ECTRIMS 2018

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PEER-REVIEWED CONFERENCE REPORT

Performance of the Revised McDonald Criteria

The revised 2017 McDonald criteria were put to the test in daily practice, showing higher sensitivity and slightly lower specificity. They increased the proportion of patients diagnosed with MS by nearly 25% at the time of a CIS.

read more on PAGE 3

Treating Progressive MS: 'the Next Frontier'

It is a huge challenge to find effective treatments for primary and secondary progressive MS, but also to design trials 'smart' enough to detect their impact. The MS-SMART trial lays a template for future trials.

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sNfL as Promising Biomarker of Disease Activity

Serum neurofilament light (sNfL) is associated with MS activity, predicts long-term outcomes, and is reduced by DMTs. This biomarker is expected to partly replace MRI to monitor disease activity.

read more on PAGE 20

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Editor Prof. Hans-Peter Hartung, University of Düsseldorf, Germany

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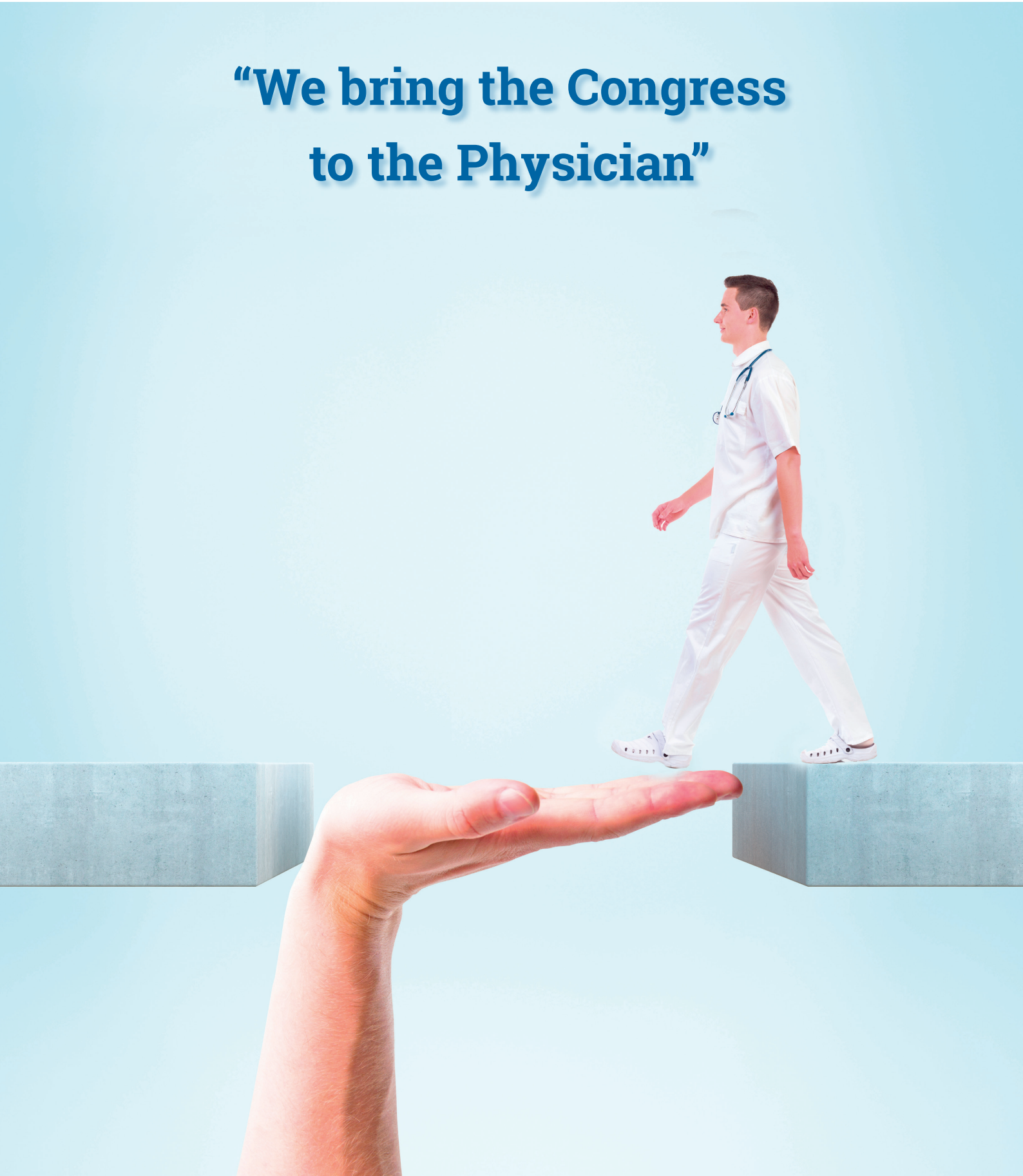

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Letter from the Editor

Prof. Hans-Peter Hartung

Dear Reader,

Almost 10,000 neurologists, researchers, and MS professionals attended the ECTRIMS 2018 in Berlin, to get updates on the new developments regarding diagnosis, treatment, pathology, and biomarker research.

The revised 2017 McDonald diagnostic criteria continue to be validated, but their use in routine practice has several implications.
Data on safety and efficacy of both novel and established biological agents are driving forward the treatment of both relapsing and progressive MS. Interesting data on head-to-head comparison of DMTs was also presented. In addition, knowing which patients to treat with which DMT, and when to discontinue or switch is of key importance and was investigated in several cohort studies.
An important topic was the undertreatment of MS symptoms such as cognitive dysfunction, affecting quality of life. An observational study suggested a neuroprotective effect of vitamin D supplementation.
Major advances are still being made in imaging technologies and it remains a hot research subject. However, the biomarker with the most attention was serum neurofilament light. The proposal of a specific cut-off value is another step forward towards its implementation as disease activity marker.

If you have not been able to experience ECTRIMS 2018 yourself, you can read about these and other highlights in this report.

Best Regards,
Hans-Peter Hartung

Biography

Prof. Hartung has been Chair of the Department of Neurology at Heinrich-Heine-University in Düsseldorf since 2001. He is also Director of the Center of Neuropsychiatry and the Department of Conservative Medicine at University Hospital Düsseldorf. He studied medicine at the Universities of Düsseldorf, Glasgow, Oxford, and London. After graduation he served an immunology fellowship at the University of Mainz. Prof. Hartung's clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies. He has been involved as steering committee member in multiple clinical trials of new drugs for the treatment of multiple sclerosis, Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy. Prof. Hartung is a former President of ECTRIMS.

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

Revised 2017 McDonald Criteria

The aims of the 2017 revision of the McDonald criteria for MS were earlier diagnosis (facilitating earlier treatment) and less frequent misdiagnosis. The revised criteria were shown to have a higher sensitivity, with a modest reduction in specificity. They increased the proportion of patients diagnosed with MS by nearly a quarter at the time of a clinically isolated syndrome.

Three major changes

In the 2017 McDonald criteria, the following changes were made to the 2010 version (Figure 1) [1]:

1. In patients with a typical clinically isolated syndrome (CIS) and clinical or MRI demonstration of dissemination in space, the presence of CSF-specific oligoclonal bands allows a diagnosis of MS (and can substitute for the requirement of dissemination in time).
2. Symptomatic lesions can be used to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome.
3. Cortical lesions can be used to demonstrate dissemination in space.

In a session dedicated to the performance of the 2017 McDonald criteria, Dr Georgina Arrambide (MS Centre of Catalunya, Spain) revealed that the revised criteria increase the proportion of patients diagnosed with MS by nearly 25% at the time of a CIS [2]. At baseline, 132 of 566 (23.3%) patients in a CIS cohort met exclusively the 2017 criteria. After a median follow-up of 6.9 years, during which 86 (65.2%) patients initiated disease-modifying treatments (DMTs), 68 (51.5%) had a second attack and 97 (73.5%) fulfilled the 2010 McDonald criteria over time.

In a Dutch cohort of 229 patients, sensitivity of the 2017 criteria was found to be higher than the 2010 criteria (68% vs 36%; P<0.001), but specificity was lower (61% vs 85%; P<0.001) [3]. Using the 2017 criteria, more MS diagnoses could be made at baseline: 97 (54%) vs 46 (26%), respectively (P<0.001). In the group with at least 5 years of follow-up, 33% of patients who were diagnosed with MS using the 2017 criteria did not experience a second attack during follow-up, vs 23% when using the 2010 criteria.

A study of 154 CIS patients also showed a higher sensitivity of the 2017 McDonald criteria, with a modest reduction in specificity [4]. Overall, the revised criteria were more sensitive (89% vs 81%) and more accurate (83% vs 79%) but were slightly less specific (73% vs 75%). When applied in patients with typical CIS, the updated criteria allowed for an earlier diagnosis of MS (57% vs 44%).

The 2017 McDonald criteria can also be applied routinely to children at any age. Compared with the 2010 version, they had higher accuracy (93.6% vs 66.0%), higher specificity (79.2% vs 54.1%), and similar sensitivity (94.1% vs 93.6%) [5]. First author Dr Yael Hacohen (Queen Square MS Centre, United Kingdom) said the improved performance in children was predominantly due to the inclusion of intrathecal oligoclonal bands. In general, an alternative diagnosis should be looked for in children who, at CIS onset, do not have evidence of intrathecal oligoclonal bands.

Figure 1 2017 McDonald criteria for the diagnosis of MS [1]

Clinical Presentation	Additional data needed to make MS diagnosis
... in a person with a typical attack/CIS at onset	
• ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemention in space (**DIS**) and dissimination in time (**DIT**) have been met.
• ≥2 attacks and objective clinical evidence of 1 lesion	**One** of these criteria: - **DIS**: additional clinical attack implicating different CNS site - **DIS**: ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions in ≥2 areas of CNS; periventricular, **juxtacortical/cortical**, infratentorial or spinal cord
• 1 attack and objective clinical evidence of ≥2 lesions	**One** of these criteria: - **DIT**: additional clinical attack - **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions - **DIT**: new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - **CSF-specific (i.e. not in serum) oligoclonal bands**
• 1 attack and objective clinical evidence of 1 lesion	**One** of these criteria: - **DIS**: additional clinical attack implicating different CNS site - **DIS**: ≥1 MS-typical **symptomatic or asymptomatic** T2 lesions in ≥2 areas of CNS; periventricular, **juxtacortical/cortical**, infratentorial or spinal cord **AND** **One** of these criteria: - **DIT**: additional clinical attack - **DIT**: simultaneous presence of both enhancing and non-enhancing **symptomatic or asymptomatic** MS-typical MRI lesions - **DIT**: by new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - **CSF-specific (i.e. not in serum) oligoclonal bands**
... in a person with progression of disability from onset	
• progression from onset	- 1 year of disability progression (retrospective or prospective) **AND** **Two** of these criteria: - ≥1 **symptomatic or asymptomatic** MS-typical T2 lesions (periventricular, **juxtacortical/cortical** or infratentorial) - ≥2 spinal cord lesions - CSF-specific (i.e. not in serum) oligoclonal bands

Coloured text = revisions compared to previous McDonald criteria.
CIS; clinically isolated syndrome, CNS; central nervous system, CSF; cerebrospinal fluid, DIS; dissemination in space, DIT; dissemination in time, T2 lesion; hyperintense lesion on T2-weighted MRI

Practical implications

Are the new McDonald diagnostic criteria controversial, making them difficult to use in clinical practice? In a 'burning debate' session, Dr Frauke Zipp (University of Mainz, Germany) agreed. She argued that the revisions force treatment too early, risking that benefits may be outweighed by possible harmful effects, such as malignancies. Dr Jiwon Oh (University of Toronto, Canada), on the other hand, argued that there is a clear scientific rationale for the update, that the new criteria are easy to apply, and that they save time and resources for the patient and neurologist. "The criteria increase the sensitivity of the diagnostic process without sacrificing much specificity."

In a poster, Prof. Gavin Giovannoni (Royal London Hospital, United Kingdom) reported on the potential implications of applying the 2017 McDonald criteria in routine neurological practice in the United Kingdom [6]. A total of 51% of neurologists with a specialist interest in MS answered a short online questionnaire on the subject. Prof. Giovannoni noted that the routine application of CSF analysis in the diagnostic process not only has practical implications for routine practice, but also has ethical, legal, and potential socioeconomic implications for people previously diagnosed as having CIS, but who now (potentially) have MS using the new criteria.

