A RESEARCH REVIEW™
CONFERENCE REVIEW

ECTRIMS 2021

Making Education Easy
13–15 Oct 2021

In this review:

Abbreviations used in this review
COVID-19 = coronavirus disease 2019
CSF = cerebrospinal fluid
DMT = disease-modifying therapy
EAN = European Academy of Neurology
ECTRIMS = European Committee of Treatment and Research in MS
EDSS = Expanded Disability Status Scale
MRI = magnetic resonance imaging
MS = multiple sclerosis
PPMS = primary progressive MS
RRMS = relapsing-remitting MS
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SPMS = secondary progressive MS

RESEARCH REVIEW™
Making Education Easy — Since 2006

Welcome to our review of the 37th Congress of the European Committee for Treatment and Research in MS (ECTRIMS) that was held online recently.

The scientific programme comprised well-known session formats such as Scientific Sessions, Hot Topics and Meet the Experts, as well as live discussions between the international faculty and participants at the end of each session. I have selected and reviewed 10 presentations from ECTRIMS 2021 that I found to be particularly interesting. All abstracts have been published in an online supplement of the Multiple Sclerosis Journal, and more information about the meeting can be found at https://www.ectrims-congress.eu/2021.html.

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

Kind regards
Dr John Mottershead
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MRI activity versus relapses as markers of disease activity in SPMS: Data from real world and pivotal clinical studies

Speaker: Gavin Giovannoni, UK

Summary: This study analysed data from the Adelphi real-world MS Disease Specific Programme (Adelphi MS DSP) and the phase 3 EXPAND study to evaluate the contribution of MRI activity and relapses in defining disease activity in patients with SPMS. 2554 patients with SPMS from the Adelphi MS DSP were categorised as having active SPMS (n=1889) or non-active SPMS (n=665). Active SPMS was defined on the basis of MRI lesions (59.1%), relapse status (12.6%), and both MRI and relapse (28.3%). Over the past 12 months, active SPMS patients had had a lower mean EDSS score (4.6 vs 5.2), a higher proportion of patients undergoing MRI (87.7% vs 58.7%), and more MRIs per patient (1.24 vs 0.87) than non-active SPMS patients. More non-active SPMS patients than active SPMS patients were without treatment (45.1% vs 23.4%). In EXPAND (n=1645), 52.6% of patients who had no relapse in the 2 years prior to screening and no Gd+T1 lesions were categorised as having non-active SPMS. Of the non-active SPMS patients who were randomised to receive placebo, 52.7% experienced on-study relapse and/or MRI activity.

Comment: This is a great study from a UK group. They have looked to see whether patients with SPMS can be meaningfully split into active and inactive groups and whether the inactive patients stay inactive. SPMS is the progressive form of MS that follows the initial relapsing-remitting phase after a latency of around 10 years in many patients. In this study, patients who had experienced neither new MRI lesions nor recent relapses had a more than 50% chance of reactivating over the next few years, with new MRI activity, relapses or both. MRI activity happened significantly more often than relapses, presumably because some MRI lesions develop in areas that are not clinically eloquent. Pharmac access criteria for initiation of DMT require a relapse in the last 12 months (or 2 in the last 24 months), plus new MRI activity on a scan within the last 2 years. This study suggests that even in patients with established SPMS, it is worth arranging an MRI to look for activity if there has been relapse activity.

Clinical aspects of MS – Diagnosis and differential diagnosis: P001

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.

