR management were strongly and diffusely hit during the first wave of COVID-19 pandemic. Concerns were mainly related to its immunosuppressive effects and the need for in-hospital administration.
Objective: To investigate changes in OCR schedule among Italian MS centers participating to the Italian MS Register during the first wave of COVID-19 pandemic and to identify factors determining such changes.
Materials and methods: A quick online survey was sent to 65 Italian MSc in order to collect from them the following data: macro-region (North, Center, South) location, number of OCR-treated patients, modifications of OCR schedule and a list of factors potentially influencing the postponement of OCR infusions (i.e. age, co-morbidity, MS phenotype, number of previous OCR cycles, disease severity/activity, CD-20 lymphocytes count, distance to MS center, fear of infection, inclusion in a research trial, infections trend, shortage of medical/paramedical staff for reallocation/infection).
Results: Among 55 MSc who answered the survey, 50 (91%) declared to have suspended or extended OCR interval dosing for at least one patient. The MSc that didn't modify OCR schedule were all from the South of Italy (33% of all South MSc). Main factors influencing OCR schedule delay were advanced age/co-morbidity (70%) and pandemic trend in the area (72%), while recent MS-disease activity hindered OCR schedule modifications (65%).
Conclusions: This study shows that most Italian MSc decided either to delay or suspend OCR treatment during the first wave of COVID-19 pandemic. Advanced age and co-morbidity and no evidence of recent MS-disease activity were the most relevant patient-dependent predictors of OCR postponement. Among patient-independent factors the most relevant factor was the local trend of infections. Contrary to what expected, the shortage of medical and/or paramedical staff in MSc did not come out as relevant. The disruption of OCR schedule during the first COVID-19 pandemic wave in Italy mostly reflected the geographical distribution and the impact on the National Health System of COVID-19 pandemic.

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EP1097

Longitudinal post-vaccine SARS-CoV-2 IgG titers, memory B cell responses and risk of COVID-19 in multiple sclerosis over 1 year

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Introduction: Some disease modifying treatments (DMTs) impair response to SARS-CoV-2 vaccines in multiple sclerosis (MS), potentially increasing the risk of breakthrough infections.

Objectives: To investigate longitudinal post-vaccine antibody dynamics and memory B cell responses after 2 and 3 SARS-CoV-2 mRNA vaccine doses, and their association with risk of COVID-19 in MS patients treated with different DMTs.

Methods: Prospective observational monocenter cohort study in MS patients undergoing SARS-CoV-2 mRNA vaccinations. Anti-SARS-CoV-2 spike IgG serum titers were measured by chemiluminescence microparticle immunoassay. Frequency of spike-specific memory B cells were measured upon polyclonal stimulation of total PBMCs and screening of secreted antibodies by ELISA.

Results: We recruited 120 MS patients (58 on anti-CD20, 9 on S1P-modulators, 15 on cladribine, 24 on teriflunomide and 14 untreated) and collected 392 samples before and up to 10.8 months after a 2nd vaccine dose. Compared to no treatment, anti-CD20 antibodies (β=-2.07, $p<0.001$) and S1P-modulators (β=-2.02, $p<0.001$) were associated with lower anti-spike IgG titers, while teriflunomide and cladribine were not. Anti-spike IgG titers progressively decreased with months since last vaccine dose (β=-0.14, $p<0.001$), independently of DMTs. Within anti-CD20 treated patients, anti-spike IgG remained constantly higher in those with greater baseline CD19+ B cell counts and were not influenced by post-vaccine anti-CD20 infusions. Anti-spike IgG titers increased after a 3rd vaccine dose on cladribine and teriflunomide and marginally on anti-CD20 and S1P-modulators. Spike-specific memory B cell responses were weaker on S1P-modulators and anti-CD20 than on teriflunomide and influenced by post-vaccine anti-CD20 infusions. Risk of SARS-CoV-2 infection was predicted by SARS-CoV-2 IgG at last sample before infection (OR=0.56, 95%CI=0.37-0.86, p=0.008).

Conclusions: Post-vaccine SARS-CoV-2 IgG antibody titers progressively decrease over time in MS regardless of DMTs, and are associated with risk of breakthrough COVID-19. Both immediate humoral and specific memory B cell responses are diminished in patients on S1P-modulator and anti-CD20 antibody treatments. Within the latter group, B cell count at first vaccine dose determines anti-spike IgG production shortly after vaccination, whereas post-vaccine anti-CD20 infusions negatively impact memory B cell responses.

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EP1098

Short and long-term serology response of MS patients treated with natalizumab following two doses of mRNA COVID-19 vaccine (Pfizer)

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Introduction: Due to the immunosuppressive mechanisms of several disease-modifying treatments, questions have been raised whether multiple sclerosis (MS) patients can be vaccinated against COVID-19. Natalizumab is an immunomodulatory drug approved for the treatment of MS. Previous studies show that the efficacy of vaccines may be minimally affected by Natalizumab.
Methods: Serology response to SARS-CoV-2 spike protein was tested in MS patients treated with natalizumab, Dimethyl-fumarate (DMF), and interferon-beta (IFNB1), 3 weeks, and 6 months after the second dose, and 1 month following the third booster-dose of the BTN162b2 mRNA vaccine.
Results: A total of 63 MS patients participated in the study. Thirty were treated with natalizumab, 24 were treated with interferon beta, and nine were treated with dimethyl fumarate. All MS patients treated with natalizumab, DMF, and IFNB1 had a positive serology response against the SARS-CoV-2 spike protein at 2–3 weeks following the second dose of the vaccine. In addition, we analysed blood samples 5-6 months following the second vaccine dose of 17 patients treated with natalizumab and 11 patients treated with IFNB1. All of MS patients treated with natalizumab and with IFNB1 had a positive serology response 5-6 months following the second vaccine dose. No difference was found between SARS-CoV-2-IgG titer of IFNB1 and natalizumab-treated MS patients 5-6 months following the second vaccine (909.70 ± 581.80 vs 911.30 ± 727.90, $p=0.99$). Following the third vaccine all MS patients treated with natalizumab (13/13) and IFNB1 (2/2) had a positive serology response.
Discussion: All MS patient in our cohort had a positive serology response. There was no significant difference in vaccine-specific serology response between MS patients treated with DMF and INFB1 and those treated with natalizumab.

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EP1099

The prevalence and associated factors of infusion-related reactions of the first full dose (600 mg) ocrelizumab instead of two doses apart

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Introduction: Ocrelizumab is a fully humanized antiCD20, known as a high efficacy disease modifying drugs (DMT) in treatment of multiple sclerosis patients. The Iranian biosimilar, known as Xacrel® (by CinnaGen), was approved by Iran Food and Drug Administration (IFDA) in 2021.The most frequent adverse effect of ocrelizumab is infusion-related reactions (IRRs). To reduce these reactions, the first dose of ocrelizumab is administered as two 300 mg infusions separated by two weeks. Next doses are prescribed as single 600 mg infusions every six months. However, in phase II trial of the drug, severe IRRs were not significantly different between two doses of 600 mg dose (two separate 300 mg doses) and 2000 mg dose (two separate 1000 mg doses).
Objective: It was necessary to reduce hospital administration due to the recent pandemic, so we decided to compare the frequency of IRRs in non-separated full (600 mg) and separated (two separated 300 mg) doses ocrelizumab.
Aim: Assessing the prevalence and associated factors of infusion-related reactions of the first full dose (600 mg) ocrelizumab instead of two doses apart.
Methods: Patients candidate for receiving ocrelizumab by an MS expert, were enrolled in an open-label randomized controlled trial. The participants received the first dose of ocrelizumab as either 600 mg in one session or two sessions of 300 mg infusion two weeks apart. IRRs during infusion and in the first 24 hours of drug were recorded.
Results: Of 332 participants, 150 received divided dose and 182 received two doses at once. No life-threatening adverse effect was observed in both groups. Overnight admission or permanently drug discontinuation were not needed for patients. Needing temporary drug discontinuation was significantly higher in nonseparated first full dose group (p value < 0.001). During the infusion,

fatigue (p value: 0.003), skin reactions (p value: 0.04), throat swelling (p value: 0.03), and dyspnea (p value: 0.01) were significantly increased. However, in the first 24 hours IRRS showed no significant association with treatment protocol (p value=0.01)
Conclusion: These findings suggest unseparated full dose (600 mg) ocrelizumab administration for the first dose is relatively safe. With some protocol modifications, it could lead to fewer patients' referrals, saving time and money.

Disclosure
The authors declare no conflict of interest.

EP1100

COVID-19 vaccination patterns and outcomes among persons with multiple sclerosis in the FlywheelMS cohort

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Background: Vaccination against SARS-CoV-2 is recommended for all persons with multiple sclerosis (pwMS) to prevent severe COVID infections and death. However, it is unknown how many pwMS are fully vaccinated or have received a booster dose and whether vaccination patterns differ across patient subgroups. In addition, there is limited research evaluating COVID outcomes by vaccination status among pwMS despite concerns that pwMS receiving immunosuppressive therapies might have an impaired immune response that could impact vaccine effectiveness.
Objective: To describe COVID vaccination patterns and COVID outcomes among pwMS in the FlywheelMS cohort and in subgroups of pwMS, including by disease-modifying therapy (DMT) status.
Methods: All pwMS included in the FlywheelMS cohort, a patient-centred study that digitises all health records for US-based pwMS across all US sites of care, were asked to complete a questionnaire on their COVID vaccination history (completed 2 July-4 May 2022). COVID diagnoses and outcomes were identified in health records. Vaccination rates were calculated for all pwMS overall and in subgroups, including by index DMT (i.e. the most recent DMT in the 6 months prior to vaccination). Breakthrough infections $>$14 days after the last dose of the primary vaccine series and COVID-related outcomes (i.e. hospitalisation, severe hospitalisation, death) were evaluated overall and in subgroups of pwMS, including by DMT status.
Results: A total of 1041 pwMS (20% response rate) completed the survey and were included in the study: 182 (17%) were unvaccinated, 11 (1%) were partially vaccinated and 848 (81%) were fully vaccinated. Among the fully vaccinated, 595 (70%) received 1 and 47 (6%) received $\geqslant$2 booster/additional doses. Fully vaccinated pwMS were more likely to be older (mean age, 50 vs 49 years), male (22% vs 13%) and treated with any DMT (76% vs 63%) compared with unvaccinated pwMS. Among all fully vaccinated pwMS, 48 (6%) had a documented breakthrough infection after vaccination. Vaccination rates and outcomes following breakthrough infections (i.e. hospitalisation, severe hospitalisation, death) for subgroups will be presented in the full poster.
Conclusions: Rates of full vaccination and boosters were higher among pwMS compared with all adults in the US. The documented breakthrough rate among fully vaccinated pwMS was low and similar to that in the general population, suggesting vaccination against SARS-CoV-2 provides benefits among pwMS.

Disclosure
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K Mace and **G Hanson** are employees and shareholders of PicnicHealth.

EP1101

Effect of ocrelizumab on leptomeningeal inflammation and humoral response to Epstein Barr-Virus in multiple sclerosis

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Introduction: Neutropenia is an infrequent complication of CD20 depleting agents and may require the administration of granulocyte-colony stimulating factor (G-CSF), which has been associated with an increased relapse risk in patients with multiple sclerosis (PwMS). The management of this side effect is still matter of debate.
Objective: To evaluate clinical features and management of neutropenia occurring in anti-CD20 treated PwMS through a single-center case series and a systematic review of the literature.
Aim: To provide practical evidence of the occurrence and management of neutropenia during anti-CD20 treatment in PwMS.
Methods: We report 3 cases of neutropenia during ocrelizumab treatment in our center along with cases identified through a systematic review of the literature, performed following the PRISMA guidelines. A PubMed/Medline research was performed with the queries "ocrelizumab AND neutropenia" and "rituximab AND multiple sclerosis AND neutropenia" (last update February, 3rd 2022). 13 records (16 patients) were included in the qualitative synthesis.
Results: 19 patients were included. 11 patients developed neutropenia during ocrelizumab treatment, 8 during rituximab treatment. Disease course was described in 16 patients: 9 were affected by relapsing remitting multiple sclerosis (MS), 3 by primary progressive MS, and 4 by secondary progressive MS. Median age was 38 years (25-69) and nearly 70% were female. Neutropenia occurred after a median of 2 (1-7) infusions and after 9.5 (1-42) months

from the first infusion. Median time from the last infusion was 90 days (2-156). About 70% of patients were symptomatic, most were treated with G-CSF and antibiotics. No relapses after G-CSF were reported. In those patients who did not suspend anti-CD20 (68.8%), neutropenia reoccurred in 18.2% of cases.
Conclusions: Neutropenia may develop in patients with both relapsing and progressive disease course, relatively early during treatment with anti-CD20 (after a median of 2 infusions). Late onset neutropenia (>4 weeks from the last infusion) encompassed most of the cases. The administration of G-CSF was not associated with relapses, suggesting that its use may be safe in PwMS. As in some cases neutropenia occurred or reoccurred after switching from RTX to OCR and viceversa, switching among anti-CD20 depleting agents, which are different in terms of humanization of monoclonal antibodies, seems not to be useful to prevent the reoccurrence of neutropenia.

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EP1102
Ocrelizumab treated patients who developed Coronavirus disease-19 despite being vaccinated

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Introduction: In the Phase III trials of ocrelizumab (OCR), the most common infections were upper respiratory infections, and several data bases have reported OCR-treated persons with MS are more susceptible to Coronarvirus disease-19 (COVID-19). In addition, patients on OCR may have a more severe course resulting in hospitalizations. The VELOCE study indicated a reduction in the immune humoral response to non-live vaccines which may contribute to the increased risk.
Objective: To report the demographics of patients who developed SAR-CoV-2 after being vaccinated.
Methods: Adult MS patients who have been prescribed OCR were eligible. Chart reviews were conducted every 6 months by a trained RN. Cases reported are patients who tested positive for COVID-19 after receiving at least one vaccine while on OCR. Demographics, disease duration, EDSS, hospitalizations, time on OCR, vaccine status, type of vaccine administered were summarized as percentages, means (SD) or medians [interquartile range (IQR) =Q1, Q3] as appropriate.
Results: Of 293 OCR patients vaccinated, 31 patients developed a documented COVID-19 infection with a mean age of 46.8 (12.7) and a median disease duration of 11.3 [4.0. 19.6] years. 17% had PMS. Median time on OCR was 42.8 [20.1, 50.4] months. 60% had been on OCR for 3 years or more. Median time from first vaccine to positive COVID-19 test was 7.3 [4.8, 8.9] months. Median time from last dose of OCR to positive COVID-19 test was 4.5 [3.2, 5.7] months. COVID-19 negative patients were older with a mean age of 52.3 (12.3), p=0.03. There were no other significant differences based on median disease duration, MS pattern, and median time on OCR. Median EDSS for patients who developed COVID-19 (19 patients) was 2 [2.0, 6.5]. 71% (22) had received the Pfizer- BioNTech or Moderna vaccines, and 45% of patients had received one booster vaccine before they developed COVID-19. Hospitalizations occurred in 9 patients with a mean age of 53.9 (12.5) years, and 4 of them were boosted. 2 patients were admitted to the intensive care unit, and 1 patient required intubation. 1 death occurred in a 62-year-old patient with an EDSS of 8.0, who had received OCR for 3.6 years and received one dose of the Johnson and Johnson vaccine.
Discussion: Patients hospitalized for a COVID-19 infection were older, and the patient who died had an EDSS of 8.0.This data is alignment with previous reports that older and more disabled patients are at risk for more severe disease.

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EP1103
A retrospective study on B-cell depleting therapies in multiple sclerosis patients: frequency of the wearing off phenomenon

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Introduction: Rituximab and its generics have been covered by public insurance in British Columbia therapy for relapsing-remitting MS (RRMS) since November 27, 2018. In contrast, Ocrelizumab (OCR) has been used in BC for RRMS via a compassion program or third party coverage and for early primary progressive MS (PPMS) with public coverage since October 1, 2017. Coverage has not been available for patients with secondary progressive MS (SPMS). Some MS patients who are treated with either of these therapies report an increase in MS-related symptoms prior to the next dose, known as the wearing-off phenomenon (WOP), which is rarely described in literature.
Objective: To investigate if OCR and other B-cell depleting therapies (OBCDTs) differ in terms of frequency of the WOP.

Aim: To compare the WOP between patients on OCR and patients on OBCDTs regardless of the source of coverage.
Methods: This was a retrospective chart review in which our sample consisted of MS patients on B-cell depleting therapies for at least 1 year between October 1, 2017, and May 1, 2022. It is standard of practice in our clinic to ask patients about their response to therapy prior to infusions. Based on patient responses, treating neurologists identify the WOP prior to the approval of treatment continuation. Differences in the WOP between groups was calculated with a Fisher's Exact Test on R software (version 4.11, R Core Team).
Results: Out of 96 patients, 69 (26% males) were on OCR and 27 (18% males) were on OBCDTs. For the OCR group, the average age was 45.3 years and duration of therapy was 3.2 years. For the OBCDTs group, it was 44.7 and 2.0 years, accordingly. On the last assessment, 16 of the patients on OCR had PPMS, 46 patients had RRMS and 7 transitioned to SPMS. For those on OBCDTs, none had PPMS, 23 had RRMS and 4 patients transitioned to SPMS. 11 patients (15.9%) on OCR and 2 patients (7.4%) on OBCDTs reported the WOP. The odds of reporting WOP were not significantly different between groups (p=0.33).
Conclusions: Groups were similar in age and sex. The occurrence of the WOP for those on OCR was not significantly different from those on OBCDTs. The different ways of detecting the WOP and its impact on the observed frequency of WOP in B-cell depleting therapies may need to be explored further to improve patient care. Future studies should consider the impact of the WOP on patient care, while considering the duration of treatment and strategies to manage it.

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EP1104

Risk of COVID-19 after vaccination among people with multiple sclerosis who are treated with disease modifying therapies

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Introduction: Alongside the advent of effective SARS-CoV-2 vaccines, came the concern of decreased effectiveness among people with multiple sclerosis(pwMS) who are treated with disease modifying therapies(DMTs). Diminished humoral response to vaccination was observed among pwMS who were treated with anti-CD20s as well as with S1P receptor modulators(S1Prm). S1Prm were also associated with compromised T-cell response.
Aim: To explore the association between treatment with various DMTs and the risk of COVID-19 after receiving mRNA SARS-CoV-2 vaccination.
Methods: Population based data from Clalit Health Services, Israel's largest health care organization, were used. All pwMS treated with DMTs without prior COVID-19 infection were included. Vaccinated participants were followed from 2 weeks after receiving one or two vaccine doses. PwMS who declined vaccination were followed from the commencement of the mass vaccination campaign on December 20, 2020. The end of follow-up was at the time of COVID-19 infection, the receipt of a third vaccine dose or until the end of August 2021, whichever came first. Multivariate Cox proportional hazard models were used to estimate hazard ratios for COVID-19 according to number of vaccination doses as time dependent variables and DMT type. Confounding variables adjusted for in the models were age, gender, EDSS, socio-economic status and comorbidities.
Results: 2511 PwMS treated with DMTs were included (Age:46.2±14.6, 70% Female, EDSS:3.0±2.1). Of whom, 2123(84.5%) received 2 vaccine doses, 347(14%) received only 1 vaccine dose and 41(1.5%) declined vaccination. On multivariate models, treatment with S1Prm as well as with Ocrelizumab was associated with increased risk of COVID-19 (HR=1.8, 95% CI: 1.08-2.84, P=0.02 for S1Prm; HR=1.5, 95% CI: 1.001-2.33, P=0.05 for Ocrelizumab). Receiving 2 doses of mRNA SARS-CoV-2 vaccination was protective (HR=0.41, 95% CI: 0.24-0.69, P=0.001). COVID-19 disease among pwMS was generally mild. Only 8 pwMS had severe infection, of whom 4 were treated with Ocrelizumab. The other 4 were treated with glatiramer, interferon, teriflunomide and fingolimod. There were no cases COVID-19 related mortality during follow-up.
Conclusion: Two doses of mRNA SARS-CoV-2 vaccination can effectively protect pwMS from COVID-19 infection. Treatment with S1Prm as well as with Ocrelizumab is associated with increased risk of COVID-19 infection, despite vaccination, however COVID-19 among vaccinated pwMS is usually mild.

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EP1105

Earlier ofatumumab treatment May reduce disease progression and relapses for patients with relapsing-remitting multiple sclerosis: results from a cost-consequence model

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Introduction: Oral disease-modifying therapies (DMTs), such as dimethyl fumarate (DMF), are the most common treatments prescribed for relapsing-remitting multiple sclerosis (RRMS) in the NHS; infusion DMTs are less frequently used.[1] Ofatumumab, a self-administered subcutaneous MS DMT, is effective at reducing relapses and slowing disease progression compared with teriflunomide, as demonstrated in the ASCLEPIOS trials.[2] During the NICE appraisal, clinical experts noted that ofatumumab could be used as a first-line treatment for RRMS.
Objectives: To evaluate ofatumumab as a first-line treatment versus second-line after initial DMF use.
Methods: A discrete time cohort Markov model based on disease progression through Expanded Disability Status Scale (EDSS) health states with annual cycles and 10-year time horizon was employed. Two cohorts, modelled separately, allowed evaluation of treatment delay. Baseline characteristics, EDSS distribution, annualised relapse rate (ARR) ratio and hazard ratio for 6-month confirmed disability progression (6M-CDP) were obtained from the ASCLEPIOS trials of ofatumumab.[2] ARR ratios and hazard ratios for time to 6M-CDP for ofatumumab and DMF (versus placebo) were obtained from a network meta-analysis.[3] Literature values for natural history of EDSS transitions, mortality and ARR data were used.
Results: Over 10 years, a patient treated with ofatumumab was predicted to have fewer relapses (3.78) than one treated with DMF for 3 years (4.23) before switching to ofatumumab, or treated with DMF only (4.67). After 5 years, 5.9% of patients receiving ofatumumab progressed to EDSS ⩾7, compared with 8.0% of those receiving DMF for 3 years and 8.7% of those receiving DMF only. After 10 years, 15.3% of ofatumumab patients progressed to EDSS ⩾7 versus 18.1% of those receiving DMF for 3 years and 20.7% of patients receiving DMF only.
Conclusion: Over 10 years, ofatumumab treatment was predicted to reduce relapse events and result in fewer patients progressing to EDSS ⩾7 when compared with those receiving delayed ofatumumab (after 3 years of DMF), or DMF only.
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1. Scolding N. Pract Neurol 2015;15:273–9; **2.** Hauser SL. N Engl J Med 2020;383:546–57; **3.** Samjoo IA. J Comp Eff Res 2020;9:1255–74.

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EP1106

A retrospective evaluation of seroconversion after COVID-19 during the early Omicron wave in fully vaccinated MS patients receiving B-cell depletion therapies

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Introduction: Patients with multiple sclerosis (MS) are commonly treated with B-cell depletion therapies (BCDTs). Reduced seroconversion following COVID-19 vaccination in patients receiving certain BCDTs has been reported, however the immune response following natural infection is poorly understood.
Objectives: This study aimed to evaluate COVID-19 antibody responses after vaccination and natural infection in BCDT-treated patients. This single-centre study evaluated COVID-19 seroconversion and spike protein antibody titres for double-vaccinated MS or neuroinflammatory disease patients treated with BCDT (n=33) with confirmed COVID-19 infection (n=16) or uninfected by COVID-19 (control; n=17).
Methods: We performed a retrospective review of patients at the Yale MS Center who had systematically checked COVID-19 spike antibody levels among patients treated with BCDTs (ocrelizumab [OCR], n=24; rituximab [RTX], n=5; ofatumumab [OFT], n=4). Data were collected from Mar 2020 to Feb 2022. All patients had received ⩾2 doses of FDA-approved COVID-19 vaccine. Qualitative spike antibody seropositivity was determined based on test-specific lab reference ranges. For a subset of patients (n=18), quantitative spike antibody levels were assessed via DiaSorin Liaison chemiluminescence assay (positive titre of ⩾13; OCR, n=13; RTX, n=3; OFT, n=2). Vaccination and COVID-19 infection dates were also recorded. Patients were monitored for health effects following COVID-19.
Results: Overall,16/33 (48%) patients seroconverted post full vaccination. After COVID-19 infection, 15/16 (94%) seroconverted, while 7/17 (41%) of uninfected patients seroconverted after vaccination. For the 18 patients with quantitative COVID-19 spike antibody titres, mean titres post-vaccination were 37.38. Mean antibody titres were significantly higher after COVID-19 infection; 540.32 vs 20.1 in the control group ($p<0.05$). Of the 16 infected patients, 15 had mild COVID-19 symptoms and 1 was asymptomatic. No hospitalizations or deaths were reported.
Conclusions: This study reports that COVID-19 spike antibody titres in fully vaccinated, BCDT-treated patients were significantly increased post-infection compared to the control group. BCDT-treated patients infected with COVID-19 displayed mild infection or were asymptomatic, with no hospitalizations or deaths. These results provide reassurance that BCDTs in double-vaccinated MS patients do not preclude an appropriate COVID-19 antibody response post infection.

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Shree Desai has no disclosures to report.
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EP1107

Tick-borne bacterium Neoehrlichia mikurensis **- an emerging safety concern during CD20-depleting therapy? – A case report**

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Introduction: Neoehrlichia mikurensis (N. mikurensis) is a newly recognized tick-borne bacterium, which is found in ticks in Europe and Asia. In humans, it is known to infect endothelium cells and is recently shown pathogenic in immunosuppressed patients with clinical syndromes ranging from febrile illness to vasculitis and as recently reported ultimately life-threatening hyperinflammation, responding excellently to doxycycline treatment. Many of the reported cases have been treated with CD20-depleting therapy.
Objectives: To describe a case of a rituximab treated multiple sclerosis (MS) patient presenting with febris continua caused byN. mikurensis.
Aims: Increase awareness on a newly recognized bacteria with pathogenicity in immunocompromised patients.
Methods: Case report.
Results: A 51-year-old man, diagnosed with secondary progressive MS and receiving rituximab, presented with fever, malaise, night sweats, and a 4-kg weight loss persisting for 1.5 months. He was referred to a fast-track cancer diagnostic center because of a suspected occult primary tumor. Whole body positron-emission tomography/computer tomography showed no signs of malignancy but revealed splenomegaly (16.5 cm). A bone marrow examination was normal. Extensive microbiologic workup was negative. Peripheral blood hemoglobin was 7.4 mmol/L (reference, 8.3–10.5 mmol/L), C-reactive protein 28 mg/L (reference, <10 mg/L), and LDH 217 (reference, 105–205 U/L). After six months of fever occurring every evening, persistent splenomegaly, and detection of interleukin-receptor-2 (1140 kU/L; reference 158-623) and sCD163 (6.13 mg/L; reference 0.69-3.86) led to a hematologist second opinion and the diagnosis; the tick-borne bacterium N. mikurensiswas detected in the blood. N. mikurensis is not found by standard blood cultures and was in this case detected by 16S profiling and specific real-time PCR targeting thegroEL gene. Symptoms, abnormal blood biochemistry and splenomegaly resolved promptly after doxycycline initiation.
Conclusions: This report adds to one previous report from Sweden of a rituximab treated MS patient presenting with fever caused by the tick-borne bacterium, N. mikurensis, with fast resolution of symptoms after doxycycline treatment. Along with reports on other immunocompromised patients, this case highlights the importance of expanding the knowledge of the bacteriumN. mikurensis among clinicians using immunosuppressive treatments.

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EP1108

Efficacy of natalizumab in MS patients with a 12-week dosing gap

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Introduction: Natalizumab (NTZ) is a highly effective treatment for multiple sclerosis (MS); however, patients who are positive for anti-JC virus antibodies have a risk of developing PML (progressive multifocal leukoencephalopathy). NTZ binds to and blocks the adhesion of VLA4 (found on the surface of leukocytes) to VCAM1, a protein found on the surface of brain endothelial cells (BEC). Thus, when blood levels of NTZ are sufficiently high, the trafficking of leukocytes into the CNS is inhibited, potentially allowing JCV to propagate and PML to develop. One approach to reducing the risk of PML is to use a dosing cycle that results in a low NTZ level allowing specific lymphocyte subsets to traffic into the CNS such that cells that drive MS disease activity are blocked but cells that allow viral immune surveillance can enter the brain.
Objective: To determine if NTZ treated patients with a 12-week dosing gap protocol would result in detectable disease activity.
Methods: The Berkovich NTZ dosing protocol, developed to minimize the risk of PML while maintaining efficacy in MS, specifies 10 doses of NTZ given q4w (SID) and then SID NTZ is resumed after a 12-week treatment gap. Study design: Visit 1: shortly before gap (SID). Visit 2: end of gap just before NTZ SID dosing resumed. Visit 3: <3 mo. after gap. Assessments: Visits 1 and 2: Clinical, blood, CSF and MRI. Visit 3: Clinical, blood and

MRI. Serum proteins (NTZ, sNfL and sVCAM) were assessed by ELISA. MRI: T_2-weighted TSE volumes were preprocessed with N4 bias field correction, histogram matching, and HD-BET brain extraction. For each subject, later timepoints were registered to the baseline T_2w volume with ANTs affine registration. Voxel-wise subtraction generated difference images, which were evaluated for new T_2 hyperintensities indicative of MS activity.
Results: MS activity as measured by sNfL and MRI appeared to be well controlled in most patients and no patient (n=12) had clinical activity. sVCAM (thought to be, a measure of cells binding to VCAM on BEC) did not appear to be dramatically higher after the gap. At the end of the dosing gap, NTZ levels were undetectable in 4/12 patients and $<$13 ug/mL in 8/12.
Conclusion: For most patients a 12-week dosing gap did not result in detectable disease activity (measured clinically, by MRI, or biomarkers). This dosing schedule of NTZ may allow selective cell trafficking into the CNS resulting in control of JCV propagation and potentially reduced PML risk.

Disclosure
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EP1109

Evaluating the efficacy and safety of transitioning patients from natalizumab to ocrelizumab

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Introduction: Natalizumab (NTZ) is an effective therapy for patients with relapsing MS (RMS) although associated with a risk of progressive multifocal leukoencephalopathy (PML) in patients infected with John Cunningham virus (JCV). Ocrelizumab (OCR) has demonstrated efficacy, yet its safety in patients previously treated with NTZ is unclear.
Objective: To present the final data from a prospective, observational study to evaluate the efficacy and safety of OCR in RMS patients previously treated with NTZ.
Methods: Clinically stable RMS patients, ages 18-65 treated with a stable dose of NTZ for $\geq$ 12 months, were started on OCR 4-6 weeks after last dose of NTZ and followed for 12 months. Relapse assessment, Expanded Disability Status Scale (EDSS), and MRI were performed prior to starting OCR and at months 3, 6, 9 (no MRI), and 12.
Results: Forty-three patients were enrolled, and 41 (95%) completed the study. 77% female with a median age at OCR start of 44 [IQR 11.5]. Participants received a median of 47 [range 7-168; IQR 65.5] NTZ infusions prior to starting OCR. Thirty-five (81%) subjects switched to OCR due to potential PML risk. Two patients had a clinical relapse, although no MRI correlate. EDSS remained unchanged at 2.5 for the patient who relapsed at month 9 but increased from 4.0 to 5.5 for the patient who relapsed at month 12. Median EDSS for the patients was 3.50 [range 1-6; IQR 2.25] at baseline and 3.50 [range 1-6; IQR 2] at month 12.
At month 3, one patient had 1 enhancing lesion and 1 new T2 hyperintensity. Another patient had 3 enhancing lesions and 3 new T2 hyperintensities. At months 6 and 12, there were no enhancing or new/enlarging T2 lesions for the entire cohort.
Infusion reactions were seen in 23 patients (54%) with the 1st infusion of dose 1 and 6 patients (14%) with the 2nd infusion of dose 1. One severe reaction was reported with the second dose.
No patient stopped the study due to an adverse event. Thirteen serious adverse events (SAEs) were reported with 10 patients being hospitalized, 2 of which were possibly related to OCR. Four of the SAEs, breast cancer, urinary tract infection, spontaneous abortion, and acute cystitis, were reported to be possibly related to OCR. No cases of PML have been reported.
Conclusion: The transition from NTZ to OCR resulted in limited disease activity with no cases of PML. The number of SAEs is concerning although majority were determined to be unlikely due to OCR.

Disclosure
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EP1110

Assessing the benefits of disease modifying therapy in relapsing multiple sclerosis using the MAGNIMS score: a post-hoc analysis of OPTIMUM study of ponesimod by early relapse status

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Introduction: The Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) scoring system has been shown to be associated with longer-term risk of disease progression and is a useful surrogate for long-term benefit.
Objectives: To compare MAGNIMS outcomes after 60 and 108 weeks of treatment with ponesimod 20 mg vs teriflunomide 14 mg among subgroups of patients experiencing a relapse (yes/no) within 12 weeks of treatment initiation in post-hoc analyses of the OPTIMUM study.
Methods: Randomized patients were categorized based on whether they experienced a relapse during the first 12 weeks.

MAGNIMS scores (range 0–2, with higher scores indicating greater long-term disease progression risk) were calculated using the cumulative number of new or enlarging T2 lesions and number of relapses over 60 and 108 weeks (0= no relapses and 0-2 lesions; 1= no relapses and ⩾3 lesions OR 1 relapse and 0-2 lesions; 2= 1 relapse and ⩾3 lesions OR ⩾2 relapses and ⩾0 lesions). MAGNIMS scores were compared between treatments within relapse subgroups at Weeks 60 and 108.