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New Compounds

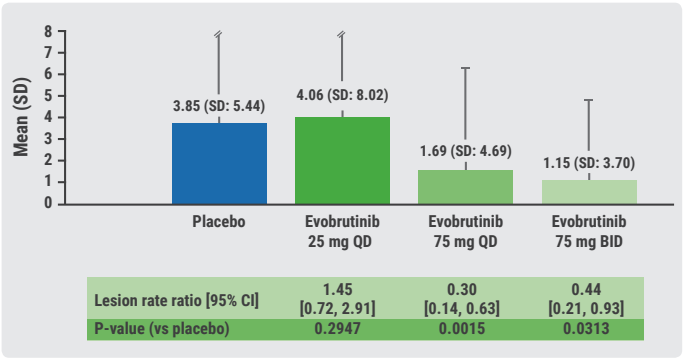
It was gratifying to see preclinical and phase 1 – 3 results of a number of new compounds, mainly for the treatment of relapsing MS. One of these was GnbAC1. This IgG4 monoclonal antibody represents a completely new mechanism of action, inhibiting TLR4-mediated pathogenic mechanisms. Another one was evobrutinib, an oral inhibitor of Bruton's tyrosine kinase (BTK) that targets both B-cells and myeloid cells. There were also positive results of satralizumab, a recycling anti-IL-6 receptor monoclonal antibody (mAb), which reduced the risk of relapse in patients with neuromyelitis optica spectrum disorder (NMOSD).

Bruton's tyrosine kinase inhibitor evobrutinib

Evobrutinib (M2951) is a highly specific, irreversible, oral BTK. Inhibition of BTK hinders M1 macrophage differentiation and skews monocytes towards an anti-inflammatory M2 phenotype, while enhancing apoptotic cell uptake by the M2 cells [1]. It could therefore have additional benefit in the treatment of MS and other autoimmune diseases, by targeting both B-cells and myeloid cells simultaneously.

In the first-in-human study, evobrutinib was well tolerated, with predictable pharmacokinetics and no prolongation of QT interval (ΔΔQTcF) in healthy volunteers [2]. Results of a phase 2 study, evaluating evobrutinib in clinically and radiologically active relapsing MS, supported a role for evobrutinib in MS [3]. In this double-blind, placebo-controlled study, 267 patients aged 18-65 years with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) with superimposed relapses were randomised to evobrutinib 25 mg a day, 75 mg a day, 75 mg twice daily, placebo, or open-label dimethyl fumarate 240 mg twice daily (reference arm) for 48 weeks. The primary endpoint was the total number of T1 gadolinium-enhancing (Gd+) lesions at weeks 12, 16, 20, and 24. An analysis of the results after 24 weeks was presented. Evobrutinib 75 mg daily and 75 mg twice daily significantly reduced the number of T1 Gd+ lesions vs placebo, with a lesion rate ratio of 0.30 (P=0.002) and 0.44 (P=0.03), respectively (Figure 2). Evobrutinib led to numerical and clinically relevant decreases in annualised relapse rate (ARR), with evidence of a dose response.

Figure 2 Total number of T1 Gd+ lesions at week 12-24 [3]



Rates of treatment-emergent adverse events (AEs) and serious treatment-emergent AEs were comparable with evobrutinib 25 and 75 mg daily and placebo, but higher with evobrutinib 75 mg twice daily (driven by asymptomatic increases in liver transaminases). There were no serious infections with evobrutinib and no other emerging safety signals.

Human endogenous retrovirus-W Env antagonist GnbAC1

"The final analyses of the CHANGE-MS phase 2b study showed consistent neuroprotective benefits with GnbAC1 [4]. Importantly, these benefits were prominent in the inactive subpopulation of patients in this study: precisely those MS patients who are suboptimally treated with currently available therapies," said Prof. Hans-Peter Hartung (University Hospital Düsseldorf, Germany), principal investigator of the study. "These results appear to be the outcome of a completely new mechanism of action targeting a cause of MS progression."

Human endogenous retroviruses (HERVs) are transposable genetic elements, representing 8% of the human genome. A pathogenic member of the HERV-W family (pHERV-W) may be transactivated by environmental factors such as Epstein-Barr Virus (EBV), a known risk factor for MS, to generate the pathogenic envelope protein pHERV-W Env. This is a potent agonist of Toll-like Receptor 4 (TLR4). The humanised IgG4 monoclonal antibody GNbAC1 targets the surface subunit of pHERV-W Env; thereby inhibiting TLR4-mediated pathogenic mechanisms.

In CHANGE-MS, 270 RRMS patients were randomised to GNbAC1 (6, 12, or 18 mg/kg) or placebo, via monthly intravenous infusion, for 24 weeks (period 1). At week 24, placebo patients were re-randomised, in a dose-blind manner, to active GNbAC1 for an additional 24 weeks (period 2). The primary endpoint was the cumulative number of Gd+ lesions on MRI at weeks 48 vs placebo.

For the highest dose (18 mg/kg), non-significant reduction of 15% in new T2 lesions was observed at week 48 vs the control group (those randomised to placebo in period 1) (P=0.48). There was a significant 63% reduction in new T1-black holes (P=0.014) from week 24-48. Also, reductions in central nervous system (CNS) volume loss were observed. Relative reductions in thalamic, cortical, and whole-brain atrophy were 72%, 31%, and 29%, respectively, with significant dose-relationships (P=0.045, P=0.014, and P=0.079, respectively). There was a consistent benefit in reducing atrophy in the non-active population. Prof Hartung added that no safety issues were found. Only 1 treatment-related serious AE was seen. Six participants withdrew from the study due to AEs. "The continued safety and tolerability," he concluded, "allow for future studies with increased dose and/or in combination with disease-modifying treatments."

Ublituximab

Results were shared of a phase 2, placebo-controlled, multicentre study of ublituximab that was primarily designed to assess the optimal dose and infusion time of ublituximab in relapsing MS subjects [5]. Ublituximab treatment resulted in rapid and robust B-cell depletion, a profound reduction in MRI activity, and suppression of relapses. Moreover, ublituximab was found to be safely delivered in infusions as fast as 1 hour.

Ublituximab is a novel mAb that targets a unique epitope on the CD20 antigen and is glyco-engineered for enhanced B-cell targeting through antibody-dependent cellular cytotoxicity (ADCC). It is hoped that the more potent ADCC will allow for lower doses and shorter infusion times than currently available anti-CD20 mAbs. In the phase 2 study, all 48 participants, including placebo subjects (post 4-week placebo phase), received 3 ublituximab infusions on days 1 and 15, and at week 24 and were followed for 48 weeks. Median B-cell depletion was >99% at week 4 and was maintained at week 24 (n=44) and week 48 (n=22), with no significant differences in B-cell depletion by cohort. Interestingly, T-cells showed a significant population shift toward naïve and regulatory phenotypes. There was a 100% reduction of T1-Gd+lesions at week 24 (n=44; baseline mean 3.80; P=0.003), which was maintained at week 48 (n=22; baseline mean 2.86; P=0.0004). Mean T2 lesion volume decreased by 8% and 10% at week 24 (n=44; P=0.004) and week 48 (n=22; P=0.016), respectively. The ARR for all patients was 0.07. No evaluable subjects demonstrated sustained disability progression. No severe AEs were reported. The most common AEs were infusion-related reactions (all grade 1-2), the risk of which did not increase with faster infusion times. Phase 3 studies ULTIMATE I and II are ongoing.

Ozanimod in early MS

In a post-hoc analysis of pooled data, ozanimod treatment resulted in lower ARR and MRI activity vs interferon (IFN) β-1a, not only in patients with advanced relapsing MS, but also in patients with early disease [6]. Ozanimod is an oral, once-daily immunomodulator selectively targeting sphingosine 1-phosphate receptors 1 and 5. In two phase 3 trials, 2,659 relapsing MS patients received daily oral ozanimod hydrochloride (HCl) 1.0 or 0.5 mg (equivalent to ozanimod 0.92 or 0.46 mg, respectively) vs weekly intramuscular IFN 30 µg for ≥12 (SUNBEAM) or 24 months (RADIANCE). Pooled data for patients with early relapsing MS were analysed. At baseline, patients with early vs advanced relapsing MS had 0.5 vs 5.7 median years since diagnosis, 2.0 vs 3.5 median Expanded Disability Status Scale (EDSS), and 1.4 vs 1.2 mean relapses within the last year, respectively.

ARR was lower with ozanimod in patients with early relapsing MS as well as advanced relapsing MS. ARR in patients with early relapsing MS was:

- ozanimod HCl 1.0 mg: 0.149;
- ozanimod HCl 0.5 mg: 0.200;
- IFN β-1a: 0.285.

Adjusted mean number of Gd+ lesions at 12 months was lower with ozanimod in patients with early relapsing MS:

- ozanimod HCl 1.0 mg: 0.263;
- ozanimod HCl 0.5 mg: 0.458;
- IFN β-1a: 0.656.

Adjusted mean new/enlarging T2 lesions over 12 months were also lower with ozanimod in patients with early relapsing MS:

- ozanimod HCl 1.0 mg: 2.952;
- ozanimod HCl 0.5 mg: 3.744;
- IFN β-1a: 4.633.

Similar effects were seen in patients with more advanced disease. These data support the potential of ozanimod as an effective treatment of both early and advanced relapsing MS.

Phase 1 studies of elezanumab, MOSPD2

In a phase 1, double-blind, placebo-controlled, escalating multiple-dose study, elezanumab was well-tolerated and did not consistently result in symptom worsening in patients who received multiple doses of up to 1,800 mg [7]. Elezanumab is a fully humanised monoclonal antibody directed against repulsive guidance molecule A (RGMa). In MS, RGMa upregulation has been observed, which inhibits axonal growth and myelination, oligodendroglial regeneration, and functional recovery after trauma or inflammation. Elezanumab treatment promoted axon regeneration, neuroprotection, remyelination, and immune modulation in several MS-relevant preclinical models.

The most common treatment-emergent AE reported was headache (5 of 20 patients: 25%). Free soluble RGMa decreased with increasing levels of elezanumab in CSF, while total RGMa (both free and antibody-bound) increased linearly with CSF elezanumab exposure. Interleukin(IL)-10 also increased in the CSF following elezanumab administration compared with placebo. From baseline through the end of the follow-up period, the majority of patients receiving elezanumab did not experience a clinically significant worsening or improvement in EDSS scores.

A preclinical study found motile sperm domain-containing protein 2 (MOSPD2) to be essential for experimental autoimmune encephalomyelitis (EAE) pathogenesis [8]. Targeting MOSPD2 using mAbs may hold promise as a remedy for MS through inhibition of monocyte accumulation in the CNS. The protein MOSPD2 is predominantly expressed on the surface of human monocytes and is essential for their migration. In MS, blood-borne monocytes are paramount for promoting myelin degradation. Therefore, inhibiting monocyte migration to the CNS of MS patients could have a therapeutic benefit. In this study, the potential of MOSPD2 as a target for treating CNS inflammation was assessed using EAE as a test model. EAE was induced by immunising mice with myelin oligodendrocyte glycoprotein (MOG) peptide 35-55. Upon immunisation with pMOG35-55, EAE development in MOSPD2 knock-out mice was suppressed. Infiltration of monocytes and T-cells to the CNS was markedly reduced. Two mAbs, VBL-632 and VBL-634, profoundly inhibited EAE development when employed in a prophylactic regimen. More importantly, VB-634 ameliorated disease severity even when administered during peak EAE.

Satralizumab in neuromyelitis optica spectrum disorder

In the SAkuraSky study, satralizumab added to immunosuppressive therapy significantly reduced the risk of relapse by 62% compared with placebo in patients with NMOSD [9]. Satralizumab was effective both in anti-aquaporin-4 (AQP4) antibody-positive and antibody-negative patients. NMOSD is an autoimmune-inflammatory disease usually associated with AQP4 autoantibodies that predominantly target optic nerves and the spinal cord. Satralizumab is a recycling anti-IL-6 receptor mAb with a long plasma circulation. Results of a randomised, double-blind, phase 3 study of satralizumab, the SAkuraSky study, were presented as a late-breaking abstract. The 83 participants were randomised to satralizumab 120 mg or placebo, given at weeks 0, 2, 4, and every 4 weeks thereafter, as add-on to baseline treatment (immunosuppressants or corticosteroids at a stable dose). The primary endpoint was time to first protocol-defined relapse.

First author Prof. Takashi Yamamura (National Institute of Neuroscience, Japan) said mean duration since NMOSD onset was 4.88 years. At baseline, mean ARR was 1.44; median EDSS was 3.5; 68/83 (81.9%) patients reported pain (Visual Analogue Scale [VAS] >0). Compared with placebo, satralizumab reduced the risk of relapse by 62% (P=0.018). The proportion of patients who were relapse-free at weeks 48 and 96 was 88.9% and 77.6% with satralizumab, and 66.0% and 58.7% with placebo, respectively. In the NMOSD AQP4 antibody-positive (n=55) and AQP4 antibody-negative (n=28) subgroups, risk of relapse was reduced by 79% and 34%, respectively (Figure 3). Throughout the mean treatment duration of approximately 2 years, satralizumab showed a favourable safety profile. The proportion of patients experiencing serious AEs was similar to placebo. Prof. Yamamura noted that more patients in the placebo arm than in the actively treated arm withdrew from the study due to AEs.