Disease-modifying treatment – if and when to stop in relapsing MS

Speaker: Ilya Kister, US

Summary: This literature review investigated whether DMTs should be used indefinitely in patients with RRMS, and discussed the pros and cons of therapy discontinuation in patients deemed to be at 'low risk' for disease reactivation. More than 12 recent studies were identified that directly addressed the question of DMT discontinuation; all of these studies were observational and many were retrospective. The available literature does not allow for an evidence-based decision of whether or when it may be safe to stop DMT, but provides a framework for a discussion of the pros and cons of DMT discontinuation. Various demographic, clinical, radiologic, and laboratory variables were identified that may be relevant for assessing the risk of post-discontinuation relapse. However, even in patients at low risk for relapses, it is unknown whether DMT discontinuation may impact progression independently of relapse activity, subclinical disease activity, and brain atrophy. The potential negative impact of DMT discontinuation needs to be weighed against the risk of prolonged immunosuppression/immunomodulation in ageing and more disabled patients, especially in the era of COVID-19. Three ongoing randomised trials of DMT discontinuation are expected to generate higher-level evidence for making this difficult decision.

Comment: More than 50% of the 3000 plus patients with MS in NZ are receiving DMTs. It is unlikely that all of them will benefit from continual treatment for the whole of their lives. But when is it safe to stop? This presentation reviewed the literature. All available studies were retrospective and mostly looked at stopping the older injectable drugs, beta-interferon and glatiramer acetate. The message seems to be that people under 45 years old, those with recent new changes on MRI, and those with recent relapse activity are at greater risk for reactivation on withdrawal of therapy. Given that older people seem to be at higher risk for serious complications from high efficacy immunomodulatory agents, there is likely to be an argument to stop therapy in older people with MS who have had no recent MRI or relapse activity. Prospective studies looking at this issue are already underway, but the outcomes may not be clear cut, given the number of factors in play.

Hot Topic 7: Disease modifying treatment – if and when to stop; 066

Disease-modifying treatment – if and when to stop in progressive MS?

Speaker: Gavin Giovannoni, UK

Summary: Stopping a maintenance anti-inflammatory DMT in more advanced or progressive MS carries the risk of rebound inflammatory activity. Evidence suggests that patients who had highly active disease when they started DMTs tend to 'reactivate' after stopping them. Factors such as immunosenescence, infection, cancer risk, vaccine-responsiveness, and comorbidities (particularly cardiovascular risk) need to be weighed up when deciding whether to continue or stop DMT. One option is a de-risking strategy (switching to safer immunomodulatory therapies) and another is to select an immune reconstitution therapy that is not associated with long-term immunosuppression in this phase of the disease. In addition, combination therapies and additional therapeutic targets may be considered instead of stopping DMTs. Randomised controlled withdrawal studies are needed to generate evidence-based criteria for stopping DMT in patients with progressive MS.

Comment: Recent changes in Pharmac funding criteria mean that many people with MS in NZ may stay on treatment until they progress to the point where they are unable to walk 100m with or without assistance. These changes are welcome, but do mean that some people may potentially stay on therapy into old age, and at relatively high levels of disability. As with the presentation on stopping treatment in relapsing MS reviewed above, many of the answers as to the right way to proceed are still unclear. One possible strategy would be to de-escalate therapy from high efficacy to lower efficacy agents in older people with no recent MRI or relapse activity. Against this, we know that the effectiveness of lower efficacy agents in progressive MS is less convincing than for the high efficacy agent ocrelizumab, although this may be in part because clinical trials used ambulation as the main outcome measure, rather than upper limb, bulbar and cognitive function which may be more sensitive to intervention in later-stage MS.

Hot Topic 7: Disease modifying treatment – if and when to stop; 067

Difficulties in diagnosis of primary progressive multiple sclerosis

Speaker: Katelijn Blok, the Netherlands

Summary: This study identified common difficulties in diagnosing PPMS in a real-world setting. The records of 322 patients with a diagnosis of PPMS in 2 MS centres were reviewed, and the diagnosis of PPMS was reassessed using a predefined set of criteria. The original diagnosis met the predefined criteria for 48% of cases. For the remaining patients, at least one of the following problems was observed: incomplete diagnostic work-up; reported episodes suggestive of remyelination in the previous medical history; failure to exclude other possible diagnoses; not meeting 2017 McDonald criteria despite full diagnostic work-up; and other concomitant diagnoses that blurred the MS disease course.

