Neurology RESEARCH REVIEW™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

Issue 81 – 2022

In this issue:

Abbreviations used in this issue
aHSCT = autologous haematopoietic stem cell transplantation
ARR = annualised relapse rate
COVID-19 = coronavirus disease 2019
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
HR = hazard ratio
MRI = magnetic resonance imaging
MS = multiple sclerosis
NfL = neurofilament light chain
pwMS = persons with MS
PTAC = Pharmacology and Therapeutics Advisory Committee
RRMS = relapsing-remitting MS
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SPMS = secondary progressive MS
TGA = Therapeutic Goods Administration

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Welcome to the latest issue of Neurology Research Review, focusing specifically on MS.

In this issue, a post hoc analysis of the ASCLEPIOS I and II trials supports the consideration of ofatumumab as a first-line therapy in recently diagnosed treatment-naïve pwMS, the SWEDISH RIFUND-MS study provides evidence that rituximab (1000mg followed by 500mg every 6 months) is superior to dimethyl fumarate in preventing relapses in patients with early RRMS, and an analysis of the EXPAND extension trial supports the clinical utility of siponimod for long-term treatment of SPMS.

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

Kind regards,
Dr Jennifer Pereira
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Efficacy and safety of ofatumumab in recently diagnosed, treatment-naive patients with multiple sclerosis: Results from ASCLEPIOS I and II

Authors: Gärtner J et al.

Summary: This post hoc analysis of the ASCLEPIOS I and II trials investigated the efficacy and safety of ofatumumab versus teriflunomide in recently diagnosed, treatment-naïve (RDTN) pwMS. 615 RDTN patients were randomised to receive ofatumumab (20mg subcutaneously every 4 weeks) or teriflunomide (14mg orally once daily) for up to 30 months. Compared with teriflunomide, ofatumumab reduced ARR by 50% (rate ratio 0.50, 95% CI 0.33–0.74; p<0.001), and reduced the risk of 6-month confirmed disability worsening by 46% (HR 0.54, 95% CI 0.30– 0.98; p=0.044) and the risk of 6-month progression independent of relapse activity by 56% (HR 0.44, 95% CI 0.20–1.00; p=0.049). Safety findings were consistent with those of the overall ASCLEPIOS population.

Comment: Ofatumumab is a humanised anti-CD20 monoclonal antibody in the same class of drugs as ocrelizumab. It has FDA approval for clinically isolated syndrome, RRMS and active SPMS, and has TGA funding for use in Australia. It is self-administered subcutaneously by an auto-injector weekly for 3 weeks then monthly ongoing, under the trade name Kesimpta®.

Reference: Mult Scler 2022;28(10):1562-75
Abstract

Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden

Authors: Svenningsson A et al.

Summary: The Swedish RIFUND-MS study investigated the safety and efficacy of rituximab versus dimethyl fumarate in patients with RRMS or clinically isolated syndrome (CIS). At 17 Swedish university and community hospitals, 200 patients aged 18–50 years with RRMS or CIS who were either untreated or only exposed to interferons or glatiramer acetate were randomised to receive oral dimethyl fumarate 240mg twice daily or intravenous rituximab 1000mg followed by 500mg every 6 months. 98 patients in the rituximab group and 97 patients in the dimethyl fumarate group were followed up for 24 months and were eligible for the primary outcome analysis. Three (3%) patients in the rituximab group and 16 (16%) patients in the dimethyl fumarate group had a protocol-defined relapse during the trial (risk ratio 0.19, 95% CI 0.06–0.62; p=0.0060). Infusion reactions were the most common adverse event in the rituximab group and gastrointestinal reactions and flush were the most common adverse events in the dimethyl fumarate group.

Comment: This non-blinded randomised controlled trial confirms that rituximab (a chimeric – part mouse – anti-CD20 monoclonal antibody) is clinically and radiologically superior to Tecfidera® (dimethyl fumarate). It consolidates what has been accepted practice, that rituximab sits with natalizumab and ocrelizumab as a high-efficacy treatment for RRMS. There have been a variety of rituximab dosing regimens advocated so this trial result also offers a proven and effective one – 1000mg on day 1 then 500mg 6-monthly ongoing. Ocrelizumab, as a more humanised monoclononal antibody, is less likely to be neutralised but whether it has superior efficacy or a superior side effect profile is not known.

