# Neurology RESEARCH REVIEW™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

Issue 71 – 2021


## In this issue:



**Abbreviations used in this issue**

**aHSCT** = autologous haematopoietic stem cell transplantation
**ARR** = annualised relapse rate
**COVID-19** = coronavirus disease 19
**DMT** = disease-modifying therapy
**EDSS** = Expanded Disability Status Scale
**HR** = hazard ratio
**MRI** = magnetic resonance imaging
**MS** = multiple sclerosis
**pwMS** = people with MS
**RRMS** = relapsing-remitting MS
**SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2
**SPMS** = secondary progressive MS


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# Welcome to this special issue of Neurology Research Review, focusing specifically on MS.

In this issue, researchers in Spain report that MS patients taking anti-CD20 treatments such as ocrelizumab and rituximab might be at increased risk for COVID-19, Italian investigators suggest an association between lymphocyte count and dimethyl fumarate efficacy, and an open-label trial in Israel reports positive results with mesenchymal stem cell transplantation in patients with active and progressive MS. A Canadian study supports an association between concussion in adolescence and future MS diagnosis, a post hoc analysis of a large phase 3 trial suggests that siponimod (not yet available in NZ) is likely to have a meaningful clinical benefit in patients with SPMS, and a US study finds that amantadine, modafinil, and methylphenidate do not improve fatigue associated with MS.

We hope you find the selected studies interesting, and welcome your feedback.

Kind regards,


**Dr Jennifer Pereira**
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## COVID-19 in multiple sclerosis patients: Susceptibility, severity risk factors and serological response

**Authors:** Zabalza A et al.


**Summary:** This retrospective study in Spain determined COVID-19 incidence and risk factors in patients with MS. Patients were identified through an email survey and clinic visits between February and May 2020. Data from 48 suspected cases and 45 confirmed COVID-19 cases were analysed (incidence 6.3%). 19 patients were hospitalised and 2 of them died. Multivariable models found that age, contact with a confirmed case, residence in Barcelona, MS duration, and time on anti-CD20 treatment were independent risk factors for presenting with COVID-19. Age was an independent risk factor for severe COVID-19 (odds ratio per 10 years, 2.71; 95% CI 1.13–6.53). 45.6% of patients who had a serological test were found to have antibodies, but only 17.6% of patients who were taking anti-CD20 therapies had antibodies.


**Comment:** COVID-19 is once again back in the spotlight in NZ. The results of this paper reiterate earlier published reports from large databases – those individuals on anti-CD20 treatment (ocrelizumab and rituximab) for the treatment of MS might be at higher risk for COVID-19 and are less likely to generate an antibody response to the infection. This is important information to convey to your patients who are already on one of these treatments or are considering starting one. This lower rate of antibody generation is also expected to be the case for individuals on anti-CD20 treatment when vaccinated against COVID. A consensus document "COVID-19 vaccine information for pwMS" written by Australian and NZ MS specialists is available on the MSRA website.


***Reference: Eur J Neurol 2020; published online Dec 19***
Abstract


### Independent commentary by Dr Jennifer Pereira BHB, MBChB, FRACP, MD

After undergraduate training in medicine at the University of Auckland, Jennifer trained in neurology at Auckland City Hospital. Postgraduate training consisted of an MS research fellowship, with the Therapeutic Immunology Group in the Department of Clinical Neurosciences, University of Cambridge (UK). There she completed her MD focused on immunological changes after treatment of MS with alemtuzumab. Jennifer then returned to Auckland and works as consultant neurologist with a special interest in neuroimmunology in the Department of Neurology at Auckland City Hospital.