Comment: PPMS amounts to around 15% of cases. It presents at an older age – often 40s or 50s, and the male to female ratio is equal. As this study shows, diagnosis is often difficult. One reason for this is the absence of characteristic relapses – in relapsing onset MS an episode of, say, optic neuritis is a big diagnostic clue. Another problem is that, as we get older, white matter lesions on MRI due to small vessel ischaemia become more commonplace, so MRI is a less reliable diagnostic tool. Hereditary spastic paraparesis, mechanical cervical myelopathy, motor neurone disease and cerebrovascular disease may all sometimes present in ways that may cause confusion with PPMS. I would be more likely to arrange CSF studies looking for oligoclonal bands when investigating older people with a non-relapsing course, especially if there were no enhancing lesions seen on MRI. Positive oligoclonal bands and/or enhancing MRI lesions provide reasonable support for a diagnosis of MS.

Clinical aspects of MS – Diagnosis and differential diagnosis; P020

Economic impact and clinical profile of the secondary progressive multiple sclerosis (SPMS) patient: The DISCOVER study

Speaker: Celia Oreja-Guevara, Spain

Summary: The DISCOVER study investigated the heath-related and non-health-related costs of SPMS. 297 patients who were treated and monitored according to routine clinical practice at 34 sites in Spain were included; the primary outcome was the estimated total annual cost per patient (including health and non-health-related direct costs and indirect costs). Mean age was 54.6 years, and patients had a median EDSS of 2.0, 5.3 and 6.0 at MS diagnosis, SPMS diagnosis and study visit, respectively. 19.9% of patients had active SPMS. The majority (89.6%) of patients were unemployed, and most (71.7%) of these patients had permanent disability. Patients with higher EDSS had a lower health-related quality of life as measured by EuroQol 5 Dimension 5 Level utility index. Total annual cost per patient was 41,448.58€, which comprised health-related resources (11,310.86€), non-health-related resources (8,775.34€), and indirect costs (21,362.37€). Costs ranged from 34,880.43€ for patients with an EDSS score of 3–3.5 to 46,218.88€ for patients with an EDSS score of 6.5.

Comment: SPMS follows on from the relapsing-remitting phase and is often only diagnosed retrospectively, after walking difficulties, bladder problems, ataxia and cognitive issues have built up gradually. This study looked at patients with established SPMS – on average these were people who would require assistance to walk more than very short distances. The findings are that there are large health-related, non-health-related and indirect societal costs. The aim of early intervention with DMTs is to reduce or delay secondary progression. Although the costs of modern treatments are high, this and other studies show that the potential financial benefits of successful treatment are very considerable. Intervening once SPMS is already established may possibly slow disability trajectories, but is unfortunately not likely to be as effective in terms of health or economic outcomes.

Clinical aspects of MS – Economic burden; P274

Real world experience with ocrelizumab in patients with primary progressive multiple sclerosis: Insights from the German NeuroTransData Registry

Speaker: Stefan Braune, Germany

Summary: This report described the real-world experience with ocrelizumab in patients with PPMS. 460 patients registered with the German NeuroTransData registry (a network of 66 neurology outpatient services across Germany) were included; 82 of whom were treated with ocrelizumab. Ocrelizumab recipients were younger (mean age 51.5 vs 62.3 years), had a shorter time from first PPMS symptoms (mean 8.69 vs 18.74 years), and had similar EDSS scores (mean 4.44 vs 4.99) compared to the overall PPMS cohort. The mean ocrelizumab treatment duration was 1.5 years. Persistence was 98.7% at 12 months and 94.8% at 24 months, and administration of infusions followed the recommended schedule. During the observation period, no significant change in EDSS score was noted.

Comment: PPMS has for a long time been resistant to treatment – the same drugs that have shown efficacy in relapsing MS have failed when tried in PPMS. This changed a few years ago when ocrelizumab, a monoclonal antibody similar to rituximab, which targets B-cells, achieved positive outcomes in a clinical trial. The benefits in slowing disability were smaller than those seen with the same drug in relapsing MS, but were nevertheless a welcome piece of good news. This study looked at the German experience with ocrelizumab in this patient population. The results are encouraging – there was high persistence on treatment and short-term stability of disability levels. Pharmac is currently looking into funding ocrelizumab for PPMS in NZ. Ocrelizumab has not been through trials in SPMS, but it would be surprising if it were not at least as effective there as it is in PPMS.