Reference: Lancet Neurol 2022;21(8):693-703
Abstract

CLICK HERE to read previous issues of Neurology Research Review

Long-term efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis

Authors: Cree BAC et al.

Summary: This study used data from the open-label extension of the EXPAND study to investigate the long-term efficacy and safety of siponimod 2 mg/day in patients with SPMS. In the extension phase (>5 years' follow up), patients who received placebo during the 2-year core study were switched to siponimod (placebo-siponimod group) and those on siponimod continued the same treatment (continuous siponimod group). Continuous siponimod reduced the risk of 6-month confirmed disability progression by 22% (HR 0.78, 95% CI 0.66–0.92; p=0.0026) and 6-month confirmed worsening in cognitive processing speed by 23% (HR 0.77, 95% CI 0.65–0.92; p=0.0047) compared with the placebo-siponimod group. Sustained effects on ARR and inflammatory disease activity were also observed. No new, unexpected safety signals for siponimod were reported.

Comment: Siponimod is a selective modulator of the sphingosine-1-phosphate receptor, and is in the same class as fingolimod (available in New Zealand for the treatment of RRMS). It is understood that siponimod crosses the blood-brain barrier where it targets the compartmentalised CNS inflammation that occurs in SPMS thereby reducing MS-related disability. In the original EXPAND trial published in 2018, siponimod was trialled against placebo in 18- to 65-year-olds with EDSS 3–6.5. There were no MRI inclusion criteria but 21% of both groups had gadolinium-enhancing lesions at baseline. The results of the EXPAND study were similar to this extension study – 26% of the siponimod and 32% of the placebo group showing sustained 3-month disability progression. The extension study shows continued reduction in disability progression (22% confirmed 6-month disability progression) in those who started on siponimod versus switched from placebo at the 2-year mark – again emphasising the need for early treatment in MS. Siponimod is available in Australia but not yet in New Zealand.

Reference: Mult Scler 2022;28(10):1591-1605
Abstract

Eighteen-month safety analysis of offspring breastfed by mothers receiving glatiramer acetate therapy for relapsing multiple sclerosis – COBRA study

Authors: Ciplea AI et al.

Summary: The retrospective COBRA study used data from the German MS and Pregnancy Registry to investigate safety outcomes in offspring of mothers with relapsing MS who received glatiramer acetate while breastfeeding. The glatiramer acetate cohort (58 mothers and 60 offspring) was compared with a matched control cohort (60 mothers and 60 offspring). 86.7% and 25% of mothers in the respective cohorts had glatiramer acetate at some point during pregnancy. Maternal demographics and disease activity were comparable in the 2 groups. During the first 18 months of life, there were no significant between-group differences in the annualised number of hospitalisations for breastfed offspring, the proportion of offspring requiring hospitalisation, the annualised number of antibiotic uses in offspring, and the proportion of offspring requiring antibiotics.

Comment: Data from the PRIMS (Pregnancy in MS) study published in 1998 indicate that off treatment in the postpartum period, the risk of relapse is at its highest with 30% of patients having a relapse in the first 3 months. This paper supports current consensus guidelines (e.g. the Association of British Neurologists' UK Consensus on Pregnancy in Multiple Sclerosis) that advise that the benefits of glatiramer acetate during breastfeeding outweigh the risks. As part of pre-pregnancy counselling, given this high postpartum risk of relapse, it is important to ensure that a treatment strategy for pregnancy and postpartum is established and that this includes a discussion about compatibility of chosen DMT with breastfeeding.

Reference: Mult Scler 2022;28(10):1641-50
Abstract

No increase of serum neurofilament light in relapsing-remitting multiple sclerosis patients switching from standard to extended-interval dosing of natalizumab

Authors: Johnsson M et al.

Summary: This study investigated changes in serum NfL concentrations after switching natalizumab dosing from 4-weekly to 6-weekly (extended-interval dosing; EID) in patients with RRMS. Two cohorts of patients with RRMS were included: one cohort received standard-interval natalizumab dosing (every 4 weeks) at baseline, and were switched to 6-weekly (EID4–6, n=45). The other cohort received EID (5–6 weekly) both at baseline and during follow-up (EID5/6, n=25). Serum samples were collected in the EID4–6 cohort at every natalizumab infusion for 12 months. Baseline mean sNfL concentration was 10.5 ng/L in the EID4–6 cohort, and it remained unchanged at 12 months. Baseline serum NfL concentrations in the EID4–6 and EID5/6 cohorts were comparable.