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## Dimethyl fumarate-induced lymphocyte count drop is related to clinical effectiveness in relapsing-remitting multiple sclerosis

**Authors:** Tsantes E et al.

**Summary:** This observational study in Italy evaluated the impact of a dimethyl fumarate-induced lymphocyte count drop on clinical effectiveness in patients with RRMS. Data were collected for 476 RRMS patients treated with dimethyl fumarate for at least 6 months who were followed-up for up to 5 years. Multivariate Cox models were used to evaluate the impact of 6-month absolute lymphocyte count (ALC) drop on time to no evidence of disease activity (NEDA-3) status loss. A greater lymphocyte decrease was associated with a lower risk of NEDA-3 status loss (HR 0.87, p=0.01). Patients with low ALC drops (<11.5%) had worse outcomes than patients in higher tertiles (p=0.008). The nadir of ALC drop (–33.6%) occurred after 12 months' treatment, as did 35% of grade III lymphopaenia cases.

**Comment:** This is the first paper I have seen suggesting an association between lymphocyte count and efficacy of dimethyl fumarate. As treating physicians, we have used the lymphocyte count in this way for patients on azathioprine. We currently monitor a full blood count 3 monthly for the first year and 6 monthly ongoing, and stop treatment if there is a sustained lymphocyte count <0.5. Based on this paper we can use this monitoring to identify those more likely to remain at NEDA-3 as well as those that need to stop due to lymphopaenia.

***Reference: Eur J Neurol 2021;28(1):269-77***
Abstract

## Autologous haematopoietic stem cell transplantation compared with alemtuzumab for relapsing-remitting multiple sclerosis

**Authors:** Zhukovsky C et al.

**Summary:** This observational study compared outcomes after treatment with aHSCT or alemtuzumab in patients with RRMS. Patients treated with aHSCT (n=69) received a conditioning regimen of cyclophosphamide and rabbit anti-thymocyte globulinerG. Patients treated with alemtuzumab (n=75) received an initial dose (60mg over 5 days), a second dose after 1 year (36mg over 3 days), and then as needed. Follow-up visits with assessment of the EDSS score, adverse events and MRI investigations were made at least yearly. Kaplan-Meier estimates of the primary outcome measure 'no evidence of disease activity' were 88% for aHSCT and 37% for alemtuzumab at 3 years (p<0.0001). Adverse events of grade 3 or higher were reported in 48 patients treated with aHSCT and 0 treated with alemtuzumab in the first 100 days after treatment initiation.

**Comment:** There is a randomised controlled trial of aHSCT versus alemtuzumab currently recruiting patients with "RRMS and breakthrough inflammatory disease activity in spite of ongoing standard immunomodulatory medication" in Europe. This paper is an observational cohort study but shows more aHSCT patients had improved and fewer (only 1%) had worsened when compared to the alemtuzumab group. The ongoing trial in Europe will determine which is the safest and most effective treatment for this small but important group of people with RRMS.

***Reference: J Neurol Neurosurg Psychiatry 2021;92:189-94***
Abstract



## Rituximab and glatiramer acetate in secondary progressive multiple sclerosis

**Authors:** Cheshmavar M et al.

**Summary:** This open-label, randomised controlled trial compared the efficacy of rituximab and glatiramer acetate in patients with SPMS. 84 patients were randomised to receive rituximab (1g intravenously every 6 months) or glatiramer acetate (40mg 3 times a week subcutaneously) for 12 months; 73 patients completed the study. Mean EDSS increased from 3.05 at baseline to 4.14 in the rituximab group and from 3.22 at baseline to 4.60 in the glatiramer acetate group. No statistically significant between-group differences in EDSS were observed.

**Comment:** In NZ, under PHARMAC criteria, we have access to funded MS therapies for those with active SPMS (those who have a progressive course but with a relapse in the past year and evidence of active disease on scan). Analysis of large databases has shown that the current available MS treatments do reduce relapse-related disability but have minimal impact on progressive disease. This trial included a small number of patients over a short period of time so the clinical relevance is limited and this is likely to be why there was no difference seen between a high (rituximab) and low efficacy (glatiramer) treatment.