Results: The MAGNIMS score at Week 108 was calculated for 1,075 patients (N=539 in the ponesimod arm and N=536 in the teriflunomide arm). Among those without a relapse in the first 12 weeks (n=463 in the ponesimod arm and n=481 in the teriflunomide arm), significantly more patients had a MAGNIMS score of 0 at week 108 in the ponesimod arm than the teriflunomide arm (57% vs 42%; odds ratio [OR] 1.9; 95% confidence interval [CI] 1.4-2.4; p-value <0.001). This was due to both a lower probability of experiencing a relapse (18% vs 32%; OR 0.5; 95% CI 0.3-0.6; p-value <0.001) and ⩾3 new/enlarging T2 lesions (29% vs 39%; OR 0.7; 95% CI 0.5-0.9; p-value 0.003) through Week 108. Among those who did experience a relapse during the first 12 weeks (n=76 in the ponesimod arm and n=55 in the teriflunomide arm), fewer patients in the ponesimod arm progressed to a MAGNIMS score of 2 over 108 weeks than in the teriflunomide arm (66% vs 84%; OR 0.4; 95% CI 0.2-0.9; p-value 0.025). This can be attributed to the lower incidence of additional relapses beyond Week 12 in the ponesimod arm (36% vs 53%; OR 0.5; 95% CI 0.2-1.0; p-value 0.051). Week 60 results were consistent with Week 108 results.

Conclusion: Continued treatment with ponesimod resulted long-term benefit compared to teriflunomide, in patients who experienced a relapse within 12 weeks after treatment initiation as well as in patients who did not.

Disclosure
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EP1111

Increased use of anti-CD20 monoclonal antibodies (anti-CD20s) in early line treatments for relapsing remitting multiple sclerosis (RRMS) patients in Europe and the United States

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Introduction: Healthcare practitioners (HCPs) have commonly adopted an escalation treatment approach for MS, but the launch of new disease-modifying treatments (DMTs) in recent years has shifted prescribing patterns; more aggressive DMTs are used at earlier lines.

Objective: To assess early line use of anti-CD20s (ocrelizumab and ofatumumab) among relapsing remitting MS (RRMS) patients in Europe and the United States and the impact on platform DMTs (Interferons, glatiramer acetate, teriflunomide, dimethyl fumarate).

Methods: A multi-centre online retrospective chart-review study of patients with MS was conducted in Q4 2019 (10/2019 – 12/2019) and Q4 2021 (10/2021 – 12/2021) across EU4+UK (UK, FR, DE, IT ES) and US. Recruited from a large access panel, neurologists (MS Nurses included in the UK) were screened for duration of practice in specialty and caseload. De-identified HCP perceptions were collected and de-identified patient charts were recorded for the next 4-10 eligible patients seen during the consultation period.

Results: 2600 and 832 (Q4-19), 2563 and 810 (Q4-21) RRMS patients in EU+UK and US were reported on, respectively. Anti-CD20 use in the patient sets increased over the 2-year period for 1st and 2nd line patients who started a DMT in 2019 and 2021 (EU: 8% Q4-19 vs 10% Q4-21; US: 8% Q4 2019 vs 13% Q4-21, 1st line/EU: 16% Q4-19 vs 21% Q4-21; US: 17% Q4-19 vs 29% Q4-21, 2nd line). This has resulted in less platform DMT use (EU: 75% Q4-19 vs 61% Q4-21; US: 65% Q4-19 vs 43% Q4-21, 1st line/EU: 39% Q4-19 vs 36% Q4-21; US: 42% Q4-19 vs 21% Q4-21, 2nd line [p<0.01]). A higher proportion of the anti-CD20 patients are reported to have highly active/RES MS vs those receiving platform DMTs (Q4-21 EU: 33% vs 1% [p<0.01]; US 10% vs 0%, 1st line/EU: 16% vs 0% [p<0.01]; US 8% vs 0%, 2nd line) and slowly progressing accumulation of disability (EU: 18% vs 11%; US 50% vs 26%, 1st line/EU: 34% vs 12% [p<0.01]; US 63% vs 43%, 2nd line).

HCP perceptions may influence the shift in prescribing habits; in Q4 2021, 67% (EU+UK) and 66% (US) of sampled HCPs associated anti-CD20s with overall efficacy compared to 41% (EU+UK), 35% US for platform DMTs [p<0.01].

Conclusions: In this study cohort, anti-CD20 uptake at earlier lines is evident, as platform DMT use declines. Lower efficacy perceptions for platform DMTs versus anti-CD20s suggests newer DMTs may be causing a shift in perceptions of MS therapies. Further investigation using comparator cohort is warranted.

Disclosure
All authors are employees of Ipsos and have nothing to disclose.

EP1112

The association of MAGNIMS score with long-term disability progression in RMS

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Introduction: The Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) scoring system has been shown to be associated with the long-term risk of disease progression among patients with relapsing multiple sclerosis (RMS) through 108 weeks in the phase 3 OPTIMUM study.

Objectives: To provide further evidence of the association of MAGNIMS with long-term disease progression risk based on the ponesimod phase 2 and extension studies with a median of 8 years of follow-up.
Methods: Data from patients who received ⩾1 dose of 10, 20, or 40 mg ponesimod during the phase 2 clinical study (or extension study) were included in the analysis. MAGNIMS scores (range 0–2) were calculated using the cumulative number of new or enlarging T2 lesions and the number of relapses at 48 weeks following initial ponesimod dose. Long-term outcomes included time to 24-week confirmed disability accumulation (CDA), defined as time from initial ponesimod dose until a 24-week sustained increase from initial ponesimod dose in Expanded Disability Status Scale (EDSS) score, and time from last EDSS assessment during the MAGNIMS assessment period to first relapse or 24-week CDA. The Kaplan-Meier (KM) method was used to estimate time to 24-week CDA and time to 24-week CDA or relapse. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated between MAGNIMS score subgroups. In addition, KM curves for time to 24-week CDA by MAGNIMS subgroup were generated and visually compared between the phase 3 data and the long-term phase 2 data.
Results: Of 435 patients in the analysis population, MAGNIMS score could be calculated for 417 (score = 0 in 302 patients [72%], 1 in 90 [22%], 2 in 25 [6%]). Baseline characteristics were similar across the three MAGNIMS subgroups. HRs (95% CIs; p-values) for time to 24-week CDA were 1.5 (0.9–2.5; 0.106) for score of 0 vs. 1 and 2.8 (1.3–5.9; 0.007) for score of 0 vs. 2 (log-rank p-value=0.011). HRs (95% CIs; p-values) for time to 24-week CDA or relapse were 2.0 (1.4–3.0; <0.001) for score of 0 vs. 1 and 3.2 (1.7–6.1; <0.001) for score of 0 vs. 2 (log-rank p-value<0.001). For both endpoints, the KM curves of each MAGNIMS subgroup were separated from one another. KM curves between the phase 3 and phase 2 data largely overlapped.
Conclusion: Over a median of 8 years of follow-up, the MAGNIMS score has been shown to be highly associated with the long-term risk of disability progression among patients with RMS treated with a disease modifying therapy.

Disclosure
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EP1113

Immune response to SARS-CoV-2 vaccines in patients with multiple sclerosis in Argentina: prospective and multicenter study

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Introduction: In Argentina, multiple sclerosis patients (MSp) are vaccinated against SARS-CoV-2 using different formulations upon availability, including viral vector/inactivated virus/mRNA vaccines, at distinct times between doses. The real-world effectiveness of these unique vaccination schedules is scarce, so asthe efficacy to mount an appropriate immune response even more in MSp under treatment (DMTs)
Aims: To analyze the presence of reactive CD4+ and CD8+ T cells for SARS-CoV-2, IgG and IgM anti-Spike and anti-RBD, in MSp after receiving a 3rd vaccine dose
Methods: 27 MSp and 9 healthy controls (HC) were included in this study. SARS-CoV-2-reactive T cells were analysed with a T Cell Analysis Kit from Miltenyi as described by the manufacturer. In brief, peripheral blood mononuclear cells (PBMCs) were cultured with a pool of lyophilized peptides, consisting of 15-mer sequences with 11 amino acids overlap, covering the complete protein coding sequence (aa 5–1273) of the surface or Spike glycoprotein ("S") of SAR-CoV-2 and controls. After stimulation, the cells were stained with the live/dead marker, washed, fixed, permeabilized and stained for lineage and activation markers as well as cytokines. Cells were analysed using a flow cytometer. Doublets, debris, and dead cells as well as CD14+ and CD20+ cells were excluded. Cells were pregated on CD3 as well as CD4 and CD8. For reactive CD4 T cells CD154 and TNF-α were assessed on CD4+ T cells while TNF-α and IFN-γ in CD8+ T cells
Results: IgG antibodies (Ab) against S and RBD were found in all analysed HC, while in 22 and 20 out of a total of 27 MSp. Levels of IgG against S were lower in MSp vs HC. IgM levels against RBD were found in all HC and MSp, but 8 MSp had low levels of those Ab.There were no differences between HC and MSp in the % of reactive CD4+ T cells to S (p= 0.151). However, we found a lower % of reactive CD8+ T cells in MSp than HC (p= 0.026). Actually, CD8+ T cells were not detected in 4 out of 5 MSp treated with Fingolimod (FTY) but were present in all patients treated with monoclonal Ab, IFN or DMF. Furthermore, MSp treated with FTY had lower values of reactive CD4+ T cells and IgG anti-RBD than patients receiving other DMTs
Conclusion: Most MSp vaccinated against SARS-CoV-2 present some humoral and cellular response to SARS-CoV-2. This humoral and cellular response would be lower in MSp treated with FTY

Disclosure
A research collaboration from GADOR was received to pay laboratories test

Therapy - Tools for detecting therapeutic response

EP1114

Relapse-free time in relapsing-remitting multiple sclerosis: a new health indicator

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Introduction and objectives: There is an ever-present need to find measurable indicators of health levels in multiple sclerosis. Such indicators are frequently used to optimize the rational use of health resources. High efficacy disease-modifying treatments (HET) have been widely demonstrated to have a profound effect in the management of Relapsing Remitting Multiple Sclerosis (RRMS), which suggests that their availability may be reflected in health levels. Our objective in this study is to evaluate whether changes in the time elapsed since the date of the last RRMS relapse reflects the widespread adoption of HET since 2006, when first HET was authorized in Europe.
Methods: We conducted a retrospective observational study. We selected patients with diagnosis of RRMS belonging to the health area of a university hospital and with an onset disease between January 1991 and December 2020. We classified the patients into two cohorts based on whether they had started the disease before or after December 31, 2005. We analyzed and compared the time from the last relapse to December 31, 2005, for the first cohort and to December 31, 2020, for the second. As secondary variables, we calculated the annualized relapse rate (ARR) from the beginning of the disease to the cut-off date, the final Expanded Disability Status Scale (EDSS) and the EDSS progression index (PI).
Results: A total of 189 patients were included in the study, 69.3% were women and the mean age at disease onset was 32.8 years ±11.6. Of these, 80 patients had started their disease between 1991 and 2005, and 109 patients between 2006 and 2020. The median of follow-up time from the start of the disease to the cut-off date was similar in both cohorts: 7.4 years (14.5 IQR) for the first cohort and 8 years (14.8 IQR) for the second cohort. The median time elapsed from the last relapse to the cut-off date in the first cohort was 1.5 years (11.6 IQR) vs 2.9 years (12.8 IQR) in the second cohort, with statistically significant differences (p=0.048). There were no differences in the ARR from the onset of the disease to the cut-off date between the two cohorts (0.5, 33.1 IQR vs 0.4, 7.86 IQR p=0.39), nor in the final EDSS (1.5, 6.5 IQR vs 2, 7 IQR p=0.22) or in the PI (0.2, 3.5 IQR vs 0.3, 11.9 IQR p=0.13).
Conclusions: Relapse-free time in RRMS reflects the impact of the availability of HET better than the ARR, the EDSS or the PI, so it could be a good new health indicator.

Disclosure
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EP1115

Cladribine treatment exerts specific effects on memory B cell immunoglobulin repertoires in multiple sclerosis patients

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Introduction: B cells are acknowledged as crucial players in the pathogenesis of multiple sclerosis (MS). Several disease modifying drugs including cladribine have been shown to exert differential effects on peripheral blood B cell subsets, however, little is known regarding functional changes within the peripheral B cell populations.
Aim: By assessing immunoglobulin heavy chain (VH) repertoires from peripheral blood B cell populations and corresponding Ig proteome peptide libraries we aim to get deeper insights into B cell biology including quantitative but also qualitative changes.
Methods: 8 patients with multiple sclerosis were treated with cladribine. VH transcriptome repertoires and Ig proteome peptides were assessed at baseline and after 6 and 12 months of treatment. VH repertoires were generated from sorted B cell subsets including naïve, double negative, memory B cells and plasmablasts by next generation mass sequencing (Illumina platform). The corresponding Ig proteome was obtained by MS/MS mass spectrometry and is currently under investigation.
Results: In line with previous results, B cell subtype percentages in the peripheral blood showed a significant decrease of memory B cells and an increase of naive B cells following cladribine therapy. The number of recovered VH sequences per population was not significantly affected during treatment. However, 6 months after initiation of cladribine, patients displayed a significantly decreased number of clones in the memory subset ($p = 0.0078$) which was sustained at 12 months (no significant effects on the other B cell subsets). Further analysis of these clones showed a significantly bigger proportion of large clones with >100 sequences ($p<0.05$) and a significantly higher diversification ($p<0.05$, Gini Index). Overlap analysis of shared clones between the different time-points showed a lower number of overlapping clones between 6 months and 12 months when compared to

baseline and 6 months pointing towards a sustained effect on the memory B cell population.
Conclusion: Our findings suggest, that peripheral B cell related treatment effects of cladribine are exerted through a depletion of clones in the memory B cell subset without disrupting the overall clonal expansion of B cells. Our results -at least partially- explain the relatively mild side effects regarding infections and the sustained immune response after vaccinations during treatment.

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EP1116

Post hoc analysis of cognitive processing speed at time of first confirmed relapse in patients with relapsing multiple sclerosis treated with ozanimod vs interferon β-1A in the phase 3 SUNBEAM trial

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Introduction: Patients with relapsing multiple sclerosis (RMS) may experience cognitive declines during relapses. In SUNBEAM, ozanimod significantly reduced annualised relapse rate (primary endpoint), improved cognitive processing speed (CPS) on the Symbol Digit Modalities Test (SDMT, a component of a secondary endpoint), and reduced loss of brain volume, including thalamic volume (TV), compared with intramuscular (IM) interferon β-1a (IFN) in patients with RMS.
Objectives: To determine whether ozanimod reduced the proportion of patients with RMS who experienced worsening in CPS during first confirmed relapse in SUNBEAM compared with IFN and the association between baseline TV and clinically meaningful CPS worsening during first confirmed relapse.
Methods: SUNBEAM (NCT02294058) was a multicenter, randomised, double-blind trial in which patients with RMS received oral ozanimod 0.92 or 0.46 mg/d or IM IFN 30 μg/wk for ⩾12 mo. The SDMT was administered at MS relapse assessments and scheduled visits. We calculated between-treatment differences in proportion of patients with clinically meaningful worsening (⩾3 or ⩾4 pt decreases) on SDMT within 7 or 30 d of first confirmed relapse in the ozanimod 0.92 mg vs IFN groups, and descriptive statistics for baseline TV in those with vs without ⩾3 or ⩾4 pt worsening on SDMT within 7 or 30 d.
Results: Fewer patients relapsed in the ozanimod 0.92 mg group (84/447 [18.8%]) vs the IFN group (132/448 [29.5%]); SDMT was available within 7 d of relapse in 81/84 (96.4%) and 119/132 (90.2%), and within 30 d in 82/84 (97.6%) and 127/132 (96.2%), respectively. Proportion with ⩾3-pt worsening on SDMT within 7 d of relapse was 34.6% with ozanimod vs 47.1% with IFN (difference: -12.5% [95% CI -26.2, 1.2]) and within 30 d was 34.1% vs 46.5% (difference: -12.3% [95% CI -25.7, 1.1]). Proportion with ⩾4-pt worsening on SDMT within 7 d was 29.6% with ozanimod vs 42.9% with IFN (difference: -13.2% [95% CI -26.6, 0.1]) and within 30 d was 29.3% vs 42.5% (difference: -13.3% [95% CI -26.3, -0.2]).Mean baseline TV was similar (14.3−15.2 cm^3) among those with and without clinically meaningful worsening on SDMT within 7 or 30 d of relapse in both groups.
Conclusion: Ozanimod reduced the number of relapses and the proportion of patients with clinically meaningful worsening of CPS measured by SDMT within 30 d of first confirmed relapse relative to IFN. There was no clear association between CPS worsening during relapse and baseline TV.

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XM: Has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past 3 years with Actelion, Alexion, Bayer, Biogen, Bristol Myers Squibb/Celgene, EMD Serono, EXCEMED, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, MedDay, Merck, Mylan, MSIF, Nervgen, NMSS, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceuticals, and TG Therapeutics
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EP1117

Effect of ocrelizumab treatment on retinal atrophy: a single-center prospective observational study

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Background: Data regarding the effect of Ocrelizumab (OCR) on retinal atrophy are still lacking.
Aims: To provide first experience data regarding the effect of OCR on retinal thinning in patients with relapsing-remitting (RR-) and progressive (P-) multiple sclerosis (MS) and investigate whether rates of peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell+inner plexiform layer (GCIPL) atrophy differ according to response to treatment over a follow-up (FU) period of 2 years.
Methods: Patients starting OCR at the MS Center of the University of Genoa underwent spectral-domain optical coherence tomography (SD-OCT) scans at baseline and at 2-years FU. Demographic characteristics and effectiveness outcomesthroughout FU were collected.NEDA3 status was defined as absence of relapses, disability worsening, MRI activity. Eyes with previous optic neuritis were excluded. Atrophy rates of pRNFL and GCIPL at different timepoints and their differences between groups were assessed with repeated measures ANCOVA accounting for age, sex, disease duration, MS phenotype and previous treatments.
Results: A total of 65 MS patients were included in this study. A total of 53 patients reached the 2-years FU and entered the final analyses [34 RR-MS and 19 P-MS; females: 57%; mean age and disease duration: 40.7+11.1 and 8.7+10.6 years; median (range) EDSS: 3.5 (0-6.5)]. No significant differences were observed between baseline and FU pRNFL (95.41±10.18vs93.86±10.75 µmrespectively:p=0.91)andGCIPL(80.37±10.12vs79.32±10.07 µm respectively: p=0.61) thickness. Retinal thinning was similar between RR-MS (pRNFL: -1.66±2.31 µm; GCIPL: -0.69±3.05 µm) and P-MS patients (pRNFL:-1.31±2.69 µm; GCIPL:-1.69±1.85µm) (p=0.79 and p=0.16, respectively). While no GCIPL atrophy was observed in patients achieving NEDA3 status during FU (baseline vs FU thickness:-0.36±3.17 µm), a reduction in GCIPL thinning was observed in patients who lost NEDA3 (baseline vs FU thickness: -1.71±2.71 µm: p=0.029). At logistic regression, mean GCIPL reduction correctly classified 77.4% of patients as NEDA3 at 2 years ($R^2$0.45; p=0.024).
Conclusions: The overall stability of pRNFL and GCIPL thickness over 2-years FU suggests a neuroprotective effect of OCR treatment in RR-MS and P-MS patients. A more pronounced retinal thinning was observed in patients loosing NEDA3 throughout FU. Our findings support the role of GCIPL in monitoring treatment response, though should be confirmed by larger studies.

Disclosure
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EP1118

High-dimensional immune profiling of peripheral blood identifies a biomarker to monitor dimethyl fumarate response in multiple sclerosis

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Introduction: Dimethyl fumarate (DMF) is an immunomodulatory treatment for multiple sclerosis (MS). Despite its wide clinical use, the immune mechanisms underlying its efficacy are not fully understood, hampering our ability to stratify patients for response to therapy.
Objectives: To develop an unbiased approach for the integration of longitudinal high-dimensional immune profiling data with clinically relevant outcomes in MS.
Aims: This study aimed to reveal immune biomarkers of therapeutic response to DMF treatment in MS.
Methods: We prospectively collected peripheral blood mononuclear cells (PBMC) from a highly characterized cohort of 44 individuals with MS before, and at 12 and 48 weeks of DMF treatment. Single cells were profiled using high-dimensional mass cytometry. To capture the heterogeneity of different immune subsets we adopted a bioinformatics multi-panel approach that allowed cell population-cluster assignment of more than 50 different parameters, including lineage and activation markers, as well as chemokine receptors and cytokines. Data were further analysed in a semi-unbiased fashion implementing a new supervised representation learning approach to capture subtle longitudinal immune changes characteristic for therapy response.
Results: With this approach, we identified a population of memory T-helper cells expressing high levels of neuroinflammatory cytokines (GM-CSF, IFNγ) as well as CXCR3, whose abundance correlated with treatment response. Using spectral flow cytometry, we confirmed these findings in a second cohort of patients. Serum neurofilament light chain levels confirmed the correlation of this immune cell signature with axonal damage. The identified cell population is expanded in peripheral blood under natalizumab treatment, further substantiating a specific role in treatment response.
Conclusions: We propose that modulation of GM-CSF-, IFNγ- and CXCR3-expressing T-helper cells is the main mechanism of action of DMF and that monitoring this population can serve as biomarker of treatment response.

Disclosure
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EP1119

Can we compare data from different fatigue PROs in MS? Mapping the fatigue symptoms and impacts questionnaire - relapsing multiple sclerosis (FSIQ-RMS) Symptoms domain and the modified fatigue impact scale (mFIS)

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Introduction: Fatigue is a highly prevalent and bothersome MS symptom. Several Patient Reported Outcome measures have been developed and used in clinical studies to assess MS fatigue, such as the FSIQ-RMS (de novo) and mFIS (legacy).
Objectives: To develop mapping algorithms to support the comparison of FSIQ-RMS and mFIS scores.
Methods: The 7-item FSIQ-RMS Symptoms (S) domain has a 24-hour recall period assessed using an 11-point (0-10) Numeric Rating Scale (NRS) deriving a standardized 0-100 weekly score over a 7-day period, with higher scores indicating greater fatigue. The 21-item mFIS has a 4-week recall period graded on a 0 to 4 verbal rating scale (VRS) deriving a total score ranging from 0 to 84, with higher scores indicating greater impact of fatigue.
Data collected at Visit 2 (Day 9) and Visit 3 (Day 87) in a non-interventional, observational study of MS patients (n=165) were used. Initially, correlations (absolute and change) between the FSIQ-RMS-S weekly score and the mFIS total score were evaluated at Visit 2 and Visit 3. Next, linear regression was conducted to derive the mapping algorithm. Modeling was conducted using the FSIQ-RMS-S weekly score as the independent variable and mFIS total score as the dependent variable (and vice versa). R-squared values and Pearson correlation coefficients were conducted for model assessments.
Results: High correlations between mFIS total score and FSIQ-RMS-S score at each visit (Visit 2=0.772; Visit 3=0.767). The regression model R-squared for Visit 2 (61.3%) and Visit 3 (58.8%) indicates a large proportion of variance in mFIS total scores can be explained by FSIQ-RMS-S scores. Moderate correlations were observed between the change scores from Visit 2 to Visit 3 (0.401). However, there were high correlations between the observed and predicted values for Visit 2 (0.783) and Visit 3 (0.767).

Conclusions: While each PRO captures MS-related fatigue symptoms they vary in recall period, content, and instructions so any mapping should be for exploratory, supportive interpretation to previous literature. Specifically, the mFIS requires MS patients to recall over a 4-week period which is quite a long period of reflection given the potential for variability of symptom experience in this patient population. The FSIQ-RMS was developed in accordance with the FDA Guidance, with direct patient input, and should be considered the gold standard measure for future studies.

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Eva Katz is an employee of Janssen Research & Development, LLC and holds company stock and/or stock options.
Carol Jamieson is an employee of Janssen Research & Development, LLC and holds company stock and/or stock options.
Stacie Hudgens is an employee of Clinical Outcomes Solutions and Clinical Outcomes Solutions received consulting fees to support the planning, analysis, and communication of this research.
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EP1120

Elevated acetate levels correlate with optimal response to ocrelizumab treatment in low inflammatory primary progressive MS patients

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Introduction: Short-chain fatty acids (SCFA) are compounds derived from gut microbiota metabolism that have a role in gut-brain axis and have been related to multiple sclerosis (MS) etiopathogenesis.
Objective: To ascertain the role of plasma SCFA levels in the response to ocrelizumab in primary-progressive multiple sclerosis (PPMS) patients.
Methods: Multicentre prospective study including 69 patients with PPMS who initiated ocrelizumab treatment, classified according to baseline presence [Gd+, n=16] or absence [Gd-, n=53] of gadolinium-enhancing lesions in brain MRI. Serum SCFA and immunoglobulin levels were measured at baseline and 6 months after ocrelizumab initiation by liquid chromatography-mass spectrometry and nephelometry, respectively.
Results: Ten (62.5%) Gd+ and 41 (77.4%) Gd- patients reached an optimal response (NEDA) defined as no disability progression and no new MRI lesions after 1 year of ocrelizumab treatment. Only in low-inflammatory Gd- patients, NEDA status associated with an increase of plasma acetate levels 6 months after the first ocrelizumab dose (p=0.0013) and this correlates with an elevation in serum IgA levels (p=0.006) and IgA/IgG ratio (p=0.0011). No differences were found in Gd+ groups.
Conclusions: In Gd- patients NEDA associated with increased plasma acetate levels, a finding that links gut microbiota and response to Ocrelizumab in PPMS patients with low inflammatory profile. Future studies are needed to confirm the relationship of microbiota composition and response to ocrelizumab in these patients.

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EP1121

Effect of disease modifying therapy on T2-flair-based neurodegenerative MRI outcomes: a longitudinal, real-world, US-based, multi-center multiple sclerosis study

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Background: The effect of disease modifying therapies (DMTs) on modulating brain atrophy in persons with multiple sclerosis (pwMS) is investigated only in highly standardized clinical trial settings or single-center academic institutions. We aimed at utilizing artificial intelligence (AI)-based volumetric analysis on routine unstandardized T2-FLAIR scans in determining the effect of DMTs on MS neurodegeneration.
Methods: The DeepGRAI (Deep Gray Rating via Artificial Intelligence) registry is a multi-center, longitudinal, observational, real-word study of 1002 relapsing-remitting (RR) pwMS from 30 United States sites. Brain MRI exams acquired as part of the routine clinical management were collected at baseline and on average at 2.5-years follow-up. The MRI scans were acquired either on 1.5T or 3T scanners with no prior standardization. Lesion volumes (LV) and active lesion count (ALC) over the follow-up were calculated using edge detection contouring technique. Thalamic volume (TV) was determined using DeepGRAI neural network architecture and lateral ventricular volume (LVV) was measured using NeuroSTREAM software.
Results: Greater TV loss, LVV expansion and higher median lesion activity were seen in untreated PwMS (n=45) (-1.1% for TV, 4.3% for LVV and 0.5 for ALC), in those who stopped their DMT (n=51) (-1.7% for TV, 7.6% for LVV and 1.0 for ALC), started their DMT later during the follow-up (n=85) (-1.3% for TV, 10% for LVV and 1.0 for ALC), or switched to different DMT over the follow-up (n=249) (-1.1% for TV, 7% for LVV and 1.0 for ALC). When compared to the active groups (n=430), PwMS that remained on the same DMT over the follow-up (n=572), had significantly lower TV loss (-0.3%, p=0.008), lower LVV expansion (4.4%, p=0.03) and lower ALC (median new/enlarging lesions of 0.0, p=0.001).
Conclusions: LVV and TV measured on T2-FLAIR scans can detect treatment-induced short-term neurodegenerative changes measured in a real-word unstandardized, multicenter, clinical routine setting. PwMS who were not treated, started, stopped or switched DMT had greater thalamic atrophy, LVV expansion and lesion activity over the short-term follow-up.

Disclosure
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EP1122

Development of an active biosensing digital application (App) for monitoring fingers' functions

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Background: Accurate assessment of various functions of the fingers is essential for monitoring the performance of daily hand activities. However, targeted digital applications for evaluating various fingers tasks are missing.
Objective: To develop a customized digital biosensing application (App) to assess fingers' functions.
Methods: We developeda digital biosensing app for smartphones and tablets using the device touch- screen. The app enables 2-min testing of fingers' movements in the vertical, horizontal, zigzag, and circle orientations for fingers 1, 2, and 5, and pinch testing for fingers 1-2, 1-3, 1-4, 1-5. Velocity in mm/sec and deviation from the required line orientation in mm, were measured for each finger and each movement orientation. Correlation was performed with age and gender. Data was collected for the dominant hand from healthy volunteers without impairments in hand function to establish population norms.
Results: 250 consecutive healthy subjects, 155 females, 95 males, mean age 36.8 ±14.19 years, were included in the study. Velocity was faster for the vertical and horizontal tests compared to all other tests, and fastest for finger 2, while the zigzag test was the slowest test for all fingers. Deviation from any required line orientation was more evident for the zig-zag test, and mainly for finger 5, while the vertical orientation was the most unerring. Analysis of the fingers' movements by age, disclosed better performance in all tests in the younger age group (<35 years); no effect of gender for both velocity and deviation were observed.
Conclusions: The screen-touch digital app enables the characterization of speed and accuracy of fingers' movements, allowing immediate evaluation of hand function. The collected population norms will be used for comparison with targeted fingers' functions in patients with MS.

Disclosure
Disclosure; All authors report no conflict of interest.

Therapy - Symptomatic treatment

EP1123

Long-term dosage and persistence of nabiximols in a randomized clinical trial and real-world registry

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Introduction: The safety and efficacy of nabiximols cannabinoid oromucosal spray were evaluated in people with multiple sclerosis (PwMS) in 4 pivotal studies. It is important to understand the dosing patterns and persistence of nabiximols over time, particularly in real-world (RW) settings.
Aims: To describe the long-term dosage of nabiximols, to evaluate RW dosing and to investigate the association between dosage and premature study discontinuation in MS-related spasticity.
Methods: A post hoc analysis was done on GWMS1137 (N=62; a randomized placebo-controlled post-authorization safety study of nabiximols in MS spasticity) and GWSR10128 (N=765; an RW observational postmarketing safety registry for nabiximols use in MS spasticity). Participants were allowed to titrate to a maximum of 12 sprays per day in both studies. Assessed were the average, minimum and maximum number of sprays at 12, 24, 36 and 48 weeks after the first dose and change from the previous visit. Time to early discontinuation of study drug for any reason was determined. The predictive impact of dose on study discontinuation, adjusting for sex and age, was modeled. Efficacy data were published elsewhere.
Results: Baseline demographics were similar between both studies. In GWMS1137, the mean average dose (sprays per day) was 7.6, 6.8, 6.4 and 6.5 sprays at 12, 24, 36 and 48 weeks, respectively, and in GWSR10128, 4.8, 4.9, 4.9 and 5.0 sprays. Female participants and those aged >45 years tended to use a lower dose of nabiximols. Mean, minimum and maximum average daily doses were stable over 12-48 weeks in both datasets, with consistently lower doses in the registry. Relative to the prior 12 weeks, mean difference in mean number of average daily sprays was −0.8, −0.3 and 0.0 in GWMS1137 and −0.2, −0.3 and −0.1 in GWSR10128 at 24, 36 and 48 weeks. In both datasets, 75% of participants continued treatment with nabiximols for 48 weeks. In the registry, the subset of participants who discontinued nabiximols took a lower dose of the drug (mean average daily dose of 3.8, 3.9, 4.0 and 4.1 sprays at 12, 24, 36 and 48 weeks, respectively). After adjusting for sex and age, the HR for study

discontinuation decreased as the average daily number of sprays increased (HR 0.6 [95% CI 0.55-0.7];P<0.0001).
Conclusions: Nabiximols dosing remained stable over time in both a randomized controlled trial (RCT) and RW registry and tended to be lower in RW settings, with a high persistence rate of 75% in both datasets.
Disclosure:
1. Scott Newsome received consultant fees for scientific advisory boards from Biogen, Genentech, Bristol Myers Squibb, EMD Serono, Greenwich Biosciences, now a part of Jazz Pharmaceuticals, inc., Novartis, and Horizon Therapeutics; is an advisor for Autobahn Therapeutics; is the Principal Investigator for a Roche clinical trial; was a clinical adjudication committee member for a MedDay Pharmaceuticals clinical trial; and has received research funding (paid directly to the institution) from Biogen, Roche, Genentech, National Multiple Sclerosis Society, Department of Defense, and Patient Centered Outcomes Institute.
2. Teresa Greco is an employee of Jazz Pharmaceuticals, Inc.
3. Jessica Alexander is an employee of Jazz Pharmaceuticals, Inc.
4. Peter Flachenecker has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, BMS-Celgene, Coloplast, Genzyme, GW Pharma, now a part of Jazz Pharmaceuticals, Inc., Hexal, Janssen-Cilag, Novartis, Merck, Roche, Sanofi, Stadapharm and Teva.

