Multiple Sclerosis Research Review™

Making Education Easy

Issue 9 - 2016

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Abbreviations used in this issue:

AE = adverse event; **ARR** = annualised relapse rate; **CIS** = clinically isolated syndrome; **DMTs** = disease-modifying therapies; **EAE** = experimental autoimmune encephalomyelitis; **EDSS** = Expanded Disability Status Scale; **GA** = glatiramer acetate; **HRQoL** = health-related quality of life; **ICV** = intracranial volume; **IFN** = interferon; **IHD** = ischaemic heart disease; **MLBG** = maximal lifetime brain growth; **MS** = multiple sclerosis; **OCT** = optical coherence tomography; **pRNFL** = peripapillary retinal nerve fibre layer; **QoL** = quality of life; **RRMS** = relapsing-remitting multiple sclerosis.

Welcome to the ninth issue of Multiple Sclerosis Research Review

The extension of the pivotal TEMSO trial assessed safety and efficacy in patients receiving teriflunomide for up to 9 years. The team reported safety observations were consistent with the core trial, with the annualised relapse rate remaining low and no new or unexpected adverse events. Results from the extension of the randomised TRANSFORMS study support a continued effect of long-term fingolimod therapy in maintaining a low rate of disease activity. Another study investigating the effects of comorbidities on disease-modifying therapies use in MS found as the total number of comorbidities increased, the likelihood of initiating a disease-modifying therapies decreased.

Other interesting findings reported in this issue include: high consumption of coffee decreased MS risk; vitamin D deficiency during early pregnancy was associated with an increased risk of MS; and larger maximal lifetime brain growth is linked to less physical disability progression in MS.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

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Minocycline added to subcutaneous interferon β-1a in multiple sclerosis: Randomized RECYCLINE study

Authors: Sørensen PS, et al

Summary: This double-blind, randomised, placebo-controlled multicentre study randomised relapsing-remitting multiple sclerosis (RRMS) patients to minocycline 100 mg twice daily (n=149) or placebo (n=155), added to subcutaneous interferon (IFN) β-1a, for 96 weeks. The team concluded the time to first qualifying relapse did not differ significantly for minocycline versus placebo. They also noted more patients discontinued because of adverse events with minocycline versus placebo.

Comment: Improving disease control by combining disease-modifying treatments with different mechanisms of action has been disappointing. Minocycline delays the conversion to multiple sclerosis (MS), as shown previously in a clinically isolated syndrome (CIS) cohort, and, in another study, a combination of minocycline and glatiramer acetate (GA) showed strong trends towards improved outcomes. In this study, the addition of minocycline to IFN β-1a had no significant effect on any clinical or MRI outcomes when compared to IFN β-1a alone. The study was limited by a large proportion of patients withdrawing before reaching the primary end-point in both groups. Both minocycline and IFN β-1a has an effect on impairing the trafficking of inflammatory cells across the blood–brain barrier into the central nervous system through inhibiting production of matrix metalloproteinases and, in this study, the similarity in mechanism of action appears not to have a synergistic effect.

Reference: Eur J Neurol 2016 May;23(5):861-70
Abstract

Brain reserve against physical disability progression over 5 years in multiple sclerosis

Authors: Sumowski JF, et al

Summary: This prospective study examined whether larger maximal lifetime brain growth (MLBG) is linked to less physical disability progression over 5 years in a cohort of 52 treatment- naïve MS patients. Physical disability was measured with the Expanded Disability Status Scale (EDSS) at baseline and 5-year follow-up, and MRI measured disease burden and MLBG. The group reported larger MLBG predicted lower risk for progression, independently of disease burden. They also observed that patients with smaller MLBG showed worse EDSS change than patients with larger MLBG.

Comment: The brain reserve hypothesis links larger MLBG, (estimated with intracranial volume [ICV]) with lower risk for cognitive decline/dementia. Larger MLBG is related to larger neuronal counts (and synaptic count) that may be more resistant to disease-related disruption. In this unique study treatment naïve MS patients were followed for 5 years. Patients with a smaller MLBG were more likely to show physical disease progression with the mean increase in EDSS almost = 1 in this group. Identifying patients with smaller MLBG at disease onset may allow targeted therapy. Larger studies are needed to replicate these findings.