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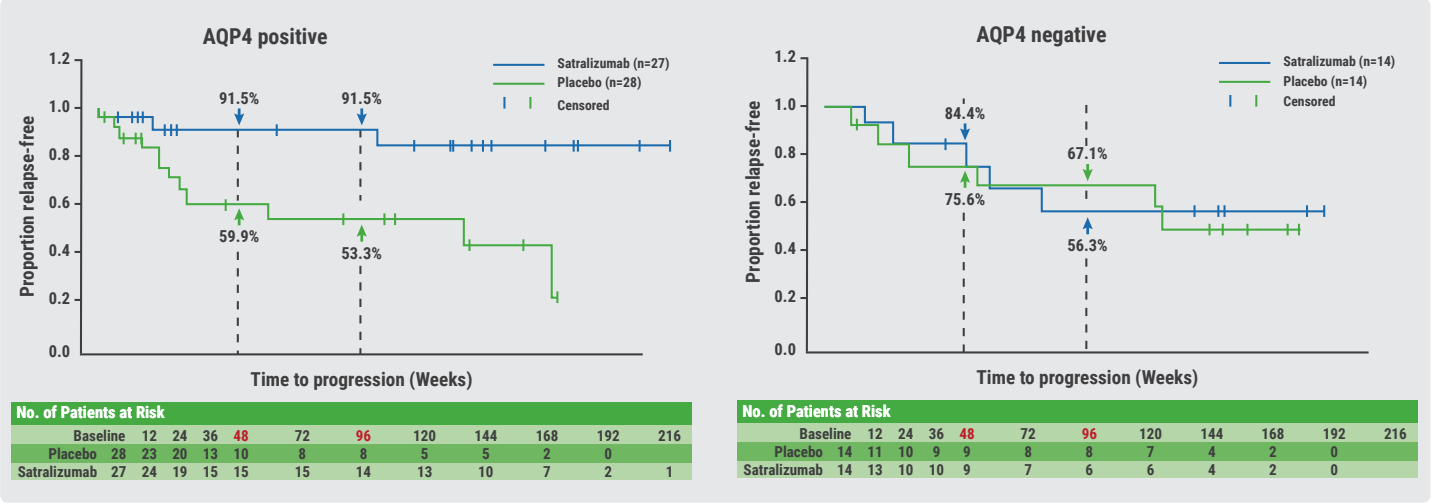
Figure 3 Reduced risk of protocol-defined relapse in both AQP4-positive and AQP4-negative subgroups [9]



Short- and Long-Term Results of Disease-Modifying Treatment

Updated results from long-term extensions of clinical phase 2/3 trials of disease-modifying treatments (DMTs) were presented, on the whole confirming efficacy and safety results that were seen in the core trials. Several observational studies confirmed that extended interval dosing (EID) of natalizumab significantly reduces the risk of progressive multifocal leukoencephalopathy (PML) without compromising its efficacy. A randomised prospective study of EID is planned. In this chapter, results of several head-to-head studies are also presented.

Alemtuzumab

Updated results from CARE-MS II patients showed that efficacy of alemtuzumab on clinical, MRI, and brain volume loss outcomes was maintained over 8 years in the absence of continuous treatment, with a consistent and manageable safety profile [1]. In the CARE-MS II phase 3 trial, 2 courses of alemtuzumab over 2 years significantly improved clinical and MRI outcomes vs subcutaneous IFN β-1a in RRMS patients with inadequate response to prior therapy. Efficacy was maintained in a 4-year extension, with 50% receiving no additional alemtuzumab or other DMTs over 6 years. Patients

could continue in TOPAZ, an additional 5-year extension study. Results of the first 2 years of TOPAZ were presented.

Of 435 patients receiving alemtuzumab in CARE-MS II, 300 (69%) completed year 2 of TOPAZ. A total of 44% received neither additional courses of alemtuzumab nor another DMT after the initial 2 courses. At year 8, ARR was 0.18, and 85% were relapse-free. EDSS scores from core study baseline were stable/improved in 70% of patients through year 8; the mean EDSS change from baseline to year 8 was 0.17. Other results through year 8:

- 64% of patients were free from 6-month confirmed disability worsening; 47% achieved 6-month confirmed disability improvement.
- 58% of patients achieved no evidence of disease activity (NEDA).
- 70% were free of MRI disease activity.
- 89% were free of new Gd+ lesions; 70% were free of new/enlarging T2 hyperintense lesions.
- The safety profile in year 8 was consistent with the previous years, and the incidence of AEs, infections, and thyroid AEs continued to decline.

In a prospective observational multicentre study from Spain, alemtuzumab was shown to be effective in controlling disease activity in patients who switched from fingolimod and natalizumab [2]. Alemtuzumab provided immunotherapeutic rescue for patients with an aggressive disease, the authors concluded. Severe AEs occurred rarely, and they resolved without problems.

Cladribine

In a post-hoc analysis, long-term sustainability of the clinical effect of cladribine tablets 3.5 mg/kg was observed in patients with high disease activity who were treated in the CLARITY core trial [3]. In CLARITY, cladribine showed strong efficacy vs placebo over 2 years in patients with relapsing MS; efficacy was sustained in years 3 and 4 without further treatment (CLARITY extension). In CLARITY, patients with high disease activity showed clinical and MRI responses to cladribine that were better than, or comparable to, those seen in the overall CLARITY population.

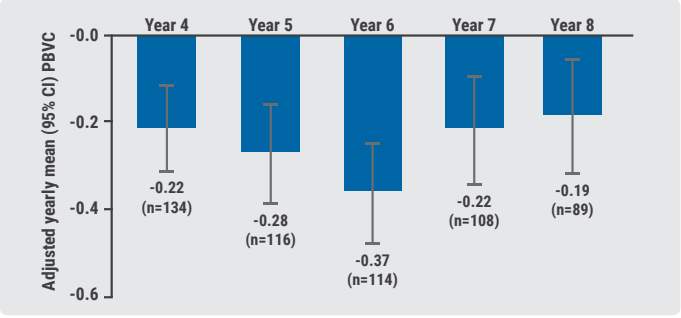
The ARR for qualifying relapses of those who switched to placebo in the extension study (n=98) was 0.15, with no difference between patients with high relapse activity and no high relapse activity. Fewer patients in the subgroups with high disease activity had confirmed 3-month EDSS progression compared with patients without high disease activity and overall groups. The proportion of patients with confirmed 3-month and 6-month EDSS progression was lower in subgroups with high disease activity in the CLARITY extension study compared with corresponding subgroups in CLARITY.

Another poster reported that the rate ratio of qualifying relapse (and all relapses) was consistently and significantly lower in the cladribine group vs placebo in the CLARITY study, for every timepoint (weeks 24, 48, and 96), including severe relapses requiring hospitalisation or steroid treatment [4]. A 2-year update of an integrated safety analysis confirms the serious treatment-emergent AE profile associated with cladribine of patients with early and active relapsing MS [5]. No new major safety findings were identified in the updated dataset, where patients were followed for up to 10 years.

Dimethyl fumarate

Long-term dimethyl fumarate treatment translates into meaningful benefits of tissue protection on MRI in RRMS patients. This was concluded from radiological outcomes in patients treated long-term with dimethyl fumarate in the ENDORSE trial. In the ongoing extension study of the phase 3 DEFINE and CONFIRM studies, lesion analysis showed a low frequency of new T1 hypo-intense lesions, suggesting axonal preservation; a low annual rate of new/newly enlarging T2 lesions, consistent with maintained anti-inflammatory effects. Annual changes in brain volume approached that of healthy individuals (Figure 4) [6].

Figure 4 Percentage brain volume change by year of dimethyl fumarate treatment [6]



A post-hoc interim analysis of ESTEEM, an ongoing, 5-year, observational study, showed that ARR at 2 years was significantly reduced compared with the year prior to dimethyl fumarate initiation in patients. The authors concluded that these data provide further evidence of real-world effectiveness of dimethyl fumarate in patients with early MS [7].

Fingolimod

Patients treated with fingolimod 0.5 mg for 5 – 10 years in the open-label LONGTERMS extension study maintained low disease activity [8]. However, the authors of this analysis could not rule out the influence of selective attrition. Reported safety was consistent with the known profile of fingolimod without the emergence of new safety concerns. The studied population included all patients (n=895) who received fingolimod 0.5 mg for at least 5 years from the first dose in the phase 2/3/3b core/extension studies. Median exposure to fingolimod 0.5

mg was 8 years. ARR gradually decreased during the study: month 0-12, 0.26; month 0-60, 0.16; month 0-120, 0.14.

Of the 697 evaluable patients at 60 months, 78.0% were free from 6-months confirmed disability progression. Mean changes from first dose in T1 hypo-intense lesion volume were similar at 60 and 120 months. The annualised rate of brain atrophy was stable throughout the study: month 12, -0.37; month 60, -0.30; month 120, -0.35. The most common AEs were viral upper respiratory tract infection (incidence rate [IR] 3.17), headache (IR 2.61) and hypertension (IR 2.08). The most common serious AEs were MS relapse (IR 0.22), basal cell carcinoma (IR 0.18), and pneumonia (IR 0.08).

Natalizumab

Evidence is accumulating that extended interval dosing (EID) of natalizumab does not compromise its efficacy but significantly reduces the risk of progressive multifocal leukoencephalopathy (PML). An 11-year study in a dedicated MS centre in Greece confirmed less frequent natalizumab dosing appeared safe and effective [9]. The authors concluded that a long wash-out period of natalizumab permits a less frequent drug dosing. Of 84 patients, none presented with PML or clinical worsening. Frequent monitoring of these patients is mandatory.

In an Italian multicentre cohort, EID regimen up to 56 days did not reduce effectiveness of natalizumab therapy at year 2 or beyond, but compared with standard interval dosing (SID; ≤35 days) it was less effective in the first year [10]. Mixed interval dosing (SID for ≥12 to ≤24 months, followed by EID) appeared to penalise efficacy of natalizumab up to year 3. Altogether, these data suggest that many patients can still achieve NEDA with EID; differences in effectiveness between EID and SID lessened with increasing treatment duration.

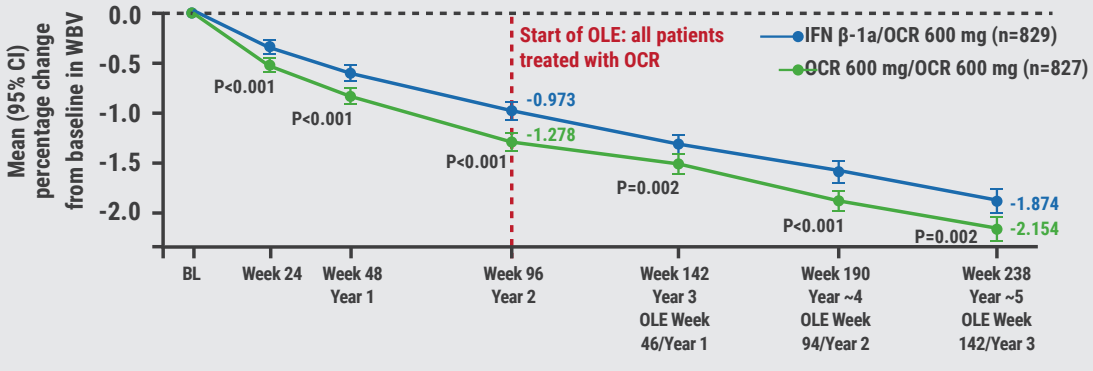
In another Italian cohort there was no evidence of a reduced efficacy of natalizumab by EID with a median interval of 4.5 to 6.3 weeks [11]. The authors concluded that a randomised study is warranted to change the standard natalizumab dosing schedule.

Ocrelizumab

The efficacy of switching from IFN β-1a to ocrelizumab or maintaining ocrelizumab was assessed after 3 years of follow-up in the open-label extension period of the OPERA I and OPERA II phase 3 trials [12]. Switching from IFN to ocrelizumab after 2 years at the start of the open-label extension period was associated with a rapid reduction in ARR. Both patient groups maintained their robust reduction in ARR through the 3-year follow-up of the open-label extension period. After 5 years, the proportion of patients with disability progression was lower in patients who initiated ocrelizumab treatment earlier and continued compared with patients who received initial IFN treatment and switched to ocrelizumab. This shows that patients who initiated ocrelizumab 2 years earlier accrued significant and sustained reductions in disability progression compared to patients switching from IFN.

Brain MRI measures of disease activity and atrophy after earlier vs delayed initiation of ocrelizumab at 5 years from core study baseline in phase 3 trials in relapsing MS was also assessed [13]. IFN-switchers had an almost complete and sustained suppression of MRI disease activity as measured by T1 Gd+ lesions and new/newly enlarging T2 lesions from year 2 to 5. Patients with 5 years of continuous ocrelizumab treatment from randomisation experienced a lower brain atrophy as measured by change from baseline in whole brain (Figure 5), white matter, and cortical grey matter volume compared with patients with a 2-year delay in ocrelizumab treatment.