EP1124

Evaluation of fampridine treatment response by triple stimulation technique

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Introduction: Prolonged release Fampridine (PRF) improves walking in 43% of patients with Multiple Sclerosis (pwMS) by restoring nerve conduction. Parameters to predict treatment response are lacking. A decrease in central motor conduction time (CMCT) under PRF has been shown, but without clinical correlation. The Triple Stimulation Technique (TST) is an electrophysiological method using motor evoked potentials and a collision technique to quantify intact nerve fibers. A reduced TST amplitude ratio (TST-AR) represents a central motor conduction deficit and correlates better with clinical deficit in pwMS than CMCT.
Objective/Aim: To evaluate if baseline (BL) TST-AR/CMCT are associated with a positive PRF response.
Methods: Ongoing clinical study, using the Multiple Sclerosis Functional Composite (MSFC) and TST (recording the abductor hallucis muscle) in adult pwMS (18-70 years (y)) with EDSS 4.0-7.0 before and during on lable treatment with PRF (day 14-21).
Results: 12 pwMS have been studied (7/12 with relapsing-remitting (RRMS), 5/12 with progressive (PMS) disease). Mean age was 55.4y (standard deviation (SD) 11.5), mean EDSS 4.6 (SD 1.1). Mean CMCT was prolonged (21.1ms, SD 8.0), mean TST-AR reduced (71.7%, SD 20.4), more pronounced in PMS (mean CMCT RRMS: 17.1ms, PMS: 27.9ms; mean TST-AR RRMS: 84.4%, PMS: 57.5%). Two subjects responded to PRF improving 20% in the Timed-25-Foot-Walk-Test (T25FWT). Both had a prolonged CMCT and reduced TST-AR at BL, one showed an improvement of 10% in both CMCT and TST-AR. However, 7/12 reported response in other domains (e.g. fatigue, walking distance). Of these, 6/7 had a prolonged CMCT and reduced TST-AR at BL. Under PRF, 4/7 showed a decrease in CMCT (mean 11.7%, SD 5.7), 4/7 an increase in TST-AR (mean 9.7%, SD 8.3), improvement in both parameters was seen in 4/7. None of the subjects without PRF response showed prolonged CMCT combined with reduced TST-AR at BL.
Conclusion: In line with previous data, we find reduced central motor conduction in pwMS associated with disease course, partially improved under PRF. We identified 2/12 'T25FWT-responders', whereas 7/12 reported functionally relevant benefits in other domains. The combination of a prolonged BL CMCT and reduced TST-AR was found in 8 of these 9 subjects with treatment benefits and in none of the patients without any PRF response.
Further investigation of a larger set of patients will elucidate if TST-AR alone or combined with CMCT allows response prediction to PRF.

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EP1125

Intermittent negative pressure applied to the lower limb of patients with multiple sclerosis and its impact on symptoms

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Introduction: Spasticity and pain are common symptoms in patients with Multiple Sclerosis (MS). A novel non-invasive medical device applying intermittent negative pressure (INP) to the lower leg increases blood flow, interacts with the veno-arterial reflex, and may stimulate other sensory receptors in the treated leg. INP treatment relieve symptoms in patients with peripheral artery disease, however, off-label use has shown promising effects on spasticity, cramps, and pain in patients with MS.
Objectives: To assess whether INP treatment could have a positive effect on spasticity related symptoms in patients with MS.
Methods: Patients with MS and spasticity related symptoms were interviewed by a neurologist via video link following treatment with INP at home for one hour per day for 2 weeks and up to 6 months. A predetermined list of questions was used to systematically interview the patients to assess the clinical status before the INP treatment, and the impact that the INP treatment had on spasticity, cramps, and pain. All patients were provided with a written summary of their response for their approval after the interviews were performed.
Results: In total 7 patients were interviewed, 6 patients reported that they had spasticity, 4 patients had pain and 3 patients had problems with cramps before the start of the treatment. After treatment with INP, 4/6 patients reported an improvement in spasticity, 4/4 patients reported an improvement in pain, 2/3 patients reported a reduction in cramps. Of the 5 patients reporting sensibility disturbances, 4 patients reported an improvement after INP treatment. All 4 patients with poor sleep quality reported an improvement after INP treatment. Several patients also reported an effect on the contralateral leg or a reduction in the overall stiffness in the body. One patient reported no effect of the treatment at all. No side effects or adverse events were reported.
Conclusion: This case series suggests that MS patients with spasticity and pain may benefit from treatment with INP. INP treatment seems to be safe with few side effects in this patient population. Further controlled clinical trials and mechanistic studies are needed to understand the potential clinical benefit and mechanism of action of INP in patients with MS.

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Gabriela Fortes: Nothing to disclose
Henrik Hoel: Head of Medical Affairs and shareholder in Otivio AS
Iacob Mathiesen: CSO and shareholder in Otivio AS

Therapy - RWE and MS registries

EP1126

Real-world outcomes of teriflunomide in relapsing-remitting multiple sclerosis: a prospective cohort study

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Introduction: Real-world studies examining the new treatment goal, no evidence of disease activity (NEDA), are lacking for teriflunomide.
Objectives: To explore efficacy (assessed by NEDA), associated impact factors, safety, and persistence of teriflunomide treatment in a real-world, relapsing-remitting multiple sclerosis (RRMS) patient cohort.
Aims: To provide real-world evidences for teriflunomide in RRMS patients.
Methods: This prospective, observational cohort study included 217 consecutive teriflunomide treated RRMS patients, 192 of which with at least 3-month persistence on teriflunomide were included in effectiveness and risk factor analyses. Multivariate Cox proportional regression analysis was performed to identify factors associated with failure of no evidence of disease activity (NEDA) 3.
Results: At baseline 82% patients were treatment naïve while 18.0% interferon-β1b treated patients had stopped treatments for more than 1 year. After treatment, 79.0% patients achieved NEDA 3 at 12-month, mean annualized relapse rate (ARR) reduced significantly (0.79 ± 0.80 vs 0.16 ± 0.70; $P<0.001$), and mean expanded disability status score (EDSS) remained stable (1.40 ± 1.67 vs 1.56 ± 1.88; $P>0.05$).Male sex (hazard ratio [HR], 1.856; 95% confidence interval [CI], 1.118–3.082, $P<0.05$), baseline EDSS score $\geqslant 4$ (HR, 2.682; 95% CI, 1.375–5.231, $P<0.01$), and frequent relapses before treatment (HR, 3.056; 95% CI, 1.737–5.377,$P<0.01$) were independent factors significantly associated with failure of NEDA 3. The most frequent adverse events (AEs) were hair thinning, alanine aminotransferase (ALT) elevation, and leukopenia, the latter two most commonly lead to teriflunomide discontinuation during the first 3 months. Persistence rates at 6, 12, and 24 months after teriflunomide initiation were 86.9%, 72.4%, and 52.8%, respectively.
Conclusions: Our results support efficacy and tolerability of teriflunomide for treatment-naïve RRMS patients in real-world practice. Female patients, patients with less relapses and less disability before treatment are most likely to benefit from teriflunomide treatment.

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EP1127

Real-world clinical and economic outcomes among persons with multiple sclerosis initiating first- vs second-line treatment with ocrelizumab

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Background: Research has demonstrated that early use of ocrelizumab (OCR), a high-efficacy disease-modifying therapy (DMT), can reduce relapses and delay progression, which is associated with reduced costs, in persons with multiple sclerosis (pwMS). However, there is limited real-world evidence on the impact of first-line (1L) OCR on clinical and economic outcomes.
Objective: To evaluate differences in relapses, healthcare resource use and costs among pwMS who initiated OCR as a 1L vs second or later line (2L+) DMT following diagnosis.
Methods: All newly diagnosed, adult pwMS were identified in deidentified Optum Market Clarity claims data (study period, 1 Jan 2015-30 Jun 2021). All pwMS were required to have 12 months' continuous eligibility prior to diagnosis and initiate OCR after diagnosis. The index date was the date of initiation of the first DMT after diagnosis. The follow-up period was the entire period of continuous eligibility after the index date. All 1L OCR pwMS were matched 1:1 to 2L+ pwMS based on months of follow-up. To account for baseline differences, pwMS in the matched cohort were weighted using stabilised inverse probability of treatment weighting (IPTW) for the probability of 1L treatment, calculated via logistic regression as a function of demographic and clinical characteristics in the 12 months prior to the index date. Differences in outcomes, including annualised relapse rate (ARR), likelihood of hospitalisation and non-DMT/MS-related costs, between 1L vs 2L+ cohorts over the follow-up period were estimated with generalised linear models using IPTW.
Results: The matched sample included 374 1L and 374 2L+ OCR pwMS. After weighting, 1L and 2L+ pwMS had similar baseline characteristics. During the entire follow-up period, 1L pwMS had a significantly lower ARR than 2L+ pwMS (1L: 0.36, 2L+: 0.51, difference: 0.15 [95% CI 0.04–0.25]). 1L pwMS had a significantly lower probability of any hospitalisation within 1 year (0.020 [95% CI 0.010–0.030]) than 2L+ pwMS (0.042 [95% CI 0.027–0.058]) over the follow-up period (P=0.017). 1L pwMS also had lower total annual non-DMT costs ($18,389 vs $26,225, P<0.001) and MS-related/non-DMT costs ($8837 vs $14,758,P<0.001) than 2L+ pwMS during follow-up.
Conclusions: Initiation of 1L OCR following diagnosis was associated with reductions in relapses, hospitalisations and costs compared with 2L+ OCR, suggesting early initiation of OCR may have benefits for both patients and the healthcare system.

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EP1128

Cladribine treatment in turkish MS patients

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Introduction: As a high-efficacy multiple sclerosis (MS) treatment, cladribine necessitates empirical data from diverse populations.
Objectives: To study the efficacy and safety data of cladribine treatment in a real-world setting.
Methods: Patients from eight MS clinics in Turkey were involved in the study. We retrieved the demographic, clinical, MRI, safety, laboratory, COVID-19, and pregnancy records of patients with at least six months of follow-up on cladribine treatment.
Results: Our study included 210 MS patients (52 males, 158 females; 193 relapsing and 17 relapsing-progressive MS). The mean age at MS disease onset was 27.6 years (±8.5). Before cladribine treatment, 56.7% of patients used first-line, and 41.9% used both first and second-line therapies. During a mean follow-up

period of 13.0 months (±4.7) following cladribine treatment, 5.7% of patients experienced a relapse. The shortest duration of relapse following cladribine administration was one week, and the longest duration was 15.3 months. Interestingly, 50% of the relapses occurred within the first three months. Among relapsing patients, five switched from fingolimod, two from dimethylfumarate, and one from ocrelizumab and interferon-β. The mean annualized relapse rate was 0.41 (±0.41) in the two years preceding cladribine and 0.11 (±0.55) one year following treatment. At baseline, the mean EDSS score was 2.47 (±1.63), and 51.9% of patients ranked below EDSS 3. EDSS progression was observed in 7.6% of patients following cladribine treatment. On cladribine, eight patients (9.4%) exhibited radiological progression. There was no difference in NEDA status between patients switching from first or second-line therapy (p=0.43). COVID was observed in 73 patients, 54 of them had a mild disease course, six had a moderate disease course, and one had a severe disease course. There have been no COVID-related fatalities. There were five pregnancies documented, three of which are currently ongoing. One of the pregnancies ended with healthy childbirth, while the other was terminated in the first trimester with a miscarriage.

Conclusions: Despite the relatively short duration of follow-up, our study demonstrates that cladribine is effective in providing NEDA. Moreover, switching from fingolimod to cladribine may increase the likelihood of early relapse.

Disclosure

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EP1129

Experience with cladribine in a real world MS cohort

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Introduction and Aims: Cladribine was approved in Spain in 2018 for the treatment of Relapsing Multiple Sclerosis (MS). Since its approval, controversy raised on whether it should be used as a first or second line treatment. The good safety profile and low monitoring requirements makes it an attractive option in mild MS patients. We present the experience of two centres in Spain in which cladribine has been used in a relatively mild MS cohort.

Methods: We included all patients that started on cladribine at Hospital General Universitario Gregorio Marañon and HM Hospitales in Madrid, Spain.

Results: Sixty patients were included in this analysis. At baseline, 83% were female, with a mean age of 39,3 years and a mean

EDSS of 1.72. Thirty-two (53,3%) patients had had a relapse in the previous year and 42% had at least one Gadolinium enhancing lesion in the baseline MRI. Mean follow-up time was 23,08 months, with 29 patients in either 2nd or 3rd years of follow-up. Half of the patients came from prior oral treatments and there were 8 naïve patients.
Lymphocyte counts decreased 43.50% after the first cycle and 57% after the second, compared to baseline. Relapse rate decreased from 0.62 to 0.25 at year 1 and to 0.08 at year 2, corresponding to a 60% and 87.1% reduction compared to baseline. Most relapses occurred during the first 6 months of treatment. EDSS remained stable throughout follow-up. No Evidence of Disease Activity through two years was reached in 45% of our sample. Three out of 6 patients switching from fingolimod experienced a rebound. Only two patients discontinued treatment due to disease activity and two patients were treated with a third course. There were no safety issues. We delayed the administration of the second course in 10 patients, in four of them due to persistent lymphopenia.
Conclusions: In our relatively low disability, low activity cohort, treatment with cladribine resulted in an excellent efficacy and safety profile.

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EP1130

Assessment of persistence to disease modifying treatments in patients with multiple sclerosis

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Introduction and objective: Planning health costs in Multiple Sclerosis (MS) is one of the main concerns of authorities. There is a need for health outcomes and persistence (PER) to Disease Modifying Treatment (DMT) may be a useful indirect outcome, and probably different between naïve and previously treated. Our aim was to assess PER and reason for discontinuation in people with MS (pwMS).
Methods: Observational retrospective study in pwMS that initiated DMTs with Interferon-β (INF-β), glatiramer acetate (GA), Teriflunomide (TRF), Dimethyl Fumarate (DMF), Fingolimod, Natalizumab or Alemtuzumab (ALZ) from January 2016 to December 2020.
PER to DMT was defined as the time elapsing from DMT initiation to discontinuation, as by Kaplan-Meier's survival analysis.
We assessed the following variables: sex, age, Expanded Disability Status Scale (EDSS), prior DMT exposure, PER, percentage of patients on DMT and reasons for discontinuation.
The sample was split between naïve patients (NP) and patients with prior exposure to DMTs (PPrev).
Results: 492 pwMS were included. 69% were female and mean age was 40,4(±10,1)years. Mean follow-up time was 21,9 months. NP were 250 (50,8%) and had significantly lower mean EDSS score than PPrev(1,2±SD vs 2,1±SD).INF-β was the most prescribed drug in NP (34%), followed by GA. In PPrev, TRF was the most frequently prescribed (35,3%), followed by DMF.
Mean PER of the full cohort was 21,9(±13,7) months. For NP, mean PER was 20,7(±13,5), with higher PER for DMF (36,2 [30,3-42,1] months) and GA (34,8[29,5-40,2] months). In PPrev, mean PER was 23,1(±SD) and significantly longer for ALZ (47,9[44,1-51,7]). No significant differences were found in PER between NP initiating a first (injectables, TRF, DMF) vs a second line DMT.
At the end of follow-up, 166 patients (33,7%) had discontinued DMT. Thirty-six per cent of NP discontinued treatment: 17,6% due to adverse events (AE) and 14,8% due to Breakthrough Disease (BD). For PPrev, 31,5% discontinued treatment: 13,7% due to AE and 12% due to BD.
PER was significantly longer in patients that discontinued due to BD than in those discontinuing due to AE, both in NP(20,5±10) vs (11,6±10,5), and in PPrev (21,1±9,9) vs (10,6±9,7).
Conclusions: In our sample, PER was high. In NP we found a trend for a longer PER with DMF and GA. In PPrev, ALZ showed a longer PER, followed by DMF. We found no difference in discontinuation due to AE or BD but PER was longer when discontinuation was due to BD.

Disclosure
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EP1131

A real-world single-centre analysis of the safety and efficacy of cladribine tablets for relapsing multiple sclerosis

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Introduction: Cladribine tablets (CT) are a highly effective immune reconstitution therapy for Relapsing Multiple Sclerosis (RMS). However, real-world data (RWD) on its safety and efficacy, certainly beyond 2 years, remains scarce.
Objectives: To evaluate safety and efficacy outcomes (no evidence of disease activity (NEDA) and its components) from our cohort of Cladribine treated RMS patients at the Rehabilitation and MS Centre (RMSC), Pelt, Belgium.
Aims: To provide novel insights into the use of CT in a diversified real-world setting.
Methods: All RMS patients who received CT between August 2018 and November 2021 were included for retrospective chart review. Patients with data for all three NEDA components (relapse, MRI, and Expanded Disability Status Scale (EDSS)), were incorporated into the efficacy analysis during follow-up. Efficacy endpoints were re-baselined at 3 months. Safety endpoints included grade of lymphopenia, liver transaminases, and adverse events. Descriptive statistics, logistic regression, and time-to-event analysis were performed, including subgroup analysis.
Results: Data from 84 eligible patients, with a mean follow-up of 22.6 ±11.5 (range: 4-43) months was analysed. Eight (9.5%) patients were treatment-naive, while 29 patients (34.5%) received at least one highly active treatment prior to CT. Most patients switched from dimethyl fumarate (21.4%) and fingolimod (19.0%), while disease activity was the most common reason for CT initiation (61.8%). Mild and serious adverse events were reported by 62 (73.8%) and 3 (3.6%) patients. Fatigue and mild infections were the most frequent (61.3% and 46.8%). Concerning the NEDA constituents, 14 (16.7%) patients experienced a relapse during follow-up, while disability progression and brain MRI activity occurred in merely 8.5% (6/71) and 6.3% (5/79) of the patients. This resulted in a cumulative NEDA-status of 86.4%, 72.4%, and 55.6% for patients reaching the 1 year- (n=59), 2 year- (n=29), and 3 year-mark (n=9). Analysis of factors predictive for disease activity after CT treatment initiation is ongoing and will be reported at the ECTRIMS Conference.
Conclusions: In our cohort of RMS patients treated with Cladribine, we observed retainment of NEDA status over 3 years in more than half of the patients following treatment initiation. Treatment with Cladribine was well tolerated and no new safety signals were seen.

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EP1132

A real-world study of four-year follow up study of patients treated with oral cladribine from 2018-2022

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Background: The administration of oral cladribine reduces relapses and slows accumulation of disability, however it is currently unknown how previous treatment with high efficacy disease modifying therapies (DMTs) may affect expanded disability status scale (EDSS).Real-world outcomes data for cladribine is limited. Real-world data provides safety and effectiveness data that is not provided through randomised controlled trials.
Objective: To explore two-year EDSS change after initiation of oral cladribine and characterise lymphocyte profile and immunoglobulin levels, to evaluate short term safety profiles and the number that need to be retreated in years 3 and 4.
Methods: In a cohort of 180 patients with MS from a single centre in Australia, lymphocyte subsets and IgG levels were measured at baseline, 12,18, 24-month time points after starting therapy with cladribine. EDSS change, and number of patients with relapse and lesion count were also captured at these time intervals. Safety data was reviewed. Patients were clinically reviewed each 6 months and if retreated further laboratory tests were conducted. The impact of COVID19 affected some clinical assessment timing.
Results: Of the total cohort treated with cladribine, 46 patients were naïve to therapy, 12 patients switched to cladribine with a treatment gap of >2 years, and the most common immediate prior DMTs were fingolimod (n=33), B cell therapy (n=38, natalizumab (n=30), and others (n=21). Mean Baseline EDSS was 4, Year 1, 3.9 and year 2 was 4.1. 85% were stable or improved and 15% had a higher EDSS. From baseline to year 2, 79% were stable or improved and 21% had worsened. CD4 cell count fell slightly, while CD8 and CD19 cell counts and IgG count remained stable from baseline, 12-month and 24-month intervals. Relapse rate fell over the 2 years to 11%. Grade 4 lymphopenia occurred in 1% of patients at the 24-month interval. 9 of 131 patients completing year 3 were given a third dose in their third year and 4 of 54 received a third dose in their 4th year.

Conclusions: Data from this cohort shows the majority of patients' EDSS scores improved or stabilised over 12-24 months, with an increasing proportion in deteriorating at 24 months. IgG levels remained stable. 10% of patients received a third dose, 6% in their 3rd year and 4% in their 4th year.

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EP1133

Effect of treating hospital on discontinuation rates of dimethyl fumarate in multiple sclerosis

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Introduction:nIn multiple sclerosis (MS), therapy switches are associated with a higher relapse rate, health care expenses, disease burden, and lower quality of life. Studies on time to discontinuation of treatment (drug-survival) for patients using dimethyl fumarate has shown varying results.
Objectives: Compare discontinuation rates of dimethyl fumarate and analyse differences in standard of care between five hospitals in Norway.
Aims: To study if some of the variation in discontinuation rates can be explained by treating hospital and their specific routines.
Method: Data was extracted from the Norwegian MS-registry from five participating hospitals in Norway. Information on the standard of care was collected through an electronic survey filled out by physicians and nurses at the participating clinics. An adjusted cox mixed effects regression analysis was preformed to examine discontinuation rates and the variation between different hospitals.
Results: We identified 802 patients with relapsing-remitting multiple sclerosis who initiated treatment with dimethyl fumarate between 01.01.2014 and 31.12.2020 at five clinics in Norway. Our analysis shows a variance of 0.04 between clinics. Including hospitals as a random effect significantly improved the model ($p<0.001$). We also found that initiating treatment with a lower dose of dimethyl fumarate decreased the risk of discontinuation, HR 0.55, $p = 0.01$. The risk of discontinuation also decreased with age, HR 0.97, $p<0.001$. However, each relapse a patient had experienced before start of treatment increased the risk of discontinuing, HR 1.07, $p=0.0032$. We found differences in standard of care between hospitals, such as use of dose-titration, consultation-time at each visit, numbers of visits during the first year of treatment and continuity in treating physician.
Conclusions: Discontinuation rates of dimethyl fumarate in MS varies between hospitals, even when individual factors are adjusted for. The use of dose-titration during the first two weeks of treatment seem to lower the rate of discontinuation.

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EP1134

Real life efficacy and tolerability of cladribine: multicentre study in galicia (CLADRIGAL)

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Introduction: Cladribine is an oral formulation which was approved as treatment of Relapsing-Remiting Multiple Sclerosis. Its efficacy and adverse events have been described in randomized controlled trials. Data from regular clinical practice are needed.
Objective: Our objetive is to describe our experience with Cladribine in terms of tolerance and clinical effectiveness after 1 year of treatment.

Patients and methods: All patients from 8 Clinical Hospitals in Galicia, Spain, that were prescribed cladribine were included. Basics demographic, clinical data, disability (EDSS scale), number of relapses, number of T2-lesions and Gd enhancing lesions on craneal MRI, lymphocyte count, adverse events and reasons for discontinuation of cladribine were reported.
Results: 128 patients (75% woman) were reviewed, included 14.8 % naive, average age 42.3 years old (±10.4), average anual relapse 0.90 (±0.75), average EDSS 2,04 (±1.44), average number Gd enhancing lesions 1.31 (±3.2), lymphocyte count 1904 (±825). 67 patients complied 1 year of treatment. Cladribine decreased average anual relapse 0.23 (±0.46) ($p<0.05$). Disability was stable 2.06 (±1.6) ($p=0.06$). Number of new lesions 1.2 (±2.5) and average number of Gd enhanging lesions was 0.35 (±1.6) ($p<0.05$). Lymphocyte count 1428 (±528) ($p<0.05$). 27 (21%) experienced adverse events, most commonly fatigue (5.6%), depression (4%), and urinary infection (3.2%). 4 had severe adverse event: Herpes Zoster (2), lymphopenia (1), amenorrhea (1), prostate cancer (1). 2 (1.6%) patients stopped the treatment, 1 (0.8%) because severe adverse event (prostate cancer) and 1 (0.8%) because inneficacy and adverse event (lymphopenia).
Conclusions: The efficacy of cladribine in real-life setting was demostrated by the stability in EDSS and reduction the number of relapses and the number of new and enhancing GD lesions on MRI. Cladribine has been well tolerated by the majority of patients

Disclosure
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EP1135

Effectiveness of cladribine tablets in the treatment of active relapsing-remitting multiple sclerosis: a multicenter, observational study

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Introduction: So far,alimited number of real-world evidence studies about the effectiveness of cladribine tablets (CT) have been published, some of them with relatively small numbers of included patients.
Aim: We aimed to study the effectiveness of CT in real-world clinical practice in three MS centers in Croatia, Slovenia, and Hungary.
Methods: This was a retrospective chart review of 159 consecutive persons with relapsing multiple sclerosis (pwMS) (114 (71.7%) females, mean age 42.4±10.0 years, median EDSS 3.0 (range 0-7), and median disease duration of6 (range 0.13-30) years) who completed two cycles of CT from 2018 to 2021. The following data were collected: gender, age at disease onset, disease duration at CT initiation, previous disease-modifying therapy (DMT), number of relapses, active MRI lesions, and EDSS in the year prior to CT initiation and every year of follow-up.
Results: All patients completed the standard dosing schedule and were followed for a median time of 2.47 (1.11-3.83) years after the initiation of treatment. 42 (26.4%) participants were treatment naïve, and 31 (19.5%) were switched from other high-efficacy DMTs. ARR in a year prior to starting CT was 1.14 and in years 1, 2, and 3 after starting CT was 0.084 ($p<0.001$), 0.149 ($p<0.001$), and 0.219 ($p<0.001$), respectively. Complete data for the 1st year after treatment (relapses, EDSS and MRI) were available for 110 pwMS, of which 73 (66.4%) achieved NEDA-3. Clinical NEDA in year 1 was achieved in 122 out of 142 participants (85.9%). Complete data for 2 years after treatment (relapses, EDSS and MRI) were available for 90 pwMS, of which 29 (32.2%) achieved cumulative 2-year NEDA-3. Cumulative 2-year clinical NEDA was achieved in 64 out of 104 participants (61.5%).
Conclusion: According to the data from our cohort of active RRMS patients we conclude CT effectiveness remains high in real-world clinical practice.

Disclosure
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GBJ, AR, AHL, UR, SSJ: Participated as a clinical investigator and/or received consultation and/or speaker fees from: Biogen, Sanofi Genzyme, Merck, Novartis, Pliva/Teva, Roche, Lek.
CR:Participated as a clinical investigator and/or received consultation and/or speaker fees or congress grants from: Biogen,Merck, Novartis,Roche,Sandoz,Sanofi Genzyme, and Teva.
PK: Nothing to disclose.

EP1136

Is there an impact on early initiation of DMTs in patients with RRMS in the German registry?

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Background: MS is a chronic progressive disease resulting in disability. Early intervention may help slow disease progression.
Aim: To compare the characteristics and outcomes of patients who initiate disease modifying treatments (DMTs) early compared to later over a 5-year period.
Methods: Data came from NeuroTransData (NTD) MS registry run by a network of Germany-wide neurologists. Study included patients initiating DMTs between Jan 1, 2009, and Oct 1, 2021.

Patient cohorts were defined based on the time of initiation of their first DMT relative to the date of RRMS diagnosis: Cohort 1 (<=12 months n=5048), Cohort 2 (> 12 months to <= 24 months, n=559), Cohort 3 (> 24 months to < 5 years, n=788), and Cohort 4 treatment (more than 5 years, n=1604).

Results: There were no meaningful differences in age, time since symptoms manifestation, or EDSS across the cohorts at time of first DMT initiation (index). Relapse activity appeared to be a leading reason for DMT initiation with at least one relapse experienced 1-year pre-index by 43.6% patients in cohort 1 compared to 31.3%, 27.2% and 18.1% of patients in cohorts 2,3,4, respectively. Glatiramer acetate/interferons were most used in cohort 1 (74.4%) and least in cohort 4 (54.5%). The use of other DMTs, including monoclonal antibodies, increased with delayed time to DMT initiation.

For cohorts 1 and 2, average (SD) annual relapse rate (ARR) was 0.4 (0.6) and 0.3 (0.6) at year 1 but declined to 0.08 (0.3) and 0.1 (0.3) by year 5, respectively. In contrast, average ARR mean (SD) was in a narrow range for cohorts 3 [0.1 (0.4)- 0.2 (0.5)] and 4 [0.05 (0.2)-0.1 (0.3)] through the study period. EDSS for patients delaying DMTs numerically worsened than those who initiated early over 5 years [e.g., mean (SD) worsening from 1.3 (1.1) at year 1 to 1.9 (1.6) at year 5 in cohort 3 compared to stable EDSS of 1.5 over 5 years in cohort 1]. EDSS results must be interpreted with caution due to high level of missingness.

Conclusions: Neurologists appear to make a reasonable prognosis regarding potential changes in patients' EDSS status over a 5-year period and whether to initiate treatment or wait and see clinical changes. A potential trade-off with the wait and see approach is that more efficacious treatments are used as initial therapy. Nevertheless, the benefit: risk of such treatments may be an important consideration along with other disease-related factors in individualizing patient treatment decisions.

Disclosure

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Maximilian Schuier, employee of Janssen-Cilag GmbH company of Johnson and Johnson and may hold stock/ stock options of Johnson and Johnson

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EP1137

Novel real world evidence from mSGo, a digital support program for secondary Progressive multiple sclerosis patients in Australia using siponimod

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Introduction: Siponimod is approved in Australia for adults with secondary progressive multiple sclerosis (SPMS). Prescreen requirements for siponimod include a CYP2C9 genotype test to determine maintenance dosing. An integrated digital platform,

'MSGo', was developed by Novartis and RxMx® to support Healthcare Professionals and their multiple sclerosis patients.
Objective: Data derived exclusively from MSGo was utilised to explore the onboarding experience of siponimod patients in Australia.
Aims: To provide real world evidence on siponimod for SPMS patients in Australia.
Methods: The study enrolled >350 adults with SPMS registered in MSGo for siponimod in Australia. Primary endpoint is the average time for onboarding with key secondary endpoints addressing adherence and variables that influence onboarding and adherence.
Results: Final data extraction on April 20th, 2022 included 368 patients (median age of 59y).CYP2C9 genotype testing took a median of 19 days (95%CI 17-21) from registration and maintenance doses of 2mg (n=166) or 1mg (n=27) were initiated as per label recommendations; 1mg was initiated for two rare allele genotypes (*1*5 and*1*11) in the absence of label recommendations. Mixture-cure modelling estimated that 58% of patients will ever initiate siponimod, with a median time to initiation of 56d (95%CI 47-59) from registration. Among those who initiated siponimod the most common reported reason for delayed initiation was 'waiting for vaccination'. Self-reporting of daily treatment, captured under the treatment reminder function in MSGo, had a drop-off of ~25% after the first week of initiation; a continued decline in reporting over time limited assessment of adherence. Continued self-reporting of daily dosing trended lower with older patients with only 28% of those >70y continuing to self-report at day 90 compared to 47-69% with the younger age groups. The study uncovered the important role of care partners, with Cox regression analyses demonstrating that SPMS patients who nominated a care partner were more likely to initiate (HR:2.1, 95%CI 1.5-3.0) and to continue self-reporting their daily medication (HR:2.2, 95%CI 1.3-3.7). A total of 90 patients discontinued the study; 48 prior to and 42 after siponimod exposure.
Conclusions: This study provides insights into siponimod onboarding for adults living with SPMS in Australia and demonstrates the impact of MSGo and care partner support during a period challenged by the COVID-19 pandemic.

Disclosure
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Therapy - Multi-disciplinary rehabilitation

EP1138
Health experiences of the multiple sclerosis community during the second year of the COVID-19 pandemic, plans for future crises

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Objectives & Aims: To investigate the health and healthcare experiences of persons with multiple sclerosis (MS) in the second year of the COVID-19 pandemic, including gathering community opinions to inform future crisis planning.
Methods: Second year data collection of a longitudinal consumer directed mixed-methods study. An online survey followed by semi structured interviews took place August-October 2021. Participants were Australian persons with MS, carers, MS-healthcare providers and MS advocates, most interviewed participants were returnees from the original 2020 interviews. The survey and interviews established health-related experiences in the second year of the pandemic and opinions on the needs of persons with MS for future crises. Qualitative data were analysed using a general inductive approach.
Results: The study was completed by 34 persons (persons with MS:18, Carers:5, healthcare professionals:6, MS advocacy employees:5) from across Australia. Themes of healthy lifestyle, accessing healthcare and medication, accessing information, and plans of action were identified. Participants discussed and suggested helpful management strategies for the MS community during future crises including mental health services, increased accessibility to preventative measures, and healthcare and rehabilitation consistency through the crisis.
Conclusion: The health and health-management implications of the COVID-19 pandemic are ongoing and represent one community crisis affecting Australians with MS. Consumer informed preparation models, such as those which include access to mental health services and consistency in healthcare and rehabilitation services are wanted by the MS community.

Disclosure
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EP1139

Body-mind therapy intervention improves quality of life in people with relapsing-remitting multiple sclerosis. A pivotal study

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Introduction: Stress and fatigue are factors that significantly impact the quality of life of people with Multiple Sclerosis (MS). These symptoms can be associated with other disorders such as depression. Current pharmacological treatments generally have a modest effect on fatigue and wellness or they may cause additional discomfort.
Objective: To evaluate the safety and benefit of Tension & Trauma Releasing Exercises (T.R.E ®) on quality of life, emotional state, fatigue and burden of treatment of people with relapsing remitting multiple sclerosis (RRMS) without worsen treatment burden disease.
Methods: Patients were invited during the appointment or via email to participate in this study. Neurological and demographic data were collected. MusiQol, (MQL) SF 36, Fatigue Severity Scale (FSS), Anxiety and depression (HADS), and Burden of Treatment (TBQ) scales were administer before and after training time.T.R.E® technique is designed to help release the deep tension created in the body during a traumatic experience or through chronic stress; It consists in 7 sequential exercises that activate the large flexor muscle groups of the body, mainly the psoas, favoring the appearance of neurogenic tremor. The sequence was introduced and coordinate for international T.R.E ® trainers and It was held three times a week for 2 months.
Results: Twenty one patients were enrolled and twenty of them finished the trial. Average attendance was 18.5 sessions (75%). Geographical and medical data showed : 18 woman, median of illness was 7 years (range 1-25) and median EDSS was 1(range 0-4). Ashworth scale was mostly normal. The median pre-training measurements for MSQ was 78.5
(range 65-92), and post-training measurement 86.5 (range 82-91; p=0.03), while the subitem "symptoms" improve from 75.75 to 82.75 (p=0.025) The remaining scales did not show significant changes comparing the pre- and post-treatment evaluations. Notably, TBQ results showed no differences before and after training (p= 0.5) meaning the intervention did not increase a burden of MS treatment.
Conclusions: The regular practice of T.R.E ® in MS patients safely improved quality of life,even more important,T.R.E ® did not increase the burden of treatment disease. It is a technique of low economic cost and very easy implementation. Future strategies needs to be done in order to implement it in daily practice.

