Neurology RESEARCH REVIEW™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

Issue 73 – 2021

In this issue:

Abbreviations used in this issue

ARR = annualised relapse rate
CSF = cerebrospinal fluid
COVID-19 = coronavirus disease 2019
CNS = central nervous system
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
HR = hazard ratio
MAGNIMS = Magnetic Resonance Imaging in MS
MRI = magnetic resonance imaging
MS = multiple sclerosis
pwMS = people with MS
RRMS = relapsing-remitting MS
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 systematic review looks at the impact of DMTs on COVID-19 risk in pwMS, an analysis of MSBase Registry data investigates pregnancy-related disease activity in women with MS, and a population-based case-control study finds that critical spinal cord lesions may be important contributors to motor progression in MS. Also in this issue, an analysis of the Tysabri Observational Program reports disability improvement in patients taking natalizumab for RRMS, and a Canadian study finds that stopping cannabinoid medications in pwMS who have depression may in fact improve their mood.

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

Kind regards,

Dr Jennifer Pereira
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COVID-19 and disease-modifying therapies in patients with demyelinating diseases of the central nervous system

Authors: Sharifian-Dorche M et al.

Summary: This systematic review investigated the impact of DMTs on COVID-19 risk in patients with demyelinating diseases of the CNS (including MS). A search of PubMed from Jan to Dec 2020 identified 84 articles that evaluated COVID-19 in a total of 2493 patients with MS. Overall, 1.8% of them died. Rituximab had the highest mortality rate of the DMTs (4%). Not many studies reported a link between DMT use and the disease course of COVID-19, but other variables such as age, higher EDSS scores, cardiac comorbidities, and obesity were independent risk factors for severe COVID-19. After infection, an attenuation of immune response was seen in patients taking fingolimod and anti-CD20 monoclonal antibodies.

Comment: As the COVID-19 pandemic was unfolding we firstly relied on expert opinion based on scientific principles, then early case series and then larger databases to inform decision making around the initiation and continuation of DMTs for pwMS. This large systematic review supports current practice to not interrupt dosing. As we head into the next phase, assessing the safety and efficacy of the COVID vaccine in pwMS on DMTs, there is no theoretical reason that the vaccines would pose a greater risk to individuals on DMTs but as suggested in this paper, the efficacy may be attenuated for those on ocrelizumab or fingolimod.

Reference: Mult Scler Relat Disord 2021; published online Jan 29

Abstract

Natalizumab, fingolimod and dimethyl fumarate use and pregnancy-related relapse and disability in women with multiple sclerosis

Authors: Yeh WZ et al., for the MSBase Study Group

Summary: This study analysed data from the MSBase Registry to investigate pregnancy-related disease activity in women with MS. 1998 pregnancies from 1619 women with RRMS or clinically isolated syndrome were included. Overall, ARR decreased during pregnancy, before increasing again postpartum. ARR spiked after delivery in all DMT groups, but breastfeeding women were less likely to relapse (HR 0.61, 95% CI 0.41–0.91; p=0.016). 5.6% of pregnancies were followed by disability progression that was predicted by higher relapse activity in pregnancy and postpartum.

Comment: This paper helps to inform management strategies for women of childbearing age planning for pregnancy. Pregnancy is "protective" for pwMS but in the treatment era those stopping fingolimod and natalizumab preconception are at risk of a relapse during pregnancy. Those at greatest risk had a preconception EDSS of ≥2 and a high preconception ARR. Early initiation of treatment postpartum is important – reducing ARR by 89%. This must be done early as the median time of relapse was 34 days postpartum.

Reference: Neurol 2021; published online Apr 20

Abstract

Critical spinal cord lesions associate with secondary progressive motor impairment in long-standing MS

Authors: Sechi E et al.

Summary: This population-based case-control study investigated whether critical spinal cord lesions are more common in patients with long-standing SPMS or long-standing RRMS. Brain and spine MRI data for 14 patients with long-standing SPMS were compared with those of 18 patients with long-standing RRMS. Median disease duration (39 vs 34 years) and relapse number (3 vs 4) were similar between groups. Compared with RRMS patients, those with SPMS more commonly had potential critical spinal cord lesions (44% vs 100% of patients, respectively), more spinal cord lesions (median 4 vs 7.5), and more brain infratentorial lesions (median 1 vs 2.5; all $p<0.05$). Multivariate analysis showed that the presence of potential critical lesions was independently associated with motor progression ($p=0.02$).