***Reference: Acta Neurol Scand 2021;143(2):178-87***
Abstract

## Beneficial effects of autologous mesenchymal stem cell transplantation in active progressive multiple sclerosis

**Authors:** Petrou P et al.

**Summary:** This trial in Israel evaluated the efficacy of mesenchymal stem cell (MSC) transplantation in patients with active and progressive MS. 48 patients with progressive MS and evidence of either clinical worsening or activity during the previous year were randomised to receive intrathecal (IT) or intravenous (IV) autologous MSCs ($1\times10^6$/kg) or sham injections in a crossover design. After 6 months, half of the patients from the MSC-IT and MSC-IV groups were retreated with MSCs, and the other half with sham injections. Patients initially assigned to sham treatment were subsequently treated with either MSC-IT or MSC-IV. The study duration was 14 months. No serious treatment-related safety issues were reported. Treatment failure was reported by significantly fewer patients in the MSC-IT and MSC-IV groups than in the sham-treated group (6.7%, 9.7%, and 41.9%, respectively).

**Comment:** MSC for the treatment of MS may offer immunomodulatory, neuroprotective and neurotrophic effects – a very different mechanism from the resetting of the immune system used in aHSCT. Intrathecal delivery of MSC is used due to compartmentalisation of the immune system in the CNS in those with progressive MS. This research group analysed intravenous or intrathecal MSC administered to a group of patients experiencing treatment failure with active MS or worsening progressive MS. This trial reported positive results. There have been a number of similar small trials with varied results – a large phase 3 trial is needed.

***Reference: Brain 2020;143(12):3574-88***
Abstract

## Concussion in adolescence and the risk of multiple sclerosis

**Authors:** Povolo CA et al.

**Summary:** This retrospective cohort study examined the association between adolescent concussion and future MS diagnosis. A search of linked administrative databases from Ontario, Canada, identified 97,965 adolescents aged 11–18 years who sustained a concussion in 1992–2011. These cases were matched 1:3 with individuals who had not sustained a concussion. A concussion during adolescence was found to be associated with a significantly increased risk of MS (HR 1.29, p=0.03), primarily in males (HR 1.41, p=0.04).

**Comment:** A role for trauma in MS disease has been postulated based on the observations that active inflammatory disease can develop along a biopsy needle track if a demyelinating lesion is sampled, and the co-occurrence of an MS plaque in the spinal cord at the level of a disc protrusion. This paper supports an association between the development of MS and earlier concussion – this is interesting but unfortunately not a modifiable risk factor.

***Reference: Mult Scler 2021;27(2):180-7***
Abstract

## Sustained disease remission after discontinuation of disease modifying treatments in relapsing-remitting multiple sclerosis

**Authors:** Pasca M et al.

**Summary:** This study investigated the disease course after DMT discontinuation in selected RRMS patients. 60 patients aged 18–65 years who had discontinued a first-line DMT were selected from a search of 1107 clinical records. Relapses, disability worsening and new brain lesions after DMT interruption were retrospectively evaluated. Median DMT treatment duration was 7.2 years, and median clinical follow-up after discontinuation was 4.6 years. No disease rebound occurred. Mean annualised disease activity and relapse rate were both significantly lower after discontinuation compared with during treatment. A 'no evidence of disease activity' (NEDA-3) period for ≥5.5 years while on treatment was associated with a low rate (7.7%) and a low risk of new disease activity (adjusted HR 0.16, 95% CI 0.03–0.78; p=0.024).

**Comment:** PHARMAC widened access to funded MS treatments from March 2021. Under the new criteria, individuals are required to stop treatment if their disability reaches an EDSS of 6.5 – unable to walk 100m with unilateral assistance. There have been no randomised controlled trials to support stopping treatment in this population group. There may be a group of patients in whom stopping treatment is appropriate and in their best interest due to the risks associated with long-term immunotherapy. This study includes only 60 patients so is too small to inform decision making but does suggest those on treatment with NEDA-3 for 5 years are more likely to remain stable if treatment is stopped.

