MS PARIS 2017

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25-28 OCTOBER 2017 • PARIS • FRANCE

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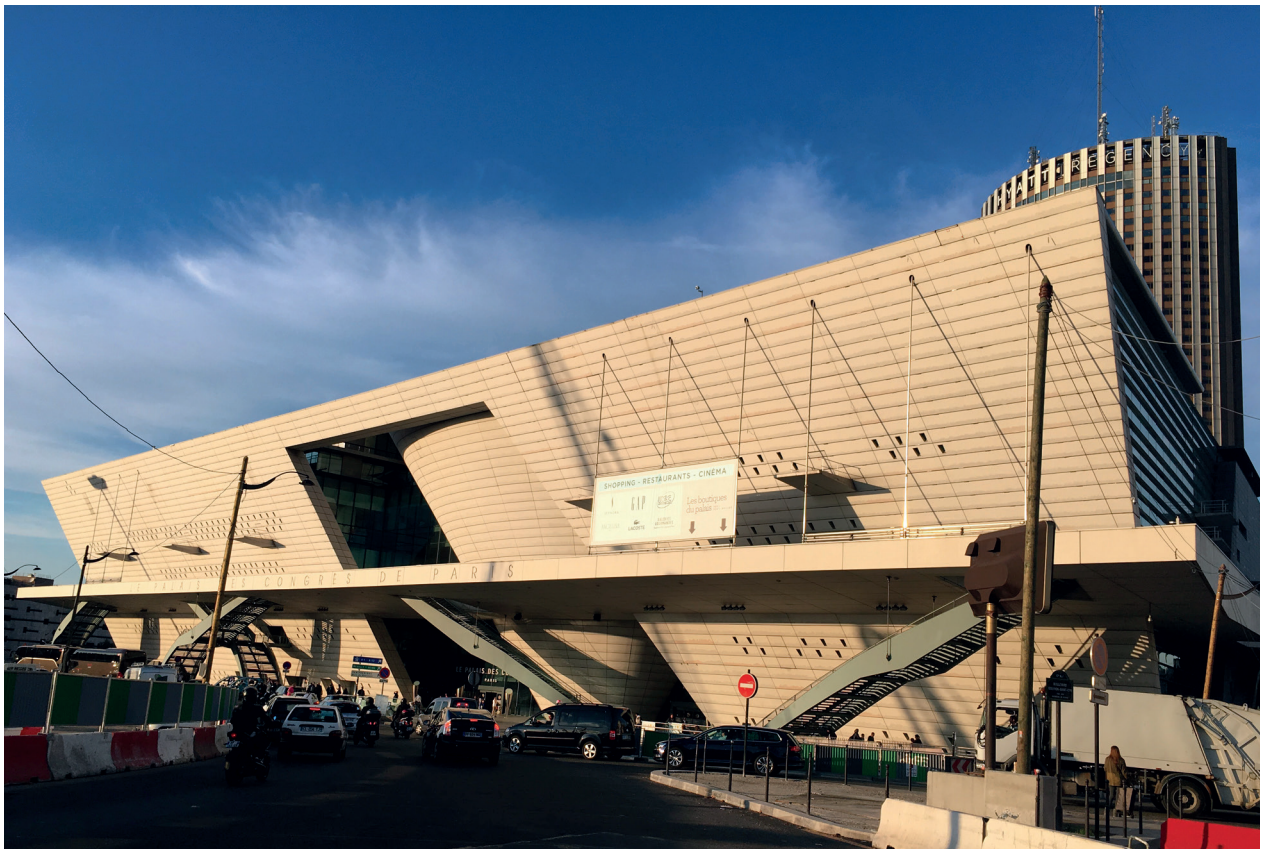

Guidelines & Criteria
The McDonald diagnostic criteria have been revised potentially allowing earlier MS diagnosis. The European and US guidelines for MS treatment have also been updated and now include DMTs.

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Early RRMS Treatment
Is it better to start treatment with high-efficacy DMTs shortly after the diagnosis RRMS or to wait until resistance to first-line therapies develops?

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Real-World Head-to-Head Studies
These unique studies were presented at MSParis, among these were cladribine vs interferon β-1a, fingolimod, natalizumab & natalizumab vs ingolimod & DMF vs fingolimod, glatiramer acetate

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Editor Prof. dr. Nikolaos C. Grigoriadis, Aristotle University of Thessaloniki, Thessaloniki, Greece

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ISSN 2468-8762 17:19

Letter from the Editor

Dr. Nikolaos Grigoriadis

Dear Reader,

At ECTRIMS 2017 in Paris, a number of clinical and scientific advances in Multiple Sclerosis, and neuromyelitis optica spectrum disorders have been presented. Among the most important findings that are expected to imminently affect clinical practice are the new McDonald diagnostic criteria and the European and US guidelines for MS treatment. Importantly enough, some promising therapeutic interventions for progressive MS have been announced. In addition, few new molecules, some of which with a novel mechanism of action were announced to be potentially effective in controlling RRMS activity. Interestingly enough, new data of either the already established or the newly approved DMTs in RRMS had been announced. Among them were the value of early high-efficacy DMTs use soon after RRMS diagnosis, particularly in the long-term disability control and the appropriate time of DMTs discontinuation, the first global study for paediatric-onset MS treatment with fingolimod and the long term benefit-risk profile of daclizumab. Among the "hot topics" of the meeting were the effect of cladribine in active RRMS and the introduction of the concept of reconstituting the immune system in MS management. A number of several head-to-head studies between well-established treatments in RRMS were also presented. Importantly enough, cognition as a key factor with considerable impact on the overall quality of life and the "cognitive phenotypes" in MS, have been highlighted. Last but not least, several fundamental research highlights such as the potential use of serum neurofilament light in the diagnosis and monitoring of MS, the identification of blood-brain barriers BBB - related molecules in neuroinflammation, the role of anti-MOG Abs in CNS immune-mediated demyelination had been presented. Some additional scientific advances in potential mechanisms related to the underlying immune and neurodegenerative process in MS, were among the most spectacular news at the meeting.

Best Regards,
Nikolaos Grigoriadis, MD, PhD

Biography

Dr. Nikolaos Grigoriadis graduated from the Faculty of Medicine of the Aristotle University of Thessaloniki. He did his PhD thesis and residency in Neurology in the same institution. He has been specialised in clinical and experimental Neuroimmunology and CNS immunopathology in a number of research centres and institutions abroad.
He is now Professor of Neurology and Head of the of the B' Dept of Neurology, AHEPA University Hospital, the MS Centre and the Laboratory of Experimental Neurology and Neuroimmunology. Professor Grigoriadis is member of various international scientific committees such as the European School of Neuroimmunology, ParadigMS, the subcommittee of ENS for Multiple Sclerosis, the ECTRIMS committee (until 2010), Co-founder and Secretary of the Hellenic Academy of Neuroimmunology. Since September 2017 he is the President of the Hellenic Neurological Society. He is ad-hoc reviewer in international scientific journals, co-ordinator in more than 40 multicentre clinical trials for MS and principal investigator in collaborative research projects for cell therapies in CNS autoimmune demyelination.
His field of interests are: neuroimmunology; multiple sclerosis; experimental models of autoimmune diseases (EAE etc); neurodegeneration; immunomodulation; cell therapies. He has published more than 150 papers in peer-reviewed journals.

New Guidelines and Criteria

At ECTRIMS 2017 in Paris, a whole session was dedicated to the proposed revisions to the 2010 McDonald diagnostic criteria for Multiple Sclerosis (MS). The new criteria should allow the diagnosis to be made earlier in many cases, as the authors stated, with an explicit role for oligoclonal bands. The first real guidelines on the use of Disease Modifying Therapies (DMTs) in MS were released by ECTRIMS in collaboration with the European Academy of Neurology (EAN). The American Academy of Neurology (AAN) was also scheduled to present its guidelines on DMTs in MS, but the data were still under embargo.

McDonald diagnostic criteria

The main revisions to the McDonald criteria were outlined by Dr J.A. Cohen from Cleveland, who co-chaired the 30-member expert panel that reviewed the latest Magnetic Resonance Imaging (MRI) and other relevant data; Cohen is also the incoming president of ECTRIMS.

He commented that the 2010 criteria performed well and that no major changes were made. "The revisions aim to simplify and clarify the criteria, facilitate earlier diagnosis, and reduce the chance of misdiagnosis." These were the 5 major changes Cohen elaborated on:

1. In a patient with a typical Clinically Isolated Syndrome (CIS) who fulfills clinical or MRI criteria for Dissemination In Space (DIS), demonstration of Cerebral Spinal Fluid (CSF)-specific oligoclonal bands, allows an MS diagnosis to be made without the previously required Dissemination In Time (DIT), if there is no better explanation for the clinical presentation. "CSF oligoclonal bands may be viewed as substitution for the dissemination-in-time requirement", Dr. Cohen said, realising that this will be regarded without a doubt as the most controversial change.
2. Both symptomatic and asymptomatic MRI lesions can be used for fulfilling MRI criteria for DIS or DIT. Under the 2010 criteria, the symptomatic lesion in a patient presenting with a brainstem or spinal cord CIS, could not be included as MRI evidence of DIS or DIT.
3. In addition to juxtacortical lesions, cortical lesions may also be used to demonstrate DIS requirements. Cohen: "This recognises that our ability to detect cortical lesions is relatively limited."
4. The requirements for the diagnosis of Primary Progressive MS (PPMS) have not changed, except that the distinction between symptomatic and asymptomatic lesions is no longer made and that cortical lesions may be used.
5. At the time of diagnosis, a provisional disease course should be determined and periodically be re-evaluated on the basis of accumulating evidence.

Dr. Cohen stressed that these criteria should not be applied mechanically, but that all clinical, imaging, and laboratory data should be synthesised. "MS is still first and foremost a clinical diagnosis."

Oligoclonal bands

MRI DIS at any time plus positive oligoconal bands was proposed as an additional criterion for MS diagnosis. Evidence exists that the presence of oligoconal bands in typical CIS increases the risk of a second attack independently of MRI findings. For this reason, the added value of oligoconal bands for MS diagnosis was further explored[1]. In an ongoing CIS cohort, MRIs were obtained 3-5 months after the CIS, at one year and every five years. In total, 565 patients with oligoconal bands determination and sufficient data on baseline brain MRI to assess 2010 DIS and DIT, were selected. The adjusted hazard ratios (aHR) were:

- 2.8 for no DIS no DIT with ≥1 lesion and negative oligoconal bands (specificity 77.6);
- 6.4 for no DIS no DIT with ≥1 lesion and positive oligoconal bands (specificity 89.1);
- 9.7 for DIS only with negative oligoconal bands (specificity 92.5);
- 14.8 for DIS only with positive oligoconal bands (specificity 88.1);
- 7.9 for DIT only (specificity 97.8).

DIS only with positive oligoconal bands had the highest sensitivity (46.2), accuracy (64.6) and Positive Predictive Value (PPV) (83.2). Although an important issue remains the possibly per centre varying quality standards for detecting oligoclonal bands.

