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# ECTRIMS 2021

European Committee for Treatment and Research in MS

13–15 OCTOBER 2021

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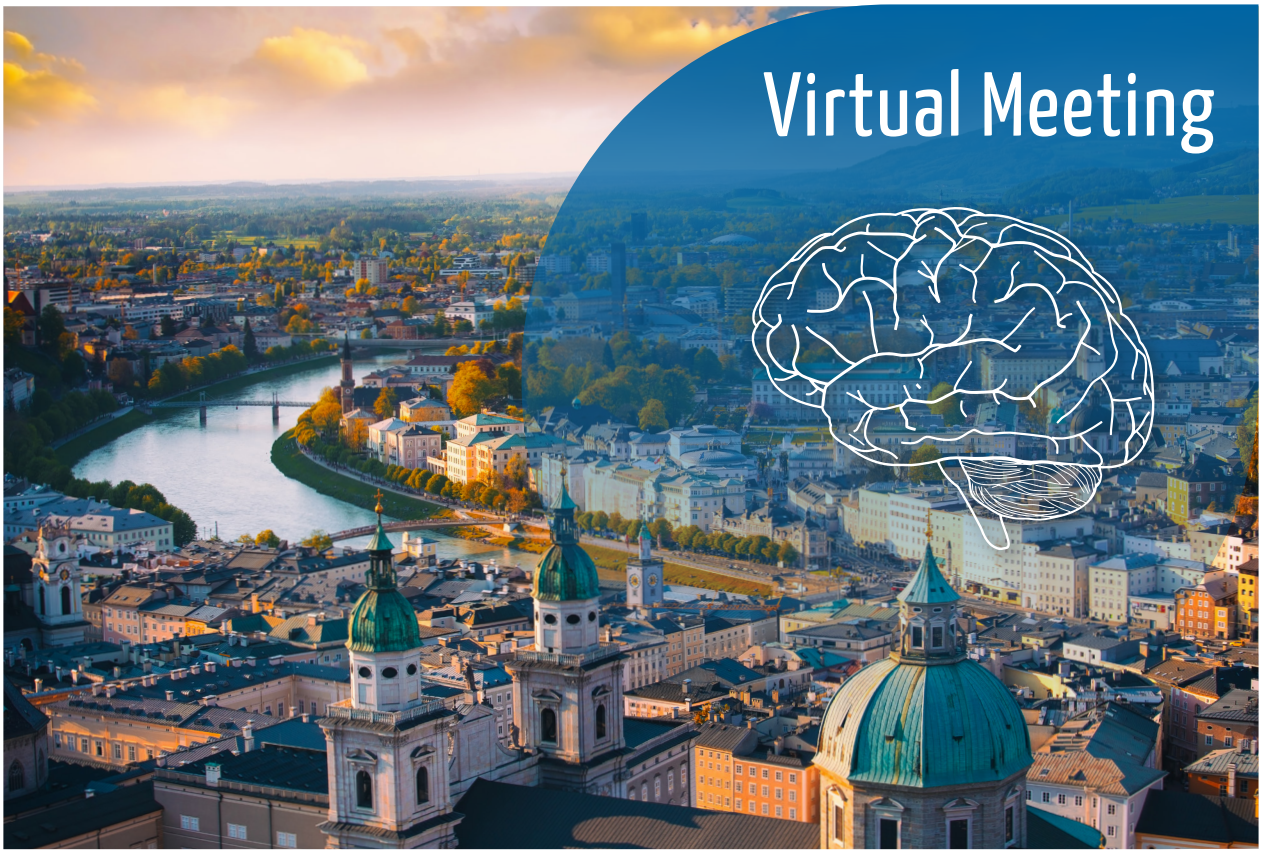


**Stem-Cell Therapy in Progressive MS**

MSC-NTF cell therapy demonstrated safety, reduced neuroinflammatory biomarkers, increased neuroprotective biomarkers, and improved clinical outcomes in patients with progressive MS.

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**Rituximab Most Effective Initial MS Therapy**

Treatment-naïve MS patients benefitted most from rituximab as initial therapy. Compared with dimethyl fumarate, natalizumab, and injectable therapies, rituximab receivers had a lower risk of relapse and MRI lesions.

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**NMOSD: Eculizumab, Satralizumab, or Inebilizumab?**

Eculizumab outperformed satralizumab and inebilizumab at lowering the risk of relapse in NMOSD, both as monotherapy and in combination with immunosuppressants.

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**Head Office**
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

**Postal address**
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom-publishers.com

# COVID-19

## MS patients at risk of hampered immune response after vaccination

**MS patients treated with ocrelizumab, rituximab, or fingolimod showed a reduced immune response after SARS-CoV-2 mRNA vaccination. In addition, higher SARS-CoV-2 antibody levels were observed in MS patients who received the Moderna vaccine compared with the Pfizer/BioNTech vaccine. Although 4 weeks after the second dose the Moderna vaccine generated higher antibody levels in MS patients receiving anti-CD20 therapies or fingolimod [1,2], it is unclear if this is of practical significance in anti-SARS-CoV-2 protective immunity.**

Disease-modifying therapies (DMTs) in MS patients are associated with a decreased immune response to antigens. A post-SARS-CoV-2 vaccination serological assessment was performed to examine the antibody response in MS patients treated with DMTs as compared with untreated patients. The current analysis of this prospective, multicentre cohort study assessed 1,339 MS patients (treated with a DMT, n=1,166; untreated, n=173) who received 2 doses of SARS-CoV-2 mRNA vaccines (Pfizer/BioNTech or Moderna). Blood samples were collected before the 1st dose, and 4 weeks after the 2nd dose. A centralised, blinded serological assessment was performed at each timepoint. Prof. Maria Pia Sormani (University of Genoa, Italy) shared the results.

Multivariate analysis revealed decreased antibody levels in patients treated with ocrelizumab (231-fold decrease, P<0.001), rituximab (20-fold decrease, P<0.001), or fingolimod (32-fold decrease, P<0.001) compared with untreated patients. Notably, patients on anti-CD20 (ocrelizumab/rituximab) therapies developed higher antibody levels when the time to the last administered infusion was longer. Patients who received the Moderna vaccine developed significantly higher antibody levels (2.9-fold) compared with those who received Pfizer/BioNTech (P<0.001). A booster vaccine may therefore be beneficial for patients with low antibody levels.


1. Sormani MP. Effect of SARS-CoV-2 mRNA vaccination in multiple sclerosis patients treated with disease modifying therapies. OP099, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Sormani MP, et al. EBioMedicine. 2021;72:103581.


## Immunotherapy in MS does not influence COVID-19 severity and mortality

**A population-based MS cohort found COVID-19 severity and mortality to depend on age, comorbidity, and degree of disability. Exposure to disease-modifying therapy (DMT) and immunosuppressive DMT was not an essential factor, except for CD20 inhibitors. This adds to the evidence that COVID-19 risk can be individually anticipated in MS patients and, except possibly for those on anti-CD20 therapies, does not generally influence treatment decisions [1–3].**

The objective of this Austrian, nationwide, population-based study was to characterise the prevalence, severity, and overall mortality of SARS-CoV-2 infection in MS patients associated with a specific DMT. Dr Gabriel Bsteh (Medical University of Vienna, Austria) explained that the study included MS patients aged ≥18 years with COVID-19 diagnosed between 1 January 2020 and 30 April 2021. COVID-19 course was classified as either mild (no hospitalisation), severe, or fatal.

Overall, 126 MS patients with COVID-19 were included, with a mean age of 43 years, and 71% were women. Median Expanded Disability Status Scale (EDSS) score was 2.0 and 18.4% had lymphopenia. The total use ratio of DMT was 71%: 38% received an immunomodulatory DMT, 33% an immunosuppressive DMT. COVID-19 course was asymptomatic in 4%, mild in 86.5%, and severe in 9.5%, of whom 3.2% died. *A priori* risk significantly predicted COVID-19 severity ($R^2$ 0.814; P<0.001) and mortality ($R^2$ 0.664; P<0.001), but DMT class did not.

Results showed that exposure to any DMT or exposure to specific immunosuppressive DMT were not significantly associated with COVID-19 severity (OR 1.6; P=0.667 and OR 1.9; P=0.426) or mortality (OR 0.5; P=0.711 and 2.1; P=0.233) compared with no DMT. Dr Bsteh added that there is a caveat for CD20-inhibitors: "Although we did not find a statistical difference in our cohort, there is evidence that CD20-antibodies may be associated with a somewhat higher risk of a severe COVID-19 course."


1. Bsteh G, et al. COVID-19 severity and mortality in multiple sclerosis do not depend on immunotherapy: insights from a nation-wide Austrian Registry. OP096, ECTRIMS 2021, 13–15 October.
2. Bsteh G, et al. PloS one. 2021;16(7):e0255316.
3. Bsteh G, et al. Mult Scler. 2021;27(14):2209-2218.

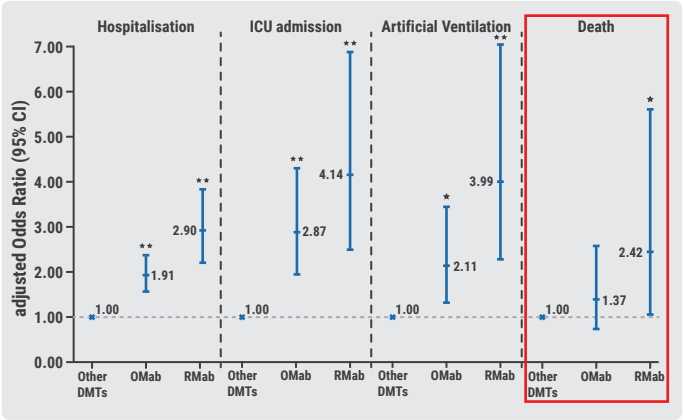
## Anti-CD20 antibodies associated with worse COVID-19 outcomes

**Findings from the COVID-19 in MS global data-sharing initiative show that the use of anti-CD20 medications (ocrelizumab and rituximab) is associated with higher COVID-19 severity, including hospitalisations and ICU admissions, compared with other disease-modifying treatments (DMTs) [1,2].**

The COVID-19 in MS global data-sharing initiative is the largest international, real-world dataset of MS patients with suspected or confirmed COVID-19, including 4,646 (83.4%) confirmed cases from 32 countries [3]. Dr Steve Simpson-Yap (University of Melbourne, Australia) shared the updated results on the associations of anti-CD20 DMTs with COVID-19 severity relative to glatiramer acetate, all other pooled DMTs, and natalizumab.

Male sex, older age, progressive MS, and higher disability were associated with worse outcomes for SARS-CoV-2 infection. The use of anti-CD20 antibodies was associated with significantly worse COVID-19 outcomes. Compared to glatiramer acetate, ocrelizumab users were 1.6 (95% CI 1.06–2.43) times more likely to be hospitalised, and rituximab users were 2.4 (95% CI 1.54–3.81) times more likely to be hospitalised. Ocrelizumab and rituximab use was also associated with a 3.1 (95% CI 1.22–8.00) and 4.7 (95% CI 1.64–12.09) times higher risk of intensive care unit admission, respectively. Rituximab users were 3.6 (95% CI 1.38–9.20) times more likely to be given artificial ventilation; ocrelizumab users were 1.9 (95% CI 0.76–4.55) times more likely to require artificial ventilation. Rituximab users also had a 2.7 (95% CI 0.68–11.09) times higher risk to die, though this effect was non-significant.

**Figure: Associations of ocrelizumab and rituximab with Covid-19 severity versus other DMTs [1]**




*P<0.05; **P<0.001

The associations of ocrelizumab (n=1,100) and rituximab (n=636) with COVID-19 severity compared with other DMTs pooled (n=2,924) are shown in the Figure. Dr Simpson-Yap pointed out that all but one association are statistically significant, including the 2.4 times higher risk of death in rituximab users and a trend towards a higher risk of death in ocrelizumab users. Compared with natalizumab users, ocrelizumab and rituximab use was only associated with a higher risk of hospitalisation, intensive care unit admission, and artificial ventilation.


1. Simpson-Yap S, et al. Updated results of the COVID-19 in MS global data sharing initiative validate consistent associations of anti-CD20 and other reported risk factors with severe COVID-19 outcomes. OP098, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Simpson-Yap S, et al. Neurology. 2021;97(19): e1870-e1885.
3. Peeters LM, et al. Mult Scler. 2020;26(10):1157–1162.


## ECTRIMS-EAN consensus on vaccination in MS patients

**The first-ever European position statement on SARS-CoV-2 vaccination for patients with MS was presented at the 2021 ECTRIMS meeting on behalf of ECTRIMS and the European Academy of Neurology (EAN). The consensus document consists of 59 recommendations on the best vaccination strategy for patients with MS, according to the latest evidence and expert knowledge [1].**

Dr Mauricio Farez (Fundacion FLENI, Argentina) presented the recommendations and conclusions from the ECTRIMS/EAN consensus for vaccination against SARS-CoV-2 in MS patients. For each clinical question, a systematic literature search was conducted considering published studies, guidelines, and position statements. The first and most relevant question that the consensus committee set out to answer was whether MS patients are at a higher risk of COVID-19 or experience a more severe form of the disease. Dr Farez explained that the studies published so far are overall reassuring and do not suggest major safety issues. The main factors associated with more serious forms of COVID-19 in patients with MS are similar to those in the general population. These include age, obesity, diabetes, sex, and ethnicity. Treatment with interferons and glatiramer acetate does not increase the risk of getting COVID-19 or worsen its clinical course. Fingolimod, teriflunomide, natalizumab, and dimethyl fumarate do not seem to negatively affect SARS-CoV-2 infection. However, several studies show that anti-CD20 antibodies and steroid pulses can increase the risk of COVID-19.