Comment: In this study, all SPMS patients had at least 1 focally atrophic lesion in the lateral column of the spinal cord. Early, effective treatment for those with active disease is likely to be the best strategy to prevent the development of these critical lesions. Also in this cohort, 44% of RRMS patients had a similar potentially critical lesion and the authors discuss the potential variation of intralesional and patient factors that determine the clinical course. Perhaps these 44% are all destined to develop SPMS or there may be important modifying factors such as "greater functional neural reserve" – further research is required to understand these factors better.

Reference: Mult Scler 2021;27(5):667-73
Abstract

Prediction of on-treatment disability worsening in RRMS with the MAGNIMS score

Authors: Kunchok A et al., for the MSBase Study Group

Summary: This analysis of MSBase data examined the prognostic value of relapses, MRI activity and the MAGNIMS score for predicting disability worsening during treatment with interferon-beta and 3 other DMTs. 2293 pwMS were included in the analysis. Cox proportional hazards models found that 3 new T2 lesions (HR, 1.60; $p=0.028$) or 2 relapses (HR, 2.24; $p=0.002$) in pwMS taking interferon-beta for 12 months were predictive of disability worsening over 4 years. A MAGNIMS score of 2 (1 relapse and ≥3 T2 lesions, or ≥2 relapses) was also associated with a greater risk of disability worsening in patients taking interferon-beta (HR, 2.0; $p=0.001$). Similar associations were seen when the data for interferon-beta were pooled with 3 other DMTs (MAGNIMS score of 2: HR, 1.72; $p=0.001$).

Comment: During a routine follow-up appointment for pwMS on DMTs we focus on the safety, efficacy and tolerability of the current treatment regimen. This piece of research uses MSBase to aid in the identification of those experiencing treatment failure. Most patients are stable but if there is evidence of ongoing clinical and/or radiological disease activity your patient should be switched to a higher efficacy agent to minimise the risk of future disability.

Reference: Mult Scler 2021;27(5):695-705
Abstract

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Functional electrical stimulation for foot drop in people with multiple sclerosis

Authors: Smith AD et al.

Summary: Foot drop is a common cause of mobility impairment in pwMS. This literature review evaluated published evidence of the use of functional electrical stimulation (FES) for the treatment of foot drop in MS. The strengths and weaknesses of FES were discussed, as well as the benefits of using it in combination with physiotherapy.

Comment: FES offers an alternative to an orthosis as a management strategy for foot drop complicating MS. It has the added benefit of being an active rather than passive measure. Electrical impulses are delivered to the common peroneal nerve and tibialis anterior. An FES device can be purchased for a cost of approximately $NZ2500. Patients who can afford to self-fund this and wish to have an assessment to determine if it would be beneficial can be referred to a neurological physiotherapist.

Reference: Mult Scler 2021;27(5):653-60
Abstract

Real-world disability improvement in patients with relapsing-remitting multiple sclerosis treated with natalizumab in the Tysabri Observational Program

Authors: Wiendl H et al., on behalf of the Tysabri Observational Program (TOP) Investigators

Summary: This analysis of TOP data investigated real-world disability improvement in RRMS patients treated with natalizumab. Confirmed disability improvement (CDI) was defined as a ≥1.0 point decrease in EDSS score from baseline. 1278 out of 5384 patients (23.9%) treated with natalizumab had CDI, with approximately half of them having improvements in the first year of treatment. Among patients with CDI, 56.6% had an EDSS decrease of ≥1.5 points and 34.4% had a decrease of ≥2.0 points. The cumulative probability of maintaining improvement for 8 years was calculated to be 52.6%.

Comment: The main aim of treatment of active MS is to stabilise and prevent future disability. The statistics provided in this paper allow an informed discussion about the potential for improvement. 24% of patients on natalizumab will experience a sustained improvement and this does not necessarily happen in the first year. It is more likely to occur in those with a shorter disease duration – ideally within 1 year after symptom onset. This improvement does translate to a meaningful clinical benefit with a third achieving a drop in their EDSS by ≥2 points.

Reference: Mult Scler 2021;27(5):719-28
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). **For full bio CLICK HERE**

Disability outcomes of early cerebellar and brainstem symptoms in multiple sclerosis

Authors: Le M et al.

Summary: This analysis of MSBase data investigated long-term disability outcomes in patients with early cerebellar or brainstem symptoms. 10,513 patients were included in the analysis; 2723 had early cerebellar symptoms and 3915 had early brainstem symptoms (patients with early pyramidal presentation were used as a comparator group). Andersen-Gill models showed that early cerebellar presentation was associated with greater risk of progression events (HR, 1.37; p<0.001) compared with patients with early pyramidal presentation. In contrast, patients with early brainstem symptoms had a lower risk of progression events (HR, 0.89; p=0.01). Neither presentation was associated with changes in the risk of relapse.