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Therapy - Symptoms Management (including cognition, fatigue, imbalance)

EP1140

Staggered steps: determining the impact of multiple sclerosis (MS) On lower limb health through scoping review and public and patient involvement

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Introduction: Multiple Sclerosis (MS) is a complex disease which affects the central nervous system. The myelin sheath that protects the nerve fibres of the body is damaged by its own immune system (demyelination). Under NICE guidelines CG186, podiatrists are not currently included within the Multiple Sclerosis rehabilitation team, with access to podiatric treatment in secondary care available for those with a specific need.

Aims:

1. To establish the impact of MS on lower limb health
2. To evaluate the benefit of Podiatric interventions, including foot health education, in the management and rehabilitation of lower limb health for increased mobility and ambulation

Objectives:

1. Establish and facilitate a Patient and Public Involvement Advisory Panel
2. Undertake a scoping review under the PRISMA-ScR guidelines

Methods: A scoping review of the effects of MS on the lower limb was undertaken to examine the extent, range and nature of any research activity that has already been completed in this area of podiatric medicine, subsequently identifying research gaps in existing literature. A PPI advisory panel was established, comprising of ten members, formed through social media recruitment, utilising Twitter as the primary platform. A search strategy was entered into the PubMed database which yielded the literature for our review in COVIDENCE.

Results: The COM-B model has been used as a framework for analysis, along with keywords used as discussion strategy. The Guidance for Reporting Involvement of Patients and Public 2 - GRIPP2 is the checklist that has been utilised to report the themes and initial findings of the PPI meetings. This guidance resembles the logic model, highlighting that evaluating participation is a complex activity, which provides the fundamental key to ensuring that public involvement and participation activities and programmes generate learning and results, and improve future participation practices. Full data extraction has been performed on the 128 articles with no indication of any podiatric involvement in studies.

Discussion: The initial findings have identified that there is scope for further research of the utilisation of podiatrists in the management and rehabilitation of lower limb health in patients with MS. The dialogue of the panel is encouraging with a host of examples provided as evidence that podiatric interventions could facilitate meaningful change to the rehabilitation service and have a great impact on both patients and carers.

Disclosure
Nothing to disclose

EP1141

Balance rehabilitation in people with multiple sclerosis: robotic versus usual care intervention protocols

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Introduction: Balance impairments, common and widespread symptoms in people with multiple sclerosis (PwMS), negatively impact daily living activities and represent a significant risk factor

for fall. Mainly for these reasons, the use of robotic-assistive platforms for rehabilitation of balance and mobility in PwMS has been growing rapidly thanks to technologies advances.
Aim: This study aimed to investigate whether a rehabilitative intervention with hunova, a robotic device developed by Movendo Technology, can be used as an alternative to traditional approaches for the improvement of balance.
Methods: Forty PwMS followed as outpatients at the AISM Rehabilitation Service of Genoa (Italy) participated in the study. PwMS, that met all eligibility criteria (an age between 18 and 70 years, relapsing-remitting MS course, without relapses or worsening in the last 3 months, an Expanded Disability Status Scale (EDSS) $\leqslant 6$ and a Mini Mental State Examination score > 24), were randomly allocated to a robotic (ROB) or traditional (TRAD) group. Both ROB and TRAD lasted 20 sessions (2 sessions/week) of 45 min each. Before (PRE) and after (POST) rehabilitation training, Berg Balance Scale (BBS), Two-Minute Walk Test (2MWT), Timed-get-up-and-go-test (TUG) and Sensory Organization Test (SOT) by EquiTest were administered to each participant.
Results: At PRE both groups did not differ for age (ROB= 54.55±10.52; TRAD= 52.85±9.17; p=.589), EDSS (ROB= 3.65±1.29; TRAD= 4.12±1.44; p=.280), disease duration (ROB= 12.60±8.44; TRAD= 12.14±9.04; p=.872), BBS (ROB= 49.68±4.84; TRAD= 49.34±4.29; p=.815), 2MWT (ROB= 103.21±17.73; TRAD= 93.20± 9.92; p=.206), TUG (ROB= 10.04±2.00; TRAD= 11.33±6.45; p=.401) and SOT composite score (ROB= 66.14±13.66; TRAD= 67.63±13.12; p=.728). Repeated-measures ANOVA showed a time (PRE-POST) effect for BBS (p=.012), 2MWT (p=.006) and SOT composite score ($p<.001$). Interestingly, for TUG a group*time interaction approaches the significance (p=.088), suggesting that ROB group improved more in balance and mobility as assessed by this outcome. Since 2MWT did not show the same trend, we could speculate that ROB rehabilitation ameliorate the sit-to-stand position more than the walking itself.
Conclusions: Results indicate that both ROB and TRAD groups improved in main outcomes of balance. Thus, this study demonstrates that hunova represents a useful and validated alternative tool to usual and traditional physiotherapy for improving balance in PwMS.

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EP1142
Energy expenditure, energy cost and relative aerobic load of walking in people with multiple sclerosis

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Background: Already early after onset people with multiple sclerosis (pwMS) may experience mobility problems. Different metabolic parameters of walking (i.e. energy expenditure, energy cost and relative aerobic load (i.e. the percentage of maximal oxygen uptake)) can contribute to these walking limitations. In general, pwMS have a slower comfortable walking speed and higher energy cost as compared to healthy peers. Furthermore, people with MS generally have a worse cardiorespiratory fitness compared to healthy peers. A reduced cardiorespiratory fitness might result in a higher relative aerobic load of walking.
Objectives: To better understand walking limitations in pwMS by investigating metabolic parameters of walking, especially focusing on the relative aerobic load.
Methods: Participants with a definite diagnosis of MS performed a 6-minute overground walk test at comfortable walking speed, to measure energy expenditure, walking speed and energy cost. Maximal aerobic capacity ($\dot{V}O_2$peak) was determined with the cardiopulmonary exercise test. Energy expenditure was divided by $\dot{V}O_2$peak to determine the relative aerobic load of walking.
Results: Thus far, data of 30 participants (mean age 50.4, 60% female, mean disease duration 16.5 years) were analysed. Mean energy expenditure of walking at comfortable walking speed was 13.91 ± 3.57 ml/kg/min oxygen. Median energy cost of walking, adjusted for walking speed (mean: 1.08 ± 0.24 m/s) was 0.21 [0.10-0.57] ml/kg/m oxygen. With a mean $\dot{V}O_2$peak of 26.09 ± 9.38 ml/kg/min, the relative aerobic load of walk was 54.63 ± 15.62%.
Conclusion: PwMS have a slow comfortable walking speed, high energy cost and a critical high relative aerobic load of walking. These gas exchange measurements can guide clinicians in treating pwMS, for example improve cardiorespiratory fitness in case of reduced cardiorespiratory fitness or improve walking (e.g. with orthosis) to reduce the energy cost of walking.

Disclosure
Conflict of interest Hanneke Hulst receives research support from ZonMW, NWO, ATARA, Biogen, Celgene/BMS, Merck and

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EP1143

Exploring the feasibility of using virtual reality for cognitive assessment in multiple sclerosis

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Introduction: Cognitive impairment (CI) occurs in up to 70% of people with multiple sclerosis (PwMS) and impacts their personal independence, employment and quality of life. Currently, most of the administered neuropsychological tasks have little resemblance to everyday life. There is a need for ecologically valid tools for assessing and predicting real-life functioning in MS. Virtual reality (VR) programs provide a platform with more realistic real-world functional assessments. However, studies using VR programs in MS are scarce.
Objectives: To explore the utility and feasibility of a VR program for cognitive assessment in PwMS.
Methods: A VR classroom embedded with continuous performance test (CPT) and naturalistic distractors was tested with 10 non-MS adults and 4 PwMS with CI (the Symbol Digit Modalities Test (SDMT) z-score $<$-1.0). Participants performed the CPT with distractors (ie. WD) and with no distractors (ie. ND). SDMT and a feedback survey on the VR program were administered.
Results: There was no difference between non-MS and PwMS in age (p=0.12) or years of education (p=0.38). For MS, the mean disease duration was 14$\pm$3.3 years, median Expanded Disability Status Scale was 3$\pm$1.5 and the mean SDMT z-score was -1.78$\pm$0.89. PwMS exhibited a higher number of commission errors than non-MS in ND (2.3$\pm$0.5 vs. 0.6$\pm$0.3, p=0.01). Additionally, PwMS showed a numerically lower correct response rate (CR) than non-MS in both WD (0.97$\pm$0.01 vs. 0.98$\pm$0.01, p=0.14) and ND (0.91$\pm$0.03 vs. 0.97$\pm$0.01, p=0.37) conditions. Higher SDMT score was associated with higher CR in both ND (r=0.62, p=0.01) and WD (r=0.50, p=0.06) conditions. 75% of the recruited PwMS reported that they enjoyed the experience with the VR system and found it could be helpful for cognitive assessments.
Conclusions:VR programs show promise in serving as ecologically valid platforms for assessing cognition in PwMS. The ongoing recruitment will guide optimization of VR application in PwMS.

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N. D. C. is on an Advisory Board for Akili Interactive and is a member of the Editorial Boards of Multiple Sclerosis Journal and Frontiers in NeuroTrauma.
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EP1144

Can demographic and clinical variables influence fatigue in people with multiple sclerosis? A cross-sectional study

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Introduction: Physical fatigue is one of the most disabling symptoms in people with Multiple Sclerosis (pwMS). Factors known to affect fatigue are gender, education, body mass index (BMI), Expanded Disability Status Scale (EDSS), working status, physiotherapy (Ph) and disease modifying therapies (DMTs). Fatigue Symptoms and Impacts Questionnaire-Relapsing Multiple Sclerosis (FSIQ-RMS) is a patient-reported outcome (PRO) used as secondary endpoint in a randomized clinical trial and which allows to define better than previous assessments the impact of fatigue in pwMS.
Aim and objectives: To use FSIQ-RMS to assess correlation between fatigue and the above-mentioned factors.
Methods: We enrolled 178 PwMS from May to July 2021 in MS centers of Sant'Andrea Hospital and Policlinico Umberto I hospital in Rome [F: 132; 83% RRMS, 17% SPMS]. The physical fatigue symptom was evaluated using the FSIQ-RMS, validated

and culturally adapted in Italian. Clinical and demographic data were collected at the same time. Each of the considered factors was subdivided into categories and comparison between categories was applied by means of student t-test or analysis of variance (ANOVA). Finally, correlation analysis, was done for the 24-hours and 7-days FSIQ-RMS scores (higher is worse) and each factor.
Results: FSIQ-RMS, both 24-hours and 7-days, was strongly correlated with BMI, with underweight subjects showing a greater level of fatigue ($p<0.001$). Moreover, both FSIQ-RMS scores correlated with a greater level of disability, assessed by EDSS ($p<0.01$). Finally, the 7-days FSIQ-RMS was correlated with not-working status and not-exercising physiotherapy ($p<0.01$).
Conclusions: The use of FSIQ-RMS in a real-word setting confirmed underweight and not-exercising physiotherapy as strong predictors of fatigue.
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EP1145

Treatment satisfaction with siponimod in patients with advancing relapsing multiple sclerosis: Interim results of the EXCHANGE study

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Introduction: Siponimod, an oral sphingosine-1-phosphate ($S1P_{1,5}$) receptor modulator, is approved in adults for treatment of relapsing multiple sclerosis (RMS) and active secondary progressive MS in the US. EXCHANGE (NCT03623243), a prospective, 6-month, multicentre, open-label, single-arm phase 3b study, is evaluating conversion to siponimod from other disease-modifying therapies (DMTs).
Objectives: Evaluate treatment satisfaction with siponimod in patients with advancing RMS in the EXCHANGE study.
Methods: The study includes patients aged 18-65 years with advancing RMS, Expanded Disability Status Scale (EDSS) score of 2.0-6.5, and on continuous oral/injectable DMTs for $\geqslant$3 months. Satisfaction was measured as a secondary endpoint, using self-reported outcomes from the Treatment Satisfaction Questionnaire for Medication (TSQM-9). The TSQM-9 is a validated tool that evaluates effectiveness, convenience and global satisfaction. Patients completed the TSQM-9 at baseline (BL) and Days 28, 84 and 168. Results are reported as mean score (SD; median) for each domain, on a scale of 0 to 100 (higher scores refer to better satisfaction).
Results: 163 patients (74.2% female; mean age 46.6 years; mean baseline EDSS score 3.9) were eligible for the analysis. At BL (n=133), mean (SD; median) TSQM-9 scores were 56.7 (19.9; 50.0) for effectiveness, 69.9 (21.0; 66.7) for convenience and 52.7 (23.7; 52.8) for global satisfaction. Numerically higher mean (SD; median) scores were reported at Day 28 (n=111; effectiveness, 68.3 [19.8; 66.7]; convenience, 84.2 [15.3; 83.3]; global satisfaction, 65.6 [21.4; 68.1]) vs BL. Mean (SD; median) TSQM-9 scores were maintained at Day 84 (n=101; effectiveness, 64.6 [21.9; 66.7]; convenience, 84.3 [15.0; 83.3]; global satisfaction, 65.0 [25.1; 68.1]) and Day 168 (n=126; effectiveness, 65.3 [23.9; 66.7]; convenience, 83.7 [15.8; 83.3]; global satisfaction, 62.4 [30.5; 69.4]). Mean (SD) change from BL to Day 168 was 8.7 (27.6), 14.0 (25.1) and 9.1 (34.3) for effectiveness, convenience and global satisfaction, respectively.
Conclusions: Patients converting to siponimod from a prior other DMT reported numerical improvements in treatment satisfaction on switching across the domains of effectiveness, convenience and global satisfaction. Improvements were maintained for the duration of the study period. These findings may help to better inform shared treatment decision-making in patients with advancing RMS.
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Disclosure
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EP1146

Disability status and cognitive functioning in patients with advancing multiple sclerosis switching to siponimod: interim results of the exchange study

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Introduction: Siponimod, a sphingosine-1-phosphate ($S1P_{1,5}$) receptor modulator, is approved in adults for treatment of relapsing multiple sclerosis (RMS) and active secondary progressive MS. Conversion to siponimod from other disease-modifying therapies (DMTs) in patients with advancing RMS is being assessed in EXCHANGE (NCT03623243), a prospective, 6-month, multicentre, open-label, single-arm phase 3b study. Exploratory outcomes included patient-reported disability and cognitive function.
Objective: Explore the effect of siponimod on short-term disease evolution and cognition in patients with advancing RMS
Methods: The study includes patients aged 18-65 years with advancing RMS and an Expanded Disability Status Scale (EDSS) score of 2.0-6.5 who received continuous treatment with DMTs for ⩾3 months. Short-term disease evolution and cognition were evaluated using Patient Determined Disease Steps (PDDS) and the Processing Speed Test (PST), respectively. The PDDS is a validated questionnaire measuring patient-reported disability on a scale from 'normal' to 'bedridden'. Patients were classified as normal (no disability) or having mild (gait impairment without device), moderate (assistive device) or severe (non-ambulatory) disability. The PST is a validated, self-administered, iPad-based tool used to measure MS-related deficits in processing speed, scoring the number of correct digits recorded over 120 sec.
Results: 163 patients (74.2% female; mean age 46.6 years; mean baseline (BL) EDSS score of 3.9) were eligible for analysis. For PDDS at BL, 20.3% (27/133) of patients were classified as normal, and 54.1% (72/133), 23.3% (31/133) and 2.3% (3/133) of patients had mild, moderate and severe disability, respectively. The percentage of patients in each category pointed to improvement at Day 84 (normal, 23.8% [24/101]; mild, 50.5% [51/101]; moderate, 23.8% [24/101]; severe, 2.0% [2/101]) and Day 168 (normal, 23.0% [29/126]; mild, 50.0% [63/126]; moderate, 25.4% [32/126]; severe, 1.6% [2/126]). For cognitive processing speed, patients achieved numerical improvement in mean [SD] PST scores on Day 84 (43.1 [18.4]) and Day 168 (46.0 [16.3]) vs BL (40.0 [17.8]).
Conclusions: Findings of this analysis suggest that patients with advancing RMS switching to siponimod reported relative stability in disease progression over the study period, including numerical improvements in self-reported physical disability and cognitive functioning.
Study Support: Novartis Pharmaceuticals

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Clinical aspects of MS - Neuropsychology

EP1147

Accelerated Long-term forgetting in multiple sclerosis-patients: application of a neuropsychological test to detect everyday memory deficits in early-stage multiple sclerosis

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Introduction:40-65% of Multiple Sclerosis (MS) patients suffer from cognitive impairment which has a higher impact on Quality of Life than motor symptoms. Standard tests only detect memory impairment over a short time interval. Accelerated long term forgetting (ALF) refers to an above average loss of information over an extended period of time, i.e. 7 days, which escapes clinical testing.
Aims: This study aims to detect memory impairment in mildly affected MS patients using the ALF concept and relate it to subjective complaints (SMI).
Methods: In this prospective observational study, 30 early-stage RR-MS patients (mean EDSS±SD=1.1±0.9) and 30 healthy controls (HC) were matched. Participants underwent ALF testing (word list (WL), geometric figure (GF), logical memory (LM)) at three time points (baseline, 30 minutes, and 7 days). SMI was reported using a scale (0-100; Higher scores indicate higher SMI). We used the Fatigue Impact Scale (FIS), the Montreal Cognitive Assessment, the Becks Depression Inventory and the Symbol Digit Modality Test. The primary outcome (PO) was defined as the quotient of the 7-day score and the 30-minute score.
Results: Demographic characteristics showed no significant differences in mean age (years±SD; MS 28.56±3.83 vs HC 29.3±6.38) or education (years±SD; MS 12.03±0.96 vs HC 12.03±1.24). We found a significant difference for PO_{WL}(MS 0.66±0.13 vs HC 0.82±0.16; $p<0.001$) and PO_{LM} (MS 0.88±0.15 vs HC 1.01±0.12; p=0.02) but not for PO_{GF} (MS 0.84±0.22 vs HC 0.88±0.17; p=0.439). Comparison of the other tests revealed significant differences for SMI (MS 35.67±15.9 vs HC 24.67±9.73; p=0.004) and for FIS (MS 36.27±21.21 vs HC 20.07±15.82; p=0.003), but not for the remaining tests. Regression analysis showed an association for PO_{WL} and FIS (coefficient B=0.003; p=0.034; 95%CI -0.005 - 0.0) and SMI (coefficient B=-0.004; p=0.01; 95%CI -0.008 - -0.001). Significantly lower and insignificant associations were found for the HC group.
Conclusions: Early-stage MS patients show higher ALF compared to a control group, although initial learning and retrieval is unimpaired. Patients showed no signs of depression, impaired cognitive function or processing speed as confounding factors. SMI can be detected using ALF-sensitive tests. Fatigue has a greater influence on memory in MS patients than in healthy controls. Our results demonstrate the relevance of ALF testing and provide important information regarding SMI and its objective diagnosis in MS.

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EP1148

Processing speed during pregnancy in multiple sclerosis: a prospective cohort study

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Introduction: Processing speed (PS) is one of the most used neuropsychological measures in people with multiple sclerosis (pwMS), as it is the most prevalent and early cognitive symptom in pwMS. It has also been pointed as a sensible biomarker for cognitive integrity.
Objectives and aims: We aimed to explore PS during pregnancy in pwMS and healthy women (HCW).
Methods: We consecutively included 27 pregnant pwMS and 37 HCW, from Hospital Universitario Gregorio Marañón between 2018 and 2022.Measurements were collected using the written version of theSymbol Digits Modalities Test(SDMT) at first and second trimesters of pregnancy. Statistical analysis was performed with Analysis of Variance (ANOVA).
Results: No differences in age and educational level were observed between pwMS and HCW.
Mean SDMT scores in the first trimester were similar between pwMS (57 (SD:8,63)) and HCW (60,27 (SD:9,39)). In the second trimester, we found significant differences in PS between groups: 53,91 (SD:6,73) for pwMS and 59,48 SDT: 6,87 for HCW, (F=3,114)p:=0,023). A subanalysis those cases that decreased a significant amount of at least 4 points in the SDMT score, data showed that this situation happened in 43% of pwMS cases, being only a 19% on the HCW side.
Conclusions: PS is a very sensitive measure of diffuse cognitive performance. PwMS might compensate for the brain damage in a normal situation. When challenged, a vulnerable brain may show a worse response. In our study, pwMS and HCW were similar at baseline, but as pregnancy evolved, that vulnerability translated into a poor PS performance only in pwMS. Whether this difference is due to a reorganization in pwMS neuronal networks or an increased brain damage in the context of pregnancy needs to be further explored.

Disclosure
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EP1149

Association between the EDSS and MS duration with cognitive impairment in a large Argentinian cohort of patient with multiple sclerosis

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Background: Cognitive impairment (CI) is a common symptom of multiple sclerosis, with a negative effect on patients' daily lives.
Objectives: 1- To describe the prevalence of CI and cognitive profile of the PwMS cohort. 2- To compare the cognitive performance of PwMS in relation to Expanded Disability Status Scale (EDSS) and MS duration. 3- To determine the association between the EDSS and MS duration with CI in a multivariate model controlling for potential confounders.
Method: Cross-sectional study. Patients from a single tertiary referral MS center in Buenos Aires were included and consecutive sampling was performed. The results of the last clinical and cognitive evaluation were included in the analysis. Measuring instruments: Clinical and cognitive variables were assessed (EDSS, Fatigue severity scale, Beck Depression Inventory, vocational status monitoring tool, BICAMS battery, PASAT, verbal fluency, 7/24 test). CI was defined as impairment in $\geqslant 2$ cognitive domains. Logistic regression model was used to predict factors related to CI, $p < 0.05$ was considered significant.
Results: 323 PwMS were recruited. Mean age: 40.71 ± 12.89 years; mean education: 13.43 ± 4.2 years; mean EDSS: 2.05 ± 1.94 (median 2.5 IQR 8) and stratified EDSS was 0-3: 61.7%; 3.5-8: 38.3%; mean MS duration: 8.51 ± 8.29 years; female 62.8%; relapsing-remitting MS (RRMS) 91.6%. Objectives: 1) The prevalence of CI at inclusion study was 47.5%. The most affected cognitive domains were: attention and processing speed followed by verbal memory, verbal fluency and visual memory. 2) Statistically significant differences were found between the stratified EDSS and MS duration with cognitive tests. Patients with EDSS between 3.5-8 presented worse performance in verbal memory test ($p < 0.01$), visual memory ($p < 0.05$), attention and processing speed ($p < 0.01$) and verbal fluency ($p < 0.05$). The PwMS duration $>$ 20 years presented worse performance in visual memory test ($p < 0.05$) and attention and processing speed ($p < 0.05$) compared to the PwMS $\leqslant$ 5 years. The PwMS duration $>$ 20 years presented worse performance in the attention and processing speed test ($p < 0.05$) compared to the PwMS 6-10 years. 3) In a multivariable logistic regression model, EDSS was an independent risk factor to reach CI when adjusted for potential confounders (adjusted Odds Ratio (OR) 1.43, 95% confidence interval (CI) 1.09-1.87, p= 0.01).
Conclusion: This study allowed us to obtain current figures on cognition in a large Argentine cohort of PwMS. The prevalence of CI and the cognitive performance in our cohort was similar to previous reports. Disability (EDSS) was an independent predictor of CI.

Disclosure
The authors have no conflicts of interest related to this study.

EP1150

Cognitive impairment in early multiple sclerosis

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Background: Cognitive impairment in multiple sclerosis (MS) negatively impacts the quality of life (QoL). Nevertheless, cognition is frequently neglected in routine clinical practice.
Objective: To determinate the cognitive profile of patients in early phases of relapsing-remitting MS (RRMS).
Methods: Naive patients with RRMS starting on teriflunomide were selected. Before treatment initiation, verbal memory (TAVEC), visual memory (BVRT), attention (D2), processing speed (SDMT), language (Boston Naming test), executive functions (Anillas), depression (Beck), and QoL (EuroQoL) was assessed. The results were standardized to a reference population, and the domain was considered affected with a standard deviation (SD) below -1 or -1.5 (less restrictive approach). Cognitive impairment was defined as $\geqslant 2$ domains altered.
Results:33 patients were included, 57.6% females, with a mean age of 41.7±9.7 years, 4.2±5.0 years of disease evolution, an annual relapsing rate (ARR) of 1.1±0.7, and an EDSS of 1.0±0.8. The domains affected were verbal memory (n=16, 48%), visual memory (n=3, 9%), executive function (n=6, 18%), attention (n=8, 24%), and processing speed (13, 39%). Cognitive impairment was detected in 14 (42%) patients and 2 (6%) with a less restrictive approach. No relation was found with age, education level, the previous relapses, the EDSS, or the QoL(p= 0.5, 0.1, 0.6, 0.8, and 0.7). The association to the evolution of the disease

and the depression was only significant with a less restrictive definition of cognitive impairment (p= 0.004 and 0.03).
Conclusion: Cognitive impairment is present even in the early stages of MS, affecting especially verbal memory, processing speed, attention, and executive function.

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EP1151
Determination of the factors affecting coping style with multiple sclerosis

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Introduction: Chronic diseases such as multiple sclerosis (MS) can bring consequences that require the individual to make psychological adjustments to the adverse effects of the disease and to cope with the disease. Coping is a factor affecting adaptation to the disease in MS, and is a time-dependent process affected by physical, behavioral, cognitive, emotional, and social components.
Aims: This study investigates the relationship between coping with the disease and affecting cognitive, physical, and psychosocial factors in people with MS (pwMS).
Methods: Ninety-seven pwMS were enrolled in this study. Demographics and clinical characteristics were recorded. Coping with MS Scale (CMSS) was used to measure coping, including seven subscales: problem-solving, physical assistance, acceptance, avoidance, personal health control, energy conservation, and emotional release. Anxiety and depression levels, stigma, neuropsychological symptoms, and personality were measured by the Hospital Anxiety and Depression Scale (HAD), EuroQol-5D Quality of Life Scale (EQ-5D), Quality of Life in Neurological Diseases (NeuroQoL) -Stigma Scale, Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) and Revised Eysenck Personality Questionnaire Abbreviated Form (EKA-GGK), respectively.
Results: A weak statistically significant positive correlation between the physical support subscale and age and the duration of the disease, and a strong positive correlation with the Expanded Disability Status Scale (r=.214, p=.035; r=.213, p=.036; r.=582, p=<.0001, respectively) were found. There was a moderate negative relationship between the Physical Support subscale and the EQ-5D Mobility, Self-Care, Pain, and Health subscales (r=-.434, p=.000; r=-.482, p=.000; r=-.526, p=<.001, respectively), a weak negative correlation with Anxiety, and a strong negative relationship with Usual Activities (r=-.379, p=<.001; r=-.243, p=.017; r=-.384, p=<.001, respectively).
Conclusions: It has been shown that coping with MS can be affected by cognitive, physical, and psychosocial factors.

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EP1152
French validation of the work difficulties questionnaire in multiple sclerosis: preliminary data focus on anxiety

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Work difficulties is a recent highlight in Multiple Sclerosis (MS). The present study aims to validate into French the MS Work Difficulties Questionnaire (MSWDQ) and evaluate the psychological and cognitive factors that may induce it. Anxiety is a frequent disorder in MS which tends to be underevaluate in clinical practice. 45 MS patients (31 recurrent remittent and 14 Progressive forms) filled a cognitive evaluation including the BICAMS and the following questionnaires: MSWDQ french adaptation, DEX for cognitive complaint, Fast BDI for depression, GAD 7 for anxiety, and EMIF for fatigue.The score of dysability at the edss correlated only with the Physical Barriers factor measured at the MSWDQ, r.37, p=.01. The cognitive complaint at the DEX strongly correlated with all three factors of MSWDQ, but mainly with the Psychological and Cognitive Barriers (PCB)factor,r=.61, p<.00001. When taking into account depression and anxiety, only the level of anxiety significantly impacted the total score and mainly on the PCB, β.35, p<.05. Physical, cognitive and social fatigues strongly correlated with all scores at the MSWDQ. Among the cognitive scores, only processing speed measured at the SDMT impacted the PCB scores, F=6, p=.01. The French validation of the MSWDQ is in progress. Cognitive complaint and anxiety strongly correlates with work difficulties. These factors could be interwined in those self reported questionnaires. Further research will aim at reducing work difficulties by proposing personalized cognitive rehabilitation including meditation practice to target anxiety effects.

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EP1153

The effects of cognitive reserve and biological sex on cognitive changes in people with multiple sclerosis: evidence from an exploratory and longitudinal study

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Introduction: Longitudinal studies on the effect of cognitive reserve (CR) on neuropsychological performance in people with Multiple Sclerosis (pwMS) are inconsistent (Amato et al., 2013; Sumowski et al., 2014), and the interaction effect between sex and CR on cognition was not fully investigated.
Aim: The aim of the study was to evaluate the effects of CR, sex, and their interaction on cognitive changes in a sample of newly diagnosed pwMS.
Materials and methods: 74 newly diagnosed pwMS (41 women, 33 men) according to 2018 McDonald criteria underwent a neurological and neuropsychological evaluation at baseline (T0; evaluation $<$12 months from diagnosis) and follow-up (T1; $\geqslant$ 1 year from T0). As for the cognitive assessment, the STROOP test was administered to assess performance on inhibitory control, whereas the Italian version of the Brief Repeatable Battery of Neuropsychological Tests was employed to evaluate levels of verbal and spatial memory (Selective Reminding Test [SRT-LTS, SRT-CLTR, SRT-D]) and Spatial Recall Test [SPART, SPART-D]), processing speed/attention (Symbol Digit Modalities Test [SDMT], Paced Auditory Serial Addition Test [PASAT]), and verbal fluency (Word List Generation [WLG]). CR was assessed by means of the italian adaptation of the Cognitive Reserve Scale (Altieri et al., 2018). To evaluate possible differences between clinical and socio-demographic variables among sexes, a t-test for independent samples was performed. To evaluate the effects of biological sex and cognitive reserve on cognitive changes, a MANOVA for repeated measures with correction for multiple comparison was performed. Within-subject factor was time (T0,T1), between-subject factors were CR (high, low) and sex (men, women), whereas the dependent variables were neuropsychological scores.
Results: T1 evaluation was performed after 20.2 $\pm$4.9 months from T0. Men reported a higher frequency of primary progressive phenotype when compared to women (p=.017), whereas women reported higher levels of CR (p=.004). The MANOVA revealed a significant main effect of i) time on SRT-LTS, SRT-D, SPART, SPART-D, SDMT, PASAT 3'', WLG, and STROOP scores (T1$>$T0), and ii) sex on SRT-CLTR, SRT-D scores (women$>$men). Moreover, the interaction effect between time, sex and CR was statistically significant on SPART ($F_{(1,70)}$=4.253, p=.043), SPART-D ($F_{(1,70)}$=7.913, p=.006), WLG ($F_{(1,70)}$=3.975, p=.05), and STROOP ($F_{(1,70)}$=4.689, p=.034) scores, with only men with high CR showing improvement at T1 evaluation.
Conclusion: The present findings suggest that cognitive decline in MS might be reversible in the short term, probably due to some influencing factors (e.g. levels of depression or anxiety, coping strategies, use of DMTs, etc) that deserve to be investigated in future studies. Moreover, only men with high CR showed an improvement on selected aspects of cognition at T1, revealing a combined role of CR and sex on cognitive changes in MS, especially on visuo-spatial memory and some executive functions.

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EP1154

Objective and subjective measures of executive functions in multiple sclerosis: implications for daily life functioning

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Introduction: The study of the relationship between objective measure of cognitive flexibility and subjective measure of executive functions (EF's) may benefit to understand the adaptation of Persons with Multiple Sclerosis (PwMS) in the real world.
Objective: To analyse the relationship between objective measure of cognitive flexibility and subjective measure of EF's with clinical and cognitive variables and Health Related Quality of Life (HRQoL) in PwMS.
Aim: To investigate the relations between executive complaints and objective executive test performance and HRQoL.
Methods: 60 PwMS were included (RR=83.9%, PP=1.8%, SP=14.3%). 73.20% female; mean age: 46.39$\pm$13.37 years; education: 14.63$\pm$2.70 years; Expanded Disability Status Scale (EDSS): 3.46$\pm$2.25; disease evolution: 18.09$\pm$11.11 years. Measuring instruments: Objective measure of cognitive flexibility: Brixton Spatial Anticipation Test; Subjective measure of EF's: Dysexecutive Questionnaire (DEX); HRQoL: Multiple Sclerosis International Quality of Life Questionnaire (MusiQol); Cognitive variables: BICAMS Battery (California Verbal Learning Test-I, Brief Visual Memory Test-Revised, Symbol Digit Modalities Test), Paced Auditory Serial Addition Test, Verbal Fluency; Clinical variables: EDSS, Fatigue Severity Scale and Beck Depression Inventory-II. Parametrics statistics were used, to define significance a value ofp$<$0.05 was accepted.