At the time of the presentation, 4 SARS-CoV-2 vaccines were licensed for the European Union. These include 2 mRNA vaccines, Moderna and Pfizer/BioNTech, and 2 adenovirus-based vaccines, from Janssen and AstraZeneca. Five other vaccines were under review. "All 4 available vaccines can be administered to patients with MS, including those receiving immunosuppressive disease-modifying therapies," Dr Farez said. He added that no red flags have been observed in MS patients receiving mRNA vaccines, but that continued surveillance for immune-mediated adverse events is warranted. So far, no signals have been observed that SARS-CoV-2 vaccines result in an increased relapse rate or disability worsening. No evidence is present for recommending a specific vaccine to MS patients, nor are there any specific contraindications.

Patients with normal lymphocyte counts taking interferons, glatiramer acetate, teriflunomide, or fumarates are most likely adequately protected. Patients with moderate to severe lymphopenia may not develop an adequate immune response to SARS-CoV-2 vaccination. Therefore, absolute lymphocyte count may be checked before vaccination. Patients taking natalizumab are also likely protected with SARS-CoV-2 vaccination. It is likely that MS patients taking alemtuzumab generate an attenuated immune cellular and humoral response to SARS-CoV-2 vaccines, especially in the first 6 months during maximum lymphopenia. If possible, vaccination should be delayed until at least 6 months after treatment. Patients who have completed both courses of alemtuzumab with complete immune reconstitution are expected to mount a full immune response. In studies, all cladribine-treated MS patients demonstrated a protective humoral immune response to the SARS-CoV-2 vaccine. The majority of patients treated with fingolimod have failed to show a protective level of antibodies following SARS-CoV-2 vaccination. Patients taking ocrelizumab do not mount an appropriate IgG response regardless of lymphocyte count or the time interval from the last ocrelizumab dose (3–9 months). It is advisable to administer a vaccine at least 12 weeks after ocrelizumab dosing and 4–6 weeks prior to the next dose.

1. Farez MF. Position statement on COVID-19 vaccinations in MS patients. OP182, ECTRIMS 2021 Virtual Congress, 13–15 October.

# Experimental Treatments

## The role of astrocyte phenotypes in acute MS lesions

**Astrocytes have been associated with both neuro-degeneration and recovery of neuronal damage in MS [1–4]. While transforming growth factor alpha (TGF-α) induces an anti-inflammatory astrocyte phenotype, vascular endothelial growth factor B (VEGF-B) induces a pro-inflammatory astrocyte polarization. Results now show that TGF-α/VEGF-B ratios can serve as a novel prognostic biomarker for acute and chronic MS lesions [5].**

Dr Veit Rothhammer (University of Erlangen-Nürnberg) discussed the role of astrocyte phenotypes in acute auto-immune inflammatory CNS lesions.

A key protein in the anti-inflammatory astrocyte phenotype is the aryl hydrocarbon receptor (AHR), which mediates protective effects of neural tissue and can be activated by binding of its ligands, originating from the gut microbiome or dietary factors. The activation of AHR is associated with an inhibition of immune cell recruitment, reduced neuron and oligodendrocyte death, and a decreased activation of monocytes [1]. A comparison of AHR ligand serum levels between patients with relapsing-remitting MS and healthy controls demonstrated a decreased level of AHR ligands in patients with MS. This result suggests that glial regeneration mechanisms are reduced in these patients, whereas inflammation, neurodegeneration, and immune cell recruitment are increased [6,7].

*In vitro* analysis of microglial AHR deletion showed that TGF-α and VEGF-B are potential up-stream regulators for astrocytes. TGF-α was associated with an anti-inflammatory phenotype of astrocytes, whereas VEGF-B induced a pro-inflammatory phenotype of astrocytes. *In vivo* analysis confirmed the role of microglia-derived TGF-α and VEGF-B in astrocyte phenotype expression [2,3].

Next, Dr Rothhammer addressed the question of whether the TGF-α/VEGF-B ratio and AHR ligand levels could serve as biomarkers in MS. A recent study showed that a decreasing TGF-α/VEGF-B ratio is significantly associated with increased disease severity in MS (P=0.0161). Similarly, reduced rates of AHR agonistic activity were associated with more severe disease (P=0.0158). Finally, AHR ligand levels predicted the time of conversion from clinically isolated syndrome to definite MS. Higher AHR agonistic activity was associated with a longer time to definite MS diagnosis (P=0.0102) [8].

In conclusion, AHR ligands are decreased in MS patients, which leads to a more pro-inflammatory phenotype of astrocytes. AHR depletion in microglia is associated with reduced TGF-α levels, and increased VEGF-B levels, indirectly stimulating a pro-inflammatory phenotype of astrocytes. TGF-α/VEGF-B ratios and AHR ligand levels have potential in measuring disease activity and predicting a patient's progression to a more severe type of MS.


1. Rothhammer V, et al. Nature Medicine. 2016;22:586–597.
2. Liddelow SA, et al. Nature. 2017;541:481–487.
3. Rothhammer V, et al. Nature. 2018;557:724–728.
4. Wheeler MA, et al. Cell. 2019;176(3):581-596.
5. Rothhammer V, et al. Astrocyte phenotypes and interactions in acute autoimmune inflammatory CNS lesions. OP058, ECTRIMS 2021 Virtual Congress, 13–15 October.
6. Rothhammer V, et al. Sci Rep. 2018;8(1):4970.
7. Rothhammer V, et al. Neurol Neuroimmunol Neuoinflamm. 2017;4(4):e359.
8. Cirac A, et al. Neurol Neuroimmunol Neuroinflamm. 2021;8(5):e1043.


## Promising results of intrathecal MSC-NTF cells in progressive MS

**Intrathecal administration of MSC-NTF cells showed a favourable safety profile in patients with progressive MS. Further post-treatment cerebrospinal fluid (CSF) analysis demonstrated a reduction in neuroinflammatory biomarkers and an increase in neuroprotective biomarkers. Additional exploratory analyses showed improvements in clinical outcome measures following intrathecal MSC-NTF cell therapy [1].**

The pathogenesis of progressive MS includes CNS inflammation, chronic demyelination, and neurodegeneration [2]. The current open-label, phase 2, BCT-101 trial (NCT03799718) aimed to investigate the safety and efficacy of MSC-NTF cells –autologous bone-marrow-derived mesenchymal stem cells, induced in culture to secrete higher levels of neuroprotective factors– in a population of patients with progressive MS. Administration of intrathecal MSC-NTF cells (dosing 100–125 x $10^6$) was performed 3 times, with 8-week intervals, in 18 patients (primary progressive MS, n=4; secondary progressive MS, n=14). Safety was the primary outcome at week 28. Secondary outcome measures included neurological biomarkers and clinical outcome measures. The findings were presented by Dr Jeffrey A. Cohen (Cleveland Clinic, OH, USA).

Headache (88.9%) and back pain (83.3%) were the most common adverse events (AEs). Dr Cohen added that most headaches were related to the lumbar punction, which was the method of therapy administration. Other common AEs were urinary tract infections (33.3%), musculoskeletal pain (27.8%), and injection site pain (22.2%). Two patients had serious AEs of arachnoiditis, one of whom discontinued the study. Regarding the efficacy of intrathecal MSC-NTF cells, CSF neuroinflammatory biomarkers displayed a trend towards reduction (VEGF, HGF), whereas CSF biomarkers of neuroprotection showed a trend of increase (MCP-1, SDF-1 and Osteopontin).

In addition, patients of the current trial were matched to patients of the CLIMB registry (n=48) and the SPRINT-MS trial (NCT01982942) (n=244). Comparing the number of patients with ≥25% improvement on the 9-Hole Peg Test (9-HPT), MSC-NTF receivers (13%) showed numerical benefits over patients from the CLIMB registry (0%), and ibudilast receivers (2%) and placebo receivers (3%) of the SPRINT-MS trial. Similarly, 2.5% Low-Contrast Letter Acuity Chart (LCLA) (≥8 letter improvement) favoured receivers of MSC-NTF cells (27%) over patients of the CLIMB registry (6%), and SPRINT-MS trial (16%, 13%). Finally, a numerically higher proportion of patients achieved ≥5 point improvement on the Symbol Digit Modalities Test (SDMT) when receiving MSC-NTF cells (47%) compared with patients of the CLIMB registry (2%) and patients of the SPRINT-MS trial (27%, 26%).

Due to the open-label, uncontrolled design of the study, clinical outcome measures need to be interpreted with caution. The results of the clinical outcome measures were largely reported descriptively, and no formal statistical analyses were performed. Therefore, a randomised, placebo-controlled trial should be conducted to confirm the results of this study. Dr Cohen mentioned that similar effects were observed for patients with primary progressive MS and patients with secondary progressive MS. However, solid conclusions on this aspect of the study cannot be made, due to the limited sample size.


1. Cohen J, et al. Multicenter Phase 2 Safety and Efficacy Study of MSC-NTF Cells (NurOwn) in Progressive Multiple Sclerosis. OP114, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Baecher-Allan C, et al. Neuron. 2018;97(4):742-768.

## Preliminary data shows positive results of ATA188 for progressive MS

**Preliminary data of a phase 1, open-label extension (OLE) trial investigating ATA188 for progressive MS showed that the drug was generally well tolerated and drove sustained disability improvement (SDI) in a significant proportion of patients. Moreover, improved magnetisation transfer ratios (MTRs) were observed in patients with SDI, suggesting possible remyelination [1].**

Evidence suggests that Epstein-Barr virus is strongly involved with the pathogenesis of MS [2,3]. To this end, the current trial assessed ATA188 as a potential therapy for patients with progressive MS. ATA188 is an investigational, off-the-shelf, allogeneic Epstein-Barr virus-targeted T-cell immunotherapy. In total, 25 patients with progressive MS followed a 12-month dose-escalation protocol of ATA188. Hereafter, patients were invited to enter a 4-year OLE period. Prof. Douglas Arnold (McGill University, Canada) presented preliminary data of the study.

SDI, based on the Expanded Disability Status Scale (EDSS) and timed 25-foot walk, was demonstrated in 7 out of 24 patients at 12 months. Six out of 7 patients who achieved SDI and 12 out of 17 patients who did not achieve SDI entered the OLE. During the OLE, 2 non-SDI patients improved to SDI. MTRs, an MRI marker of myelin density, improved significantly in patients who achieved sustained EDSS improvement at any time compared with patients who did not. MTRs improved in T2 lesions at 12 months, with a median change for patients with sustained EDSS of 0.134 versus -0.030 in patients without sustained EDSS (P=0.021), and at 6 months (P=0.080). Moreover, numerical MTR improvements in normal-appearing brain tissue were observed at 12 months (median change for sustained EDSS, 0.082 vs no sustained EDSS, 0.005; P=0.162). In general, the authors detected a trend supporting an association between improvement in MTR signal and a reduction in EDSS score. Prof. Arnold argued that the MTR data showed that structural changes, suggestive of remyelination, may be the mechanism behind sustained EDSS improvement.

In total, 25 patients received at least one dose of ATA188 and were assessed for safety. A favourable safety profile was observed. No grade >3 adverse events, dose-limiting toxicities, cytokine-release syndrome, or graft-versus-host disease were reported. One grade 3 MS relapse –that was possibly related to treatment– occurred. A randomised, placebo-controlled trial is needed to confirm the encouraging results of this trial.


1. Bar-Or A, et al. Updated open-label extension clinical data and new magnetization transfer ratio imaging data from a Phase 1 study of ATA188, an off-the-shelf, allogeneic Epstein-Barr virus targeted T-cell immunotherapy for progressive multiple sclerosis. P638, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Abrahamyan S, et al. J Neurol Neurosurg Psychiatry. 2020;91(7):681–686.
3. Bar-Or A, et al. Trends Mol Med 2020;26(3):296–310.


## Evobrutinib reduces relapses and MRI lesion activity

**Evobrutinib significantly reduced MRI activity and the number of MS patients with qualified relapses, regardless of baseline blood neurofilament light chain (NfL) levels. However, high levels of serum (s)NfL at baseline were highly predictive of increased relapse and MRI lesion activity [1]. Additionally, high dose evobrutinib reduced the volume of slowly expanding lesions (SELs) in patients with relapsing MS [2].**

NfL is an established biomarker of neuro-axonal damage in MS. In a post-hoc analysis of a phase 2, randomised trial (NCT02975349), evobrutinib 75 mg twice daily significantly lowered blood NfL levels at weeks 12 and 24 [3]. In a new analysis, the interaction of sNfL levels and the effects of a Bruton's tyrosine kinase (BTK) inhibitor in MS patients was evaluated for the first time. Prof. Jens Kuhle (University Hospital Basel, Switzerland) shared the results.

A total of 162 patients were included in the modified, intention-to-treat population for whom sNfL values at baseline were available (excluding the dimethyl fumarate control arm of the original study). Participants were stratified by high dose (evobrutinib 75 mg once or twice daily; n=74) or placebo/low dose (placebo or evobrutinib 25 mg once daily; n=88). They were also stratified by mean sNfL levels on baseline as high (n=80) or low (n=82) sNfL, with a cut-off value of 11.36 pg/mL. Treatment effect on qualified relapses was evaluated over 24 weeks, and on gadolinium-enhancing (Gd+) T1 and T2 lesions over 12, 16, 20, and 24 weeks.