Figure 5 Percentage change in whole brain volume from baseline to year 5 [13]



No. of patients at risk							
IFN β-1a/OCR 600 mg	707	682	614	545	422	353	316
OCR 600 mg/OCR 600 mg	743	708	673	594	485	383	342

Siponimod

The longer-term safety of siponimod 2 mg for up to 6 years was assessed, using pooled data from the BOLD and EXPAND trials and their extensions [14]. No increase was observed in the incidence rates of AEs nor any other new safety finding. Low lymphocyte counts were not associated with an increased infection rate.

Efficacy and safety of siponimod was evaluated for relapsing MS patients in the phase 2 trial BOLD, and for SPMS patients in the phase 3 EXPAND study. In the long-term pool, patients were included who received ≥1 dose of siponimod 2 or 10 mg in core/extension phases (n=1,737). In the long-term pool, AEs were reported in 90% of patients, serious AEs in 20.7%, and AEs that led to study discontinuation in 9.6%. IRs of the most common AEs (incidence ≥10%) in the long-term pool were consistent with those reported with siponimod 2 mg in the core pool:

- nasopharyngitis (9.1 vs 9.7);
- headache (7.9 vs 11.3);
- urinary tract infection (6.9 vs 8.3);
- fall (5.5 vs 7.9);
- hypertension (4.9 vs 7.4).

Teriflunomide

Long-term efficacy and safety data, with a follow-up of up to 12.8 years, from a pooled analysis of the phase 2/3 TEMSO, TOWER, and TENERE core and extension studies was presented [15]. ARR was significantly lower among patients treated with teriflunomide 14 mg vs placebo (Figure 6). No new safety signals were reported.

There were 812 and 896 patients in the pooled placebo and teriflunomide 14 mg intention-to-treat groups, respectively. The cumulative treatment exposure for teriflunomide 14 mg was 1,357 patient years; mean exposure was 154 weeks.

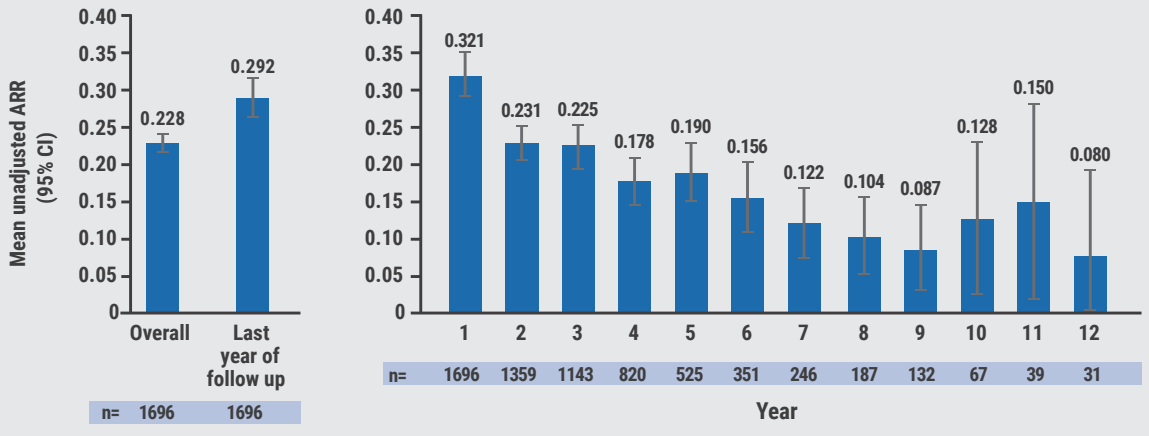
Adjusted ARR was significantly lower among patients treated with teriflunomide 14 mg (0.38) compared with placebo (0.59), representing a relative reduction of 35% (P<0.0001). The overall ARR in teriflunomide 14 mg groups was 0.228. The ARR in the first year was 0.321; in year 12 it was 0.080. The annual percentage of patients free from relapses was high and stable: 75% in year 1, 93% in years 8 and 9, and 80% in year 12. EDSS score also remained stable. In the teriflunomide 14 mg and placebo groups, the percentage of patients with AEs was 89.7% and 86.4%, respectively. The percentage of patients with serious AEs was 12.8% and 12.4%, and the percentage of patients who discontinued treatment due to AEs was 13.1% and 6.9%, respectively.

In post-hoc analyses of the phase 3 TEMSO study, significant treatment effects of teriflunomide 14 mg on brain volume loss were observed compared with placebo [16]. In the adjusted model, mean percentage brain volume change was -1.01% in the 14 mg group and -1.30% in the placebo group, with an estimated treatment effect of 0.30% (P=0.0207). Most of the effects on brain volume were independent of teriflunomide's effect on focal lesions and relapses. The authors therefore concluded that the effect on brain volume loss may be due to reducing diffuse neurodegeneration, rather than being secondary to ameliorated focal inflammation.

Head-to-head studies

- For the first time, the relative efficacy of teriflunomide and dimethyl fumarate has been assessed [17]. After 1 and 2 years of treatment, and after correction for confounders, their efficacy was similar in terms of relapse risk and worsening of EDSS. However, significantly more patients treated with teriflunomide experienced new T2 lesions after 2 years, which was supported by an increased

Figure 6 Mean annualised response rate in patients treated with teriflunomide [15]



treatment withdrawal for lack of efficacy in this group. This was found in a prospective French study in 1,770 RRMS patients participating in the national OFSEP cohort. The proportion of patients with at least one relapse at 1 and 2 years of treatment in teriflunomide and in dimethyl fumarate-treated patients was 21.6% vs 20.2% in the first year, and 30.4% vs 29.5% at 2 years. A similar percentage of patients has a higher EDSS score at one year (27.4% s 27.1%) and 2 years (41.6% vs 40.6%). The proportion of patients with at least one new T2 lesion at 2 years was 60.8% in the dimethyl fumarate group vs 72.2% in the teriflunomide group (OR: 0.6).

- Another study comparing teriflunomide and dimethyl fumarate in a real-world setting found no differences in 6-months confirmed EDSS worsening, but did find lower relapse rates, increased time to first relapse and lower incidence of discontinuation due to disease breakthrough in dimethyl fumarate compared with teriflunomide-treated patients [18]. A total of 1,696 patients from the Danish Multiple Sclerosis Registry (DMSR) were included in the study: 1,178 on teriflunomide and 518 on dimethyl fumarate. After a mean follow-up of 2.0 years, the mean ARR in teriflunomide and dimethyl fumarate was 0.19 and 0.11, respectively. Discontinuation due to disease breakthrough for teriflunomide and dimethyl fumarate was 22.1% and 10.2%, respectively. Discontinuation due to AEs was 17.4% and 16.2%.
- In an Italian monocentric cohort of RRMS patients, dimethyl fumarate and fingolimod had comparable efficacy outcomes, but the time to treatment discontinuation was shorter in the dimethyl fumarate group [19]. The effects on MRI activity were larger in fingolimod patients. In 196 fingolimod-treated patients and 350 dimethyl fumarate-treated patients, higher MRI activity was observed in the dimethyl fumarate group (OR: 1.73). NEDA was observed in 60.4% and 54.3% of fingolimod- and dimethyl fumarate-treated patients, respectively. Two-year rate of discontinuation was 22.8% and 17.1% (P=0.003); time to discontinuation was significantly shorter for dimethyl fumarate (P<0.005). The differences in MRI activity were even more profound in treatment-naïve patients.

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Data from Observational Studies

Initiated in 2001, the German MS Registry is one of the largest databases worldwide with over 49,000 patients. An analysis revealed that MS symptoms, such as fatigue, are undertreated, and that the rate of fully employed MS patients is still low. Results from an observational Australian cohort justify continuing disease-modifying treatments (DMT) use in secondary progressive multiple sclerosis (SPMS) patients who are actively relapsing. A Norwegian study showed vitamin D elevation and smoking cessation after clinical onset may protect cognitive function in clinically isolated syndrome (CIS) patients.

MS symptoms often untreated

An update on healthcare situation, employment status, and baseline data of the German MS Registry suggested more favourable outcomes than 10 years earlier, which is in line with cohorts from other countries [1]. Three quarters of MS patients received DMTs, but symptoms of MS were undertreated.

As Prof. Peter Flachenecker (Neurologisches Rehabilitations-zentrum Quellenhof, Germany) explained, data from 18,030 MS patients was available for analysis. Mean duration of MS was 10.6 years, median Expanded Disability Status Scale (EDSS) was 3.0. The disease course was relapsing-

remitting MS (RRMS) in 77.4%, SPMS in 16.8%, and primary progressive MS (PPMS) in 5.8%. Most participants (75.2%) were treated with DMTs, mostly with interferons (27.1%), followed by fingolimod (15.4%), glatiramer acetate (14.4%), dimethyl fumarate (14.4%), natalizumab (11.3%), and teriflunomide (8.3%). Prof. Flachenecker remarked that low disability in terms of EDSS score does not reflect the impact of neuropsychological symptoms with their putative impact on quality of life. He observed that MS symptoms were often not treated (Table 1); for example, of patients with fatigue, only 29.7% received treatment for this. Only 37.5% of the cohort was fully employed, while 22.5% was prematurely retired (Table 2). Prof. Flachenecker: "The low rate of fully employed MS patients underlines the need for more effective strategies that help maintain their functional level and social participation."

Table 1 MS symptoms and their treatment [1]

Symptom	Frequency (%)	% not treated
Fatigue	8,447 (52.3%)	70.3%
Mobility impairment	8,607 (49.9%)	16.0%
Spasticity	5,408 (33.1%)	14.0%
Bladder dysfunction	5,280 (33.1%)	47.0%
Ataxia/tremor	4,492 (27.6%)	30.0%
Cognitive dysfunction	4,247 (26.7%)	71.7%
Pain	4,184 (26.0%)	21.1%
Depression	3,656 (22.7%)	25.6%
Bowel disturbances	1,276 (8.2%)	52.8%

Table 2 Employment of MS patients [1]

	2005/2006	Since 2014
Number of patients	4,242	16,014
Fully employed	26.2%	37.5%
Partially employed	8.4%	19.5%
Retired early	37.1%	22.5%
Unemployed	5.7%	4.5%
Retired (age related)	5.7%	6.0%

Disability progression in SPMS

In randomised controlled trials, most DMTs have failed to show benefit during the progressive phase of SPMS. However, results from an observational Australian cohort justify continuing DMT use in SPMS patients who are actively relapsing [2]. Dr Nathaniel Lizak (University of Melbourne, Australia) suggested that ongoing relapse activity is a suitable treatment target in SPMS. He also noted earlier conversion to SPMS predicts subsequent faster disability progression.

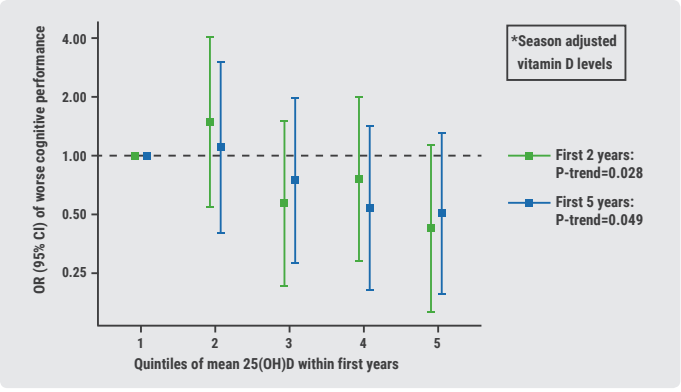
The aim of the analysis was to evaluate factors influencing the rate of disability progression during SPMS, including the effects of DMTs. From MSBase (n>53,000), 1,622 patients with definite SPMS and EDSS follow-up available from ≤24 months of diagnosis to ≥12 months post-SPMS onset were identified. Of these, 662 (41%) had superimposed relapses. Early RRMS DMT use was not associated with SPMS disability slope. A lower EDSS at SPMS conversion and a higher relapse rate during SPMS were associated with increased SPMS disability slope for all patients (β=0.02, P<0.001; β=0.04, P=0.04, respectively). For SPMS with superimposed relapses, DMT use during SPMS was associated with a lower disability slope (low efficacy: β=-0.09, medium efficacy: β=-0.10, high efficacy: β=-0.12; P≤0.008). This was not observed in patients without relapses during SPMS. Secondary analyses confirmed these results.

Vitamin D, smoking, and cognition

Vitamin D elevation and smoking cessation after clinical onset might protect cognitive function and neuronal integrity long-term in CIS patients. This was the conclusion of a prospective study that was presented as a late-breaking abstract [3]. The results were presented by Prof. Marianna Cortese (Haukeland University Hospital, Norway).

Among the 468 CIS patients participating in BENEFIT (Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment), higher serum 25-OH vitamin D levels predicted better, and smoking predicted worse long-term cognitive function, compared with median scores. A 50 nmol/L increment in mean vitamin D within the first 2 years was related to 65% lower odds of scoring worse on the Paced Auditory Serial Addition Test (PASAT-3) at year 11 (Figure 7; P=0.028). Standardised PASAT scores were lower in smokers and heavy smokers than non-smokers (P-trend=0.036). Associations with neurofilament light (NfL) concentrations at year 11 corroborated the main findings. A 50 nmol/L increase in mean 25-OH vitamin D the first 2 years was associated with 20% lower NfL (P=0.05). Smokers had 29% higher NfL levels than non-smokers (P=0.006). Prof. Cortese concluded: "Vitamin D supplementation during the first years after a CIS may have some neuroprotective effects."