Results: Objective and subjective measures of EF's were unrelated ($p>0.05$). More errors in the cognitive flexibility task were negatively and moderate to large correlated with learning (r=-0.50; p=0.00) and verbal episodic memory (r=-0.53; p=0.00), processing speed (r=-0.54; p=0.00), working memory (r=-0.50; p=0.00) and phonological fluency (r=-0.44; p=0.00). In addition, number of errors were associated with high EDSS (r=0.34; $p<0.05$), less MusiQol index (r=-0.36; $p<0.05$) and did not correlate with depression and fatigue ($p>0.05$). DEX were unrelated with cognitive performance and EDSS ($p>0.05$), but correlated positively with depression (r=0.64; p=0.00), fatigue (r=0.49; p=0.00) and negatively with MusiQol index (r=-0.37; $p<0.05$). In multiple regression analysis, short-term memory recall and EDSS were significant predictors of cognitive flexibility (R^2:.390; p:<.001). Depression was statistically significant predictor of perceived EF's difficulties (R^2=.408,p:<.001).
Conclusion: High physical disability and poor short-term memory recall predicts cognitive flexibility performance; meanwhile depression predicts EF's complaints suggesting they may primary indicate depression. Both measures may be clinically relevant to understanding PwMS daily life functioning.

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EP1155

Self-efficacy influences depression and anxiety in a cross-sectional cohort of people with multiple sclerosis

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Background: Around 50 percent of people with multiple sclerosis (pwMS) experience symptoms of anxiety and depression at some point during the disease course. These symptoms might in part be explained by lower levels of self-efficacy, indicating a reduced belief in one's own controllability of or competence to handle difficult situations.
Objective: The aim of this study was to investigate whether self-efficacy could serve as predictor for anxiety and depression in pwMS, independent from demographics and clinical variables.
Methods: We analysed cross-sectional data of 149 pwMS (62% female; age=39.3±9.9 years; disease duration=9.8±7.3 years) who underwent clinical and neuropsychological assessment. Self-efficacy expectations were assessed using the "Self-Efficacy Scale". The "Hospital Anxiety and Depression Scale" (HADS) was used to assess anxiety and depression scores. We analysed Pearson correlations and hierarchical linear regressions to predict anxiety and depression levels by including sex, age, and years of education in the first step, expanded disability status scale (EDSS) score, disease duration and annualized relapse rate in a second step and self-efficacy in the third step.
Results: In our cohort, clinically relevant (scores > 7) anxiety was present in 30 pwMS (20 %) and clinically relevant depression was present in 21 pwMS (14 %). The level of self-efficacy was strongly correlated with anxiety (r=-0.42; $p<0.001$) and depression (r=-0.54; $p<0.001$). The only significant predictor for severity of anxiety was self-efficacy (b=-0.41; $p<0.001$), explaining 16% of variance. Severity of depression was predicted by EDSS (8% explanation of variance; b=0.25; $p<0.001$) and self-efficacy (28% incremental explanation of variance; b=-0.54; $p<0.001$), all predictors together explaining 36% of variance. No other demographic or clinical variables were significant predictors (all $p>0.05$).
Conclusions: Our results indicate that independent from demographics and clinical data, the level of self-efficacy strongly contributes to prediction of depressive symptoms and levels of anxiety in pwMS. Increasing self-efficacy by standardized training might therefore be a promising tool to improve quality of life in pwMS.

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EP1156

The effect of fampridine on cognition in patients with multiple sclerosis (MS): a systematic review and meta-analysis

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Introduction: Cognitive impairment (CI) is a disabling complication in patients with multiple sclerosis (MS). Fampridine is used to improve cognitive status in MS while the results of various studies did not show the same results. So, we designed this

systematic review and meta-analysis to estimate pooled effects of fampridine on cognition in patients with MS.
Methods: Two independent researchers searched PubMed, Scopus, EMBASE, Web of Science, google scholar, and also gray including references of the references and conference abstracts. We extracted data regarding the total number of participants, first author, publication year, the country of origin, mean age, mean disease duration, mean Expanded Disability Status Scale(EDSS), duration of low up, type of cognition test, and scores before and after the treatment.
Results: We found 4972 studies in the first literature search. After deleting duplicates, 2607 remained. Two researchers screened the title and the abstracts, removing 2590 studies. Finally, 15 studies remained for meta-analysis. The included studies were published between 2013 and 2021, the most frequent country of origin was Denmark. The mean age of participants of the studies ranged between 39 and 53 years and the mean EDSS ranged between 4 and 5.8, respectively. The SMD of SDMT (after-before treatment) was 0.45(95%CI: 0.06-0.84)(I^2=75.3%, $p<0.001$). The SMD of PASAT (after-before treatment) was 0.25(95%CI: 0.13-0.37) (I^2=84.3%, $p<0.001$) .
Conclusion: The results of this systematic review and meta-analysis show that fampridine significantly improves cognition in patients with MS.

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EP1157

Demographic and clinical characteristics of persons with multiple sclerosis with psychiatric disorders

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Introductions: Psychiatric disorder is one of the most common comorbidities in person with multiple sclerosis (MS, pwMS). It has been demonstrated that psychiatric disorders such as depression, anxiety, and bipolar disorder are more common in pwMS than in general. However, the reasons for this relationship are still unknown.
Aims: We aimed that identify demographic and clinical characteristics of pwMS with psychiatric comorbidities and compare them with pwMS without psychiatric disorders.
Methods: In total, 2732 (1886 female; 846 male) pwMS followed by the outpatient MS Clinic of Dokuz Eylül University Hospital were included in the study. Psychiatric disorder, age, gender, disease duration, duration of diagnosis, age of onset, and MS course of pwMS were recorded.
Results: 383 (14%) of pwMS had a diagnosis of psychiatric disorder and 352 of those were diagnosed with a psychiatric disorder after MS. There was no significant difference between two groups in terms of disease duration and duration of diagnosis. There were significant differences regarding age, gender, age of onset and MS course between two groups. The age and age of onset of pwMS with comorbidities were higher than pwMS without comorbidities (age: 45.89±11.50, age of onset: 44.09±12.57; age: 30.42±9.81, age of onset: 29.29±9.74, respectively). The rate of female pwMS with a psychiatric disorder (%76.4) was higher than female pwMS without a psychiatric disorder (%67.8). In terms of MS course, while 81% of those who had psychiatric disorder pwMS were relapsing-remitting MS (RRMS), 15.6% were secondary progressive MS (SPMS) and 3.4% were primary progressive MS (PPMS); 85.4% of those who had no psychiatric disorder pwMS were RRMS, 11% were SPMS and 3.6% were PPMS.
Conclusion: Our study demonstrated that the most important factors related to psychiatric disorders in MS were age, gender, age of onset andMS course. for Studies involving other clinical features and cognitive functions are needed to better understand the psychiatric disorders in MS.

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EP1158

Emotional expressions and evaluation of quality of life in patients with multiple sclerosis and their relatives

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Introduction: Multiple sclerosis (MS) presents patients and their families with an array of issues that affect psychological functioning. The psychological well-being of the patient and the patient's entire family is critically important for the successful treatment of individuals with multiple sclerosis (MS).
Aims: The aim of this study is to evaluate the emotional expressions of multiple sclerosis patients and their relatives simultaneously with the hopelessness levels of the patients and the quality of life of their relatives.
Method: The emotional expressions of the patients and their relatives was determined by the LEE Scale (Level of Emotion) and the EE Scale (Expressed Emotion). In addition, the BECK Hopelessness Scale and the short form SF-36 were administered.
Results: We included 50 patients (35 females and 15 males) and their relatives (20 females and 30 males) into our study. All SF-36 scores were significantly lower in the patients than in the relatives ($p<0.001$). We found moderate positive correlation between Expressed Emotion Scale (EE) Total score and all Level of Expressed Emotion Scale (LEE) scores ($p<0.001$). We found a

moderate positive correlation amongst the LEE Total score, Emotional Response, Attitude towards Illness, and Tolerance/Expectation subgroup scores ($p<0.001$,$p=0.001$ and $p=0.002$), while there was a low positive correlation between EE Criticism/Hostility score and LEE Intrusiveness score ($p=0.006$). We found a moderate positive correlation amongst the Beck Hopelessness Scale score and all LEE scores($p<0.001$), EE Total score, and EE Criticism/Hostility score ($p=0.001$ and $p<0.001$). There was a moderate negative correlation amongst the Beck Hopelessness Scale score and the patients' SF-36 Physical Function($p<0.001$), Physical Role Limitations ($p<0.001$), General Health($p<0.001$), Vitality/Energy scores($p<0.001$), Social Functioning($p<0.001$) and Emotional Role Limitations scores ($p=0.001$).

Conclusion: Various psycho-social problems experienced by multiple sclerosis patients affect both their own treatment processes and the relatives of the patients who go through the difficult process with them. As seen in this study, the behaviors, attitudes and reactions of patient relatives interact with the patient's condition. Based on the data obtained, providing support to patients and their relatives in line with their needs can increase their quality of life.

Disclosure

All authors have nothing to disclose.

EP1159

Moving beyond the number of correct responses as an outcome measure in symbol-digit substitution testing using Konectom™ smartphone-based cognitive processing speed test

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Introduction: Smartphone-based Konectom cognitive processing speed (CPS) test was previously shown to have good test-retest reliability and correlated with symbol-digit modalities test (SDMT). The Konectom CPS test includes a symbol-to-digit (S2D) substitution test followed by a digit-to-digit (D2D) matching test to account for visuomotor reaction time. CPS substitution time (ST) is a novel response time feature derived by subtracting D2D correct response time (RT) from S2D correct RT to limit the influence of visuomotor reaction time on the assessment of CPS.

Objectives: To assess the discriminative validity, sensitivity to cognitive impairment (CI), and influence of age, sex, and education on CPS score (number of S2D correct responses) and response time features (CPS ST, S2D correct RT, D2D correct RT). To assess the clinical relevance of CPS ST by exploring substitution time by employment status.

Methods: The DigiToms study (NCT04756700) is enrolling people with multiple sclerosis (PwMS) aged 18-64 years, with Expanded Disability Status Scale (EDSS) score $\leqslant 6.0$, and healthy control (HC) subjects matched for age, sex, and education. Konectom CPS was self-administered remotely up to 28 days and in-clinic. For PwMS, CI was defined as z-score $\leqslant -1.5$ on any single Brief International Cognitive Assessment for MS (BICAMS) test, calculated from published BICAMS French normative data.

Results: Data from 35 PwMS and 12 HCs were used in this analysis. Influence of age, sex, and education on CPS ST was less (total R-squared=17.7%) than it was for CPS score, S2D and D2D correct RT (total R-squared=27-49%). Further analyses were adjusted for age, sex, and education. CPS score and response time features significantly differed between HC and PwMS, with largest effect sizes seen for CPS score and ST (Cohen's d=1.40 and 1.29 respectively). All features appeared sensitive to CI in PwMS, while CPS ST and S2D correct RT had greatest sensitivity (Cohen'sd=1.81 and 1.73 respectively). CPS ST was significantly higher in unemployed vs partially or fully employed PwMS ($p=0.025$).

Conclusions: CPS score and response time features are sensitive to cognitive impairment and show discriminative validity between PwMS and HC. CPS ST appears less confounded by age, gender, and level of education than other features and differed significantly by employment status, suggesting Konectom captures clinically meaningful neurocognitive capacities beyond the CPS score.

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EP1160

The role of personality traits on clinical and neuropsychological variables of people with MS in Argentina

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Background: Personality traits are relatively stable over time, specific between individuals and, therefore, behavioral predictors. The aim of this study is to analyze the relationship between personality traits and clinical and neuropsychological manifestations in people with multiple sclerosis (PwMS).
Methods: The sample included 75 PwMS, 94.3% with relapsing remitting MS, 61.3% were women; average age: 39.16 ± 11.70 years; education: 13.57 ± 3.79 years; EDSS: 2.62 ± 2.23; evolution MS duration: of the disease 8.21 ± 6.83 years. Measuring instruments: Clinical variables: EDSS; Fatigue severity scale; Beck Depression Inventory II. Cognitive variables: BICAMS battery; the NEO Five-Factor Inventory (NEO-FFI) personality traits include neuroticism, extraversion, openness, conscientiousness, and agreeableness. Parametric and non-parametric statistics were used, to define significance a value of $p < 0.05$ was accepted.
Results: The neuroticism trait was associated with greater reported fatigue ($p<0.01$) and greater depressive symptomatology ($p<0.01$). On the contrary, the conscientiousness trait was negatively associated with the presence of fatigue ($p=0.030$) and depression ($p<0.01$). Significant statistical differences were found between PwMS with and without cognitive impairment. Those patients with cognitive impairment presented a higher level of neuroticism ($p=0.038$).
Conclusion: Personality traits have a negative impact on cognitive performance, depression, and reported fatigue. Identifying these personality traits gives us valuable information to personalize the therapeutic approach.

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Therapy - Neurobiology & Rehabilitation

EP1161
Measuring the impact of common exercise programs on subjective fatigue and metabolic efficiency during daily living activities in people with multiple sclerosis: a randomized controlled pilot trial

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Introduction: Fatigue is one of the most disabling symptoms of people with multiple sclerosis (MS, PwMS), affecting the activities of daily living (ADL), motor function, and social life. While the pathophysiology of fatigue in MS is not fully clarified, evidence supports exercise therapy as a safe and effective tool to counteract fatigue impact on PwMS.
Objectives: Since firm evidence is lacking on which exercise programs are most effective to manage fatigue in MS, we aimed at doing so by evaluating, both subjectively and objectively, real-life fatigue and to define which protocol is capable to positively impact on patient's function and health-related quality of life (QoL).
Aims: Aim of the study was to compare the effects of 4 common forms of exercise on subjective and objective fatigue burden and QoL elating to physical health and on mobility and muscle strength.
Methods: Design was set as a parallel, 4-armed randomized pilot trial. Thirty-two PwMS with fatigue as their main complaint underwent assessment via Modified Fatigue Impact Scale (MFIS), physical health QoL via MSQoL-54 before and after completing one of the following 8-week (2-session/week) interventions: aerobic reconditioning, strength training, aerobic+strength training (COMBO) and global rehabilitation. Secondary outcomes were mobility, strength, cardio-fitness, and mood.
Repeated-measures ANOVA with corrected pairwise comparisons were run to test for changes in the endpoints of treatment, with significance set at $p<0.05$.
Results: No adverse events and/or relapses were reported. Within-subjects comparisons showed significant changes for COMBO in MFIS_total (-18.2 pts; $p=0.006$), MFIS_physical (-12.3 pts; $p=0.003$), MSQoL_physical_health (-17.1 pts; $p=0.003$), health_perception (-2.3 pts; $p=0.02$), and energy_fatigue (-1.4 pts; $p=0.04$). Only COMBO resulted in reductions in depression of mood (-7.7 pts; $p=0.001$) and gains in distance covered in 6 minutes (+47 m; $p=0.03$), and strength of the knee flexors (+4.5 kg; $p=0.03$), extensors (+ 7.5 kg; $p<0.001$), and ankle plantarflexors (+3.7 kg; $p=0.03$). Conversely, only global rehabilitation resulted in increased walking speed (+0.3 m/s; $p<0.001$). Between-group statistics revealed superiority of COMBO over the other interventions for MFIS (all $p\leqslant0.02$), MSQoL (all $p\leqslant0.02$), and muscle strength (all $p\leqslant0.01$).
Conclusions: Preliminary data seem to introduce superiority for COMBO over the other interventions, on MS-related fatigue.

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Therapy - Others

EP1162

The global inequality of neurological research: a systematic analysis of clinical trials between 2017 and 2021

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Introduction: Clinical trials provide the framework for medical decision-making. Generalisation of study results requires the proportional representation of populations of interest. However, knowledge of clinical trial distribution among neuroscientific studies in high-income (HIC) and low- and middle-income countries (LMIC) is lacking.
Objectives: We aimed to understand the global neuroscientific landscape and discuss future challenges of research globalisation.
Methods: Data was acquired by searching the following databases between 2017 and 2021: Clinical Trials.gov, EudraCT, JAPIC. The continents of South and Central America, Africa and Asia were defined as LMIC. North America, Europe and Australia were considered as HIC. Descriptive statistical analysis was performed to interrogate differences between HIC and LMIC.
Results: 26,208 interventional trials including a total of 3,197,626 patients and 7798 non-interventional studies and patients' registries including a total of 75,581,848 patients were analysed. A disproportional amount of interventional and observational clinical trials across neuroscientific indications take place in HIC. Phase 1 studies are predominantly conducted in North America, while phase 2 and 3 as well as observational studies were mostly conducted in Europe and North America. Interventional studies saw a continuing growth in LMIC as compared to HIC, whereas non-interventional studies displayed no clear trend. The number of neuroscientific studies correlated with health care expenditure per capita.
Conclusion: Structural changes are needed to overcome the staggering inequality of neuroscientific research and foster the potential of clinical research in LMIC. Local solutions might improve public health in a resource-limited setting to include outcomes of patient groups currently underrepresented in clinical trials.

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EP1163

Discontinuation of high- versus middle-efficacy disease-modifying treatment in middle-aged patients with multiple sclerosis

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Background and Purpose: There has been scant research on the consequences of discontinuing high-efficacy disease-modifying treatment (DMT) in middle-aged patients with multiple sclerosis (MS). The objective of the present study was therefore to examine the occurrence of focal inflammatory activity after the discontinuation of high versus middle-efficacy DMT in patients with MS over 45 years.
Methods: Patients with MS who had been treated for at least 6 months with high (natalizumab, fingolimod, anti CD20) or middle-efficacy DMT and who then stopped their DMT were retrospectively included in this two-center study. Kaplan–Meier survival curves were used to study the occurrence of relapse and MRI activity according to the type of DMT stopped. Proportional hazard Cox models were calculated to identify factors associated with focal inflammatory activity. The annualized relapse rate was calculated under treatment and for every 3 months after DMT discontinuation.
Results: We included 232 patients with MS (median age at DMT discontinuation: 52.8 years), 49 of whom stopped high-efficacy DMT. The probability of having a relapse within the year following discontinuation was 6% in patients who had been receiving middle-efficacy DMT, 9% for fingolimod and 43% for natalizumab. In multivariate analysis, the probability of relapse after DMT discontinuation was significantly increased with natalizumab compared to middle-efficacy DMT (HR= 3.24; 95% CI (1.52; 6,90)). A peak of relapse was observed at 0-3 months after stopping natalizumab or fingolimod.
Conclusion: Our study suggests that the risk of focal inflammatory activity is greater after discontinuation of natalizumab compared to other DMT, even in middle-aged patients with MS. As for younger patients, natalizumab discontinuation should only be considered if there is an adequate substitution of a different highly effective therapy.

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EP1164

Adherence to treatment in multiple sclerosis. The importance of personality, executive functions, and social support

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Introduction: Adherence to Multiple Sclerosis (MS) medical treatment is fundamental for a successful therapeutic response. Adherence to treatment may be influenced by emotional, cognitive, and social factors. Therefore, identifying those factors could be important.
Objectives: To test whether adherence to treatment in patients with MS is influenced by cognitive variables (executive functions), personality, and social support.
Methods: This is a pilot observational, descriptive, cross-sectional study. A sample of 60 patients with RRMS (73.33% female; age: 41.41 ±14.00) undergoing medical treatment (41 patients received oral treatment -teriflunomide, cladribine, dimethylfumarate, fingolimod-, 13 monoclonal ac. -natalizumab, antiCD20- and 6 injectables -interferon, glatiramer acetate-). These were subjected to a comprehensive multi-component evaluation including: cognition, social support (using the self-reported record of social support scale), personality (using the NEO-FFI questionnaire) and evaluation of treatment adherence using the Morisky Green Levine Medication Adherence Scale.
Participants were divided into two groups according to their adherence to medical treatment, low vs. high adherence was defined using a cutoff score of 4. Differences between groups were evaluated using Student's t-test with a significance level of $p<0.05$, the effect size was calculated with Cohen's d test.
Results: Groups did not differ significantly in age, sex, type of treatment, Montreal Cognitive Assesments or neuropsychiatric (MoCA), scales of depression and anxiety (HADS). Regardless of treatment type, 63.33% of the patients had high treatment adherence. Significant differences between groups were found in the Global Index of Social Support (p=0.016, Cohen's d= 0.73) and the responsibility factor of the NEO-FFI (p=0.048, Cohen's d= 0.20). Conversely, no significant differences were found in executive functions (p=0.8), Openness (p=0.062), Extraversion (p=0.5), Neuroticism (p=0.4) and Agreeableness (p=0.8).
Conclusions: Social support and the responsibility factor of personality are significantly different between MS patients with high and low adherence to medical treatment. The study of social support and personality may be a key component in improving adherence strategies.

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EP1165

Factors influencing patient decisions when choosing disease modifying therapy for multiple sclerosis

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Introduction: The expanding number of disease modifying therapies (DMTs) available to patients with multiple sclerosis (MS) has made the DMT decision-making process more complex for patients. Understanding the factors that are most important to patients when making DMT decisions is crucial to facilitating successful shared decision-making. While prior studies have shown that disability prevention, risk of severe adverse events, and route/frequency of DMT administration are among the most important factors to patients, there are limited data on how demographic and disease-related variables influence these factors. Additionally, updated data in the era of newer DMTs are needed.
Objectives: The objective of this study is to improve clinicians' understanding of how patients make decisions when choosing DMTs for MS.
Aims: This study seeks to identify factors that patients report as influential when choosing DMTs, as well as correlations with demographic and disease-related variables.
Methods: Study participants (N = 90) were patients in a comprehensive MS center who were considering starting or switching DMTs. Participants completed an online survey that included questions about demographics, disease-related attributes, current and prior DMT use, attitudes about medications, psychological measures, and factors that may influence DMT decision-making.
Results: The factors that subjects agreed or strongly agreed were most likely to influence DMT decisions included disability prevention (87.8%), MRI lesion prevention (83.3%), relapse prevention (75.6%), healthcare provider recommendation (75.6%), and the risk of severe adverse events (66.7%). Subjects with lower Patient Determined Disease Steps scores were more likely to rate disability and relapse prevention as important factors. Younger subjects and subjects with higher anxiety scores on the Hospital Anxiety and Depression Scale were more likely to rate relapse prevention as an important factor. Nonwhite subjects were more likely to rate the risk of severe adverse events as an important factor.
Conclusions: Disability prevention is the most important factor to patients with MS when choosing a DMT, especially among those who are less disabled, while prevention of inflammatory disease activity and safety concerns are highly important factors as well. Clinicians should provide patients with information about these factors in discussions about DMTs and should communicate clearly if any specific recommendations exist.

Disclosure
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EP1166

Heterogeneous virtual multiple sclerosis patients for analysis of personalized treatment responses

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Introduction: One of the major challenges in the treatment of Relapsing-remitting Multiple Sclerosis (RRMS) is the diversity and unpredictability of RRMS disease courses. Currently, a wide array of treatment options with different efficacy and safety profiles is available on the market, and development of new therapies is ever ongoing. However, answering the question of the most appropriate drug for a patient, and the most appropriate target population for a new drug, is no easy task. Here, a population of virtual patients (VPs) with RRMS was generated and treatedin silicowith several different treatment options. The response of the VPs to the treatments was analysed in terms of individual differences in efficacy.
Objectives: To analyse interpersonal efficacy response differences to treatments in RRMS VPs.
Aims: To support personalized treatment in RRMS through characterization of individual patients optimal efficacy profiles.
Methods: VPs were generated with MS TreatSim, a web-based, cloud-based VP and clinical trial simulator available at mstreat.insiliconeuro.com. MS TreatSim VPs are individualized instances of a mechanistic immune system simulator that has been induced to develop RRMS. The VPs, with active RRMS, were simulated for 260 weeks with four different treatment protocols – no treatment, interferon β-1a, teriflunomide and natalizumab. Efficacy responses were then quantified within each VP to obtain individual analyses of the differences in treatment responses and stratified for further analysis.
Results: Without treatment, the 50 VPs had an annualized relapse rate of 0.33 ± 0.29 (mean ± SD). With treatment, rates fell to 0.10 or lower and damage to the oligodendrocytes – a continuous measure of relapse activity and neural damage incorporated in the VP - decreased by means of 58% (interferon β-1a), 80% (teriflunomide), and 72% (natalizumab), respectively. To investigate inter-individual differences, the responses of VPs to the different treatments were then more closely investigated. Patients were stratified by ratios of treatment responses, and differences in efficacy patterns were identified.
Conclusion: MS TreatSim generates VPs with heterogeneous immune initializations and treatment responses. Analysis of these

VPs in terms of not only efficacy, but also leukocyte number-based safety profiles, can help to characterize the optimal efficacy-safety profile for a patient, as well as which patients are the optimal targets for a treatment.

Disclosure
Fianne Sips: is an employee of InSilicoTrials Technologies.
Alberto Palazzin: is an employee of InSilicoTrials Technologies.
Roberta Bursi: is an employee of InSilicoTrials Technologies.

EP1167

Did the introduction of the Sars-Cov-2 vaccine influence the choices of therapy in patients with a new diagnosis of multiple sclerosis?

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Introduction: Since the beginning of the Sars-Cov-2 pandemic, several evidences have been gathered on the use of Disease Modifying Drugs (DMTs) in patients with Multiple Sclerosis (MS) .The introduction of the Sars-Cov-2 vaccine marked a turning point for MS patients, considered "fragile patients".
Aims: The objective of this study is to describe changes about the use of first-line DMTs in patients with a new diagnosis of MS, comparing the semester before and after the start of vaccination campaign for Sars-Cov-2.
Methods: The study included patients newly diagnosed with MS according to McDonald's 2017 criteria. The proportion of patients initiated into the use of Interferon Beta (IFN), Dimethylfumarate (DMF) and Teriflunamide (TERI) was defined as a proportion for the previous semester (October 2020- March 2021) and subsequent (April 2021–September 2021) to the avaibility of Sars-Cov-2 vaccine. The determinants of the choice of first-line DMTs were evaluated through regression analysis.
Results: The study included 134 patients, including 40 (29.9%) male, average age of 38.3 ± 12.3 years, disease duration of 3.0 ± 4.6 years, average EDSS of 1.7 ± 1.1. Among these, 75 (56%) patients started a first-line DMTs in the semester before the start of vaccination campaign [IFN 13 (9.7%), TERI 6 (4.5%), GA 28 (20.9%), DMF 28 (20.9%)], while 59 (44%) in the following semester [IFN 4 (3%), TERI 11(8.2%), GA 12 (8.9%) and DMF 32 (23.9%)]. A reduction of 40% and 53% respectively in the use of GA and IFN was observed in the semester following the start of the vaccination campaign. In contrast, an increase of 29 % in the use of TERI and 6% in the use of DMF respectively was reported in the same semester. The regression analysis shows the use of injection therapies (IFN, GA) being associated with female gender (p= 0.032) and with the previous semester to the availability of Sars-Cov-2 vaccine (p=0.006). In contrast, the use of TERI is associated with male gender (p=0.031) and with the following semester the introduction of the vaccine (p=0.05). About the use of DMF, a relationship with the post-introduction semester of the vaccine has been observed (p=0.037) the relapse rate in the previous 2 years is the strongest determinant in the choice of this treatment (p=0.001).
Conclusions: Our data show how the start of the vaccination campaign for Sars-Cov-2 influenced the use of first-line immunotherapies in patients with new diagnosis of MS.

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EP1168

Intravenous transplantation of bone marrow-derived mesenchymal stromal cells in patients with multiple sclerosis, a phase I/II, double-blinded, randomized, controlled, crossed over clinical trial

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Introduction: Multiple sclerosis (MS) is a neurodegenerative, progressive, and demyelinating disease of the central nervous system. This disease is immune-mediated and leads to disability especially in young adults. Even though 18 approved MS therapies exist, they slightly inhibit disease progression and do not induce regeneration and repair in nervous system. Mesenchymal stromal cells (MSCs) have emerged as a new therapeutic modality in regenerative medicine, tissue engineering, and immunomodulation.
Methods: We have designed a double-blinded, randomized, controlled, crossed-over clinical trial. Twenty-one patients with confirmed MS were enrolled. These patients received systemic transplantation of autologous bone marrow-derived MSCs intravenously. Patients were allocated in two distinct groups: early and late treatment. We followed up the patients for 18 months after cell transplantation. Follow-ups included regular visits, paraclinical evaluation, and imaging analysis.
Results: No severe immediate or late adverse events were observed in both groups after intervention. We didn't find any significant differences in the rate of relapses, Expanded Disability Status Scale (EDSS) score, and cognitive condition between the two treatment groups. Moreover, there were no noteworthy differences in Magnetic Resonance Imaging (MRI) findings or in some biomarkers of cerebrospinal fluid in the two groups.

Conclusions: Transplantation of autologous bone marrow-derived mesenchymal stromal cells is a safe and feasible procedure. The efficacy of transplantation of these cells should be evaluated through designing randomized clinical trials with larger sample sizes, other administration routes, as well as longer follow-up periods.

Disclosure
There is no conflict of interest by the authors.

RIMS - Physical exercise and lifestyle changes

EP1169
Physical activity level in people with multiple sclerosis in the Czech Republic

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Introduction: Regular physical activity is part of the comprehensive treatment of people with multiple sclerosis (MS).
Aim: Therefore was the aim of the study evaluate physical activity levels in people with MS and to compare the proportion of physical activities in patients with MS and individuals of the general population (GP).
Methods: Data were obtained using a questionnaire survey. The respondents of both interviewed groups filled in the standardized Godin-Shephard Leisure-Time Physical Activity Questionnaire. The data was obtained from 630 individuals of the GP (individuals without chronic disease) and from 354 patients with MS in the age range of 25-70 years with EDSS 0 – 6.5. The data of both interview groups were analyzed using descriptive statistics and statistical testing of the Chi-Square.
Results: It was observed that a total of 54,8 % of individuals of the GP and 38,4 % of individuals with MS are insufficiently physically active (they do not follow the minimum recommendations regarding physical activity). In people with MS the most popular activity include cycling, walking and swimmimg. There was weak relationship between gender and Godin score and no relationship between age, BMI and Godin score in both groups. Regarding motivation for physical activity 67,8 % people with MS want to do something for themselves, 35,9 % want to improve fitnes.
Conclusions: The results show that people with MS and GP do not engage in physical activity regularly and sufficiently according to existing recommendations. It seems necessary to work sufficiently with motivation of people with MS.

Disclosure
Nothing to disclose.

EP1170
Sit to stand tests can be an interesting tool for disability and ability to ambulate in pwMS

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Introduction: Multiple Sclerosis (MS) is a demyelinating and and chronic disease, which can lead to moderate-severe disability. Variable symptoms as fatigue, balance disorders, loss of coordination, strength and sensation are present in the disease. There are different scales which score the ability of ambulation and the quality of walking, such as 6 minute walking test, 2 minutes walking test and Ambulation Index (AI). Only few papers took into consideration the 5 times sit to stand (STS) or the 30 seconds chair stand test (30CST), which are good indicators in other neurological diseases.
Objectives: We focused on these two easy and fast tests: 30CST consists in recording the number of stands a person can complete in 30 seconds as fast as possible, and STS, which measures the time of 5 stands.
Aims: The aim of our research is to verify the validity, the reliability and the responsiveness of the two tests, since we believe that they are very feasible, fast and useful tools to investigate the ability of walking and the level of disability of pwMS.
Methods: pwMS with EDSS $\leqslant$6.5, followed as outpatients at the AISM rehabilitation center of Genoa, were enrolled in the study. We performed a correlation of the two scales with the AI and the EDSS scale, considered a gold standard scale for people with MS (pwMS); a test-retest reliability test (the two tests have been performed by two different operators after a week); and a comparison between the first evaluation and the last one after 10-12 sessions of physiotherapy is still ongoing.
Results: We collected the preliminary data of 12 pwMS (6 M/6F, EDSS range 1.5-6.5). In our results, EDSS correlates significantly with 30SCT ($p<0.05$) and STS ($p<0.05$) and AI also correlates significantly with both (30SCT $p<0.001$; STS $p<0.0001$). The test-retest analysis shows a very high correlation between the two evaluations (r Pearson 0.979) and Cronbach's alpha is 0.989.
Conclusion: Data suggest that 30SCT and STS seem to be valid and reliable tools. Moreover, they can predict walking concerns on patients and probably both are responsive to change, even though we need further studies with more patients to show it statistically. In conclusion, these 2 tests are simple, reliable, easy to administer and data confirm that they can be included in the evaluation of pwMS.

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Monti Bragadin M - nothing to disclose
Prada V - nothing to disclose

EP1171

Activity and efficacy of radial shock wave therapy in reducing spasticity in people with multiple sclerosis

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Introduction: Spasticity is frequent in People with Multiple Sclerosis (PwMS). Stretch reflex can be studied using surface electromyography (sEMG). Radial shock wave therapy (RSWT) has been widely used to treat spasticity in several neurological conditions.
Objectives: Activity and efficacy of RSWT in treating spasticity in PwMS through sEMG.
Aims: The study aims to evaluate the efficacy of RSWT in treating spasticity in PwMS and the effect on spasticity patterns at sEMG.
Methods: Inclusion criteria: MS diagnosis, age>18, MAS⩾1. Assessments: Modified Ashworth Scale (MAS), Medical Research Council (MRC), Numeric Rating Scale (NRS) spasticity, NRS pain, sEMG (stretch reflex), Timed Up and Go test (TUG), Timed 25 Foot Walking Test (T25-FWT), Global Perceived Effect (GPE).
The sEMG patterns evaluated before and after the treatment were the following: activity in dynamic phase (DSR-alone); activity in dynamic and static phase (DSR+SSR); spastic dystonia (SD), activity in dynamic and static phase (SD+DSR+SSR); SD and activity in dynamic phase (SD+DSR); noEMG activity.
Treatment: 4-session, 1-week interval. Each session: 2000 shots, frequency of 4 Hz, pressure of 1.5 Bars.
Results: A total of 16 PwMS were recruited (5F/11M, mean age 50.38 [SD= 7.39] years, mean EDSS 5.31 [SD=1.28], mean disease duration 11.31 [SD=7.59] years, 7 relapsing-remitting MS, 5 secondary progressive MS and 4 primary progressive MS course). Muscles treated were: 12 right plantar flexors, 9 left plantar flexors and 1 right knee extensor.
Muscles sEMG patterns before RSWT: 16 DSR-alone, 29 DSR+SSR, 21 SD+DSR+SSR.
Muscles sEMG patterns after RSWT: 24 DSR-alone, 21 DSR+SSR, 18 SD+DSR+SSR, 3 noEMG activity.
Activity measured at DSR during stretch reflex before RSWT was 21.56 [SD=12.88] uV, while it was 17.42 [SD=14.45] uV after treatment, and resulted statistically different between the two time points. Regarding evaluation measures performed, scorse before RSWT were: T25-FWT 12.89 [SD=9.03] s, TUG 19.65 [SD=15.91] s, MAS 1.59 [SD=0.36], MRC 4.5 [SD=0.9], NRS pain 0.73 [SD=2.39], NRS spasticity 3.32 [SD=3.86]. After RSWT: T25-FWT 12.78 [SD=8.51] s, TUG 18.15 [SD=13.59] s, MAS 1.48 [SD=0.72], MRC 4.59 [SD=0.94], NRS pain 0.00 [SD=0.00], NRS spasticity 2.68 [SD=2.86]. Mean GPE for subjective perception was 5.13 [SD=0.96]; 11 subjects perceived a subjective benefit (GPE⩾5).
Conclusion: RSWT is a new approach to treat spasticity in PwMS and sEMG could be a useful tool to assess treatment effect.