Patients with high sNfL had a higher disease burden at baseline, with more clinical relapses in the past 2 years, a higher Expanded Disability Status Scale (EDSS) score, more Gd+ T1 lesions, and a higher T2 lesion volume. Treatment results showed the following:

- The odds of qualified relapse were significantly higher in the high baseline sNfL group (OR 6.07; P=0.038), and were

significantly reduced in the evobrutinib high dose group versus placebo/low dose (OR 0.12; P=0.003).

- Patients with high sNfL at baseline had higher Gd+ T1 activity. The cumulative number of Gd+ T1 lesions was significantly reduced in the high evobrutinib dose group: both the high sNfL group (RR -69.2%; P=0.002) and the low sNfL group (RR -69.4%; P=0.010).
- Patients with high sNfL at baseline also had higher T2 lesion activity. New or enlarging T2 activity was observed for the high evobrutinib dose group, regardless of sNfL. In the high sNfL group, RR=54% (P=0.046), in the low sNfL group, RR=73.4% (P=0.001).

The authors concluded that these outcomes further support the value of blood NfL levels as a prognostic marker of MS disease activity.

A different post-hoc analysis assessed the effect of evobrutinib on SELs. These chronic active lesions have been associated with disease progression and long-term disability in patients with MS [4]. Prof. Douglas Arnold (McGill University, Canada) presented the findings.

The results displayed a dose-dependent effect of evobrutinib on SEL volume: the 25 mg once daily arm showed a mean numerical volume reduction of -136.5 $mm^3$ (95% CI -618.0 to 309.0; P=0.505), whereas the 75 mg twice daily arm demonstrated a mean volume reduction of -474.5 $mm^3$ (95% CI -1,098.0 to -3.0; P=0.047). The effect was evident in patients with the largest SEL volumes. Moreover, the effect was more pronounced in patients with higher baseline EDSS scores (EDSS ≤3.0, -73.0 vs EDSS ≥3.5, -652.0) and longer disease duration (disease onset <8.5 years, -12.0 vs disease onset ≥8.5 years, -729.3). Prof. Arnold argued that the suppression of SEL volumes by evobrutinib suggests that this agent has an influence on myeloid cells, including microglia and macrophages, within the CNS.


1. Kuhle J, et al. Evobrutinib significantly reduces relapses and magnetic resonance imaging outcomes in patients with multiple sclerosis: association with baseline neurofilament light chain levels. OP116, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Arnold DL, et al. Effects of evobrutinib, a Bruton's tyrosine kinase inhibitor, on slowly expanding lesions: an emerging imaging marker of chronic tissue loss in multiple sclerosis. OP115, ECTRIMS 2021 Virtual Congress, 13–15 October.
3. Montalban X, et al. N Engl J Med 2019;380(25):2406–17.
4. Elliot C, et al. Brain. 2019;142:2787–99.


## Primary endpoint of opicinumab for relapsing MS not met in AFFINITY trial

**Opicinumab did not meet the primary or key secondary efficacy endpoints in patients with relapsing MS. Subgroup analyses demonstrated potential benefits of opicinumab for older patients, patients with longer disease duration, patients with higher Expanded Disability Status Scale (EDSS) scores, and patients who received dimethyl fumarate as a disease-modifying therapy (DMT) [1].**

Opicinumab is a human monoclonal antibody, blocking LINGO-1, a leucine-rich repeat protein. The SYNERGY trial (NCT01864148) –a previous opicinumab study– did not demonstrate a significant improvement of disability following opicinumab treatment, compared with placebo in patients with relapsing MS [2]. However, further analysis showed that a subgroup of patients, defined by disease duration, magnetisation transfer ratios, and diffusion tensor imaging-radial diffusion in pre-existing T2 lesions, may benefit from opicinumab. Therefore, the current phase 2, AFFINITY trial (NCT03222973) enrolled patients with similar imaging characteristics as those who showed a promising therapy response, to assess the efficacy and safety of opicinumab. The population was expanded with patients who did not have this favourable imaging profile. Patients were randomised to opicinumab (750 mg, intravenous, every 4 weeks; n=120) as add-on therapy, or placebo (n=120), next to background DMT. The primary endpoint was the Overall Disability Response Score (ODRS) at week 72. Prof. Peter Calabresi (Johns Hopkins University, MD, USA) presented the results.

ODRS scores did not demonstrate a statistical difference between patients receiving opicinumab (adjusted mean 0.11) and placebo (adjusted mean -0.04) at week 72 (difference 0.15; P=0.148). Similarly, the key secondary endpoint – confirmed disability improvement (CDI) at week 12– was not met. Prespecified subgroup analyses showed larger efficacy signals of opicinumab in patients >40 years, patients with EDSS scores ≥3, patients with a disease duration ≥6 years, and patients from the imaging core group. However, the EDSS score ≥3 subgroup was the only subgroup that demonstrated a significant benefit of opicinumab compared with placebo (ODRS difference 0.36; P=0.025). Patients who were on dimethyl fumarate as primary DMT showed numerically higher improvements of opicinumab compared with placebo (ODRS difference 0.31; P=0.105) than interferon beta users (ODRS difference 0.02), or natalizumab users (ODRS difference 0.13). Differences between imaging subgroups and DMT subgroups on pre-defined MRI endpoints were small and non-significant. The safety analysis did not reveal new safety issues of opicinumab and the results were consistent with the known safety profile of the drug.

Prof. Calabresi argued that, despite the non-significant results of the trial, further analyses of the AFFINITY and SYNERGY datasets regarding patient population and MRI biomarkers may help in the design of future trials aiming to enhance remyelination in patients with MS.


1. Calabresi PA, et al. Efficacy and Safety of Opicinumab in Participants with Relapsing Multiple Sclerosis: A Randomized, Placebo-Controlled Phase 2 Trial (AFFINITY Part 1). OP147, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Cadavid D, et al. Lancet Neurol. 2019;18(9):845–856.


## Elezanumab did not outperform placebo in progressive and relapsing MS

**Elezanumab did not improve physical function or disability in patients with relapsing or progressive MS. The drug showed favourable safety and tolerability profiles and is currently investigated in other neurological conditions [1].**

Elezanumab is a fully humanised, monoclonal antibody, selectively binding to repulsive guidance molecule A (RGMa). This molecule is an inhibitor of axon regeneration, neurite outgrowth, and remyelination in the CNS. Antibody neutralisation of RGMa has been linked to enhanced neuronal regeneration and increased neuroprotection in animal models [2]. RADIUS-R (NCT03737851; n=208) and RADIUS-P (NCT03737812; n=123), 2 randomised, double-blind, placebo-controlled, phase 2 trials investigated the efficacy and safety of elezanumab as add-on treatment in patients with relapsing MS and progressive forms of MS, respectively. In both trials, patients were randomised 1:1:1 to elezanumab 1,800 mg (intravenous, every 4 weeks), elezanumab 400 mg, or placebo, in addition to standard-of-care disease-modifying therapy. The most common co-treatment was ocrelizumab, which was used by >50% of the patients in each trial. The primary endpoint was the mean Overall Response Score (ORS) at week 52. Prof. Bruce Cree (University of California, CA, USA) presented the results.

Elezanumab 1,800 mg or 400 mg did not improve the ORS at week 52 compared with placebo in patients with relapsing MS or progressive MS. In addition, the key exploratory endpoints –Symbol Digit Modalities Test (SDMT), Low Contrast Visual Acuity (LC-VA), Modified Fatigue Impact Scale (MFIS), and brain and cervical spinal cord MRI– did not demonstrate clinically significant changes following elezanumab therapy. Similarly, other biomarkers, such as daily step count, neurofilament light, or glial fibrillary acidic protein did not display benefits of elezanumab over placebo in these populations. Elezanumab was generally safe and well tolerated and the patient retention was excellent, with 88% of the patients completing treatment with the study drug in each trial. There was no imbalance in treatment emergent adverse events (AEs) across the arms of the trials. The most common AEs were urinary tract infections, falls, infusion-related reactions, fatigue, headache, arthralgia, and muscular weakness.


1. Cree BAC, et al. Safety and Efficacy of Elezanumab in Relapsing and Progressive Forms of Multiple Sclerosis: Results From Two Phase 2 Studies, RADIUS-R and RADIUS-P. OP149, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Demicheva E, et al. Cell Rep. 2015;10:1887–1898.


## Ibudilast reduced retinal atrophy in primary progressive MS

**Ibudilast was associated with reduced retinal atrophy compared with placebo in patients with primary progressive MS (PPMS) but not in patients with secondary progressive MS (SPMS). The ganglion cell and ganglion cell-inner plexiform layer (GCIPL) were mostly responsible for the detected differences in retinal layer thickness between participants [1].**

Ibudilast is an amino-modulatory, small molecule inhibitor targeting phosphodiesterase and toll-like receptor 4. The phase 2, randomised, placebo-controlled SPRINT-MS trial (NCT01982942) demonstrated retinal conserving qualities of ibudilast in patients with progressive MS [2]. The current post-hoc analysis aimed to compare the thickness of several retinal layers between ibudilast receivers and placebo receivers, measured by optical coherence tomography (OCT). Retinal layers included were GCIPL, the inner nuclear layer (INL), and the outer nuclear layer (ONL). Subgroup analyses were performed to differentiate between PPMS and SPMS patients. Analyses were adjusted for differences in baseline characteristics. Results were compared with MRI brain measures. In total, 248 participants and 2,217 OCT scans were assessed. Dr Henrik Ehrhardt (Johns Hopkins University, MD, USA) presented the findings.

GCIPL atrophy rates were significantly higher in placebo participants (-0.272 µm/year; 95% CI -0.471 to -0.074) than in ibudilast participants (-0.20; 95% CI -0.220–0.181; P<0.003). Subgroup analysis revealed that this declined atrophy rate was present in PPMS patients (ibudilast -0.081; 95% CI -0.372–0.209, placebo -0.598; 95% CI -0.884 to -0.312; P<0.001), but not in SPMS patients (ibudilast -0.196 vs placebo -0.119; P=0.543). Dr Ehrhardt added that future research should aim to unravel the observed differences in atrophy rates between MS subtypes.

Furthermore, baseline GCIPL thickness, age, sex, and disease duration were not associated with atrophy rates in patients with PPMS or SPMS. No significant associations were found between INL or ONL atrophy rates and the treatment arms. Finally, results of OCT scans of retinal layer atrophy and MRI measures (brain parenchymal fraction, grey matter fraction, white matter fraction) correlated significantly in this population. "These findings support the use of OCT measures in similar trials and may provide information on the relation between damage in various parts of the CNS," Dr Ehrhardt concluded.


1. Ehrhardt H, et al. Ibudilast slows retinal atrophy in progressive multiple sclerosis: post-hoc analyses of the SPRINT-MS Phase II randomized controlled trial. OP151, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Robert JF, et al. N Engl J Med 2018;379(9):846–855.


# Treatment Trials and Strategies

## ECTRIMS/EAN Clinical Guidelines on MS treatment: an update

**At a joint session on behalf of ECTRIMS and the European Academy of Neurology (EAN), an update was presented of the ECTRIMS/EAN Clinical Guidelines on the treatment of people with MS. At the time of the presentation, this document had not yet been published [1].**

Prof. Xavier Montalban (Vall d'Hebron University Hospital, Spain) summarised the 2021 update of the ECTRIMS/EAN guidelines. The update is divided into 8 topics, of which the first is efficacy of disease-modifying therapy (DMT). The following recommendations were included:

- Offer interferon or glatiramer acetate to patients with clinically isolated syndrome (CIS) highly suggestive of MS and an abnormal MRI with lesions suggestive of MS who do not fulfil criteria for MS.
- Offer treatment with siponimod to patients with secondary progressive MS (SPMS) with evidence of inflammatory activity (relapses and/or MRI activity). Treatment with other DMTs used for relapsing MS may also be considered, taking into account their efficacy, the patient's expectations, as well as safety and tolerability issues.
- Consider treatment with siponimod or anti-CD20 monoclonal antibodies for patients with SPMS without evidence of inflammatory activity, particularly in young patients and those in whom progression has started recently.
- Consider ocrelizumab for patients with primary progressive MS (PPMS), particularly in early and active (clinically and/or radiologically) disease.
- Consider treatment with mitoxantrone in patients with active SPMS when there is no other therapy available, taking into account –in discussion with the patient– its efficacy and specifically the well-documented, concerning, safety issues and tolerability profile.

Topic 2 comprised early treatment decisions. One of the recommendations is to consider choosing a higher efficacy DMT early on, according to disease activity (either clinically or on MRI) and patient particulars.

Topic 3 is disease/treatment response monitoring and treatment modifications. The central recommendation in this topic is to offer a more efficacious drug to patients treated with DMTs who show evidence of disease activity.

Topic 4 is concerned with suspension of treatment and disease reactivation. Prof. Montalban highlighted these 2 recommendations:

- When treatment with a high-efficacy DMT is stopped, either due to inefficacy or risk of adverse events, consider starting another high-efficacy DMT, taking into account the following factors: 1) clinical and MRI disease activity before and during treatment; 2) pharmacokinetics and biological activity of the previous DMT; 3) the potential for resumed disease activity or even rebound, particularly with natalizumab and S1P modulators.
- In the stable patient (clinically and on MRI) who shows no safety or tolerability issues, consider continuing treatment with DMT, taking into account the following patient circumstances:
  1) patient characteristics and comorbidities;
  2) drug safety profile;
  3) family planning;
  4) patient values and preferences.

Additional practical issues were addressed in some other topics. For example, when treating patients with natalizumab,

and after a period of stability, you can consider switching to a 6-week interval regimen in order to minimise the risk of progressive multifocal leukoencephalopathy (PML). Treatment with high-efficacy DMT including natalizumab can be considered in patients with high disease activity in which a quick therapeutic effect is required, taking into account the risk of PML in John Cunningham virus-positive patients (specifically for natalizumab) as well as the therapeutic lag of the different DMT.

