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CONFERENCE REVIEW

ACTRIMS Forum 2021

Making Education Easy

25–27 Feb 2021

In this review:

Abbreviations used in this review
CNS = central nervous system
COVID-19 = coronavirus disease 19
DMT = disease-modifying therapy
GI = gastrointestinal
MRI = magnetic resonance imaging
MS = multiple sclerosis
RRMS = relapsing-remitting MS
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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RESEARCH REVIEW™
Making Education Easy — Since 2006

Welcome to our review of the ACTRIMS (Americas Committee for Treatment and Research in Multiple Sclerosis) Forum that was held online in late February.

I have selected and reviewed 10 presentations from the virtual meeting that I found to be particularly interesting. More information about the meeting can be found at https://forum.actrims.org/.

I hope you find this conference review informative and relevant to your practice.

Kind regards
Dr John Mottershead
johnmottershead@researchreview.co.nz

Low sun exposure is a risk factor for paediatric-onset multiple sclerosis

Authors: Sebastian P et al.

Summary: This case-control study evaluated whether low sun exposure is a risk factor for paediatric-onset MS. 332 children with MS and 534 age- and sex-matched controls were recruited from multiple centres in the US. Logistic regression analysis adjusted for confounding factors found that, compared with children who spent <30 min outdoors daily during the most recent summer, those who spent 30–60 min outdoors daily had a 61% lower risk of MS (odds ratio [OR] 0.39, 95% C] 0.17–0.86; p<0.05), and those who spent 1–2 hours outdoors daily had an 87% lower risk (OR 0.13, 95% CI 0.06–0.31; p<0.001). Higher summer ambient UV radiation levels were also protective against MS. It was estimated that a person living in Florida would have a 20% lower risk of MS than a person living in New York.

Comment: Low sun exposure is an established risk factor for the development of MS. The effect may be mediated via exposure levels in pregnancy, as well as during an individual's early life. There is accumulating evidence that this effect may be due to protective effects of higher levels of vitamin D. The large scale clinical trials required to show whether treatment with vitamin D will be beneficial after diagnosis with MS have not yet been done. This study looked at the special case of paediatric-onset MS. The protective effect associated with higher sun exposure was striking – a 60% reduction in risk of MS where exposure was 30–60 minutes per day. The role of vitamin D could not be determined in this study, as levels checked following diagnosis were potentially complicated by MS cases being given supplementation. Other risk factors for MS include smoking, obesity and Epstein-Barr virus exposure.

Session 1.3: Emerging Concepts in MS
Abstract

Independent commentary by Dr John Mottershead

Dr John Mottershead is a Neurologist at SDHB. He trained at Oxford University as a medical student and after qualification and junior doctor jobs was involved in research into uses of MRI in MS under the supervision of Professor Ian McDonald at Queen Square, London, before completing his neurology training in the South West of England. From 2002 to 2009 he was a neurologist in Manchester, where he gained further experience in general neurology and worked in the busy MS disease-modifying treatment clinic that served Greater Manchester. In 2009 he and his family moved to Dunedin. In 2013 he received an MSc in Clinical Education, with Distinction, from Edinburgh University. He continues to have a clinical interest in MS and other demyelinating disorders.

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Adult-onset genetic leukodystrophies misdiagnosed as multiple sclerosis in clinical practice

Authors: Carlson A et al.

Summary: This study described the clinical and imaging features of patients with adult-onset genetic leucodystrophies (gLD) who were initially misdiagnosed with MS. 19 patients who were referred to a single MS centre for white matter abnormalities (WMAs) on brain MRI, who initially had a suspected or established MS diagnosis but then received a confirmed diagnosis of gLD, were included. The most common presenting symptoms were spastic paraplegia (37%) and headache (16%). Ultimately, 79% of patients developed spastic paraplegia, while 63%, 47%, 42% and 37% had sensory, cognitive, urinary, and visual symptoms, respectively. 21% of patients had extra-neurological symptoms. gLD diagnoses included cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leucoencephalopathy (CADASIL; 21%), and hereditary spastic paraplegia (26%). WMAs fulfilled the criteria for dissemination in space in 37% of patients, but were atypical in most patients. 11% of patients had oligoclonal bands. Primary progressive MS was suspected in 68% of patients, and RRMS in 21%.