Figure 7 Vitamin D and cognitive function at year 11



Smoking and vitamin D as prognostic factors

Another study concluded that smoking and low vitamin D levels are both key modifiable prognostic factors that show a dramatic interaction with risk of EDSS progression [4]. This observation was based on a dynamic model for predicting long-term prognosis incorporating age, sex, topography of CIS, oligoclonal bands, and number of T2 lesions, which was further updated by adding vitamin D and cotinine serum levels (as a surrogate for smoking status).

From 1995 to 2016, 1,088 CIS patients were prospectively recruited for clinical assessment and brain MRI follow-up. Patients were stratified in 3 groups: low risk (n=442; HR 1.0 reference), medium risk (n=561; HR 3.0), and high risk (n=51; HR 9.6). Vitamin D deficiency increased the risk for EDSS progression; patients with low risk moved to the medium risk group and patients with medium risk moved to high risk. In patients already at high risk, the impact of vitamin D deficiency was minor. An interaction was also observed for smoking and risk group. High cotinine levels increased the risk for EDSS progression; patients with low risk moved to the medium risk group and patients with medium risk moved to high risk. In the high-risk group, adding smoking status raised their HRs from 13.8 to 64.2.

10-year risk of ambulatory disability

The RoAD score (Risk of Ambulatory Disability) was proposed as a useful tool to orient treatment strategy in MS. This was the outcome of the first study ever to evaluate the effect of DMT on long-term disability progression by a scoring system in which parameters of treatment response and clinical baseline factors are considered together [5]. This scoring system is based on sex, age, disease duration, baseline EDSS score, and number of relapses and new T2 lesions after the first treatment year. Its ability to predict the 10-year risk of ambulatory disability in patients starting an injectable DMT was evaluated.

Data was collected of 1,224 patients who started IFN β or glatiramer acetate and had an EDSS ≤3.5 at DMT start. At 10-year follow-up, 162 (13%) reached an EDSS ≥6.0. A risk score based only on 1-year disease activity showed a sensitivity of 58% and specificity of 81% (AUC=0.67). The RoAD score, based on a combination of baseline factors and one-year variables, yielded an increased sensitivity of 72% and specificity of 82% (AUC=0.83; P<0.001).

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Primary and Secondary Progressive MS

Improving disease activity in the progressive phase of MS is 'the next frontier' in MS care. The past few years have seen some positive results, but these were modest and largely restricted to subsets of patients. One of the problems is that clinical progressive MS trials are not 'smart' enough. This could not be said of the MS-SMART trial, the first ever multi-arm, multi-stage (MAMS) phase 2 trial in MS. None of the three interventions had any noticeable therapeutic effect, but a template for future trials has been laid. Other clinical trial results of progressive MS treatments involved a labdane diterpene (IB-MS), high-dose biotin (MD1003), and ocrelizumab.

Which progressive MS patients to treat

Four drugs are registered for the treatment of progressive MS: IFN β-1a, mitoxantrone, ocrelizumab for the treatment of active secondary progressive MS (SPMS), and ocrelizumab for the treatment of primary progressive MS (PPMS). As Prof. Xavier Montalban (St Michaels Hospital, Canada) stressed, their effectiveness is modest and mainly restricted to patients with active inflammation. He pointed out a number of reasons why drugs fail or show modest effects at best in progressive MS trials:

- The pathogenic mechanisms in the progressive phase of MS are completely different from those in the relapsing phase.
- Patient populations included in trials are not appropriate.
- Clinical outcome measures are not sensitive enough, and clinical trials are not smart enough to detect the worsening of disease during follow-up.

"For a treatment to be successful, it is very important that there is at least some degree of inflammatory reactivity," Prof. Montalban said. Trial populations should be carefully

chosen. The prototype of a progressive MS patient who is likely to have a relatively good response to treatment has or is:

- prior relapses;
- rapidly evolving disease;
- active disease on baseline MRI;
- younger;
- shorter disease duration;
- treatment-naïve;
- lower EDSS score.

Some progressive MS trials may fail because the definitions of treatment effect are inadequate and rely too heavily on RRMS trials. In active progressive MS, treatment failure may be defined as persistence of relapses; but should disability worsening also be part of the definition? In progressive non-active progressive MS, disability worsening and appearance of relapses signal treatment failure, according to Prof. Montalban. Then what should the (minimum) treatment duration be to consider treatment efficacy? Clinical trials are often not powered to show effects in progressive MS. Also, how sensitive are the outcome measures that have been used? May nothing but improvement be considered proof of treatment efficacy? Even in progressive MS trial design, many questions are left unanswered. Established treatment targets and trial protocols remain elusive.

MS-SMART trial: a multi-arm strategy

In a late-breaking abstract, results were shared from the first ever multi-arm, multi-stage (MAMS) phase 2b trial, comparing 3 different interventions in progressive MS [1]. A MAMS design is an example of a flexible, seamless phase 2/3 randomised controlled trial. This approach allows for several treatments, different doses of the same treatment, or combinations of treatments to be assessed simultaneously against a common control group. The MAMS design provides an efficient method for acquiring prospective randomised data in less time and needing fewer patients.

The 3-in-1 MS-SMART trial was successfully performed, in a timely and economic fashion, with excellent patient, clinician, and MS charities support, said Dr Jeremy Chataway (National Hospital for Neurology and Neurosurgery, United Kingdom). The trial aimed to determine if drugs targeting different candidate pathways in the pathobiology of progression, which had early phase 2a success, could reduce whole brain atrophy. No therapeutic effect was seen from any of the 3 interventions. The chosen drugs and their postulated mechanisms were: amiloride (acid-sensing ion channel-1 antagonist; reducing calcium and sodium influx), fluoxetine (increased production of brain-derived neurotrophic factor; enhanced astrocyte glycogenolysis), and riluzole (reduction in glutamate release; antagonism of voltage gated sodium channels). A total of 445 patients with SPMS were randomised 1:1:1:1 to 96 weeks of treatment with amiloride (5 mg), fluoxetine (20 mg), riluzole (5 mg), or matched placebo. The median EDSS was 6.0. There were no statistically significant differences between any of the treatments and placebo in the rate of brain atrophy, disability progression, or cognitive decline. The primary outcome was the percentage of brain volume change between baseline and 96 weeks, derived from structural MR brain imaging data using Structural Image Evaluation, using Normalisation, of Atrophy (SIENA). One of the major secondary outcomes was to establish that a multi-arm trial strategy is an efficient way of screening drugs in SPMS. There was a statistically significant decrease in the number of MRI-detected relapses (T2 lesions) after 96 weeks between patients treated with fluoxetine vs placebo (P=0.012). However, Dr Chataway heeded his audience not to attach too much importance to this result. He concluded: "In the MS-SMART trial, 15 years of work were completed in 5 years," laying a template for future trials.

Slowly evolving lesions in secondary progressive MS

In a cohort of SPMS patients from the MS-SMART trial, slowly evolving lesions (SELs) were identified to explore their relationship with physical and cognitive disability [2]. The results showed that patients developing SELs at follow-up had higher physical and cognitive disability at baseline. Data were available for 79 out of 176 SPMS patients. Median age was 54.2 years, disease duration 23.3 years, EDSS score 6.0, Multiple Sclerosis Functional Composite (MSFC) 0.24, and Symbol Digit Modalities Test (SDMT) score 48. This cohort underwent brain FLAIR and 3D T1-weighted imaging at baseline, 24, and 96 weeks. Out of 4,756 T2 lesions screened, 1,140 were identified as 'candidate lesions' and 140 were classified as SELs (2.9%). Of 79 patients, 61 (77%) were SEL-positive. In the SEL-positive group, the median SEL volume per patient was 1.84 mL. At baseline, SEL-positive patients showed higher physical disability (MSFC score -0.42; P=0.004) and worse cognitive performance (SDMT -6.04; P=0.04). Baseline EDSS did not differ. The authors plan to extend this analysis to all trial patients and investigate the association between SELs and disability progression.

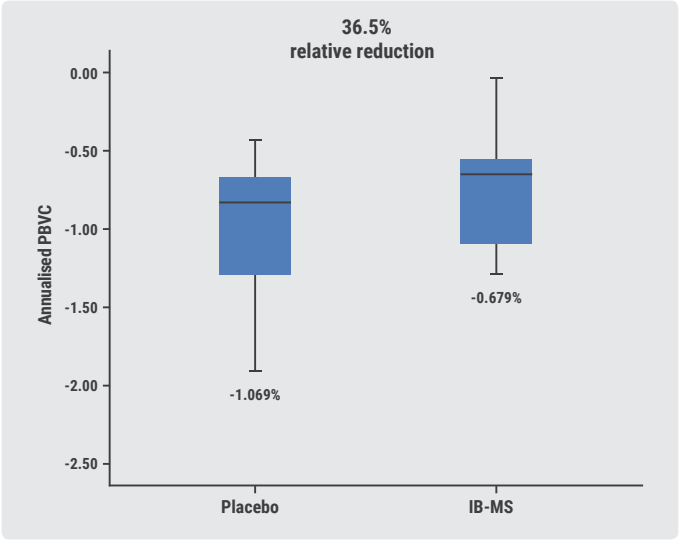
Labdane diterpene IB-MS

Another progressive MS trial with negative results that were still deemed to be encouraging in some respects, was the single-centre, placebo-controlled trial of IB-MS [3].

This labdane diterpene, isolated from the plant *Andrographis paniculata*, may be effective in the treatment of autoimmune diseases. The main outcome was the efficacy of IB-MS in reducing brain atrophy as measured by SIENA over a period of 24 months, with an estimated sample size of 68 patients. This endpoint was not met, nor was the expected sample size achieved. However, progression and disability outcomes suggest a potential role of IB-MS in reducing neurodegeneration in inactive progressive MS, according to the authors.

Forty-three patients with inactive progressive MS were recruited. They had been without DMT for at least 6 months, had an EDSS score <8.0, and an MMSE >24. Patients were randomly assigned to oral IB-MS 140 mg twice a day (n=23) or placebo (n=20). Twenty-nine patients (17 IB-MS, 12 placebo) completed the study. Percentage brain volume change was lower in the IB-MS group compared with placebo (Figure 8). The IB-MS group had a lower 24 month mean EDSS score compared with placebo (P=0.036). In the IB-MS and placebo group, 29.4% and 41.6% of patients had confirmed disability progression (P=0.02). Tolerability and safety seemed comparable between the groups. Larger multicentre studies are needed to determine the magnitude of the contribution of IB-MS in reducing neurodegeneration.

Figure 8 IB-MS reduces mean annualised percentage brain volume change compared with placebo [3]



Observational study of ocrelizumab

Ocrelizumab induction regimen appeared to be safe in a real-life Italian cohort of patients with longstanding PPMS, and more advanced age and disability than those enrolled in clinical trials [4]. PPMS patients were enrolled in the ocrelizumab compassionate use program before EMA pronouncement on prescription restrictions. According to regulators, strict clinical and paraclinical criteria must be met for the use of ocrelizumab in PPMS, i.e. early PPMS in terms of disease duration, level of disability, and MRI activity.

Thirty-four patients were included in the analysis, with a mean age of 52 years. The median follow-up was 4.5 months. Mean and median disease duration at ocrelizumab initiation were 12.4 and 9.3 years, respectively. Median pre-treatment EDSS was 6.0. Ten patients (29%) were treatment-naïve at ocrelizumab treatment onset. Infusion-related AEs were experienced by 4 patients, serious AEs by 1 patient. Radiological activity was found in 6 patients. Only 4 of 34 patients (12%) fulfilled all EMA criteria for PPMS treatment with ocrelizumab, but there was no significant difference in AEs and serious AEs between the two groups (P=0.32).

Biotin in a real-world setting

MD1003 (high-dose biotin) 300 mg/day was confirmed to be effective and well-tolerated in the treatment of PPMS and SPMS in a real-world clinical setting in France [5]. At 1 year of treatment, 23% of patients experienced improvement in MS-related disease activity. MD1003 is being prescribed to progressive MS patients in France under an expanded access programme. In this single-centre study, 220 patients had received MD1003 at the cut-off (May 2018) in the Centre Hospitalier Universitaire of Toulouse. Results were presented of 91 patients that had 1 year of follow-up.

