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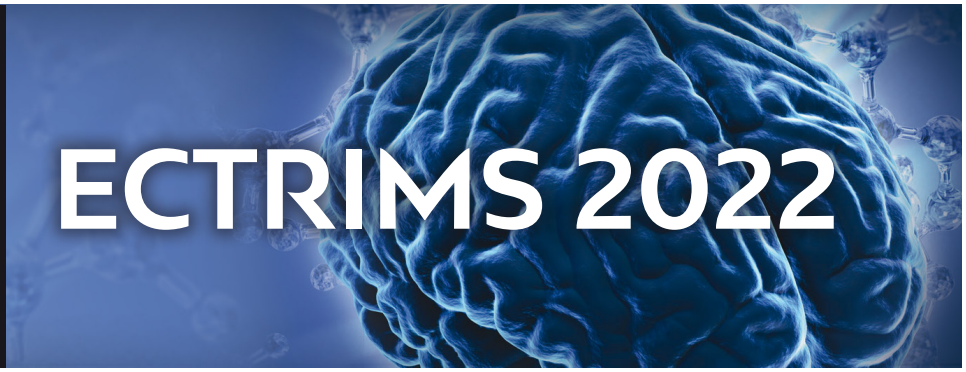
CONFERENCE REVIEW



ECTRIMS 2022

Making Education Easy

26-28 October, 2022

In this review:

Abbreviations used in this review
AE = adverse effects
ARR = annualised relapse rates
CI = confidence interval
CNS = central nervous system
DMT = disease-modifying therapy
EDSS = expanded disability status scale
Gd = gadolinium
HAD = highly active disease
HR = hazard ratio
Ig = immunoglobulin
IV = intravenous
MRI = magnetic resonance imaging
MS = multiple sclerosis
OR = odds ratio
RCT = randomised controlled trial
RIS = radiologically isolated syndrome
RRMS = relapsing remitting multiple sclerosis
TEAE = treatment-emergent adverse effects

RESEARCH REVIEW™
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Welcome to our review of the 38th Congress of the European Committee for Treatment and Research in MS (ECTRIMS) that I recently attended online.

The scientific programme included 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 2022 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://2022.ectrims-congress.eu/.

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

Kind regards
Dr John Mottershead
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Multi-center, randomized, double-blinded assessment of dimethyl fumarate in extending the time to a first clinical demyelinating event in radiologically isolated syndrome (ARISE).

Speaker: D.T. Okuda

Summary: This study assessed the effect of therapeutic intervention at preventing first symptom manifestation during the RIS stage of MS. A multi-center, double-blind RCT was conducted in people with RIS. Participants (n=87) were randomised to dimethyl fumarate (DMF – 240 mg BD) or placebo. The primary end-point was time to onset of clinical symptoms attributable to a CNS-demyelinating event at week 96. The risk of a first demyelinating event during the 96-week study period was significantly reduced in both the unadjusted HR (HR 0·18; p=0·007) and the adjusted HR (0·07; p=0·005). After adjusting for Gd-enhancing lesions at baseline, the number of new or newly-enlarging T2-weighted hyperintense lesions in the DM was significantly reduced, compared to placebo (p=0.042). There were more moderate adverse reactions in the DMF arm (31.8%) than the placebo arm (20.9%), but the rate of severe events was similar. DMF treatment was associated with >80% risk reduction for a first clinical event related to CNS demyelination, relative to placebo.

Comment: DMF is funded in NZ for treatment of relapsing onset MS. Since July 2022, this includes people who have only experienced a single clinical episode if they fulfil McDonald 2017 diagnostic criteria for MS. This study is the first trial of treatment in people with RIS - these are individuals who have had an MRI done for other reasons (the biggest group in the trial had had the scan because of headache) and are unexpectedly seen to have MRI findings typical of MS. The results were that around 40% of the placebo group had a clinical episode over the 96 weeks of the trial. This risk was reduced by around 80% in patients treated with DMF. RIS is currently only seen rarely, but this will change with greater availability of MRI. We should expect pressure for funding of treatment for RIS, but this will not be likely to happen in NZ until there is more evidence of a long-term benefit from such an approach.

Scientific Session 18 – Late Breaking Abstracts: 0179

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.