***Reference: Mult Scler Relat Disord 2021;47:102591***
Abstract

## Siponimod and cognition in secondary progressive multiple sclerosis

**Authors:** Benedict RHB et al.

**Summary:** This secondary analysis of the EXPAND study investigated the effects of siponimod on cognition in patients with SPMS. 1651 patients were randomised 2:1 to receive siponimod 2 mg/day or placebo in a double-blind design. Cognitive function was assessed using the Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), and Brief Visuospatial Memory Test-Revised (BVMT-R). Improvements in SDMT scores from baseline were significantly better in siponimod than placebo recipients at 12 months, 18 months, and 24 months. Siponimod recipients were less likely to have a 4-point sustained decrease in SDMT score (HR 0.79, 95% CI 0.65–0.96; p=0.0157), and more likely to have a 4-point sustained increase in SDMT score (HR 1.28, 95% CI 1.05–1.55; p=0.0131) than placebo recipients. PASAT and BVMT-R scores did not differ significantly between groups.

**Comment:** This post hoc analysis of a large phase 3 trial shows improved cognitive outcomes for those with SPMS treated with siponimod. This result, and the phase 3 trial results showing significant delay to the time to 3-month confirmed disability progression compared to placebo, suggests this drug is likely to have a meaningful clinical benefit for patients. Siponimod is a small molecule and it is believed it is effective in SPMS as it is able to cross the blood-brain barrier to exert an anti-inflammatory effect. It is not yet available or funded in NZ.

***Reference: Neurology 2021;96(3):e376-86***
Abstract



## Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis

**Authors:** Nourbakhsh B et al.

**Summary:** This randomised controlled trial evaluated the efficacies of amantadine, modafinil, and methylphenidate when used for fatigue in patients with MS. 141 patients who reported fatigue and had a Modified Fatigue Impact Scale (MFIS) score >33 were randomised to receive each of the 3 drugs and placebo according to a 4-sequence, 4-period, crossover, double-blind design. Oral amantadine (up to 100mg twice daily), modafinil (up to 100mg twice daily), methylphenidate (up to 10mg twice daily), and placebo were each given for up to 6 weeks, separated by 2-week washout periods. The primary outcome measure was MFIS while taking the highest tolerated dose at week 5 of each medication period. Estimated mean MFIS scores were 51.3 at baseline, 40.6 with placebo, 41.3 at week 5 of amantadine, 39.0 at week 5 of modafinil, and 38.6 at week 5 of methylphenidate (p=NS). Adverse events were reported by 31% of patients taking placebo, 39% taking amantadine, 40% taking modafinil, and 40% taking methylphenidate.

**Comment:** This randomised controlled trial showed the commonly prescribed medications for MS- related fatigue offered no significant benefit over placebo. This study enrolled only a small number of patients so there may still be some benefit from these treatments. However, using other methods to treat fatigue will likely lead to better results. Options for those on MS treatments reviewing the efficacy of DMT include assessing the indication for drugs with side effects of sedation and considering non-medical fatigue management strategies.

***Reference: Lancet Neurol 2021;20(1):38-48***
Abstract

## Effects of ibudilast on MRI measures in the phase 2 SPRINT-MS study

**Authors:** Naismith RT et al.

**Summary:** This secondary analysis of the SPRINT-MS study investigated the effects of ibudilast on brain volume and new lesions in patients with progressive forms of MS. 255 patients were randomised to receive ibudilast (up to 100 mg/day) or placebo. At 96 weeks, new or enlarging T2 lesions were observed on MRI in 37.2% of ibudilast recipients and 29.0% of placebo recipients (p=NS), and new T1 hypointense lesions were observed in 33.3% and 23.5% of patients in the respective groups (p=NS). Compared with placebo, treatment with ibudilast reduced grey matter atrophy by 35% (p=0.038), and progression of whole brain atrophy by 20% (p=0.08).

**Comment:** Ibudilast is a small molecule, phosphodiesterase inhibitor. Results from the phase 2 SPRINT-MS trial and this planned secondary analysis suggest that ibudilast may treat the neurodegenerative component of MS through a mechanism that is independent of inflammation. However, as detailed in the accompanying editorial, studies to date have shown only a small beneficial effect on disability progression and no significant impact on neurofilament light – a nerve cytoskeletal protein considered a biomarker for neurodegeneration in pwMS. More research is needed to determine if these MRI outcomes translate into a clinically meaningful benefit for patients.

***Reference: Neurology 2021;96(4):e491-500***
Abstract

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