At baseline, 70.3% had SPMS, mean EDSS was 5.9, mean timed 25-foot walk was 50.7 seconds, 9-hole peg test in the dominant hand was 35.1, and the mean number of previous relapses was 5.1. After 1 year of treatment with MD1003, 19 patients (23% of patients with data) experienced improvement in EDSS and 15 (23% of patients with data) experienced ≥20% improvement in timed 25-foot walk. Active disease, a clinically defined relapse, and/or a Gd+ T1 lesion was found in 9 patients (11% of those with data). In a cohort of 103 patients with non-active progressive MS, 12-month MD1003 treatment resulted in significant improvement from baseline in cognition, quality of life, and dexterity [6]. Improvement tended to be greater for patients with baseline EDSS 6.0-6.5 (compared with baseline EDSS 4.5-5.0 and EDSS 7.0-7.5. The authors noted that clinical therapeutic evaluations could be adapted to disability score to detect improvement in progressive MS.

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Treatment Strategies

The advent in the last decade of 'high-efficacy' disease-modifying treatments (DMTs), such as fingolimod, natalizumab, and alemtuzumab, has drastically changed MS treatment, including treatment goals, treatment strategies, and switching strategies. An urgent question is in which patients and in which stage of MS high-efficacy DMTs should be used. Another urgent topic is when to switch therapies, and to gain insight into the consequences. The third question addressed here is whether DMT treatment can and should be discontinued with older age.

When to start high-efficacy treatment

As a treatment strategy for MS, either escalation or induction therapy is usually applied. Escalation therapy consists of starting with first-line DMTs (IFN β, glatiramer acetate, teriflunomide, dimethyl fumarate), and switching to second-line 'high-efficacy' drugs if first-line drugs are not sufficiently effective. Induction therapy consists of the early use of immunosuppressant drugs, immediately pursuing higher efficacy, but also accepting more safety risks. This approach uses an individualised benefit-risk assessment taking into account the patient's risk of disease progression. Induction treatment is usually limited to patients with very active or aggressive disease, where the risk of early disability outweighs the risk of side effects. The past few years have seen a debate about whether induction therapy should be applied to a wider range of patients.

Real-world data from the Big Multiple Sclerosis Data (BMSD) network indicate that the optimal time to start DMTs in MS to prevent long-term accumulation of disability is within 6 months from disease onset [1]. For this study, a cohort of 11,871 RRMS patients with ≥10 years follow-up, ≥3 years cumulative DMTs exposure, and EDSS scores ≥3 was retrieved. A set of pairwise (1:1) propensity score matching analyses with 10 different cut-offs for early vs delayed treatment (>0.5 year up to >5.0 years, using 0.5-year intervals) have been conducted to allow an unbiased comparison between groups. The median age at onset was 27.7 years, median follow-up was 13.2 years, and median time to the first DMT start was 3.8 years. During follow-up, 12 months-confirmed EDSS progression was reached by 4,138 (34.9%) patients. The lowest hazard ratio (HR) with relative 95% CI for propensity score matched models was obtained by a cut-off of treatment start within 6 months from disease onset (n=873 per group). Early treatment significantly reduced the risk of reaching an EDSS progression: HR 0.72 (95%CI 0.59-0.90; P=0.003). None of the other comparisons between early and delayed treatment resulted in statistically significant differences.

According to the guidelines, DMTs should be offered as early as possible in MS, whether they be first-line or second-line drugs. A study that was performed in Sweden showed that early treatment initiation is associated with a better outcome (or rather, income), i.e. a lower risk to lose earnings [2]. In total, 3,593 MS patients were included in the analysis. Patients initiating treatment later had a greater risk of losing earnings, defined as time from treatment initiation to a 95% decrease in annual earnings compared with each patient's baseline level (at treatment initiation). For example, patients starting treatment after 2 years from MS onset were at a 20% higher risk of losing 95% of their earnings sooner (adjusted HR 1.20).

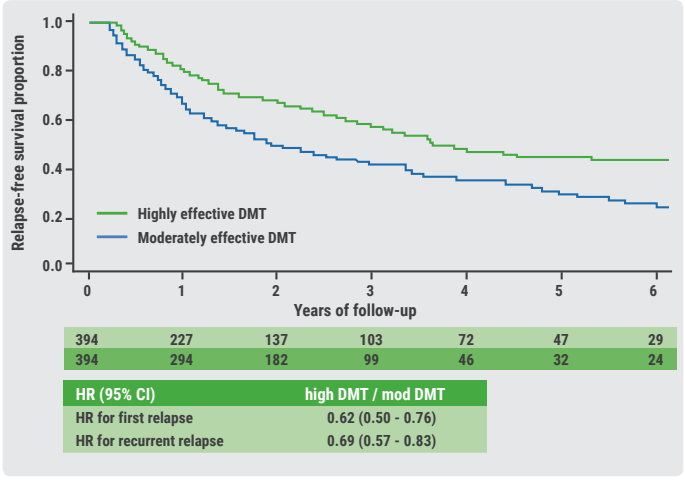
When to switch treatment

Determining whether and when to switch therapies, Dr Fred Lublin (Mount Sinai Hospital, USA) called "one of the most vexing issues in treating patients with MS". He identified several problems, most notably a lack of data to predict effectiveness of a treatment on an individual level, the unpredictable clinical course of MS, and the absence of a reliable marker of therapeutic response. While head-to-head studies provide some data on comparative efficacy on a group level, they cannot guide individual decisions and do not address switching. Observational studies are significantly limited in terms of generalisability. Most switch studies have serious design flaws limiting their value. Newer biomarkers of treatment response, such as NfL, may assist in decision making.

One of the studies on switching that was presented, showed that treatment escalation (i.e. switching to a highly effective DMT) leads to fewer relapses than switching to another moderately effective DMT. Danish researchers found a statistically non-significant trend towards reduced time to first 1-point EDSS worsening over the short-to-medium term [3]. This cohort study relied on data from the Danish Multiple Sclerosis Registry (DMSR) on all adults with relapsing-remitting MS (RRMS), with EDSS <6, who experienced a relapse

while treated with a moderately effective DMT, and switched to either another moderately effective DMT or to a highly effective DMT. The matched cohort consisted of 814 patients, 407 in each group, that was followed for a median of 3.2 years. The group of patients who switched to a highly effective DMT had a 38% lower risk of reaching first relapse (Figure 9; HR 0.62). ARRs were 0.21 and 0.34 for patients who switched to a highly and to a moderately effective DMT, respectively. Relapse rate ratio for highly vs moderately effective DMTs was 0.62. The group who switched to a highly effective DMT had 13% lower HR of 1-point EDSS worsening. The authors recommend escalation therapy after relapses on a moderately effective DMT to improve control of relapse activity.

Figure 9 Risk of relapse in patients switching to a highly effective or another moderately effective DMT [3]



Switching from fingolimod to alemtuzumab

A particularly high reactivation of MS has been reported in patients who received alemtuzumab after fingolimod, in particular in case of a short washout period. In an Italian cohort, however, rapid start of alemtuzumab after fingolimod did not increase the risk of MS reactivation. Alemtuzumab dramatically reduced inflammation, both in terms of relapses and new T2/Gd+ lesions, compared with the previous fingolimod treatment and the washout period [4].

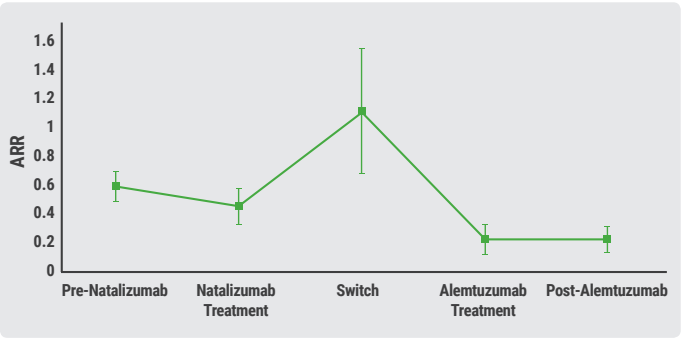
A total of 77 patients from 11 centres were enrolled. Median disease duration was 13.7 years. Of these patients, 37 received more than one course of alemtuzumab. The mean washout period was 2.7 months. The ARR during fingolimod was 0.60, during washout 1.33, and during alemtuzumab 0.20. After switching to alemtuzumab, 7 patients experienced 1 relapse, and 2 subjects 2 relapses. The median time to first relapse during washout was 28 days, after staring alemtuzumab it was 315 days. The last MRI during fingolimod treatment showed new T2 and Gd+ lesions in 45/65 (69.2%) and 34/58 (58.6%) patients, respectively. The first MRI during alemtuzumab showed these lesions in 5/48 (10.4%) and in 1/46 (2.2%) patients, respectively. Lymphocyte count was normal in about half of the cohort.

Switching from natalizumab to alemtuzumab

Another sequence of DMTs discussed during the ECTRIMS 2018 meeting was the switch from natalizumab to alemtuzumab in rapidly evolving severe MS. Long-term data from 13 UK and Irish sites showed no unexpected safety signals from the use of alemtuzumab after natalizumab. A shorter switch period without bridging was associated with better outcomes and no evident risk [5].

A total of 79 patients were included; 51 were followed for over 2 years after their initial alemtuzumab infusion. Independent blinded MRI analysis was conducted in 20 patients. The median switch period was 115 days. Mean EDSS increased from 3.4 before natalizumab to 4.7 in the switch period, but then fell to 4.4 in the alemtuzumab period and 4.3 in the post-alemtuzumab phase (>2 years after first alemtuzumab infusion). Mean ARR decreased from 2.3 before natalizumab to 0.8 on natalizumab, and was 0.4 on alemtuzumab and 0.5 in the post-alemtuzumab phase (Figure 10). The mean number of new or worsened MRI lesions was highest during the switch period (4.32/MRI/year), lowest in alemtuzumab (0.006/MRI/year), and remained low post-alemtuzumab (0.017/MRI/year). ARR increased during the switch period in proportion to increasing duration, and EDSS increased when the switch period exceeded 3 months. Significant infections were seen in 10 patients; in 2 of them they were serious. Twelve patients developed thyroid disease.

Figure 10 Annualised relapse rate by treatment phase [5]



When to withdraw treatment

Perhaps an even more vexing issue than switching is withdrawing MS treatment. Observational data clearly shows recurrence of disease activity in young patients; but can and should DMT treatment be discontinued with older age?

In a lecture on the subject, Prof. John Corboy (University of Colorado, USA) said the answer is not yet clear. One of the arguments in favour of discontinuing MS treatment is the disease's natural history: risk of relapses and new MRI changes decreases significantly with age. Thus, the need to continue MS medication may also decrease, especially in patients who have been free of relapses or MRI changes for prolonged times. There is potential harm in continuing DMT treatment in older MS patients, Prof. Corboy added. Some risks may increase with age: for example, the risk of PML in patients over 50 on dimethyl fumarate, fingolimod JVC-positive rate increases with age; as well as the risks of comorbidities – cancer, diabetes, hypertension, infections – relevant to the use of DMTs.

However, it is still unknown at what age treatment might be safely discontinued, and in which patients: there are no firm markers of low risk. Maybe discontinuing one drug is safer than the next. The risk attached may, for example, be higher with natalizumab, said Prof. Corboy. "There is a lack of controlled data: no randomised controlled trials for discontinuing DMTs have been performed." He went on to outline a randomised controlled discontinuation trial (NCT03073603). The DISCOMS study sets out to recruit 300 RRMS or progressive MS patients of ≥55 years from 15 sites in the USA, who have inactive MS (no relapse or any change on MRI). Follow-up will be 2 years. Outcomes are the percentage of patients with new relapse(s) or T2/FLAIR lesions; the percentage of patients with EDSS change; and patient reported outcomes.

Fingolimod discontinuation

In a retrospective analysis of a real-world MS cohort, recurrence of disease activity (RDA) after discontinuation of fingolimod occurred in around 30% of all cases. Younger MS patients with shorter disease duration and evidence of disease activity on treatment with fingolimod carried a higher risk of RDA [6]. DMTs such as fingolimod, reducing lymphocyte trafficking into the central nervous system, have been associated with a higher risk and severity of RDA after discontinuation. In a single-centre study, characteristics of RDA within 6 months after fingolimod discontinuation were described. RDA was defined as either clinical and/or MRI activity; severe RDA as either severe relapse (EDSS increase ≥2 points) and/or pronounced MRI activity.

Of the 433 Swiss patients who initiated fingolimod treatment, 110 discontinued fingolimod after a mean treatment duration of 26.2 months. Within 6 months after fingolimod discontinuation, RDA was observed 41 times (23 both clinical and radiological, 12 clinical only, 6 MRI activity only) in 39 patients (36 RRMS, 3 SPMS). RDA occurred 15 times in patients with no subsequent DMT, 4 times in patients who discontinued fingolimod <6 months, and 22 times in patients who switched to another DMT. Patients with RDA had higher disease activity in the year before stopping fingolimod (relapses 52.4% vs 37.7%; MRI activity 54.8% vs 39%), were younger at the time of discontinuation (34.4 vs 43 years), and had a shorter disease duration (6.6 vs 10.6 years). Severe RDA was observed 14 times in 12 patients.

Discontinuing fingolimod due to pregnancy

Despite the natural protection of pregnancy, at least one third of women treated with fingolimod before or up to pregnancy experienced a relapse during pregnancy in a German registry. Women who stopped fingolimod >2 months prior to the last menstrual period experienced more relapses before pregnancy and in the first trimester of pregnancy [7].