Effectiveness of autologous haematopoietic stem cell transplantation in comparison with natalizumab in progressive MS

Speaker: T. Kalincik

Summary: This study compared the effectiveness of autologous haematopoietic stem cell transplantation (AHSCT) versus natalizumab in progressive MS. Patients with secondary or primary MS from 6 AHSCT centres were combined with patients from MSBase. Eligible patients had received AHSCT or natalizumab during progressive MS. Propensity matching scores were used to create pairwise-censored groups for analysis. The 39 patients treated with AHSCT (mean age 37 years, mean EDSS = 5.7) experienced similar on-treatment relapse frequency as the 65 matched natalizumab patients during ≤6 years (mean ARR ±SD 0.08±0.28 vs. 0.07±0.25). The cumulative hazards of 6-month confirmed EDSS worsening and improvement were also similar. Adverse events in the AHSCT group included serum sickness (9 patients), ICU admission (6), febrile neutropenia during mobilisation (3), and 36 patients experienced complications after discharge. AHSCT was not superior in reducing disability progression or allowing reduction of disability in this group of patients with progressive MS.

Comment: AHSCT is of proven efficacy in the treatment of RRMS, and there are promising signs that the availability of this intervention may be about to improve in NZ. There is far less evidence for the use of AHSCT in progressive MS, although some centres around the world will treat patients with progressive MS who have evidence of recent MRI activity, particularly if they are relatively young. Natalizumab is a high efficacy drug in RRMS, but a trial in advanced secondary progressive MS was negative for the primary outcome (based around ambulation). This new study used retrospective analysis of groups of patients with primary or secondary progressive MS matched for clinical confounding prognostic variables. The secondary progressive group were enriched for recent relapse activity (because many AHSCT centres stipulate relapse activity within the last year as a criterion for access to this treatment). The results showed that 45% of patients receiving AHSCT experienced disability progression over the next 5 years, and that the results were similar in the natalizumab group. Unfortunately, these findings strengthen the suspicion that neither AHSCT nor natalizumab is likely to be especially effective in advanced progressive MS.

Scientific Session 18 – Late Breaking Abstracts: 0181

Immunadsorption versus double-dose methyl prednisolone in steroid-refractory multiple sclerosis relapses: results from the INCIDENT-MS study

Speaker: S. Pfeuffer

Summary: This study compared the safety and effectiveness of immunoadsorption (IA) versus intravenous methyl prednisolone (IVMPS) in acute MS relapses. Patients (n=42) with a significant persisting disability following a first course of IVMPS received either 6 courses of tryptophan-IA (n=16) or a second course of IVMPS (n=26). At discharge, the adjusted OR for any treatment response towards escalation treatment favoured IA (p=0.005). At 3-month follow-up, the OR for best clinical response was 50.7 favouring IA (p<0.001). The findings for evoked potentials and neurofilament light-chain levels were similar. Immunophenotyping revealed a marked reduction of B cell subsets following IA treatment that was correlated to treatment response and was not seen following IVMPS. Tryptophan-IA appears to produce favourable outcomes in patients with steroid-refractory MS relapses, compared to a second course of IVMPS. The investigators did not detect any new security signals with IA which contrasts with the serious risks associated with double-dose IVMPS, including infections or even psychosis.

Comment: A substantial minority of patients with severe MS relapse do not have a good outcome after an initial course of steroids (often 1000mg IV methylprednisolone for 3-5 days). Current practice is often to consider plasma exchange if the patient has major residual disability from a relapse e.g. blindness, paraplegia. This small prospective study compared a double-dose steroid treatment course with IA (which is similar to plasma exchange). The results suggest that, at least if done early (the average delay before IA was 17 days here) IA achieves very good improvements for many patients and is far more effective than high-dose steroid.

Immunomodulation/Immunosuppression E-poster: P282

Discontinuation of first-line disease-modifying therapy in multiple sclerosis

Speaker: E.M. Coerver

Summary: The safety of discontinuing first-line DMT in relapse onset MS patients is poorly understood. This study aimed to investigate the characteristics of patients who discontinued DMT and the development of clinical and radiological inflammatory disease activity thereafter. Data was collected from 130 patients with relapse onset MS who had discontinued first-line DMT with no intention of restarting or switching treatment. The median duration of follow-up after discontinuation was 59.5 months. MRI activity after DMT discontinuation was seen in 62 patients (47.7%), 33 of whom did not have a clinical relapse. A relapse was experienced by 40 patients (30.8%), 25 of whom also displayed MRI activity. Recommencement of DMT occurred in 22.3% of patients. Increased age at discontinuation was associated with a lower risk of subsequent MRI activity, a lower total number of new T2-lesions, and a lower risk of relapse. No other statistically significant predictors of disease activity were found.

