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PEER-REVIEWED CONFERENCE REPORT

Risk of COVID-19 Not Increased in MS

People with MS are not more susceptible to COVID-19 infection than others. Age and EDSS are risk factors of severe COVID-19. Anti-CD20 DMTs seem associated with worse COVID-19 outcomes.

read more on PAGE 3

Biomarkers

Abundance of *Blautia* gut microbiota is associated with risk of relapse in paediatric-onset MS. sNfL may qualify as biomarker for disease activity during pregnancy. MWI can offer an *in vivo* biomarker for cognition.

read more on PAGE 5

Novel Treatment Directions

BTK inhibitors may suppress microglia-driven neuroinflammation. The RXR agonist bexarotene promotes remyelination. Masitinib may be a treatment option for progressive MS. Anti-MOSPD2 mAbs hold potential in all MS stages.

read more on PAGE 16

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Contents

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Letter from the Editor

Prof. Hans-Peter Hartung

Dear colleagues,

Scientists, physicians, healthcare professionals were eagerly looking forward to the joint ACTRIMS/ECTRIMS meeting held every third year, scheduled to take place in Washington DC in September. The organisers met the challenges of putting together the first virtual ACTRIMS/ECTRIMS meeting with some 45,000 'digital attendants'.

The extensive teaching and scientific program covered all aspects of MS research, treatment, and care. New insights into the pathobiology, particularly of progressive MS, epidemiological aspects and lifestyle risk factors, MR and PET imaging, newer outcome measures, digital monitoring devices, data mining of trial extension studies, large scale registries, and experimental therapeutics were presented. The comprehensive trials of various Bruton's tyrosine kinase inhibitors modulating B cell and microglial functions were discussed. Noteworthy was the positive outcome of the study using the tyrosine kinase inhibitor masitinib.

Eagerly awaited data from national and international registries including the MS Data Alliance on Covid-19 and MS were presented and showed concurrently a higher frequency and severity of Covid-19 infections in people with MS undergoing B cell depleting treatments. Conversely, interferon-β-treated patients contracted Covid-19 less frequently.

Research into cause, pathomechanisms, phenotypes, and treatments of related autoimmune CNS disorders (NMOSD, MOGAD) was also discussed.

Despite the *ad hoc* emerging challenges to completely transform a real into a virtual meeting, this joint conference was yet again a great success in the series of joint ACTRIMS/ECTRIMS conferences.

Hans-Peter Hartung

Biography

Prof. Hartung has been chair of the Department of Neurology at Heinrich-Heine University Düsseldorf since 2001. He was also appointed director of the Center for Neurology and Neuropsychiatry in 2012 and Medical Director of the Department of Conservative Medicine.
Prof. Hartung received his undergraduate training at the Universities of Düsseldorf, Glasgow, Oxford, and London. After graduating *magna cum laude* he served an immunology fellowship at the University of Mainz. His clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies.
He has been involved as member of the Steering Committee in numerous international multi-centre therapeutic phase 2 and 3 trials in Multiple Sclerosis, Guillain-Barré Syndrome, and chronic inflammatory demyelinating polyneuropathy.
He is former President of ECTRIMS and is a Fellow of the American Academy of Neurology, Fellow and general assembly member of the EAN, has been chair/member of the management group of the EAN scientific panels on general neurology and multiple sclerosis, amongst others. He is/was also member of the Editorial Board of a number of international journals.

Conflict of Interest Statement:
Hans-Peter Hartung has received fees for consulting, speaking, and serving on steering committees from Bayer Healthcare, Biogen, GeNeuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi Genzyme, CSL Behring, Octapharma, Teva, TG Therapeutics, and Viela Bio, with approval by the Rector of Heinrich-Heine University.

COVID-19 and MS

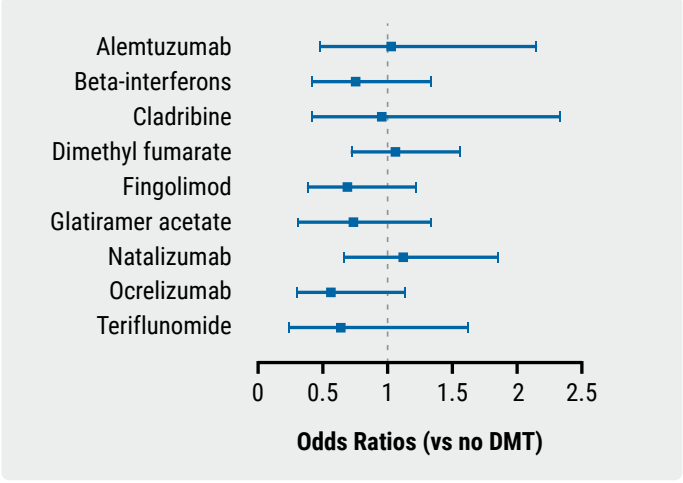
Risk of COVID-19 not increased in MS patients

Results of the largest community-based study of COVID-19 in MS worldwide suggest that people with MS are not more susceptible to SARS-CoV-2 infection than the UK general population [1]. During lockdown, with strict physical distancing measures, disease-modifying treatment (DMT) use or physical disability did not increase the likelihood of contracting COVID-19 nor affected recovery from COVID-19.

Participants of the United Kingdom MS Register (UKMSR) were asked to answer a COVID-19-related survey at admission and a follow-up survey every 2 weeks, depending on whether they reported COVID-19. The mean age of the 5,309 participants was 52.4 years, 76.1% were female. The overall incidence of self-diagnosed COVID-19 in this cohort was 535 (10.1%). In a time when testing facilities were still very limited, 75 of these 535 COVID-19 cases were confirmed by RT-PCR test. The COVID-19 incidence in this cohort peaked during the second week after lockdown started on 23 March 2020 (13.2%) and dropped to 3.5% in the 10th week. Almost half of the MS patients (47%) went into self-isolation during lockdown (23 March–23 June 2020).

The strongest predictor for self-isolation was higher web-based EDSS score (OR 1.389; 95% CI 1.333-1.447). Other predictors were having progressive MS and using monoclonal antibodies or fingolimod as DMT. Older age (OR 0.969; 95% CI 0.957–0.982) and having progressive MS (OR 0.595, 95% CI 0.422–0.838) lowered the risk of COVID-19. This was not surprising, as these populations were more likely to self-isolate. MS duration nor physical disability altered the risk of contracting COVID-19. A multi-variate analysis is required to more accurately predict clinical and demographic risk factors. There was no DMT that was associated with an elevated risk of COVID-19 (see Figure). Of 336 COVID-19 patients of whom data on disease course was available, 249 (74.1%) recovered. The preliminary findings of this study did not show an association between faster recovery and MS-related factors, including EDSS score or DMT use.

Figure: Odds ratios of contracting COVID-19 while on DMT versus no DMT [1]



1. Garjani A, et al. COVID-19 in people with MS: A large community-based study of the UK MS Register. MSVirtual 2020, Abstract SS02.01.

Age and EDSS are risk factors for severe COVID-19

In an observational French cohort study, EDSS and age were independent risk factors for severe COVID-19, while immunomodulating disease-modifying treatment (DMT) was independently associated with lower COVID-19 severity [1]. There was no association between immunosuppressive therapies and severity of COVID-19.

The study cohort (COVISEP registry) that was analysed included 405 MS patients with confirmed or highly suspected SARS-CoV-2 infection between 1 March 2020 and 14 July 2020. Included were patients who met at least one of the following criteria:

- biologically confirmed COVID-19 diagnosis based on SARS-CoV-2 RT-PCR positivity;
- typical thoracic CT abnormalities (ground-glass opacities) in epidemic areas;
- sudden-onset anosmia or ageusia in the absence of rhinitis or nasal obstruction; or
- typical symptoms (triad associating cough, fever, asthenia) in the epidemic zone of COVID-19.

Mean age was 44.7 years, mean MS duration was 13.4 years, and 293 patients (72%) were female. Median EDSS was 2.0

(range 0.0-9.5) and 326 patients (80.5%) used a disease-modifying treatment (DMT). COVID-19 severity was assessed on a 7-point ordinal scale, ranging from 1 (not hospitalised, no limitations on activities) to 7 (death). Cut-off score was at 3 (hospitalised, not requiring supplemental oxygen). The presented results were a follow-up on previously published results in JAMA Neurology [2].

Of 405 participants, 78 (19.3%) had a COVID-19 severity score ≥3 and 12 patients (3.0%) died from COVID-19. Most of the very severe COVID-19 patients did not use any DMT. The percentage of patients with a COVID-19 severity score ≥3 in patients with and without a DMT was 14.4% versus 39.2% (P<0.001). Independent risk factors for COVID-19 severity score ≥3 were higher age (OR 1.8 for 10 years) and higher EDSS (OR 4.5 for EDSS ≥6). Obesity and cardiac comorbidity were also associated with severe COVID-19 (OR 2.58 and 2.39, respectively). Immunomodulatory treatment with interferon or glatiramer acetate was associated with a lower risk of COVID-19 severity score ≥3 (OR 0.2) compared with no treatment. Knowing these risk factors should help to guide individualised clinical management of MS patients during the COVID-19 pandemic.

1. Louapre C, et al. Clinical Characteristics and Outcomes in Patients with Coronavirus Disease 2019 and Multiple Sclerosis. MSVirtual 2020, Abstract SS02.06
2. Louapre C, et al. JAMA Neurol. 2020;77(9):1079-88.

Anti-CD20 DMTs associated with worse COVID-19 outcomes

The first results of the COVID-19 in MS Global Data Sharing Initiative suggest anti-CD20 disease-modifying treatment (DMT) is consistently associated with hospitalisation, intensive care admission, and artificial ventilation [1]. These results suggest that anti-CD20 DMT among MS patients at risk for COVID-19 exposure may be a risk factor for more severe COVID-19 disease. Confirmation with Roche's pharmacovigilance program is however needed.

Clinician-reported data from 21 countries all over the world were aggregated into a dataset of 1,540 patients. Of these, 476 (30.9%) with suspected and 776 (50.4%) with confirmed COVID-19 were included in the analysis.

Older age, progressive MS, and higher EDSS were associated with a higher likelihood of hospital admission but being female with a lower likelihood. Progressive MS and higher disability were associated with a higher risk of intensive care unit admission. Mortality risk was elevated in patients with progressive MS, older age, and higher disability.

The adjusted prevalence ratios (aPRs) of hospitalisation (313 events) were established per DMT, with dimethyl fumarate as comparison. Use of anti-CD20 DMT ocrelizumab and rituximab was positively associated with hospital admission (aPRs 1.19 and 1.58), intensive care admission (aPRs 3.53 and 4.12), and the need for artificial ventilation (aPRs 3.17 and 7.27). There was no association between any DMT and death. Risk of all 3 clinical outcomes was higher in anti-CD20 users (n=343) compared with all other DMT users (n=492): hospitalisation aPR 1.49; intensive care admission aPR 2.55; and ventilation aPR 3.05. These risks were also higher compared with natalizumab: hospitalisation aPR 1.99; intensive care admission aPR 2.39; ventilation aPR 2.84. Associations persisted when restricting analysis to confirmed COVID-19 cases only.

There are different possible explanations for the consistently stronger association with COVID-19 severity of rituximab versus ocrelizumab. The most simple and appropriate explanation is the difference in affinities, with rituximab binding the exact same epitope on CD20 but binding more strongly.

An update from Roche's pharmacovigilance program did not confirm the above findings for ocrelizumab. Notwithstanding the limitations of the data sources, the experience of ocrelizumab-treated MS patients with COVID-19 appeared in line with the data reported from the general population and MS datasets [2]. The majority of SARS-CoV-2 infections in MS patients treated with ocrelizumab across Roche clinical trials (n=51; 26 confirmed) and post-marketing spontaneous reports (n=307; 263 confirmed) with reported severity, resulted in mild-to-moderate disease. Case fatality rates in ocrelizumab-treated MS patients were in line with the general population and MS datasets overall. Ocrelizumab-treated patients with risk factors associated with worse COVID-19 outcomes appeared to experience more severe disease, which is also in line with published experience.