Pregnancies were prospectively collected in the German MS and pregnancy registry (n=140) and by 6 international collaborators (n=16) up to September 2017. Six pregnancies are ongoing. The patients were divided into 2 groups: those who stopped fingolimod while planning a pregnancy (group A; n=46) vs those who stopped fingolimod with a positive pregnancy testing (group B; n=110). Ten (22%) women in group A experienced a relapse between fingolimod stop and the beginning of pregnancy. After conception, in group A, 13 women (28%) had 17 relapses during pregnancy; in group B, 26 women (24%) had 33 relapses (P=0.203). Significant more women in the unexposed group relapsed during the first trimester (P=0.04). EDSS remained stable in the majority of the women, but 1 woman (5%) in group A and 9 (8%) in group B showed a substantial EDSS worsening of ≥2 points 6 months postpartum (P=0.732). In total, 39 (25%) women had 45 relapses in the first 6 months postpartum. Relapses during pregnancy were the only significant predictor for relapses postpartum (OR 5.82).

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Imaging

Conventional MRI measures may be helpful in identifying patients with early MS who are at a high risk of developing cognitive disability. Brain MRI-defined leptomeningeal enhancement (LME) may identify a subset of patients at risk for disease progression. Relapsing-remitting MS (RRMS) patients who converted to secondary progressive MS (SPMS) early, already showed more severe structural changes and a more abnormal functional network, most notably thalamus atrophy, at baseline.

Biomarker for cognitive decline

The extent of focal inflammatory activity in the brain in patients with early relapse-onset MS, as measured by conventional MRI, was associated with long-term cognitive performance [1]. A total of 104 patients with a CIS had brain/spinal cord MRI at onset and after 1 year. When they were followed up after 15 years, 83 (80%) patients had MS and 35 (34%) were cognitively impaired (all MS). Baseline Gd+ lesions (1+) was independently associated with reduced performance on tests of information processing speed, memory, and executive function (all P<0.01) at 15 years. New supratentorial lesions at 1 year was also associated with information processing speed (P=0.01) and memory (P<0.01), and new supratentorial (P<0.01) and spinal cord lesions (P=0.02) at 1 year with executive function. Baseline normalised brain volume and percentage brain volume change at 1 year were not associated with cognition at 15 years independent of lesion measures.

Leptomeningeal enhancement

Recently, brain MRI-defined LME has been observed in MS and may reflect meningeal inflammation. A study demonstrated a high prevalence of LME in RRMS, as detected by 7T MRI, and a link to cortical pathology [2]. These results suggest that LME might identify a subset of patients at risk for disease progression, given that cortical damage is more common in progressive MS. Thirty RRMS subjects (mean disease duration 12.6 years, EDSS score 2.0) and 15 age-matched and sex-matched healthy controls were studied. Subjects underwent Gd+ 7T brain MRI using a 3D high-resolution protocol, including MP2RAGE and FLAIR, with 0.7 mm3 isotropic voxels. LME was found in 20/30 (66.7%) of RRMS subjects and in 1 of 15 (6.7%) controls. LME-positive RRMS subjects had 2.8 LME foci (range 1-6). Compared with LME-negative subjects, they had:

- longer disease duration (14.9 vs 8.1 years; P=0.028);
- a markedly increased number (21.5 vs 5.5; P<0.001) of cortical lesions;
- a markedly increased total volume (0.80 vs 0.13 mL; P=0.016) of cortical lesions.

LME status was not associated with age, gender, ambulation time, or EDSS score.

Award-winning posters

Imaging was the subject of 3 out of 5 best oral presentations given by young investigators (age ≤35). The first one was by Dr Kim Meijer (Amsterdam UMC, the Netherlands). She presented results of a longitudinal study aiming to identify structural and functional MRI measures that may predict conversion from RRMS to SPMS [3]. Dr Meijer found that RRMS patients who converted to SPMS within 5 years, already demonstrated more severe structural changes and a more abnormal functional network compared with matched RRMS patients who did not convert (Figure 11). A backward logistic regression model showed that atrophy of the thalamus, one of the most important hubs in the brain network, was the strongest MRI predictor of conversion to SPMS within 5 years.

The second presentation was by Dr Russell Ouellette (Karolinska Institute, Sweden), who studied the histopathological specificity, robustness, and clinical value of REMyDI (rapid estimation of myelin for diagnostic imaging) based on time-efficient multi-parametric MRI [4]. His group recruited a cohort of 71 MS patients, with a main disease duration 12 years, along with 21 age/sex-matched controls. All underwent 3T MRI, including REMyDI. A subset of 13 patients and 19 controls underwent repeatability scanning. Dr Ouellette found that the REMyDI correlated well with histopathology, provides robust in vivo myelin quantification, and is related to MS disability. Furthermore, it detects demyelination in normal-appearing tissue, which is related to cognition. REMyDI is therefore a suitable biomarker to monitor myelination dynamics in MS and potential remyelinating therapies.

The third presentation was by Dr Sara Collorone (Sapienza University of Rome, Italy) on the use of Neurite Orientation

Dispersion and Density Imaging (NODDI) and 23Na-MRI to investigate early changes in the normal and lesional brain tissue of patients at onset of a CIS. Dr Collorone concluded that at CIS onset, sodium accumulation in MS lesions, known as a marker of acute inflammation and axonal loss, seems to be related to early pathological processes, occurring irrespective of blood-brain barrier permeability and fibre loss [5]. Neurite density index confirmed to be a potential further marker of axonal loss and demyelination, independently correlated with clinical parameters.

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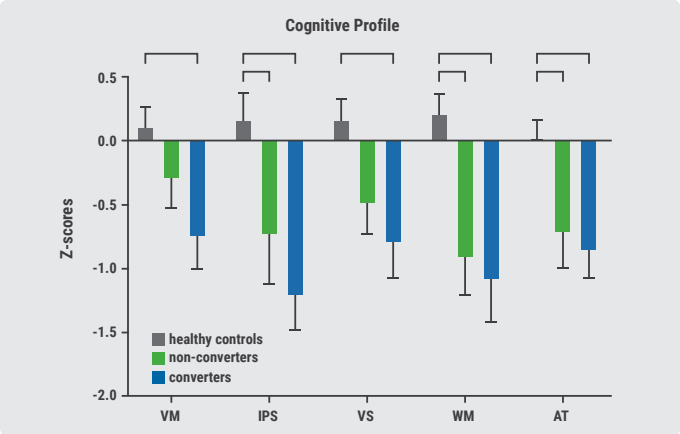
Figure 11 Cognitive impairment is worse in patients converting from RRMS to SPMS [3]



VM, verbal memory; IPS, information processing speed; VS, visuospatial memory; WM, working memory; AT, attention

Serum Neurofilament Light

Neurofilament light (NfL) was one of the truly hot topics at the ECTRIMS 2018 meeting. NfL is a cytoskeletal protein that is released into the CSF and eventually in blood following neuroaxonal injury. NfL levels can be measured in CSF but also in serum, which is usually done with a highly sensitive Single Molecule Array (Simoa) assay. Serum NfL (sNfL) is associated with disease activity, predicts long-term clinical and imaging outcomes, and is reduced by disease-modifying treatments (DMTs) in relapsing-remitting MS (RRMS) patients. A cut-off value of >16 pg/mL was proposed. sNfL may replace MRI – in part – as a means to monitor disease activity.

Prognostic biomarker

The predictive value of sNfL for future disease activity in RRMS patients with DMT was investigated in the Swiss MS Cohort Study [1]. The results support the value of sNfL levels for treatment monitoring in MS clinical practice, the authors concluded. Baseline and yearly follow-up sNfL were measured by the Simoa assay in samples from patients on fingolimod (n=182), natalizumab (n=27), or IFN β or glatiramer acetate (n=28). sNfL independently increased with age (2.1%/year; P<0.001), EDSS (5.7%/step; P=0.006), and relapse within 120 days (19.4%; P=0.05). sNfL decreased with time on DMT (-3.2%/year; P=0.006). This decrease was -12.8% steeper in patients on natalizumab (P=0.003) and -6.8% steeper in patients on fingolimod (P=0.009) compared with patients on IFN/glatiramer acetate. In patients on fingolimod, higher baseline sNfL levels were associated with higher relapse rates within the following 2 years.

Another study found that sNfL fulfils a critical requirement as a prognostic biomarker in RRMS: it predicts long-term physical disability progression in patients with RRMS [2]. This was a post-hoc analysis that included data from patients on fingolimod 0.5 mg in the phase 3 FREEDOMS trial and the LONGTERMS extension. Patients with the highest quartile of NfL were twice as likely to have 6-month confirmed disability progression compared with the lowest quartile when using the geometric mean NfL over 1 year, and 2.3 times as likely over 2 years (Figure 12). Patients with the highest quartile of NfL were 3.69 times more likely to reach EDSS ≥4 compared with the lowest quartile over 1 year (P=0.014), and 8.7 times as likely over 2 years (P=0.0014).

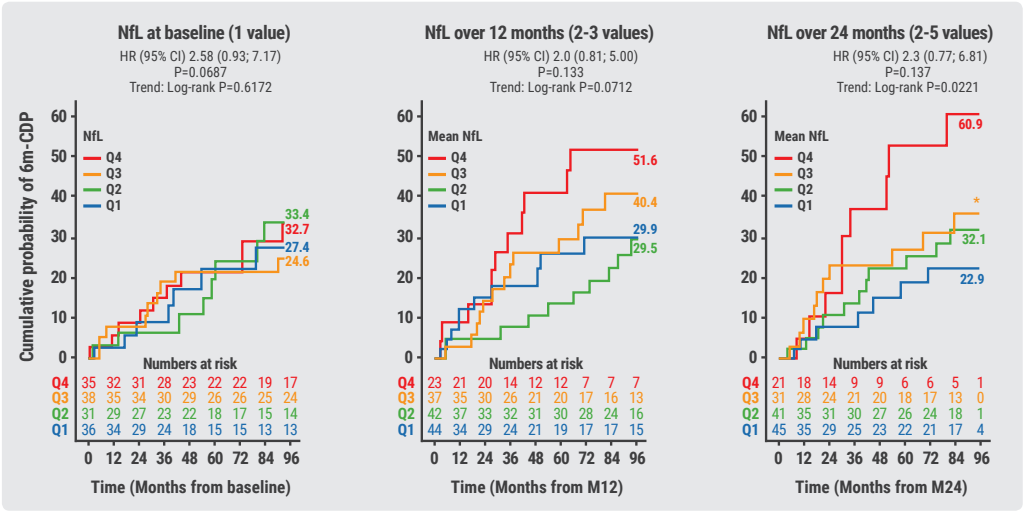
Monitoring treatment effects

Findings from a real-world study supported the use of sNfL for monitoring treatment effects in RRMS [3]. Age-adjusted baseline sNfL values were associated with the number of previous relapses, in turn having a significant impact on levels at 12 months. This suggests a slow degree of normalisation or lingering disease activity at 12 months. The

investigators obtained samples at the start and at 1 year from 915 Swedish RRMS patients on teriflunomide (n=100), fingolimod (n=253), dimethyl fumarate (n=314), or natalizumab (n=248). NfL was determined using the Simoa assay.

Age-adjusted baseline NfL values were associated to the number of previous relapses (coefficient relapses = 0.16, P<0.001). Change in sNfL from baseline to 12 months was influenced by baseline NfL (explaining 20% of variance), DMT (explaining 10%), and age (explaining 4%).

Figure 12 Probability of 6-month confirmed disability progression against patients with RRMS, categorised into quartiles of baseline NfL levels, over 12 months, and over 24 months [2]



Natalizumab patients had the highest baseline NfL values, and teriflunomide the lowest. On-treatment sNfL levels were significantly lower with natalizumab, dimethyl fumarate, and fingolimod as compared with teriflunomide, due to a more pronounced decrease in sNfL levels.

Primary and secondary progressive MS

Conventional MR measures show only modest association with disease evolution in progressive MS and are poor efficacy markers in trials. sNfL also seems to be of value to measure disease progression or response to therapy in both patients with primary progressive MS (PPMS) or secondary progressive MS (SPMS). In a study comparing SPMS patients (n=1,452) and PPMS patients (n=378), sNfL levels were found to be higher in SPMS patients, independent of age [4]. In both MS subtypes, sNfL predicted future brain atrophy and 3-months confirmed disability worsening. As Prof. Ludwig Kappos (Universitätsspital Basel, Switzerland) explained, the SPMS and PPMS patients participated in a phase 3 trial of siponimod (EXPAND; n=1452) and of fingolimod (INFORMS; n=378), respectively. NfL levels at baseline were higher in SPMS patients than in PPMS patients: 32.1 vs 22.0 (P<0.001). Similarly, patients with no Gd+ lesions at baseline had sNfL levels of 29.2 and 21.0 in SPMS and PPMS, respectively, while patients with Gd+ lesions had NfL levels of 45.0 in SPMS and 34.0 in PPMS. The Gd+ lesion count and T2 lesion volume at baseline correlated best with baseline sNfL (P<0.0001, all). In both SPMS and PPMS patients, high (> 60) sNfL at baseline was associated with higher percentage of brain volume loss at month 12. Prof. Kappos: "Our data suggest that NfL should be considered as an informative endpoint for phase 2 studies in SPMS."