Clinical aspects of MS – Progressive MS; P117

Comparing humoral immune response to SARS-CoV2 vaccines in multiple sclerosis and healthy controls

Speaker: Gabriel Bsteh, Austria

Summary: This multicentre trial in Austria evaluated humoral immune response to SARS-CoV-2 vaccines in 467 patients with MS compared with 124 healthy individuals. Preliminary analyses show that 89.9% of MS patients and 97.6% of healthy controls developed protective levels of anti-SARS-CoV-2 immunoglobulin G antibodies. Positivity rate was significantly lower in patients on immunosuppressive DMTs (63.8%) than in patients not on DMTs (91.7%) or on immunomodulatory DMTs (92.9%). Seroconversion was lowest in patients taking anti CD-20 monoclonal antibodies (55.2%) or sphingosine-1 receptor modulators (75%).

Comment: COVID-19 vaccination is very much in the news. This study adds to previous data, especially from Israel, which show that vaccination seems to be safe in MS, with no signal to suggest that relapses are triggered. Immunity levels following vaccination are similar to those seen in healthy controls, apart from for those patients taking sphingosine-1-phosphate modulators like fingolimod, or anti CD-20 monoclonal antibodies like ocrelizumab, who have lower antibody responses. When choosing a treatment, potential effects on vaccine-related protective immunity are now a significant consideration, and often the approach may be to delay initiation until a patient has been doubly vaccinated, if other factors suggest that ocrelizumab or fingolimod is the best agent to use. The prospect of booster vaccinations obviously complicates things further, and I now talk through these issues before finalising treatment choice with the individual. Things are simpler with the other funded drugs, which seem to have little or no effect on vaccine response.

Scientific Session 18: Late Breaking News; 186

The impact of smoking cessation on multiple sclerosis disease progression

Speaker: Jeff Rodgers, UK

Summary: This study investigated the impact of smoking cessation on disease progression in patients with MS. 7983 adults with confirmed MS who were registered on the UK MS Register were included. 4130 (51.7%) participants had ever smoked, of whom 1315 (16.5%) were still smokers and 2815 (68.2%) were former smokers. For all patient-reported outcomes, adults who were still smokers at the time of completing their first questionnaire had higher disability than those who had never smoked. There was no improvement in patient-reported outcomes with increasing time since quitting in former smokers. A prospective parallel group analysis (n=922) demonstrated that normalised MS Physical Impact Scale, normalised MS Walking Scale, and Hospital Anxiety and Depression Scale (HADS) depression worsened significantly over a period of 4 years, whereas HADS-anxiety remained stable. Post-hoc analysis showed that being a still smoker was associated with a worse score than never smokers for the MS Physical Impact Scale and MS Walking Scale, whereas former smokers were no different from never smokers.

Comment: Smoking has been found to be a risk factor for development of MS in many studies, and may also be associated with a less favourable clinical course. This large UK registry study presented both retrospective and prospective data. The most interesting results were that, despite starting at the same patient-reported disability level, current smokers progressed more rapidly than former smokers and experienced higher levels of mood disturbance as well as increased disability. It seems likely that this is a causal effect, unless there is something about the biological situation of a person who is more likely to progress that makes it harder for them to give up smoking. The practical take-home message is that people with MS should be encouraged to stop smoking, not just for the usual reasons, but also because their MS prognosis may be better if they are successful. Lifestyle advice is increasingly a part of MS management, with exercise and dietary factors also worthy of attention.