1. Simpson-Yap S, et al. First results of the COVID-19 in MS Global Data Sharing Initiative suggest anti-CD20 DMTs are associated with worse COVID-19 outcomes. MSVirtual 2020, Abstract SS02.04.
2. Hughes R, et al. COVID-19 in persons with multiple sclerosis treated with ocrelizumab: pharmacovigilance update. MSVirtual 2020, Abstract SS02.05.

Black MS patients have poorer COVID-19 outcomes

In the North-American COViMS registry, Black MS patients have an increased risk for less favourable outcomes compared with White MS patients, even after adjusting for comorbidities at the time of COVID-19 [1].

COViMS is a North American clinician-based registry for MS patients with COVID-19. Cases are reported after 7 days and when the outcome of infection is reasonably certain. The main objectives of the registry are to see how MS patients as a group fare with COVID-19, and to evaluate how individual disease-modifying treatment (DMT) affects outcomes of COVID-19.

The 2 race groups that were considered for the analysis that was presented as a late-breaking abstract were non-Hispanic White and Black or African-American (AA) patients with MS and clinically isolated syndrome (CIS). A total of 858 MS patients were reported in COViMS, 503 (58.6%) were reported as non-Hispanic White and 223 (26.0%) as Black/AA. The latter group were more likely to be younger (P<0.001), be a never-smoker (P=0.014), and have a shorter MS duration (P<0.001). There were no significant differences in DMT use (P=0.06): 80% of White patients and 85% of Black/AA patients were on DMT treatment. A higher proportion of Black/AA patients had cerebrovascular disease (P=0.006), chronic lung disease (P=0.006), diabetes (P=0.005), hypertension (P=0.001), and morbid obesity (P=0.004).

Overall mortality was similar in both race groups: 6.3% in White patients versus 5.4% in Black/AA patients. A multivariable logistic regression analysis did not reveal an effect of race on mortality alone (P=0.30), after adjustment for covariates. Overall rates of mortality and/or intensive care admission was 12.8% in White patients and 16.9% in Black/AA patients. An independent association of race was identified with mortality and/or intensive care admission: risk for Black/AA MS patients was over 3 times higher (OR 3.7; 95% CI 1.6–8.2; P=0.002). The overall rate of mortality, intensive care admission, and/or hospitalisation was 30.2% in White patients and 35.8% in Black/AA patients (OR 1.7; 95% CI 1.02–2.84; P=0.04). One of the study's limitations may be a reporting bias towards severe cases.

1. Salter A, et al. Comparison of COVID-19 outcomes between racial groups in the COViMS registry. MSVirtual 2020, Abstract SS02.02.

Biomarkers

Gut bacteria associated with relapse in paediatric-onset MS

A relative abundance of a gut microbiota species within the *Blautia* genus and its interconnected variants was associated with an elevated risk of relapse in patients with paediatric-onset MS [1]. *Blautia stercoris* has also been linked to disease activity in other immune-mediated diseases, such as systemic lupus erythematosus.

Commensal gut microbes are known to affect host immune function and may play a role in the pathogenesis of MS. It is largely unknown to what extent gut microbiota may contribute to subsequent disease activity. To investigate this association in paediatric-onset MS patients, stool samples of 53 patients (of whom 38 girls) were collected and analysed using 16S rRNA sequencing in the V4 region. Amplicon sequence variants (ASVs) were identified using the Divisive Amplicon Denoising Algorithm-2. At the time of sample collection, mean age was 15.5 years and disease duration was 1.1 years; 48 used a disease-modifying therapy.

A total of 270 individual ASVs were included in the analyses. Of these, 20 ASVs were nominally significant (P<0.05). An example was *Blautia stercoris*, the presence of which was associated with higher relapse risk (HR 2.50; 95% CI 1.43-4.37). Higher values of 1 module's eigengene were significantly associated with higher risk of relapse (HR 1.23; 95% CI 1.02-1.50). In this module, 4 ASVs were individually, nominally associated with higher relapse risk (P<0.05): *Blautia massiliensis*, *Dorea longicatena*, *Coprococcus comes*, and a species in the genus *Subdoligranulum*. Of 309 MetaCyc pathways, 10 were significantly associated with relapse risk (false discovery rate q<0.2).

1. Horton M, et al. Network analysis identifies gut bacteria associated with multiple sclerosis relapse among pediatric-onset patients. MSVirtual 2020, Abstract LB01.05.

Predictive value of CSF Aβ and tau proteins in MS

A prospective study showed that 2 neurodegenerative biomarkers in cerebrospinal fluid (CSF) –beta-amyloid (Aβ) and especially tau– can help identify early-onset disability and unfavourable prognosis in MS patients, independent of age [1].

Not a single biomarker of axonal damage in MS is routinely used in clinical practice. An Italian group set out to evaluate if CSF Aβ and tau protein concentrations collected at diagnosis can predict early MS disability. They also investigated if these 2 biomarkers correlate with other radiological prognostic markers collected at baseline, i.e. global T2 white matter lesion load and spinal cord lesions. Demographic, clinical, and radiological data were collected at baseline and at the most recent clinical follow-up. Early disability was measured using the MS Severity Score (MSSS) and the MSSS age-related score (ARMSS) at the most recent follow-up. A total of 109 MS patients (82 with relapsing-remitting MS) were followed for a mean period of 4 years.

Patients with higher CSF tau levels at baseline had higher MSSS (R=0.3361; P=0.0003) and ARMSS (R=0.3088; P=0.001) at follow-up. There was no correlation between CSF Aβ and markers of early disability. Patients with spinal cord involvement showed a trend towards higher tau levels. In patients with higher white matter lesion load, there was a trend towards higher tau and lower Aβ. There was a significant correlation between CSF tau and early disability, measured either with MSSS (β=0.258; P=0.009) or ARMSS (β=0.252; P=0.001).

These results led the researchers to conclude that CSF tau and Aβ may correlate with negative prognostic factors at MS diagnosis, particularly with high lesion load and spinal cord involvement. CSF tau may be able to help predict early disability.

1. Virgilio E, et al. Biomarkers of neurodegeneration, in particular Tau protein, may predict early disability in Multiple Sclerosis patients. MSVirtual 2020, Abstract PS03.02.

Serum NfL as biomarker for suboptimal treatment response

Serum neurofilament light chain (sNfL) levels are independently associated with clinical and MRI measures of MS disease activity in MS patients [1]. Increased sNfL in patients on disease-modifying therapies for at least 3 months therapy predicted relapses, EDSS worsening, and MRI activity in the subsequent year. Current sNfL levels predicted future clinical disease activity, can detect subclinical disease activity in NEDA-3 patients and may serve as independent of standard metrics for treatment monitoring, and can detect subclinical disease activity in NEDA-3 patients.

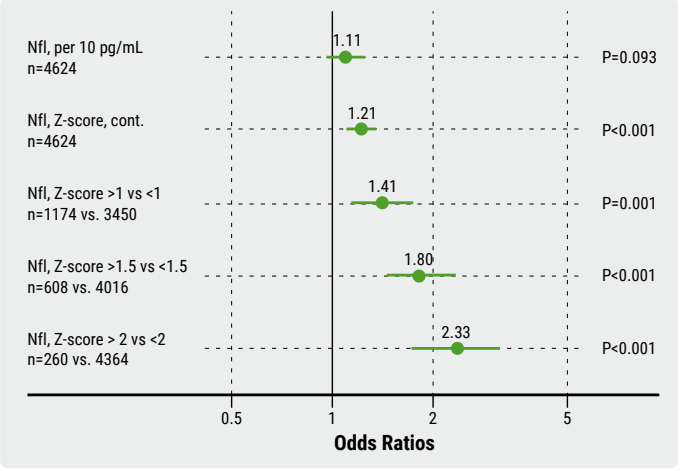
Participants were 1,062 patients from the Swiss MS Cohort Study, of whom 95.9% had relapsing-remitting MS and 4.1% clinically isolated syndrome (CIS). Median age was 39.7 years, median EDSS 2.0, and median follow-up 5 years. All patients were on disease-modifying therapy for at least 3 months. sNfL was measured every 6 or 12 months with the NF-light® assay. A total of 5,192 longitudinal samples were analysed and compared with 8,865 samples of healthy controls.

Clinical events (EDSS worsening or relapse; n=4,624) in the following year were predicted by the sNfL z-score (OR 1.21; P<0.001). There was a "dose-effect relationship" with increasing sNfL z-score (see Figure). Results for the prediction of future new/enlarging T2 lesions and brain volume loss were similar. In a multivariable mixed logistic regression model, new/enlarging T2 lesions (OR 1.88; P=0.016) and sNfL z-score >1.5 (OR 2.18; P=0.009) predicted future clinical events (n=853); previous EDSS worsening, previous relapses and current contrast enhancement did not. Even in NEDA-3 patients, change of sNfL z-score could predict clinical events (relapses, EDSS worsening, contrast enhancing or new/enlarging T2 lesions in brain MRI; n=587) in the subsequent year (OR 1.37; P=0.025).

These study results in a well-characterised, large, real-world cohort support the use of sNfL to monitor treatment effects in MS clinical practice. According to the authors, sNfL gives a unique signal that is not captured by other markers.

1. Yaldizli Ö, et al. Value of serum neurofilament light chain levels as a biomarker of suboptimal treatment response in MS clinical practice. MSVirtual 2020, Abstract PS09.05.

Figure: sNfL z-score predicts relapse or EDSS-worsening in the following year [1]



Interrupting DMT due to pregnancy increases NfL levels

Interrupting disease-modifying treatment (DMT) leads to higher serum neurofilament light chain (sNfL) levels during pregnancy and the DMT-free postpartum period [1]. This elevation was independent of relapses, suggesting increased subclinical disease activity during this time span. sNfL may qualify as a sensitive and minimally-invasive measure of MS disease activity during pregnancy.

A total of 72 pregnancies in 63 relapsing MS patients were evaluated. Median age was 31.4 years, median disease duration 7.1 years, median EDSS 1.5 at last visit before birth, and median follow-up 6 years. Of 433 included samples, 167 were taken before pregnancy, 92 during pregnancy/DMT-free postpartum, and 174 after pregnancy. Most patients (n=39) were treated with fingolimod or natalizumab as last medication before birth; 4 patients did not use a DMT before, during, and after pregnancy. In 14 of 72 pregnancies, DMT exposure during pregnancy was >6 months; in 39 pregnancies, exposure was limited to the first 2 trimesters; in 15 pregnancies, treatment was discontinued before getting pregnant.

Relapses were more likely in the first trimester and the first 3 months postpartum. sNfL levels increased towards the last trimester and in the first 3 months postpartum, not only in women who relapsed. Mean sNfL levels were 22% higher during pregnancy (β=1.22; P<0.001). During the postpartum, 29 relapses occurred. Relapses were associated with 98% higher sNfL (β=1.98; P<0.001). Mean sNfL was 13% higher during the postpartum period (β=1.13; P=0.009). However, this difference lost significance after including DMT exposure into the model (β=1.07; P=0.178). Patients sampled during DMT had on average 12% lower sNfL levels compared with patients without (β=0.88; P=0.019). The authors concluded that strategies allowing to continue DMT during pregnancy may be warranted.

1. Yaldizli Ö, et al. Interrupting disease modifying treatment for pregnancy in multiple sclerosis – effect on disease activity and serum neurofilament light chain. MSVirtual 2020, Abstract LB01.06.

Predicting autoimmunity in patients treated with alemtuzumab

The use of alemtuzumab in highly active MS has been limited by adverse events (AEs) in the form of secondary autoimmune disorders, especially involving the thyroid gland. A low percentage of blood circulating CD19+ B cells –cut-off value 7.6%– before starting alemtuzumab treatment may predict a lower risk of autoimmune AEs [1].

A multicentre, prospective, longitudinal study evaluated whether patients' blood lymphocyte profile before the initiation of alemtuzumab treatment may help predict the development of later autoimmunity. The Spanish study included 54 relapsing-remitting MS (RRMS) patients (34 female), with a median age of 35 years and a median follow-up of 2.8 years. Of these, 14 patients (25.9%) experienced autoimmune AEs, in all cases dysthyroidism. No immune thrombocytopenia or nephropathies were observed.