Disclosure:
- D.G. R declares no potential conflict of interest
- G. E. declares no potential conflict of interest
- B. M. declares no potential conflict of interest
- M. F. G. declares no potential conflict of interest
- P. L. declares no potential conflict of interest
- T. C. declares no potential conflict of interest
- C.S. has served on scientific advisory boards for Almirall, Merck-Serono; received research support from Merck-Serono, Italian Multiple Sclerosis Foundation; received support for travel and congress from Biogen, Roche, Merck-Serono; received honoraria for speaking engagement from Merck-Serono, Almirall, Amgen.

RIMS - (Tele)Rehabilitation (physical, neuropsychological and psycho-social approaches)

EP1172

Music moves – co-creating a music-supported exercise programme with and for people with multiple sclerosis

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Introduction: People with multiple sclerosis (pwMS) expressed their desire for a music-supported exercise programme and motivated us for this project. Patient and Public Involvement and Engagement (PPIE) refers to the involvement of patients or the public as partners in research and provided the study framework.
Aims: To actively involve pwMS in the co-development of a music-supported exercise programme. To evaluate satisfaction with PPIE-activities, levels of involvement and emotional states in pwMS in the context of the cooperation between co-researchers and researchers.
Objectives: To explore levels of involvement in pwMS as members of advisory, monitoring, steering and research groups. To

evaluate lessons learned from bidirectional information exchange and peer-to-peer interviews. To co-create, co-examine and co-adapt a music-supported exercise programme for pwMS with different levels of disability.
Methods: Using various rounds of researcher-supported peer-to-peer focus groups and individual interviews, information was gathered on musical preferences and exercise needs at two centres, based on which the exercise programme is co-developed and co-refined. Tasks were transparently distributed according to people's knowledge and interests and communication was on eye level. Levels of involvement were assessed using a PPIE Evaluation Questionnaire (PPIE-EQ) and Semantic Differential (SD). Emotional states were measured using the Self-Assessment Manikin (SAM). Lessons learned were analysed qualitatively and synthesised with respect to broader implications for the research culture at the study sites and beyond.
Results: Out of 58 study participants, 16 pwMS, 2 caregivers and 3 patient organisation representatives are involved in the project as co-researchers, 4 of them with a musical background. Fifteen are female, with a median (min-max) age of 49.7 (29.8-63.9) years, Expanded Disability Status Scale score of 3.5 (1.5-7.0) and 12.8 (10-22) years of education. High levels of involvement were found by median PPIE-EQ scores of 5 (4-5) and SD scores of 5 (3-5). Positive emotional states were shown by SAM pleasure, arousal, and dominance scores of 8 (5-9), 4 (1-9) and 5.5 (2-9), respectively. Co-researchers' lived experience led to major changes in interview questions and development procedures that will be presented at the congress.
Conclusions: Outcomes represent a two-way learning that will lead to shared decisions about future research content and methods.

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EP1173

Multiple sclerosis patients perform tandem gait with additional upper-limbs movements: proposal of an inefficiency index

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Objectives: While early detection of balance and gait impairments in multiple sclerosis (MS) is very important to propose early rehabilitation and to improve patient's follow-up, it is also challenging. By reducing the area of support and the step width, tandem gait highly challenges dynamic balance and requires additional body segments movements to maintain balance.
The aim of the present study was to propose an index to quantify upper limbs and trunk movements during tandem gait in early-stage MS patients compared to matched healthy participants.
Methods: Fifteen patients with remitting-relapsed MS, with a median Expanded Disability Status Scale of 2.5 [0-4] and a disease duration of 10.9 ± 7.9 years, were compared to 15 matched healthy participants. Three-dimensional motion analysis was performed during tandem gait to calculate spatiotemporal parameters and an inefficiency index based on the linear momentum of body segments. This index measured the right and left upper and lower limbs and head-trunk-pelvis additional movements to achieve tandem gait. The higher the inefficiency index is for a given body segment, the less efficient this segment is for the forward body progression.
Results: Compared to healthy participants, MS patients performed tandem gait with higher speed (p=0.03), longer step length (p=0.03) and an increased distance between the feet (p=0.02). The right and left upper limbs inefficiency indexes were significantly higher in MS patients (p=0.02 and p=0.03, respectively).
Conclusion: Even at the early stage of the disease, MS patients presented a less accurate tandem gait execution. The inefficiency index revealed that MS patients largely increased their upper limbs movements. These additional movements could contribute to balance recoveries and indirectly illustrate the balance performance of MS patients. This index could be used as a physical marker to follow balance deterioration and to assess the efficiency of the rehabilitation, even at the early stage of the disease.

Disclosure
nothing to disclose

EP1174

Effect of the synchronized telerehabilitation-based upper extremity training program on hand-arm functions in people with multiple sclerosis: a pilot study

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Introduction: Between 60% and 75% of people with multiple sclerosis (MS, pwMS) reports having upper extremity dysfunction that occurs unilaterally or bilaterally from the early stages of the disease process. Synchronized telerehabilitation provides immediate feedback, customized treatment, and a social

environment; beyond clinical service delivery. There are limited evidence of synchronized telerehabilitation-based training for upper extremity function in pwMS.
Aims: The study examines the effects of an 8-week synchronized telerehabilitation-based upper extremity training program on hand-arm function in pwMS and compares these effects with the asynchronous treatment group.
Methods: PwMS followed by the Outpatient Multiple Sclerosis Clinic of Dokuz Eylül University Hospital were randomly divided into two groups; synchronous-based telerehabilitation group (SbTG) (n=10) and asynchronous-based telerehabilitation group (AbTG) (n=10). SbTG was applied online, including upper extremity exercises 2 days a week by a physiotherapist. The same exercises were performed via exercise videos in AbTG. All the participants were assessed at baseline and after 8 weeks (post-treatment) by assessors blinded to the group allocation. Upper extremity function was assessed with the Nine-Hole Peg Test (9HPT), the JAMAR Hand Dynamometer, and The Arm Function Questionnaire in Multiple Sclerosis (AMSQ).
Results: The SbTG group had significant improvement in 9HPT (26.17±5.89 vs. 24.28±5.32) ($p<0.05$). There were no significant differences in terms of JAMAR (19.96±8.31 vs. 22.37±5.76) and AMSQ (71.57±29.54 vs. 58.90±28.55) ($p>0.05$) in SbTG. There were no significant differences in terms of 9HPT (24.24±8.46 vs. 27.02±15.23), JAMAR (22.0±10.12 vs. 23.69±10.97), and AMSQ (66.14±35.93 vs. 61.0±20.72) ($p>0.05$) in AbTG after 8 weeks.
Conclusions: Based on the improvement in 9HPT scores, which is shown as the gold standard in upper extremity assessment in pwMS, supports the use of synchronized-based upper extremity training. The advantages of interaction between physiotherapists and patients in synchronous-based telerehabilitation group could be the reason for group differences.

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EP1175

Assessment of telerehabilitation in people with multiple sclerosis: from the patient's perspective

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Introduction: Telerehabilitation is a sub-branch of telehealth aiming to remote control and monitor rehabilitation using telecommunication technologies. Considering the importance of accessing rehabilitation in chronic diseases with heterogeneous symptoms such as multiple sclerosis (MS), remote rehabilitation is gaining importance. In addition, treatment compliance, success, and effectiveness of this access advantage provided to patients should be evaluated.
Aims: The study aims to evaluate telehealth and telerehabilitation from the patient perspective in people with MS (pwMS). It also reveals the difference in perspective between people who access synchronized and asynchronous rehabilitation.
Methods: Twenty-two pwMS (13 synchronized telerehabilitation, 9 asynchronous telerehabilitation) followed by the Outpatient MS Clinic of Dokuz Eylül University Hospital who had access to an exercise program with telerehabilitation twice a week for 8 weeks were included in the study. Each pwMS evaluated their telemedicine-based education with the 'Telehealth Usability Questionnaire (TUQ)' consisting of 21 questions, and the 'Telemedicine Satisfaction Questionnaire (TSQ)' consisting of 14 questions. The Expanded Disability Status Scale (EDSS), age, gender, and disease duration were recorded.
Results: The clinical and demographic profiles of the participants were the following: the age range was between 23 and 67 (43.91±10.84), EDSS range was between 1.0 and 6.0 (3.18±1.60), disease duration range was between 0.50 and 34.75 (12.21±9.43). The mean TUQ and TSQ score were 127.95±23.24 (min/max: 74/147) and 63.68±9.18 (min/max: 39/70), respectively. No significant difference was found between synchronized and asynchronous telerehabilitation groups in age, EDSS score, and disease duration. Also, there were no significant differences in terms of TUQ (synchronized (137.84±8.64) and asynchronous (113.66±30.29)) and TSQ (synchronized (67.30±2.59) and asynchronous (58.44±12.62)) between the groups receiving synchronized and asynchronous telerehabilitation. There was no significant relationship between age, EDSS, disease duration, and TUQ and TSQ scores ($p>0.05$).
Conclusions: Our results indicated that the telerehabilitation method could be used both synchronized and asynchronous. Moreover, we found that satisfaction and usability of these methods are not related to age, EDSS score, and disease duration, which means it could apply to a large population of MS.

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EP1176

Individual telerehabilitation program for improving balance in people with MS

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Introduction: During the Covid-19 pandemic, the provision of rehabilitation care to people with MS was significantly reduced (in addition, many patients were afraid to visit medical and sports facilities). An alternative (in these cases) could be telerehabilitation (ie the provision of rehabilitation services at a distance).
The aim of our pilot study was to evaluate the feasibility of this form of rehabilitation in people with MS with balance disorders.
Methods: Our pilot study included 20 patients with MS with balance disorders. The intervention lasted 12 weeks. The experimental group underwent individual telerehabilitation (twice a week, 45 individual telerehabilitation), which consisted of balance and strength exercises with a physiotherapist, using the Homebalance system and other simple tools). The control group received regular rehabilitation care (outpatient individual physiotherapy). Functional tests were selected to assess the gait and balance disorders: Timed Up and Go (TUG), TUG with dual cognitive task and Berg Balance Scale (BBS). Subjective perceptions of gait, balance and fatigue disorders were evaluated with standardized questionnaires: Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Walking Scale-12 (MSWS-12), Falls Efficacy Scale International (FES-I), Activity Balance Confidence Scale (ABC Scale).
Results: The mean age of participants was 51 years (34-65 years), with the mean disease duration was 17 years (4-29 years) with a median neurological disability EDSS 5 (3-6.5). There was a significant improvement in the experimental group in the functional mobility test-TUG (p=0.048), balance-BBS (p=0.002) and in the standardized ABC Scale questionnaire (p=0.041).
Conclusion: The results of the pilot study suggest that individual telerehabilitation could be an alternative to routine rehabilitation care for the treatment of balance and mobility disorders in patients with MS (suitable, for example, for people with a more distant place of residence or in case of new pandemic restrictions).

Disclosure
Nothing to disclose

EP1177

Evaluating preliminary efficacy of a Cognitive Occupation-Based programme for people with Multiple Sclerosis (COB-MS): a feasibility cluster-randomised controlled trial

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Introduction: Cognitive difficulties experienced in MS impact areas such as work, socialising, self-care and many activities of daily living. There is a high prevalence of cognitive difficulties in MS, but despite this there are few programmes targeting cognition that focus on the ability to function well in everyday life. The COB-MS programme, an occupation-focused cognitive intervention, was developed to address this. It focuses on both the functional difficulties and the wide-ranging symptoms that present in MS, including the ability to maintain employment, social activities, home management and self-care.
Objective: Here we report on the results of feasibility and initial efficacy of the COB-MS as a cognitive intervention for people with MS.
Methods: Although initially designed for in-person delivery, the COB-MS was adapted for online delivery due to the COVID-19 pandemic. Data was collected from people with MS experiencing cognitive difficulties at baseline, post-intervention, 12-weeks, and 6-month follow-up. The primary outcome measure was the Goal Attainment Scaling at 12 weeks. Data was also collected in cognition, quality of life, and mood.
Results: One hundred and twenty-five people with MS and cognitive difficulties were randomised to either usual care or COB-MS intervention. Ninety-four participants were retained at 6-month follow-up. Fidelity data was collected and analysed for occupational therapist conducting the intervention. A qualitative evaluation of the COB-MS from the perspective of participants also took place. All feasibility results will be presented- preliminary efficacy, participant experiences, intervention fidelity, and overall outcomes from the trial.
Conclusion: The results provide recommendations for a future definitive trial of COB-MS, with respect to both feasibility and preliminary, clinical efficacy.

Disclosure
This study was conducted within a trial funded by a Health Research Board Definitive Intervention and Feasibility Awards (DIFA-FA-2018-027).

EP1178

Developing a web-based tele-neurorehabilitation system and implementation in multiple sclerosis patients

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Introduction: There is increasing interest in technology-supported exercise programs in MS rehabilitation. It is important to offer not exercise training but also evaluation and follow-up in one platform for patients with MS.
Objectives & Aims: Developing and examining the effectiveness of a telerehabilitation system that allows evaluation, follow-up and training in MS patients who have difficulties in participating in physiotherapy and rehabilitation services due to personal and environmental reasons.
Methods: A website (www.telenororehab.com) that include exercise videos, photos andexplanations, informative videos and texts was developed. The 5 Times Sit To Stand Test (5XSST), Romberg Test and Tinnetti Balance Test, and Fatigue Severity Scale (FSS) were used to assess the changes in functional performance, static and dynamic balance, and fatigue, respectively. Exercise programs were defined for the patients after the first evaluation with an online interview with the physiotherapist on the system. The patients performed the exercises defined for them through the videos included in the system 3 days a week for 8 weeks. 5 MS patients (3 female, 2 male, mean age=39.2±8.16 year, mean EDSS=3.8±1.3) were included in this pilot study.
Results: Statistically significant improvement was observed in 5XSST (p=0.043), Romberg Test (p=0.042), and Tinnetti Balance Test (p=0.042) after the treatment. There was no significant change in the FSS (p=0.080).
Conclusions: A web-based tele-neurorehabilitation system has a potential to improve functional performance and balance in patients with MS.
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EP1179

Postural control and lower extremity isokinetic muscle strength in people with newly diagnosed multiple sclerosis with no disability

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Introduction: Even early-phase Multiple Sclerosis (MS) is accompanied by considerable impairments across multiple domains, such as strength and balance. Although the Expanded Disability Status Scale (EDSS) is the gold standard for the classification of disability, we think that it is insufficient to detect mild involvement in the very early period
Aims: This study aimed to evaluate balance performance and knee muscle strength in patients with newly diagnosed MS and clinically asymptomatic under different conditions and to compare them with healthy controls.
Methods: People diagnosed with MS (<6 months), with an EDSS of 1.5 and below, and healthy individuals with similar age, gender, and body mass index were included in the study. Isokinetic knee flexor and extensor strengths were assessed with Biodex Multi-Joint System at the angular velocity of 60°/s. The modified Clinical Test of Sensory Integration of Balance (m-CTSIB) was used to evaluate postural sway in four different conditions (open eyes on firm and foam surfaces, closed eyes on firm and foam surfaces). Also, the Balance Error Scoring System (BESSTest) was used to assess postural sway in feet together and tandem stance, on firm and foam surfaces.
Results: Our study was completed with 23 MS and 20 healthy individuals. Hamstring strength was significantly different between groups (p: 0.019, p: 0.015 for right and left, respectively) however quadriceps strengths were similar (p: 0.511, p: 0.670 for right and left, respectively). There was no difference between groups in the open eyes-firm surface (p:0.121), but a significant difference in postural sway was found in all other m-CTSIB conditions (p: 0.004, p: 0.039, p<0.001, respectively). A significant difference was found in all BESSTest conditions (p: 0.001, p< 0.001, p: 0.001, p< 0.001, respectively).
Conclusions: The hamstring muscle weakness starts before the quadriceps involvement in individuals with newly diagnosed and clinically asymptomatic MS. Balance performance is also affected in the early period, and as the balance task becomes more difficult, postural control problems become more pronounced compared to healthy controls. Balance and muscle strength parameters should be evaluated objectively from the early period and intervention should be done with early rehabilitation approaches before the level of exposure increases.

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Clinical aspects of MS - Paediatric MS

EP1180

Age-related blood transcriptional regulators affect disease progression in pediatric multiple sclerosis

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Introduction: Pediatric onset multiple sclerosis patients (POMS) is defined as multiple sclerosis with an onset before the age of 18 years. Compared to adult onset multiple sclerosis (AOMS), POMS has more severe disease activity at onset, but better recovery. Little is known about the molecular mechanism responsible for the differences in the clinical presentations.
Objectives: To assess the role of age-related transcriptional changes that could control the underlying molecular mechanism responsible for the differences in clinical presentation between POMS and AOMS.
Methods: Peripheral Blood Mononuclear Cells samples were taken from 22 POMS patients (mean age 14.1±2.4 years, 15 females, 7 males), and 16 AOMS patients, (mean age 30.8 ±6.1 years,10 females, 6 males), and gene-expression were analyzed using Affymetrix Inc. HU-133-A2 microarrays. Differentially Expressed Genes (DEGs) that significantly distinguished between POMS and AOMS with a p.value <0.05 after false discovery rate correction were evaluated using Partek software. Twenty-one matched age and gender control was applied to clarify age-related changes. Clinical assessment was performed by analysis of the expanded disability status scale (EDSS) and brain MRI lesion loads. Gene functional analysis was performed by Ingenuity Pathway Analysis software.
Results: Compared to AOMS, POMS had higher EDSS (3.0 IQR 2.0-3.0 and 2.0 IQR 2.0-3.0, p=0.005), volume of T1 (2.72 mm^3, IQR 0.44-8.39 mm^3 and 0.5 mm^3 IQR 0-1.29 mm^3respectively, p=0.04) and T2 (3.70 mm^3, IQR 1.3-9.6 and 0.96 mm^3, IQR 0.24-4.63 respectively, p=0.02) brain MRI lesions. The POMS transcriptional profile was characterized by 551 DEGs enriched by cell cycling, B lymphocyte signaling and senescent pathways ($p<0.02$). Of these, 183 DEGs significantly correlated with T2 lesions volume. The POMS MRI correlated DEGs (n=183) and their upstream regulators (n= 718) overlapped with age related DEGs obtained from healthy subjects (n=497). This evaluated common DEGs (n= 30) defined as POMS age-related regulators, suggesting to promote effect on disease severity.
Conclusion: Our finding of higher transcriptional levels of genes involved in cell cycle, cell migration and B cell proliferation that are promoted by the transcriptional levels of age-associated genes and transcription factors, allow a better understanding of the more aggressive clinical course that defines the POMS.

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EP1181

Shifting from natalizumab to alemtuzumab in pediatric-onset multiple sclerosis

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Introduction: Pediatric-onset multiple sclerosis (POMS) is characterized by an aggressive course and early development of physical and cognitive disability. The introduction of highly effective treatments at disease onset (such as natalizumab) is strongly recommended. However, the JCV seroprevalence rate progressively increases in POMS, indicating the withdrawal of natalizumab and the shift to a different highly active treatment.
Objective: To evaluate in POMS withdrawing natalizumab for safety reasons the efficacy of alemtuzumab on clinical and radiological parameters.
Methods: All POMS shifting from Natalizumab to Alemtuzumab between and August 2016 and October 2021 were enrolled in this single-centre, prospective study. Patient were evaluated every 6 months both clinically and radiologically and followed up for 30.4±18.7 months (6-64 months). No radiological (i.e., no evidence of new/enlarging white matter lesions nor gadolinium-enhancing lesion) or clinical (i.e., no evidence of clinical relapse or EDSS worsening) evidence of disease activity (rNEDA and cNEDA respectively) were evaluated at 12 and 24 months. In addition, survival analysis for overall NEDA condition (i.e., radiological and clinical) was also analyzed.
Results: Eleven POMS were enrolled in this study. After the first course 2 patients experienced a clinical relapse (18.2%), while in 4 (36.4%) MRI disclosed inflammatory disease activity. After the second course, one patient, who had at month 12 an active white matter lesion, experienced a clinical relapse, while none had a radiological relapse. Overall, at month 24 63.6% were NEDA. Since during the follow up 4 (36.4%) patients had further evidence of radiological disease activity, 5 (45.4%) POMS were NEDA at the end of their follow-up (mean: 30 months). However, last EDSS was stable (median of 1.0 at baseline and follow-up, p=0.33).
Conclusions: In POMS shifting from natalizumab, alemtuzumab is an effective option. The moderate NEDA condition needs to be further evaluated compared with pediatric cohorts not treated with alemtuzumab and with alemtuzumab-treated adult-onset MS.

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Clinical aspects of MS - Progressive MS

EP1182
Understanding the unmet need for the treatment of patients with progressive forms of multiple sclerosis (MS) In Europe and the United States

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Introduction: Whilst disease-modifying therapies (DMTs) available for relapsing forms of MS are successful in reducing the frequency and severity of relapses, there are fewer treatment options available for progressive forms of MS.
Objective: To assess the size of the unmet need among patients with non-active secondary progressive MS (naSPMS) and primary progressive MS (PPMS).
Methods: A multi-centre online retrospective chart-review study of patients with MS was conducted in Q4 2021 (10/2021-12/2021) across EU4+UK (UK, FR, DE, IT, ES) and US. Recruited from a large access panel, neurologists (MS Nurses included in the UK) were screened for duration of practice in specialty and caseload. De-identified HCP perceptions were collected and de-identified patient charts were recorded for the next 4-10 eligible patients seen during the consultation period.
Results: 274 & 78 (naSPMS), and 314 & 113 (PPMS) were reported on in EU4+UK and US respectively. In EU4+UK, 47% of the naSPMS and 43% of the PPMS patients were untreated versus 29% (naSPMS) and 24% (PPMS) in the US. Suffering from progressive/ severe MS was primarily why the naSPMS patients were untreated (EU4+UK: 48% US:43%); lack of a suitable DMT (54% EU+UK) andpatient refusal (44% US) were the top reasons for the PPMS cohort. Among reported DMT treated naSPMS and PPMS patients, disease progression was still evident: 64% (EU4+UK) and 62% (US) of treated SPMS patients and 74% (EU4+UK) and 79% (US) of treated PPMS patients were reported to have slowly/ rapidly progressing accumulation of disability. 48% (EU4+UK) and 36% (US) of treated SPMS patients experienced an EDSS score increase over the previous 24 months, whilst treated PPMS patients had a mean EDSS point increase of 1.47 (EU) and 1.33 (US) over the previous 24 months. 'Treatments for progressive MS' (EU) and 'neuroprotection and remyelination' (US) were ranked as the most interesting topics for the future of MS treatment by the surveyed HCPs (n=245 EU4+UK, n=116 US).
Conclusions: In this study cohort, a proportion of progressive MS patients remain untreated, whilst evidence of progression is still seen among those treated with DMTs. Further research using comparator cohort is warranted to better understand the opportunity for additional treatment options for progressive patients.

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All authors are employees of Ipsos and have nothing to disclose.

EP1183
mTOR and the unfolded protein response conversely regulate oligodendrocyte maturation in vitro **and are active in chronic demyelinating lesions of cuprizone**

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Multiple sclerosis **(MS)** starts as an immune mediated-demyelinating disease that later progresses into a neurodegenerative condition resulting in accumulation of permanent disabilities. In progressive phase of MS, remyelination declines despite the presence of oligodendrocyte progenitor cells (OPCs) within the lesions. This is in contrast with acute demyelinating lesions where remyelination occurs partially or completely. Elucidating the cellular and molecular mechanisms underlying impaired OPC maturation in chronic lesions can aid in identifying novel treatments to promote remyelination in progressive phase of MS. Using two mouse models of MS, the experimental autoimmune encephalomyelitis (EAE) and the cuprizone-induced demyelination, we show that mTOR activity is increased transiently during acute demyelinating and remyelinating stages through the complex mTORC1 and its downstream effector pS6K suggesting a role for mTOR pathway in acute remyelination. Additionally, we found that unfolded protein response (UPR) is upregulated in acute demyelinating lesions of cuprizone mice and its downregulation correlates with successful remyelination. In contrast, upregulated level of UPR persists in chronically demyelinating cuprizone lesions even after introduction of normal diet in recovery phase that correlates with remyelination failure. To date, the role of mTOR and UPR pathways in regulating OPC properties under

MS-like conditions are not fully understood. Here, we have used direct in vitro systems and cuprizone induced demyelination in PDGFRα-Cre reporter mice to investigate the role of these pathways in regulating OPC maturation, oligodendrogenesis and remyelination in chronic demyelinating lesions. Our direct in vitrodata show that mTOR inhibition with rapamycin impedes OPC proliferation and maturation and reduces morphological complexity of oligodendrocytes and normal expression of myelin basic protein, which has a major role in myelination. We also identified a significant reduction in OPC proliferation after tunicamycin-induction of the UPR, and a decline in OPC differentiation into mature oligodendrocytes and reduced oligodendrocyte arborization. We are currently investigating these pathways in chronic demyelinating lesions of the cuprizone mice. These findings are an interesting starting point for elucidating the role of mTOR and UPR pathways in regulating oligodendrocytes and remyelination in chronic progressive MS.

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EP1184

Profiling cognitive-motor interference in cognitively impaired persons with progressive multiple sclerosis

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Introduction: Performing cognitive-motor dual tasks (DT) may result in reduced walking speed and cognitive performance in persons with Multiple Sclerosis (MS) and the effect in persons with progressive MS having cognitive dysfunction is unknown.
Objectives: To profile DT performance during walking in cognitively impaired persons with progressive MS and examine DT performance by disability level.
Methods: Secondary analyses were conducted on baseline data of the CogEX study. Participants, enrolled with SDMT⩽1.282 SD below normal, performed a single cognitive task (alternating alphabet), single motor task (walking) and a DT (both). Outcomes were walking speed, number of correct answers on the alternating alphabet task, and the DT cost on walking (DTC_{motor}) and cognitive ($DTC_{cognitive}$) performance. Outcomes were given overall and given and compared by EDSS (<6 vs. ⩾6). Spearman correlations were conducted between the DTC_{motor} with clinical measures and patient reported outcomes.
Results: Overall, participants (n=303, EDSS: 6.0, 4.5-6.5) walked slower and had fewer correct answers on the DT versus ST (both $p<0.001$), with a DTC_{motor} of 15.7% and $DTC_{cognitive}$ of 2.3%. Participants with lower EDSS walked faster than those with higher EDSS ($p<0.001$), but did not differ on cognitive performance or DTCs.
Conclusions: DT affects walking and cognitive performance in cognitively impaired persons with progressive MS. This interference did not differ by overall disability level.

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EP1185
SPMS diagnosis: a Canadian practice audit

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Introduction: An estimated 50% of relapsing-remitting multiple sclerosis (RRMS) patients develop secondary-progressive disease (SPMS) within 15-20 years of MS onset; average age at onset is 45 years (Tremlett 2008,Tutuncu 2013). The lack of consensus on diagnostic criteria contributes to clinician uncertainty and a considerable diagnostic delay (Katz Sand 2014).
Objectives: To examine the clinical characteristics of potentially transitioning RRMS and SPMS populations in the Canadian practice setting.
Methods: A retrospective chart review was completed in Canadian MS specialized centres and community neurology practices of MS patients with EDSS 3.0-6.5 who received an RRMS diagnosis 10-20 years ago.
Results: Data were collected for 708 patients at 15 centres (59% from 10 MS clinics, 41% from 6 community practices). A majority were aged >50 years (58%). The average duration of MS was 15.2 years (range 13.3-17.1 years). The SPMS group (n=223) was older (76% aged >50 years vs. 49%), had a higher current

Expanded Disability Status Scale (EDSS) score (mean 5.6 vs. 3.9) and a longer time from MS diagnosis (mean 16.1 vs. 14.7 years) compared to the RRMS group (n=485). Clinical and radiological disease activity in the preceding two years were similar in both groups. The proportion of RRMS vs. SPMS patients with relapses (22% vs. 16%) and new/expanding magnetic resonance imaging (MRI) lesions (27% vs. 30%) was also similar. A higher proportion of SPMS vs. RRMS patients had not undergone MRI within the past 2 years (19% vs. 6%).

Records were examined for the incidence of three MS-related symptoms. A higher proportion of SPMS patients had bladder dysfunction/urinary incontinence (84% vs. 43%), sexual dysfunction (29% vs. 12%) and signs of cognitive impairment (49% vs. 26%) compared to the RRMS group.

A majority of SPMS patients (119/223, 53%) were not receiving a disease-modifying therapy (DMT). The most common DMTs were oral agents (29%) and first-line injectables (9%). In contrast, 84% of RRMS patients were currently on treatment. The most common DMTs were oral agents (40%) and monoclonal antibodies (28%).

Conclusions: SPMS is generally diagnosed about 16 years after MS onset when patients are aged >50 years and already have moderate-to-severe disability. The above data could not determine if an SPMS diagnosis is delayed. Improved detection of worsening symptoms may enable earlier diagnosis of SPMS in younger patients before the onset of irreversible disability.

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EP1186

Demographic and clinical characteristics of persons with severe disability: the descriptive study from Turkey

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Introduction: A better understanding of severe disability is essential for optimizing treatment in this subtype of MS.

Aims: Our aim was to identify the characteristics of patients with MS with severe disabilities.

Methods: We analyzed the demographics and clinical characteristics of 417 participants with an EDSS score of 6 and above registered in our database.

Results: The majority of participants (81.77%) had a secondary progressive MS (SPMS), whereas %18.23 of the sample had a primary progressive MS (PPMS). The mean EDSS of the total sample was 6.6±0.6. The female/male ratio was 1.68; the mean disease duration was 18.74±9.7 years; the mean age at onset was 32.85±11.23 years. The mean diagnosis age was 36.48±11.61, the mean disease duration at the first visit was 3.62±4.92, and the mean onset age was 32.85±11.23. The mean age at conversion from relapsing-remitting MS to SPMS was 42.46±10.38. The disease onset age of patients with PPMS was 38.01±12.56. 11.5% of patients had known familial history, and 8.63% had pediatric-onset MS. Regions of lesions at onset were spinal cord (48.9%), optic (32.1%), and supratentorial (24.7%).

Conclusion: Our results confirm that older age at onset is a risk factor for more severe MS, consistent with the literature. However, the prevalence of familial MS and pediatric MS is not greater than the rate reported in studies covering the entire disability spectrum. Further follow-up studies are needed to define clinical markers for severe disability.

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EP1187

When does progression start and do objective classifiers provide help for the clinicians in defining secondary progressive multiple sclerosis?

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Introduction: A period of diagnostic uncertainty characterizes the clinical transition from relapsing remitting multiple sclerosis (RRMS) to secondary progressive MS (SPMS), since SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course. Previous observational studies have indicated the usefulness of objective classifiers (OCs) to identify patients with SPMS.
Objectives: Our study aims to investigate the length of the uncertainty period associated with the transition to the secondary progressive phase in a Danish population and the usefulness of selected OCs in the diagnostic process.
Methods: Using the Danish Multiple Sclerosis Registry, we identified all patients linked to the Danish Multiple Sclerosis Center with clinically assigned SPMS (CA-SPMS) from 2010 to 2021. We then read through patient records, searching for the date of first mentioned sign of progression. The time difference between this date and the date of CA-SPMS was defined as the uncertainty period. Finally, we applied two OCs, the MSBase and the Karolinska Decision Tree (KI-DT), to generate suggested dates of transition to compare with the dates from the patient records.
Results: A total of 141 patients were included. At the time of CA-SPMS, the mean age was 53.6 years (standard deviation (SD): 9.5), mean disease duration was 19.5 years (SD: 9.7), median EDSS was 6.5 (Q1-Q3: 6-7), and the number of females was 86 (60.9%). In total, 40 patients (28.4%) reported relapse activity up to two years prior to the date of CA-SPMS.
We found a median uncertainty period of 2.1 years (Q1-Q3: 0.59-3.80). The selected OCs generated a suggested transition date that was 4.6 years (SD: 5.60) and 3.8 years (SD: 5.00) earlier than the date of CA-SPMS. This indicates an earlier transition start of 1.9 years (SD: 5.88) for MSBase and 1.1 years (SD: 5.17) for KI-DT compared to our findings of first mentioned sign of progression.
The OCs did not detect a transition in all included patients. However, they provided an earlier SPMS transition date in respectively 66.7% and 50.4% of the study population.
Conclusions: Our findings emphasize that the period surrounding the transition from RRMS to SPMS disease course is associated with uncertainty. Furthermore, the results show that OCs might help in shortening the length of the uncertainty period, but the need for paraclinical tests to help clinicians detect the start of the SPMS phase in time is still present.