1. Montalban X. Updated recommendations on the treatment of patients with MS. OP184, ECTRIMS 2021 Virtual Congress, 13–15 October.

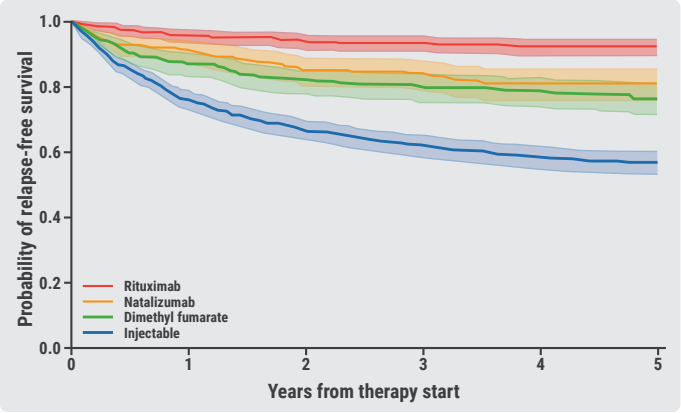
## Rituximab most effective initial MS therapy in Swedish real-world study

**Rituximab was associated with lower relapse risk and MRI lesions in treatment-naïve MS patients, compared with dimethyl fumarate, natalizumab, and injectable therapies (interferon-β, glatiramer acetate). Expanded Disability Status Scale (EDSS) score at 3 years was similar to dimethyl fumarate and natalizumab. The probability of switching therapy was lowest in rituximab users [1].**

The register-based, COMBAT-MS (NCT03193866) study evaluated the effectiveness of the most frequently prescribed initial MS therapies in Sweden. MS patients ever-treated with initial rituximab (n=472), natalizumab (n=269), dimethyl fumarate (n=339), or injectables (interferon-β, glatiramer acetate; n=858), were followed between 2010 and 2020. Outcome measures were first relapse (time to event), MRI lesion rate, EDSS score, and time to treatment discontinuation. Rituximab served as the reference therapy. Mr Peter Alping (Karolinska Institutet, Sweden) shared the results.

Initial treatment with injectables demonstrated the highest probability of relapse (HR 6.0), followed by dimethyl fumarate (HR 2.9) and natalizumab (HR 1.8; see Figure). However, baseline characteristics showed that natalizumab users were on average younger and had experienced more relapses prior to the study onset. Rate ratios of MRI lesions favoured initial rituximab therapy over injectables (rate ratio 4.5), dimethyl fumarate (4.8), and natalizumab (1.9). Interestingly, only injectables demonstrated significantly higher EDSS scores than rituximab. Time to treatment discontinuation was shortest for injectables, followed by dimethyl fumarate and natalizumab. Reasons to discontinue dimethyl fumarate or injectables were mainly adverse events or inadequate efficacy. Natalizumab was frequently discontinued due to John Cunningham virus positivity and concerns of progressive multifocal leukoencephalopathy.

**Figure: Time to first relapse for initial MS treatments [1]**




1. Alping P, et al. Effectiveness of initial MS treatments in the COMBAT-MS trial: injectables, dimethyl fumarate, natalizumab and rituximab. OP34, ECTRIMS 2021 Virtual Congress, 13–15 October.

## Ublituximab meets primary endpoint for relapsing MS

**Ublituximab was more efficacious than teriflunomide in patients with relapsing MS. Annualised relapse rates and MRI parameters demonstrated superiority of ublituximab over teriflunomide. These results, along with a favourable safety profile, showed that ublituximab has the potential to become the first 1-hour anti-CD20 infusion therapy in relapsing MS patients [1].**

Prof. Lawrence Steinman (Stanford University, CA, USA) presented the 96-week results of the identical phase 3, randomised, multicentre, double-blind ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) trials. Subjects with relapsing MS (n=549, n=545) were randomised 1:1 to 450 mg intravenous ublituximab every 24 weeks or 14 mg oral teriflunomide once daily. The primary endpoint was the annualised relapse rate (ARR) at week 96.

Ublituximab significantly reduced the ARR in the ULTIMATE I (59.4% reduction) and II (49.1% reduction) trials compared with teriflunomide. The relative reductions of contrast-enhancing T1 lesions for patients in the ublituximab arms were 96.7% and 96.5%, respectively, compared with teriflunomide. The relative reductions of new or enlarging T2 lesions were similar. In both trials, the proportion of patients who showed No Evidence of Disease Activity (NEDA) were higher in the ublituximab group (44.6%; 43.0%) than in the teriflunomide group (15.0%; 11.4%).

Multiple Sclerosis Functional Composite (MSFC) scores showed patients benefited from ublituximab (0.469; 0.521) over teriflunomide (0.266; 0.275). A favourable safety and tolerability profile was observed for ublituximab. Any adverse events (AEs) were reported in approximately 88% of the patients, regardless of treatment. Infusion-related reactions, headache, and nasopharyngitis were the most frequently reported AEs in the ublituximab groups. Serious AEs, mainly infections and infestations, were observed in 9.5% of patients treated with ublituximab.

1. Steinman L, et al. Phase 3 results of the ULTIMATE I & II global studies: ublituximab versus teriflunomide in relapsing multiple sclerosis. OP117, ECTRIMS 2021 Virtual Congress, 13–15 October.

## Dynamic scoring system aids decision to switch MS therapies early

**A newly developed dynamic scoring system has been developed and validated to support the decision of switching at an early stage from first-line to second-line MS therapies. Based on 5-year relapse-free survival, it was concluded that at least one-third of relapsing-remitting MS (RRMS) patients might benefit from an earlier switch [1].**

Early identification of suboptimal response could prevent irreversible disability progression by timely switching from a first-line to a more potent second-line disease-modifying therapy (DMT) [2]. With this in mind, Dr Camille Sabathé (French Institute of Health and Medical Research, France) and colleagues developed a dynamic scoring system to aid the early decision of switching therapies. They had at their disposal a French cohort of 12,823 adult RRMS patients who had started a first-line treatment between 2008 and 2018. Patients who switched to a second-line treatment because of inefficacy were compared with patients remaining on first-line treatment, by use of a 1:1 emulated clinical trial (ECT) based on time-dependent propensity scores. The main outcome measure was time to first relapse after matching.

The cohort was divided at random into a learning sample (n=8,549) and a validation sample (n=4,274). To compute the propensity scores and to match patients, in a first ECT (n=2,028) a frailty Cox model was set up that could predict the time to relapse in the patients who switched (n=1,014) versus those who did not (n=1,014). The switch benefit was found to be higher for patients who:

- were younger at disease onset;
- had a low Expanded Disability Status Scale (EDSS) score (≤5) at first-line treatment initiation;
- had ≥1 relapse under first-line treatment;
- had ≥1 gadolinium-enhancing T1 lesion on MRI under first-line treatment.

Based on these outcomes, the individual hazard ratio (iHR) of relapse in case of switch versus waiting was established. Patients with iHR ≤0.69 significantly benefited from a switch, patients with iHR >0.69 did not. This scoring system was then applied on a first validation ECT of 348 patients with iHR ≤0.69. Five-year relapse-free survival was 0.14 (95% CI 0.09–0.22) in non-switchers and 0.40 (95% CI 0.32–0.51) in switchers. In a second validation ECT of 518 patients with iHR >0.69, 5-year relapse-free survival was 0.37 (95% CI 0.30–0.46) and 0.44 (95% CI 0.37–0.52), respectively, a non-significant difference.

1. Sabathé C, et al. Improving the decision to switch from first to second-line therapy in MS: a dynamic scoring system. OP035, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Ziemssen T, et al. Mult Scler Relat Disord. 2015;4(5):460–469.

## Long-term suppression of MRI disease activity with ocrelizumab

**Patients receiving ocrelizumab maintained near complete suppression of focal MRI disease activity. Advantages were gained both in patients receiving continuous ocrelizumab and in those who switched to ocrelizumab later. Specifically, both relapsing MS (RMS) and primary progressive MS (PPMS) patients showed a reduction of T2 and T1 lesion volume accumulation as well as reduced global/regional volume loss at the 5th year of follow-up [1].**

In the original, phase 3 OPERA I/II (NCT01247324; NCT01412333) and ORATORIO (NCT01194570) trials, the efficacy and safety of ocrelizumab versus interferon beta-1a (IFN) in RMS and versus placebo in PPMS were demonstrated [2]. In the open-label extension (OLE) period of these studies, the effect of switching to/maintaining ocrelizumab therapy on various MRI measures was assessed. Scans were acquired at the 6th and 5th year of follow-up after starting the OLE for RMS and PPMS, respectively. Interim results of 3 years after OLE have already been published [3].

RMS patients receiving continuous ocrelizumab, compared with those who switched to ocrelizumab later, showed no differences in number of T1 gadolinium (Gd)-enhancing and new or enlarging T2 lesions (P=0.617 and P=0.760, respectively), but showed less brain structure volume loss, and significant/nominal differences in lesion volume accumulation. Percentage reduction at the 6th year of ocrelizumab-ocrelizumab versus IFN-ocrelizumab were:

- whole brain volume (WB): -6.9%, P=0.070;
- cortical grey matter volume (CGM): -6.2%, P=0.047;

- white matter volume (WM): -8.3%, P=0.240;
- thalamus volume (THAL): -21.3%, P<0.001;
- cerebellum volume (CBL): -11.0%, P=0.203;
- T2 lesion volume: -92.3%, P=0.034;
- T1 lesion volume: -11.5%, P=0.502.

PPMS patients initially randomised to ocrelizumab showed no difference in T1 Gd-enhancing lesions, a small difference in new or enlarging T2 lesions (ocrelizumab-ocrelizumab versus placebo-ocrelizumab rate: 0.010 and 0.069; P=0.0145), significant/numerical differences in brain volume loss and lesion volume accumulation. Percentage reduction at the 5th year of ocrelizumab-ocrelizumab versus placebo-ocrelizumab were:

- WB: -4.9%, P=0.388;
- CGM: -0.3%, P=0.948;
- WM: -3.1%, P=0.741;
- THAL (4th year): -17.0%, P=0.012;
- CBL (4th year): -15.7%, P=0.070;
- T2 lesion volume: -70.0%, P<0.001;
- T1 lesion volume: -28.1%, P=0.022.

Switching to/maintaining ocrelizumab therapy showed an almost complete suppression of focal MRI disease activity. Additionally, for both RMS and PPMS patients, reduction of T2 and T1 lesion volume accumulation as well as global/regional volume loss tended to persist.


1. Arnold DL. Long-term suppression of MRI disease activity and reduction of global/regional volume loss: results from OPERA I/II and ORATORIO open-label extension. P407, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Hauser SL, et al. N Engl J Med 2017;376(3):221–234.
3. Hauser SL, et al. Neurology. 2020;95(13):e1854–e1867.


## Stopping DMT: when or if at all?

**A hot topic session addressed the question of whether disease-modifying therapy (DMT) can be stopped at some point. In patients with relapsing-remitting MS (RRMS), older age (>55 years) and longer No Evidence of Disease Activity-3 (NEDA-3; >5 years) consistently predict a successful DMT discontinuation [1]. In progressive MS (PMS), one of the options worth considering may be a de-risking strategy, by switching onto safer immunomodulatory therapies [2].**

Prof. Ilya Kister (NYU Grossman School of Medicine, NY, USA) explained during her presentation that most DMTs are approved for indefinite use, but it is unclear whether they should be used indefinitely and, if not, on which variables the decision to stop DMT should depend. Prof. Kister presented a review of over a dozen recent, retrospective, observational studies of DMT discontinuation in RRMS [1]. These studies have identified various variables that may help to predict low risk of relapse after discontinuing therapy: most notably older age, prolonged disease stability, lower disability rank, absence of MRI activity, and low neurofilament light chain (NfL). However, it is unknown whether stopping DMT impacts progression independent of relapse activity (PIRA), subclinical disease activity, and brain atrophy.

Studies with a required period of disease stability prior to stopping DMT showed RRMS patients <45 years of age were at high risk of disease activity after stopping DMT even following a period of disease quiescence. Patients with no relapses for >5 years did not appear to benefit from continuing an injectable DMT. Studies with a required age threshold at DMT stop showed that the risk of relapse after stopping injectable DMT was low, among older patients. Finally, studies that required neither age threshold nor stability showed that older age (>55 years) and longer NEDA-3 (>5 years) predicted a successful DMT stop. Combining these variables may help identify subgroups of RRMS patients with very low risk of disease reactivation after stopping DMT.

Prof. Gavin Giovannoni (Queen Mary University of London, UK) discussed stopping criteria for patients with progressive forms of MS [2]. The older the patient, the more likely they are to have progressive MS, and the less likely to have evident disease activity (EDA) on stopping DMT. It is unknown if this is related to age or to the biology of the disease. "What I do know is that –on a population level– if the patient has been free of disease activity for 4 years, this predicts continuing to be free of disease activity on stopping." However, if patients had highly active MS when starting DMT (especially natalizumab or fingolimod), the disease tends to 'reactivate'.

As patients with progressive MS are older and tend to have more comorbidities, the risk-benefit ratio changes. Factors such as immunosenescence, infection and cancer risk, vaccine responsiveness, and comorbidities, in particular cardiovascular risk, need to be weighed up when deciding to continue or stop DMT [3]. Prof Giovannoni believes there should be a focus on de-risking strategies: switching patients onto safer immunomodulatory therapies. Another option is to select an immune reconstitution therapy that is not associated with long-term immunosuppression in this phase of the disease.