There were no significant differences in clinical and demographic baseline characteristics (e.g. EDSS) in patients who developed autoimmune AEs versus those who did not. Patients who experienced autoimmune AEs before treatment onset did have a higher percentage of baseline blood CD19+ B cells (P=0.001), with a higher relative percentage of naïve B cells and plasmablasts. In total cell numbers, only plasmablast levels remained significant (P=0.02). Previous treatments did not significantly influence the percentage of B lymphocytes. There was a lower risk of autoimmune AEs after alemtuzumab treatment among patients with <7.6% of blood CD19+ B cells (OR 14.67; 95% CI 3.4-54.5; P<0.0001).

1. Walo Delgado P, et al. Predictive biomarkers of the development of autoimmunity in patients treated with alemtuzumab. MSVirtual 2020, Abstract PS09.03.

Serum glial fibrillary acidic protein predicts relapses in NMOSD

The astrocyte-specific marker glial fibrillary acidic protein (GFAP), measured in serum, can predict relapses in neuromyelitis optica spectrum disorders (NMOSD) during remission. Two other biomarkers, S100B and neurofilament light chain (NfL) failed to do so [1].

In acute phases of NMOSD, the astrocyte-specific biomarkers GFAP and S100B are elevated in cerebrospinal fluid (CSF) and serum or plasma, as is the neuron-specific biomarker NfL. GFAP is already used to set appropriate treatment regimens and monitoring response. In a new study, the prognostic potential of these 3 biomarkers for future relapses in NMOSD with aquaporin-4-IgG was evaluated. Median baseline biomarker values were determined from 47 serum samples from 18 patients in remission. Cut-off levels were established for "high" and "low" GFAP (141.6 pg/mL), S100B (8.6 pg/mL), and NfL (33.9 pg/mL). When a patient relapsed, another serum sample was taken and analysed. In total, 25 post-relapse samples were analysed (11 patients had 1 relapse, 7 had 2 relapses).

Patients with high baseline GFAP had earlier future relapses (after a median of 922 days) than those with low GFAP levels (3,710 days; P=0.0047). They were also at higher risk of future relapses (adjusted HR 9.5; P=0.0061). These differences were absent in the high versus low S100B and NfL groups.

Presenting author Prof. Mitsuru Watanabe (Kyushu University, Japan) suggested that S100B may have failed in this study because it is not specific to astrocytes and because it has a short half-life compared to GFAP. The failure of NfL may be explained by the pathogenesis of NMOSD, in which astrocytopathy is of primary and neuro-axonal damage only of secondary importance.

1. Watanabe M, et al. Serum glial fibrillary acidic protein, but not S100B or neurofilament light chain predicts future relapses in neuromyelitis optica spectrum disorders. MSVirtual 2020, PS03.04.

Assessing demyelination using myelin water imaging

Myelin water imaging (MWI) is an *in vivo* MRI technique that images water trapped between the lipid bilayers of myelin, providing a quantitative measure of myelin: the myelin water fraction (MWF). MWI provides evidence for unique anatomical-functional relationships between myelin damage and cognition in MS. It can be used to monitor changes in myelination and its relationship to cognitive worsening or improvement [1].

This study aimed to determine possible anatomical-functional relationships between myelin content and myelin damage location and cognitive performance. A sample of 76 patients with clinically definite MS and 22 age-, sex-, and education-matched healthy controls was used. MS patients had a median EDSS of 3.2 (range 1.0 – 8.5) and median disease duration of 15.5 years (0.3 - 48.0). They all underwent cognitive testing and MRI. Cognitive testing was performed with assessments drawn from cognitive batteries validated for use in MS. Non-parametric permutation testing was used to determine which white matter MWF voxels were associated with cognitive test performance. This resulted in test-specific maps of associated white matter areas (cognitive test-specific white matter regions). For each cognitive test, MS patients were categorised into 1 of 3 groups:

i. cognitively impaired: z-score ≤1.5;
ii. mildly impaired: z-score >-1.5 to ≤1;
iii. cognitively preserved: z-score ≥1.

In MS patients, significant associations were observed between MWF and performance on the Symbol Digit Modalities Test, Selective Reminding Test, and Controlled Oral Word Association Test. No significant associations were found between myelin measures and cognitive performance in controls. The results showed an anatomical-functional relationship between myelin damage and cognitive performance in MS with unique white matter patterns for different cognitive domains. Mean MWF in cognitive test-specific white matter regions was significantly lower in cognitively impaired versus cognitively preserved MS patients, and was significantly associated with cognitive test performance.

With new MS treatments moving towards remyelination, these findings can be translated to clinical trials. The results suggest that MWI can offer an *in vivo* biomarker feasible for use in clinical trials investigating cognition, providing a means for monitoring changes in myelination and its association with symptom worsening or improvement.

1. Abel S, et al. Myelin water imaging provides evidence for unique anatomical-functional relationships between myelin damage and different cognitive domains in MS. MSVirtual 2020, Abstract LB1197.

Grey matter network measures predict disability and cognition

Data-driven, MRI network-based measures of co-varying grey matter volumes predict disability progression better than volumetric measures of grey and white matter lesion loads, a new study found [1]. Independent component analysis (ICA) of MRI can help select clinical MS study participants who are more likely to respond to treatment.

Baseline MRI and longitudinal clinical data were used from 988 participants of the randomised, double-blind, placebo-controlled ASCEND trial, which evaluated the effect of natalizumab on disease progression in secondary progressive MS. Spatial ICA was applied to baseline structural grey matter probability maps to identify co-varying grey matter regions. Correlations between ICA components and EDSS, 9-Hole Peg Test (9HPT), and Symbol Digit Modalities Test (SDMT) scores were computed.

A total of 15 clinically relevant networks of co-varying grey matter patterns were identified. Compared with conventional MRI measures, SDMT and 9HPT baseline scores correlated

more strongly with ICA components, especially main basal ganglia components including the thalamus, caudate, putamen, and frontal and temporal lobes. EDSS correlated more closely with an ICA component involving cerebellum, brainstem, and temporal and parietal lobes (R=-0.11; P<0.001). EDSS progression was predicted by baseline caudate volume (HR 0.81; P<0.05). Descending SDMT scores were best predicted by 2 ICA components (HR 1.26; P<0.005; and HR 1.25; P<0.005). Two other ICA components predicted worsening of 9HPT scores (HR 1.30; P<0.01; and HR 1.21; P<0.05).

1. Colato E, et al. Predicting disability progression and cognitive worsening in multiple sclerosis with gray matter network measures. MSVirtual 2020, Abstract PS07.03.

Lesion-specific perfusion levels affect myelin loss and repair

Remyelination in MS lesions is heterogeneous and often fails. A key factor to explain this may be the level of perfusion of single MS lesions, which is critical for myelin repair. A new study analysed the relationship between perfusion and subsequent myelin content changes in the white matter lesions in 15 relapsing-remitting MS patients using ^{11}C-PIB PET and 3T MRI. It was found that lesion-specific perfusion at baseline is an independent predictor of successful myelin repair [1].

^{11}C-PIB PET allows to simultaneously map demyelination and remyelination *in vivo* and to generate quantitative maps of brain perfusion. In 15 relapsing-remitting MS patients, ^{11}C-PIB PET and 3T MRI were performed at baseline and 2-4 months later. At baseline, 904 lesions were identified on T2-weighted scans. Gadolinium-enhancing lesions were excluded. Successful repair of lesions was defined as remyelination of ≥50% of demyelinated voxels, and demyelination over the follow-up in <25% of voxels that were classified as normally myelinated at study entry.

There was lower perfusion in white matter lesions than in normal-appearing white matter (0.43 vs 0.49; P<0.001). However, single-lesion R1 values were very heterogeneous (range 0.08-2.5). In single lesions, higher baseline perfusion was associated with more extensive remyelination (β=0.32; P<0.001) and reduced demyelination (β=-0.28; P<0.001). Lesion-specific perfusion at baseline was an independent predictor of successful myelin repair (OR 8.4; P<0.001).

1. Colombi A, et al. Lesion-specific perfusion levels affect myelin loss and repair in multiple sclerosis: a positron emission tomography study. MSVirtual 2020, Abstract PS11.03.

Treatment Strategies and Results

Management of progressive MS with approved DMT

In an invited lecture, Prof. Xavier Montalban (Vall d'Hebron University Hospital, Spain) discussed the management of primary and secondary progressive MS (PPMS and SPMS) with approved disease-modifying treatment (DMT) highlighting their limitations and reasons they have failed [1]. For PPMS in particular, current treatment options are limited to ocrelizumab, but the ongoing trials were discussed.

Drugs considered for active SPMS in the 2018 ECTRIMS/EAN MS treatment guidelines are interferon-1a or -1b, taking into account the dubious efficacy as well as the safety and tolerability profile [2]. Other options mentioned for active SPMS are mitoxantrone, ocrelizumab, or cladribine. Possible additions to this list are siponimod and ozanimod, which were recently approved for relapsing MS, and ofatumumab, which was approved for active SPMS (among others) by the FDA in August 2020.

For PPMS, only 1 DMT has been approved specifically, which is ocrelizumab. Prof. Montalban pointed out several reasons why drugs fail in PPMS trials. First, pathogenic mechanisms in the progressive phase are completely different from the relapsing phase. Second, patient populations included in PPMS trials are generally not appropriate. Third, generally used clinical outcome measures are not sensitive enough, meaning clinical trials are not "smart" enough to detect PPMS worsening over a relatively short time span. Among drugs that failed to show any effect on PPMS are fingolimod and glatiramer acetate.

Natalizumab could have a role in the treatment of SPMS "for specific cases of very active disease," according to Prof. Montalban. In the phase 3 trial ASCEND, natalizumab did not reduce progression on the primary multicomponent disability endpoint over 2 years, but it did reduce progression on its upper limb component, the 9-Hole Peg Test (9-HPT) [3]. Siponimod is an example of an MS drug showing some efficacy in SPMS patients who have a particular profile. Response is better in patients with prior relapses, rapidly evolving disease, active baseline MRI, younger age, shorter disease duration, no prior treatment, and a lower EDSS score [4].

More DMTs have been tested in SPMS in the past decade, ranging from interferon-β to agents that are not registered for any form of MS. For example, MD1003 (biotin) showed very positive results that could, unfortunately, not be replicated in a second pivotal phase 3 trial [5,6]. A phase 3 trial of high-dose simvastatin in SPMS (n=1,180) is ongoing. A potentially promising therapy in both PPMS and SPMS is ibudilast [7]. The potential benefit of opicinumab is less clear [8]; an additional phase 2b trial is underway. Clemastine showed short-term improvement in visual evoked potentials [9], but the clinical relevance of these results is as yet unclear. Amiloride, fluoxetine, and riluzole yielded basically negative results in the MS-SMART study [10]. Lipoic acid showed a "very important" 68% reduction in annualised percent change brain volume [11], but these results have to be replicated in a larger trial.

Prof. Montalban stressed that a major complicating factor in treating progressive MS is the lack of consensus on the definition of treatment failure. In active progressive MS, is it persistence of relapses, or disability worsening? In non-active PPMS, is it disability worsening and/or appearance of relapses? How long should the time on treatment be when evaluating efficacy? Can only improvement be considered as proof of efficacy? All these questions are still waiting to be answered.

1. Montalban X, et al. Management of Progressive MS with Approved DMT. MSVirtual 2020, Abstract PS05.02.
2. Montalban X, et al. Mult Scler. 2018;24(2):96-120.
3. Kapoor R, et al. Lancet Neurol. 2018;17(5):405-15.
4. Kappos L, et al. Lancet. 2018;391(10127):1263-73.
5. Tourbah A, et al. Mult Scler. 2016;22(13):1719-1731.
6. Coulome L, et al. Mult Scler. 2019;1352458519894713.
7. Fox RJ, et al. N Engl J Med. 2018 Aug 30;379(9):846-855.
8. Cadavid D, et al. Lancet Neurol. 2019 Sep;18(9):845-856.
9. Moghaddasi M, et al. Clin Neurol Neurosurg. 2020 Jun;193:105741.
10. Connick P, et al. BMJ Open. 2018 Aug 30;8(8):e021944.
11. Spain R, et al. Neurol Neuroimmunol Neuroinflamm. 2017 Jun 28;4(5):e374.