Neuromyelitis optica

At the same session, Dr. R. Marignier from Lyon presented an evaluation of the diagnostic accuracy of three different sets of NeuroMyelitis Optica (NMO) criteria, among patients

suspected being part of the NMO spectrum disorders[2]. In the absence of a gold standard for the diagnosis of NMO, three main sets of diagnostic criteria have been proposed in the past 20 years: Wingerchuk 1999, Wingerchuk 2006 and International Panel for NMO Diagnosis (IPND) 2015. The more recent ones (IPND 2015) are considered to improve the diagnostic yield. These three sets were applied retrospectively on 235 patients referred by three French tertiary centres, for serum AQP4-IgG assay. To evaluate the specificity, MS criteria (Polman 2015) were also applied. Of the 235 studies patients, 75 fulfilled NMO criteria in one or more sets and 76 MS criteria, while a large group (n=94) did not satisfied any criteria. Among the 75 NMO patients, 69/75 (92%) were identified by the 2015 criteria, 38/75 (51%) by the 2006 ones and 35/75 (46%) by the 1999 ones. Thus, the IPND 2015 criteria confirmed a higher sensitivity, but did not catch all previously identified cases. Interestingly, the study pointed out an overlap between MS and NMO: 10 patients fulfilling NMO criteria also satisfied MS criteria, 8 of whom were AQP4-Ab positive. The MOG antibodies were not available for the entire patient population thus this may affect the sensitivity results. Among the 94 patients not fulfilling any criteria, 46 presented as isolated or recurrent inflammatory optic neuritis/transverse myelitis, associated with negative brain MRI. Finally, among 42 patients tested positive for AQP4-Ab, 41 were considered NMO and one as atypical PMS.

New European and US guidelines for MS treatment

The ECTRIMS/EAN guidelines on the use of DMTs were presented by Dr. Montalban from Barcelona. He explained that the guidelines committee used GRADE, a systematic approach to rating evidence. To every recommendation a strength has been assigned: strong or weak, or consensus statement. Montalban: "Strong recommendations should be acted on, weak recommendations should be considered." Montalban then proceeded to simply read out the guidelines, 20 in total. The following are a dozen of them:

- The entire spectrum of disease-modifying drugs should be prescribed only in centres with adequate infrastructure to provide proper monitoring of patients, comprehensive assessment, detection of side effects, and capacity to address them properly. (Consensus statement)
- Offer interferon or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
- Offer early treatment with disease-modifying drugs in patients with active Relapsing-Remitting MS (RRMS), as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong).
- For active RRMS, choosing among the wide range of available drugs from the modestly effective to the highly effective will depend on patient characteristics and comorbidity, disease severity, drug safety profile, and accessibility of the drug. (Consensus statement)
- Consider treatment with mitoxantrone in patients with active Secondary Progressive MS (SPMS), taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
- Consider ocrelizumab for patients with PPMS. (Pending European approval).
- Offer a more efficacious drug to patients treated with interferon or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
- When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
- In treatment decisions, consider the possibility of resumed disease activity or even rebound when stopping treatment, particularly with natalizumab. (Weak).
- Advise all women of childbearing potential that disease-modifying drugs are not licensed during pregnancy, except glatiramer acetate. (Consensus statement)
- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using interferon or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; or treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

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Promising Treatments of Progressive MS

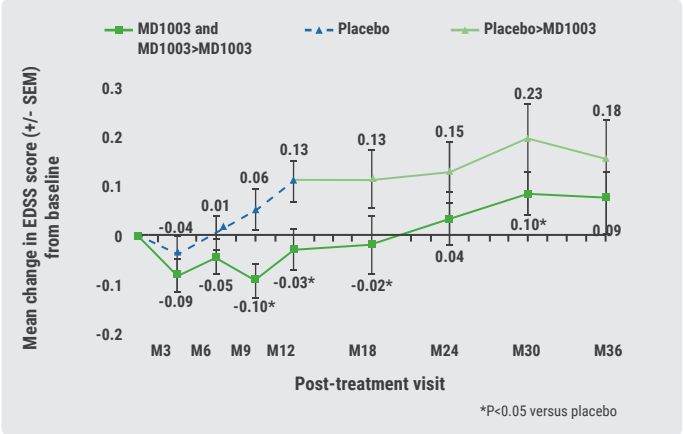
A topic that took centre stage in the 2017 edition of ECTRIMS was treatment of MS in its progressive phases. At long last treatments are emerging that seem to be able to slow disease progression in this stage, or perhaps even reverse the disease course to a certain extent. This is all the more exciting because the research faces huge barriers. The biological processes that cause progression are still poorly understood. As progression is often slow, trials exploring progressive MS treatments usually take a lot of resources, patients, time and patience. Nonetheless, high-dosed biotin, ibudilast, siponimod, ocrelizumab, and natalizumab all showed more of less promising results in progressive MS.

High-dose biotin: MD1003

One of the interesting aspects of the 12-month placebo controlled MS-SPI study of high-dose biotin (MD1003) in patients with non-active progressive MS (PMS), is the relatively low number of participants (n=154)[1]. Nonetheless the results were remarkable and suggest that this targeting of neuronal metabolism in PMS may represent a new class of long-term DMT in PMS.

In Paris, the results after 36 months in the open-label extension phase were presented, in which all patients received MD1003[2]. The results indicate that the effects of MD1003 are sustainable over time; that disease progression halts when patients switch from placebo to MD1003; that delayed treatment in PM patients results in higher disability over time; and that MD1003 is well tolerated over 36 months. The extension phase included 133 patients, of whom 91 had received active treatment from baseline (MM), and 42 had received placebo in year 1 (PM). Another intersting aspect is the primary endpoint of confirmed Expanded Disability Status Scale (EDSS) or timed 25-foot walk (TW25) improvement. This was significantly higher for MM vs PM patients at 9 months (13% vs 0%, P<0.05); the trend was similar at 18 months (13% vs 7%) and 30 months (10% vs 2%). Mean EDSS change from baseline slightly decreased in MM and worsened in PM patients after 12 months (−0.03 vs 0.13, P=0.01). When all patients were treated with MD1003 at 12 months, mean EDSS remained stable, without a significant difference between groups: 0.04 vs 0.15 at 24 months (P=0.13); 0.09 vs 0.18 at 36 months (P=0.35). However, the two mean EDSS evolution curves remained parallel, suggesting that earlier treatment leads to a lower disability at 36 months. The proportion of patients unable to complete TW25 (or with time >180 sec) increased in both groups in the first year, with a trend for less increase in the MD1003 group, baseline: 1% vs 2%; month 12: 6% vs 19%. Clinician and Subject Global Impression of Change scale (CGI and SGI) results were significantly better in the MD1003 group at 12 months (CGI: 4.05 vs 4.62, P<0.0001; SGI: 4.27 vs 4.76, P=0.009). After the first year, scores remained stable for MM patients and improved for PM patients. At month 36, adverse events had been experienced by 67% vs 79% of patients in MM and PM groups.

Figure 1 Mean change in EDSS score from baseline in the double-blind and extension phase



SEM, standard error of the mean

MD1003: subgroup and MRI analyses

Results of subgroup analyses revealed no evidence that any specific subgroup did not benefit from MD1003 treatment in patients included in the MS-SPI trial[3]. The total population (n=154) was split into the following subgroups: EDSS low (4.5–5.5) or high (6–7) (n=35 vs 119); concomitant use of fampridine or not (72 vs 82); PPMS or SPMS (55 vs 99); concomitant use of DMT or not (61 vs 93); and undergoing new intensive physical therapy during the study or not (29 vs 125).

Results of a brain volumetric MRI/DTI follow-up sub-study were presented by Dr. D. Arnold from Montreal[4].These indicated a decrease in whole brain volume and gray matter

volume in the MD1003 arm compared to placebo. A decrease in these volumes was also observed in the placebo group switched to MD1003 in the second year. Dr. Arnold said the effects of MD1003 were attributable to the reversal of virtual hypoxia. This in turn explains the pseudo-atrophy phenomenon observed in this sub-study, which is linked to a decrease in brain water volume following the initiation of treatment with MD1003. This phenomenon may be a consequence of increased energy production triggered by high-dose biotin. Dr. Arnold concluded: "The MRI/Diffusion Tensor Imaging (DTI) results are suggestive of possible remyelination."

Ibudilast

Also highly anticipated were the results of the SPRINT-MS/NN 102 phase II trial of ibudilast (MN-166) in progressive MS[5]. Ibudilast slowed the rate of brain atrophy by 48% without inducing significant toxicity compared with placebo. Ibudilast is an oral inhibitor of Macrophage Migration Inhibitor Factor (MMIF), PDE-4, PDE-10, and Toll-like receptor 4, with potential neuroprotective effects. Ibudilast has been approved in Japan since 1989 as a treatment for complications following stroke and asthma. Dr. R.J. Fox from Cleveland presented the results as a late-breaking abstact. In the SPRINT-MS trial, 255 patients with PPMS or SPMS were randomised 1:1 to placebo or ibudilast at escalating doses (60, 80, or 100 mg/day), based on tolerability. Annual change in brain atrophy, as measured by Brain Parenchymal Fraction (BPF), was -0.00105 in the ibudilast group compared with -0.00202 in the placebo group (P=0.040). These findings were supported by relative reductions in MTR-progression of 77–82% vs placebo. For normal appearing brain tissue, the MTR at year 1 was -0.00558 vs -0.03064 (P=0.047). For normal-appearing gray matter, the MTR rate change was -0.00753 vs -0.0321 (P=0.054). There was no significant difference in DTI, but there was a trend favouring ibudilast. Adverse events (AEs) occurred in 88% and 92% in the placebo and ibudilast group, respectively, a difference which was not significant (P=0.26). There were 58 total serious AEs (Serious AEs) in the trial, which occurred in 44 patients; the rates of Serious AEs were similar between the two arms. The discontinuation rate in the ibudilast group was about 5% higher. Dr. Fox: "Treatment-related adverse events were mostly gastrointestinal, as well as rash, depression, and fatigue. There was no increased rates of serious adverse events and, importantly, no signals of opportunistic infections or cancer."

More analyses are underway, Dr. Fox added – notably of OCT, cortical atrophy, and clinical outcomes, as well as additional safety and laboratory analyses – which will also shed more light on the anti-inflammatory effects of ibudilast.

Siponimod

Siponimod (BAF312) is a new sphingosine 1-phosphate receptor agonist which selectively modulates the sphingosine 1-phosphate receptor (S1P1,5). The ongoing phase III EXPAND trial is a multicentre, randomised, double-blind study comparing the efficacy and safety of siponimod to placebo in patients with SPMS. MRI outcomes from EXPAND emphisesed the positive impact of treatment with siponimod in patients with SPMS[6]. The results showed that siponimod 2 mg significantly reduced change in brain volume and T2 lesion volume (T2LV), new and enlarging T2 lesions, gadolinium-enhancing and T1 (Gd+T1), and brain volume loss assessed by Percent Brain Volume Change at 12 months, with effects sustained at 24 months. NB: In the second year of the study patients with confirmed disability progression were allowed other DMTs as well. MRI scans were performed at baseline and every 12 months thereafter. Post-baseline MRI data were available from >80% of the 1,651 randomised patients. The adjusted mean differences in the change from baseline vs placebo for the full data set were:

- A reduction of 73% and 86% in T2LV at month 0–12 and month 12–24 (P<0.0001 for all);
- A reduction of 87% and 42% in T1Gd+ lesion count at month 12 and at month 24 (P<0.001 for all);
- A reduction of 39% and 15% in percent brain volume loss at month 0–12 and at month 0–24 (P<0.0001 for all).

Dr. Fox said these results were encouraging, even though the magnitude of the effects was lower after 2 years than after 1 year. He added: "Positive effects on brain volume loss and disability progression support the potential neuroprotective effects of siponimod."