Comment: Extended dosing of intravenous natalizumab (from the standard 300mg 4 weekly to 6 weekly infusions) is now a routine part of clinical practice. Extended dosing first began as a consequence of a theoretical reduction in the risk of progressive multifocal leukoencephalopathy (PML). In 2019 Ryerson et al. published an analysis of the TOUCH data showing a 94% relative risk reduction in PML in those dosed every 5–6 weeks. The efficacy of 6-weekly natalizumab was unknown until the results of a randomised controlled trial (the NOVA trial) that was just published in 2022. With now accepted efficacy, supported by this NfL data, and the wish to avoid infusion centres in the COVID era, the majority of patients in Auckland receive natalizumab 6 weekly.

Reference: Mult Scler 2022; published online Jul 20
Abstract

Immunological consequences of cladribine treatment in multiple sclerosis

Authors: Rolfes L et al.

Summary: This longitudinal real-world study in Germany evaluated the effects of cladribine on immune cell reduction and reconstitution during the first 2 years of treatment. 80 pwMS who received cladribine at 2 tertiary centres underwent monthly laboratory testing. There were selective alterations in immune cell populations following cladribine treatment, with the most marked effects observed in the second year of treatment. A rapid reduction in CD56+ natural killer cells was followed by a greater reduction in CD19+ B cells and a moderate decrease in CD4+ and CD8+ T cells. Despite the marked effect on B cells, immunoglobulin levels were unaffected. Clinical disease activity was unrelated to the observed immune alterations. The most common adverse event was lymphopenia (86.3% of patients), and the cumulative incidence of infections (mostly mild or moderate) was 55%. 19 herpes infections were reported in 8 (10%) cladribine recipients.

Comment: With the reopening of the borders you may, like me, be inheriting patients who have received cladribine overseas. The lymphopenia that occurs as part of the immune reconstitutive mechanism of action of cladribine is the most common side effect. In the phase 3 trials, lymphopenia was associated with an increased risk of herpes zoster infection. On-treatment monitoring includes a full blood count at month 2 and 6. If the lymphocyte count is less than 0.5, more frequent clinical and laboratory monitoring is advised and prophylactic anti-viral medication is indicated if the lymphocyte count is 0.2 or below. Cladribine is approved by PTAC and awaiting PHARMAC funding.

Reference: Mult Scler Relat Disord 2022;64:103931
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. **For full bio CLICK HERE**

Response to COVID-19 booster vaccinations in seronegative people with multiple sclerosis

Authors: Tallantyre EC et al.

Summary: This study evaluated responses to a COVID-19 vaccine booster in pwMS treated with anti-CD20 therapies and fingolimod. 79 pwMS without a detectable immunoglobulin (Ig)G response after COVID-19 vaccines 1 and 2 provided a dried blood spot ± venous blood sample 2–12 weeks after COVID-19 vaccine 3. Twenty-six out of 79 (33%) participants had anti-SARS-CoV-2-spike IgG seroconversion post-COVID-19 vaccine 3, and 26 out of 40 (65%) who provided a whole blood sample had a positive T-cell response. Overall, 31 out of 40 (78%) patients who provided a whole blood sample demonstrated either humoral or cellular immune response post-COVID-19 vaccine 3.

Comment: PwMS on fingolimod and ocrelizumab are now eligible for their second COVID boosters. Please ensure your patients have had the 2 boosters and their 3 vaccines as part of the primary course. This same group is also eligible for COVID treatments within 5 days of getting COVID – advise your patients to contact their general practitioner. Available therapies are Paxlovid®, molnupiravir and remdesivir. As of 25 August 2022, this same group fall within the PHARMAC eligibility criteria for COVID-19 pre-exposure prophylaxis with tixagevimab and cilgavimab, brand name Evusheld®. Evusheld® comprises 2 monoclonal antibodies that bind to the spike protein on the virus. It is administered as 2 sequential intramuscular injections.

Reference: Mult Scler Relat Disord 2022;64:103937
Abstract

Evaluation of liver injury in multiple sclerosis patients receiving pulsed steroid therapy

Authors: Namaei P et al.