Outcomes in patients on alemtuzumab with thyroid adverse events

In alemtuzumab-treated patients from the CARE-MS core and extension trials, the thyroid adverse events (AEs) encountered over 6 years were independently characterised [1]. Graves' disease was the most common thyroid AE detected in 40% of the patients within 4 years after the last alemtuzumab course. The favourable MS disease outcomes over a 6-year period were however similar in patients with or without thyroid AEs.

An expert panel of 3 independent endocrinologists reviewed all reported thyroid-related laboratory abnormalities and AEs from the CARE-MS trials.

Over 6 years, 378 of 811 (47%) patients treated with alemtuzumab had a laboratory abnormality (n=36) or thyroid AE (n=342; 44 serious). A consensus on thyroid AEs was reached in 292 cases, adjudicated as follows:

- Graves' disease: 40%;
- Hashimoto's disease: 17%;
- transient thyroiditis: 8%;
- Graves' disease switching to hypothyroidism 6%;
- Hashimoto's disease switching to hyperthyroidism: 3%; and
- uncertain: 2%.

More than 97% of thyroid AEs were detected within 4 years of the last alemtuzumab course; 83% within 2 years. Patients with or without thyroid AEs received similar numbers of alemtuzumab courses. MS disease outcomes were similar in both groups in terms of annualised relapse rate, EDSS score change, brain volume loss, and being disease activity-free on MRI.

Treatment of thyroid AEs consisted of oral thyroid medications in 84%, primarily levothyroxine/levothyroxine sodium (64%) or thiamazole (43%). Another 11% underwent thyroidectomy, 9% had radioiodine therapy. At the most recent follow-up, cases were recovered (53%), ongoing (46%), or unknown (0.3%).

1. Dayan C, et al. Outcomes in Alemtuzumab-Treated Patients With Thyroid Adverse Events: 6-Year Pooled CARE-MS Data. MSVirtual 2020, Abstract P0128.

Safety and efficacy of dimethyl fumarate: 13 years of follow-up

The overall benefit-risk ratio of dimethyl fumarate (DMF) remained favourable during a 13-year follow-up period [1]. Low rates of relapse were sustained throughout the 10-year treatment period. Rates of confirmed disability progression, serious infections, and malignancies were also low.

The final safety and efficacy results of DMF 240 mg twice daily (the approved dosage) were reported in patients with relapsing-remitting MS who were followed for 13 years in the ENDORSE trial (2 years DEFINE/CONFIRM and >10 years

in ENDORSE). Patients were either treated with placebo in year 0-2 followed by DMF in year 3-10 (PBO/DMF) or with DMF continuously (DMF/DMF). Overall, 1,736 patients were enrolled in ENDORSE and 750 completed the study, 501 of whom received DMF/DMF and 249 PBO/DMF.

Annualised relapse rate (ARR) remained low throughout the study (see Figure). In the DMF/DMF group, ARR was 0.20 in year 1 and 0.11 in years 9-10. In the PBO/DMF group, ARR was 0.33 during placebo and 0.15 during DMF treatment. In the DMF/DMF and PBO/DMF group treated for up to 10 years, 45% and 42% of patients remained relapse-free, respectively, indicating that earlier treatment yields more favourable results. The percentage of patients with EDSS ≤3.5 over 10 years in the DMF/DMF group was 86% and 77% after 2 and 10 years, respectively; and 82% and 74% in the PBO/DMF group. In the DMF/DMF and PBO/DMF group, respectively, 72% and 73% of patients had no 24-week confirmed disability progression over 10 years.

Overall, 551 (32%) patients experienced serious adverse events (AEs); most were MS relapse and falling. One case of progressive multifocal leukoencephalopathy was reported; there was no increased incidence of other infections or serious infections. AEs caused 16% of patients (n=282) to discontinue treatment, most commonly due to gastrointestinal and nervous system disorders. Absolute lymphocyte count decreased over the first 48 weeks, and then generally remained stable. The proportion of patients with other AEs of special interest (including opportunistic infection, malignancy, and serious herpes zoster) was similar regardless of absolute lymphocyte count. The authors concluded that these data further support DMF as a long-term option for patients with relapsing forms of MS.

1. Gold R, et al. Safety and Efficacy in Patients Treated With Dimethyl Fumarate and Followed For 13 Years: Final Results of ENDORSE. MSVirtual 2020, Abstract FC02.05.

Update on estimated PML risk related to fingolimod

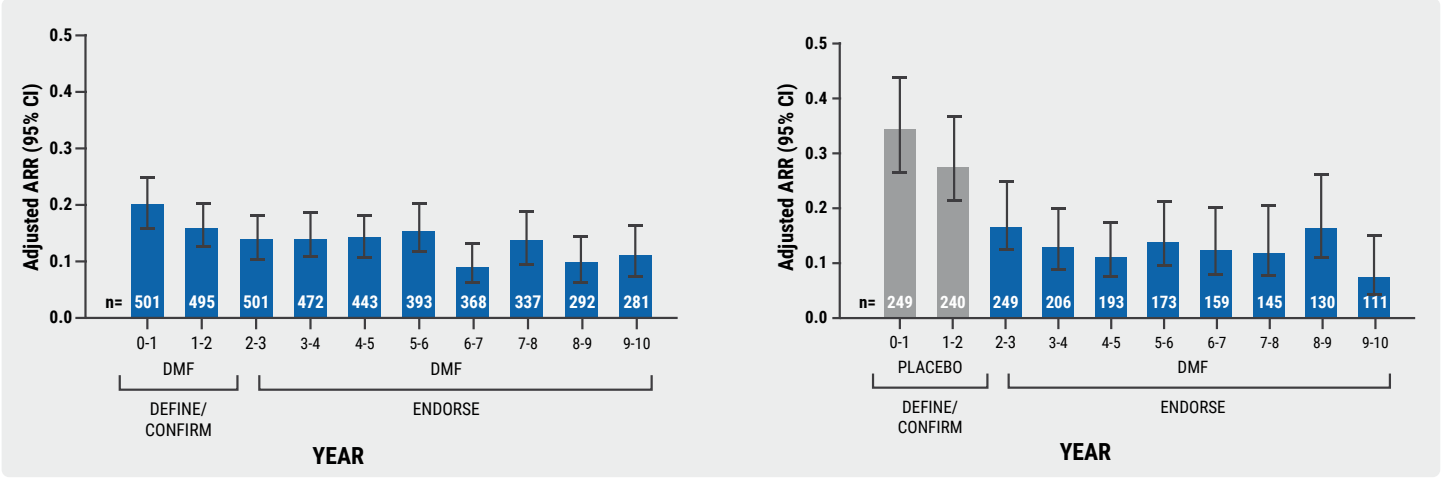
An updated estimate on the global risk of progressive multifocal leukoencephalopathy (PML) in 299,600 MS patients receiving fingolimod showed that the PML risk associated with fingolimod is low, estimated at 0.13 per 1,000 patients over a 5-year period [1]. The risk appears to increase with cumulative exposure. PML risk could be increased if fingolimod treatment is started at a relatively high age.

Potential PML cases from the manufacturer's safety database (data cut-off 28 February 2020) were reviewed by an independent PML adjudication committee. The number of confirmed PML cases was compared with the estimated global number of fingolimod-treated patients and patient-years of exposure. Approximately 299,600 patients were treated with fingolimod globally, covering >778,900 patient-years (PYs) of exposure.

The number of suspected PML cases reported and evaluated was 188. Of these:

- 37 cases were associated with fingolimod treatment;
- 17 cases were attributed to previous natalizumab treatment; and
- 134 cases were not confirmed as PML based on reported information.

Figure: Adjusted ARR by yearly interval in patients continuously treated with DMF or who switched from placebo after 2 years [1]



Based on these numbers, the estimated crude incidence was 0.12 (95% CI 0.09-0.17) per 1,000 patients. The estimated incidence rate was 4.75 (95% CI 3.34-6.55) per 100,000 PYs. The incidence of PML appeared to increase with treatment duration, approaching a plateau in year 5 at ~0.13 per 1,000 patients, with a wide confidence interval.

The exact pattern of the relationship to duration of treatment remains unclear. PML incidence appeared to increase between 30 and 50 years of age and then stabilise or even decrease, but the exact shape of the relationship with age is also uncertain. For both treatment duration and age at treatment initiation, the incidence estimates lacked precision due to the small number of cases.

1. Fox R, et al. Update on the risk estimates of progressive multifocal leukoencephalopathy related to fingolimod. MSVirtual 2020, Abstract FC02.02.

Less thalamic atrophy in patients initiating ocrelizumab earlier

In the open-label extension (OLE) of the phase 3 trials OPERA I/II and ORATORIO, patients with relapsing and primary progressive MS who were initially randomised to ocrelizumab experienced less thalamic volume loss than those initiating ocrelizumab later [1]. Baseline thalamic volume may predict confirmed disability progression (CDP) and CDP-9-Hole Peg Test (9HPT) score in relapsing MS.

Thalamic atrophy occurs early and consistently over the course of MS, at a rate that is faster than in healthy controls. MS has both a direct effect on the thalamus by neuronal loss, and an indirect effect due to axonal transection in lesions which affects afferent and efferent projections of the thalamus. Thalamic atrophy may therefore be a useful marker of therapeutic effects. This study assessed the efficacy of switching to or maintaining ocrelizumab therapy on thalamic atrophy in patients with relapsing and primary progressive MS participating in OPERA I/II and ORATORIO, and evaluated if baseline thalamic volume predicts disability progression during the double-blind period of both trials.

The OPERA I/II trials compared ocrelizumab (n=827) to interferon β-1a (n=829) in relapsing MS patients; ORATORIO compared ocrelizumab (n=488) to placebo (n=244) in primary progressive MS patients.

Ocrelizumab significantly reduced thalamic atrophy in patients who were initially randomised to ocrelizumab compared with those initiating ocrelizumab later (all P<0.001; see Table). The correlation of thalamic volume with CDP as measured by 9HPT, EDSS, and timed 25-feet walk was significant in both trials, albeit modest.

Table: Percentage change in thalamic volume from baseline in OLE of OPERA I/II and ORATORIO trials [1]

	OPERA I/II		ORATORIO	
	IFN β-1a-OCR	OCR-OCR	PBO-OCR	OCR-OCR
OLE day 1	n.a.	n.a.	−3.46	−2.44
Week 46/48	−2.88	−2.12	−3.93	−2.61
Week 94/96	−3.31	−2.36	−4.30	−3.25
Week 142/144	−3.61	−2.78	−4.86	−3.62
Week 190	−3.68	−3.03	n.a.	n.a.
Week 238	−4.07	−3.41	n.a.	n.a.

IFN β-1a, interferon β-1a; OCR, ocrelizumab; PBO, placebo; OLE, open-label extension.

1. Arnold D, et al. Reduced thalamic atrophy in patients initiating earlier versus delayed ocrelizumab therapy: results from the OLE of OPERA I/II and ORATORIO. MSVirtual 2020, Abstract FC03.05.

No new safety signals in ofatumumab open-label data

Only a few weeks prior to the MSVirtual 2020, the fully human anti-CD20 monoclonal antibody ofatumumab was approved by the FDA for the treatment of relapsing forms of MS. In the open-label extension study ALITHIOS, ofatumumab's very good safety profile was consistent with data from the core phase 3 ASCLEPIOS I/ASCLEPIOS II trials [1,2].

The indication of ofatumumab is to include clinically isolated syndrome (CIS), relapsing-remitting MS, and active secondary progressive MS in adults. In the ASCLEPIOS trials, ofatumumab demonstrated superior efficacy versus teriflunomide and a favourable safety profile in relapsing-remitting MS patients [2]. Long-term safety data continues to be collected from the open-label phase 3b ALITHIOS extension study.

The overall safety data of all participants in ALITHIOS was reported [1]. This data included 1,230 patients who were randomised to ofatumumab in the core phase 2 APLIOS (12 weeks) or phase 3 ASCLEPIOS I/II (up to 30 months) trials and continued in ALITHIOS, or completed/discontinued the core study and continued the safety follow-up; and 643 patients who were randomised to teriflunomide in ASCLEPIOS I/II and switched to ofatumumab in ALITHIOS. The overall exposure was 2,118 patient-years.