Comment: This study showed that patients with genetic disorders who had been misdiagnosed with MS usually had atypical features such as non-specific MRI abnormalities and negative oligoclonal bands in CSF. A progressive course (especially lower limb spasticity) was also seen in the majority of cases, suggesting that clinicians should be more cautious about diagnosing primary progressive MS than relapsing onset forms of MS. Almost half the genetic cases were diagnosed with either CADASIL (these patients have migraine and small-vessel strokes) or hereditary spastic paraparesis. The greater availability and lower cost of genetic testing means that it is now much more feasible to screen patients while working them up for a possible diagnosis of MS. This is important, as inappropriate exposure to MS disease-modifying agents is costly and potentially harmful. There are also emerging therapies for some gene disorders.

Session 1.4: Emerging Concepts in MS
Abstract

Tolerability of diroximel fumarate in relapsing-remitting multiple sclerosis patients with gastrointestinal co-morbidities at baseline

Authors: Singer BA et al.

Summary: This analysis of the ongoing EVOLVE-MS-1 trial evaluated the gastrointestinal (GI) tolerability of diroximel fumarate in patients with MS and coexisting GI disorders. 130 EVOLVE-MS-1 participants had a GI disorder at baseline, and 38.5% of these patients reported adverse GI effects while taking diroximel fumarate (median drug exposure was 1.7 years). The most frequently reported adverse GI events were diarrhoea (12.3%), nausea (10.8%), constipation (6.2%), upper abdominal pain (4.6%), and vomiting (3.8%). Most events were mild in severity; <1% of patients discontinued treatment due to poor GI tolerability.

Comment: Dimethyl fumarate is a funded oral treatment for relapsing MS in NZ. A proportion of patients do not tolerate dimethyl fumarate because of GI side effects. Diroximel fumarate is a similar drug – in fact it has the same active metabolite – and seems to have better tolerability with similar efficacy. This study looked specifically at people with pre-existing GI problems. The findings showed that the GI side effects of diroximel fumarate were mostly mild and did not persist. Diarrhoea, nausea and constipation were the most commonly reported adverse effects. Improvements in the tolerability of drugs are an important way to increase the time on treatment for people with MS. As the management of MS is a long-term project for each patient, time on treatment can be as important as treatment efficacy.

ePoster 049
Abstract

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Analysis of ocrelizumab treatment in aged patients at an academic MS centre

Authors: Luxenberg E et al.

Summary: This analysis of a real-life cohort examined the efficacy of ocrelizumab in MS patients aged >55 years. 59 patients with MS treated with ocrelizumab at the University of Washington MS Centre's infusion suite were included. 30 of them were aged 56–60 years, 12 were aged 61–65 years, 10 were aged 66–70 years, and 7 were aged >70 years. During follow-up, patients stopped ocrelizumab treatment because of MS progression (n=5), repeated or severe infections (n=5), unfavorable risk/benefit ratio (n=2), worsening psoriasis (n=1), and receiving autologous stem cell transplant (n=1). Limited data showed prolonged B-cell depletion for up to 1.5 years after the last ocrelizumab infusion in those aged >70 years.

Comment: Ocrelizumab is a monoclonal antibody that reduces B-lymphocyte populations. It has high efficacy in relapsing MS and is also the first drug to show benefit (albeit more modest) in primary progressive MS. There is understandable concern about long-term risks of infection in people treated with ocrelizumab, because of suppression of antibody formation. This observational study did find that these older, more disabled patients had significant rates of discontinuation due to serious infection. In patients older than 55 years, 5 out of 59 stopped ocrelizumab because of infection. Interpretation of these findings needs to take into account that more disabled, older people are already more vulnerable to infection, so not all of these infections are necessarily related to ocrelizumab. Nevertheless, prescribers will need to counsel patients about infection risk when using this drug.

ePoster 069
Abstract

Long term trajectories of employment status, work hours and disability pension status after an initial episode of CNS demyelination

Authors: Zarghami A et al.

Summary: This analysis of the AusImmune Longitudinal (AusLong) study determined trajectories of employment-related outcomes in 279 patients aged 18–59 years presenting with a first clinical diagnosis of CNS demyelination who were followed-up for at least 11 years. Distinct trajectories were found for employment status, average work hours per week and disability pension status. Female sex was associated with a higher risk of being in part-time work (relative risk [RR] 4.2, 95% CI 2.0–8.6) and having early deterioration in work hours (RR 2.7, 95% CI 1.4–5.3). Women also had a consistently higher risk of deteriorated work hours trajectories than men. An increased number of relapses during the 5 years after first clinical diagnosis was associated with an increased risk of early deteriorated or stable part-time trajectories. Patients who progressed to clinically definite MS and those with a higher number of comorbidities at baseline were more likely to be granted a disability pension.

