The Importance of Early Intervention in Multiple Sclerosis

This symposium intended for healthcare professionals took place on 18th and 19th September 2024, as part of the 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) held in Copenhagen, Denmark.

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Meeting Summary

A satellite symposium titled 'Transforming MS Care: Early Intervention and Sustained Safety' held at the 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) discussed current challenges and future advances in the management of multiple sclerosis (MS). The symposium discussed the importance of early intervention with disease-modifying therapy (DMT) in people with MS. The session explored the effects of DMT switching in patients with MS, and discussed data on the persistence, patient satisfaction, and long-term safety associated with DMTs. The DAYBREAK OLE trial investigating once-daily ozanimod showed that early treatment with high-efficacy DMT is essential to improve disability outcomes, preserve cognition, and delay MS disease progression.

Transforming Multiple Sclerosis Care: Early Intervention and Sustained Safety

Multiple Sclerosis as a Disease Spectrum: Understanding the Need for Early Intervention

A number of concurrent mechanisms drive tissue injury and disease progression in people with MS. Hersh, Cleveland Clinic Lou Ruvo Center for Brain Health, Nevada, USA, opened the first session by outlining that these include axonal degeneration, chronic parenchymal and interstitial inflammation, neuronal degeneration, oxidative stress, white matter cortical demyelination, acute white matter inflammation, and failure of remyelination.[1] This combination of pathological mechanisms, including inflammation and neurodegeneration, result in tissue injury and clinical disease progression (i.e., the accumulation of irreversible clinical disability), which can vary between individuals. Differences in these underlying biological mechanisms may explain the heterogeneity in disease presentation and progression between people with MS. Consequently, people with MS may have similar clinical presentations but with different underlying pathologies owing to a unique mix of genetic, biological, and environmental factors.

Hersh outlined the topographical model of MS, which illustrates how an admixture of inflammation and neurodegeneration drives the disease course.[1] According to this model, functional neurological reserve is influenced by factors such as the effective use of DMTs, the presence of comorbidities (e.g., hypertension, hyperlipidaemia, and Type 2 diabetes), and lifestyle choices (e.g., tobacco smoking) that can further drive ongoing neurodegeneration as patients age.[1]

Early use of high-efficacy DMTs may disrupt the underlying heterogeneous pathophysiological processes that contribute to disability progression in MS, including inflammatory activity (clinical relapse, new lesion formation) and disease progression (accumulation of irreversible clinical disability and neurodegeneration).[2] Hersh concluded by stating that, "time is brain".

The Power of Early Intervention in Multiple Sclerosis: New Perspectives

Why Does Early, Effective Treatment Matter?