Comment: There are now a lot of patients in NZ on DMTs. From subgroup analyses of clinical trials, we know that older patients have a less favourable response to treatment. We also know that MRI and relapse activity, which are two of the main outcomes affected by DMTs, are lower in older individuals with MS. Furthermore, older people are more vulnerable to infections and other risks of DMT usage. Neurologists are increasingly asking when the right time to consider stopping treatment may be. This retrospective study found that MRI and relapse activity was less likely after discontinuation in older patients, especially if there had been no MRI activity in the 4 years leading up to discontinuation. Although it is tempting to offer discontinuation to clinically and radiologically inactive patients who are aged over 55, it would be good to have data from prospective randomised studies - this study does not tell us what would have happened if the patients had stayed on treatment. Data on disability outcomes will also be important.

Immunomodulation/Immunosuppression E-poster: P302

MRI, efficacy, and safety of tolebrutinib in patients with highly active disease (HAD): 2-year data from the phase 2b Long-term safety (LTS) Study

Speaker: R.J. Fox

Summary: This is a phase 2 trial reporting on the safety and efficacy outcomes of the Bruton's tyrosine kinase inhibitor tolebrutinib at week 96 in relapsing MS patients with HAD. In the double-blind section of the study (Part A, n=60) patients continued their study tolebrutinib dose (5, 15, 30 or 60 mg/day) and in the open-label section (Part B, n=59) all patients received 60 mg/day. New Gd-enhancing lesion counts stayed low in the 60/60-mg arm through W96 and dropped in other arms by W48 through W96, except for the 5/60-arm. Low new/enlarging T2 lesion counts persisted for the 15/60, 30/60, and 60/60 mg arms. The T2 lesion volume was unchanged for the 60/60-mg arm. A dose-response relationship for TEAE/serious AE was not observed in Part A and no new safety signals for patients switching to 60 mg in Part B were reported. The ARR for patients who received tolebrutinib 60 mg/day ≥8 weeks was 0.10 and 92.9% remained relapse-free at W96.

Comment: BTK inhibitors are of proven efficacy in certain haematological malignancies. They are currently of great interest as potential treatments for MS. They penetrate the blood-brain barrier and are expected to modulate B-lymphocyte and microglial activity, both of which are important in MS progression. It is hoped that BTK inhibitors may slow disability progression in primary and secondary progressive MS, rather than being yet another class of drug whose main utility is in relapsing MS. Phase 3 studies in relapsing and progressive MS are underway using several different BTK inhibitors. This phase 2 study showed good efficacy in suppressing enhancing lesions and reducing the number of enlarging lesions in people with highly active MS.

Immunomodulation/Immunosuppression E-poster: P292

B-lymphocyte-guided retreatment contributes to establish a good effectiveness/safety profile in MS patients treated with rituximab

Speaker: J.L. Chico Garcia

Summary: This prospective study aimed to establish the best B lymphocyte (BL) value for rituximab retreatment in MS and to confirm efficacy and safety. An exploratory cohort involved 10 MS patients with BL assessed every 3 months following rituximab infusion with retreatment made at BL values ≥0.5%. The confirmatory cohort involved 41 MS patients (87.8% with secondary progressive MS, median disease duration 14.1 years, EDSS score=5.5) treated with rituximab in the same manner as the exploratory cohort. A BL value ≥0.2% was established from the exploratory cohort as the optimal retreatment value. In the confirmatory cohort, rituximab reduced the ARR (0.56 vs 0.125; p<0.001), the proportion with new/enlarged T2 lesions (63.4% vs 12.2; p<0.001), Gd-enhancing lesions (39% vs 0%; p<0.001) and confirmed disability progression (55% vs 27.5%; p=0.037). NEDA-3 was achieved by 53.7% of patients and none experienced severe infections, although 10.7% did experience reduced IgG levels.