1. Kister I. In relapsing MS. OP066, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Giovannoni G. In progressive MS. OP067, ECTRIMS 2021 Virtual Congress, 13–15 October.
3. Hartung H.P., et al. Curr Opinion Neurol 2021; 34(4):598-603.

# Biomarkers

## Early predictors of disability progression in paediatric-onset MS

**Progression of disability in patients with paediatric-onset MS can be predicted by relapse frequency, greater number of relapses with incomplete recovery, higher disability during the first year of the disease, older age at symptom onset, and the presence of pyramidal, visual, or cerebellar symptoms. In contrast, persistent treatment with high-efficacy disease-modifying therapies (DMTs), brainstem relapse, and complete recovery from the first relapse demonstrated a protective effect against disease progression [1].**

Paediatric-onset MS patients (3–10% of the total MS population) demonstrate higher relapse rates than adult-onset MS patients in the first year of the disease [2,3]. Moreover, these patients reach irreversible disability milestones at an earlier age than adult-onset patients: over 50% of the patients with paediatric-onset MS are classified as secondary progressive MS patient by the age of 30 years [2,4]. Treatment with high-efficacy DMTs potentially slows down disease progression in this population [5]. The current study aimed to identify early predictors of disease worsening in paediatric-onset MS, to aid decision makers in the initiation of high-efficacy DMTs. In total, 672 patients <18 years at symptom onset were followed via biennial visitations. Multiple Sclerosis Severity Score (MSSS) and Expanded Disability Status Scale (EDSS) worsening were the outcome measures of interest. Dr Sifat Sharmin (University of Melbourne, Australia) presented the late-breaking results.

Older age at MS onset (OR 1.09; 95% CI 1.03–1.16), high EDSS score during the first 12 months of the disease (OR 1.32; 95% CI 1.21–1.45), relapse frequency (OR 1.04; 95% CI 0.96–1.13), and the presence of pyramidal (OR 1.34; 95% CI 1.13–1.58), visual (OR 1.28; 95% CI 1.10–1.48), or cerebellar symptoms (OR 1.17; 95% CI 1.00–1.37) were significantly associated with MSSS worsening. Longer duration of high-efficacy DMT treatment (OR 0.96; 95% CI 0.93–0.99), complete recovery from first relapse (OR 0.78; 95% CI 0.63–0.96), and brainstem relapse (OR 0.79; 95% CI 0.67–0.92) demonstrated a protective effect. Dr Sharmin added that 76% of patients with paediatric-onset MS worldwide are treated with DMTs, of whom only 27% are treated with high-efficacy DMTs. The results of the current study could aid clinicians in identifying patients at risk of disability worsening at an early stage of the disease, enabling them to initiate high-efficacy DMTs swiftly.


1. Sharmin S, et al. Early predictors of disability in paediatric multiple sclerosis: evidence from a multi-national cohort. LB187, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Banwell B, et al. Lancet Neurol. 2007;6(10):887–902.
3. Gorman MP, et al. Arch Neurol. 2009;66(1)54–59.
4. Waldman A, et al. Lancet Neurol. 2014;13(9):936–948.
5. Amato MP, et al. Brain. 2020;143(10)3013–3024.


## High-sensitive biomarker detection in MS via novel ELISA assay

**An international research team developed a novel high-sensitive ELISA assay to detect antibodies to myelin lipid antigens in the serum of patients with MS. Their analysis demonstrated that IgM antibodies reactive with phosphatidylcholine (IgM-PC) can be a sensitive biomarker for MS [1].**

The detection of specific antibodies reacting with lipids in myelin, the main target in MS, has been troublesome due to technical issues and antibody parameters in serum samples of MS patients. To this end, the current study aimed to develop a high-sensitive technique to detect antibodies to lipids in MS patients. Furthermore, IgM and IgG antibodies in reaction with PC or lactosylceramide (LC) were assessed as potential biomarkers in these patients. The team collected serum samples of 362 MS patients (clinically isolated syndrome, n=17; primary progressive MS, n=37; relapsing-remitting MS, n=62; secondary progressive MS, n=50; benign MS, n=36), 80 control participants, and 10 patients with non-MS myelin diseases. Prof Maria Cruz Sádaba (Private University San Pablo CEU, Spain) presented the results.

The novel, ultra-sensitive ELISA assay, developed by the researchers, was able to significantly differentiate between the serum levels of IgM-PC in MS patients (optical density (OD) mean 0.192) and control subjects (OD mean 0.078; P=0.001) [2]. Furthermore, the tool was able to distinguish between patients with clinically isolated syndrome (OD mean 0.281; P=0.035) and relapsing-remitting MS (OD mean 0.244; P=0.011) on the one hand, and patients with progressive forms

of the disease on the other hand (primary progressive OD mean 0.170; secondary progressive OD mean 0.200). Progressive forms of MS could be differentiated from benign MS based on IgM-PC serum concentration. An additional analysis confirmed these results: a higher proportion of patients with clinically isolated syndrome displayed IgM-PC in serum samples (88.2%), compared with patients with secondary progressive MS (58.0%; P=0.037), primary progressive MS (59.5%; P=0.034), benign MS (11.1%; P=0.0001), control participants (25.0%; P=0.0001), and non-MS myelin disease (30.0%; P=0.004). In patients with relapsing-remitting MS, 88.7% showed IgM-PC in serum samples, significantly more than patients with benign MS, progressive forms of MS, and healthy controls, respectively. IgG-PC, IgG-LC, and IgM-LC levels did not differ between MS patients and controls.


1. Sádaba MC, et al. Detection of IgM to phosphatidylcholine in serum samples is a major diagnosis marker in MS. P003, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Sádaba MC, et al. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e765.


## Cortical lesions predict cognitive impairment 20 years after MS diagnosis

**The number of cortical lesions at the time of MS diagnosis could accurately predict cognitive impairment 20 years after the diagnosis of the disease. A predictive model showed that patients who displayed 3 or more cortical lesions at diagnosis had a 4-fold higher risk of developing severe cognitive impairment at 20 years of follow-up [1].**

Cortical lesions reflect brain damage in patients with MS [2]. However, the role of early cortical lesions in predicting long-term cognitive impairment has yet to be clarified. Therefore, the current study aimed to assess the prognostic capacity of cortical lesions at MS diagnosis regarding cognitive impairment after 20 years of MS. The study included 170 patients with MS, who received a 1.5T MRI scan within 3 years from MS diagnosis to evaluate cortical lesions. Furthermore, a neuropsychological assessment was conducted to assess cognitive status at 20 years follow-up. Mr Stefano Ziccardi (University of Verona, Italy) presented the study results.

Patients who were cognitively impaired at 20 years of follow-up had a significantly higher number of cortical lesions at diagnosis (median 3.0) than patients without cognitive impairment at follow-up (median 0.0). Moreover, there was a significant difference in the number of cortical lesions at diagnosis between patients with mild cognitive impairment (median 2.0) and patients with severe cognitive impairment (median 4.0). Logistic regression analysis showed that patients with ≥3 cortical lesions at diagnosis had approximately a 4-fold risk of cognitive impairment at follow-up (OR 3.70; 95% CI 1.8–7.5; P<0.001). In addition, these patients were at higher risk of severe cognitive impairment after 20 years of disease (OR 3.33; 95% CI 1.49–4.17; P=0.01). These results suggest that early cortical lesion evaluation in MS patients could predict cognitive alterations in the future. Early recognition of these lesions is necessary in order to improve the diagnosis and monitoring of cognitive abilities in patients with MS, and to enable swift interventions.


1. Ziccardi S, et al. Cortical lesions at diagnosis predict cognitive impairment in multiple sclerosis: a 20-year follow-up study. OP49, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Calabrese M, et al. Arch Neurol. 2009;66(9):1144–50.


## Applicability of sNfL measurement in clinical practice

**Elevated baseline serum neurofilament light (sNfL) levels were associated with longitudinal brain atrophy and the development of new T2 lesions in patients with MS. The results were consistent across demographical and clinical subgroups [1]. First small steps were proposed towards the routine use of sNfL measurements in clinical practice [2].**

NfL is a neuronal protein that reflects axonal damage in the cerebrospinal fluid of patients with MS [3]. Serum NfL levels can be used as a marker of drug response and can predict future disease activity in patients with MS [4]. According to Prof. Elias Sotirchos (Johns Hopkins University, MD, USA) there is evidence that sNfL is linked to clinic-radiological measures of inflammatory disease activity. However, assessments of sNfL in large heterogenous MS populations are scarce. The study evaluated the relation between sNfL levels, longitudinal brain atrophy, and new T2 lesion development in patients from the real-world, multicentre, prospective MS Partners Advancing Technology and Health Solutions (MS PATHS) network cohort. Biospecimens were collected from 6,968 participants from the MS PATHS cohort and 201 healthy controls. The assessment of sNfL levels was performed via high-throughput immunoassay and was adjusted for demographic and clinical variables. sNfL levels >97.5$^{th}$ percentile in healthy controls were considered elevated.

Among the MS patients eligible for analysis (n=3,705), 615 (16.6%) participants displayed elevated sNfL levels at

baseline. The prospective assessment showed that elevated sNfL levels were associated with higher rates of longitudinal brain atrophy, as measured by brain parenchymal MRI fraction (elevated sNfL annualised change 0.27% vs normal sNfL 0.16%; P<0.001). This result was consistent across disease subtypes, and age and sex stratification. Furthermore, elevated sNfL was related to an increased risk of developing new T2 lesions (OR 1.90; 95% CI 1.43–2.51; P<0.001). This finding was significant across the pre-defined subgroups.

Prof. Jens Kuhle (University Hospital Basel, Switzerland) argued that the routine use of sNfL measurement in clinical practice is approaching. "At the moment, normative data from a general population is being analysed to enable the differentiation between pathological and physiological (i.e. age- or-BMI related) changes of sNfL levels." He added that a recent study has shown that fixed cut-off points lead to false negatives and false positives in young and old patients with MS, respectively [4]. According to Prof. Kuhle, a personalised approach of sNfL measurement, including factors such as disease duration, Expanded Disability Status Scale (EDSS) score, treatment type, and the number of contrast-enhancing lesions shows promising results in an ongoing trial at the University of Basel. Moreover, an internet-based application to calculate sNfL Z-scores is under development, supporting the use of sNfL measures in clinical practice. On a more critical note, Prof. Kuhle mentioned that pre-clinical studies should provide more insight regarding NfL metabolism and kinetics and that standardisation of sNfL measurement is needed to create a uniform tool to use in clinical practice.


1. Sotirchos ES, et al. Serum Neurofilament Light Chain is Associated with Longitudinal Brain Atrophy and Radiological Disease Activity in the MS PATHS Network. OP088, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Kuhle J. Neurofilaments: ready for routine clinical use? OP085, ECTRIMS 2021 Virtual Congress, 13–15 October.
3. Kuhle J, et al. Mult Scler. 2016;22(12):1550–1559.
4. Kuhle J, et al. Neurology. 2019;92(10)e1007–e1015.


## MRI more sensitive for disease activity than relapses in SPMS

**In both real-world and clinical trial setting, MRI activity was found to be a more sensitive tool to measure disease activity than relapses in secondary progressive MS (SPMS). Thus, the frequency of MRI monitoring is driving detection of disease activity. Even after 2 years without relapse and no MRI activity at baseline, disease activity returned in >50% of patients with previously 'non-active' MS on placebo [1].**

Patients with SPMS are often categorised as active (aSPMS) or non-active (naSPMS) based on evidence of their disease activity, explained Prof. Gavin Giovannoni (Queen Mary University of London, UK). However, the relative contribution of MRI activity and/or relapses in defining disease activity is not well understood. Therefore, differences between aSPMS and naSPMS were evaluated. Data was used from the Adelphi real-world MS Disease Specific Programme (Adelphi MS DSP), and the phase 3 EXPAND study (NCT01665144).

Adelphi MS DSP is a non-interventional, real-world study of 37,318 MS patients, including 3,580 patients with SPMS who were surveyed between 2011 and 2019. This group was categorised into aSPMS (≥1 new lesion on the most recent MRI and/or ≥1 relapse in the last 12 months; n=1,889) and naSPMS (n=665). In the 1,651 participants of the EXPAND study, aSPMS was defined as ≥1 relapse in the 2 years prior to screening and/or ≥1 gadolinium-enhancing (Gd+) T1 lesion at baseline. According to this definition, 779 patients had aSPMS and 866 naSPMS.

"In patients from the real-world cohort categorised as having aSPMS, disease activity was more commonly detected via MRI than relapse activity," Prof. Giovannoni observed. They were considered aSPMS based on relapse status alone (12.6%), on MRI status alone (59.1%), or on both MRI and relapse status (28.3%). In the past 12 months, naSPMS patients had a higher mean Expanded Disability Status Scale (EDSS) score versus aSPMS patients (4.6 and 5.2, respectively), were less frequently monitored with MRI (58.7% vs 87.7%), and had a lower number of MRIs per patient (0.87 vs 1.24). A higher proportion of naSPMS patients had moderate-to-severe disease, and were not on any DMT (45.1% vs 23.4%).

In EXPAND, 52.7% of naSPMS patients on placebo had on-study relapse and/or MRI activity: MRI (41.8%), relapses (4.6%), or both MRI and relapse (9.2%). "What's driving the detection of disease activity in this population is the frequency of MRI monitoring," said Prof. Giovannoni. He concluded that incorrectly defining patients as naSPMS can result in reduced monitoring and decreases the chance to detect and treat any new disease activity in these patients.


1. Giovannoni G, et al. MRI activity versus relapses as markers of disease activity in SPMS: Data from real world and pivotal clinical studies. P001, ECTRIMS 2021 Virtual Congress, 13–15 October.