The most frequently reported adverse events (AEs) were injection-related reactions and upper respiratory tract infections.

Most AEs were mild to moderate in severity; the incidence of AEs, serious AEs, or grade 3/4 AEs did not increase in either group. There were no deaths. The overall safety profile was consistent with reports from the core ASCLEPIOS I/II trials. In the newly switched group, injection-related reactions were mild to moderate; none were serious or led to treatment discontinuation. Concerning AEs of special interest: there were no opportunistic infections, hepatitis B reactivation, or progressive multifocal leukoencephalopathy (PML) events. There were no new cases of malignancies in the continuous or newly switched patients either.

1. Cross AH, et al. Safety experience with extended exposure to ofatumumab in patients with relapsing multiple sclerosis from Phase 2 and 3 clinical trials. MSVirtual 2020, P0234.
2. Hauser SL, et al. N Engl J Med. 2020;383:546–57.

Long-term safety and efficacy of ozanimod in RMS

In the ongoing DAYBREAK trial, ozanimod was associated with low annualised relapse rate (ARR) and low new/enlarging T2 and gadolinium-enhancing lesion counts in relapsing MS patients over time [1]. Most participants were relapse-free and did not experience disability progression. Ozanimod was generally well tolerated; no new safety concerns emerged with long-term use.

DAYBREAK is an open-label extension (OLE) study of relapsing MS patients who participated and completed an ozanimod phase 1, 2, or 3 trial. In the OLE, patients received ozanimod 0.92 mg/day, equivalent to ozanimod HCl 1 mg. The analysis included 2,494 participants with a mean ozanimod exposure of 35.4 (range 0.03–50.2) months in the OLE.

Ozanimod was associated with a low (adjusted) ARR in the OLE of 0.112 (95% CI 0.093–0.135). After 24 months, 79% of participants were relapse-free; after 36 months this was 75%. Six-month confirmed disability progression was observed in 8.6%. Mean number of new/enlarging T2 lesions per scan was low and remained similar throughout (range 1.57–1.90 at month 36), as was mean number of gadolinium-enhancing lesions (range 0.2 0.4).

No new safety concerns emerged. In the OLE, 2,039 participants (81.8%) had any treatment-emergent adverse event (AE), 236 (9.5%) had a serious treatment-emergent AE, and 56 (2.2%) discontinued treatment due to a treatment-emergent AE. The most common treatment-emergent AEs were nasopharyngitis (17.9%), headache (14%), upper respiratory tract infection (9.9%), and lymphopenia (9.6%). There were no serious opportunistic infections. During the parent trials and DAYBREAK combined, 1.2% of participants exposed to either dose of ozanimod developed malignancies, which is consistent with malignancy rates among patients treated with other disease-modifying treatments.

1. Selmaj K, et al. Long-term safety and efficacy of ozanimod in relapsing multiple sclerosis in DAYBREAK: an open-label extension study of ozanimod phase 1–3 trials. MSVirtual 2020, Abstract P0217.

Low-dose rituximab as effective as high-dose, but safer

Results of a Spanish two-centre study suggest that low doses of rituximab are equally as effective as high doses, but have a superior safety profile [1]. A standardised treatment schedule for this anti-CD20 monoclonal antibody has yet to be established. The study authors think these results will change clinical practice.

The efficacy and safety of 2 rituximab regimens were compared at 2 large MS centres in Barcelona and Girona. The Barcelona centre (BC; n=249) applied higher doses of rituximab than the Girona centre (GC; n=54). In the BC, at least 3 cycles of 2 g intravenously (IV) were followed by 1 g every 6 months; in the GC, a minimum of 1 cycle of 2 g IV was followed by 500 mg every 6 months. For the 303 study participants, clinical progression plus inflammatory activity was the main reason to start rituximab in the BC (45.8%) as well as the GC (79.6%).

At baseline, mean annualised relapse rate (ARR) was 0.37 (BC) and 0.33 (GC), median EDSS was 5.5 and 6.0, and the proportion of MRI with contrast-enhancing lesions was 32.4% and 42.6%, respectively. In the BC and GC, mean ARR decreased to 0.05 (87.5%, P<0.001) and 0.03 (90.3%, P=0.018), respectively, in the first year of treatment. In the third year, ARR was 0.08 (88.3%, P=0.016) and 0.0 (100%, P=0.172). Of participants with progressive MS, EDSS remained stable or improved in 79.4% (BC) and 71.4% (GC). The proportion of patients with contrast-enhancing lesions and new T2 lesions were 2.7% and 19% (BC) and 8% and 16% (GC) after 1 year; this decreased 0% and 12% (BC) and 0% and 0% (GC) after 3 years.

In the first year, the incidence of adverse events was 14.8% in the BC and 4.1% in the GC cohort. There were no differences in the dynamics of CD19 lymphocyte percentages. Throughout the first 3 years, IgG values decreased significantly in the BC but not in the GC cohort.

1. Midaglia L, et al. Rituximab treatment for MS: an observational multicentric dose comparison. MSVirtual 2020, PS01.05.

TERIKIDS trial extension of teriflunomide in paediatric MS

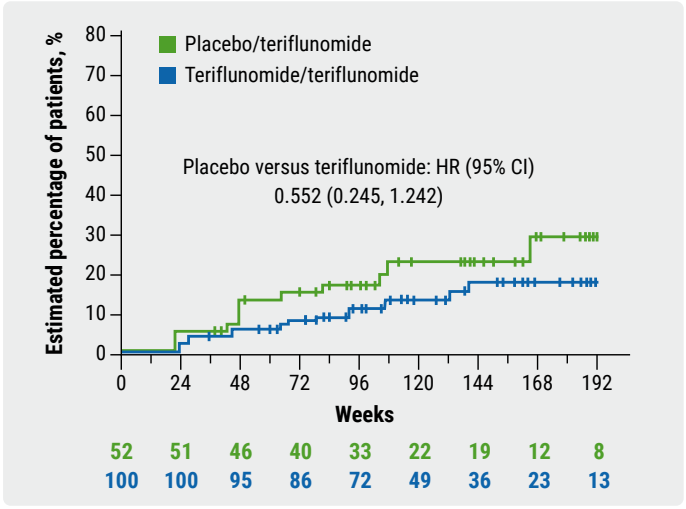
During the combined double-blind and open-label periods in the TERIKIDS-trial, continuous teriflunomide numerically lowered clinical relapses and the risk of 24-week sustained disability progression compared with delayed initiation of teriflunomide after placebo [1]. Teriflunomide was well tolerated and had a manageable safety profile.

TERIKIDS (NCT02201108) is a 2-year, multicentre, multi-national, randomised, double-blind, placebo-controlled, parallel-group phase 3 study of teriflunomide in children and adolescents of 10-17 years at baseline with relapsing MS. It is followed by a 96-week open-label period, of which interim results were shared. All participants in the open-label period (n=152) received teriflunomide at a dose based on body weight, equivalent to 14 mg in adults.

The primary endpoint in the double-blind period, median time to first confirmed relapse, was 75.3 weeks with teriflunomide and 39.1 weeks with placebo (HR 0.66; 95% CI 0.39–1.1). This difference was not statistically significant versus placebo (P=0.29). In a prespecified sensitivity analysis, median time to first disease activity was significantly reduced by teriflunomide (HR 0.57; 95% CI 0.37-0.87; P=0.041).

Differences in key secondary outcomes were also significant. There was relative reduction of 75% in the number of T1 gadolinium-enhancing lesions versus placebo (P<0.0001), and a relative reduction of 55% in the number of new/enlarging T2 lesions (P=0.0006). Median time to first confirmed relapse in the double-blind and open-label period combined was numerically lower with continuous teriflunomide versus placebo/teriflunomide (HR 0.61), as was time to disability progression (HR 0.552; see Figure). The number of new/enlarging T2 lesions per MRI scan was reduced with continuous teriflunomide versus placebo/teriflunomide (6.3 vs 13.0; P=0.0006). The number of T1 gadolinium-enhancing lesions was 4.2 versus 1.9 (P=0.0106).

Figure: Time to disability progression sustained for 24 weeks [1]



Incidence of adverse events during the open-label period was lower with continuous teriflunomide than with placebo/teriflunomide: 68.0% versus 82.7%. In 8 patients, adverse events (2 serious) led to treatment discontinuation during the open-label period.

1. Chitnis T, et al. Teriflunomide efficacy and safety in pediatric patients with relapsing forms of MS: Interim analysis of open-label TERIKIDS trial extension. MSVirtual 2020, Abstract FC02.04.

Teriflunomide improves satisfaction versus prior DMT regardless of age

In the phase 4, real-world Teri-PRO study, teriflunomide improved treatment satisfaction regardless of age in relapsing MS patients switching from other disease-modifying therapies (DMTs). Improvements occurred as early as week 4 and persisted at week 48 of treatment [1].

The presented subanalysis of Teri-PRO assessed changes in treatment satisfaction over 48 weeks in relapsing MS patients, stratified by age, who switched to teriflunomide 14 mg from prior DMTs. Four groups were identified:

- ≤35 years (n=85);
- >35 to ≤45 years (n=167);
- >45 to ≤55 years (n=175); and
- >55 years (n=129).

Patients rated their satisfaction using the highly-validated Treatment Satisfaction Questionnaire for Medication (TSQM), version 1.4. Its 4 domains are: global satisfaction, effectiveness, side effects, and convenience. Scores are between 0 and 100, from lower to higher satisfaction. Assessment was done at baseline, when actually the prior DMT was evaluated, and again at week 48, when patients rated satisfaction over the past 2-3 weeks or since last use of medication.

Least-squares mean change (LS) in each TSQM domain was significantly improved at week 48 compared with baseline in all patients aged >35 years:

- >35 to ≤45 years: global satisfaction, 15.0 (P<0.0001); effectiveness, 6.3 (P=0.0157); side effects, 20.6 (P<0.0001); convenience, 31.6 (P<0.0001).
- >45 to ≤55 years: global satisfaction, 15.4 (P<0.0001); effectiveness, 8.3 (P<0.0001); side effects, 20.4 (P<0.0001; convenience, 31.0 (P<0.0001).
- >55 years: global satisfaction, 11.3 (P=0.0001); effectiveness, 9.3 (P=0.0001); side effects, 11.7 (P<0.0001); convenience, 29.8 (P<0.0001).

In the group of patients aged ≤35 years, improvements in 2 domains reached significance: side effects (26.2, P<0.0001) and convenience (28.7, P<0.0001); the other 2 domains showed a numerical positive trend.

1. Coyle P, et al. Treatment Satisfaction Across Age Groups in Patients Who Switched to Teriflunomide: Analysis of the Real-world Teri-PRO Study. MSVirtual 2020, Abstract P1065.

Safety and efficacy of cladribine, glatiramer acetate, and more

Interim data on long-term efficacy and durability of effect of **cladribine tablets** from CLASSIC-MS, with a median of 10 years follow-up, were presented [1]. Interim results of 147 participants of this phase 4 study suggested sustained efficacy of cladribine following 2 annual treatment cycles, with a substantial proportion of patients requiring no further treatment with a disease-modifying treatment or assistive ambulatory device. Median time since last parent study dose (LPSD) was 10 (range 8-14) years. Of 147 patients, 139 (94.6%) did not use a wheelchair/were not bedridden in the 3 months prior to CLASSIC-MS; 123 (83.7%) did not need an ambulatory device (EDSS <6) at any time since LPSD. The majority of patients (93/147: 63.3%) received no subsequent DMT after LPSD, and 59.1% maintained active employment.

The safety, tolerability, and efficacy in terms of NEDA-3 of **glatiramer acetate** long-acting injection in the subpopulation of 10 relapsing-remitting MS patients who completed the core study and finished 3 years of the study extension were encouraging [2]. Mean EDSS score after 4 years showed no change versus baseline. There were no relapses or MRI activity. NEDA-3 over 4 years was achieved by 90% of the per protocol population. The number of adverse events was significantly reduced during the extension study. No unexpected adverse events were reported. According to the authors, these results further support the assumption of the potential of glatiramer acetate long-acting injection to improve MS treatment by significantly reducing the frequency of injections, increasing adherence, and providing a therapeutic benefit.