Reference: Neurology 2016 May 24;86(21):2006-9
Abstract

Health-related quality of life in multiple sclerosis: Direct and indirect effects of comorbidity

Authors: Berrigan LI, et al

Summary: Adults with MS (n=949) were recruited from 4 Canadian MS clinics. Health-related quality of life (HRQoL) was assessed using the patient-reported Health Utilities Index Mark 3. EDSS scores, physical comorbidity, depression, anxiety, and fatigue were also evaluated as predictors of HRQoL. The researcher concluded all predictors were significantly associated with HRQoL and together accounted for a large proportion of variance (63%). Overall, disability status most strongly affected HRQoL (β = -0.52), closely followed by depressive symptoms (β = -0.50).

Comment: Quality of life (QoI) studies in MS have been conflicting and associations between QoI and physical disability in particular have been unclear. This meticulous study from several Canadian centres addresses an important knowledge gap in MS. The authors found that neurologic disability, symptoms of depression and anxiety, fatigue, and physical comorbidity were all associated with HRQoL and, together, accounted for a large proportion of variance in HRQoL. Improving HRQoI in MS patients can be achieved by initiating treatments that reduce neurologic disability but addressing the symptoms of MS and comorbidities are essential. This included strategies to improve depression, anxiety, fatigue, and other physical comorbidities.

Reference: Neurology 2016 Apr 12;86(15):1417-1424
Abstract

Examining the effects of comorbidities on disease-modifying therapy use in multiple sclerosis

Authors: Zhang T, et al

Summary: This retrospective observational analysis utilised Canadian population-based health databases to assess the effects of comorbidity on initiation of injectable disease-modifying therapies (DMTs) in MS. Of the 10,698 persons with incident MS identified, half had ≥1 comorbidities. The study found as the total number of comorbidities increased, the likelihood of initiating a DMT decreased. Comorbid anxiety and ischaemic heart disease (IHD) were associated with reduced initiation of a DMT. However, patients with depression were 13% more likely to initiate a DMT compared to those without depression.

Comment: As with any chronic disease, comorbidities are common in MS and can adversely affect outcomes. The authors' finding that a greater number of comorbidities results in a lower likelihood of a DMT being started is consistent with the trends seen in hypertension and cancer for example. When examining individual comorbidities, IHD and anxiety were associated with the greatest likelihood of DMT not being initiated. It is likely that multiple comorbidities can be barriers that may influence access to, and decisions regarding treatment. Alternatively, delays may reflect diagnostic issues. Mental comorbidities such as anxiety is important to recognise when considering DMT initiation in MS. Anxiety can complicate communication between patients and clinicians and amplify concerns regarding drug treatment especially fear of adverse effects. All efforts should be made to treat MS early and effectively and developing strategies to manage treatment initiation barriers are important.

Reference: Neurology 2016 Apr 5;86(14):1287-95
Abstract

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Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study

Authors: O'Connor P, et al

Summary: This extension of the pivotal phase 3 Teriflunomide Multiple Sclerosis Oral (TEMSO) trial included a total of 742 patients. The teriflunomide-treated patients continued the original dose; those previously receiving placebo were randomised 1:1 to teriflunomide 14 mg or 7 mg. The team reported safety observations were consistent with the core trial, with no new or unexpected adverse events (AE) in patients receiving teriflunomide for up to 9 years. Disease activity decreased in patients switching from placebo and remained low in patients continuing on teriflunomide.

Comment: There are several reassuring aspects to the publication of the 7-year extension data from the TEMSO trial. Firstly, efficacy continues with the annualised relapse rate (ARR) remaining low throughout the study and very few confirmed EDSS progression events noted. AEs were similar to that described in the core TEMSO study and occurred early. No malignancies were observed due to teriflunomide exposure. Peripheral neuropathy was confirmed for 8 patients receiving teriflunomide 14 mg and 5 patients receiving 7 mg. Of these, 3 resolved with sequelae and 4 without. Three patients discontinued owing to peripheral neuropathy (of these, 2 were classed as polyneuropathy). The only opportunistic infection documented was oral herpes (5-7%). Hypertension was reported in 6.3 to 10.8% but not deemed serious. As with any longterm extension study, there is no placebo group, and outcomes may be biased by retaining only patients who are responding well to treatment.