Ocrelizumab

Ocrelizumab is the first approved therapy for PPMS, albeit in Europe so far only in Switserland. Ocrelizumab, a humanised monoclonal antibody that selectively targets CD20+ B cells, had superior efficacy versus placebo in patients with PPMS in the double-blind period (DBP) of the phase III ORATORIO study. Results from the extended controlled treatment period confirmed the positive impact on sustained reduction in confirmed disability progression (CDP)[7].Patients had

Table 1. Relative risk reductions in CDP, composite CDP, ≥20% increase in T25FW and ≥20% increase in 9HPT

Endpoint (OCR vs PBO)	Double-blind period relative risk reduction	Extended controlled period relative risk reduction
CDP (12-week; primary endpoint)	24% (P=0.032)[1]	25% (P=0.020)
CDP (24-week; key secondary endpoint)	25% (P=0.037)[1]	25% (P=0.006)
Composite CDP (12-week; exploratory endpoint)	26% (P<0.001)[1]	25% (P<0.001)
Composite CDP (24-week; exploratory endpoint)	29% (P<0.001)[1]	25% (P<0.001)
≥20% increase in T25FW (12-week; exploratory endpoint)	25% (P=0.005)[1]	25% (P=0.008)
≥20% increase in T25FW (24-week; exploratory endpoint)	27% (P=0.006)[1]	25% (P=0.002)
≥20% increase in 9HPT (12-week; exploratory endpoint)	44% (P<0.001)[1]	25% (P<0.001)
≥20% increase in 9HPT (24-week; exploratory endpoint)	45% (P<0.001)[1]	25% (P=0.002)

pHPT, 9-hole heg test; CDP, confirmed disability progression; OCR, ocrelizumab; PBO, placebo; T25FW, timed 25-foot walk

been randomised 2:1 to ocrelizumab 600 mg or placebo every 24 weeks for ≥120 weeks, until a prespecified number of CDP events had occurred during the DBP. Time to onset of CDP from baseline sustained for at least 12 or 24 weeks, a composite 12/24-week CDP (cCDP) and confirmed 20% increase in Timed 25-Foot Walk Test (T25FW) after 12 and 24 weeks were evaluated. Data from 488 and 244 patients randomised to ocrelizumab and placebo respectively, were analysed. Relative RR versus placebo seen in the DBP for 12- and 24-week CDP (24% and 25%), slightly increased in the Extracorporeal Photopheresis (ECP) 25% and 30%. Relative RRs in the DBP for 12- and 24-week cCDP (26% and 29%) also slightly increased during the ECP: 27% and 30%. The Relative RRs during the DBP for ≥20% worsening in T25FW with 12 or 24-week confirmation (25% and 27%) remained consistent during the ECP: 24% and 28%.

A poster was presented in which ocrelizumab was shown to lower the risk of progression of upper limb functional impairment in patients with PPMS in the ORATORIO study[8]. Upper limb function was measured by the validated 9-Hole Peg Test (9HPT). Compared with placebo, ocreliumab reduced the time to 12- and 24-week confirmed progression of ≥15% on 9HPT by 37% (Hazard Ratio (HR): 0.627; P=0.001) and 39% (HR: 0.607; P=0.002) for both hands; by 30% (HR: 0.699; P=0.011) and 40% (HR: 0.599; P< 0.001) for better hand; and by 29% (HR: 0.705; P=0.016) and 28% (HR: 0.717; P=0.040) for worse hand.

Natalizumab in SPMS

In the ASCEND trial, natalizumab did not meet the primary endpoint of reducing disability progression in mostly nonrelapsing SPMS patients. However, natalizumab did significantly delay upper limb disability progression and was associated with greater levels of disability improvement than placebo; this suggests that natalizumab treatment benefits in this population may be a combination of reduced sustained worsening and increased sustained improvement. A post-hoc analysis of ASCEND used Area-Under-the-Curve (AUC) methodology to integrate disability worsening with improvement outcomes[9]. The results show natalizumab significantly improved the overall disability experience for walking and upper limb function compared with placebo in this population. Treatment effects on integrated disability worsening and improvement were measured using the EDSS, T25FW and 9HPT. Significant improvements from baseline to week 96 with natalizumab vs placebo were observed in the median AUC of T25FW (natalizumab, 19.18; placebo, 24.5; P=0.020) and 9HPT (average hand: natalizumab, −1.59; placebo, 2.58; P=0.006), but not EDSS (natalizumab, 0; placebo, 0; P=0.733). These results correspond to 28% and 77% reductions in T25FW and 9HPT mean AUC, respectively, for natalizumab vs placebo. The authors noted that the negative median AUC on the 9HPT suggests most natalizumab-treated patients experienced an overall favourable disability experience relative to baseline on upper limb function.

Take-home message

Progressive MS is recognised as the most difficult form of MS to treat. Until recently, there were no clear successful therapeutic approaches. Building upon earlier unsuccessful studies, clinical trial designs in progressive MS have improved and provide clearer outcomes, said Dr. F.D. Lublin from New York at a session on therapeutic perspectives in progressive MS. "Lessons we have learned from recent pivotal studies in primary and secondary progressive MS are, that it is treatable, although the effectiveness of tested drugs are modest so far; that we need neuroprotective approaches in addition to anti-inflammatory therapies; that we need better outcome metrics; and that improvement as an outcome measure is possible, as is shown by the aggressive and daring outcome measure of disease reversal in the MS-SPI trial of high-dose biotin." Dr. Lublin added that the pipeline of agents for progressive MS, contrary to 20 years ago, is well-filled.

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New Compounds

Results on several new compounds for the treatment of RRMS were presented. One of these is the humanised IgG4 monoclonal antibody GnbAC1, which represents a novel therapeutic approach: blocking a potential causal agent (pHERV-W Erv protein), without directly affecting normal immunity, as well as promoting remyelination via disinhibition of Oligodendroglial Precursor Cells (OPC) maturation blockade. There were also positive results of the first-in-class, highly selective partial PPARγ agonist CHS-131, of laquinimod, ublituximab, and ozanimod; the latter showing no cardiac signals.

GNbAC1

Post-hoc evidence was found that GNbAC1 lowers the cumulative number of Gd+ lesions at 24 weeks at the highest tested dose of 18 mg/kg. Evidence of remyelination was also found[1]. "These results plus the excellent safety profile are encouraging", said Dr. H-P. Hartung from Düsseldorf, who was looking forward to the results at 48 weeks, which will be available in early 2018. Human Endogenous Retroviruses (HERVs) are latent in the human genome, of which they represent about 8%. Pathogenic HERV-W envelope protein (pHERV-W Env) is associated with MS. GNbAC1 targets the surface subunit of pHERV-W Env. It thereby inhibits TLR4-mediated pathogenic mechanisms, including activation of peripheral macrophages and microglia to pro-inflammatory phenotypes. Furthermore, direct inhibition of remyelination via TLR4 expressed on OPCs during maturation and expression of ICAM-1 on blood-brain barrier endothelium. Dr. Hartung presented the results of an international, placebo-controlled phase IIb study of GNbAC1 as a late-breaking abstract. A total of 270 RRMS-patients were randomised 1:1:1:1 to GNbAC1 (6, 12 or 18 mg/kg) or placebo, via monthly, IV infusion, for 24 weeks (period 1). At week 24, placebo patients were re-randomised 1:1:1 to active GNbAC1 for another 24 weeks (period 2). The primary endpoint was the cumulative number of Gd+ lesions on monthly brain MRI from weeks 12-24 versus placebo. Safety and tolerability were "excellent", according to Dr. Hartung. There was no effect on any MRI or clinical measure from week 12–24 at any dose. The number of lesions in the 6 mg, 12 mg, 18 mg/kg and placebo group was 510, 407, 339 and 666, respectively. The trend toward effect prompted the authors to perform a post-hoc analysis, which revealed a significantly lower rate of Gd+ lesions in the group with the highest dose (18 mg/kg). "Admittedly, this was found in a post-hoc analysis", said Dr. Hartung. He added that in the same (18 mg/kg) group, evidence of remyelination in normal-appearing white matter was found. "Individual normal-appearing white matter and cortical bands showed dose-dependent trends in favour of GNbAC1. There was an increase of about 2 MTR percentage units, with statistical trends in favour of GNbAC1 at 18mg/kg." MTR lesion analyses were inconclusive for week 12-24. "Week 48 data may be more informative."

PPARγ agonist CHS-131

In a recent phase II-b study, daily treatment with 3 mg oral CHS-131 was well-tolerated, decreased Gd+ lesions and attenuated neural atrophy[2]. CHS-131 is a first-in-class, highly selective partial PPARγ agonist, which crosses the blood-brain-barrier and appears to be anti-inflammatory in the CNS without demonstrable immunosuppression. At ECTRIMS 2017 the first part of a study with a 2-part design was presented[3]. Part 1 had a double-blind, placebo-controlled design to evaluate safety and efficacy of CHS-131 in treatment-naïve RRMS patients. The 227 participants from 21 Russian sites were randomised 1:1:1 to 1 or 3 mg/

day CHS-131, or placebo. In Part 2 the subjects were given the choice to continue treatment with 1 mg daily of CHS-131. The patients underwent monthly MRI examinations with contrast to identify new inflammatory lesions. CHS-131 treatment resulted in a dose-dependent reduction in cumulative contrast-enhanced lesions over 6 months. Treatment with 1 mg/day reduced contrast-enhanced lesion burden by 21% compared to placebo. Three mg daily yielded more robust results, reducing contrast-enhanced lesion burden by 52% compared to placebo (4.2 vs 7.8 lesions; P=0.003). New/enlarged T2 lesions were reduced by 14% and 30% in the 1 mg/day and 3 mg/day group, respectively, compared to placebo. In addition to the dose-dependent anti-neuroinflammatory effects, CHS-131 treatment appeared to attenuate gray matter volume loss at 6 months. Compared to placebo, there was 34.2% less cortical volume loss and 50% less whole brain volume loss in the 3 mg cohort. CHS-131 was safe and well-tolerated; no treatment-emergent Serious AEs were reported.

Laquinimod

Prior phase III studies of laquinimod (ALLEGRO[4] and BRAVO[5]) showed better effects on the secondary endpoint of disability progression than on the primary endpoint of relapse rate in RRMS. In the CONCERTO trial however, which used time to CDP as its main endpoint, the difference with placebo at 3, 6, or 9 months was not significant[6]. As Prof Dr. G. Comi from Milan pointed out, laquinimod 0.6 mg did demonstrate a nominally significant effect on reducing brain volume loss and clinical relapses, and was generally well tolerated in patients with RRMS. CONCERTO was a randomised, double-blind, placebo-controlled phase III study. Patients (n=2199) were randomised 1:1:1 to receive oral laquinimod 0.6 mg or 1.2 mg or placebo once daily. The laquinimod 1.2 mg dose arm was discontinued due to findings of cardiovascular events at high doses in CONCERTO and in ARPEGGIO, an ongoing study of laquinimod in PPMS. The primary endpoint was time to 3-month CDP, which was not met (HR, 0.94; P=0.71). Secondary endpoints of 6- and 9-month CDP did not show a significant treatment effect either. However, laquinimod significantly lowered the risk of first confirmed relapse (HR 0.72; P<0.0001). It also significantly lowered the mean RR, which was an exploratory endpoint (RR 0.75; P=0.0002). In CONCERTO, laquinimod was also associated with significantly fewer Gd+ lesions at 15 months (RR 0.70; P=0.0064), but this difference was no longer significant at 24 months. The clinical safety profile of laquinimod 0.6 mg was confirmed in CONCERTO. The lesson, as Dr. R.J. Fox from Cleveland would later comment, is that reduction of relapse activity does not always imply slowing down disability progression.