Effects of **ponesimod** on prespecified MRI-based endpoints and NEDA status in relapsing MS patients in the phase 3 OPTIMUM study were evaluated [3]. Patients were randomised to ponesimod or **teriflunomide** for 108 weeks. Of 1,133 participants, 985 (86.9%) completed the study. For all MRI outcomes, including whole brain volume loss, ponesimod showed more benefit than teriflunomide. A significantly higher percentage of patients treated with ponesimod achieved NEDA-3 and NEDA-4 status. At week 108, 28.2% and 18.3% of patients in the ponesimod and teriflunomide groups, respectively, achieved NEDA-3 (OR 1.70; P=0.0004); 15.0% and 8.5% achieved NEDA-4 (OR 1.85; P=0.0026).

The clinical effectiveness of **natalizumab**, **fingolimod**, and **BRACETD** (interferon-β, glatiramer acetate, dimethyl fumarate, or teriflunomide) was compared in patients with rapidly evolving severe relapsing-remitting MS in a real-world setting [4]. Mean follow-up was approximately 3 years. Annualised relapse rate was lowest with natalizumab, followed by fingolimod and BRACETD (ARR 0.18 vs 0.29 vs 0.39, respectively; P<0.001 for all comparisons). Risk of first relapse was lower with natalizumab versus fingolimod or BRACETD (HR 0.63 and 0.41; P<0.001 for both) and with fingolimod versus BRACETD (HR 0.66; P<0.001). Confirmed disability improvement was more likely with natalizumab than with fingolimod (HR 1.25; P=0.047) or BRACETD (HR 1.46; P=0.002).

1. Giovannoni G, et al. CLASSIC-MS: Long-term efficacy and real-world treatment patterns for patients receiving cladribine tablets - interim data with 8–14 years follow-up. MSVirtual 2020, Abstract LB1229.
2. Fletcher S, et al. Glatiramer Acetate Depot (Extended-Release) Phase IIa Study in Patients with RRMS: Safety, Tolerability and Efficacy Four-Years Analysis. MSVirtual 2020, Abstract LB1228.
3. Kappos L, et al. Effect of oral ponesimod on clinical disease activity and MRI-based outcomes in patients with relapsing multiple sclerosis: Phase 3 OPTIMUM study. MSVirtual 2020, Abstract P0071.
4. Spelman T, et al. Comparative effectiveness of natalizumab, fingolimod, and first-line therapies for rapidly evolving severe relapsing-remitting multiple sclerosis. MSVirtual 2020, Abstract P0859.

Novel Treatment Directions

Functional potential of gut microbiome in paediatric MS

A study using metagenomic sequencing found differences in the functional potential of the gut microbiome of patients with paediatric-onset MS compared with controls at various metabolic pathways [1]. Exposure to disease-modifying therapy (DMT) was associated with enrichment of pathways involved in promoting central nervous system remyelination.

A Canadian group examined the gut microbiome functional diversity and potential by metagenomic analysis of stool samples from 20 patients ≤21 years old (mean age 16.1 years) with paediatric-onset MS and from 20 matched controls. Exposure to antibiotics or corticosteroids 30 days prior to sampling was not allowed. MS patients were either DMT-naïve (n=8) or used interferon-beta or glatiramer acetate (n=12).

There were no significant differences in functional alpha-diversity by disease or DMT status. However, differential analysis of metabolic pathways revealed that MS patients exhibited higher *Archaea*-related methanogenesis, flavin biosynthesis (producing vitamin B and flavin cofactors), viral activity, metabolism of heavy metals, and degradation of L-glutamate (which produces the short-chain fatty-acid propionate). These differences were not significant for the DMT-naïve versus DMT-exposed MS patients. Homolactic fermentation (lactate production, associated with anti-inflammatory effects) and bacterial carbohydrate degradation were lower in MS patients than in controls. In patients using a DMT, an enrichment of pathways involved in promoting CNS remyelination was observed versus DMT-naïve MS patients. For example, choline biosynthesis was enriched in DMT-exposed patients (log-fold change 21; 95% CI 12–29; P<0.0001).

1. Mirza A, et al. Functional survey of the pediatric multiple sclerosis microbiome. MSVirtual 2020, Abstract PS10.03.

Modulating BTK-dependent inflammatory signalling in microglia

Using the cuprizone-induced toxicity model, the role of Bruton's tyrosine kinase (BTK) signalling in modulating inflammation in microglial cells was assessed [1]. Results showed that BTK-dependent inflammatory signalling in these cells can be modulated using brain-penetrant BTK inhibitors *in vivo*. This treatment may suppress microglia-driven neuroinflammation in MS progression.

BTK is expressed in B-lymphocytes and monocytes/macrophages as well as in microglia. It is assumed to modulate the activity of both adaptive and innate immune cells. In B cells, BTK is centrally involved in the B-cell receptor signalling pathway, regulating proliferation, maturation, antigen presentation, and production of secreted immunoglobulins. The research that was reported focused on the possible role of BTK in regulating microglial deleterious inflammatory signalling.

This role was evaluated applying immunohistochemistry, Western blotting, and RNA sequencing in 3 different settings: primary murine microglial cells *in vitro*, a rodent model of cuprizone-induced demyelination, and *post mortem* MS brain tissue.

In mouse microglial cells, basal BTK activity was enhanced by stimulation with immune complexes and silenced with a BTK inhibitor. In autopsy tissue specimens, expression of BTK could be demonstrated in B cells and microglial cells; in MS lesion samples, levels were increased. Furthermore, a BTK-dependent transcriptional profile in brains from cuprizone-treated mice was identified. It was postulated that a brain-penetrant BTK inhibitor might provide therapeutic benefit within the CNS. Oral administration was found to downregulate the BTK-dependent gene expression signature in the mouse model.

1. Gruber R, et al. Decoding Bruton's tyrosine kinase signalling in neuroinflammation. MSVirtual 2020, Abstract P0311.

Therapeutic potential of anti-MOSPD2 monoclonal antibodies

Human proof-of-concept data showed that 2 monoclonal antibodies against motile sperm domain-containing protein 2 (MOSPD2) significantly inhibit the migration of monocytes from MS patients *ex vivo*, regardless of patient diagnosis, disease severity, or treatment applied [1]. Anti-MOSPD2 monoclonal antibodies, therefore, hold therapeutic potential for MS in all stages.

MOSPD2 is a surface protein expressed on monocytes and plays a key role in these cells' ability to migrate to inflammatory sites, in a chemokine-agnostic manner. Study results of 2 anti-MOSPD2 monoclonal antibodies with distinct epitopes were presented.

Blood samples from 25 relapsing-remitting, 4 primary progressive, and 4 secondary-progressive MS patients were analysed. Isolated monocytes were tested for chemotaxis in the presence of 2 anti-MOSPD2 drug candidates, here referred to as mAb1 and mAb2. An isotype control antibody was used as a reference.

Incubation with mAb1 and mAb2 profoundly inhibited monocyte migration in all tested MS patients, by up to 97%. This effect was independent of disease stage, gender, and MS medication used. These human data provide, for the first time, proof of concept for the possibility to target monocyte migration in MS patients. This is a different mechanism from existing treatments (mostly targeting T and B cells), which helps explain that both anti-MOSPD2 monoclonal antibodies showed an additional efficacy to any therapy participants already used. The results indicate that this approach may be implemented in all types and stages of MS. A first-in-human study is planned for the second half of 2021.

1. Salem Y, et al. Targeting monocyte migration for treatment of MS: Human ex-vivo proof-of-concept for Anti-MOSPD2 mAbs in patients with RR and progressive MS. MSVirtual 2020, Abstract P0402.

Masitinib: a first-in-class TKI as treatment of progressive MS

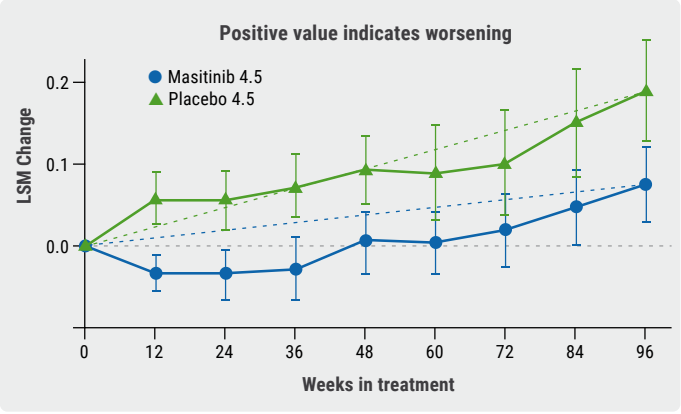
Results of a randomised phase 3 trial indicate that masitinib may be a new treatment option for both primary progressive MS and non-active secondary progressive MS [1]. Treatment with this tyrosine kinase inhibitor (TKI) resulted in a significant and sustained change in EDSS score over 2 years.

Masitinib has a novel mechanism of action which is thought to have an impact on the innate immune system by selectively inhibiting mast cell activity (measured by c-KIT, LYN, and FYN) and microglia activity (measured by CSF1R).

Results of a randomised, double-blind, placebo-controlled, phase 2b/3 trial were presented. The trial had novel design features, evaluating 2 independent parallel groups: 4.5 mg/kg/day versus matched placebo, and titrated 6.0 mg/kg/day versus placebo. Efficacy results from the high-dose parallel group were inconclusive and not reported. The study of masitinib 4.5 mg/kg/day included 300 patients with either primary progressive MS or non-active secondary progressive MS. Mean age was 49.3 years, median baseline EDSS score 5.5. Patients received masitinib (n=199) or placebo (n=101) for 96 weeks. The primary endpoint was overall mean absolute EDSS change from baseline.

Masitinib was significantly more effective than placebo: EDSS change was 0.001 versus 0.098 (P=0.0256: see Figure). This treatment effect was numerically maintained when stratifying the non-active secondary progressive (n=120 vs 56) and primary progressive MS (n=79 vs 45) groups. Sensitivity analysis showed that masitinib was associated with a significant 39% increase in the probability of either reduction in EDSS progression or increase in EDSS improvement (P=0.0446). There was also a significant 42% lower relative risk of first progression (P=0.034) and a 37% lower relative risk of 12-weeks confirmed progression (P=0.159). Masitinib treatment effects were irrespective of baseline inflammatory status. Safety was consistent with the known profile of masitinib. In the experimental and placebo-group respectively, 94.5% and 87.1% experienced ≥1 adverse event.

Figure: Absolute changes from baseline in EDSS measured every 12 weeks up to week 96 [1]



1. Vermersch P, et al. Masitinib in primary progressive (PPMS) and non-active secondary progressive (nSPMS) multiple sclerosis: Results from phase 3 study AB07002. MSVirtual 2020, FC04.01.

Gold nanocrystals may improve brain metabolic profile

Interim results from two phase 2 studies provide evidence that orally delivered CNM-Au8 (gold nanocrystals) have catalytic effects on key bioenergetic metabolites in the brain of patients with MS or Parkinson's disease (PD) [1]. The observed metabolic homeostasis may be neuroprotective.

CNM-Au8 is a suspension of clean-surfaced, faceted, gold nanocrystals that promotes remyelination and neuroprotection by catalysing nicotinamide adenine dinucleotide (NAD) and adenosine triphosphate (ATP) production and by reducing oxidative stress. Treatment effects are evaluated using high-resolution ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS). With this quantitative technique, bioenergetic metabolites can be monitored, as well as phospholipid and myelin precursors.

Preliminary target engagement data from 2 ongoing open-label imaging trials were presented: REPAIR-MS and REPAIR-PD. Treatment consisted of CNM-Au8 30 mg/day. 7T ^{31}P-MRS was conducted at baseline and after 12-16 weeks of treatment. Results of 4 completers with MS and 6 with PD were available.

For key bioenergetic markers, percentage change from baseline at the end-of-study visit highly correlated with baseline levels. Whole-brain baseline NAD levels below the mean significantly increased at end-of-study visit. However, baseline NAD levels higher than the mean normalised to mean baseline levels. These dynamics were not only seen for total NAD levels (r^2=0.6384; P=0.0056), but also for β-ATP (r^2=0.8723; P<0.0001), and several other ^{31}P-metabolites.