# Imaging

## Changes in GABA-receptor binding among cognitively impaired MS patients

**[11C]flumazenil (FMZ) positron emission tomography (PET) demonstrated higher GABA-receptor binding for cognitively unimpaired MS patients, compared with cognitively impaired MS patients and healthy controls. In addition, cognitively impaired patients showed lower perfusion rates, suggesting possible brain atrophy. These results suggest that [11C]FMZ may have clinical applicability in MS patients with cognitive impairment [1].**

Cognitive impairment is frequently observed in patients with MS and changes in the GABAergic system have been associated with cognitive impairment in this population [2,3]. This study aimed to investigate GABA-receptor binding via [11C]FMZ PET. The optimal method of analysis was assessed for [11C]FMZ PET in MS patients and the GABA-receptor binding between cognitively impaired and cognitively unimpaired patients was compared. MS patients (n=17: cognitively impaired, n=11; cognitively unimpaired, n=6) and healthy controls (n=11) underwent 60-minute dynamic PET, using plasma input data. Two models (1-tissue 2-rate-constant (1T2K); 2T4K) measured the influx rate and volume of distribution of 7 brain regions relevant for cognitive function. Akaike information criterion was used to determine the best-fitting model.

By margins, the 2T4K model was preferred over the 1T2K model: in 55.6% of the analysed brain regions, the 2T4K model outperformed the 1T2K model. However, Prof. Hanneke Hulst (Amsterdam UMC, the Netherlands) argued that both models could reliably estimate radiotracer delivery. Mean perfusion rates were significantly lower for cognitively impaired patients (0.29 µL/min) compared with cognitively unimpaired patients (0.33) and healthy controls (0.33). The volume of distribution was higher in cognitively unimpaired patients (5.73 mL of plasma/$cm^3$ of tissue) than in cognitively impaired patients (4.95) and healthy controls (4.87). This implicates a higher GABA-receptor binding in cognitively unimpaired patients.


1. Hulst H. [11C]flumazenil positron emission tomography in multiple sclerosis: model validation and clinical applicability in cognitive impairment. LB188, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Benedict RHB, et al. Lancet Neurol. 2020;19(10):860–871.
3. Freeman L, et al. Ann Neurol. 2015;78(4):554–567.


## T2 lesions independently predict early conversion to SPMS

**Results from a 10-year longitudinal study showed that cervical spinal cord T2 lesions independently predict early conversion to secondary progressive MS (SPMS). The occurrence and number of T2 lesions at the time of a clinically isolated syndrome (CIS) were significantly higher in patients who converted to SPMS than patients who did not. These results highlight the importance of SC-T2L at CIS diagnosis [1].**

Brain MRI T2 lesions (B-T2L) at time of CIS are a well-known risk factor for developing SPMS. However, longitudinal data studying the influence of cervical spinal cord T2 lesions (SC-T2L) are lacking. The prognostic value of SC-T2L on MRI performed at the time of CIS was assessed in a retrospective study of prospectively gathered data of patients with a CIS suggestive of demyelinating disease. All participants had a brain and cervical spinal cord MRI at diagnosis. Dr Laura Lacruz-Ballester (Health Research Institute La Fe, Spain) presented the results.

The study cohort consisted of 242 patients, with a mean age of 32 years and 71.1% women. Mean follow up was 12.7 years. Of these 242 patients, 205 (85.6%) were treated; 87 (41.8%) began treatment after the first relapse, and 120 (58.2%) after the second relapse. Of the CIS patients, 224 (92.6%) had a second relapse; 36 (14.9%) evolved to SPMS. The median total number of B-T2L lesions was higher in SPMS (20.5) than in relapsing-remitting MS/CIS patients (11.9; P=0.009). So was the number of SC-T2L lesions (1.75 vs 1.0; P=0.00005). Dr Lacruz-Ballester said: "In a regression model, adjusting for sex, age, treatment initiation at CIS, B-T2L, SC-T2L, and the presence of oligoclonal bands, SC-T2L was the only independent factor to predict conversion to SPMS, with an odds ratio of 2.2 (95% CI 1.06–4.97)."

Dr Lacruz-Ballester concluded that this data should stimulate studies of how spinal cord lesions can trigger neurodegeneration in progressive MS, for example by inducing corticospinal tract atrophy, or via a chronic inflammatory mechanism.


1. Lacruz-Ballester L. Cervical spinal cord T2 lesions independently predict early conversion to secondary progressive multiple sclerosis: a longitudinal 10-year study. OP137, ECTRIMS 2021 Virtual Congress, 13–15 October.

## Natural killer-like CD8+ T cells as a reservoir of clonal cells related to MS activity

**Memory CD8+ T cells with natural killer-like (NK)- properties are increased in MS patients and associated with disease activity. These cells belong to a reservoir of oligoclonal cells that infiltrate the CNS and exert cytotoxicity independent of T-cell receptor (TCR) involvement [1].**

Although memory CD8+ T cells are more predominant than CD4+ T cells in MS lesions and drive autoimmune inflammation, they have not yet been identified. The current study set out to identify a cell involved in MS with a specific phenotypic and functional pattern in the periphery subtype.

Single-cell, high-dimensional profiling of peripheral memory CD8+ T cells was combined with TCRβ sequencing in a cohort of 17 MS patients and 11 healthy controls. An effector memory CD8+ T cell subtype could be identified that was increased in MS patients. Interestingly, this subtype was preferentially found during relapse episodes and belongs to a reservoir of peripheral oligoclonal cells. RNA sequencing confirmed the expression of NK-related molecules and their high cytotoxic potential. These NK-like CD8+CD94+ T cells were found to infiltrate the CNS. They were present in MS lesions, particularly in chronic active lesions. Functional assays showed that NK-like CD8+CD94+ T cells exert a cytotoxic function against the K562 cell line. Since this line is devoid of MHC molecules, the observed cytotoxicity is independent of TCR involvement.

1. Dugast E. High dimensional single-cell profiling identifies NK-like CD8+ T cells with high cytotoxic properties that are the reservoir of clonal cells related to disease activity in multiple sclerosis. OP133, ECTRIMS 2021 Virtual Congress, 13–15 October.

## The importance of MS progression independent of relapses

**Confirmed disability accumulation (CDA) in MS may occur as Relapse-Associated Worsening (RAW) or Progression Independent of Relapse Activity (PIRA). Three presentations focused on the role and importance of PIRA. PIRA is present from disease onset, predominates in later-onset MS, and is associated with increased brain atrophy rates in patients with relapsing MS [1–3].**

A Spanish study assessed clinical and MRI features of patients who develop PIRA early on after the first attack of MS, or in the absence of recent inflammatory activity [1]. In 754 patients with a clinically isolated syndrome (CIS) or early MS who were followed for >20 years, 209 (28%) developed PIRA after a median of 7.2 years. Presenting with PIRA after a CIS is not uncommon and implies an unfavourable, long-term prognosis, concluded Dr Carmen Tur (Vall d'Hebron University Hospital, Spain). Among all PIRA patients, one-third developed early PIRA, i.e. within 5 years after the CIS. Generally, patients with early PIRA were older at the time of CIS, with more spinal cord lesions and fewer relapses over time than late PIRA. Patients with late PIRA, on the other hand, were younger at CIS, with a higher inflammatory burden. "This suggests that late PIRA occurs as a predominantly inflammation-driven process." Of all PIRA patients, a third will develop "pure PIRA", i.e. PIRA in the absence of recent inflammatory activity on MRI. Pure PIRA shares many characteristics with early PIRA. Dr Tur concluded that identifying those CIS patients who are at risk of developing any form of PIRA may have important therapeutical implications.

An Italian group investigated the rate and predictors of RAW and PIRA in paediatric (PO), adult (AO), and late-onset (LO) MS. In a relapsing MS cohort of 5,287 patients assessed within 1 year from onset, CDA events were more frequent in LOMS (61.3%) than in AOMS (45.9%) and POMS (41.0%; P<0.001) after a mean 11.4 years. PIRA accounted for about two-thirds of disability worsening, Dr Angelo Bellinvia (University of Florence, Italy) concluded. "Underlying MS progression is detectable early in the disease course also in POMS patients and is more prevalent than RAW in AOMS and LOMS patients at the first demyelinating event. This data suggests that MS can be seen as a continuum from the very onset, and that age at onset seems to be one of the main determinants of CDA subtype, with RAW being more prevalent in POMS and PIRA in LOMS." Early treatment with a disease-modifying therapy (DMT) was effective in preventing any CDA in all age groups and appeared to slow down the transition to the progressive phase. This underscores the importance of prompt initiation of DMTs in MS patients.

A Swiss group found that PIRA is associated with increased brain atrophy rates [3]. In a retrospective, longitudinal study including 516 relapsing-remitting MS patients, 334 were stable, 122 had relapsed, and 46 experienced PIRA. Both focal inflammatory activity and PIRA were associated with increased brain atrophy rates, without significant differences between the 2. The association between PIRA and diffuse neurodegeneration underscores the necessity to better stratify MS patients in clinical practice, as well as to optimise treatment to prevent accumulation of irreversible neuro-axonal loss.

1. Tur C. Progression independent of relapse activity is present from disease onset: a complete view of the phenomenon in the CIS/early MS cohort of Barcelona. OP155, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Bellinvia A. Progression independent of relapse activity in paediatric, adult and late-onset multiple sclerosis patients. OP154, ECTRIMS 2021 Virtual Congress, 13–15 October.
3. Cagol A. Progression independent of relapse activity is associated with increased brain atrophy rates in patients with relapsing-remitting multiple sclerosis. OP156, ECTRIMS 2021 Virtual Congress, 13–15 October.

# Neuromyelitis Optica Spectrum Disorder

## Eculizumab, satralizumab, or inebilizumab for NMOSD?

**An indirect comparison analysis suggests that eculizumab is more effective than satralizumab and inebilizumab at lowering the risk of relapse in adults with neuromyelitis optica spectrum disorder (NMOSD) who are positive for aquaporin-4 protein autoantibodies (AQP4-IgG+). Not only was eculizumab superior to the other 2 agents with regard to time to first relapse, but superiority was observed both as a monotherapy and in combination with immunosuppressive treatments (ISTs), such as mycophenolate, azathioprine, or glucocorticoids [1,2].**

Prof. Dean Wingerchuk (Mayo Clinic Phoenix/Scottsdale, AZ, USA) explained that given the absence of any head-to-head studies, his team conducted an indirect comparison based on published studies up to September 2020 from controlled trials testing eculizumab, satralizumab, and inebilizumab individually. He also acknowledged that there are limitations to this type of analysis, and pointed out that all 3 agents are very effective in treating AQP4+ NMOSD.

The meta-analysis incorporated data from 29 studies from 4 placebo-controlled clinical trials — collectively including 551 patients: N-MOmentum phase 2/3 clinical trial (NCT02200770), PREVENT phase 3 trial (NCT01892345), and SAkuraStar (NCT02073279) and SAkuraSky (NCT02028884) phase 3 trials. Time-to-first relapse was the only outcome measure reported across all trials and was therefore used in the comparison efficacy analysis.

The researchers conducted 3 separate analyses: 1 comparing the 3 therapies alone, another comparing eculizumab with satralizumab, given alone or in combination with ISTs, and the 3rd comparing the eculizumab-IST combination with the satralizumab-IST combination. The results showed that eculizumab alone led to a significantly reduced risk of first relapse, compared with both satralizumab (by 90%) and inebilizumab (by 89%). When given alone or in combination with ISTs, eculizumab was also associated with a 76% reduced risk of first relapse relative to satralizumab. Furthermore, patients treated with combination eculizumab-IST therapy were 59% less likely to experience the first relapse, compared with those receiving combination satralizumab-IST therapy, but this difference did not reach statistical significance (see Table).

Table: Hazard ratios for time to first relapse [1]

| Network | Treatment Comparison | Hazard Ratio (95% CI) |
|---|---|---|
| Mono or Combination Therapy | Eculizumab ± IST (n=96) vs Satralizumab ± IST (n=104) | 0.24 (0.06–0.98) |
| Monotherapy | Eculizumab (n=21) vs Satralizumab (n=63) | 0.10 (0.01–0.65) |
| | Eculizumab (n=21) vs Inebilizumab (n=161) | 0.11 (0.02–0.68) |
| Combination Therapy | Eculizumab + IST (n=75) vs Satralizumab + IST (n=41) | 0.41 (0.07–2.34) |

IST, immunosuppressant therapy

Prof. Wingerchuck concluded: "Based on current evidence, monotherapy and mono-combination therapy with eculizumab appear to be more efficacious at preventing relapses than satralizumab or inebilizumab for the treatment of adults with AQP4+ NMOSD. These findings suggest that C5 complement inhibition with treatments such as eculizumab prevent relapses more effectively than other mechanisms involving IL-6 receptor or CD19 inhibition among adults with AQP4+ NMOSD." However, multiple factors need to be considered in the differential treatment decision process [3].


1. Wingerchuck DM, et al. Indirect comparison analysis of FDA-approved treatment options for adults with aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder. OP118, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Wingerchuck DM, et al. Neurol Ther 2021;Nov 13. DOI:10.1007/s40120-021-00295-8.
3. Hartung HP. Ann Neurol. 2021 Jun;89(6):1084–1087.