Reference: Neurology 2016 Mar 8;86(10):920-30
Abstract

High consumption of coffee is associated with decreased multiple sclerosis risk; results from two independent studies

Authors: Hedström AK, et al

Summary: This retrospective study assessed data collected from two population-representative case-control studies; a Swedish study comprising 1620 cases and 2788 controls, and a US study comprising 1159 cases and 1172 control. Compared with those who consumed no coffee, the risk of MS was substantially reduced among those with a consumption exceeding 900 mL daily (OR 0.70 (95% CI 0.49 to 0.99) in the Swedish study, and OR 0.69 (95% CI 0.50 to 0.96) in the US study.

Comment: Caffeine has been shown to have neuroprotective effects in experimental autoimmune encephalomyelitis (EAE) models by upregulating adenosine 1A receptors. Here, in a case-control study using retrospective data of coffee consumption, two large populations have been analysed with regards to the risk of MS. Controlled logistic regression analyses showed a reduction in the risk of developing MS of 30 and 31% if >900ml of coffee were consumed per day compared to those who drank no coffee. The results are interesting and support the neurobiological effect of caffeine. However, recall bias is a weakness of the study design and it should be noted that a large number of controls did not complete all questions. It was also assumed that patients' coffee consumption remained consistent throughout. Further studies are needed and it would be premature to advise patients at risk to consume large amounts of coffee!

Reference: J Neurol Neurosurg Psychiatry 2016 May;87(5): 454-60
Abstract

Long-term (up to 4.5 years) treatment with fingolimod in multiple sclerosis: Results from the extension of the randomised TRANSFORMS study

Authors: Cohen JA, et al

Summary: The TRANSFORMS trial was a 12-month, phase 3, double-blind, randomised study that demonstrated significant benefits of fingolimod 0.5 or 1.25 mg over IFNβ-1a in RRMS patients. This paper reports the results of long-term (up to 4.5 years) extension of the study. Patients randomised to fingolimod in the core phase continued the same dose in the extension, whereas those on IFNβ-1a were re-randomised (1:1) to fingolimod (IFN: 0.5/1.25 mg). Of the 1027 patients who entered the extension, 772 completed the study. The team reported ARR in patients on continuous-fingolimod 0.5 mg was significantly lower than in the IFN-switch group. They also noted after switching to fingolimod, patients initially treated with IFN had a 50% reduction in ARR, reduced MRI activity and a lower rate of brain volume loss.

Comment: Owing to the low patient numbers in the IFN to fingolimod switch groups (IFN-switch 0.5 and 1.25 mg), the authors only present pooled data for both the fingolimod doses (IFN-switch group) for efficacy outcomes. To avoid further bias when interpreting AEs, these are only presented for the continuous fingolimod 0.5 mg and IFN-switch 0.5 mg groups. Side-effects were similar to that seen in the core TRANSFORMS study with nasopharyngitis, lymphopaenia and headache the most common. The most common serious AEs in both groups were basal cell carcinoma (2%) and MS relapse. Herpes viral infections were reported in 36 (10.1%) patients in the continuous-fingolimod group and 25 (15%) patients in the IFN-switch group. Efficacy was confirmed with evidence that earlier treatment with fingolimod provided additional benefit when compared to those who switched from IFN.

Reference: J Neurol Neurosurg Psychiatry 2016 May;87(5):468-75
Abstract

Vitamin D status during pregnancy and risk of Multiple Sclerosis in offspring of women in the Finnish maternity cohort

Authors: Munger KL, et al

Summary: This prospective, nested case-control study identified individuals with a diagnosis of MS whose mothers were in the Finnish Maternity Cohort and had an available serum sample from the pregnancy. The team matched 176 cases with 326 controls and found the mean maternal vitamin D levels were higher in maternal control than case samples (15.02 ng/mL vs 13.86 ng/mL). They concluded maternal vitamin D deficiency (25[OH]D levels <12.02 ng/mL) during early pregnancy was associated with a nearly 2-fold increased risk of MS in the offspring compared with women who did not have deficient 25(OH)D levels.