Ublituximab

Preliminary results of a phase 2 trial in RMS patients revealed that ublituximab is well tolerated and highly efficacious in reducing MRI activity after 24 weeks[7]. As the authors emphasised, ublituximab can be delivered in shorter infusions than other anti-CD20s, providing a convenience benefit for patients. Ublituximab is a novel, chimeric monoclonal antibody which targets a unique epitope on the CD20 antigen; it has been glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, demonstrating greater antibody-dependent cellular cytotoxicity activity than rituximab. The phase 2 trial that was presented at ECTRIMS 2017 was designed to assess the optimal dose and infusion time as well as safety/tolerability of ublituximab in RMS subjects[7]. Laboratory, clinical and MRI analysis were also performed. At baseline, the 38 participants showed a total number of 104 Gd+ T1 lesions (mean 7) and a total T2 lesion volume of 16.1 mL. No Serious AEs were reported, including the subjects receiving rapid infusions. So far, MRI data from 16 of 38 enrolled subjects (42%) had been analysed up to week 24 of the 52-week study, encompassing two infusions. In this subgroup, total number of Gd-enhancing T1 lesions at baseline was 51 (mean 3); T2 lesion volume was 19.2 mL. At week 24, the total number of Gd+ T1 lesion was 0, with a 100% decrease compared to baseline (P=0.004); the total number of new or enlarging T2 lesion was 5 (mean 0.3), while the T2 lesion volume showed a 6% decrease compared to baseline (P=0.01).

In another analysis of the same trial, ublituximab demonstrated rapid and robust B-cell depletion, a profound reduction in Gd+ enhancing lesions, with clinical stability observed at week 24[8]. At week 4, median B-cell depletion in 16 analysed patients was 99% from baseline in the ublituximab group, which was maintained to week 24. No relapses or Gd+ lesions were reported in any subject during the first 24 weeks, while 83% of subjects had ≥1 relapse in the year prior to screening. Mean EDSS at baseline was 2.7 (±1.3) and 1.9 at week 24. There were no Serious AEs or clinically significant lab abnormalities. The most commonly reported AEs were infusion related reactions (grade ≤2). Faster infusion times did not increase the frequency of these reactions.

Ozanimod

Full data from two phase 3 trials of ozanimod (RPC1063) in RMS were presented for the first time at ECTRIMS 2017,

called RADIANCE and SUBEAM. The results confirmed the superiority of ozanimod to interferon β-1a on relapse and MRI endpoints and a favourable benefit-risk profile. Ozanimod is an oral, once daily immunomodulator selectively targeting sphingosine 1-phosphate 1 and 5 receptors. The SUNBEAM study was a multicentre, randomised, double-blind, double-dummy, parallel-group study of daily oral ozanimod 0.5 or 1 mg vs weekly interferon β-1a, 30 µg intramuscular injection[9]. A total of 1,346 RMS patients were enrolled in 20 countries. Mean treatment duration was 13.6 months. The absolute risk reduction, which was the primary endpoint, was 0.241 and 0.181 for ozanimod at 0.5 mg and 1.0 mg vs 0.350 for interferon β-1a, representing a 31% (P=0.0013) and 48% (P<0.0001) improvement, respectively. There was also a 25% (P=0.0032) and 48% (P<0.0001) reduction in new/enlarging T2 lesions for ozanimod at both doses, respectively. A consistent dose response was observed across efficacy endpoints for the two ozanimod doses. Overall, ozanimod was generally safe and well tolerated.

The results of the two-year RADIANCE study were presented as a late-breaking abstract by Dr. J.A. Cohen from Cleveland[10]. A total of 1,313 patients were randomised to 0.5 or 1 mg ozanimod, or interferon β-1a. The annualised relapse rate was 0.21 and 0.17 for both doses of ozanimod and 0.27 for interferon β-1a, which amounts to a relative reduction of 21% and 36%, respectively (P=0.01 and P<0.0001). There was a also a 34% and a 42% relative reduction in new/enlarging T2 lesions (P<0.0001 and P=0.0001). Similarly, there was a 47% and a 53% relative reduction in the number of Gd+ lesions (P=0.0006 and P=0.0003).

In a pre-specified pooled analysis of the SUNBEAM and RADIANCE results, ozanimod did not significantly prolongue time to 3-month CDP. However, disability progression was very low across all treatment groups. In SUNBEAM, the number of patients with 3-month CDP by the end of the study was 13 (2.9%) and 17 (3.8%) in both ozanimod groups compared with 19 (4.2%) in the interferon β-1a group.

In both trials, most treatment-emergent AEs were mild, with a low incidence of serious AEs, and similar across treatment groups. The rate of discontinuation due to AEs was likewise low and alike over treatment groups. No first dose, clinically relevant cases of bradycardia and no atrioventricular blocks of second degree or higher were reported. The largest mean supine heart rate reduction was 0.6 bpm at hour 5. Serious cardiac AEs were 0.7% and 0.0% for 0.5 and 1 mg ozanimod respectively, and 0.5% for interferon β-1a.

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RRMS Management

Is it better to start treatment with high-efficacy DMTs shortly after the diagnosis RRMS or to wait until resistance to first-line therapies develops? A study showed high-efficacy therapies are superior in preventing accumulation of disability, but that the gap with first-line therapies diminishes over time. The impact of DMTs on development of new relapses and MRI changes is considerable, but much less so on slowing progression. Which is why a randomised trial of discontinuation of DMTs in MS patients 55 and older is on its way. As in every year, ECTRIMS saw many presentations om DMTs adding yet another year of real-world data on long-term efficacy and safety; e.g. of fingolimod in POMS, of alemtuzumab and daclizumab beta, and of cladribine, approved by the EMA only 3 months before.

Early treatment with high-efficacy DMTs

Based on outcomes from the global MSBase cohort study, early vs delayed commencement of high-efficacy DMTs in RRMS provides superior control over relapse activity. However, disability outcomes on high-efficacy DMTs were largely independent of the timing of therapy[1].

Dr. T. Kalincik from Melbourne explained that his team compared relapse and disability outcomes between 430 patients who started high-efficacy DMTs (alemtuzumab, natalizumab or fingolimod) and 1,295 patients who started low-efficacy DMTs within 4 years after diagnosis. Patients treated early with high-efficacy DMTs experienced less relapses (annualised relapse rate 0.22 vs. 0.42, P=10-54) and were more likely to recover from disability (HR 1.5, P=0.04) than those commencing low-efficacy DMTs. They also compared patients who commenced high-efficacy DMTs within 4 years of diagnosis vs after 6 years (n=619 and n=1,210, respectively). No differences in disease outcomes were observed. Finally, they evaluated the association between the time of commencing therapy and disease outcomes in 500 patients who received high-efficacy DMTs vs 1,949 who received low-efficacy DMTs. The difference in annualised relapse rate between the high- and low-efficacy DMTs diminished with time. In contrast, no time-dependent flux in disability outcomes was observed. Dr. Kalincik summarised: "High-efficacy therapies are superior in preventing accumulation of disability, particularly in younger patients. The gap between high-efficacy and first-line therapies diminishes with time, age, and greater disability."

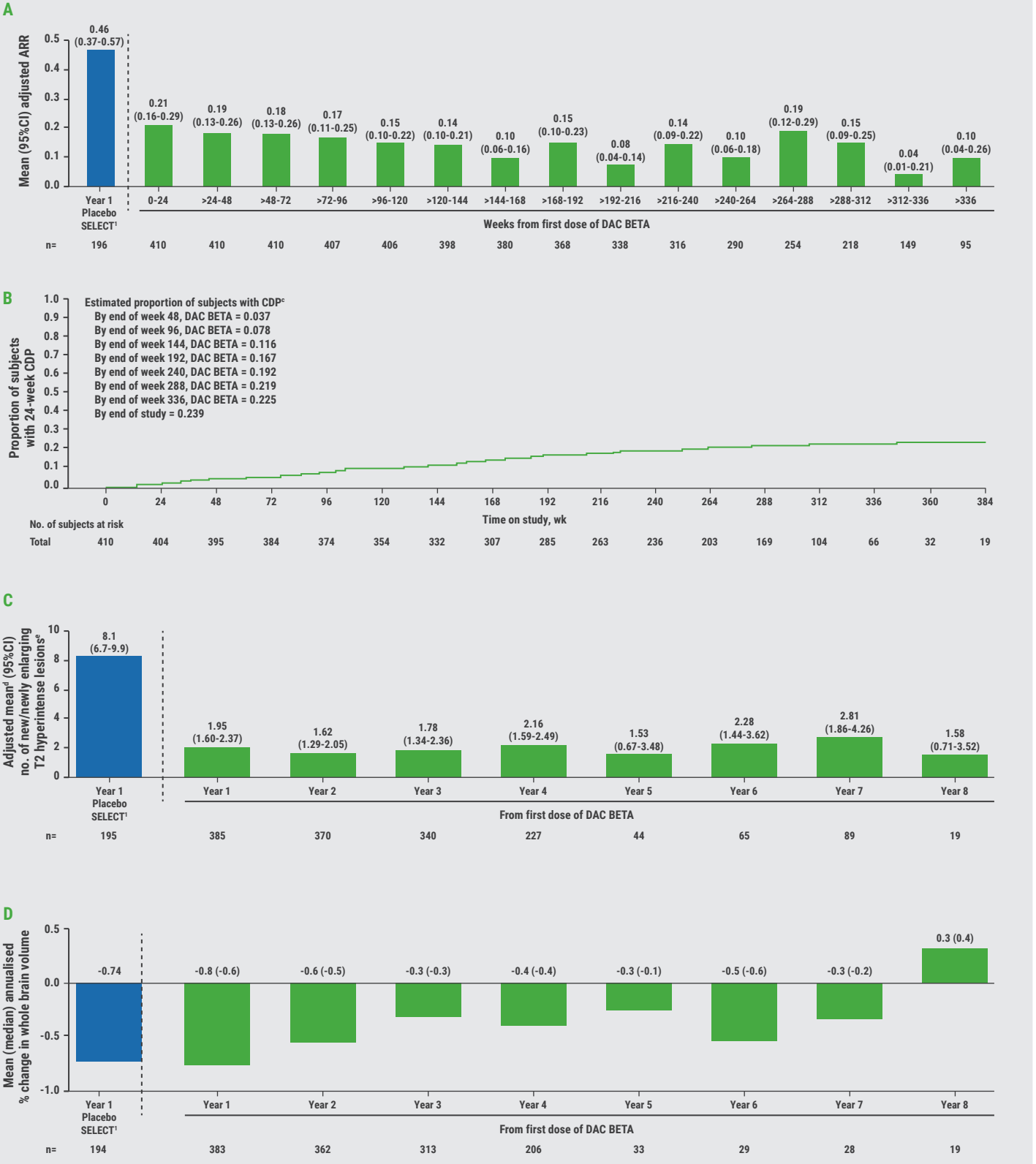
Discontinue DMTs in the elderly?