## Long-term efficacy of satralizumab for NMOSD

**New, long-term data shows that more than 70% of patients with aquaporin-4 IgG-seropositive neuromyelitis optica spectrum disorder (AQP4-IgG+ NMOSD) treated with satralizumab remained relapse-free after 4 years, with a favourable safety profile [1].**

Satralizumab, a subcutaneously administered, IL-6 receptor antagonist, significantly reduced the risk of relapse in patients with AQP4-IgG+ NMOSD in the 2 double-blind, randomised-controlled, phase 3 SAkuraSky (NCT02028884) and SAkuraStar

(NCT02073279) trials. In both trials, a favourable safety profile was observed in the double-blind phase [2,3]. The current study, presented by Dr Ingo Kleiter (Ruhr-Universität Bochum, Germany), assessed the long-term efficacy of satralizumab. Patients who received ≥1 dose of satralizumab in the double-blind phase or the open-label extension (OLE) period were included in the analysis (n=111). Satralizumab dose in the OLE period was 120 mg, administered every 4 weeks. Efficacy endpoints were investigator-assessed protocol-defined relapses (iPDRs), severe iPDRs (≥2-point increase on the Expanded Disability Status Scale (EDSS), and sustained EDSS score worsening (≥24 weeks) at week 192. Dr Kleiter said: "Just one NMOSD relapse can lead to lifelong disability. An early accurate diagnosis followed by effective treatment is vital to conserving the quality of life of people with this chronic disease."

At a median duration of 3.7 years (192 weeks) exposure to satralizumab, 71% (SAkuraSky) and 73% (SAkuraStar) of the patients were free from relapse. This corresponded to a mean annualised iPDR rate of 0.20. In addition, most patients were free from severe relapse (SAkuraSky 90%; SAkuraStar 91%). Sustained EDSS worsening was observed in 10% (SAkuraSky) and 14% (SAkuraStar) of the patients. These results demonstrate that the robust efficacy observed in the studies' double-blind periods is sustained long-term for satralizumab, as both a monotherapy and in combination with immunosuppressive therapy.

The data also demonstrated a favourable safety and tolerability profile for satralizumab in the overall treatment period of up to 7 years, comparable to the double-blind treatment periods in both SAkuraStar and SAkuraSky studies. Rates of adverse events (AEs) and serious AEs during the overall treatment periods were consistent with satralizumab and placebo in the double-blind periods. The most common AEs observed were headache, arthralgia, white blood cell count decrease, hyperlipidemia, and injection-related reactions. No new safety signals were observed.


1. Kleiter I, et al. Long-term efficacy of satralizumab in aquaporin-4-IgG seropositive neuromyelitis optica spectrum disorder (NMOSD). Results from the open-label extension periods of SAkuraSky and SAkuraStar. P024, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Yamamura T, et al. N Engl J Med 2019;381(22):2114–2124.
3. Traboulsee A, et al. Lancet Neurol. 2020;19(5):402–412.


## Long-term efficacy data: inebilizumab for NMOSD

**Inebilizumab demonstrated favourable long-term safety and efficacy outcomes for patients with neuromyelitis optica spectrum disorder (NMOSD). Results showed that the risk of attack in NMOSD participants treated with inebilizumab remained low. Moreover, long-term use of inebilizumab did not result in the occurrence of unexpected serious adverse events [1].**

Inebilizumab is a humanised anti-CD19 monoclonal antibody depleting B cells, that is approved in the USA for the treatment of NMOSD patients who are seropositive for immunoglobulin G autoantibodies against aquaporin-4 (AQP4-IgG+) [2]. Prof. Bruce Cree (UCSF Multiple Sclerosis Center, CA, USA) presented the final efficacy and safety data of the 5.5-year follow-up, open-label extension (OLE) period of the randomised-controlled, phase 2/3 N-MOmentum trial (NCT02200770).

NMOSD AQP4+ patients (n=230) were randomised 3:1 to inebilizumab (300 mg, intravenous, administered at day 1 and 15) or placebo. After 6 months, patients could enter the OLE period, during which all enrolled participants received inebilizumab every 6 months. In total, 174 patients completed the OLE period. The primary outcome was the time to the first attack.

The results of the randomised-controlled period showed that inebilizumab outperformed placebo: 87.0% of the patients on inebilizumab were attack-free, compared with 59.9% of the placebo receivers (risk reduction 72.8%; P<0.001) [1,3]. After completion of the OLE period, 87.7% of the patients continuing inebilizumab, and 83.4% of patients switching from placebo, were attack-free. The mean treatment duration was 3.2 years, with a reported annualised attack rate of 0.092. Treatment-emergent adverse events (AE) occurred in 39.6% of the patients. Urinary tract infections (26.2%), nasopharyngitis (20.9%), and arthralgia (17.3%) were the most frequently reported AEs. The rate of infections did not increase with continued treatment (116.3 per 100 person-years in year 1 vs 55.1 in year 4). Transient low IgG levels (<700 mg/dL) were reported in 105 subjects. However, no association between IgG levels and the occurrence of infections was observed. One patient died from complications of an NMOSD attack after 9 days of inebilizumab treatment. Two other patients died after 224 and 1,225 days of inebilizumab therapy, due to a CNS event of unclear aetiology and following a SARS-CoV-2 infection, respectively.


1. Cree BAC, et al. Safety and efficacy of inebilizumab in NMOSD over a mean duration of 3.2 years: end of study data from the N-Momentum trial. P037, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Frampton JE. Drugs. 2020;80(12):1259–1264.
3. Cree B, et al. Lancet 2019;394(10206):1352–1363.

# Progressive MS

## Charcot Award 2021: Progressive MS, a personal perspective

**The 2021 Charcot Award was awarded to Prof. Alan J. Thompson (University College London, UK). "The Charcot Award is viewed by the MS community as the ultimate accolade for a lifetime's work, and I'm absolutely delighted to be the 2021 recipient," Prof. Thompson said. As part of this honour, Prof. Thompson gave the Charcot Lecture at the ECTRIMS 2021 meeting [1].**

"Approximately 1 to 1.5 million people are currently suffering from progressive forms of MS worldwide," Prof. Thompson started his lecture. "The increasing disability, reduced quality of life, and costs for the individual and the community that are a result of this condition demonstrate the need to focus on progressive MS." Prof. Thompson argued that most therapies in the last 3 decades were developed for relapsing-remitting MS, leaving progressive MS underexposed. "In primary progressive MS, ocrelizumab is the only effective therapy that has been developed in the last 30 years. Fortunately, in recent years the international focus has been shifting towards progressive MS."

Prof. Thompson emphasised that the key to developing effective therapies lies in understanding the injury mechanisms driving progression. "Studies into slowly expanding lesions [2,3] taught us that progression is largely independent of relapse. Moreover, we have learned that neurodegeneration starts before MS is clinically manifested. The current clinical course descriptors are not necessarily reflecting what is happening pathologically. Therefore, therapies should be initiated before symptoms or progression of symptoms are clinically present." In addition, Prof. Thompson mentioned that research in progressive MS should focus on how to match clinical descriptors with underlying pathological mechanisms.

Machine learning has shown value in this aspect, according to Prof. Thompson. A machine learning model was able to differentiate between MS subtypes (cortex-led, normal-appearing white matter-led, lesion-led) based on MRI data. These subtypes were predictive of treatment response and thus providing clinical benefits [4]. Prof. Thompson stressed that MRI markers are needed for the early stages of the disease. "If we initiate treatment after compensatory mechanisms collapse and biological ageing exerts its influence on patients, it is probably too late."

Prof. Thompson continued by addressing drug targets in MS. "The majority of drugs in MS have an immune-modifying effect. We should focus more on remyelination and neuroprotection in progressive MS." The REBUILT trial (NCT02040298) and the SPRINT-MS trial (NCT01982942) are 2 recent trials that showed efficacy of this approach in patients with MS. "I believe we should continue to develop and investigate neuroprotective and remyelinating agents in the future."

Concluding his lecture, Prof. Thompson expressed his hope for the future: "the International Progressive MS Alliance puts effort into understanding the mechanisms behind progression in MS, accelerating clinical trials, and enhancing the quality of life of patients with progressive MS. If we continue this hard work, I hope we can establish early initiation of effective therapies in order to prevent progressive MS from arising."


1. Thompson AJ. Charcot award 2021: Progressive MS, a personal perspective. Plenary Session 2, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Absinta M, et al. JAMA Neurol. 2019;76(12):1474–1483.
3. Calvi A, et al. Mult Scler. Sep 23, 2020. DOI: 10.1177/1352458520958589.
4. Eshagi A, et al. Nature Commun. 2021;12(1):2078.


## Top score poster: Meta-analysis on the effect of DMTs

**A new meta-analysis of over 10,000 participants in 16 randomised trials investigating disease-modifying therapies (DMTs), including patients with progressive forms of MS, showed a 13% reduction of confirmed disability progression (CDP). A subsequent subgroup analysis indicated that this benefit was almost entirely attributable to the response in patients with active disease [1].**

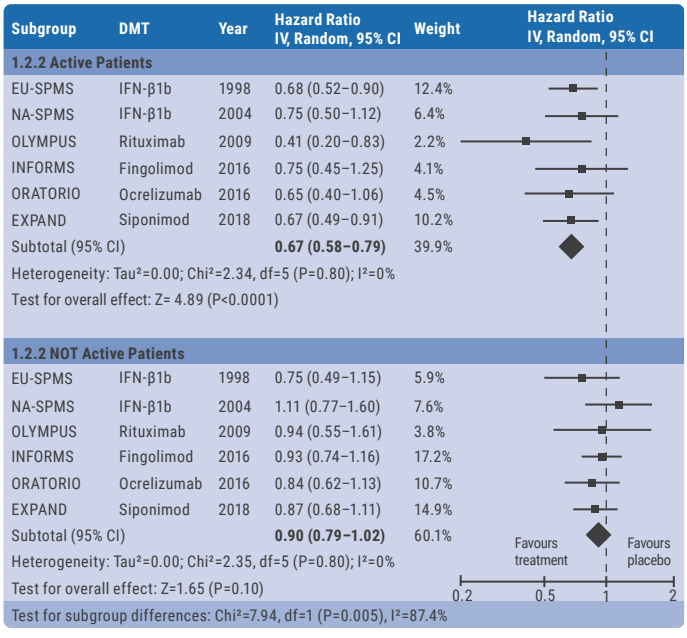
Although relapsing-remitting MS has several available therapies, only limited options are available for progressive forms of MS, such as primary (PPMS) and secondary progressive MS (SPMS) [2]. The current study investigated

the benefit of DMTs on reducing the progression of disability in progressive forms of MS and the efficacy of DMTs on participants with more active/inflammatory MS. Dr Mirko Capanna (University of Genoa, Italy) presented the study that was awarded a Top Score Poster prize at ECTRIMS 2021.

A meta-analysis of 16 randomised studies was performed using time to CDP as endpoint, all of which used the Expanded Disability Status Scale to assess treatment effect. A total of 10,562 participants (3,489 PPMS and 7,073 SPMS) were included in the analysis. The meta-analysis demonstrated a statistically significant benefit in treating patients with progressive forms of MS, quantifiable with a 13% CDP rate reduction (HR 0.87; 95% CI 0.81–0.93; P<0.0001). Further evaluation indicated that there was a low risk of bias in the studies; heterogeneity between the studies was estimated to be only 2%.

Subsequent subgroup analyses from 6 of these studies compared the effect of DMT on patients with "active" or "not active" MS, using the burden of enhancing brain MRI lesions to define disease activity. According to this analysis (see Figure), the "active" subgroup of progressive MS patients had a 33% reduction in CDP from intervention with DMT (HR 0.67; 95% CI 0.58–0.79), whereas the "not active" subgroup only had a 10% reduction (HR 0.90; 95% CI 0.79–1.02). The interaction between these groups was highly significant (P=0.005).

**Figure: Forest plot for subgroup analysis according to disease activity [1]**




CI, confidence interval; DMT, disease-modifying therapy; HR, hazard ratio.

Dr Capanna concluded that reduction of CDP with immunomodulatory/immunosuppressive DMTs has a clear clinical benefit in progressive MS, but this benefit appears to be largely confined to progressive patients with active inflammatory disease.


1. Capanna M, et al. Effect of disease-modifying therapies on progressive multiple sclerosis: a meta-analysis of randomised clinical trials. P626, ECTRIMS 2021 Virtual Congress, 13¬–15 October.
2. Tsivgoulis G, et al. PLoS One. 2015;10(12):e0144538.


## Cortical lesions predict disease progression and disability accumulation

**The presence and number of cortical lesions (CLs) at the time of MS diagnosis predicted the development of secondary progressive MS (SPMS) and disability accumulation in a 20-year follow-up study. The analysis also showed that a 1.5T MRI scan at diagnosis could be used as a prognostic tool for SPMS and disease burden [1].**

Recent studies have confirmed that CLs are predictive of the development of progressive MS and worsening of disability in MS patients [2,3]. The objective of this study, presented by Dr Gian Marco Schiavi (University of Verona, Italy), was to assess the prognostic value of CLs after 20 years when CLs were determined at an early stage of the disease. For this purpose, 220 patients with MS (relapsing-remitting MS, n=162; clinically isolated syndrome, n=45; primary progressive MS, n=12) were followed for a median of 20 years. At diagnosis and within 4 years of the clinical onset of the disease, they underwent a 1.5T brain MRI and a spinal cord MRI scan. The number of CLs, the number of white matter lesions, and the presence of spinal cord lesions were evaluated. Primary endpoints were the correlation of early MRI features with conversion to SPMS types and Expanded Disability Status Scale (EDSS) scores at the end of follow-up.

After 20 years of follow-up, 152 patients were relapsing-remitting, 44 had converted to SPMS, and 12 continued with clinically isolated syndromes. Post-hoc analyses showed that the number of CLs at diagnosis was higher in patients who converted to SPMS (mean 6.28) than in non-SPMS patients (mean 1.16; P<0.001). Moreover, higher EDSS scores were associated with higher numbers of CLs at baseline (P<0.001). Corresponding mean EDSS scores ranged from 1.5 in patients without CLs to 6.0 in patients with >3 CLs at baseline.