Comment: The authors report that children of women who were vitamin D deficient early in their pregnancy had a doubled increased risk of developing MS as an adult. Most (70%) of the maternal samples were collected during the first trimester of pregnancy and the question of increased risk of MS due to deficient vitamin D levels in the second and third trimester cannot be answered here. It should be noted that there was no information or adjustment for other environmental risk factors such as Epstein-Barr virus infection, high body mass index in childhood/adolescence, cigarette smoking, or human leukocyte antigen DRB1*1501 status. In addition, the results can also possibly be explained by vitamin D deficiency in childhood and early adulthood in the people who developed MS. It seems reasonable to recommend vitamin D replacement therapy to deficient mothers early in pregnancy.

Reference: JAMA Neurol 2016 May 1;73(5):515-9
Abstract

Independent commentary by Dr Anneke van der Walt, who is a Neurologist at Royal Melbourne Hospital and a Senior Research Fellow at the Melbourne Brain Centre at Royal Melbourne Hospital, Department of Medicine, University of Melbourne. Her research focuses on predicting outcomes in MS. She has a particular interest in optic neuritis as a model for neurodegeneration in MS, novel treatment of tremor in MS and MS cognition. Her work is funded by the NHMRC.

Interferon-beta exposure during first trimester is safe in women with multiple sclerosis—A prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry

Authors: Thiel S, et al

Summary: This group compared pregnancy outcomes of women exposed to interferon-beta (n=251) with pregnancies unexposed to disease-modifying therapies (n=194). Ninety eight per cent of women discontinued interferon-beta treatment during first trimester. The group reported there was no differences regarding mean birth weight, mean birth length, preterm birth, spontaneous abortion, and congenital anomalies were observed between the two groups.

Comment: The results of this study regarding early pregnancy exposure to IFN-beta, a large molecule with a short half-life time, are pharmacologically plausible as the human foetus gains most of its weight at the end of pregnancy. It contradicts previous studies that were notably small (n=17) or had greater numbers of women who smoked during pregnancy. Corticosteroid exposure during pregnancy can also decrease birth weight by average 100g and it should be noted that patients not exposed to IFN-beta before pregnancy had a higher risk of relapses in the first trimester. Overall, the results are reassuring and suggest that IFN-beta can safely be continued up until confirmed pregnancy.

Reference: Mult Scler 2016 May;22(6):801-9
Abstract

Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: A cohort study

Authors: Martinez-Lapiscina EH, et al

Summary: This study assessed the role of peripapillary retinal nerve fibre layer (pRNFL) thickness and macular volume as a biomarker of disability worsening in a cohort of patients with CIS (n=74), RRMS (n=664), or progressive multiple sclerosis (n=141) without previous optic neuritis. The authors concluded patients with a pRNFL of less than or equal to 87 µm or less than or equal to 88 µm had double the risk of disability worsening at any time after the first and up to the third years of follow-up, and the risk was increased by nearly four times after the third and up to the fifth years of follow-up. There were no meaningful associations for macular volume identified.

Comment: The search for individualised predictors of disability progression has long focused on markers of retinal axonal loss but definitive evidence of correlations between loss of retinal nerve fibre layer and disability in MS has been lacking. This large, collaborative study, demonstrates a pRNFL threshold of 87 µm (Cirrus OCT) or 88 µm (Spectralis OCT) in eyes without past optic neuritis, predicts a two-fold increase in disability worsening. Sequential measurements of pRNFL were not done during this study and the degree of change in the pRNFL over time cannot be estimated from these results. Repeating OCT tests within a 2-year period in eye without prior optic neuritis is however unlikely to be helpful using current technology (repeating retinal ganglion cell layer measurements may however be more useful). The results suggest that measuring pRNFL thickness in eyes without optic neuritis can provide information about a person with MS risk of worsening disability and is therefore worthwhile doing.

Reference: Lancet Neurol 2016 May;15(6):574-84
Abstract

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