Disclosure
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EP1188

Construction of a resource for advance care planning in multiple sclerosis (ConCure-SM): results of cognitive debriefing with users

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Introduction and objectives: Advance care planning (ACP) promotes discussion between patients, health care professionals (HPs) and, if the patient wishes, family members to ensure that future care will be consistent with the values disclosed, especially at the end of life. A recent guideline on palliative care in people with progressive multiple sclerosis (PwPMS) found no evidence available on ACP in this condition. The aims of the present study were to further develop an ACP booklet concerning acceptability, comprehensibility, and clarity to the target population (PwPMS and their significant others, SOs); and to assess its usability within ACP conversations from the perspective of HPs.
Methods: We conducted a multicentre, qualitative study applying the cognitive interview technique with PwPMS and SOs, and including a focus group meeting (FGM) with HPs. We analysed the interviews using the framework method, and the FGM using thematic analysis.

Results: Ten PwPMS and three SOs were interviewed. Interview analysis yielded three overarching themes: comprehensibility and clarity, content acceptability and emotional impact, and suggestions for improvement. Seven neurologists, three psychologists, one nurse, and one physiotherapist participated in the FGM, the analysis of which identified two themes: content importance and clarity, and challenges to ACP implementation.
Conclusions: Study findings suggest that the user's appraisal of the ACP booklet was key to improve its comprehensibility and clarity, but we ascertained common misunderstandings about the role of the HP in this process. HPs highlighted the main barriers to implementing ACP, which were in line with the most recent literature in other settings.

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EP1189

Active inflammation in primary progressive multiple sclerosis: a systematic review

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Background: Active inflammation in multiple sclerosis (MS) is defined as the presence of relapses, gadolinium enhancing lesions (GEL) and/or new or unequivocally enlarging lesions (NEL) on MRI scans. In patients with progressive MS, active inflammation is associated with improved efficacy of anti-inflammatory therapies. However, the prevalence of active inflammation in primary progressive MS (PPMS) is unknown.
Aim: To summarize active inflammation in PPMS as reported in literature, and identify influencing factors for the prevalence of active inflammation in PPMS cohorts.
Methods: A systematic literature search was conducted in EMBASE, MEDLINE, Web of science Core Collection, COCHRANECENTRAL register of trials, and GOOGLE SCHOLAR. Keywords included PPMS, inflammation, and synonyms. Two readers performed abstract and full-text screening. Only original research papers written in English were included if data of at least 5 adult PPMS patients with sufficient data on disease activity were available. We extracted relevant cohort characteristics and outcome data for relapses, GEL and NEL. These data were used to perform descriptive statistics and perform metaregression analyses to identify influencing factors for prevalence of active inflammation in PPMS cohorts.
Results: Out of 3649 hits, we included 34 articles (based on 7137 PPMS patients) for analyses. Twenty articles (4154 patients) reported data on relapses, with a median prevalence of 4.3% (IQR 0%-20.0%). Twenty-four articles (3558 patients) reported data on radiological disease activity (GEL and/or NEL), with a median prevalence of 31.9% (IQR 8.3%-63.6%). In multivariable metaregression analyses including mean age at inclusion, mean EDSS, sex and mean disease duration, a younger mean age at inclusion of study was associated with a higher prevalence of overall active inflammation (relapses, GEL and NEL combined) (p=0.014). This multivariable model had a $R^2$of 25.1. Additional meta-analyses are being performed on separate outcomes of disease activity.
Conclusion: Radiological disease activity is more common than relapses in PPMS. Mean age is an important factor influencing the prevalence of active inflammation. There is a high variability in reported prevalence of active inflammation in PPMS cohorts, which is not fully explained by differences in mean age, EDSS, disease duration and sex. Further research is necessary to determine the causes of the between-study differences in prevalence of active inflammation.

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EP1190

A novel, patient-centred real-world evidence study designed to better understand active and non-active progressive multiple sclerosis using health records in the United States

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Introduction: Multiple sclerosis (MS) has only one diagnosis code despite different outcomes in progressive multiple sclerosis (PMS) and relapsing MS. To better understand the burden and unmet need in PMS, proper patient identification is needed.

Aim: To describe the design, patient demographics, and healthcare resource utilization of patients with active and nonactive PMS who are currently enrolled in the novel, patient-centred real-world evidence study using health records in the United States (US).
Methods: Data are being collected using the PicnicHealth digital record platform, a patient-centred real-world health record aggregator, and included de-identified data from medical records in the US. Adult patients (⩾18 years of age) across the US with confirmed MS enrolled in this study starting in July 2021. Patients with documented PMS (primary progressive [PPMS] and secondary progressive [SPMS]) were included. All available medical records from routine clinical care were obtained, and relevant clinical data were structured from narrative text into a de-identified dataset by the PicnicHealth platform. Data, along with provider and care site metadata, were extracted from inpatient and outpatient records, as well as procedure and radiographic reports. Patients were categorized as active if they were diagnosed with relapsing/active disease or had any relapses or enhancing lesions reported in the last 2 years; nonactive is those who do not meet these criteria. Descriptive statistics were reported.
Results: Of the 177 patients with PMS enrolled, 11% had active MS (17 PPMS, 2 SPMS) and 89% had nonactive MS (74 PPMS, 84 SPMS). Median (Q1, Q3) age was 54 (46, 62) years and 75% were female. Most patients were White (83%, 13% Black, 4% other) and not Hispanic/Latino (93%). Patients were geographically represented across the different US regions with 18% in the Northeast, 24% in the Midwest, 35% in the South, and 23% in the West. Patients had a median (Q1, Q3) of 5 (2, 8) years of visits available from 3 (1, 4) care sites and 6 (3, 15) providers. Of the 45% (79/177) of patients who had a hospitalization, median length of stay was 4 (2, 8) days.
Conclusion: Most patients in this study had nonactive MS disease and demographics were consistent with the PMS population in the US. With a median of 5 years of visit data available for patients, this ongoing novel, patient-centred study has robust real-world data that can be used to generate meaningful future insights.

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EP1191

Magnetic resonance imaging outcomes, neurofilament light, smoking, and treatment with erythropoietin, methylprednisolone, natalizumab or placebo in progressive multiple sclerosis

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Introduction: Disease-modifying treatment options for patients with progressive MS are limited and are mainly efficacious in patients with clinical or magnetic resonance imaging (MRI) activity.
Objectives: To investigate the effects of treatment with erythropoietin (EPO), methylprednisolone (MP) and natalizumab (NTZ), serum concentrations of neurofilament light chain (sNFL) and smoking on MRI outcomes in an exploratory study using data from phase 2 trials in progressive MS.
Aims: To compare effects on lesion activity, brain atrophy and microstructure of lesions, normal-appearing white matter (NAWM) and cortical grey matter (CGM) in progressive MS.
Methods: In a phase 2 double-blind study, 26 patients were randomized to treatment with high-dose EPO and 26 to placebo for 24 weeks followed by a 24 weeks observation period. In phase 2 open-label studies, 24 patients were treated with NTZ and 30 patients with monthly MP pulse treatment for three days for a total of 60 weeks. The trials are registered at clinicaltrials.gov as NCT01144117, NCT01077466 and NCT01305837. Baseline sNFL was measured using SIMOA technology (Quanterix) and corrected for age. MRI was performed using a standardized protocol at baseline and week 48 (EPO/placebo study) or at week 12 (rebaseline scan) and 60 (MP and NTZ studies) on a 3T Siemens Trio scanner. New lesions, enlarging lesions, percentage brain volume change and changes in magnetization transfer ration, mean diffusivity and fractional anisotropy in lesions, NAWM and CGM were analyzed using multivariable generalized and general linear models.
Results: The rate ratio in a multivariable Poisson model for new T2 lesions was 1.20 (95% confidence interval [CI] 0.70-2.06) for patients treated with EPO; 0.44 (95% CI 0.20-0.96, p=0.039) for patients treated with NTZ; and 0.32 (95% CI 0.14-0.72, p=0.006) for patients treated with MP compared to placebo. The rate ratio for new T2 lesions was 2.35 (95% CI 1.36-4.05, p=0.002) in current smokers and 1.97 (95% CI 1.07-3.64, p=0.030) in former smokers compared to never smokers in the multivariable model. Serum NFL concentrations and clinical and demographic

variables were not associated with T2 lesion activity. None of the factors studied were consistently associated with other MRI outcome measures.
Conclusions: Treatment with NTZ and MP is associated with lower risk and smoking is associated with increased risk of T2 lesion activity in progressive MS.

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F. Sellebjerg has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche and Sanofi Genzyme. His laboratory has received research support from Biogen, Merck, Novartis, Roche and Sanofi Genzyme. R. Ratzer has served on scientific advisory boards for Merck and Roche and has had travel expenses reimbursed by Sanofi. Jeppe Romme Christensen has received speaker honoraria from Biogen. K. Schreiber has received support for congress participation from Biogen Idec, Genzyme, Merck Serono, Novartis and Teva, and served on advisory board for Novartis. M. Magyari has served in scientific advisory board for Sanofi, Novartis, Merck, and has received honoraria for lecturing from Biogen, Merck, Novartis, Roche, Genzyme, Bristol Myers Squibb. Cecilie Ammitzbøll has nothing to disclose. H. Lundell is inventor on patents related to MRI methods not used in this study. Hartwig .R. Siebner has received honoraria as speaker from Sanofi Genzyme, Denmark, Lundbeck AS, Denmark,and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark, Lophora, Denmark, and Lundbeck AS, Denmark, and as editor-in-chief (Neuroimage Clinical) and senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany and from Gyldendal Publishers, Copenhagen, Denmark. Per Soelberg. Sørensen has received personal compensation for serving on scientific advisory boards, steering committees, independent data monitoring committees or have received honoraria as speaker from Merck, Novartis, TEVA, GlaxoSmithKline, SanofiAventis/Genzyme, and BMS/Celgene.

Clinical aspects of MS - Natural course

EP1192
Concentric sclerosis of baló: Description of six patients from a cohort of Rio de janeiro and review of the literature of antemortem diagnosed cases

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Introduction: Balo's Concentric Sclerosis (BCS) is a rare demyelinating disease of the central nervous system characterized by the presence of concentric rings and traditionally described as an acute or progressive disease with a fatal course diagnosed by autopsy or histopathology. In the 1980s, with the advent of magnetic resonance imaging (MRI), ante-mortem diagnosis began to be made and benign and recurrent forms were recognized.
Objective: To describe the clinical and neuroimaging characteristics of patients from a cohort in the state of Rio de Janeiro (RJ) with BSE and compare them with data from a systematic literature review.
Methods: A series of cases diagnosed with ante-mortem BSE between 1985 and 2021 were selected from the Hospital Federal da Lagoa (HFL) database with clinical and laboratory information from 1500 patients with inflammatory demyelinating disease (IDD). Patients were followed longitudinally with registration of identification data, clinical history and neurological evaluation of all events in the medical records and with available exams. This series was compared with cases from the literature selected through a systematic review by electronic search on Pub Med with the terms "Balo disease and magnetic resonance" between 1989 and 2021. The following data were extracted from the RJ series and from the literature: sex, age in the first event, clinical manifestations in the first and all events, type and location of lesions on MRI.
Results: Six cases were selected from the RJ cohort. From the electronic search, 102 articles were identified and 30 were selected according to inclusion criteria. Of these, 63 clinical descriptions of ECB diagnosed ante mortem were found.
Conclusion: Six patients were described, corresponding to 0.4% of the DDI cases registered in the HFL. Higher frequency was found in females with great variability in age at onset. Hemiparesis/hemihypoesthesia was the predominant neurological manifestation in the first and all events. Regarding the form of presentation, four patients met the criteria for "like" MS, one presented the "like" NMO form with positive AQP4 and another "like" ADEM. When comparing the cases in RJ with those in the literature, the clinical manifestations and neuroimaging characteristics were similar in the two groups, with predominance of hemiparesis/hemihypoesthesia in the events and neuroimaging with concentric lesions in brain topography.

Disclosure
Not to disclosure

EP1193
Further analysis of cognitively resilient adults with MS:Assessing effects of DMT and neuroimaging indices

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Introduction: Up to 70% of individuals with MS are known to have cognitive impairment but little is known about individuals with MS without cognitive limitations.In recent work, we found that there was a discrete group of individuals with MS who were subjectively and objectively cognitively intact.The cognitively resilient group was found to have less mood disturbance, less pain

interference, and higher baseline intellect, and a trend toward greater cognitive strategy use.FLAIR lesion volumes were comparable between groups.
Objectives: The present study was designed to further explore this cognitively resilient group regarding disease-modifying therapy (DMT) use and neuroimaging correlates. We particularly examined whether or not DMT usage is associated with the better cognitive status of the resilient group. We also tested for neuroimaging features that distinguish those with cognitive resilience.
Methods: Participants included 119 adults with MS who were categorized as cognitively resilient (MScr) or not (MSncr).Criteria for MScr were: no neuropsychological test scores lower than 1 standard deviation below control norms and no subjective impairment based on self- or informant reports.Groups (MScr n=23 and MSncr n= 96) did not differ in age, gender, disease subtype, EDSS, or disease duration (i.e., years since diagnosis, years since symptom onset).DMT were tabulated using both patient report and medical record review.High-resolution T1-weighted anatomic scans were segmented using previously reported methods.
Results: The percentage of patients on DMT did not differ between groups, with 66.7% on treatment in the MScr group and 80.2% in the MSncr group (Chi-Square (1) = 1.23, p=.40). Separate analyses of covariance showed effects of age and sex for whole brain volume and gray matter volume and an effect of education for white matter volume, but only subtle trends toward significance for group differences (MScr v. MSncr) in whole brain volume (p=.08) and white matter volume (p=.09) adjusted for intracranial volume (ICV).There were no group differences in gray matter volume or thalamic volume adjusted for ICV.
Conclusions: Taken together with our prior research, these findings indicated that this unique subgroup of MS patients who exhibit cognitive resilience differ on psychosocial factors but not disease-related factors such as DMT use or brain volumes.This motivates further research into lifestyle factors that may be related to cognitive resilience in MS.

Disclosure
Nothing to disclose

EP1194

Peripheral nervous system impairment in multiple sclerosis patients: ultrasound and electrodiagnostic study

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Background: Peripheral nervous system (PNS) involvement has not been thoroughly visited in multiple sclerosis. Different methods have been used to assess PNS involvement in MS such as electrodiagnostic and magnetic resonance neurography. Some of these studies have demonstrated peripheral nervous pathology to some extent.
Aim: evaluation of the peripheral nervous system involvement in patients with MS in different stages of the disease using ultrasound and electrodiagnostic tests. Subjects and methods: Sixty-one MS patients (RRMS 60.7%, SPMS 29.5%, PPMS 9.8%, mean age 27±7 years and mean duration of disease 8±5 years) underwent electrodiagnostic and ultrasound examination of right median and posterior tibial nerves as well as left ulnar and left common peroneal nerves. Sixty control subjects underwent nerve ultrasound.
Results: Overall median, ulnar and posterior tibial nerves showed statistically significant increase in cross-sectional area (CSA) of nerve compared to controls. No significant increase in CSA was shown in common peroneal nerve yet it showed a higher frequency of abnormal fascicule enlargement. Electrodiagnostic abnormalities were detected in a small proportion of patients with median and common peroneal nerve (CPN) showing the higher frequency of abnormal conduction velocity (31.1% and 6.6 % of patients respectively). Higher frequency of amplitude abnormalities was detected in CPN (9.8%). In ulnar nerve lower duration of the disease and lower EDSS was related to higher CSA.
Conclusion: Ultrasound examination of Peripheral nervous system of MS patients demonstrated abnormal structure, yet, only a small proportion had functional impairment by electrodiagnostic study.

Disclosure
Nothing to disclose

EP1195

Clinical and demographic characteristics of late-onset multiple sclerosis

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Introduction: There are delays in the diagnosis of late onset MS (LOMS) cases due to differential diagnosis differences; comorbid diseases, polypharmacy and drug interactions complicate treatment management.
Aims: It was aimed to evaluate the demographic data, clinical features, presence of OCD and presence of spinal lesion in the study group.
Methods: A five thousand nine hundred patients who were followed up between January 2020 and December 2021 in 8 different MS centers in our country were screened; 136 patients aged 50 and over with a definite diagnosis of MS were included in the study.

Results: Mean age of the study group; 60.96 ± 6.42 (51-79), mean age at diagnosis; It was found to be 54.94±4.30, (F/M; 1.89). When the first attack characteristics of the study group were examined; motor onset and optic neuritis onset were the most common (21.3% and 16.2%, respectively). The mean time from the first episode to diagnosis was 3.33±5.62 years, and the mean disease duration was 73.03±55.64 months. 64% of the study group were RRMS, while 16.2% were PPMS. OCB positivity rate was 79.3%, spinal lesion was detected in 83.8% of the study group. 97.1% of the study group were using any disease modifying drugs.The average number of attacks in the study group, which was followed regularly for about 6 years
It was 2.24 ± 1.70 and the EDSS score at the time of diagnosis; The EDSS score evaluated at the last visit was 2.44±1.46; It was determined as 3.15±2.14. The mean EDSS scores in all evaluation periods were found to be higher in the patient group with a clinically poor prognostic factor compared to the group without. The EDSS scores of the patients with spinal lesion were higher than those without spinal lesion in all periods. The presence of comorbid disease, age at diagnosis and duration of diagnosis did not have a significant effect on EDSS.
Conclusions: In cases of LOMS, the diagnosis process may be delayed by the contribution of comorbid diseases. It is thought that a good definition of the LOMS group, in which it is difficult to monitor both disease activity and progression, will provide important data in the treatment decision and follow-up.

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EP1196
Prognostic role of visual evoked potentials at multiple sclerosis diagnosis

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Introduction: No biomarker for relapses in patients with Multiple Sclerosis (PwMS) is available and the diagnosis is still clinical with an important risk of misdiagnosis. Small Extracellular Vesicles (sEV) have gained significant interest in MS as potential biomarkers due to their synthesis by immune cells and their ability to cross the blood-brain barrier. Once thought to be primarily driven by T cells, B cells are emerging as central players in MS immunopathogenesis. the majority of Bmem populating the CSF display an isotype-switched phenotype (71%; CD19+ CD27+ IgD- IgM-)
Objective: To explore the changes in sEV concentrations in PwMS during a relapse (RP) or in remission (rP) and the difference with healthy volunteers (HV).
Methods: sEV from patients in relapse (RP) and remission (rP) and healthy volunteers (HV) were isolated by plasma samples using Dual-Mode Chromatography. Isolated sEV were labelled with CD9+ (specific sEV biomarker) and CD19+CD200+ (B naïve marker) or CD19+CD27+ (B memory marker) and were analysed by flow cytometry using Cytoflex S equipment. Differences in EVs levels between different MS-treatments were also analysed.
Results: Higher CD19+CD27+ sEV were found in relapse vs remission ($p<0,005$). Higher CD19+CD200+ sEV levels were found in HV versus PwMS, independent of disease activity ($p<0,005$). Finally, our study revealed that anti-CD20 treatments alter these patrons.
Conclusions: Our study demonstrates that B-cell phenotypes could be used as potential activity biomarkers in MS, as PwMS in RP presented higher Bmem sEV in comparison with remission. Bmem in peripheral blood may prove useful for monitoring therapeutic effects in MS.

Disclosure
None

Clinical aspects of MS - Epidemiology

EP1197
The risk of parkinson's disease in multiple sclerosis and neuromyelitis optica spectrum disorder: a nationwide cohort study in South Korea

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Introduction: Neuroinflammation is a major pathogenesis of multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), but neurodegeneration is also associated with pathogenesis of both diseases. Parkinson's disease (PD) is

a representative neurodegenerative disease with pathogenesis similar to that of MS and NMOSD. However, there have not been many studies to evaluate whether MS or NMOSD is associated with risk of PD.

Objectives & Aims: The present population-based cohort study investigated the risk of PD in patients with MS or NMOSD compared with control populations within the Korean National Health Insurance Service (NHIS) database.

Methods: MS and NMOSD cohorts were collected from the NHIS between January 1, 2010, and December 31, 2017, using International Classification of Diseases 10th revision diagnosis codes and information in the Rare Intractable Disease management program. The PD incidence rate that occurred after a 1-year lag period was calculated and compared with that of a control cohort matched for age, sex, hypertension, diabetes, and lipid panel results in a 1:5 ratio.

Results: The adjusted hazard ratio of PD was 7.73 (95% confidence interval [CI], 3.87-15.47) in MS patients and 2.61 (95% CI, 1.13-6.02) in NMOSD patients compared to matched controls. The incidence probability of PD in MS and NMOSD patients was higher than that of their control groups. In both MS and NMOSD patients, there was no significant difference in relative risk when stratified by sex, age, diabetes, hypertension, and dyslipidemia.

Conclusions: The PD risk was higher in MS and NMOSD patients compared to healthy controls and was particularly high in MS patients. Further investigations should be performed to determine the pathophysiology and occurrence of PD in MS and NMOSD patients.

Disclosure

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EP1198

Characterization of patient and treatment characteristics in SPMS and at risk for SPMS patients in clinical routine: final results from the pangaea 2.0 evolution study

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Background: Until today, the diagnosis of patients with secondary progressive multiple sclerosis (SPMS) and especially identification of the transitional phase from relapsing remitting multiple sclerosis (RRMS) to SPMS remains challenging since reliable clinical diagnostic criteria and tools are missing or are not yet established.

Objective: The aim of the PANGAEA 2.0 EVOLUTION study was to evaluate and compare clinical parameters and patient reported outcomes of patients with RRMS at high risk to develop SPMS with SPMS patients in order to characterize the transition between these two stages of MS.

Methods: In the prospective non-interventional study PANGAEA 2.0 EVOLUTION 600 patients with either SPMS or RRMS at high risk for SPMS were followed independently of treatment for up to 2 years. As there are no standard criteria for the transition state from RRMS to SPMS, physicians independently assigned patients to the 'high risk for SPMS' cohort after a comprehensive evaluation of the patient's symptoms according to their daily practice. At 6-month intervals routine clinical measurements, quality of life and socioeconomic parameters are documented.

Results: Final results from the 600 patients will be presented including baseline characteristics as well as up to 24-month follow-up data. First data shows that SPMS patients are older than RRMS patients at risk for SPMS (53.6 vs 49.5 years), have a longer disease duration (17.2 vs 13.8 years) and a higher EDSS (5.1 vs 4.2). Cognition (assessed by SDMT) and motor fatigue (assessed by FSMC) are more pronounced in SMPS patients (SDMT: 38.0 SPMS vs 43.0 high risk for SPMS; FSMC: 68.1 SPMS vs 63.9 high risk for SPMS). Here we will expand on these data to show how the patients in the two groups progressed during the observational period of up to 24 months.

Conclusions: PANGAEA2.0 EVOLUTION allows comparing SPMS patient profiles to RRMS patients at risk for SPMS in a real world, yet well-structured setting. Combining clinical and non-clinical parameters for a patient profile may help to establish standard early diagnosis criteria and therapy of SPMS patients.

Disclosure

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EP1199

Cross-sectional analysis of stressful life events and relapse, disability, depression-risk, and fatigue in people with MS

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Background: Studies suggest stress increases the risk of relapses and reduces quality of life in people with MS but few have examined the effect of stressful life events (SLEs) on disease progression.

Objective: To investigate the associations between SLE number and individual SLEs and the frequencies of relapse, disability severity, depression-risk, and fatigue in people with MS.

Methods: Cross-sectional analysis of data from an online cohort of people with MS was performed (n=948). SLEs were assessed using a subset of 16 SLEs from the Holmes-Rahe Social Readjustment Rating Scale. SLE relationships with relapse,

disability severity, depression-risk, and fatigue were assessed by log-binomial or log-multinomial regression, as appropriate, adjusted for age, sex, education, MS type, disability, fatigue, comorbidities, ongoing relapse symptoms, and antidepressant/anti-fatigue medication, as appropriate.

Results: The average number of SLEs was 1.8(range 0-9). SLE number was associated with 10%(95%CI;1-20) and 8%(95%CI;3-14) more frequent depression-risk and fatigue, respectively, but no associations with relapse or disability were found. Depression-risk was more frequent in individuals with serious illness [30%(95%CI;3%-64%)], work/school/career crisis/serious disappointment [38%(95%CI;0%-88%)], and new family members [2.47-fold(95%CI;1.21-5.07)]. Fatigue was more frequent in individuals with serious illness [22%(95%CI;7%-39%)] and starting/resuming serious relationships [2.31-fold(95%CI;1.78-2.98)].

Conclusion: SLE number and individual SLEs were associated with greater depression-risk and fatigue. Defining the impact of SLEs on health outcomes may help inform behavioural and/or intervention strategies to improve health outcomes in people with MS.

Disclosure

Jeanette Reece has no conflicts to disclose.

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Steve Simpson-Yap has no conflicts to disclose.

EP1200

Neighborhood level social determinants of health and their association with ambulatory and cognitive disability in multiple sclerosis

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Introduction: An association between neighborhood-level social determinants of health (nlSDOH) using census tract and health outcomes has been reported but remains poorly understood at the individual level in multiple sclerosis (MS). Furthermore, few studies exist that account for neighborhood context in Hispanic and Latinx patients with MS.

Objective: To examine the association between nlSDOH and MS-related disability measures and to ascertain the variance of each measure.

Methods: We developed a nlSDOH index using personal information from 241 self-identified Hispanic and Latinx patients from the United States[US and Puerto Rico(PR)] with early MS (diagnosis of<5 years). Employment status, region-specific household median income, education, language, homeownership and crowding (>4 household) were used to characterize nlSDOH [range:2-9, mean(SD):4.86(1.72), higher score: worse]. Acculturation was assessed using Short Acculturation Scale for Hispanics. The association between nlSDOH and early disability in MS via structured EDSS, 25-foot walk (25-FTW), Hauser ambulatory index (H-index), and symbol digit modality testing (SDMT) was investigated using multivariable linear regression (age/sex-adjusted in the base model and additionally for acculturation).

Results: Most participants were female (73.7%), had relapsing MS (85.7%), self-identified as White (69.8%), had a mean (SD) age of first symptom and disease duration of 33.86(10.17) years, and 1.83(1.42) years, respectively. Approximately 14.5% were unemployed, 36.2% < high school education, 59%<median income (US$65,000; PR$20,000) and 79% lived in a household with ⩾5. SDMT, H-index, EDSS and 25-FTW mean (SD) were 46.3(12.6), 1.36(1.7), 2.3(1.9), and 7.1(2.8) seconds, respectively. After controlling for age and sex, each unit increase in nlSDOH was associated with 2.76 (95%CI:-3.42,-1.85) decrease in SDMT, 0.46(95%CI:0.24,0.68) increase in H-index, 0.36 (95%CI:0.21,0.51) increase in EDSS, and 0.30(95%CI:0.18,0.43) second increase in 25-FTW. Low acculturation accounted for 9.4% and 11.1% of the effect of nlSDOH on SDMT and EDSS, respectively. Furthermore, each unit increase in nlSDOH was associated with 58%(OR:1.58,95%CI:1.18,2.10) increased odds of severe ambulatory disability (EDSS⩾6).

Conclusion: Neighborhood level disparities exist in MS and explain a large amount of the variability in MS-related disabilities observed in this cohort. Whether these living conditions contribute to delays in care and diagnosis is unknown. Understanding the reasons for these disparities may inform prevention and treatment strategies.

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EP1201

Incidence of COVID-19 after vaccination in people with multiple sclerosis in Argentina: data from the nationwide registry RelevarEM

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Objective: The objective of the study was to evaluate the incidence of COVID-19 after complete vaccination in people with multiple sclerosis (PwMS) included in the Argentinean MS and NMOSD registry (RelevarEM, NCT 03375177).
Methods: cohort study conducted between May 2021 and December 2021. The primary outcome was the appearance of infection during the follow-up time (at least three months after complete vaccination (second dose)). Data was collected through the contact between the treating physician and the patient. Specific information was requested (date, symptoms, need for hospitalization, ventilatory assistance, treatment, and evolution). The contact was made every 30 days during the period of 3 months after the full dose vaccination. A positive COVID-19 case was defined according to the definition established by the Ministry of Health in Argentina. Cumulative incidence was reported by Kaplan Meier survival curves as well as incidence density.
Results: A total of 576 PwMS were included, mean age 45.2 ± 13 years, 432 (75%) RRMS, 403 (70%) were female. The mean and median time of follow-up after the second dose was 91 ± 17 and 94 ± 21 days respectively. Most frequent first and second dose received was Astra-Zeneca vaccine, followed by Sputnik V vaccine. During follow-up a total of 20 COVID-19 cases were observed for a total exposure time of 39557 days. The overall cumulative incidence for the observed period was 3.4% (SE 0.4%) with an overall incidence density of 5 x 10.000 patients/day (95%CI 0.7-12). We observed more cases in woman than men with an incidence density of 6x10.000 patients/day (95%CI 0.9-9) vs. 3x10.000 patients/day (95%CI 0.2-6) respectively, but not significantly different (IRR 1.7 95% CI 0.56-7.37 p= 0.15).
Conclusion: we found an incidence density of breakthrough COVID-19 infection of 5 x 10.000 patients/day (95%CI 0.7-12) after vaccination in Argentina.

Disclosure
Authors declare no potential conflicts of interest regarding this research, authorship and/or publication of this article

EP1202

COVID-19 and the risk of CNS demyelinating diseases: a systematic review

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Background: Viral infections are thought proposed as a possible cause of central nervous system (CNS) demyelinating diseases, including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). During the past two years, CNS demyelinating events associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported, but causality is unclear.
Objective: To investigate the relationship between CNS demyelinating disease development with antecedent and/or concurrent COVID-19 infection.
Methods: A systematic literature review of all publications describing either a new disease onset or relapse of CNS demyelinating diseases (MS, NMOSD, MOGAD) in association with SARS-CoV-2 infection was performed utilizing PRISMA

guidelines. Descriptive statistics were used for data analysis, using a case analysis approach.
Results: Fifty articles were meet inclusion criteria for the study. Most of the reported cases ofNMOSD (n=10., 66.7% of reported cases)and MOGAD (n=12, 92% of reported cases) were of new disease onset, presenting with typical clinical and radiographic features of these conditions, respectively. In contrast, reported MS cases varied amongst newly diagnosed cases (n=11, 13% of reported cases), relapses (n=48, 56.5%) and pseudo-relapses (n=26, 30.5%). Median duration between COVID-19 infection and demyelinating event onset was 9 days (range 0-30 days) in NMOSD, 4 days (range^{-}7-$^{+}$21 days) in MOGAD, and 13.5 days (range^{-}21-$^{+}$180 days) in MS. Most cases received high-dose corticosteroids with a good clinical outcome.
Conclusions: Based upon available literature, the rate of CNS demyelinating events occurring in the setting of preceding or concurrent SARS-CoV-2 infection is relatively low given the prevalence of infection. The clinical outcome of new-onset or relapsing MS, NMOSD or MOGAD associated with antecedent or concurrent infection is mostly favorable. Larger prospective epidemiological studies are needed to better delineate the impact of COVID-19 on CNS demyelinating diseases.

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EP1203

Socioeconomic status of Iranian patients with multiple sclerosis in relation to disease-induced disability

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Background: Socioeconomic status (SES) is believed to alter the course of multiple sclerosis (MS).
Aim: To investigate the SES determinants of Iranian MS patients and their relation to disability and disease progression.
Methods: This population based study conducted of all MS patients in nationwide MS registry of Iran (NMSRI) up to January 8, 2022.
Results: A total of 5153 MS patients were evaluated. The majority of cases were female (74.5%), unemployed (65.1%), married (70.8%), and without an academic degree (53.8%). Of all, 1444 (28%) participants did not own a house. Median family size was four. Only a minority (n = 79, 1.5%), did not have any health insurance coverage. Family history of MS was positive in 926 (18%). Expanded Disability Status Scale (EDSS) was $\geqslant$ 6 in 239 (4.6%) patients. Assistance equipment was used by 371 (7.2%), and rehabilitation by 677 (13.1%).Considering EDSS $\geqslant$ 6 as the outcome measure, gender, age, and MS type were fixed in the multivariate model. Of all socioeconomic determinants, unemployment (OR: 3.75, 95% confidence interval (CI): 2.26 – 6.23) and not being married (OR: 2.60, 95% CI: 1.77 – 3.81) were significantly associated with EDSS $\geqslant$ 6. Time to progression was significantly less in the unemployed group (p value: 0.03). Besides, a significant negative correlation was found between time to progression and age at disease onset (rho: - 0.22, p value $<$ 0.001).
Discussion: Investments in supporting MS patients and their families, financially and socially, could decrease the individual and social burden of the disease.

Disclosure
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All authors declare no conflict of interest.