Summary: This prospective observational study investigated the incidence and risk factors for liver injury in MS patients receiving pulsed methylprednisolone therapy. 314 pwMS who were treated for relapse with methylprednisolone pulse therapy at Sina Hospital in 2020–2021 underwent liver function tests. Liver injury was diagnosed if there was an elevation of serum aminotransferase levels above the upper normal limit (45 IU/L). The prevalence of liver injury after pulsed methylprednisolone therapy was 2.86%. None of the cases of liver injury were severe. Multivariate regression analysis showed that hyperlipidaemia and history of alcohol abuse were significantly associated with liver injury.

Comment: Standard advice for patients receiving the standard 5 days of 500mg methylprednisolone for the treatment of an MS relapse is to watch for side effects of sleep disturbance, gastric irritation, mood disturbance or psychosis. I prescribe a short course of omeprazole and zopiclone alongside the steroids. The individuals included in this paper potentially received a higher dose – a maximum 10,000 mg/day for 5 days with a 10- to 15-day prednisone taper. This article highlights a particular group that is at increased risk for liver injury. Although based on this study liver injury is rare and not severe, with the maximum alanine transaminase in the group at 342, aspartate transaminase 250, alkaline phosphatase 200, and resolved within 1 week to 1 month.

Reference: Mult Scler Relat Disord 2022;65:103968
Abstract

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Impact of previous disease-modifying treatment on safety and efficacy in patients with MS treated with aHSCT

Authors: Kvistad SAS et al.

Summary: This retrospective observational study evaluated the impact of previous long-lasting DMTs on the safety and efficacy of aHSCT in pwMS. 104 patients with RRMS who received aHSCT in Sweden and Norway in 2011–2021 were grouped according to the last DMT used ≤6 months prior to aHSCT. Mean follow-up after aHSCT was 39.5 months. 66% of patients developed neutropenic fever after aHSCT, but there was no treatment-related mortality. 20 patients (19%) were diagnosed with autoimmunity during follow-up. Occurrence of neutropenic fever, length of hospital stay or secondary autoimmunity did not vary according to the last DMT used prior to aHSCT. A total of 84 patients (81%) achieved No Evidence of Disease Activity (NEDA-3) status, including 100% of patients who used rituximab, alemtuzumab or cladribine before aHSCT.

Comment: aHSCT is a treatment for aggressive, medically refractory RRMS. Individuals who meet selection criteria and undergo this treatment in New Zealand will be effectively "switching" therapy from natalizumab, ocrelizumab or fingolimod. Ocrelizumab can lead to long-lasting B cell depletion. This study, using the cyclophosphamide/rabbit antithymocyte globulin conditioning regimen, showed that being on an anti-CD20 agent (17% of the cohort were on rituximab, 6% on alemtuzumab and 2% on cladribine) did not appear to pose greater transplant-related risk than "switching" to aHSCT from another standard agent (natalizumab 19%, fingolimod 14%, dimethyl fumarate 5%).

Reference: J Neurol Neurosurg Psychiatry 2022;93(8):844-8
Abstract

Time to first treatment and risk of disability pension in relapsing-remitting multiple sclerosis

Authors: Wandall-Holm MF et al.

Summary: This population-based cohort study used data from the nationwide Danish MS Registry to investigate the association between treatment delay from MS onset and the hazard of disability pension. 5208 patients with onset of RRMS in 1996–2016 were followed up until disability pension or a competing risk/censoring event. Patients were categorised according to time from onset to first treatment: within 1 year (early; n=1922), between 1 and 4 years (intermediate; n=2126) and from 4 to 8 years (late; n=1160). Cox regression estimates adjusted for clinical and socioeconomic confounders showed that, compared with the 'early' group, the hazard of receiving a disability pension increased with increasing delay of treatment initiation (HR 1.37, 95% CI 1.12–1.68 for the intermediate group; and HR 1.97, 95% CI 1.55–2.51 for the late group).

Comment: This paper offers socioeconomic support for early treatment of active MS. In this study "early" is defined as being within 1 year of disease onset. The data for this study come from a mandatory Danish MS registry where patients are entered at diagnosis and at which time retrospective information on time of onset and prior relapses is recorded and then prospective data are collected from there. In New Zealand, PHARMAC has widened the access to MS treatments, funding treatment from the first clinical attack of MS. As of 1 July 2022, patients that fulfil McDonald 2017 MS diagnostic criteria with an active scan and an EDSS of 0–6.5 are eligible for treatment. Assess your patients carefully – they will now mostly NOT need to wait for that second attack.

Reference: J Neurol Neurosurg Psychiatry 2022;93(8):858-64
Abstract