According to the authors, these observations indicate that CNM-Au8 has a homeostatic effect on brain bioenergetics. Full analyses will be conducted once the 2 trials are completed. Another ongoing study, called VISIONARY-MS, will further explore the possible neuroprotective effects of the brain metabolic homeostasis observed with CNM-Au8 treatment.

1. Ren J, et al. Effects of nanocatalysis on CNS bioenergetic markers in patients treated with CNM-Au8: Interim results from two Phase 2 ^{31}Phosphorous imaging studies. MSVirtual 2020, P0206.

Retinoid-X receptor agonist promotes remyelination

In a double-blind, placebo-controlled phase 2a trial, the non-specific retinoid-X receptor agonist bexarotene promoted remyelination in MS patients [1]. Bexarotene was very poorly tolerated and its use in MS is not recommended by the authors. However, they believe that their data support the development of selective retinoid-X receptor gamma agonists.

The trial assessed the safety and efficacy of bexarotene, which is licensed for the treatment of cutaneous T cell lymphoma, as a remyelinating therapy in people with relapsing-remitting MS. The 52 randomised participants were aged 18-50 years, had an EDSS score of 6 or less and at least 5 MRI brain lesions, and were stable on dimethyl fumarate for at least 6 months. They were randomised 1:1 to bexarotene 300 mg/m^2 or placebo for 6 months. The primary efficacy endpoint was change in magnetisation transfer ratio (MTR) of those lesions with the lowest tissue integrity at baseline, that is those with MTR values below the "within-patient" median (the submedian). Analysis was by intention to treat.

The primary efficacy outcome was not met. There was no significant difference in mean submedian lesion MTR change. This difference, adjusted for baseline MTR, EDSS, age, gender, and site, was 0.16 pu (0.25 pu in the bexarotene group vs 0.09 pu in the placebo group; P=0.54). In an exploratory analysis at lesion level, the treatment difference in submedian lesions was significantly greater than in supermedian lesions (P=0.001-0.007). This suggests a biological effect of bexarotene on MTR which depends on baseline lesional MTR. When lesions were divided by location, there were statistically significant treatment differences in cortical grey matter lesions, deep grey matter lesions, and brainstem lesions. Furthermore, bexarotene reduced full field visual evoked potential (VEP) latency versus placebo in all eyes and in the 52 eyes with delayed VEPs at baseline.

All 26 patients in the bexarotene group experienced adverse effects: 6.12 on average. Patients in the placebo group experienced on average 1.63 adverse events. In the experimental group, 100% experienced hypothyroidism, and 92% hypertriglyceridaemia, while 50% had rash and 38% neutropenia. In the bexarotene and placebo group, there were 0 and 1 serious adverse events, respectively.

1. Brown J, et al. Phase 2 clinical trial evidence that a retinoid-X receptor agonist promotes remyelination in people with relapsing-remitting multiple sclerosis. MSVirtual 2020, LB01.02

Neuromyelitis Optica Spectrum Disorders

Gut dysbiosis in NMOSD promotes CNS autoimmunity

Neuromyelitis optica spectrum disorders (NMOSD) faecal microbiota increases susceptibility for experimental autoimmune encephalomyelitis (EAE) in a rodent model [1]. Reduction in the number of regulatory T cells may contribute to EAE exacerbation.

Dysbiosis of gut microbiota has been shown both in MS and NMOSD, suggesting that the gut microbiome may regulate inflammatory responses. A San Francisco-based group hypothesised that the gut microbiota from NMOSD patients play a role in NMOSD pathogenesis. To investigate this, they colonised wild-type C57BL/6 germ-free mice with faecal samples from an untreated NMOSD patient (n=10), a household healthy control (HHC; n=9), or vehicle (n=13) for 5 weeks. In the month after that, susceptibility to MOG p35-55-induced EAE was evaluated.

Results showed that EAE was more severe in mice colonised with faecal microbiota from NMOSD and HHC (3.1 and 2.6, respectively) than in mice from the vehicle group (1.9; P≤0.01). The mean clinical score of mice colonised with NMOSD gut microbiota was significantly higher than mice colonised with gut microbiota from HHC or vehicle (P≤0.001). The amount of CD4+Foxp3+CD25+ regulatory T cells was decreased in lamina propria of small (LP-SI) and large (LP-LI) intestine, Peyer's patches, and mesenteric lymph node compartments in the NMOSD and HHC groups versus the vehicle group (P≤0.01). The amount of CD4+Foxp3+Helios+ T cells was significantly decreased in mesenteric lymph nodes and LP-SI in the NMOSD and HHC groups compared to the vehicle group (P≤0.01).

These results suggest that different mechanisms may be involved in EAE enhancement in NMOSD and HHC. The researchers intend to test more samples of NMOSD patients and healthy controls; to extract tissues and phenotype immune cells at the peak of the disease; and to perform 16sRNA analysis, to correlate bacterial compositions between samples and immunophenotyping of different tissues.

1. Moinfar Z, et al. Gut dysbiosis in neuromyelitis optica promotes CNS autoimmunity. MSVirtual 2020, Abstract PS10.05.

NG-specific biomarkers differentiate NMOSD from MS

Neutrophil granulocyte (NG)-specific biomarkers have high sensitivity and specificity for rapid differentiation between acute NMOSD, anti-MOG antibody-associated disease (MOGAD), and relapsing-remitting MS, even in auto-antibody-negative cases. NG-biomarkers can be measured within a few hours and may help determine treatment choice in the acute phase.

Neuromyelitis optica spectrum disorder (NMOSD), MOGAD, and MS have a different aetiology and pathogenesis and are difficult to differentiate clinically. The diagnostic gold standard for NMOSD and MOGAD is measuring aquaporin-4 and MOG antibodies, but sensitivity is limited and laboratory turnaround time is up to 2 weeks. There is a need for better and also quicker tests.

The objective of the presented study was to test whether NG-derived biomarkers in CSF could be used to differentiate NMOSD and MOGAD from MS and whether the results can be used for therapeutic decision-making in the acute disease phase. CSF samples were available of 42 patients with NMOSD (18 acute, 24 stable), 6 with MOGAD, and 41 with relapsing-remitting MS (18 acute, 23 stable). Four NG-markers were measured: elastase, MPO, MMP-8, and NGAL. They were compared with 2 known markers of neuronal (NfL) and astrocytic (GFAP) damage in NMOSD and MS, and with an additional astrocytic marker, i.e. S100B. CSF from 25 healthy controls served as reference.

The results showed that NG-markers appeared both in NMOSD and MOGAD. Their levels correlated both with the highest and lowest NG cell count in CSF. In acute NMOSD, all 4 NG-markers were increased compared to controls and acute relapsing-remitting MS (all P<0.01). Elastase, MPO, and MMP-8 were increased in MOGAD versus controls (P<0.025) and acute relapsing-remitting MS (P<0.04). GFAP levels were increased only in NMOSD, mainly in the acute phase (P<0.01). NfL was elevated in all disease groups compared with controls (P<0.01). Neither GFAP nor NfL were suitable as a diagnostic

marker to distinguish between NMOSD and MS, but they can be useful disease activity markers. Increased S100B and GFAP levels differentiated acute NMOSD from MOGAD.

1. Watanabe M, et al. Neutrophil granulocyte markers in cerebrospinal fluid differentiate NMOSD and anti-MOG antibody associated disease from MS in acute disease phase. MSVirtual 2020, Abstract LB01.03.

Eculizumab reduces long-term relapse risk in AQP4-positive NMOSD

Results of a long-term post-hoc analysis support the long-term effectiveness and safety of eculizumab monotherapy in aquaporin-4 (AQP4)-positive NMOSD. Over 90% of patients who had experienced 1 or 2 relapses in the year prior to the start of the PREVENT trial remained relapse-free through 192 weeks of eculizumab monotherapy [1].

PREVENT was a randomised, double-blind phase 3 trial in which eculizumab was associated with a significantly lower risk of relapse than placebo among patients with AQP4-positive NMOSD and was well tolerated [2]. The presented long-term results centred on the 33 patients who received eculizumab as monotherapy during PREVENT and/or its open-label extension (OLE), for a total of 85.3 patient-years (PY). In PREVENT, 1 of these 33 patients had experienced an adjudicated relapse versus 7 of 13 with placebo alone.

After 192 weeks, 96.2% and 93.8% of patients who received eculizumab monotherapy or eculizumab with concomitant immunosuppressive therapy (IST), respectively, were relapse-free. No patients receiving eculizumab monotherapy were hospitalised for a relapse or started IST.

Eculizumab has generally been well tolerated in the short- and longer term in patients who received the drug in the PREVENT study and/or its ongoing OLE. The number of adverse events (AEs) after 192 weeks that were related to treatment with eculizumab monotherapy (PREVENT + OLE) were similar to placebo alone in PREVENT: 181.0 and 186.0 events per 100 PY, respectively. The infection rate was also similar: 174.1 versus 186.0 events per 100 PY. There were no meningococcal infections or deaths. Actually, there were less treatment-related serious AEs with eculizumab monotherapy than with placebo (5.7 vs 23.3 per 100 PY).

1. Pittock S, et al. Long-term efficacy and safety of eculizumab monotherapy in AQP4+ neuromyelitis optica spectrum disorder. MSVirtual 2020, Abstract FC01.01.
2. Pittock SJ, et al. N Engl J Med. 2019;381(7):614-25.

Satralizumab lowers risk of severe relapse in NMOSD patients

Patients treated with satralizumab had a 79% lower risk of severe relapse and were less likely to receive acute relapse therapy compared with placebo, in addition to having a lower relapse risk overall [1]. This was the main conclusion from a pooled analysis of results across the double-blind periods of two phase 3 trials, SAkuraSky and SAkuraStar.

Satralizumab reduced relapse frequency and had a favourable safety profile in the placebo-controlled trials SAkuraSky (satralizumab + baseline immunosuppressants) and SAkuraStar (satralizumab monotherapy) trials. In both studies, participants were randomised to satralizumab 120 mg or placebo at weeks 0, 2, 4, and Q4W thereafter for 24 weeks.

The pooled analysis used data from the intention-to-treat (ITT) populations in the double-blind periods of 24 weeks (n=178). The impact of treatment on relapse severity was assessed by comparing the EDSS score at relapse and prior to relapse. A similar analysis was performed using visual Functional Systems Score (FSS) to assess impact on optic neuritis relapses. A protocol-defined relapse was severe if it resulted in a change of ≥2 points on the EDSS or visual FSS.

In the ITT-population, 27 of 104 patients (26%) in the satralizumab group had a protocol-defined relapse versus 34 of 74 patients (46%) in the placebo group. In the subgroup of aquaporin-4-positive patients, 12 of 68 patients (18%) versus 25 of 51 patients (49%) had a protocol-defined relapse, respectively. The proportion of severe protocol-defined relapses was also lower in patients receiving satralizumab: 5 of 27 events (19%) versus 12 of 34 events (35%) in the placebo group. This equals a relative risk reduction of 79% (OR 0.21; 95% CI 0.07–0.61; P=0.002). In aquaporin-4-positive patients, 4 of 12 events (33%) in the satralizumab group and 11 of 25 events (44%) in the placebo group were severe (OR 0.18; 95% CI 0.06–0.58; P=0.002). Optic neuritis relapses were severe in 2 of 8 events (25%) versus 5 of 13 events (39%). In the ITT population, acute relapse rescue therapy was prescribed in 39 of 104 patients in the satralizumab group (38%) versus 43 of 74 patients (58%) in the placebo group (OR 0.46; P=0.015). As the number of patients with severe protocol-defined relapses was low, results should be interpreted with caution.

1. Palace J, et al. Effect of satralizumab on relapse severity in neuromyelitis optica spectrum disorder (NMOSD): results from the Phase III SAkura studies. MSVirtual 2020, Abstract FC01.03.

Clinical features of a recently identified disease: GFAP autoimmunity

Glial fibrillar acidic protein (GFAP) autoimmunity is a recently identified disease at the interface between autoimmune encephalitis and gliopathies. Results of a French cohort study showed that GFAP autoimmunity was generally associated with a favourable outcome, and monophasic course with low risk of relapse [1].