Dr. J. Corboy from Aurora in the US discussed the rationale for a randomised, controlled, blinded two-year trial (DISCOMS NCT03073603) of discontinuation of DMTs in MS patients 55 and older at 15 US sites who have had no new relapses or brain MRI scan changes for at least five years while continuously taking a DMT[2]. Data addressing the possibility of a trial off of DMTs are sparse and have significant methodological limitations, but suggest it may be reasonable to consider a trial off DMTs, especially for older patients who have been clinically quiescent for a prolonged time. This is because the inflammatory component of MS seems to be maximal in the young, while the degenerative component, especially as manifested by worsening brain and spinal cord atrophy, begins early and is persistent throughout aging with MS. DMTs have significant impact on development of new relapses and MRI changes, but much less effect on slowing progression. Almost all clinical trials identifying the benefit of MS DMTs have had a maximum age of 55, and subgroup analyses by age reveal that response to DMTs is often greatest in younger patients, especially those under age 40. Dr. Corboy said he hoped to have data from the DISCOMS trial by 2020, that will further guide clinicians in this area. For him, the relative futility of presently available DMTs in aging MS patients, especially those with progressing symptoms, argues strongly for approaches that diminish neurodegeneration and enhance CNS recovery and/or regeneration.

Fingolimod in POMS

The PARADIGMS trial is the first global, controlled trial investigating the efficacy and safety of fingolimod in patients with paediatric-onset MS (POMS). "PARADIGMS study met its primary endpoint, showing a significant lower annualised relapse rate up to month 24 with fingolimod versus interferon β-1a", observed Dr. T. Chitnis from Boston[3]. It also shows randomised trials in the paediatric MS population are feasible. PARADIGMS is an up to 2-year, double-blind, parallel-group, multicentre study, followed by a 5-year fingolimod open-

Figure 2 Clinical and radiological measures of efficacy in DAC BETA–treated subjects in SELECTED: (A) adjusted annualised relapse rate by 6-month intervals;[a] (B) 24-week CDP;[b] (C) number of new/newly enlarging T2 hyperintense lesions; (D) annualised percentage change in whole brain volume.



ARR = annualised relapse rate; CDP = confirmed disability progression; DAC BETA = daclizumab beta;[a] Adjusted ARR was estimated for a Poisson regression adjusted for number of relapses in the year before study entry;[b] Confirmed disability progression was defined as ≥1.0-point increase in Expanded Disability Scale (EDSS) score from a baseline score of 0, sustained for 24 weeks;[c] Date of first dose of DAC BETA is used as the start date. Estimated time to progression and proportions of subjects with progression was based on on the Kaplan-Meier product limit method;[d] Adjusted mean was estimated from a negative binomial regression adjusted for baseline number of T2 hyperintense lesions;[e] Adjusted mean number of new/newly enlarging T2 hyperintense lesions since the previous year's magnetic resonance imaging scan

label extension phase in paediatric patients with MS aged 10 to less than 18 years at randomisation. Patients were randomised (1:1) to receive oral fingolimod once daily (0.25 mg or 0.5 mg, dependent on body weight) or interferon β-1a 30 µg intramuscular once weekly. The mean age of the patients at the time of randomisation was 15.3 years, with a mean disease duration of 1.2 years, a mean number of relapses in the 12 months before screening of 1.5, and a number of Gd+ T1 lesions of 3.1; the median EDSS score was 1.5. The primary endpoint, annualised relapse rate during the randomised study phase, was 0.12 and 0.67 in the fingolimod and control group, respectively. This amounts to a relative reduction of 81.9% (P<0.001). "85.7% vs 38.8% of patients in the fingolimod and interferon β-1a group, respectively, were free of confirmed relapse for the entire study duration," Dr. Chitnis added. Time to three-month CDP was also significantly delayed with fingolimod: 95.2% vs 84.7% of patients were free of three-month CDP at month 24. Fingolimod significantly reduced the annual rate of brain atrophy up to month 24 vs interferon β-1a: change -0.48 vs -0.80.

In the fingolimod and control group, 88.8% and 95.3% of patients experienced one or more AEs. Most common were upper respiratory tract infections, pyrexia, influenza and influenza-like illness. Serious AEs were more frequent in the fingolimod group: 17.8% vs 9.3%. These included among others leucopenia (n=2), and seizure/epilespy (n=4). Dr. Chitnis: "The safety profile of fingolimod in the PARADIGMS trial was consistent with that seen in adult clinical trials."

Daclizumab bèta

The efficacy of daclizumab bèta (DAC BETA) on clinical and radiologic MS disease activity outcomes was sustained across yearly treatment intervals for up to 8 years[4]. No new safety concerns were identified in the SELECTED study population. The results demonstrated that the favourable benefit-risk profile of DAC BETA was sustained in subjects who remained on treatment for up to ~8 years of treatment.

SELECTED was an open-label single arm extension study that evaluated treatment with DAC BETA for up to 6 additional years in patients with RMS who completed the randomised SELECT and SELECTION studies. Of 455 subjects who completed SELECT and SELECTION, 410 (90%) enrolled in SELECTED. DAC BETA efficacy was maintained in subjects continuing treatment throughout the study. The annualised relapse rate and number of new/newly enlarging T2 lesions remained stable and low over time. The proportion of subjects with 24-week CDP remained low with extended treatment; by the end of SELECTED, 23.9% of subjects had 24-week CDP. Annualised percentage change in whole brain volume decreased over time on DAC BETA treatment to levels in the range in healthy controls. The overall incidence and severity of AEs remained stable throughout the DAC BETA treatment period and did not increase with long-term exposure. Overall, 87% of subjects experienced an AE, 26% had serious AEs (excluding MS relapse) and 22% had AEs leading to treatment discontinuation. Yearly incidence of AEs during SELECTED remained stable through year 5. Nine percent of subjects had elevated levels of alanine aminotransferase or aspartate aminotransferase >5 × upper limit of normal and 4% of subjects had alanine aminotransferase or aspartate aminotransferase levels >10 × upper limit of normal.

Alemtuzumab

Durable clinical and MRI efficacy over a period of 7 years was reported for alemtuzumab, despite 59% receiving no additional treatment since the initial 2 courses of alemtuzumab. Results from the TOPAZ study revealed alemtuzumab continued to be efficacious in treatment-naive patients, 37% of whom also showed improvement in disability[5]. Over 7 years, alemtuzumab also reduced MRI disease activity and slowed brain volume loss[6].

In CARE-MS I, alemtuzumab significantly improved clinical outcomes vs subcutaneous interferon β-1a over 2 years in treatment-naive patients with active RRMS. Durable efficacy of alemtuzumab was demonstrated over 6 years in a completed extension study in the absence of continuous treatment after 2 initial courses. CARE-MS I patients received 2 courses of alemtuzumab 12 mg/day. In the extension, they could receive as-needed alemtuzumab retreatment or another DMT. Patients completing at least 48 months of CARE-MS extension could enrol in the 5-year TOPAZ study for further long-term evaluation.

321 of 349 (92%) CARE-MS I patients who entered the extension remained on study until the end of year 6 and then entered TOPAZ; 299 (93%) remained on study through year 7. The annualised relapse rates remained low at 0.13; a proportion of patients with stable or improved EDSS remained high (78%). Through 7 years, 74% were free from 6-month confirmed disability worsening, 37% achieved 6-month confirmed disability improvement, and the majority achieved No Evidence of Disease Activity (NEDA) each year. Incidences of overall AEs, infusion-associated reactions, and infections decreased over time and were reduced vs the 2-year core study. Thyroid AE incidence declined after peaking at year 3. The MRI results were equally positive

and durable[6]. At year 7, 68% of patients remained free of MRI disease activity and of new/enlarging T2 lesions. 91% were free of new Gd-enhancing lesions and 85% were free of new T1 hypointense lesions. Alemtuzumab consistently slowed median yearly brain volume loss, derived by relative change in BPF. BPF change over 2 years, remaining low in the 5 years thereafter (BPF change in year 1 to 7: -0.59%, -0.25%, -0.19%, -0.14%, -0.20%, -0.17% and -0.16%). The conversion rate from RRMS to SPMS through 6 years among CARE-MS alemtuzumab-treated patients was low[7]. Patients in CARE-MS I were treatment naive; in CARE MS-II they had inadequate response to prior therapy. Median baseline disease duration in CARE-MS I and II was 1.7 and 3.8 years, respectively. Of alemtuzumab-treated CARE-MS I and II patients, 1.1% and 3.7% converted to SPMS through 6 years. Sensitivity analyses confirmed the low conversion rates.

Cladribine

Cladribine tablets 3.5 mg/kg (CT3.5), which have been approved by the EMA in August 2017, were a 'hot topic', in view of the dozens of presentations and posters on a wide variety of aspects of the drug.

A post-hoc analysis of the CLARITY study revealed that in patients with high-disease activity, treatment with CT3.5 produced comparable efficacy in reducing MRI markers of disease activity to the overall study population[8]. Two definitions of high disease activity were used:

1. High-relapse activity (HRA), defined as ≥2 relapses during the year before study entry, whether on DMD treatment or not;
2. HRA plus treatment non-response (HRA+TNR) with TNR defined as ≥1 relapse AND ≥1 T1 Gd+ or ≥9 T2 lesions during the year before study entry while on therapy with other DMDs.

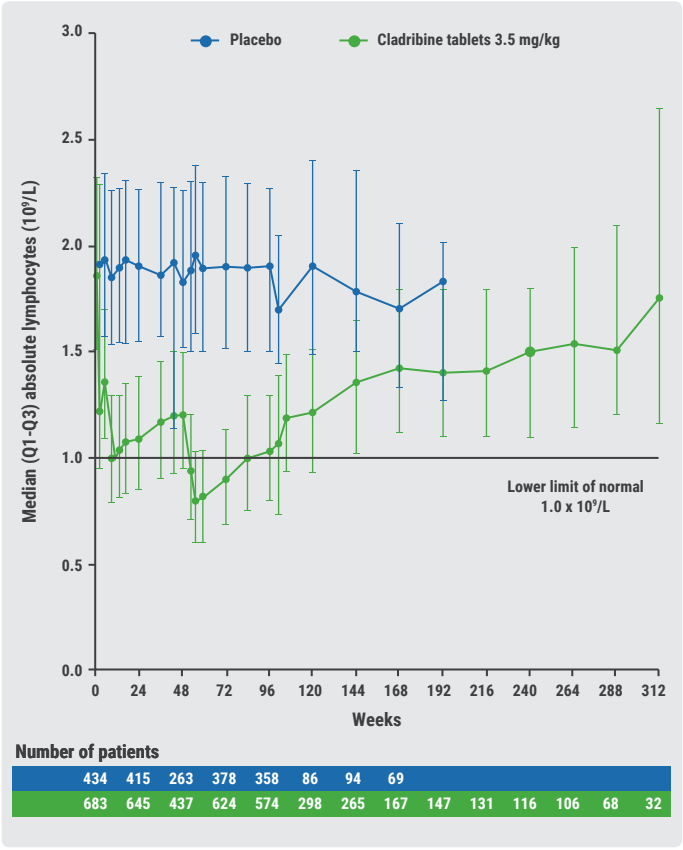
For cumulative new T1 Gd+ lesions, the relative risk ratio in the HRA subgroup (0.087) was significantly lower in favour of CT3.5 (n=130) over placebo (n=131). In the HRA+TNR subgroup, the relative risk ratio (0.077) also significantly favoured CT3.5 (n=140) vs. placebo (n=149). The risk reductions (91% and 92%, respectively) were similar to the 90% reduction in the overall CLARITY population (0.097; P<0.0001). For cumulative active T2 lesions, the relative risk ratio also significantly favoured CT3.5 vs. placebo for HRA (0.263) and HRA+TNR (0.254): risk reductions of 74% and 75%, reflecting the 73% reduction in the overall population (0.272; P<0.0001). The relative risk ratio for cumulative combined unique lesions significantly favoured CT3.5 vs. placebo for HRA (0.212) and HRA+TNR (0.203): risk reductions of 79% and 80%, reflecting the 77% overall population reduction (0.234) (P<0.0001 for all comparisons above). Comparable results were seen in the non-high-disease activity counterparts.