Comment: Rituximab is an anti-CD20 monoclonal antibody which reduces B-lymphocyte populations. It is not funded for use in MS in NZ, but a newer drug with a similar mechanism (ocrelizumab) is. Rituximab is used extensively to treat MS in other countries, and is a very frequent DMT choice in Sweden, for example. Regarding drugs which deplete B-cells, there are concerns that long term use leads to progressive lowering of Ig levels, with a resultant vulnerability to infections. Because of these concerns, clinicians are exploring whether delaying retreatment until CD19 B-cells have started to return to the circulation can achieve equivalent control of MS activity compared to regular infusions every 6 months. If this can be done, it is hoped that progressive immunoparesis will be less likely. There would also be cost savings. I am currently using a similar strategy for selected patients on ocrelizumab. This study from Spain showed promising data for this approach.

Immunomodulation/Immunosuppression E-poster: P300

Cyclophosphamide in acute treatment of severe neuroinflammatory disorders

Speaker: A. Osen

Summary: This retrospective chart review assessed outcomes for patients with severe CNS neuroinflammatory conditions who failed first-line immunosuppressive therapy and were subsequently treated with cyclophosphamide. Patients were divided into non and atypical MS, or typical MS. Primary outcomes included targeted neurologic deficits (TNDs) and radiologic activity. The review identified 46 patients (median age 35) and 82.2% had improvement in TNDs with 62.2% having scores ≥2. In general, the two groups showed similar improvements, but the non and atypical MS group experienced a more robust clinical response. Rates of improvement persisted at second follow-up (median 6 months). Adverse effects developed in one-third of patients with nausea, vomiting, alopecia, and headache being the most common. One patient was diagnosed with uterine cancer 5 years after cyclophosphamide exposure; no other malignancies were reported over a median of 7 years of follow-up. It was concluded that cyclophosphamide treatment can stabilise severe CNS neuroinflammatory conditions.

Comment: There are some patients who have a poor outcome despite treatment of an MS relapse with steroids and then plasma exchange/immunoadsorption. It would seem logical that a highly potent immunosuppressive drug like cyclophosphamide, which has major effects on T-lymphocytes, might be effective in this situation. There is, however, very little evidence for using cyclophosphamide to treat refractory MS relapses, because very few studies have been done. This retrospective uncontrolled study from a single centre in Chicago looked at disability and MRI outcomes in 27 patients with MS and 19 with other inflammatory CNS disorders. The results look promising - most patients were stable or improved at follow-up, and there was little new MRI activity following cyclophosphamide treatment. More than 50% of MS patients enjoyed at least a moderate improvement in the relapse-related deficit. We do not have enough weapons available to treat severe relapses, and this is useful information.

Immunomodulation/Immunosuppression E-poster: P315

Alternative diagnosis in first-line referral for suspected MS

Speaker: K. Brochu

Summary: This study assessed the frequency and predictors of early MS diagnosis and identified alternative diagnoses in patients evaluated by neurologists. The investigators reviewed all MS referrals (n=121) made from general practitioners during 2018, 85% of which were for diagnostic confirmation and 12% for follow-up of a previous diagnosis. A MS diagnosis was confirmed in 12/103 patients with MS suspicion and 13/15 in previously diagnosed MS. Overall, 94/121 (78%) had an alternative diagnosis, the most common being non-specific sensory symptoms (38%), musculoskeletal injuries (13%), peripheral nerve lesions (7%) and headaches (7%). A total of 98 patients had an MRI prior to neurology consultation, with 51 having non-specific cerebral white matter lesions and 19 normal MRI. Interpretation by a neuroradiologist was associated with a higher probability of MS diagnosis compared to a general radiologist (32% vs 9%; p=0.01). It was concluded that strict application of diagnostic criteria is paramount, particularly in the context of typical MS syndromes.

Comment: I usually like these studies which show final diagnoses in people suspected to have MS, as they provide useful context and lessons for our own clinical practice. This one is from Quebec and shows that their neurological and primary care services must be set up a little differently to ours in NZ. Patients were referred to neurology by primary care having mostly already had MRI studies. Only 12/103 patients referred for confirmation of a diagnosis of MS were thought to have MS. Non-specific sensory symptoms, particularly if there were also non-specific white matter lesions on MRI (which are a common finding, especially in older people), seemed to be a particularly difficult diagnostic scenario for non-specialists. I agree with the authors that caution should be exercised in making an MS diagnosis, especially if the initial clinical presentation is not well defined.

