Neurology RESEARCH REVIEW™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

Issue 77 – 2021

In this issue:

Abbreviations used in this issue

BTK = Bruton tyrosine kinase
COVID-19 = coronavirus disease 2019
DMT = disease-modifying treatment
EDSS = Expanded Disability Status Scale
MENACTRIMS = Middle East North Africa Committee for Treatment and Research in MS
MRI = magnetic resonance imaging
mRNA = messenger ribonucleic acid
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 the latest issue of Neurology Research Review, focusing specifically on MS.

In this issue, a French cohort study finds that long-term use of DMT in RRMS delays the development of moderate disability and conversion to SPMS, an analysis of the MSBase Registry finds that the risk of disability worsening after switching to ocrelizumab is reduced by short treatment gaps, and the phase 2 APLIOS study of subcutaneous ofatumumab suggests we could be at beginning of a new and more convenient era for DMT. Also in this issue, we review a succinct summary of the current recommendations for COVID-19 vaccination in pwMS, and a dose-response study of the BTK inhibitor tolebrutinib in relapsing and progressive forms of MS provides rationale for further development of the drug.

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

Kind regards,

Dr Jennifer Pereira
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Cumulative effects of therapies on disability in relapsing multiple sclerosis

Authors: Rollot F et al.

Summary: This nationwide cohort study in France investigated the relationship between treatment exposure and disability risk in patients with RRMS. Associations between treatment duration and risk of disability were assessed using a novel weighted cumulative exposure model in 2285 adult patients (mean age 33.4 years, 75.0% female). The risk of disability decreased with increasing duration of exposure to DMTs. Compared to a 5-year treatment starting 10 years ago, a 15-year continuous treatment starting 20 years ago was associated with a 26% decrease in risk of irreversible EDSS 4, and a 34% decrease in risk of conversion to SPMS.

Comment: We know from randomised controlled trials in RRMS and their extension studies that immunotherapies reduce relapse rate and cumulative disease activity. These data provide additional evidence that the use of sustained long-term immunotherapy prevents cumulative disability and conversion to secondary progressive disease. This analysis was performed between 1996 and 2017 and the most frequently used DMTs were interferons (44.7%) and glatiramer acetate (11.9%) – low efficacy MS therapies, so the effects seen are likely to be greater in our current treated RRMS population. This study showed sustained treatment to be of greater benefit than early treatment. We aim for both early and sustained.

Reference: Mult Scler 2021;27(11):1760-70

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.

Prediction of multiple sclerosis outcomes when switching to ocrelizumab

Authors: Zhong M et al.

Summary: This analysis of MSBase Registry data evaluated predictors of relapse and disability progression in patients with RRMS when switching from another DMT to ocrelizumab. Prior DMTs included interferon-beta/glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod and natalizumab. Multivariable Cox proportional hazard regression models showed that the risk of relapse was higher when switching from fingolimod compared with other DMTs, but only in the first 3 months of ocrelizumab therapy (hazard ratio [HR] 3.98, 95% CI 1.57–11.11; p=0.004). The adjusted risk for 6-month confirmed disability progression increased with increasing washout duration (2–6 months vs <1 month: HR 9.57, 95% CI 1.92–47.64; p=0.006).

Comment: We switch patients from fingolimod to ocrelizumab for a variety of reasons including breakthrough disease or complications of treatment such as macular oedema, low lymphocyte count or deranged liver function tests. The washout period between treatments cannot be standardised as the timing of ocrelizumab infusion may be impacted by the reason to switch. In this retrospective study, 14.3% of patients with a >2-month washout had a relapse during the washout and 9.9% had a relapse during the first year on ocrelizumab. The lowest risk of an on-ocrelizumab relapse when switching from fingolimod was when the washout was <1 month (2.8%). It appears from earlier studies quoted in this paper that ocrelizumab is able to deplete B cells sequestered in lymph nodes. The drug has a half-life of 26 days so it can target the repopulating peripheral lymphocytes as it happens (6–8 weeks after stopping treatment). If you are switching due to breakthrough disease you need to minimise the washout period – prospective data are still required.