Scientific Session 7: Epidemiology in MS – what we know, don't know and why; 065

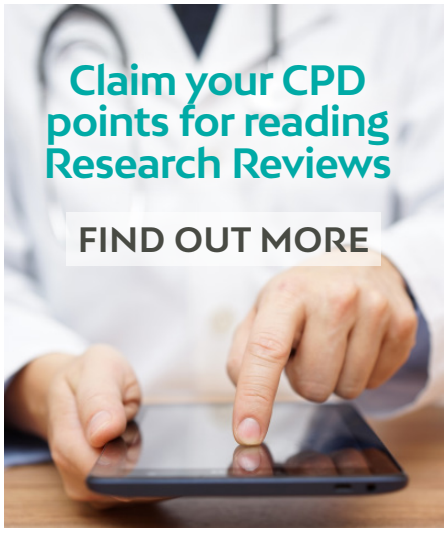
Recommended standards for vaccinations in MS patients

Speaker: Susana Otero-Romero, Spain

Summary: This joint statement on behalf of the ECTRIMS-EAN presented evidence-based guidelines for vaccination in patients with MS. Current evidence indicates that vaccines are not associated with an increased risk of relapse or disability accrual in MS patients with or without DMTs, and the benefits of immunisation greatly outweigh any potential risks.

Comment: The COVID-19 pandemic has thrown the whole area of vaccination into greater focus. As a result, clinicians are thinking more about vaccination status in general when dealing with people who may need to start immunomodulatory treatments. In this work, a European committee has drafted guidelines for vaccination in MS patients. They reviewed available evidence and then used a modified Delphi process to achieve at least 80% consensus on recommendations. Broadly speaking, they suggest that immunisation status should be ascertained early on in people with MS, and where there are gaps, vaccination should be offered against measles-mumps-rubella, diphtheria-pertussis- tetanus, varicella zoster virus, and in some patients hepatitis B, human papillomavirus, herpes zoster, pneumococcus and influenza. Inactivated vaccines may be given safely to patients on immunosuppressive drugs, but efficacy may be reduced. Live attenuated vaccines should be given prior to starting immunosuppressive therapy, if indicated. The benefit of dealing with immunity gaps soon after diagnosis is that there will not need to be any delay in starting immunosuppressive therapy later on.

ECTRIMS-EAN Session; 181



An RXR agonist causes age-dependent remyelination in people with relapsing remitting MS

Speaker: Christopher E McMurran, UK

Summary: The phase 2a CCMR One trial showed that the retinoid-X receptor agonist bexarotene improved neurophysiological and radiological markers of remyelination in RRMS patients aged 25–50 years. This post-hoc analysis of the results investigated whether the remyelination associated with bexarotene varies with patient age. For eyes with chronic optic neuropathy, bexarotene shortened full-field visual evoked potential (VEP) P100 latency maximally in younger patients. P100 improvement in the treatment group diminished by 0.45 ms/year, such that bexarotene had no significant benefit over placebo in patients aged ≥42 years. There was a similar age-related decline in deep grey matter remyelination, with no significant treatment effect in patients aged ≥42 years. In the other 2 brain regions sensitive to bexarotene (cortical grey matter and brainstem), remyelination did not significantly decline with age.

Comment: Remyelination occurs naturally in people with MS, resulting in plaques changing from having a bright white appearance on T2-weighted MRI to become grey "shadow plaques". Unfortunately, a lot of demyelinated areas fail to remyelinate. Treatments that promote successful remyelination are being actively studied. This paper looked at a trial of a retinoid-X receptor agonist, bexarotene. The small clinical trial showed promising signals for efficacy, as assessed by improvements in VEPs and MRI measures of myelination. Unfortunately, toxicity issues mean that this drug will not go forward to phase 3 trials. The beneficial effects seemed to be restricted to people under the age of 42, mirroring results in experimental rats, where remyelination is more successful in younger animals, partly because of the biochemical environment, and partly because the oligodendrocytes in older animals become less responsive to stimulation. We must hope that other drugs in this class will prove to be safe and effective, preferably for people of all ages.

Free Communication 4: Treatment trials – Neuroprotection and remyelination; 148

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