Another post-hoc analysis of the CLARITY trial showed CT3.5 to significantly increase the proportion of patients with high-disease activity that had NEDA compared with placebo[9]. The same two definitions of high-disease activity were applied here. In both high-disease activity subgroups, the proportion of patients who fulfilled individual NEDA criteria was higher with CT3.5. In the HRA subgroup, 76% of CT3.5-treated patients (n=130) were relapse-free and 84% were T1 Gd+ lesion-free vs 49% and 31%, respectively, for placebo (n=131). In the HRA+TNR subgroup, 77% were relapse-free and 85% were T1 Gd+ lesion-free with CT 3.5 (n=140) vs 50% and 32%, respectively for placebo (n=149). Composite NEDA score: 43.2% and 43.7% of actively treated patients in both subgroups were free of disease activity compared with 8.7% and 9.0% (OR 8.02 and 7.82) respectively, of placebo recipients. In the overall CLARITY population, the composite NEDA score also favoured CT3.5 (n=433) over placebo (n=437): OR 4.46 (P<0.0001 for all comparisions).

Lymphocyte counts

Lymphopenia was the most commonly reported AE in CLARITY, which is consistent with the mechanism of action of cladibrine. However, lymphocyte recovery begins soon after treatment, with the absolute lymphocyte count (ALC), CD19+ B cells and CD4+ T cells reaching threshold values by 7.5 months, 12 months and 18 months, respectively, after the last dose in year 2. CD8+ cells never dropped below the threshold value[10]. This is the conclusion from pooled data from patients randomised to CT3.5 over 2 years in CLARITY or CLARITY Extension, including time spent in the PREMIERE registry (n=685). Median ALC at baseline was 1.86×10^9/L. In year 1, ALC reached nadir at 9 weeks post-treatment with CT3.5 (1.00×10^9/L) and then gradually increased. During year 2, ALC reached nadir at week 55 (0.81×10^9/L), by week 96 recovered to the normal range (≥1.00×10^9/L), and continued to increase thereafter. ALC had returned to the normal range in 75% of patients by week 144. Median CD4+ lymphocytes were 851 cells/μL at baseline. After treatment in year 1, they reached nadir at week 16 (385 cells/μL) and then gradually increased. After treatment in year 2, CD4+ reached nadir at week 60 (292 cells/μL). Values reached the threshold of 350 cells/μL around week 120, continuing to improve thereafter. Median CD8+ lymphocytes were 378 cells/μL at baseline. They reached nadir in the first and second year at week 16

Figure 3 Median absolute lymphocyte counts over time



Visits with sample size ≥30 are displayed

(239 cells/µL) and week 72 (232 cells/µL), respectively. CD8+ recovered quickly after treatment and never dropped below 200 cells/µL. Median CD19+ lymphocytes were 205 cells/µL at baseline. In the first and second year, they reached nadir at week 9 (18 cells/µL) and week 52 (31 cells/µL). CD19+ reached the threshold of 100 cells/µL by week 96 and continued to improve thereafter.

Another study demonstrated the effectiveness of of lymphocyte-based treatment criteria in minimising the incidence of severe, sustained lymphopenia during 4 years of treatment with CT3.5[11]. In a subgroup of patients treated according to guidelines – i.e. Grade 0 lymphopenia before the first course and Grade 0 or 1 before up to 3 subsequent annual courses of CT3.5 – at least 86% of patients recovered to Grade 0 or 1 lymphopenia by the end of each treatment year. Grade 3 was uncommon, and no patient experienced Grade 4 lymphopenia.

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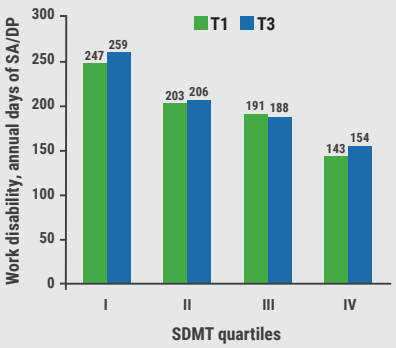
Cognition

Cognition in MS has been treated as a dichotomous variable: patients are either impaired or not. This fails to consider heterogeneity within the group of patients with cognitive impairment, which affects between 40-70% of adults with MS and can have a very considearble impact on quality of life and working status. A group from New York described isolated memory impairment and isolated speed impairment as "cognitive phenotypes". An Italian study showed cognitive reserve to be a key protective factor for subject cognitive and socio-professional outcome.

Cognitive phenotypes

Dr. V.M. Leavitt from New York described cognitive phenotypes in MS and characterised their neural correlates using cognitive measures and structural MRI parameters, respectively[1]. Dr. Leavitt described how 188 MS patients (mean disease duration 8.2 years, 175 RRMS, 13 SPMS) completed cognitive assessments. Latent variables were derived for MEMORY (verbal and visual measures) and SPEED (Symbol Digit Modalities Test, Stroop Test, Trail Making). Cortical thickness maps for 68 discrete neuroanatomic regions were laid out. Approximately 40% of the participants were cognitively impaired. Distinct cognitive phenotypes were represented within this group: 18% had isolated memory impairment; 6% had isolated speed impairment; 15% were impaired in both. Distinct cortical thickness regions were related to SPEED and MEMORY. Across phenotype groups, the cortical thickness pattern predicting MEMORY was differentially expressed (P=0.0064). Dr. Leavitt said recognising different cognitive phenotypes and their distinct neural correlates is essential for the development of targeted cognitive treatments. Cognitive function in MS patients is highly associated with work disability, even after adjusting for other factors, as was confirmed by a Swedish study[2]. Its authors found the Symbol Digit Modalities Test to be a simple and time-effective screening instrument for cognitive impairment, that may serve as a tool to identify MS patients who are at high risk of short- and long-term sickness absence or disability pension.

Figure 4 Predicted marginal means of work disability (SA+DP) among MS patients



Conclusions
Cognitive function is to a high extent associated with MS patients' work disability (sickness absence (SA) + disability pension (DP), even after adjusting for other factors.
Symbol Digit Modalities Test (SDMT) is a simple and time effective screening instrument for cognitive impairment and could be used as a potential tool to identify MS patients who are at high risk of short and long-term SA and DP.

Cognitive reserve

Cognitive reserve (CR) is a key, potentially modifiable, protective factor for subject cognitive and socio-professional outcome, an Italian study demonstrates[3]. Comparing cognitive outcome and socio-professional attainment in adult- and pediatric-onset MS (AOMS and POMS) patients and the relevant demographic and clinical correlates, CR was found to be lower in POMS. Our findings underscore the importance of interventions focusing on intellectual enrichment, particularly in the paediatric MS population, in order to achieve better cognitive, social and professional performances in adulthood.

A group of 111 (adult) POMS and 115 AOMS patients were enrolled in 5 Italian centres. Compared with AOMS, adult POMS subjects were younger (32.0 vs 38.8 years) and had a longer disease duration (16.9 vs 12.1 years). CR tended to be decreased in POMS compared to AOMS (P=0.05). Proportion of cognitive impairment was 36% and 33%, respectively (P=0.64). There was no difference in social and professional attainment between the groups. CI was associated with older age (OR=1.03; P=0.039), higher EDSS (OR=1.42; P=0.001) and lower CR (OR=0.92; P<0.001). Better social and professional attainments were associated with CR (Beta 0.98-1.35, P<0.01), male sex (Beta 7.79, P=0.005) and lower EDSS (Beta 0.40, P<0.001). Another Italian study also concluded that CR seems able to independently predict cognitive performance in RRMS patients[4]. Cortical grey matter volume and CR were predictors of performance on tests assessing verbal and visual memory, attention and information processing speed; thalamic volume and CR were independent predictors of performance on verbal, visual memory and inhibitory control.

Researchers from New York found that CR independently contributes to both cognitive efficiency and memory over and above disease burden in PMS (and in RRMS in an earlier study)[5]. Brain reserve protected against disease-related cognitive inefficiency, but not against memory problems. The authors also conclude lifestyle choices protect against cognitive impairment independently of genetic factors.

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Real-World Head-to-Head Studies

Head-to-head studies were presented of, among others, cladribine vs interferon β-1a, fingolimod and natalizumab; natalizumab vs fingolimod; dimethyl fumarate vs fingolimod and vs glatiramer acetate.

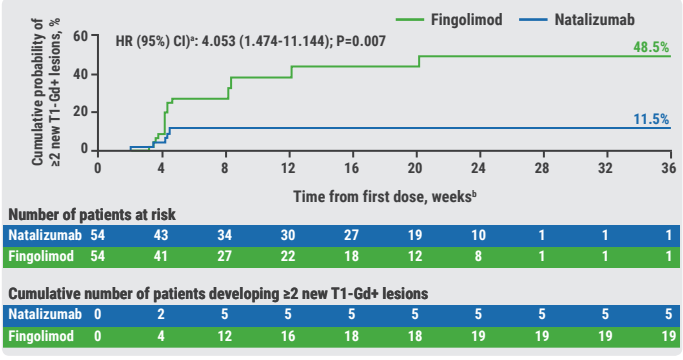
Cladribine vs interferon β-1a, fingolimod, natalizumab

The effect of cladribine on relapses is comparable to fingolimod; its effect on disability accrual is comparable to interferon β-1a and fingolimod. Cladribine could be associated with better recovery from disability than interferon β-1a, fingolimod and natalizumab. These were the main results from a propensity score-matched analysis from MSBase comparing 1-year relapse and disability outcomes of cladribine with interferon β-1a, fingolimod and natalizumab[1]. The cohorts consisted of 37 patients treated with cladribine, 1,940 with interferon β-1a, 1,892 with fingolimod and 1,410 with natalizumab. The probability of remaining relapse-free on cladribine was higher than on interferon β-1a (P=0.05), similar to fingolimod (P=0.31) and lower than on natalizumab (P=0.042). The probability of remaining free from disability accumulation on cladribine was similar to interferon β-1a (P=0.37) and fingolimod (P=0.089), but lower than natalizumab (P=0.021). The probability of disability improvement was higher on cladribine than interferon β-1a (P=0.00017), fingolimod (P=0.0025) or natalizumab (P=0.00099). Sensitivity analyses largely confirmed these results.

Natalizumab vs fingolimod

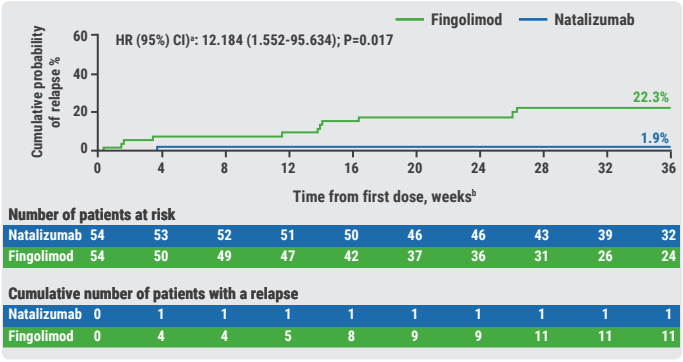
The phase 4 REVEAL study was designed to compare onset of efficacy with natalizumab and fingolimod. Although closed prematurely within 1 year (for non-safety/non-efficacy reasons), the study's results confirm that natalizumab has benefits soon after initiation, demonstrating that onset of reduced disease activity occurred more rapidly, and to a greater extent, with natalizumab than with fingolimod in patients with active RRMS[2]. Available data did not permit primary endpoint evaluation however, so these results should be interpreted with caution. Patients were assigned to open-label intravenous natalizumab 300 mg every 4 weeks (n=54) or oral fingolimod 0.5 mg once daily (n=54). Data permitted comparison of effects occurring shortly after treatment initiation. Patients in the natalizumab group were less likely than those in the fingolimod group to develop new Gd+ lesions. Cumulative probability of developing ≥1 lesion was 40.68% vs 57.99% (HR 1.678; P=0.126) and of developing ≥2 lesions 11.54% vs 48.48% (HR=4.053 P=0.007). The

Figure 5 Cumulative probability of developing ≥2 new T1-Gd+ lesions in natalizumab- and fingolimod-treated patients



[a]Fingolimod vs natalizumab based on a Cox model adjusted for number of T1-Gd+ lesions, age, baseline EDSS score and years since first symptom.
[b]For presentation, the x-axis has been truncated at week 36, as no events were observed after week 36.