Results of another study confirmed the use of sNfL to measure disease progression or response to therapy in SPMS [5]. In the phase 3 ASCEND study, natalizumab reduced sNfL levels compared with placebo in SPMS patients with and without acute inflammatory activity. These results suggest that sNfL may not only reflect inflammation-driven neuro-axonal damage but also non-inflammatory neurodegeneration in MS patients. Baseline sNfL levels were significantly associated with baseline age (P<0.05), number of Gd+ lesions, T2 lesion volume, timed 25-foot walk time, 9-hole peg test time, and brain atrophy over 96 weeks (P<0.0001, all). At week 96, sNfL levels were significantly higher in patients with progression, defined by EDSS (P<0.01), timed 25-foot walk (P<0.05), or 9-hole peg test (P<0.01). Finally, sNfL levels at week 48 and week 96 were significantly lower in natalizumab-treated patients compared with those on placebo: ratio 0.84 and 0.80 (P<0.001, both).

Implementation and cut-off values

Integration of sNfL into clinical practice requires a standardised, validated assay as well as defined clinically-meaningful cut-off values, validated with real-world data. Prof. Peter Calabresi (Johns Hopkins School of Medicine, USA) presented a study that aimed to define sNfL levels relevant to disease severity classification and treatment monitoring in RRMS patients [6]. The findings support the clinical relevance of sNfL levels and establish a relevant cut-off value (>16 pg/mL) for disease severity stratification and treatment monitoring in RRMS patients.

Samples and data from more than 1,000 patients enrolled in 4 Biogen phase 3 clinical trials were used: ADVANCE (peginterferon β-1a in RRMS, n=594), CHAMPS (IFN β-1a in CIS), MSCRG

(IFN β-1a in RRMS, n=164), and SENTINEL (natalizumab in RRMS, n=122). sNfL was measured with the Simoa assay or a laboratory method in serial samples. "The Simoa assay is a technically validated, sensitive, preferred, and widely used assay for evidence generation," Prof. Calabresi said.

Baseline sNfL levels were associated with the number of Gd+ lesions (P<0.0001) and accumulation of new T2 lesions over time (P<0.0001). Patients with no evident disease activity had consistently low sNfL levels; those with active disease, especially with high brain atrophy rates, had elevated sNfL. A cut-off value for sNfL of >16 pg/mL indicated high probability of disease activity over the following year and was also associated with worse long-term clinical and imaging outcomes: EDSS progression (12 years, P<0.05), T2 lesion volume (10 years, P<0.00001), and brain atrophy (5 years P<0.00001). Prof. Calabresi added that sNfL levels were also found to be lowered by DMTs. Natalizumab reduced sNfL below 16 pg/mL in 96% of patients.

Age dependent cut-off levels for sNfL in healthy individuals were also provided, in order to correctly interpret NfL levels in MS patients [7]. In healthy individuals, NfL levels were shown to increase considerably with age, especially above the age of 60. The 95th percentile cut-off sNfL levels for the age ranges of 40-50 years, 50-60 years, 60-70 years, and >70 years were 31.5, 34.7, 58.9, and 78.6 pg/mL, respectively. Using this model, baseline sNfL values correctly predicted follow-up levels in 87.5% of patients.

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Basic Science

At a session concluding the ECTRIMS 2018 meeting, Prof. Scott Zamvil (University of California, USA) and Dr Louisa Klotz (University of Münster, Germany) presented their scientific highlights, most of which are mentioned below. They praised one of these highlights as a possible "game changer": research revealing the role of 'autoproliferation' of T-cells and B-cells in MS. Autoproliferating T-cells recognise antigens expressed in B-cells and brain lesions.

Autoproliferation of peripheral T-cells

MS is caused by an interplay of genetic - most importantly HLA-DR15 - and environmental risk factors. How these etiologic factors generate and maintain an autoreactive CD4+ T-cell repertoire is unclear. Swiss researchers demonstrated that self-reactivity, defined as 'autoproliferation' of peripheral Th1 cells, is elevated in patients carrying the HLA-DR15 haplotype [1]. Autoproliferation of T-helper cells was found to be directly mediated by the interaction of memory B-cells via HLA-DR – T-cell receptor contact. Depletion of B-cells in vitro and therapeutically in vivo by anti-CD20 (rituximab) drastically reduces T-cell activation and autoproliferation, while it is increased with rising circulating memory B-cells in natalizumab-treated patients. T-cell receptor deep sequencing showed that in vitro autoproliferating T-cells are enriched for brain-homing T-cells. The researchers identified RASGRP2 as a target autoantigen that is expressed in the brain and B-cells. These findings will be instrumental to address important questions regarding pathogenic B- and T-cell interactions in MS, and possibly also to develop novel therapies.

How does anti-CD20-mediated absence of B-cells affect frequency, cytokine production, and activation of myeloid antigen-presenting cells, which are tightly regulated by B-cells? Mechanistic studies revealed that the cytokine environment generated by B-cells can differentially shape the activity and antigen-presenting capacity of myeloid cells [2]. Some MS patients displayed an accentuated activation of immune cells following anti-CD20 treatment. The researchers hypothesise that the individual B-cell phenotype before anti-CD20 treatment predicts the respective immunological changes occurring thereafter.

Gut-brain axis

Could mucosal addressing cell adhesion molecule 1 (MadCAM-1) be a novel therapeutic target? Immune cell

trafficking into the gut is mediated by binding of leukocytes to MadCAM-1, expressed on endothelial cells. A MadCAM-1-associated modulation of CNS autoimmunity within the intestinal tract was demonstrated, adding insight into a functional role of the intestine in neuroinflammation [3]. MadCAM-1 deficient mice were significantly less susceptible to actively induced EAE than controls. This was accompanied by decreased numbers of immune cells in the lamina propria, as well as reduced immune cell infiltration into the spinal cord. Another group investigated the role of IgA and IgA-producing cells in gut dysbiosis and along the gut-brain axis in RRMS. Their data indicated that the oligodendroglial differentiation block observed in MS is predominantly due to extrinsic inflammatory mediators and is not caused by intrinsic oligodendroglial factors [4]. In particular, factors secreted by T-cells appear to be important. These findings may help to develop new treatment options that promote remyelination in MS.

Pathogenesis of synapse loss

A study of cortical neuroinflammation revealed the structural and functional dynamics of cortical pathology and subsequent compensation [5]. It provides a cellular and subcellular mechanistic framework for synaptic loss in inflammatory lesions, and demonstrates a potential treatment strategy with possibilities for translation into MS patients.

Chronic two-photon calcium imaging of neuronal activity showed a drop of neuronal firing in cortical projection neurons, which started within three days of onset of cortical neuroinflammation. A sharp and acute reduction in synapse numbers on the dendritic arbours of pyramidal neurons was observed throughout the cortical layers. Subcellular imaging of calcium concentrations in neurites revealed local calcium overload in individual spines which tagged them for subsequent removal.

Pharmacological interference with phagocyte activation lead to a significant protection from spine loss.

How Th17 cells kill neurons

The role of Th17 cells in mediating direct neuronal injury is still highly debated because neurons do not express MHC-II molecules necessary for T-cell receptor-dependent recognition. New research results helped to unravel the role of Th17 cells in neuroinflammation [6]. They show that Th17 cells themselves can secrete glutamate triggered by cell-cell contact with neurons leading to neuronal injury. The results suggest a novel pathway of immune-neuron interaction, regulated by VCAM1 - β1-integrin/KV1.3 signalling, wherein glutamate release is initiated by a direct cell-cell contact-specific interaction of Th17 cells with neurons.

References

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Miscellaneous

The crucial role of the Epstein-Barr virus (EBV) in MS was corroborated by an analysis of a large cohort of patients with early MS. Clarification of the mechanisms through which EBV exerts its effects in MS remains a key question. In 'aggressive' MS, autologous haematopoietic stem cell transplantation (AHSCT) improved median EDSS scores by 2.5 and could have a role as a first-line therapy. The central vein sign (CVS) was shown to have a high specificity in differentiating MS from non-MS and can support the diagnosis of MS.

Crucial role Epstein-Barr virus

In a cohort of 901 patients with a clinically isolated syndrome (CIS) or relapsing-remitting MS (RMSS) all individuals were found to be EBV seropositive [1]. This result further strengthens the already strong evidence for a crucial role of EBV in MS, according to Prof. Klemens Ruprecht (Charité Universitätsmedizin Berlin, Germany), who led the research. He said it also suggests that a negative EBV serology in a patient with suspected inflammatory central nervous system disease should alert clinicians to consider diagnoses other than MS.

Antibodies to Epstein-Barr nuclear antigen-1 (EBNA-1), measured by a chemiluminescent assay, were detected in 839 of 901 patients with a CIS (n=380) or early RRMS (n=521) from the German National MS cohort. Of the 62 EBNA-1 antibody seronegative patients, 45 had antibodies to viral capsid antigen. All 17 remaining patients had antibodies to EBV as detected by EBV immunoblot. Thus, all 901 (100%) patients with CIS/RRMS investigated in this study were EBV seropositive. Prof. Ruprecht explained that this result was likely related to the very stringent inclusion criteria, and to the use of a sensitive stepwise approach for detection of EBV antibodies. He added that these results were consistent with those of a recent study in which only 1 of 1,047 MS-patients was truly EBV-negative [2].

Stem cell transplantation

AHSCT is a very effective treatment in patients with highly active RRMS who failed to respond to standard DMTs. In a cohort of 20 patients with 'aggressive' MS in 5 centres, AHSCT was safe and highly effective in inducing rapid and sustained remission; it was associated with a significant improvement of patients' level of disability [3].

Median age at diagnosis was 33 (19-52) years. Median pre-treatment EDSS score was 6.5 (1.5-9.5). Median follow-up was 30 (6-118) months. Median EDSS score at the last follow-up was 2.0 (0-6.5). Median improvement between pre-treatment and last follow-up EDSS scores was 2.5 (0-8), which was statistically significant ($P<0.05$). None of the 20 patients had any clinical relapse following AHSCT. Three patients were noted to have new T2 lesions on MRI at the first follow-up, but no further new or enhancing lesions were observed in subsequent scans. No treatment-related mortality was observed. These results demonstrate the potential role of AHSCT as first-line therapy in 'aggressive' MS.

Central vein sign in MS diagnosis

The central vein sign (CVS) has a high specificity in differentiating MS from non-MS and may thus be used to support the diagnosis of MS. The sensitivity is moderate on susceptibility weighted imaging and increases when using optimised T2*weighted imaging [4]. These were the main conclusions from a multi-centre study in 606 subjects evaluating the sensitivity and specificity of various CVS-based criteria in differentiating MS from non-MS on clinical 3T MRI. The CVS was examined on parcellated 3T T2*weighted or susceptibility weighted imaging. In total, 4,447 lesions were analysed. The median proportion of a positive CVS was 50% in CIS/RRMS, and 0% in non-MS. A 35% threshold was the best CVS-proportion-based cut-off, with a specificity and sensitivity of 82.9%, and 68.1% respectively. In addition, a three-CVS-positive-lesion threshold had a specificity and sensitivity in differentiating between RRMS/CIS and non-MS of 89.0%, and 61.9%, respectively.

MS and family planning

During a session concluding ECTRIMS 2018 and presenting clinical highlights of the meeting, Dr Jaqueline Palace (University of Oxford, United Kingdom) summarised data on the use of DMTs around and during pregnancy as follows:

- The summary of product characteristics (SmPC) is always over-cautious concerning pregnancy.
- The risk of the foetus has to be balanced against that of the mother.
- Most MS drugs are not teratogenic; be careful with newer drugs and small molecules.
- Interferons and glatiramer acetate are safe up to conception and probably beyond.
- More information on DMT-exposed pregnancies is needed for newer drugs.
- Include exposed pregnancies in registries.
- Ask MS drug companies for updated information on the number of exposed pregnancies.
- Most women with MS will not experience an increase in permanent disability from a postpartum relapse.
- Breastfeeding is not harmful – exclusive breastfeeding may be beneficial in women with milder disease (low pregnancy relapse frequency and severity). Breastfeeding should not be discouraged in favour of resuming MS medication in most women.
- If a woman does not wish to breastfeed, start MS treatment early (7-14 days postpartum).
- In women with highly active disease (controlled pre-pregnancy only by natalizumab, fingolimod, or cyclophosphamide) foregoing nursing, resuming medication as soon as possible may be necessary.
- In highly active disease when planning: consider a depleting antibody with long-lasting effect, e.g. cladribine; on natalizumab, continue natalizumab until week 34.

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