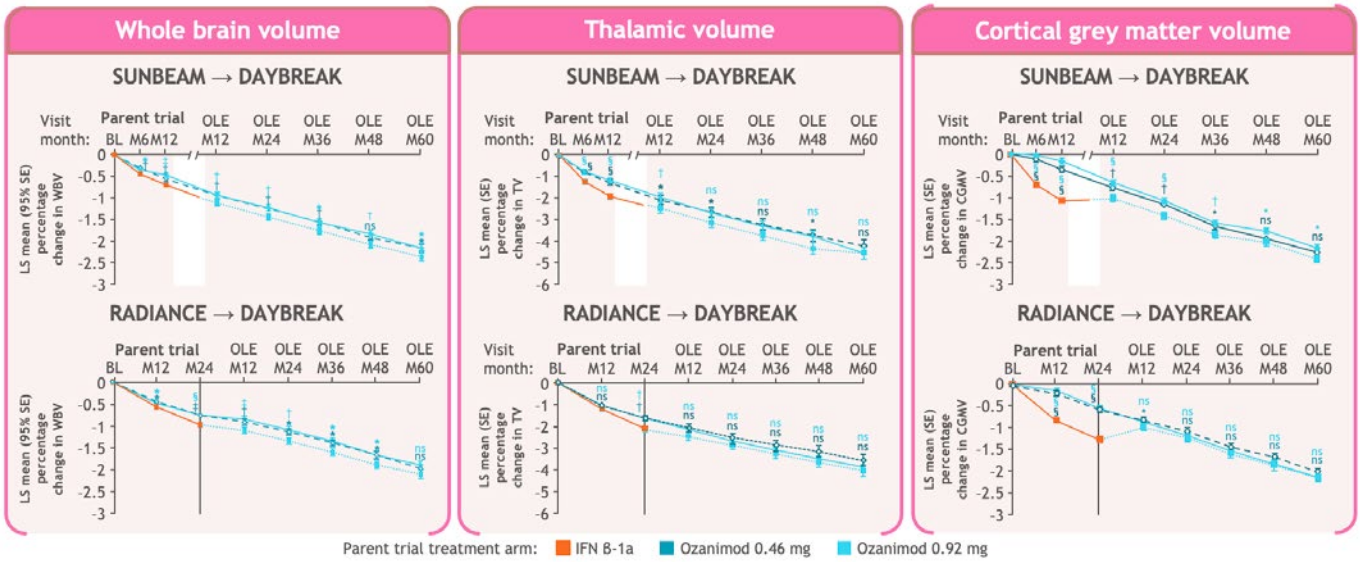
Havrdová, Charles University, Prague, Czechia, highlighted that cognitive impairment, thought to be caused by inflammation in the CNS, may be present in people with MS from early in the disease course and independent of physical disability.[3] Indeed, brain volume loss is greatest in the first 5 years after MS onset.[4] Cognitive impairment in people with MS correlates with measurements of brain atrophy, which is caused by inflammation.

It was revealed in studies over a decade ago that early treatment with interferon (IFN) β-1b delayed disease progression and improved cognitive outcomes in patients with clinically isolated syndrome.[5,6] More recently, in an Italian MS registry study (n=2,702), early intensive treatment with a high-efficacy DMT (fingolimod, natalizumab, mitoxantrone, alemtuzumab, ocrelizumab, or cladribine) was shown to improve disability outcomes measured by Expanded Disability Status Scale (EDSS) scores compared with an escalation approach, in which patients received either glatiramer acetate, IFNs, azathioprine, teriflunomide, or dimethyl fumarate (DMF) for 1 year before escalation to a high-efficacy DMT.[7]

Latest results From DAYBREAK OLE: Impact of Early Treatment on Brain Atrophy

Evidence for the benefits of early treatment with high-efficacy DMT is also available from clinical trials. Havrdová presented results from DAYBREAK OLE, which was open to participants who completed any of the parent trials for ozanimod. The two Phase III registrational trials for ozanimod, SUNBEAM and RADIANCE, investigated once-daily oral ozanimod 0.46 mg or 0.92

Figure 1: Brain atrophy measurements up to Month 60 in the DAYBREAK OLE trial.[9]



*P<0.05
†P<0.01
‡P<0.001
§P<0.0001

BL: baseline; CMGV: cortical grey matter volume; IFN: interferon; LS: least squares; M: Month; MS: multiple sclerosis; NS: not significant; OLE: open-label extension; RMS: relapsing multiple sclerosis; SE: standard error; TV: thalamic volume; WBV: whole brain volume.

mg versus once-weekly IFN β-1a 30 µg for a period of either 12 months (SUNBEAM) or 24 months (RADIANCE). In DAYBREAK OLE, participants received once-daily oral ozanimod 0.92 mg.[8]

As Havrdová explained, outcomes at Month 60 of DAYBREAK OLE were evaluated according to whether participants were treatment (DMT)-naïve or treatment-experienced at parent trial baseline. Outcomes for participants who were DMT treatment-experienced at parent trial baseline were consistently improved versus those who were DMT treatment-naïve, highlighting the importance of early DMT treatment in people with MS. These improvements were observed in annualised relapse rate and MRI observations, which included the number of new/enlarging T2 lesions.[8]

In a separate analysis, evaluation of brain atrophy assessed whole brain volume, thalamic volume and cortical grey matter volume at DAYBREAK OLE Month 60 according to treatment allocation in the parent trial (Figure 1).[9] Switching from IFN β-1a to ozanimod at DAYBREAK OLE baseline consistently reduced rates of whole brain volume loss and thalamic volume loss by Month 60. Furthermore, participants continuously treated with ozanimod (in both parent trial and DAYBREAK OLE) had reduced whole brain volume loss compared with those switching from IFN β-1a, with the least amount of brain volume loss in the continuous ozanimod 0.92 mg group. In addition, loss of cortical grey matter volume (which Havrdová stated is connected to cognition) rapidly stabilised when participants switched from IFN β-1a to ozanimod treatment.