Comment: We have 7 different treatments available in NZ for active MS. These have varying efficacy and side-effect profiles. Treating neurologists advise patients on the best option for them based on clinical and prognostic factors. 10% of pwMS present with an early cerebellar relapse and as detailed in this paper are at risk of more significant disability than those with a pyramidal presentation. Consider these individuals for high-efficacy agents – natalizumab and ocrelizumab.

Reference: Mult Scler 2021;27(5):755-66
Abstract

Breastfeeding and treatment of multiple sclerosis

Authors: Celius EG

Summary: Breastfeeding may not be sufficient to prevent postpartum relapses in women with highly active MS, so the reinitiation of DMTs is usually indicated. Most DMTs are contraindicated in breastfeeding mothers due to known potential effects in the baby, lack of knowledge about transfer to breast milk, or lack of knowledge about possible uptake in the baby. It is unethical to perform clinical trials in pregnant or breastfeeding women, so clinical practice and prescribing information can only be updated through case reports and case series. Recent evidence suggests that the period of stopping breastfeeding after a treatment course of cladribine may possibly be reduced from 7 to 1–2 days after each treatment cycle. Further studies on MS treatments are needed to help guide the increasing number of women with MS who wish to breastfeed their babies.

Comment: Pregnancy and breastfeeding must be considered together when discussing DMTs with women of childbearing age. Cladribine is an oral reconstitution therapy not yet funded by PHARMAC. It is administered in treatment courses – 5 days of tablets in week 1 and week 5 of year 1 and repeated in year 2 with efficacy anticipated through until the end of year 4. It is teratogenic and patients should not conceive or father a child for 6 months after a treatment course. According to the Association of British Neurologists' guidelines published in *Practical Neurology* in 2019, women should not breastfeed during a treatment course and for 7 days after it.

Reference: Mult Scler 2021;27(5):801-2
Abstract

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Discontinuing cannabis improves depression in people with multiple sclerosis

Authors: Feinstein A et al.

Summary: This Canadian study investigated whether symptoms of depression change when pwMS discontinue cannabis use. 40 cognitively impaired pwMS who smoked cannabis almost daily were randomised to either a cannabis continuation group or a cannabis withdrawal group and were followed up for 28 days. Depression scores on the Hospital Anxiety and Depression Scale in pwMS who were using cannabis to manage their depression remained unchanged at day 28 in the cannabis continuation group, but improved in the cannabis withdrawal group (p=0.006).

Comment: In the midst of a busy MS clinic, ascertaining what patients are taking for symptomatic management is important. Often patients are prescribed multiple centrally acting drugs – these need to be rationalised particularly if the patient has symptoms of fatigue, cognitive disturbance or depression. Patients may not volunteer they are taking tetrahydrocannabinol, cannabidiol, or a combination. This paper indicates that stopping cannabinoid medications in those with depression who have cognitive impairment may in fact improve their mood.

Reference: Mult Scler 2021;27(4):636-9
Abstract

Defining the course of tumefactive multiple sclerosis

Authors: Di Gregorio M et al.

Summary: This multicentre retrospective study determined the clinical characteristics and prognostic factors of tumefactive multiple sclerosis (TuMS). Demographic, clinical, MRI, and laboratory data were reviewed for 102 patients with TuMS. TuMS affected women more than men (female to male ratio: 2.4), with a young adulthood onset (median age 29.5 years). At onset, 52% of patients had involvement of more than 1 functional system and 24.5% of them had multiple tumefactive demyelinating lesions (TDLs). Over a third (38.7%) of TDLs had an infiltrative MRI pattern, and approximately three-quarters of patients (76.6%) had immunoglobulin G oligoclonal bands (OCBs) in CSF. 25.3% of patients were treated with more than 1 acute-phase treatment, and 46.6% were treated with high-efficacy treatments. After a median follow-up of 2.3 years, median EDSS score was 1.5. Independent risk factors for reaching an EDSS score ≥3 were higher age at onset, a higher number of TDLs, and the presence of infiltrative TDLs at baseline.

Comment: Early diagnosis of TuMS is challenging as over 50% of patients with this condition present with a multifocal presentation and striking MRI changes that differ from typical MS. This retrospective cohort study identifies where there are similarities – these patients are predominantly female with a mean age of onset of 30 years, 77% have OCBs and detailed analysis of the radiological features shows typical MS lesions in the brain and spinal cord in 85% of patients.

Reference: Eur J Neurol 2021;28(4):1299-1307
Abstract