Comment: This Australian study looked at employment status and disability pension receipt over time following initial presentation with MS. The results are worrying – remember that Australia has very high levels of access to DMTs for MS. Despite this, over the 11 years analysed from initial presentation with MS, there was a significant and progressive change in employment status for many individuals, with fewer hours worked over time, and higher rates of claiming for disability pension. These trends were much higher in females than males, for reasons that are unclear. Reduction in working hours was also slightly higher in people with other baseline co-morbidities and in those with higher MS relapse activity. It is to be hoped that earlier use of more modern effective treatments for MS will eventually improve employment prospects, but there is clearly still much to be done.

ePoster 088
Abstract

Reference: 1. TECFIDERA (dimethyl fumarate) Data Sheet, 5 March 2020. **2.** Gold R *et al. Neurol Ther* 2015;4:93–104. **3.** Hellwig K *et al.* Poster presented at ACTRIMS–ECTRIMS: September 11–13 2020. Virtual conference. **4.** Gilenya (fingolimod) Data Sheet, 20 July 2020. **5.** Aubagio (teriflunomide) Data Sheet, 18 August 2020 / Aubagio (teriflunomide) Product Information, 17 September 2020. **6.** Fampyra (fampridine) Data Sheet, 31 January 2020. **7.** Mavenclad (cladribine) Data Sheet, 11 May 2020 / Mavenclad (cladribine) Product Information, 15 January 2021. **8.** Gold R *et al. Ther Adv Neurol Disord* 2020;13:1–17. **9.** Desai A *et al. Eur J Pharm Med Res* 2016;3(5):197–205.

Vaccination responses in setting of different types of MS DMTs

Authors: Bar-Or A et al.

Summary: While direct data are lacking, it is expected that different DMTs will have varying effects on COVID vaccine responses. It is thought that these differences will depend on the particular DMT mechanism of action and the timing of vaccination relative to DMT administration. Cell-depleting therapies, including those that deplete B-cells (such as a CD20, cladribine, and alemtuzumab) are not likely to affect pre-existing humoral immunity, but are expected to attenuate vaccine-induced antibody responses.

Comment: With vaccines beginning to be rolled out in NZ, decisions about their use in special patient groups have become very relevant. As none of the vaccines is live, they are all expected to be safe in people on immune-modulating treatments. There is no evidence so far to suggest that COVID-19 vaccines will exacerbate MS. For the majority of MS agents funded in NZ (teriflunomide, beta-interferon, glatiramer, natalizumab and dimethyl fumarate), vaccination may be done just as normal. For patients about to start fingolimod (a drug that may attenuate the immune response to vaccination), it is recommended that the second vaccine dose be given ≥4 weeks before starting fingolimod, if this is feasible. For patients about to start ocrelizumab, it is also recommended that there should be a 4-week delay from the second vaccine dose. Additionally, patients already receiving ocrelizumab should ideally be vaccinated ≥12 weeks after their last dose of ocrelizumab, with 4 weeks again being allowed following the second vaccine dose before the next dose of ocrelizumab is given. Encouragingly, it is not thought that people who already have immunity due to vaccination or exposure will have that immunity reduced by treatment with MS drugs.

Session CE1.2: Cutting Edge Developments
Abstract

COVID-19 and MS-registry information

Authors: Salter A

Summary: This presentation discussed global efforts to determine COVID-19 outcomes and risks in patients with MS. In particular, the findings of a registry-based study of patients with MS and SARS-CoV-2 infection (COViMS) in North America were presented.

Comment: Although we have been fortunate to avoid high levels of COVID-19 in the community in NZ, patients understandably often ask about factors related to MS. This presentation looked at various registries from around the world. What emerged is that more severe COVID-19 is seen in older and more disabled MS patients, and also those with obesity. This is very similar to the risk profile for severe COVID-19 in the general population. There were mixed results related to the potential for more severe COVID-19 in MS patients taking anti CD-20 drugs such as ocrelizumab or rituximab, and interpretation here may be complicated by confounding factors – ocrelizumab may be used more than other drugs in disabled patients with primary progressive MS. Encouragingly, it appears that outcomes are improving over time for MS patients with COVID-19, possibly because of improved management of severe cases.