LS mean percentage change from parent-trial baseline and the between-treatment differences were estimated using mixed model for repeated measures. Model included percentage change from parent-trial baseline in brain volume as the dependent variable; stratification factors (region [Eastern Europe versus rest of world], baseline Expanded Disability Status Scale score category [≤3.5 versus >3.5]), age at parent-trial baseline, treatment, time point, and the interaction between treatment and time point as fixed effects; parent-trial baseline volume; age at parent-trial baseline, and treatment duration in parent trial for OLE time points as continuous covariates; and subject as a random effect. For OLE visits, treatment duration in parent trial was added as a fixed effect in addition to the effects stated above.

In a separate analysis, cognitive processing speed up to Month 72 of DAYBREAK OLE was improved or preserved over time with continuous ozanimod treatment.[10] Havrdová concluded that the results from DAYBREAK OLE show that "IFN treatment does not appear to protect the brain, even in people with MS that is considered to be benign".

Staying the Course in Multiple Sclerosis: Long-term Safety of Disease-Modifying Therapies

The Effects of Disease-Modifying Therapy Switching

As MS is a heterogenous disease, treatment interruption, switching and discontinuation are familiar challenges encountered in clinical practice. Stürner, Christian-Albrecht University of Kiel, Germany, stated: "Although patients may feel that switching treatments means there has been a treatment failure, switching is normal." The most frequently cited reasons for treatment switch or discontinuation in people with MS are lack of efficacy, intolerance, and occurrence of adverse events.[11] However, although many patients with MS discontinue or switch DMTs, treatment switching leads to increased risk of disability accumulation, and is associated with a risk of relapse or rebound.[12] Consequently, Stürner emphasised the need to have a treatment plan in place for each patient.

When establishing a treatment plan, it is important to consider individual treatment attributes. A retrospective analysis of the US IQVIA database from 2019–2022,

evaluated real-world rates of treatment switch or discontinuation in people with MS (n=3,278; Figure 2).[13] In this analysis, the risk of treatment switch or discontinuation was approximately 50% lower with ozanimod than with teriflunomide and more than two times lower with ozanimod versus DMF or diroximel fumarate (DRF).[13]

Evidence from MS and other therapy areas suggests that patients have higher adherence to treatments with a once-a-day dosing regimen (e.g. teriflunomide and fingolimod) versus a twice-a-day dosing regimen (e.g. DMF and DRF).[14] Stürner stated that once daily dosing is a potential advantage that should be communicated to the patient when treatment options are being discussed.