Figure 6 Cumulative probability of relapse in natalizumab- and fingolimod-treated patients

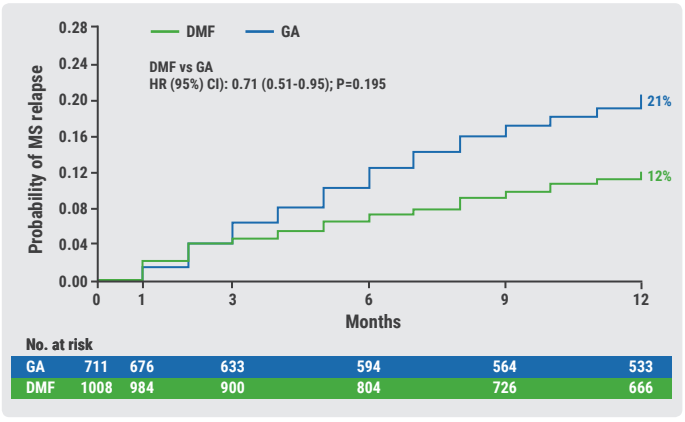


Number of patients at risk										
Natalizumab	54	53	52	51	50	46	46	43	39	32
Fingolimod	54	50	49	47	42	37	36	31	26	24

Cumulative number of patients with a relapse										
Natalizumab	0	1	1	1	1	1	1	1	1	1
Fingolimod	0	4	4	5	8	9	9	11	11	11

[a]Fingolimod vs natalizumab based on a Cox model adjusted for number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom.
[b]For presentation, the x-axis has been truncated at week 36, as no events were observed after week 36.

Figure 7 Proportion of patients relapsed at 1 year after DMF/GA initiation



No. at risk						
GA	711	676	633	594	564	533
DMF	1008	984	900	804	726	666

DMF = delayed-release dimethyl fumarate; GA = glatiramer acetate; HR = hazard ratio; MS = multiple sclerosis. Time to first MS relapse after DMF/GA initation estimated using the Kaplan-Meier product limit method. Kaplan-Meier was obtained as a pooled estimate of propensity score, strata-specific estimate, which was weighted proportionate to the number at risk.

natalizumab group consistently had 63%-72% fewer Gd+ lesions, with between-group differences apparent within 4 weeks and reaching significance by week 16 (P=0.025). The annualised relapse rate was 83% lower with natalizumab than with fingolimod (0.05 vs 0.29; P=0.0236), and cumulative probability of relapse was 1.85% with natalizumab vs 22.28% with fingolimod (HR=12.18; P=0.0174).

DMF vs fingolimod, GA

In the first-ever head-to-head controlled trial comparing delayed-release DiMethyl Fumarate (DMF) with fingolimod in RRMS, no difference across all clinical effectiveness outcomes assessed was found.3 However, patients on fingolimod had a significantly longer time to treatment discontinuation compared to DMF, in both the all-comer and EU fingolimod label patient population (EUF) populations. This was the main finding of a pair-wise propensity-score matched German cohort from the NeuroTransData MS registry. Patients meeting either the EU fingolimod label patient population (EUF) or an all-comer population were assessed for the primary outcome of time to first relapse and secondary outcomes of annualised relapse rate, time to treatment discontinuation and time to 3- and 6-month EDSS confirmed disability progression (TTCDP3, TTCDP6). DMF patients were 1:1 matched to fingolimod all-comers (n=457) and fingolimod EUF (n=99) patients. In the all-comer population, >77% had ≥1 prior DMT, whereas in the EUF population 100% was pre-treated. There was no evidence of difference in time to first relapse between DMF vs fingolimod all-comers (HR 0.91; P=0.532) and fingolimod EUF (HR 1.10; P=0.714). Consistent results were observed for annualised relapse rate, TTCDP3, and TTCDP6. Fingolimod all-comer and fingolimod EUF patients had significantly longer time to treatment discontinuation vs DMF (HR 1.76; P<0.0001) and (HR 3.31; P=0.0002), respectively.

The retropspective, observational EFFECT study compared real-world effectiveness of RRMS patients treated with DMF or with glatiramer acetate (GA). Over 12 months, treatment with DMF was associated with a statistically significant higher proportion of relapse-free patients and a lower annualised relapse rate.4 A total of 816 DMF-treated patients and 1042 GA-treated patients from 17 countries were included in the full analysis set. At 12 months, 117 (14%) of DMF-treated and 211 (20%) of GA-treated patients had discontinued therapy; the primary reason was tolerability for both DMF (9%) and GA (9%) arms. The estimated proportion of DMF-and GA-treated patients that relapsed at 12 months was 11.6% and 20.8% (HR 0.71), representing a significant decrease of 29% (P=0.0195). At 12 months the adjusted annualised relapse rate ratio for DMF was 0.66, representing a significant decrease of 34% (P=0.0033) versus GA.

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Fundamental Research Highlights

For years, research has tried to pin down the possible value of serum neurofilament light (NfL) in the diagnosis of MS and as a marker of disease severity and treatment effect. New highly sensitive tests have accelerated the production of results, which is promising. Future research will reveal if NfL testing may be even more sensitive in measuring treatment effects of e.g. fingolimod, rituximab, and natalizumab, than MRI. Among many more scientific highlights was a session on blood-brain-barriers, which showed that the integrin alpha-8 and EGFL7 are interesting therapeutic targets for future studies.

Diagnostic value of NfL

In clinically suspected MS, Swedish researchers found NfL to have diagnostic value, but not Glial Fibrillary Acidic Protein (GFAP) or BPF. They conclude NfL may therefore be included in the diagnostic work-up of MS[1]. In a prospective study 276 patients with clinical features of suspected MS onset were included and categorised: CIS/early relapsing MS (n=100), relapsing MS with disease duration of 2 years or more (n=80), and non-MS/symptomatic controls (SC; n=96). In addition healthy controls (n=51) and progressive MS (PMS; n=23) were included as control subjects. All MS phenotypes had increased NFL (CIS/early MS 92.3%, MS>2 years 85%, PMS 72.7%) compared to healthy controls and SC. The NFL levels were within the normal range in all healthy controls and SC.Increased GFAP was associated with progressive MS but not with other phenotypes of MS. Lower BPF, indicating increased brain atrophy and degeneration, was associated with longer disease duration. BPF could not distinguish between healthy controls, SP and CIS/early MS however, suggesting that neurodegeneration had not reached a significant magnitude in patients with recent clinical onset of CIS/early MS, or that synthetic MRI was unable to detect brain atrophy of low rate.

NfL as marker for disease and treatment monitoring

Other findings indicated serum NfL is a promising candidate marker for disease and treatment monitoring in MS[2]. Serum NfL was measured at baseline and week 48 in 272 patients from the phase 3 ADVANCE study of PEG-interferon β-1a. In patients with NEDA, NfL levels remained consistently low; in patients with Evident Disease Activity (EDA), NfL levels appeared consistently elevated and more variable, while decreasing on PEG-interferon β-1a treatment. In 40 patients from the placebo group, comprising 20 patients with NEDA (no relapses, no Gd+ and no new T2 lesions over 2 years), and 20 patients with EDA (≥1 relapse, ≥1 Gd+ and/or new T2 lesions at year 1 and year 2) serum NfL was measured every 3 months, using a sensitive single molecule array assay. Serum NfL levels at baseline were significantly associated with number of Gd+ lesions and T2 lesion volume at baseline, number of new T2 lesions at year 2, and percent brain volume change over 2 years ($P<0.0001$ for all comparisons). In patients with elevated baseline NfL (>10 pg/mL), mean NfL levels decreased significantly more in the PEG-interferon β-1a compared vs the placebo group (55% vs 26%, $P<0.05$). Patients with NEDA revealed consistently low and stable NfL levels, similar to those in healthy individuals (mean 7.9 pg/mL). In patients with EDA, serum NfL levels were significantly higher at each time-point (mean 28.9 pg/mL $P<0.0001$) and more variable.

NfL as endpoint for phase 2 studies

"NfL is a very promising endpoint for phase 2 studies that captures both inflammatory and degenerative aspects of MS", said Dr. M.P. Sormani from Genoa, presenting as a late-breaking abstract an analysis of NfL after 6 months with 2-year T2 lesion formation, relapse activity, percent brain volume loss and disability progression in 258 patients enrolled in the FREEDOMS study[3]. This 24-months, placebo-controlled phase 3 trial evaluated the effect and safety of fingolimod 0.5 mg in RRMS. Median blood NfL levels at baseline were similar in the two arms: 28 and 26 pg/mL in the fingolimod and placebogroup, respectively. By month 6, levels were significantly lower in the fingolimod arm: 18 vs 26 pg/mL ($P<0.001$). NfL at 6 months was correlated to measures of disease activity and severity at 24 months: nT2 lesions ($r=0.46$, $P<0.001$), number of relapses ($r=0.25$, $P<0.001$), percent brain volume loss ($r=-0.41$, $P<0.001$) and 6 months confirmed disability progression (HR=1.7, $P=0.02$). The correlations of NfL at 6 months with relapses at 24 months, percent brain volume loss and disability progression are similar to those of active T2 lesions at 6 months. The proportion of treatment effect on relapses at 24

months explained by the effect on NfL at six months and that explained by the effect on nT2 lesions was 30%, respectively. The proportion of treatment effect on percent brain volume loss was clarified by the effect on month-6 NfL which was 58%, and that was explained by nT2 lesions at 6 months was 39%. Dr. Sormani: "The sample size to detect with 90% power a reduction of NfL between treated and placebo arms by 30% or 40% is close to the sample size of phase 2 studies based on MRI lesions. In our analysis it was 64 or 30 per arm, and for comparison of two active arms it was 80 or 40 per arm."

Blood-brain barrier

At ECTRIMS 2017, an entire session was dedicated to the blood-brain barriers (BBB) in MS. Results from one of the presentations suggest that the integrin alpha8 may be an effective therapeutic target to prevent disease activity and progression in MS[4].

Widespread expression of alpha4beta1 across leucocyte subsets causes natalizumab treatment to be associated with impaired immune surveillance and susceptibility to severe viral infections. The goal of this analysis, therefore, was to identify novel beta1 integrin partners involved in the specific migration of pathogenic T lymphocytes across the CNS vasculature. Proinflammatory TH17 cells were found to express integrin alpha8, which heterodimerises exclusively with integrin beta1. Alpha8 was specifically expressed by activated CD4+ and CD8+ T lymphocytes and upregulated in pro-inflammatory conditions in healthy controls and MS patients. Alpha8+ T-cell infiltrates were found in the brains of MS patients and animal models of experimental autoimmune encephalomyelitis (EAE). Furthermore, both BBB and blood-meningeal barrier endothelial cells expressed the main ligand of alpha8, nephronectin. Blockade of the alpha8 binding site decreases TH1 and TH17, but not TH2 cell migration across a monolayer of BBB-endothelial cells in vitro. Injections of alpha8 blocking peptide ameliorated clinical severity and limited proinflammatory T lymphocyte infiltration into the CNS in MOG35-55 actively induced EAE mice.