Clinical aspects of MS - Diagnosis and differential diagnosis: EP0809

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Treating active MS following induction therapies

Speaker: G. Edan

Summary: Induction therapies for active MS have been trialed with at least 3 approved medicines: mitoxantrone, alemtuzumab and more recently cladribine. Induction with mitoxantrone in highly active relapsing MS, followed by interferon beta-1b maintenance, resulted in delayed time to sustained confirmed disability over 3 years. Ten years after 3 or 6-monthly courses of mitoxantrone, the majority of early highly active patients remained untreated or treated with a first-line maintenance DMT, with a low mean ARR and a mean EDSS score remaining significantly improved for up to 10 years. In patients with aggressive RRMS, alemtuzumab demonstrated a persistently low ARR for up to 8 years and a stable mean EDSS. Two years of treatment with oral cladribine followed by 2 years of placebo produced clinical benefits similar to 4 years of cladribine, with a low risk of severe lymphopenia or clinical deterioration. The induction effect of rituximab appears to be limited to approximately 30 months after a single course, mirroring the repopulation of CD19+ B cells. Accumulated data from long-term follow-up studies in highly active MS support this innovative strategy.

Comment: The idea of induction therapies is attractive. A patient receives a short course of treatment to reset their immune system (immune reconstitution) and is then monitored and only receives further treatment (either more of the induction agent or one of the continuous therapies like natalizumab, ocrelizumab, fingolimod, teriflunomide or dimethyl fumarate) if there is breakthrough clinical or MRI activity. This makes things like pregnancy planning potentially easier and may lead to cost savings if the patient enjoys very long-term stability. The downside is that the induction therapies may be more toxic in the short term. Mitoxantrone has cardiac toxicity that means it can only be safely used for a few courses, and it carries a risk of treatment-associated leukaemia and persistent amenorrhoea. Alemtuzumab leads to autoimmune thyroid disease in a substantial group of patients and has other risks including infection and immune thrombocytopaenia. Cladribine is perhaps less potent than alemtuzumab but has lower risks and there are hopes that it may be funded in NZ in the future.

Hot Topic 5: Escalating and de-escalating DMTs: O049

Predicting the risk of long-term relapse in MOGAD

Speaker: A. Francis

Summary: This prospective study aimed to determine if early relapse of MOG-antibody associated disease (MOGAD), and predictors of early relapse, predicts relapse beyond one year. A cohort of 192 MOGAD patients without long-term immunosuppressive treatment during the first year were included. Relapse at any stage was experienced by 118 (61%) of patients, 49 (25.5%) of whom had early relapses. Univariate analysis showed a higher risk of long-term release with any early relapse (HR 1.6), relapses in the first or the last 3-month epoch (HR 2.24 and 2.66 respectively), increased number of early relapses (HR 1.48), and non-white race (HR 1.94). Longer duration of early corticosteroid treatment was protective. Multivariate analysis revealed the number of early relapses, relapse in the first and third 3-month epochs, days on corticosteroids, and non-white race were significant. The specificity for long-term relapses in the first 5 years in those with ≥1 and ≥2 early relapses was 84% and 99% respectively, with respective sensitivities of 20% and 5%. These results suggest that early relapses are associated with an increased risk of long-term relapse, possibly indicating the need for long-term immunosuppression.

Comment: MOGAD is increasingly being diagnosed now that the antibody test is easily available. It can present in children and adults, with optic neuritis, spinal cord inflammation and encephalitis being the more common manifestations. This paper looks at factors which may predict who will have recurrent disease and who will have a monophasic course. The results suggest that relapses during the first 12 months after presentation and non-white race are risk factors for further relapses beyond this time, and that a longer initial course of steroids may be protective. This will help clinicians to decide whether to use a disease-modifying agent from an early stage to help protect against future disease activity. However, we are still learning how to treat this condition. There have not been any proper trials of DMTs, but mycophenolate is probably the most widely used.

Clinical aspects of MS – MOGAD: P022