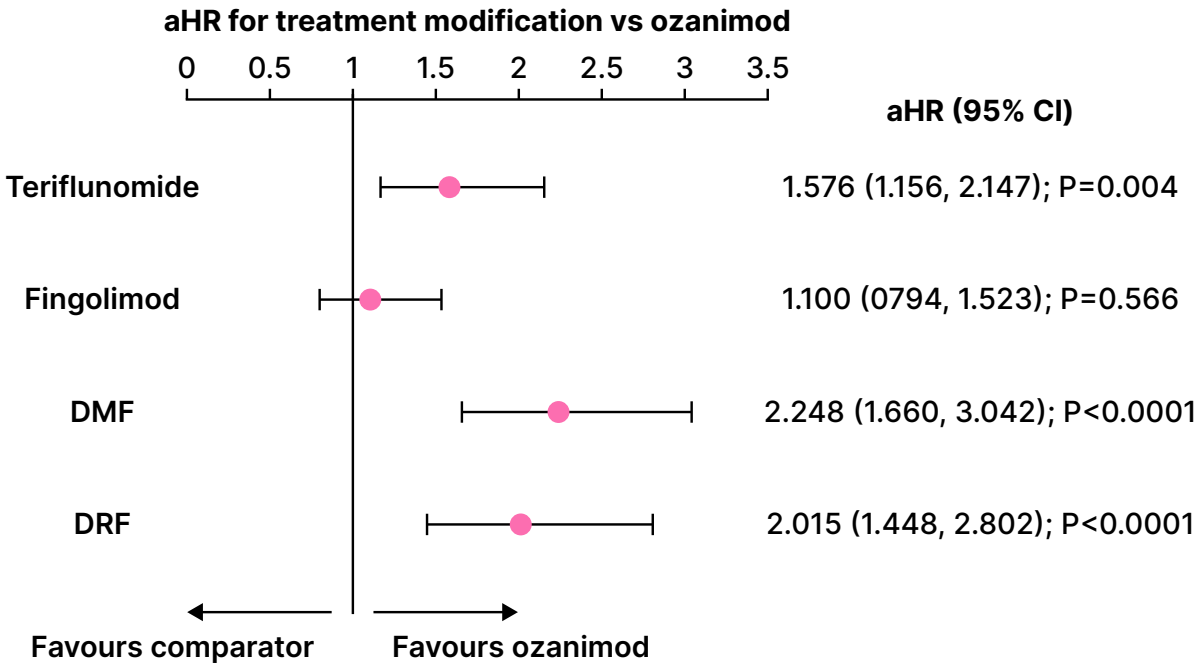
The Long-Term Safety of Disease-Modifying Therapies

Benefit-risk profiles vary between MS DMTs and should be discussed with patients. Stürner explained that safety concerns vary across MS DMTs, and can include infections, cardiac abnormalities, hepatic abnormalities, gastrointestinal symptoms, and malignancies (e.g., lymphoma, melanoma, carcinoma).[15]

Stürner presented long-term safety outcomes with ozanimod from DAYBREAK OLE.[16] At Month 60, the incidence rates of overall treatment-emergent adverse events (TEAE) and serious TEAEs in the continuous ozanimod 0.92 mg group (n=881) decreased or remained stable over time compared with the parent trials (i.e., SUNBEAM or RADIANCE; Figure 3).[16]

Stürner stated that there was no evidence of rebound (as characterised by severe exacerbation of disease or severe persistent increase in disability) following ozanimod discontinuation in DAYBREAK OLE. In total, 55/1,679 participants (3.3%) had known post-discontinuation return of disease activity characterised by MS relapse. Out of the 55 patients who discontinued the

Figure 2: Rates of treatment switch or discontinuation for disease-modifying therapies versus ozanimod in the US IQVIA real-world database (2019–2022; n=3,278).[13]



aHR: IPTW-adjusted hazard ratio; DMF: dimethyl fumarate; DRF: diroximel fumarate; IPTW: inverse probability treatment weighting; RWE: real-world evidence.

Figure 3: Incidence rates of overall and serious treatment-emergent adverse events in the DAYBREAK OLE trial up to Month 60.[16]

BL: baseline; IR: incidence rate; M: month; NA: not applicable; OLE: open-label extension; PY: patient-years; TEAEs: treatment-emergent adverse events.

majority of relapses were mild (36.4%) or moderate (61.8%) rather than severe (1.8%) relapses.[17] No participants who relapsed following discontinuation of ozanimod had a persistent severe increase in disability, with 76.4% of patients completely recovered and 20.0% partially recovered at last follow-up.

Panel Discussion

In a stimulating panel discussion, the faculty agreed that it is essential to build a good relationship with the patient from the earliest consultations. The patient should be provided with reliable sources of information on different treatment options and encouraged to take an active part in treatment decisions, as they will need to commit fully to their treatment to gain the greatest benefit. Moreover, it is now apparent that early, high efficacy DMT can lead to robust control of the microinflammatory stages of disease and lead to improved outcomes versus delayed treatment. The faculty agreed that lifestyle factors and brain health are also key factors to discuss with patients to help them achieve the best outcomes that they can from the onset of MS.

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