During the same session, a possible beneficial role of EGFL7 in neuroinflammation was revealed[5]. EGFL7 can limit CNS infiltration of pro-inflammatory leukocytes by promoting BBB integrity, decreasing MCAM expression and tethering activated CD4 T lymphocytes to the extracellular matrix. The authors think it may therefore represent a new therapeutic principle in MS.

Other findings identify for the first time a second, inducible barrier to CNS entry at the astrocytic glia limitans[6]. It is composed of reactive astrocyte TJ proteins consisting of CLDN-1, CLDN-4 and JAM-A subunits. In a human co-culture model, CLDN-4-deficient astrocytes were unable to control lymphocyte segregation. In models of CNS inflammation and MS, mice with astrocytic CLDN-4 deletion displayed exacerbated leukocyte and humoral infiltration, neuropathology, disability and mortality. The authors assume this second barrier may be therapeutically targetable in inflammatory CNS disease.

Observations from a French study indicate, for the first time, that endothelial cells acting as semi-professional antigen-presenting cells could also be involved in infectious or inflammatory CNS diseases[7].

MOG-antibodies

Presented as a late-breaking abstract, German research showed the pathological potential of human antibodies against myelin oligodendrocyte glycoprotein (MOG-Abs)[8]. These occur in a proportion of patients with inflammatory demyelinating diseases of the CNS. Dr. E. Meinl from Martinsried in Germany explained his team had achieved affinity-purification of Abs from blood that recognise conformationally intact MOG and showed their pathogenic activity in transfer experiments in two animal models. They selected two patients with a high reactivity to MOG and cross-reactivity to rodent MOG; both had recurrent optic neuritis. The team managed to affinity-purify a proportion of their MOG-Abs. These were pathogenic upon intrathecal injection in two different EAE models in the Lewis rat. The Abs enhanced T-cell infiltration and induced microglial activation in the subpial parenchyma; they also induced demyelination associated with deposition of the terminal complement complex C9neo, resembling an MS type II pathology.

In a second approach, recombinant Abs from single-cell sorted MOG-binding B cells were obtained from one of the two patients. To affinity purified Abs, MOG was bound with low affinity only by ELISA, but not in a cell-based assay and not in tissue sections. Dr. Meinl concluded that Abs affinity-purified from the blood of patients with inflammatory demyelinating disease induce pathological changes in vivo upon co-transfer with myelin-reactive T cells, suggesting that these Abs are similarly pathogenic in patients.

Highlights in short

- For the first time the role of IgA in mucosal and systemic immunity in MS was analysed. The results reveal MS-associated changes in immunorecognition of gut bacteria by IgA both in the intestinal lumen

and systemically, which suggests a potential mechanism for gut microbiota-dependent regulation of humoral autoimmunity[9].

- A link between adaptive immunity and remyelination has been established. MS patient lymphocytes exhibit intrinsic capacities to coordinate myelin repair. The genetic profile of patients can predict their remyelination efficacy[10].
- Kir4.1 function contributes to early oligodendrocyte development, but it has a major role in maintaining myelin and axon integrity during aging. It seems that KIR4.1 downregulation in MS is maladaptive[11].
- A Canadian cuprizone model of EAE provides a proof-of-concept showing that primary endogenous myelin changes can secondarily elicit inflammatory demyelination in an immune-primed host. It also identifies protein-arginine deiminase as a potential mechanism through which inside-out inflammation occurs[12].
- The axon initial segment has been identified as a novel site of neuronal dysfunction in MS. Axon initial segment alterations may contribute to MS pathophysiology and open up new therapeutic avenues[13].

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Miscellaneous

The existence and definition of 'benign MS' are often debated; a study with a 30-year follow-up confirms that it does exist and is not all that uncommon. PMS patients with higher depression scores at the start of intensive motor neurorehabilitation treatment show a better improvement in fatigue, depression and a trend for motor and physical scales. Furthermore, there is a risk of vaccination-associated relapses among patients with neuromyelitis optica spectrum disorder (NMOSD), but only if they are untreated.

Does benign MS exist?

It is not uncommon for people with relapse-onset MS to have only mild or no physical or cognitive dysfunction approximately three decades after clinical onset[1]. In a 30-year follow-up of a CIS onset UK cohort, 31 out of 80 participants are known to have MS, and had no or mild physical disability, of these subjects, only 1 out of 20 who were tested had cognitive impairment. The original cohort consisted of 132 people. At 30-year follow-up, 29 had deceased (19 of whom had MS). Of the remaining 103, clinical outcome data was obtained from 91. It was found that 30 remained CIS, 35 had RRMS, and 26 had SPMS. Only 11 had received a DMT at some time. Of the 35 RRMS patients, 31 (88%) had an EDSS score ≤3.0. All of these 31 patients remained in employment, or had retired at the national state pension age. Z-scores from the Brief International Cognitive Assessment for Multiple Sclerosis were available in 20 of the 31 individuals, with only one subject scoring lower than -1.5.

Swedish researchers assessed the difference between benign MS and non-benign MS patients in long-term progression of physical disability and decline of cognitive function[2]. They defined benign MS as an EDSS score of ≤3.0 fifteen years or more after disease onset. They found that the difference in physical disability between benign MS and non-benign MS patients is already shaped early in the disease

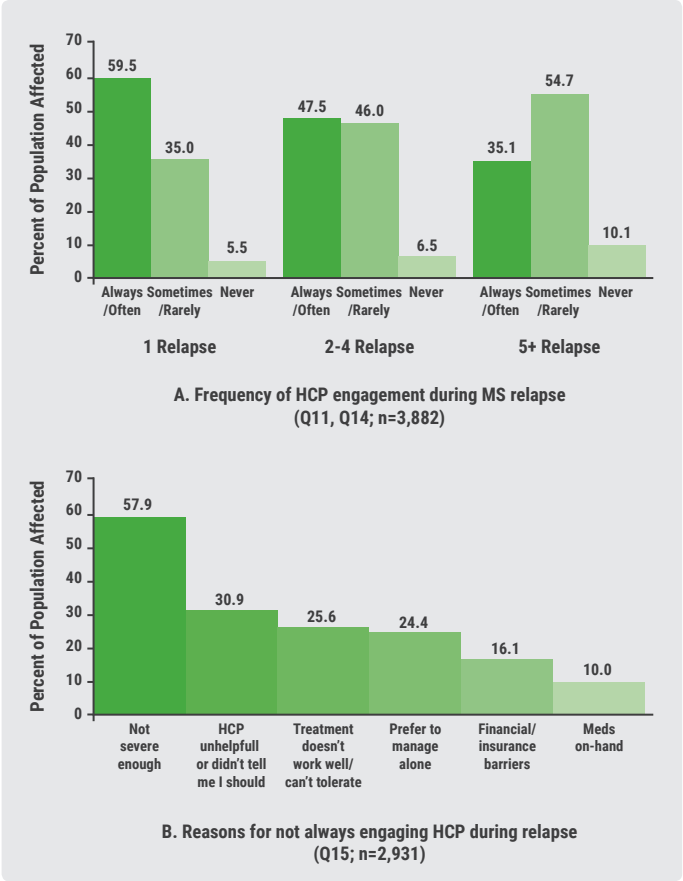
course, as the rate of progression between these two groups was similar after 15 years of disease duration. Benign MS patients showed a significantly better cognitive performance than non-benign MS patients and the overall cognitive decline rate was much lower. At baseline, at 15 years of disease duration, BMS patients were more often female (75% vs. 69%), had a younger onset age (28.4 vs. 33.7 years) and were less likely to have been exposed to first- and second-line DMTs (53% vs 65% and 14% vs 42%, respectively) during the first 15 years of MS (P<0.001 for all comparisons). From year 15 to the latest clinical examination, mean EDSS score of non-BMS patients (n=4724) was 3.76 higher than that of BMS patients, but the rate of clinical progression was similar. The single digit modalities test score of non-BMS patients was a mean 8.9 points lower than of BMS patients, showing a decline of -0.7 single digit modalities test points per year.

Patients not reporting relapses

Over half of MS patients do not always report their relapses to healthcare providers (HCPs) according to results of an online survey in which 5,311 American MS patients participated. When patient do engage with their HCPs, many report untimely or no follow-up at all[3].

During a relapse, 46.9% said they often or always engage their HCPs. The main reasons for not always doing so were 'that relapses were not always severe enough to warrant it', and 'I prefer to manage my relapses on my own'. Patients who engage their HCPs during a relapse said relapse-related symptoms/severity, prescription medications/treatments, and treatment effectiveness (resolution) are most discussed. Frequency of HCP engagement during a relapse was positively related to breadth of topics discussed (relapse-related, MS-related) and negatively related to number of relapses. 35.0% of patients reported HCP follow-up within 1 month of communication of relapse, 50.3% said at a next office visit, and 14.7% said there usually is no follow-up. Given a positive relationship with breadth of discussion and a negative relationship with relapse frequency, the authors concluded, HCP-patient engagement during and after relapse to ensure appropriate resolution and treatment should be prioritised.

Figure 8 HCP engagement during MS relapse



A. Frequency of HCP engagement during MS relapse.
B. Reasons for not always engaging HCP during relapse.

Neurorehabilitation improves fatigue, depression

Italian researchers explored the effect of pre-existing depressive symptoms on the outcome of intensive motor neurorehabilitation treatment in PMS. They found a better improvement in fatigue and depression and a trend for motor and physical scales in patients with higher depression scores at the start of such a treatment program[4]. The authors consider these data consistent with the view that underlying depression may confound motor and fatigue measures and underline importance to address psychological factors that enhance the positive outcome of rehabilitation on treatment and its maintenance. Recruited were 40 consecutive PMS patients (median EDSS 5.85) participating in a randomised trial on repetitive transcranial magnetic stimulation coupled with neurorehabilitation. The results showed patients with mild/severe depression at baseline (beck depression inventory >14, n=11, 28%) significantly improved in fatigue (delta fatigue severity scale 1.48 vs 0.16; P=0.036) and depression (delta beck depression inventory 9.4 vs 1.7; P=0.025). They also had a tendency to improve at T3 in the 6 minutes walking test (55.3 vs 19 mt; P=0.06), and MS walking scale (35.2 vs 9.6; P=0.054).

Vaccination and NMOSD

There is a risk of vaccination-associated relapses among untreated patients with NMOSD; immunosuppressive therapy

at time of vaccine halts this risk[5]. These conclusions were based upon results of a multi-centre retrospective analysis of 90 patients, who received 211 vaccinations in total and experienced 340 relapses over a median disease course of 6.6 years. The researchers identified 7 NMOSD patients who relapsed within 30 days of a vaccination, 6 between 31-60 days, and 4 between 61-90 days. Only among patients who were not on preventive immunotherapy was the rate of vaccine-associated relapses within 30, 60, and 90 days significantly higher than the likelihood of a relapse spontaneously occurring within each of the given time frames (P<0.011, 0.003, 0.009, respectively). Among NMOSD patients who were on immunotherapy to prevent relapses, there was no significant risk of relapse associated with vaccines. Additionally, among patients on immunotherapy, the annualised relapse rate of those who received routine vaccinations was significantly lower than in unvaccinated patients.

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