Reference: Mult Scler 2021; published online Oct 8
Abstract

Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis

Authors: Bar-Or A et al.

Summary: The phase 2 APLIOS study evaluated the bioequivalence of subcutaneous ofatumumab when administered by an autoinjector versus a prefilled syringe, and explored the effect of ofatumumab on B cell depletion. 256 patients with relapsing MS received subcutaneous ofatumumab 20mg every 4 weeks (after initial doses on days 1, 7, and 14). Patients were randomised 10:10:1:1 to receive an autoinjector or prefilled syringe dose in the abdomen, or an autoinjector or prefilled syringe dose in the thigh, respectively. The pharmacokinetics of abdominal ofatumumab were bioequivalent for the autoinjector versus prefilled syringe (geometric mean area under the curve, 487.7 vs 474.1 h × µg/ml; maximum plasma concentration, 1.409 vs 1.409 µg/ml). Ofatumumab rapidly decreased B cell counts in all groups, from a median 214.0 cells/µl at baseline to 2.0 cells/µl on day 14.

Comment: Subcutaneous delivery of high efficacy MS treatments will save time, minimise hospital exposure in the COVID era and reduce the pressure on our busy infusion centres. Ofatumumab has been through phase 3 trials in this formulation and natalizumab has proven efficacy in phase 2 trials. Subcutaneous ocrelizumab trials are currently underway. It could be the beginning of a new and more convenient era!

Reference: Mult Scler 2021; published online Oct 4
Abstract

MENACTRIMS practice guideline for COVID-19 vaccination in patients with multiple sclerosis

Authors: Yamout BI et al.

Summary: This practice guideline offers recommendations for vaccinating pwMS during the COVID-19 pandemic. A group of regional experts selected by MENACTRIMS reviewed the available evidence regarding COVID-19 vaccines in pwMS, and preliminary recommendations were developed by a subcommittee. They recommended that pwMS should be vaccinated against COVID-19 promptly. All COVID-19 vaccines are effective and do not appear to carry any additional risk for patients with MS. Once vaccinated, pwMS should continue to practise standard and recommended precautions against COVID-19. COVID-19 vaccines are safe to use in pwMS treated with DMTs, and there is no evidence that patients with MS are at higher risk for complications than the general population.

Comment: This paper offers a succinct summary of the current recommendation for COVID-19 vaccination in pwMS. It does not cover third vaccination which is available in NZ to individuals who are immunosuppressed. Third doses are advised between 8 weeks and 6 months after the second Pfizer vaccine dose and are indicated for pwMS on ocrelizumab and fingolimod.

Reference: Mult Scler Relat Disord 2021;56:103225
Abstract

Humoral and T-cell response to SARS-CoV-2 vaccination in patients with multiple sclerosis treated with ocrelizumab

Authors: Brill L et al.

Summary: This study in Israel investigated SARS-CoV-2 vaccine-specific humoral and cellular responses in pwMS treated with ocrelizumab. 49 pwMS treated with ocrelizumab, 40 healthy controls, and 23 untreated pwMS received 2 doses of the Pfizer/BioNTech (BNT162b2) COVID-19 vaccine between Dec 2020 and Apr 2021. Blood samples were taken 2–4 and 2–8 weeks after the second dose for antibody and T-cell assessments, respectively. 89.7% of patients treated with ocrelizumab and all of the healthy controls had SARS-CoV-2-specific T cells after vaccination (mean 15.4 and 14.3 spot-forming cells, respectively). Mean antibody titres and positive serology rates were lower in patients treated with ocrelizumab than in healthy controls and untreated patients, with a positive association with time from ocrelizumab infusion (p=0.04).

Comment: Early data of seroconversion post COVID infection and COVID vaccination for pwMS on anti-CD20s has (not unsurprisingly) shown an attenuated B cell response. Early data show about 35% have no antibodies after the second dose of the Pfizer vaccine. To further understand the efficacy of the vaccine response for patients on these treatments, the analysis of the T cell response has been eagerly awaited. This study shows that the T cell response is equivalent to that of healthy controls. This is good news but it remains unknown how these laboratory data translate into real-world efficacy and protection against COVID infection.