GFAP autoimmunity (autoimmune GFAP astrocytopathy) was first described in 2016 by researchers of the Mayo Clinic (USA) [2]. GFAP is a type III intermediate filament protein with several isoforms and is expressed by astrocytes and ependymocytes in the central nervous system. Auto-antibodies against GFAPα are a biomarker of autoimmune GFAP astrocytopathy.

In a French cohort study, all patients from 2 referral centres who tested positive for GFAP antibodies were included (n=46). Clinical, biological, and imaging features were reported, as well as clinical course and outcomes. Median age at onset was 43 years; 65% were male.

Other autoimmune diseases were found in 22%, coexisting neural autoantibodies in 11% (including MOG-IgG and AQP4-IgG). Infectious prodromal symptoms were reported in 82%. The most frequent presentation was meningoencephalitis (61%) and meningoencephalomyelitis (24%). Other/associated clinical presentation included: myelitis (30%), visual tract involvement (35%), and peripheral nervous system involvement (28%).

Cerebrospinal fluid showed pleocytosis (98%), oligoclonal bands (77%), and low glucose level (15%). MRI findings were heterogeneous: radial enhancement was found in 26%, periventricular diffuse T2 hyperintensity in 39%, brainstem involvement in 33%, leptomeningeal enhancement in 23%.

There is no standard treatment regimen for GFAP autoimmunity, which is one of the unmet needs. Immunotherapy was given to 17 patients. Though high severity at presentation was common, 39/46 patients had a monophasic course, associated with a good outcome at last follow-up (Rankin Score ≤2: 89% at 15.5 months).

1. Gravier Dumonceau A, et al. GFAP auto-immunity: a French cohort study. MSVirtual 2020, Abstract FC01.05.
2. Fang B, et al. JAMA Neurol. 2016 Nov 1;73(11):1297-1307.

Miscellaneous Topics

Gender-based approach to MS therapeutics: a missed opportunity

Most pivotal disease-modifying treatment (DMT) trials miss an opportunity to evaluate and understand sex differences. There seem to be unexplored sources of bias in observational and interventional studies. Greater attention is warranted to evaluate sex-specific experiences, especially regarding safety and side effects. This was argued by Dr Riley Bove (Weil Institute for the Neurosciences, USA) in an invited lecture [1].

The female:male ratio is about 3:1 in MS. Overall, men and women tend to reach disability milestones at a similar age, despite numerous differences in the disease course. For example, men tend to be older at diagnosis, have more often a progressive onset of MS, have a lower relapse rate (with a greater proportion of motor relapses), and experience more rapid disability progression in relapsing-onset MS.

In women, the risk of developing adverse health outcomes is nearly doubled compared with men. After menopause, women may experience increased disability progression, but also less inflammatory activity. Many gaps in scientific knowledge surround postmenopausal women, including the unknown effectiveness of hormone supplementation in stabilising symptoms or even offering neuroprotection.

Drug volume of distribution, metabolism, and elimination are likely to be influenced by sex differences in anatomy, body composition, and physiology. Despite known differences, most drugs have had no sex-specific dosage recommendations in their labels.

In the major clinical trials, evaluation of sex differences in enrolment characteristics, DMT efficacy, and/or side effects are incomplete. Dr Bove described in detail a study she recently published, reporting sex differences in a total of 29

clinical MS trials of DMT [2]. She found that:

- 0 of 29 trials reported baseline comparison of demographic or clinical characteristics according to sex;
- 10 of 29 trials reported a pre-planned analysis of efficacy based on sex (but without evaluating baseline sex differences);
- 0 of 29 trials performed a pre-planned analysis of major adverse events based on sex;
- 8 of 29 trials published post-hoc comparisons of sex differences in efficacy and safety outcomes; and
- 0 of 29 trials commented on statistical power to report sex differences.

Dr Bove also stressed that adjusting for sex differences is not the same as evaluating and understanding these differences. She would recommend at a minimum the following steps for reporting sex differences in future trials:

- giving attention to statistical power and pharmacokinetics/pharmacodynamics;
- harmonisation of baseline characteristics;
- evaluation of efficacy and safety; and
- consideration of sex-specific experiences or risks.

Ethical concerns complicate proper research in the area of pregnancy and lactation, but it could also be argued that it is the status quo which is "unethical". An example of an ethical approach in research is to evaluate transfer of DMT into breast milk without exposing the infant. Obviously, DMT selection in women of childbearing potential is very important, including the issue of whether and when to discontinue a DMT, and how to avoid rebound risk. Dr Bove added that there is mounting evidence that B cell-depleting agents support disease control surrounding pregnancy, as B cell depletion can extend well beyond drug elimination.

1. Bove R. Gender Based Approach to MS Therapeutics. MSVirtual 2020, Abstract PS12.01.
2. Houtchens MK & Bove R. Front Neuroendocrinol. 2018;50:123-34.

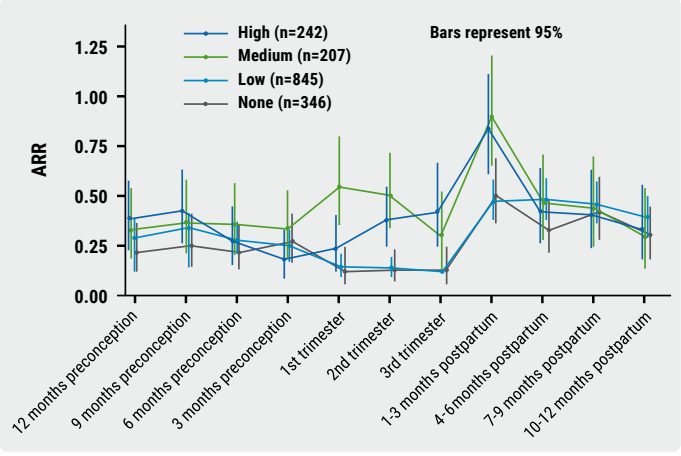
Disease activity during pregnancy in a modern MS cohort

Women with relapsing-remitting MS treated with moderate- or high-efficacy disease-modifying treatment (DMT) are at greater risk of relapse during pregnancy [1]. Apparently, immunomodulatory changes during pregnancy are not sufficient to suppress MS disease activity among these women. This is of great clinical interest because pregnancy has historically been associated with a reduced risk of relapse.

The presented study aimed to compare the characteristics and relapse rates of a modern cohort of women on different classes of DMT (low-, moderate-, and high-efficacy) before conception, and to determine factors that predicted relapse. The study included data of 1,640 pregnancies in 2011-2019, conceived from 1,452 women. DMT use in the year before conception was no DMT (n=346), low-efficacy (n=845), moderate-efficacy (n=207), and high-efficacy (n=242).

EDSS ≥2 at the time of conception was more common in higher-efficacy DMT groups (high-efficacy DMT 41.3%, no DMT 20.2%). Annualised relapse rate (ARR) in the year prior to conception was relatively similar in the 4 DMT groups, averaging 0.29. ARR slightly decreased during pregnancy in the no-DMT or low-efficacy DMT groups, but steadily increased throughout in the high-efficacy group (0.42 vs 0.14 on low-efficacy, in third trimester). In the moderate-efficacy group, ARR increased in the first trimester (0.55 vs 0.14 on low-efficacy), then decreased to a trough in the third. In the first trimester postpartum, there was a spike in ARR in all groups, which was highest in the moderate- and high-efficacy groups (see Figure). Pre-conception ARR and preconception use of medium- or high-efficacy DMT predicted relapse activity during pregnancy. Continuing high-efficacy DMT into pregnancy predicted reduced relapse risk (OR 0.80), as did older age (≥35 years).

Figure: Annualised relapse rate by DMT class



The authors concluded that careful pregnancy management and use of long-acting high-efficacy DMT pre-conception, or continuing high-efficacy DMT into pregnancy beyond the first trimester, may prevent relapse in pregnancy.

1. Yeh W, et al. Pregnancy in a modern day multiple sclerosis cohort: Predictors of relapse during pregnancy. MSVirtual 2020, Abstract PS12.04.

Cardiovascular risk factors may contribute to brain atrophy in MS patients

The presence of cardiovascular (CV) risk factors is associated with brain atrophy in MS patients ≤50 years, who are unlikely to have small vessel disease. An Italian cross-sectional observational study suggests CV risk factors have synergistic effects in MS [1].

The impact of CV risk factors on T2 hyperintense lesion volume and brain atrophy in MS patients aged ≤50 years was evaluated in 124 MS patients (relapsing-remitting MS, n=79; progressive MS, n=45) and 95 matched healthy controls. Participants underwent a complete neurological assessment and brain 3D T2-weighted and FLAIR MRI, as well as 3D T1-weighted MRI. Assessed traditional CV risk factors were smoking ≥5 pack-years, hypertension, dyslipidaemia, and (pre-)diabetes. More stringent cut-offs were also assessed: smoking ≥10 pack-years, and hypertension, dyslipidaemia, or diabetes while on medication. Of the 124 MS patients, 48 had 1 traditional CV risk factor, 15 had 2 or more. Of 95 healthy controls, 19 had 1 risk factor, 4 had more (P<0.001). Thirty MS patients had 1 stringent risk-factor, and 8 had more than 1, as did 10 and 3 healthy controls (P=0.01). The most common CV risk factor was smoking.

In MS patients, having 2 or more traditional CV risk factors was associated with reduced normalised grey matter volume (nGMV; P=0.01), white matter volume (nWMV; P=0.03), and whole brain volume (nBV; P=0.003), but not with T2-lesion volume (T2-LV; P=0.27). Only hypertension was associated with MRI measures (nWMV and nBV). Having 1 stringent CV risk factor was associated with reduced nGMV (P=0.006), nWMV (P=0.003), and nBV (P<0.001), and higher T2-LV (P=0.03). In healthy controls, neither traditional nor stringent risk factors significantly impacted the abovementioned measures.

1. Bonacchi R, et al. Cardiovascular risk factors affect brain volume in young MS patients. MSVirtual 2020, Abstract PS04.05.

Amantadine, modafinil, and methylphenidate for MS-related fatigue

For fatigue, one of the most prevalent subjective symptoms in MS patients, methylphenidate, modafinil, and amantadine are commonly prescribed. Substantial evidence supporting their efficacy is however lacking. In the randomised crossover TRIUMPHANT-MS trial, none of these 3 agents was superior to placebo in improving MS-related fatigue, but they did cause more adverse events [1].

The TRIUMPHANT-MS trial compared the efficacy of twice-daily oral methylphenidate, modafinil, and amantadine against each other and placebo. Eligible patients had MS-related fatigue with a Modified Fatigue Impact Scale (MFIS) score of >33. EDSS score at the time of screening ranged from 0.0 to 7.0. A total of 141 adult patients received 1 of 4 treatment sequences:

i. amantadine, placebo, modafinil, methylphenidate;
ii. placebo, methylphenidate, amantadine, modafinil;
iii. modafinil, amantadine, methylphenidate, placebo; or
iv. methylphenidate, modafinil, placebo, amantadine.

Each medication was titrated over 4 weeks to the participants' highest tolerated dose or pre-defined highest dose. Each intervention was given up to 6 weeks, with a 2-week washout period between treatments. The primary outcome measure was the MFIS score in week 5, when the highest tolerated dose was used.

The estimated mean value of the MFIS total score at baseline was 51.3. In week 5 of treatment, the MFIS total score was 41.2 with amantadine, 39.0 with modafinil, 38.7 with methylphenidate, and 40.7 with placebo (P=0.20 for overall medication effect). In the subgroup of patients with a higher baseline daytime sleepiness (Epworth Sleepiness Scale) score, both modafinil and methylphenidate were superior to placebo in improving MFIS score (-4.1 for both interventions).

In the amantadine, modafinil, and methylphenidate groups, 38.6%, 40.0% and 39.5% of participants reported adverse events, respectively, versus 30.6% in the placebo group. The authors concluded that these agents should not be used indiscriminately for the treatment of MS-related fatigue.

1. Nourbakhsh B, et al. Randomized Trial of Amantadine, Modafinil and, Methylphenidate for Multiple Sclerosis Fatigue. MSVirtual 2020, Abstract PS13.03.