Dr Schiavi concluded that their data supports the notion that the presence of CLs at the time of diagnosis is associated with long-term disability and transition to a secondary

progressive disease course. Nevertheless, further research is needed to validate CLs as a biomarker for clinical practice, e.g. whether CL burden can be used to guide therapeutic decision-making in MS.


1. Schiavi GM, et al. Cortical lesions at diagnosis predict conversion to secondary progressive multiple sclerosis and accumulation of disability: a 20-year follow-up study. P105, ECTRIMS 2021 Virtual Congress, 13¬–15 October.
2. Scalfari A, et al. Neurology. 2018;90(24):e2107–e2118.
3. Haider L, et al. Brain. 2021;144(5):1384–1395.


## Ocrelizumab shows long-term benefits in primary progressive MS

**Patients with primary progressive MS (PPMS) who were originally receiving ocrelizumab had a lower risk of disability progression than patients originally receiving placebo after 8-years of follow-up, despite later cross-over in the open-label extension (OLE) period of the phase 3 ORATORIO trial. In addition, patients originally receiving ocrelizumab had a significantly reduced rate of recurrent 48-week confirmed disability progression (CDP) events, compared with participants who received ocrelizumab only later in the trial [1].**

Ocrelizumab outperformed placebo in patients with PPMS in the 144-week, double-blind plus extended controlled periods of the randomised, phase 3 ORATORIO trial (NCT01194570). The OLE of this trial assessed the long-term efficacy and safety of ocrelizumab for patients (n=517) maintaining or switching (prior placebo receivers) to ocrelizumab therapy.

The primary endpoint of this trial was time to first 48-week CDP on the Expanded Disability Status Scale (EDSS) of ≥1 point (in patients with EDSS ≤5.5 at baseline), or ≥0.5 points (in patients with EDSS >5.5 at baseline). Prof. Jerry S. Wolinsky (University of Texas Health Science Center at Houston, TX, USA) presented the 8-year follow-up study results.

At week 408, initial ocrelizumab users displayed fewer 48-week CDP-EDSS events (55.9%) than delayed treatment receivers (67.5%). Combining all periods of the study, the reduced risk of CDP-EDSS events was 29% for patients receiving ocrelizumab from the start. The risk of repeated 48-week CDP-EDSS events was lower in ocrelizumab receivers as well: the mean cumulative number of repeated CDP-EDSS was 0.944 in early ocrelizumab users versus 1.207 in delayed ocrelizumab users. Over 8 years, the risk of achieving 48-week CDP-EDSS score of ≥7, representing wheelchair dependence, was numerically lower (33%) in subjects receiving ocrelizumab at the start.

In summary, compared with a delayed ocrelizumab start, early treatment significantly reduced patients' risk of CDP-EDSS. Early ocrelizumab receivers' need for walking aid was reduced by approximately a third as well. In short, a 2-year delay in initiating ocrelizumab "comes at a cost to patients," suggesting a clear benefit for clinicians to start this therapy from the get-go.


1. Wolinsky JS, et al. Sustained reduction in 48-week confirmed disability progression in patients with PPMS treated with ocrelizumab in the ORATORIO OLE: 8-year follow-up. OP158, ECTRIMS 2021 Virtual Congress, 13–15 October.


# Other

## WNT9B-gene variant associated with doubled relapse risk in MS

**In a study looking for genetic factors that may account for differences in MS relapse rate, a rare variant –*rs11871306* within the *WNT9B* region– was associated with a more than doubled risk for a relapse. These findings imply that genetic variation within the cross-talking Wnt signalling and vitamin D pathways contributes to differences in relapse occurrence [1].**

Over the years, more than 230 gene variations have been identified that contribute to the risk of developing MS, but the role of gene variants in disease heterogeneity remains unclear [2]. Ms Marijne Vandebergh (KU Leuven, Belgium) and colleagues aimed to identify genetic variation associated with relapse risk in MS. To this end, they conducted a large gene study in 991 participants with relapsing MS before they began disease-modifying therapies (DMTs). As Ms Vandebergh explained, a genome-wide association study (GWAS) was performed in a discovery cohort and the genome-wide significant variants were investigated further in a replication cohort. In these cohorts, a total of 2,231 relapses were captured before the start of any immunomodulatory treatment.

In the discovery cohort, age at baseline was 31 years and duration of disease 4.0 years (range 1.35–12.07), while the replication cohort had a baseline age of 33 years and disease duration of 0.50 years (range 0.25–2.57). The low-frequency genetic variant *rs11871306* within *WNT9B* reached genome-wide significance in predicting relapse risk, with an HR of 2.03 (95% CI 1.55–2.67) in the discovery cohort (n=506), 2.53 (95% CI 1.58–4.05) in the replication cohort (n=485), and 2.15 (95% CI 1.70–2.78) in the 2 cohorts combined (P<0.0001). A pathway analysis identified an association of the pathway 'response to vitamin D' with relapse risk (P<0.0001). The MS genetic risk scores were not associated with relapse risk.

Ms Vandebergh concluded: "We have demonstrated the applicability of GWAS to longitudinal data. We have identified an association between genetic variation in *WNT9B* and relapse risk. This study provides genetic support for a protective role of naturally occurring higher vitamin D levels in MS relapse risk. In contrast, we observed no effect on relapse risk of genetically related increases in body mass index."


1. Vandebergh M. Genetic variation in WNT9B increases relapse hazard in multiple sclerosis. OP078, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Cotsapas C, Mitrovic M. Clin Transl Immunol. 2018;7(6):e1018.


## Melatonin associated with improved sleep quality in MS patients

**A randomised, double-blind, controlled pilot study demonstrated that melatonin improved sleeping time in MS patients. Sleep disturbances and fatigue may be alleviated by this low-cost, low-risk, over-the-counter supplement [1].**

Patients with MS often suffer from sleep disturbances, but therapeutic options targeting sleep in these patients are scarce [2]. A pilot study examined the effect of exogenous melatonin on sleep quality and sleep disturbances in MS patients. Patients with MS and confirmed sleep disturbances (n=30) were randomised 1:1 to a dose-escalating regimen of melatonin (0.5–3 mg, oral, once daily) or placebo for 2 weeks. Patients followed the opposite regimen from weeks 2–4. Sleep time and sleep efficiency were measured with an actigraphy device. Furthermore, several sleep-related patient-reported outcomes (PROs) were recorded. Dr Wan-Yu Hsu (University of California San Francisco, CA, USA) shared the results.

The total sleep time was significantly longer in the melatonin group (mean 6.96 hours) compared with the placebo group (mean 6.67 hours; P=0.03). Moreover, sleep efficiency was numerically higher in melatonin users (84.7%) versus placebo users (83.2%). Mean improvements on the Insomnia Severity Index (ISI) (melatonin -3.5 vs placebo -2.4), the sleep quality component of the Pittsburgh Sleep Quality Index (PSQI) (-0.03 vs 0.0), and the Neuro-Quality of life-Fatigue questionnaire (-4.7 vs -2.4) numerically favoured melatonin users (see Table).

**Table: Results of objective outcome measures and PROs in MS patients receiving melatonin or placebo [1]**

| Outcome measures (mean [SEM]) | Melatonin (n=30) | Placebo (n=30) | P-value |
|---|---|---|---|
| Mean total sleep time | 6.96 (0.19) | 6.67 (0.25) | 0.03 |
| Mean sleep efficiency (%) | 84.7 (1.2) | 83.2 (1.4) | 0.06 |
| ISI change | -3.5 (0.8) | -2.4 (0.8) | 0.07 |
| PSQI, component 1 change | -0.3 (0.1) | -0.0 (0.1) | 0.07 |
| ESS change | -1.2 (0.7) | -1.1 (0.7) | 0.92 |
| NeuroQoL-Fatigue change | -4.7 (1.9) | -2.4 (2.2) | 0.06 |
| MSWS 12 (%) change | -3.0 (2.0) | -2.0 (2.0) | 0.45 |
| HADS-Anxiety (HADS-A) change | 0.4 (0.6) | 0.5 (0.5) | 0.92 |
| HADS-Depression (HADS-D) change | 0.03 (0.42) | 0.03 (0.50) | 0.81 |
| HADS-Total (HADS-T) change | 0.44 (0.65) | 0.44 (0.80) | 0.94 |
| Step count | 66.802 (4675.7) | 67.573 (5423.6) | 0.84 |

HADS, Hospital Anxiety and Depression Scale; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; MSWS-12, Multiple Sclerosis Waling Scale – 12; PROs, patient-reported outcomes; PSQI, Pittsburgh Sleep Quality Index; SEM, standard error of the mean.


1. Hsu W-Y, et al. Effects of melatonin on sleep disturbances in multiple sclerosis: a pilot study. P881, ECTRIMS 2021 Virtual Congress, 13–15 October.
2. Freal JE, et al. Arch Phys Med Rehabil. 1984;65(3):135–8.


## "Expanded Disability Status Scale 0 is not normal"

**High-challenge tests can reveal performance differences between healthy controls and MS patients with an Expanded Disability Status Scale (EDSS) score of 0. Correlations between challenge task performance and imaging markers (T2LV and nThal) encapsulate both lesional burden of disease and a volumetric measure of brain reserve [1].**

Detection of MS in the early stages is complicated due to the absence of above-threshold symptoms. Sub-threshold MS lesions are compensated by functional reserve and yield no physical deficits. The threshold above which clinical deficits are recognised depends on the sensitivity of the assessment techniques. The widely used EDSS defines a score of 0 as 'neurologically normal.'

"We are only as sensitive as our tests allow," Dr Stephen Krieger (Mount Sinai Hospital, NY, USA) explained. "The recent

concept of silent progression has been highly discussed. But it is only silent if we are not listening." Recognition of sub-threshold deficits in apparently neurologically normal MS patients may help to better understand and predict the disease course. Dr Krieger and his colleagues hypothesised that higher-challenge tasks may be more sensitive to sub-threshold deficits, with neuroimaging correlates. "Patients with an EDSS score of 0 should be the same as healthy controls, but are they?"

To answer this question, 63 recently (<5 years) diagnosed MS patients in the RADIEMS cohort with an EDSS of 0 were compared with 50 matched healthy controls on standard tasks, including the timed 25-foot walk (T25FW) and high-challenge measures of upper extremity coordination (9-Hole Peg, Grooved Pegboard) and balance (NIH Toolbox Balance, Balance Boards).

Results showed that patients with an EDSS score of 0 also had normal T25FWs (median 3.95; interquartile range 3.75–4.24). However, patients performed worse than controls on:

- upper extremity (P=0.039);
- balance (P=0.005);
- overall function (P=0.006).

The higher overall function was associated with lower T2 lesion volume (T2LV; r=-0.344; P=0.006) and higher normalised thalamic volume (nThal; r=0.461; P<0.001). Dr Krieger concluded: "These results show that EDSS 0 is not normal. This challenges the existing dogma of how we define MS severity right from the beginning." He added that correlations between challenge task performance and imaging markers (T2LV and nThal) encapsulate both lesional burden of MS and a volumetric measure of brain reserve.

1. Krieger S, Sumowski J. Subclinical burden of multiple sclerosis at EDSS 0. OP122, ECTRIMS 2021 Virtual Congress, 13–15 October.

## Personality trait alterations in MS patients

**Personality traits that are often seen in patients with a recent MS diagnosis (<2 years ago) are, first and foremost, being highly agreeable, followed by being conscientious, open, and neurotic. Extraversion is less prominent. Women are significantly more likely to be agreeable and conscientious than men [1].**

Neuropsychiatric changes, including personality disturbances, are common in patients with MS. Personality traits may help explain differences on an individual level in disease acceptance, coping styles, and psychological well-being. As such, these traits impact patient care, compliance, and quality of life, and they influence healthy behaviour, symptoms, and comorbidities. Little is known about the personality of MS patients at the earliest stages of the disease.

To this end, the MS clinic of the Western University in Canada performed a retrospective chart review on adult patients that had been recently diagnosed with MS. Comprehensive baseline psychometric testing of MS patients, including NEO-Five Factor Inventory (NEO-FFI), is a standard of care in this centre. The study aimed to determine if an "MS personality" exists and which personality traits would then predominate. Dr Laura Chu (Memorial University of Newfoundland, Canada) shared the results.

The study included NEO-FFI results of 390 patients, collected within the first 2 years after the diagnosis. Of these, 363 (93%) patients had relapsing-remitting MS, about two thirds were female, and nearly all were white. The mean age was 38 years and median Expanded Disability Status Scale (EDSS) score was 2.0 (0.0–6.0). The most frequently prescribed treatments were interferon beta/glatiramer acetate (32.8%), dimethyl fumarate (15.9%), or teriflunomide (7.4%); a large proportion (39.0%) received no treatment at all.

Overall, the personality trait most predominantly present was being (highly) agreeable: 53.9% of participants were rated "high" or "very high", and 29.0% "average." A slight tendency towards higher rates of conscientiousness, openness, and neuroticism was detected. Being extravert was generally less prominent: 38.0% scored "low" or "very low", while 27.2% scored "high" or "very high". On average, women had significantly higher degrees of agreeableness (P<0.001) and conscientiousness (P=0.007). No significant differences between women and men for neuroticism, extraversion, or openness were detected.

1. Chu L. Is there a multiple sclerosis (MS) personality? Personality characteristics in persons with recently diagnosed MS at a single Canadian centre. P078, ECTRIMS 2021 Virtual Congress, 13–15 October.

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