Reference: JAMA Neurol 2021; published online Sep 23
Abstract

Association of disease-modifying treatment and anti-CD20 infusion timing with humoral response to 2 SARS-CoV-2 vaccines in patients with multiple sclerosis

Authors: Disanto G et al.

Summary: This observational cohort study investigated the humoral response to two COVID-19 mRNA vaccines in pwMS treated with DMTs. 120 pwMS (mean age 55 years; 61.7% women) from the Neurocentre of Southern Switzerland were included. Patients were receiving anti-CD20 therapies (n=58), teriflunomide (n=24), cladribine (n=15), sphingosine-1-phosphate receptor (S1P) modulators (n=9) and no therapy (n=14). All participants received 2 SARS-CoV-2 mRNA vaccine doses and had serum samples collected within 2 weeks prior to the first vaccine dose and 21–35 days after the second dose to determine immunoglobulin G (IgG) production. All patients on teriflunomide or no therapy had appropriate humoral responses to SARS-CoV-2 vaccination, but 48.2% of those in the anti-CD20 group, 33.3% in the S1P modulator group, and 7.1% in the cladribine group remained seronegative 21–35 days after the second vaccine dose.

Comment: This study included 120 pwMS receiving the Moderna or Pfizer COVID-19 vaccine. Participants' serological response pre and 21–35 days post second vaccine dose was measured. 48% of those receiving anti-CD20 treatment and 33% of those in the S1P modulator group were seronegative after the second vaccine. In the anti-CD20 group there was a steady increase in the SARS-CoV2 IgG titre with time since last infusion. These data support earlier studies indicating that positive titres are more likely to occur 6 months after ocrelizumab and in proportion to the B cell count. If a robust B cell vaccine response is needed (rather than relying on the T cell response) to prevent serious COVID infection in individuals on these therapies, delaying ocrelizumab infusion may be the best strategy (with timing of vaccine guided by B cell repopulation), acknowledging the potential risk for MS-related relapse.

Reference: JAMA Neurol 2021; published online Sep 23
Abstract

Depression in multiple sclerosis across the adult lifespan

Authors: Chan CK et al.

Summary: This analysis of MS PATHS data examined the burden of depressive symptoms across the adult age span in 13,821 pwMS compared with age-matched non-MS controls. The prevalence of depression was higher in pwMS than non-MS controls across the adult age span, but did not differ significantly between men and women across ages. Multivariable-adjusted regression models showed that the association between depression and processing speed (PST) or walking speed varied by age whereby depressed younger individuals had 0.45 standard deviation (SD; 95% CI –0.62, –0.29) worse PST z-scores than non-depressed younger individuals, and older depressed individuals had 0.20 SD (95% CI –0.32, –0.08) worse PST z-scores than non-depressed older individuals.

Comment: In this large study of 13,821 pwMS, the investigators examined the association between depression and measures of MS severity. Earlier studies estimated a lifetime prevalence of depression in pwMS of 50%. This study concluded that low mood can impact on physical and cognitive performance. 30% of pwMS in this study were being treated with an antidepressant and despite treatment 28% continued to report moderate to severe depression. Ask about symptoms of depression and response to current therapy for your patients – maximising treatment may not only improve mood but MS-related symptoms as well.

Reference: Mult Scler 2021;27(11):1771-80
Abstract

Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis

Authors: Spelman T et al.

Summary: This cohort study used data from the Danish and Swedish national MS registries to investigate the impact of different DMT strategies for RRMS. 4861 pwMS who started treatment with DMT in 2013–2016 were followed up for a mean 4.1 years. 92.3% of the Danish patients initiated a low to moderately effective DMT (42.0% teriflunomide) and 7.6% initiated a highly effective DMT. In contrast, only 65.5% of Swedish patients initiated a low to moderately effective DMT (2.4% teriflunomide) and 34.5% initiated a highly effective DMT. Relative to the Danish treatment strategy, the Swedish strategy was associated with a 29% reduction in the rate of post-baseline 24-week confirmed disability worsening (p=0.004), a 24% reduction in the rate of reaching EDSS 3 (p=0.03), and a 25% reduction in the rate of reaching EDSS 4 (p=0.01).