Session CE1.1: Cutting Edge Developments
Abstract

An increased normal appearing white matter perfusion: A possible radiological inflammatory marker in relapsing-remitting multiple sclerosis

Authors: Lapucci C et al.

Summary: This study used dynamic susceptibility contrast-enhanced (DSC) perfusion to evaluate brain haemodynamic changes in RRMS patients in clinical relapse (REL) or without relapse in the previous 2 months (REM). 45 patients underwent 3T MRI scans (including 3D-FLAIR, 3D-T1MPRAGE, DSC epiT2* and T1SE post gadolinium administration sequences) to determine cerebral blood flow, cerebral blood volume, and mean transit time. DSC perfusion showed a relative hyperperfusion of normal appearing white matter (NAWM). The correlations between perfusion of NAWM, disease duration and annualised relapse rate in the previous year in REM patients suggests that increased perfusion of NAWM may be a radiological marker of higher inflammatory activity.

Comment: Although the usage of three letter abbreviations (TLA) makes this study difficult to read, the findings are interesting. Measuring regional brain perfusion using MRI, the investigators found higher cerebral blood flow in the NAWM of patients with shorter disease duration and higher relapse activity. This suggests that blood flow may be a marker of inflammatory disease activity that is partly independent of the more obvious MRI plaque formation. This is important, as disability progression may occur in people who are not developing new MRI lesions, and the mechanism of this "silent progression" is not well understood.

ePoster 103
Abstract

Prevalence and use of disease modifying therapy in radiologically isolated syndrome (RIS)

Authors: George IC et al.

Summary: This study examined the use of DMT in people with RIS. A search of medical records identified 49 patients diagnosed with RIS at Mass General Brigham in 2005–2020 who were followed-up for at least 2 years (38 female, mean age at diagnosis 41 years). 20 patients (40.8%) were treated with a DMT (median treatment duration 2.67 years). These patients were younger than those who were not treated with DMTs (mean age at diagnosis 37.6 vs 44.1 years, p=0.03), and most (73.5%) met >2 Barkhof criteria. The reasons for DMT initiation were MRI change over time (including newly gadolinium-enhancing lesions, 65%), clinical suspicion of high risk of conversion to MS (30%), and/or a high burden of CNS demyelinating disease on MRI (20%). Dimethyl fumarate was the most common first-line agent, followed by glatiramer acetate, teriflunomide, ocrelizumab and fingolimod. Seven patients required a second-line agent (5 due to poor tolerability and 2 for MRI activity). 1 patient developed clinically isolated syndrome during follow-up.

Comment: In NZ, access to funded DMT is restricted to patients who have had at least 2 clinical relapses. Patients with a single relapse and MRI findings consistent with MS have a very high risk of future relapse and are treated in many other countries. This study looks at patients who have MRI changes consistent with MS, but have never had a relapse. Such patients have usually undergone MRI for other reasons, such as investigation of headache. Here we see that 40% of these radiologically isolated cases were started on immunomodulatory agents, often prompted by the development of new abnormalities on repeat MRI. I can see the temptation to do this, but without robust evidence of prognostic benefit, I would be happy to wait for the first clinical episode.

ePoster P168
Abstract

Pain locations, prevalence, severity and interference in ambulation in people with multiple sclerosis and self-reported spasticity

Authors: Hugos CL et al.

Summary: This study evaluated the impact of an education and lower extremity stretching programme (Spasticity: Take Control, STC) on chronic pain in people with MS and spasticity. 66 individuals with MS and spasticity were randomised to STC or a programme focused on education and range of motion (ROM). Both groups had two 2-hour group sessions and were asked to track their exercise for 6 months. At baseline, 35 of 66 patients (53%) reported chronic pain, mostly in the lower back and/or legs. Both pain severity and interference improved significantly from baseline after 6 months in the STC group, but improvements were smaller and not significant in the ROM group.

Comment: Pain is common in people with MS. This study looked at pain in people with lower limb spasticity. The most common areas for reported pain were lower back, leg, upper back, head and arm. The authors also investigated 2 different exercise-based interventions. Although both interventions were associated with improvement in reported pain, these findings could be due to regression to the mean, so more detailed studies would be needed to confirm any potential benefit. Exercise-based interventions that do not require direct therapist supervision would be very useful, and intuitively you would think that some patients would benefit, at least for pain related to spasticity. I have generally found that medications are only helpful in the short term when used to treat spasticity and associated pain.

ePoster P222
Abstract