EP1204

Life and death in multiple sclerosis: 20 years-later reappraisal of a cohort of patients residing in Verona, Italy

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Introduction: Multiple sclerosis (MS) is one of the most disabling diseases affecting young adults, with a severe socio-economic impact. Earlier age at death and increased excess mortality in people with MS (pwMS) have been previously demonstrated, although more recently it has been postulated a rise in survival occurring in the last 20 years.
Objectives and aims: The aim of our study is to assess survival in a cohort of pwMS residing in the town of Verona, Italy, over 20 years.
Methods: We evaluated a cohort of pwMS comprising all the prevalent cases residing in Verona at 31/12/2001. We retrospectively investigated the survival state of each pwMS at 31/12/2021 through the consultation of medical records of the Neurology Units of the two Verona Hospitals – referral centers for MS – to assess if patients were still on follow-up; for those with no records at 31/12/2021, we surveyed the death certificates from Verona municipality to verify death notification and date. We evaluated mean age to death of MS patients compared to the general population of Verona province and mean time from disease onset to death by age and disease course.
Results: Among 270 MS prevalent cases (158 females, F) at 31/12/2001, on 31/12/2021 59 (36 F) patients had died, while 155 pwMS (119 F) were alive and currently undergoing clinical follow-up; 137 of them were still residing in Verona. 10 cases (4F) had been lost at follow-up while for 46 of them the investigation is still ongoing. Mean age at disease onset was 32±11 years for both F and M; mean age at prevalence day was 47±14 years for F and 47±12 years for M. Mean age at death was 68±13 years (67±12 in males (M) and 68±14 in F), as compared with a mean of 81±1 years of the general population of Verona province between 31/12/2001 and 31/12/2021; mean time from disease onset to death was 31±13 years (36±13 M and 28±13 F, $p<0.001$; mean age at MS onset for the dead group: 39±11 for F and 31±13 for M); it was significantly lower in patients with primary progressive MS (27±13 years) than in those with relapsing-remitting or secondary progressive MS (34±13 years, $p<0.001$).
Conclusions: Mean age at death is lower in pwMS compared to the general population as shown in previous studies; we surprisingly observed a lower time from disease onset to death in females than in males, for which further investigation is needed to clarify if the result is attributable only to the different age at onset in the two groups or to other factors.

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Riccardo Orlandi: nothing to disclose
Alberto Gajofatto: nothing to disclose
Francesca Calabria: nothing to disclose

EP1205
Rising prevalence of multiple sclerosis in Tunisia

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Introduction: The epidemiology of multiple sclerosis (MS) has been studied recently in many countries of the Middle East and North Africa (MENA) region showing globally an increased rate. Data on the prevalence of MS in Tunisia come back to more than twenty years ago.
Objectives: Our study aimed to determine the current prevalence of MS in Tunisia
Methods: To estimate the total number of Tunisians with MS residing in Tunisia and in the absence of a national information system to identify all cases of MS, we based on the following established indicators for the year 2019: the number of patients with MS benefiting from the Integral Supported Affections regime in 2019, the number of insured and eligible as of December 31, 2019, and the Tunisian population estimated on July 1, 2019. Referring to data from the National Health Insurance Fund, the number of patients with MS benefiting from the condition fully supported regime was 3,649 and the proportion of insured persons and eligible represented approximately 53.7% of the Tunisian general population estimated at 11,658,341.
Results: The total number of subjects with MS in Tunisia, as of December 31, 2019, was estimated at 6,801. The prevalence of MS in the Tunisian population corresponds to the estimated total number of subjects with MS multiplied by 100,000 and reported to the Tunisian population which is 6,801 x 100,000 / 11,658,341 leading to a prevalence rate of 58.3 per 100,000 inhabitants.
Conclusions: The prevalence of MS has significantly increased in Tunisia over the last twenty years. The current rate showed that MS prevalence tripled compared to the last published one of 20,1 per 100 000 in 2000. It ranks Tunisia in a high prevalence MS zone worldwide. It is near to that recently reported in Lebanon but is still lower than that in the western countries and even in other MENA countries like Kuwait, Qatar and the United Arab Emirates. This new MS prevalence in Tunisia needs to be investigated to conclude about leading factors and should be considered in the future management of healthcare resources.

Disclosure
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EP1206
Cognitive and motor impairment in multiple sclerosis and their relative impact on employment status: Preliminary findings from the north american registry for care and research in multiple sclerosis (NARCRMS)

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Introduction: The North American Registry for Care and Research in MS (NARCRMS) is a longitudinal registry studying the course of MS in the disease-modifying era.
Objectives: Under or unemployment in multiple sclerosis (MS) is caused by multiple impairments, among them cognition and motor impairment.In this study we examine the relative roles of cognition and motor function in under or unemployment in patients with MS.
Methods: Cognitive and motor impairment were examined in a subgroup of patients enrolled into NARCRMS at the enrollment visit.Their employment status was recorded and if employed part-time, patients were queried if their status was based on their self-perceived impairments due to MS.
Results: Complete data was available on 351 subjects where cognition was examined by the 3-second Paced Auditory Sequential Addition Test (PASAT 3).Patients ranged from 20 to 64 years (median 39 years) and M:F ratio of 1:2.5.The median extended disability status scale (EDSS) was 1.50, mean dominant 9 hole-peg test (9HPT) 23.07 seconds, 25-foot timed walk (25FTW) 5.82 seconds, and fatigue was reported by 63.41%. Approximately a third of the subjects were unemployed and 15% reported part-time employment and 44% indicated that the impairments from MS precluded full-time employment.Patients were grouped into quartiles based on the PASAT scores from the highest functioning subjects in the 1st quartile to the lowest performers in the 4th. Significant interquartile differences were not observed for EDSS or motor function.Although motor function approached but did not meet significance, employment status was statistically significant favoring the higher functioning subjects (Q1 v. Q4, p=0.0375).
Conclusions: Preliminary studies from this limited data set reaffirms that under or unemployment in those diagnosed with MS correlated best with cognitive rather than motor impairment in this cohort of subjects with relatively early MS.

Disclosure
Dr. Kottil Rammohan received honoraria for consultation and adboards from Biogen, EMD Serono, Genzyme, Genentech, Novartis, Alexion, Horizon and TG Therapeutics; he also received grants from Biogen, Genzyme, Genentech, Novartis, Alexion, and TG Therapeutics.
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Dr. Ramon Flores Gonzalez: nothing to disclose.

EP1207

Significant negative associations of stressful life events with mental quality of life in an international sample of people with MS

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Background: There is increasing evidence for a role for stress and stressful life events (SLE) in the progression of MS. The impacts of SLEs on quality of life (QoL) is understudied.
Objectives: To assess the cross-sectional relationship of SLE number and load and individual SLEs with QoL in an international cohort of people with MS.
Methods: Data derived from the 7.5-year review of the Health Outcomes and Lifestyle in a Sample of people with Multiple sclerosis (HOLISM) study. Participants queried for 16 SLEs in the preceding 12 months assessed by Holmes-Rahe Social Readjustment Scale. SLE number summated and weighted SLEs summated to estimate SLE load. QoL assessed by MSQOL-54, estimating physical and mental QoL composite scores, as well as QoL subdomains. Associations of SLEs with QoL assessed by linear regression, adjusted for age, sex, MS type, disability, clinically significant fatigue, depression, comorbidity number, antidepressant medication use, and ongoing symptoms due to recent relapse.
Results: 724 participants contributed to physical QoL analyses and 891 to mental QoL analyses. Median SLE number=2 and median physical and mental QoL=68.87 and 78.21. SLE number and load associated with lower physical QoL but this did not persist on further adjustment. SLE number and load associated with significantly lower mental QoL, robust to adjustment: those with 2+ SLE number had 3.2% lower QoL (ptrend=0.048) and in the top quartile of SLE load with 4.7% lower QoL (ptrend=0.016). Of individual SLEs, close family deaths, participant injury/illness, participant assault, friend/family assault, and loss of employment were associated with significantly lower mental QoL.
Conclusion: SLE number and load, as well as select individual SLEs, showed appreciable and robust negative effects on mental QoL in this international sample of people with MS. These results may suggest efforts to aid coping with stress and SLEs may help improve mental QoL in people with MS.

Disclosure
Jeanette Reece has no conflicts to disclose.
Maggie Yu has no conflicts to disclose.
Sandra Neate is the author of Overcoming Multiple Sclerosis Handbook: Roadmap to Good Health and has previously received remuneration from facilitation of Overcoming MS residential workshops.
Nupur Nag has no conflicts to disclose.
Steve Simpson-Yap has no conflicts to disclose.

EP1208

Prevalence and factors associated with COVID-19 vaccination in people with multiple sclerosis compared to the general population in Croatia

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Background: The aim of this study was to determine the pooled prevalence of COVID-19 vaccination among people with multiple sclerosis (pwMS) compared to the general population in Croatia.
Methods: Data from all pwMS entered in the MS Base register until24.03.2022 were extracted including age, sex, MS phenotype, disease-modifying therapy (DMT), COVID-19 vaccine, and date of vaccination (1st, 2ndand/or 3rddose). Data on the general population of Croatia were obtained from the vaccination register of the Croatian Institute of Public Health.
Results: 464 pwMS (317 females, with a median age of 38.1 years, disease duration of 6.1 years, EDSS 1.5) were included in the analysis. 386 (83.2%) pwMS had relapsing-remitting, 26 (5.6%) primary progressive, 19 (4.1%) secondary progressive phenotypes, and 16 (3.4%) clinically isolated syndrome. Fifty-six (12.1%) pwMS were treatment naïve, 21 (4.5%) were not on DMT at the moment of the last visit, 134 (28.9%) were on injectable DMTs, 84 (18.1%) on 1stline oral DMTs, and 169 (36.4%) were on high efficacy DMTs. 295 (63.6%) pwMS were fully COVID-19 vaccinated compared to 59.7% of the general population (p=0.089). However, in the age groups, 20-24 and 35-39 significantly more pwMS received 2 doses compared to the general population (p=0.001 and p=0.03, respectively). Vaccinated pwMS were older (40.5 vs 37.6 years, p=0.01),had higher EDSS (2.0 vs 1.0, p=0.025), and longer disease duration (6.39 vs 5.35 years, p=0.02), were more likely to have progressive disease course (p=0.049) and on high efficacy DMTs (p=0.045) compared to unvaccinated pwMS.In a multivariable logistic regression model, there were no predictors for COVID-19 vaccination in pwMS.
Conclusion: There was a similar prevalence of vaccinated individuals in pwMS and the general population. However, in younger age groups significantly more pwMS were vaccinated when compared to the general population.

Disclosure
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EP1209

Russian multiple sclerosis e-registry: preliminary results of a four-year study

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Introduction: Large-scale epidemiology studies are a promising approach to improving multiple sclerosis (MS) diagnosis, as well as defining treatment needs in various geographic regions. In 2017, an electronic registry of adult patients with MS who live in the Russian Federation was initiated. We present preliminary results of a four-year experience of maintaining a local e-Registry of patients with MS.
Objectives: to identify key epidemiological indicators of the Russian population of MS patients: prevalence of MS clinical forms, features of disease course, initial diagnosis, time to confirmed diagnosis, use of disease-modifying therapies (DMTs), and switching between DMTs.
Aims: the purpose of the study was to analyse a set of data derived from the local MS e-Registry in order to identify practical issues of diagnosis and treatment of MS in Russia.
Methods: The Russian MS e-Registry is a prospective multicenter non-interventional study, with retrospective analysis of available medical records at the time of the patient's enrollment. An individual electronic registration form was created in order to collect demographic, clinical, laboratory, and neuroimaging data.
Results: Between September 2017 and May 2022, data on 5201 patients aged from 18 to 78 were collected. Mean age of MS patients was 37.7 (31.3; 45.5) years; 66.2% (3443) were female. Mean age at symptom onset was 29 (23; 36) years. Relapsing-remitting MS (RRMS) was observed in 83% (4317) of all registered cases, secondary progressive MS (SPMS) — in 12% (614) of cases (active SPMS – in 4.8% (250)), primary progressive MS – in 5% (270) of all patients. Mean time to diagnosis was 12 (1; 41) months. The most prominent diagnostic delay (40 (7; 97) months) among all disease forms was observed in patients with initial diagnosis of SPMS. In 38.1% of all cases, initial diagnosis was not a neurological condition, since patients were mostly addressed to general practitioners (GPs) and other clinicians (not specializing in neurology). Mean time between diagnosis of MS and DMTs initiation was 4 (1; 25) months.
Conclusions: Our findings suggest that diagnosis and treatment of MS in Russia has several major issues, such as delayed diagnosis and late initiation of DMTs that contribute to earlier transition of RRMS to a secondary progressive course. Raising GPs awareness of MS manifestations may result in a decrease in the average diagnostic delay in MS in Russia.

Disclosure
Anna Abramova: has received honoraria for lectures and speaking in the past 3 years for Roche.
Ivan Kochergin: has received honoraria for lectures and speaking in the past 3 years for Roche, Novartis.
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Inna Smagina: nothing to disclose.

EP1210

Multiple sclerosis in the campania region (South Italy) 2015-2020: incidence algorithm validation

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Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system, whose onset is usually in young adults. More than 2.8 million people live with MS around the globe, with a median incidence rate of 2.1 per 10,000. However, spatial and temporal variations in MS incidence and prevalence are expected as a consequence of different factors.
We aim to develop and validate an algorithm relying on routinely-collected healthcare datasets, to identify multiple sclerosis (MS) incident cases in the Campania Region (South Italy) and estimate spatial trends in relative MS risks. We included MS patients living in the Campania Region from 2015 to 2020. To identify incident cases, we merged this cohort to the actual date of diagnosis from a clinical registry and validated the minimum interval from the starting point of our study (January 1, 2015) to the first MS registration in administrative datasets. We tested four variants of the algorithm, which differed in the length of the time interval between the study baseline and index date (12,18, 24 and 36 months) and we assessed the discrimination power by calculating sensitivity, specificity, positive and negative predictive values, as well as area under the curve (AUC). To explore the geographical distribution of MS relative risk in the Campania region, we adopted the Bayesian approach also including the deprivation index as a covariate in the estimation model. We used the capture-recapture method to estimate the proportion of undetected cases.
The study included 7,431 people with MS in the Campania region (46.11 ±13.55 years of age; 64.10% females). The 12-month interval algorithm detected included 2,150 incident MS cases, with 74.4% sensitivity (95%CI =64.1%, 85.9%), 95.3% specificity (95%CI =90.7%, 99.8%), 0.85 ROC area (95%CI = 82.3%, 87.8%).The cumulative incidence obtained was 36.68 (95%CI =35.15, 38.26) per 100,000 from 2016 to 2020. The annual incidence of MS for Campania Region was 7.34 (95%CI =7.03, 7.65) per 100,000 people-year. The geographical distribution of MS relative risk showed a mountain-to-seadecreasing gradient. The number of expected MS cases was 11% higher than detected cases.
We have validated a case-finding algorithm based on administrative data to estimate the up-to-date incidence of MS, and its spatial/temporal. This algorithm will be used in future studies to evaluate changes in MS incidence with different risk factors.

Disclosure
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EP1211

impact of the COVID-19 pandemic on personal networks and neurological outcomes of people with multiple sclerosis: a case-control cross-sectional and longitudinal analysis

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Introduction: Personal social networks impact the quality of life of people living with multiple sclerosis (pwMS).
Objective / Aims: To evaluate the dynamic associations between personal network features and neurological function in pwMS and control participants during the COVID-19 pandemic and compare with the pre-pandemic period.
Methods: We first analyzed data collected from 8 cohorts of pwMS and control participants during the COVID-19 pandemic from March-December 2020. We then leveraged data collected between 2017-2019 in 3 of the 8 cohorts for longitudinal comparison. Participants completed a personal network questionnaire, which quantified the structure and composition of each person's personal network, including the health behaviors of network

members. Neurological disability was quantified by three interrelated patient-reported outcomes: Patient Determined Disease Steps (PDDS), Multiple Sclerosis Rating Scale – Revised (MSRS-R), and Patient Reported Outcomes Measurement Information System (PROMIS)-Physical Function. We identified the network features associated with neurologic disability using paired t-tests and covariate-adjusted regressions.

Results: In the cross-sectional analysis of the pandemic data from 1130 pwMS and 1250 control participants, percentage of network members perceived to have a negative health influence was associated with greater neurological symptom burden in pwMS (MSRS-R: Beta[95% CI]=2.181[1.082, 3.279], $p<.001$) and worse physical function in control participants (PROMIS-Physical Function: Beta[95% CI]=-5.707[-7.405, -4.010], $p<.001$). In the longitudinal analysis of 230 pwMS and 136 control participants, the percentage of people contacted weekly or less ($p<.001$) decreased during the COVID-19 pandemic for both pwMS (0.30 ± 0.26 v. 0.19 ± 0.22) and controls (0.23 ± 0.25 v. 0.15 ± 0.21) when compared to the pre-pandemic period. PwMS further experienced a greater reduction in network size ($p<.001$), increase in constraint (a measure of close ties of the network, $p<.001$) and decrease in maximum degree (highest number of ties of a network member, $p<.001$) than controls during the COVID-19 pandemic. These changes in network features were not associated with worsening neurological disability.

Conclusions: Our findings suggest that negative health influences in personal networks are associated with worse disability in all participants and COVID-19 pandemic led to contraction of personal networks to a greater extent for pwMS than controls.

Disclosure

Dr. Claire Riley has received compensation for consulting or advisory services from EMD Serono, TG Therapeutics, Genentech, Novartis, Janssen Global, Bristol Myers Squibb, Biogen, and TRV Cell Therapy. Dr. Amit Bar-Or participated as a speaker in meetings sponsored by/and received consultant fees and/or grant support from: Accure, AtaraBiotherapeutics, Biogen, BMS/Celgene/Receptos, GlaxoSmithKline, Gossamer, Janssen/Actelion, Medimmune, Merck/EMD Serono, Novartis, Roche/Genentech, Sanofi-Genzyme. Dr. Philip De Jager serves as a consultant for Roche and Biogen. Dr. Zongqi Xia received research support from the National Institute of Health, the Department of Defense, and Octave Biosciences. Dr. Xia has served on the scientific advisory board for Genentech/Roche.

EP1212

Anti-SARS-CoV-2 vaccination immune response in MS patients: interim results of a multicentre, prospective cohort study

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Introduction: Understanding the impact of disease-modifying drugs (DMDs) on vaccine-mediated immunity and knowledge of a patient's immunisation status are essential for balancing medical decisions between beneficial multiple sclerosis (MS) therapy and protection against SARS-CoV-2.

Methods: This ongoing study investigates the immune response to authorised SARS-CoV-2 vaccines in MS patients (planned sample size: n=200) by collecting clinical and serological data at 10 centres across Germany. Eligible patients include those with planned vaccination, first dose given, vaccination completed within the last 6 weeks, or vaccination completed >6 weeks ago and booster dose planned within the next 90 days. In addition, patients must have recovered from any previous COVID-19 infection. The primary endpoint is the number (%) of patients with immune response approx. 30 days after their last vaccination (baseline for SARS-CoV-2 S1-specific IgG after booster dose: serum level ⩾3 months after complete vaccination). The persistence of humoral immunity after initial and booster doses is followed over time.

Results: At data cut-off (12 April 2022), 156 patients (66.0% female, age: 41.7 ± 10.7 yrs) had been enrolled of whom 117 (75.0%) had received 3 vaccine doses, 32 (20.5%) 2 doses, 3 (1,9%) 1 dose, and 1 (0.6%) 4 doses. Most patients were on MS DMDs at inclusion (136/156, 87.2%). After the first booster, 54/82 patients (65.9%) showed IgG-S1 response (increase >100 BAU/mL vs baseline). Adequate immune response was less frequent among patients treated with anti-CD20 agents or S1P-R modulators (7/32, 21.9%) compared to untreated patients or those treated with other DMDs (47/50, 94.0%). Tozinameran (Comirnaty) was the most frequently used vaccine (367/422 vaccinations, 87.0%); of the triple-vaccinated patients, 83 (70.9%) had received 3 tozinameran doses and 22 (18.8%) 2 tozinameran doses with an elasomeran (Spikevax) booster (other vaccine combinations: <5%). Patient-reported vaccine tolerability was 'as expected' or 'better than expected' for 348/422 (82.5%) vaccinations. Tolerability of the second dose was more often rated as 'worse than expected' than the first dose (11.3% vs 7.2%). Eight patients developed COVID-19 during the study, and 2 patients experienced an MS relapse.

Conclusions: The preliminary results of this ongoing study show that the immune response to SARS-CoV-2 vaccination is

generally good in MS patients but may be impaired under treatment with certain DMDs.

Disclosure

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EP1213

Multiple sclerosis incidence in Latin America and the Caribbean (EMELAC Project) - Uruguayan results

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Introduction: The worldwide incidence of multiple sclerosis (MS) is estimated to be 0.5-10 cases per 100,000 person-years and is probably increasing. Incidence in Uruguay was estimated to be 1.2 cases per 100,000 person-years in a 2015 study.

Objectives/Aims: Following the EMELAC protocol (MS in Latin America and Caribbean), we conducted an observational, prospective, population based study to determine MS incidence in Uruguay.
Methods: The population studied included people older than 18 years old, living in Uruguay between 7-1-2019 and 6-30-2021. The diagnosis was based on the 2017 McDonald criteria.
Multiple data sources were employed. All possible cases of MS were reviewed by the research team. Cases with diagnostic uncertainty were re-reviewed by an outside co-author (DO). Capture-recapture method was used to estimate incidence and exhaustivity.
Results: 155 new MS cases were confirmed after review, of which 111 were females (71.6%). The sex ratio was 2.5:1 female to male. Age range was 18 to 62 with a median of 35 and an interquartile range of 27-43.25. 19 patients (12.25%) were diagnosed with late onset multiple sclerosis (LOMS).
The crude incidence rate was 2.89 cases per 100,000 person-years, 3.95 in females and 1.72 in males. Incidence rate estimated using capture-recapture method was 3.18 (CI 95% 3.02-3.34). The highest incidence was observed in the 25-29 years old group (5.74 cases per 100,000 person-years). 113 patients were reported by their neurologist and 99 patients were reported by more than one data source.
Discussion: According to MS Atlas, Uruguay has a low incidence rate (2.0-3.99), even though it is one of the highest in Latin America. Our country aligns with the global trend of increasing incidence when comparing to the 2015 study, though different methodological approaches were used.
Age and gender distribution were similar to other studies, with a high incidence of patients with LOMS. The capture-recapture method suggests the exhaustivity of our investigation.

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EP1214

Comorbidities and multiple sclerosis: prevalence and relationship to disease characteristics in a cohort of 1023 patients with multiple sclerosis

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Introduction: Several comorbidities are associated with multiple sclerosis (MS). Moreover, comorbidities modify clinical presentation of MS, increase disability and have implications for treatment choice, adherence, and outcome.

Aims: To establish a detailed prevalence of comorbidities in a French monocentric MS cohort and to define clinical profiles of patients with MS (PwMS) depending on comorbidities.
Methods: PwMS were identified since 1.01.2016 to 30.06.2019 from computerized medical records. A predefined list and a non-selective search collected comorbidities using an artificial intelligence (AI) tool to read medical correspondence. Descriptive analysis, logistic regressions and multiple component analysis (MCA) were performed. Then an Ascending Hierarchical Classification (AHC) was implemented to determine the optimal number of PwMS groups on a dendogram.
Results: 1023 PwMS were included (mean age 52.3 yrs.; median EDSS: 5.5). The 3 most frequent comorbidities are urinary (49.8%), orthopedic (32.6%) and cardiovascular (25.5%) diseases.
MCA can defined four classes:
Class1 >63 years, EDSS⩾ 6, MS duration >17 yrs., progressive form without disease modifying therapy (DMT) presenting urinary (50%) and locomotor (30%) diseases but few cardiovascular, metabolic, or psycho-emotional diseases.
Class2:⩽ 43 years, EDSS ⩽ 3.5, remittent-recurrent MS (RRMS) treated with immunosuppressive DMT (50%) presenting few comorbidities (< 14%).
Class3: > 53 years, EDSS ⩾ 6, progressive form (50%), MS duration > 17 years and no DMT presenting cardiovascular, metabolic, and urinary diseases (>50%) and locomotor and psycho-emotional diseases (50%).
Class4: < 53 years, more women, EDSS ⩽ 5.5, RRMS, MS duration ⩽ 17 years, treated with immunosuppressive DMT presenting urinary (50%), locomotor (38%) and psycho-emotional diseases (22%).
Classes constituted by the AHC highlight a graduation of the disease state related to the associated comorbidities: class2 < class4 < class1 < class3.
Conclusions: A.I strategy highlights an exhaustive view of comorbidities. The MCA and HAC method classify PwMS in 4 groups according comorbidities and MS characteristics.

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Clinical aspects of MS - MS and gender

EP1215
Menstrual cycle, MS symptom fluctuations, and impact of hormonal contraceptives: a pilot study

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Introduction: In clinical practice, patients with multiple sclerosis (MS) report fluctuation of symptom severity over the course of the menstrual cycles. Oral contraceptives (OCs) stabilize hormonal fluctuations, particularly continuous contraceptives (i.e. 11+ weeks of continuous exogenous hormones, followed by one week of placebo).
Objectives: We aimed to prospectively capture neurologic and generalized symptoms over the course of successive menstrual cycles to evaluate (1) the effect of menstrual cycle phases on symptoms and (2) the impact of contraceptive mechanisms on day-to-day symptoms.
Methods: In this two-center (UCSF and Yale) pilot prospective observational cohort study, we collected menstrual cycle information and weekly symptom-related surveys (SymptoMS, MSQOL-54, MFIS, PHQ9, PSS10) for up to 6 months from cycling women aged 18-45 years with a diagnosis of MS. Contraceptive use was categorized into: cyclical OC, continuous OC, hormonal intrauterine device (IUD), or mechanical/no birth control.
Results: Altogether, 45 women provided >4 weeks of data and were analyzed (from 69 enrolled). Mean (SD) age was 35.0 (0.9) years, median (IQR) EDSS was 1.5 (1-2), and mean SymptoMS (SD) score was 10.4 (9.6).
When we compared menstrual cycle phases, patients on no OC reported worse quality of life (MSQOL-54 mental health component p=0.000; MSQOL-54 physical health component p=0.053) and more fatigue (MFIS) (p=0.038) in the perimenstrual timepoint as compared to the luteal phase.
Women on continuous OCs reported numerically less severe symptoms across most domains when compared to women on either cyclic OC or no OCs; these were significant for PHQ9 (p=0.014 and 0.020, respectively) and Daily Hassles survey (p=0.023 and 0.072, respectively).
Conclusions: In this pilot study, we found some evidence of worse neurologic and systemic symptoms in the perimenstrual timepoint for MS patients. There was a trend for improved symptoms in patients on continuous OCs. The study is limited by study retention; 35.7% of participants provided less than 4 weeks of data. Future strategies could include patient incentivization or large enrollment for shorter timeframes (1-2 cycles).

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EP1216

Free testosterone levels in untreated men with multiple sclerosis are not associated with relapses or disability status

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Background: Studies of men with multiple sclerosis (MS) and the animal models of experimental autoimmune encephalomyelitis have indicated that testosterone has a neuroprotective and anti-inflammatory effect, however, results have been ambiguous.
Objectives: We aimed to investigate if disease activity or disability status are associated with levels of free testosterone in more than 200 untreated Danish men with MS.
Methods: Testosterone and sex-hormone binding globulin (SHBG) were measured by a Cobas 8000 and neurofilament light (NfL) by single molecule array (SiMoA) in serum samples from 203 MS patients taken before their first disease modifying treatment with interferon-beta. The clinical disease activity measures, expanded disability status scale at baseline (BL) and last follow-up (LF) and relapses 2 years prior to treatment and number of relapses 2 years after treatment start, were available from all MS patients. Age related MS severity (ARMSS) and MSSS scores were calculated at BL and LF and correlated with testosterone and NfL. Number of relapses before and after treatment were investigated by Poisson or negative binomial regression analyses for association with testosterone and NfL adjusting for age in the analysis. Free testosterone levels were calculated using SHBG and an age corrected NfL-ratio was calculated. Questionnaire data on smoking status and body mass index (BMI) was available from 125 men.
Results: Free testosterone did not correlate with ARMSS or MSSS at BL (r=-0.037, p=0.61; r=-0.080, p=0.37) or LF (r=-0.065, p=0.36; r=-0.075, p=0.29) or the age-corrected NfL concentrations (r=0.047, p=0.51). Free testosterone levels were not associated with smoking or BMI but showed a significant negative association with age. No significant associations were seen between number of relapses 2 years prior and after treatment and free testosterone levels (incidence rate ratio (IRR)=0.54, p=0.30; IRR=0.93, p=0.96), respectively, or with the NfL-ratio. Dichotomic analyses of patients with high (84%) compared with low (16%) levels of testosterone did not show significant associations with relapses or disability status.
Conclusions: We did not find testosterone levels to be associated with inflammation or neurodegeneration as measured by number of relapses and disability measures in a larger study of Danish men with MS. This could indicate that testosterone predominately acts as a MS susceptibility risk factor, as supported by several studies.

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EP1217

Incongruence between objective measure of cardiorespiratory fitness and subjective reports of physical activity especially in men with multiple sclerosis

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Introduction: Cardiorespiratory fitness is a significant health and performance predictor in people with multiple sclerosis (PwMS), primarily influenced by physical activity.
Objectives/Aims: Research examining gender-related issues in MS is increasing, but very few studies explored gender differences in fitness and physical activity.This study aimed to investigate the gender differences in fitness and the relationship between fitness and self-reported physical activity in PwMS.
Methods: This cross-sectional sample included 107 PwMS (mean age 47.24 ± 10.19 years) (77 women; 72%) recruited from MS clinics. Fitness was measured as maximal oxygen uptake (VO_2max) during a graded exercise test using a whole-body recumbent stepper. VO_2max values were converted to percentile ranks accounting for age and sex. Moderate-vigorous PA (MVPA) was assessed as the amount of time spent engaging in any activity ⩾3 metabolic equivalents (MET) during the previous day, and the MET-minutes were calculated by multiplying the activity MET value by the duration of the activity in minutes.
Results: Two-thirds of both genders were below the 50th percentile for VO_2max, suggesting poor to fair fitness levels. The time spent on MVPA was similar between the sexes, while the mean MVPA MET-minutes (781.82 ± 752.01) in men were

significantly higher than in women (588.30 ± 520.63; p=0.039). Men reported higher intensity activities than women. A positive relationship between MVPA and VO_2max values was found among females (r=0.279; p=0.014) but not among males, suggesting that males overestimated their MVPA. While MET-minutes were not associated with disability, VO_2max values were negatively correlated with disability in both genders.
Conclusions: Although reported MVPA values were well above recommended guidelines (>450 METs), both men and women had low levels of objectively measured fitness. Subjective physical activity correlated with aerobic fitness only in females. Our findings suggest that PwMS, especially men overestimate their level of physical activity.

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Sexual dysfunction in premenopausal Spanish women with relapsing multiple sclerosis: a multicenter study

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Introduction: Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system that affects young people, is more frequent in women and, in them, a high prevalence of sexual dysfunction has been observed. Patient-reported outcomes (PROs) are gaining increased relevance in detection of patients' needs.
Objectives: This project aimed to assess sexual dysfunction in Spanish premenopausal women with relapsing MS with the purpose of assessing the degree of sexual dysfunction and designing a personalized therapeutic strategy.
Methods: Multicenter observational clinical study in a transversal cohort of 133 premenopausal women with relapsing MS. All participants completed the Spanish version of the Female Sexual Function Index (FSFI) and clinical-demographic data was collected. Data analysis was performed using non-parametric tests to compare distributions (U Mann Whitney) or correlate quantitative variables (Spearman test). R software was used for analysis.
Results: No statistically significant clinical or demographic differences were observed between centers. Median age in the cohort was 39 years old (32.5 – 42) and disability measured as EDSS was 1.75 (1 – 2.5).The median FSFI score in our cohort of women with relapsing MS was 28 (21-32). Using the published threshold value (26.55), 66% of the women presented sexual dysfunction. The most affected spheres were desire and arousal, and the least, pain. The clinical-demographic data that had a negative influence in FSFI scores were coexisting sphincter symptoms (P = 0.034) and the use of psychoactive drugs to treat MS-related symptoms (P = 0.0018). Women with active profession and stable partner (>10 years) presented better scores (P = 0.0003; P = 0.007). FSFI scores did not correlate with disease duration but did correlate with neurologic disability at time of completion of the questionnaire (Rho = -0.329; P = 0.00136).
Conclusions: Premenopausal women with MS frequently present sexual dysfunction, especially in areas related to desire and arousal. Sexual dysfunction was associated with the degree of neurological disability, the use of symptomatic medications, and the presence of sphincter sequelae.

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EP1219

A pilot study on sex hormones and cognition in men with MS

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Introduction: The presence of sexual dysfunction, adding to physical problems in male patients in early adulthood, further exacerbates the adverse impression of Multiple sclerosis (MS) on quality of life.
Aims: The goal of our study is to evaluate the relationship between sex hormons, serum antimullerian hormone (AMH) values, spermiogram characteristics and disease severity, sexual dysfunction, cognition in male MS patients.
Methods: Twenty-eight MS patients and 14 age- and education-matched healthy controls were included in the study. To assess the cognitive status; California Verbal Learning Test (CVLTII), Symbol Digit Modalities Test (SDMT), Revised Brief Visuospatial

Memory Test (BVMT-R), trail-making test (TMT) and to evaluate sexual functions; male sexuel healt questinore (MSHQ) and international index of erectile function (IIEF) scales were used. Serum AMH level, FSH, LH and total testosterone levels were evaluated.

Results: Serum testosterone levels were significantly lower in the MS group than in the healthy group (4.28 ± 1.20 and 4.50 ± 2.24, respectively; $p = 0.012$). Sexual functions were evaluated using the MSHQ and IIEF, and the MSHQ-ejaculation function scores were statistically significantly lower in the patient group than in the control group ($p = 0.014$). Erectile function was assessed using the IIEF. ED was detected in 11 (39%) patients, and four patients could not provide semen analysis specimens due to severe ED. BVMT and CVLT scores were statistically significantly lower in the ED group than in non-ED group, while TMT times were significantly longer ($p = 0.008$, $p = 0.008$, and $p = 0.026$).

Concluisons: The importance of sex hormones in the course of MS has been demonstrated by both clinical scales and cognitive tests. In this pilot study investigating sperm parameters in individuals with MS and investigating the role of AMH in men with MS, the relationship between MS and sex hormones was evaluated as remarkable.

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