Comment: We are fortunate in NZ to be able to individualise treatment based on MS disease severity and factors such as pregnancy planning and patient choice. There are no head-to-head randomised controlled trials of moderate or high efficacy agents. There is, however, increasing evidence from observational studies that using high efficacy therapy early leads to better MS-related disability outcomes. This cohort study analysing nationwide registry data shows that the clinical practice in Sweden (using high efficacy rituximab or natalizumab as first line, or early escalation to a high efficacy agent) led to better treatment outcomes than the Danish approach (teriflunomide as first line with a tendency to switch to a still moderate efficacy agent, fingolimod, for breakthrough disease).

Reference: JAMA Neurol 2021;78(10):1197-1204
Abstract

Safety and efficacy of tolebrutinib, an oral brain-penetrant BTK inhibitor, in relapsing multiple sclerosis

Authors: Reich DS et al.

Summary: This phase 2b study determined the dose-response relationship between oral tolebrutinib and the reduction in new active brain MRI lesions in patients with relapsing MS. At 40 centres in 10 countries in Europe and North America, 130 patients aged 18–55 years with relapsing MS (either RRMS or SPMS) were randomised to receive tolebrutinib 5, 15, 30, or 60mg once daily, or placebo. MRI scans were performed at screening and every 4 weeks thereafter. At treatment week 12, there was a significant dose-dependent reduction in the mean number of new gadolinium-enhancing lesions in tolebrutinib recipients (1.39, 0.77, 0.76 and 0.13 with tolebrutinib 5, 15, 30, and 60mg, respectively), compared with placebo recipients (1.03). Headache was the most common non-serious adverse event reported with tolebrutinib, and no safety-related discontinuations or treatment-related deaths occurred.

Comment: The BTK enzyme plays a key role in B cell receptor signalling that regulates B cell proliferation, maturation, antigen presentation, and immunoglobulin production. BTK is not only expressed in B cells but also innate immune cells such as the microglia that reside in the CNS and contribute to the "smouldering plaque". It is hoped that these agents (at least 4 under development) will work similarly to the anti-CD20s but without the cellular depletion and with the added bonus of penetrating the CNS, acting locally to reduce inflammation in chronically active lesions. A phase 3 trial of tolebrutinib versus 14mg of teriflunomide for the treatment of RRMS is underway, as are 2 other studies evaluating this medication for the treatment of primary progressive MS and SPMS.

Reference: Lancet Neurol 2021;20(9):729-38
Abstract

Epilepsy as a predictor of disease progression in multiple sclerosis

Authors: Grothe M et al.

Summary: This case-control study used data from the German MS register to examine whether epilepsy in MS leads to increasing disability over time. Analysis of data for 31,052 pwMS showed that secondary progressive disease course, age, and disability were associated with the 5-year prevalence of epilepsy. Patients who developed epilepsy during the course of the disease had a higher EDSS score at disease onset (2.0 vs 1.5), higher disability at final 15-year follow-up (EDSS 4.4 vs 3.4) and lower employment status (40% vs 65%) than matched control patients.

Comment: MRI studies have found that more extensive MS cortical pathology correlates with higher levels of disability and an increased risk of seizures. This case-control study analysed disability levels over time in patients with MS who also had epilepsy – EDSS scores were analysed over 15 years. Interestingly, those with epilepsy had higher EDSS scores after the first year of diagnosis, and as expected more rapid progression and increased disability over the course of the study. In a sub-cohort, the authors found time from disease onset to first treatment and exposure time to a DMT did not alter epilepsy prevalence. This is disappointing but fits with our understanding that cortical MS pathology is neurodegenerative or due to meningeal-related lymphoid aggregates, neither of which are treatable with our current immunotherapies.

Reference: Mult Scler 2021; published online Oct 1
Abstract

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