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CONFERENCE REVIEW

ECTRIMS 2024 Conference Review

Making Education Easy

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In this review:

Abbreviations used in this review:
CSF = cerebrospinal fluid
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
IgG = immunoglobulin G
MRI = magnetic resonance imaging
MS = multiple sclerosis
PPMS = primary progressive MS
RMS = relapsing MS
SPMS = secondary progressive MS

Welcome to our review of the 40th Congress of the European Committee for Treatment and Research in MS (ECTRIMS) that was held recently in Copenhagen.

The conference featured speakers from all over the world who presented scientific and educational sessions to an estimated 9000 delegates. I have selected and reviewed 11 presentations from ECTRIMS 2024 that I found to be particularly interesting. Abstracts presented at the congress have been published in an online supplement of the Multiple Sclerosis Journal, and more information about the meeting can be found at https://ectrims.eu/ectrims2024/.

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

Kind regards,
Dr John Mottershead
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Revised McDonald criteria 2023

Presenter: Xavier Montalban (Spain)

Summary: A committee of 55 experts from a wider range of global regions than used previously has produced provisional revisions to the McDonald diagnostic criteria for MS, which were last revised in 2017. Experts voted on changes, with an 80% agreement generally being required. The proposed revisions are:

- radiologically isolated syndrome (RIS) is MS in certain situations;
- the optic nerve is added as a fifth region for demonstration of dissemination in space (DIS) – the other four are periventricular, infratentorial, juxta/intracortical and spinal cord;
- dissemination in time (DIT) is no longer required;
- kappa free light chains in CSF are considered equivalent to positive oligoclonal bands (OCB);
- a single set of criteria will be used to diagnose both PPMS and RMS;
- preclinical evidence will be required to diagnose MS (i.e. it is no longer possible to make a diagnosis solely using clinical factors) – MRI, CSF, evoked potentials or ocular coherence tomography (OCT) must be abnormal in a way that supports the diagnosis;
- stricter criteria for individuals over 50 years, or with headache disorders, or with vascular disorders (because of the lower incidence of MS presenting over 50 years and the higher likelihood of similar lesions on MRI in people of this age or with these conditions);
- addition of new MRI lesion types – central vein sign (CVS) and paramagnetic rim lesions (PRLs) as tools for diagnosis in certain situations;
- laboratory testing for myelin oligodendrocyte glycoprotein (MOG)-IgG antibody is recommended in children and adolescents.

Comment: These proposed new diagnostic criteria, which will be finalised subject to further discussion, were the biggest news at ECTRIMS. The changes reflect the discovery of new, sensitive and specific MRI lesion types (CVS and PRLs) as well as results from prospective cohort studies that show high rates of conversion from RIS to MS – 72% after 15 years. The presenter acknowledged that the proposed new criteria are complicated and confusing. In NZ, access to the modern MRI techniques needed to demonstrate CVS and PRLs is very restricted, but this should improve in time. It makes sense for optic nerve MRI lesions or changes on visual evoked potentials or OCT to count towards diagnosis, as optic neuritis is a common and relatively specific feature of RMS. DIT has been largely dropped from the criteria, because people who fulfil enough of the other baseline criteria generally fulfil DIT eventually anyway, so a requirement for DIT does not greatly improve accuracy and leads to diagnostic delay. The criteria for RIS are interesting – MS may be diagnosed in a patient with positive MRI but no clinical findings or relevant history provided they fulfil DIS and DIT (DIT is otherwise removed from the criteria for everyone else), or fulfil DIS plus have OCB, or fulfil DIS and have six or more CVS lesions. In a nutshell, the proposed changes leverage increasingly sophisticated investigational findings to allow earlier diagnosis of MS, but the resultant diagnostic algorithms are very complex.

Scientific Session 1: New diagnostic criteria

Evaluating the effectiveness of simvastatin in slowing the progression of disability in secondary progressive multiple sclerosis (MS-STAT2 trial)

Presenter: Jeremy Chataway (UK)

Summary: The multicentre phase 3 MS-STAT2 trial evaluated the effects of high-dose simvastatin on the progression of disability in patients with SPMS. At 31 UK hospitals, 964 patients with SPMS were randomised 1:1 to simvastatin (40 mg/day for 1 month then 80 mg/day) or matching placebo for up to 4.5 years. Key eligibility criteria were age 25–65 years, confirmed diagnosis of SPMS with steady progression, and EDSS score of 4.0–6.5. The primary outcome was confirmed disability progression (increase of at least 1 point in EDSS score from baseline if baseline EDSS score was <6, or a confirmed increase of 0.5 point if baseline EDSS score was ≥6). The primary outcome did not differ significantly between simvastatin and placebo groups during 54 months of follow-up.

Comment: A phase 2 study of simvastatin in SPMS, published in 2004, showed a substantial slowing of brain atrophy on MRI. This phase 3 study in the UK looked at clinical outcomes, with disability progression (EDSS) being the primary outcome measure. The trial looked to be methodologically sound and appropriately powered, with 365 progression events occurring over the 3- to 4-year trial period. Disappointingly, there was no effect of simvastatin versus placebo on any of the measures of disability presented. The patients recruited were on average in their mid-fifties and relapse activity was very low – this group of patients has so far been largely resistant to disease modification. There are more results to come from this study, including effects on cognitive outcomes, but it seems unlikely that simvastatin will be an effective treatment for MS.

Late Breaking Oral Presentations; abstract no. 4018/0134
Abstract

Efficacy and safety of tolebrutinib versus placebo in non-relapsing secondary progressive multiple sclerosis: Results from the phase 3 HERCULES trial

Presenter: Robert J. Fox (US)

Summary: The phase 3 HERCULES trial evaluated the efficacy and safety of tolebrutinib in patients with non-relapsing SPMS. Across 31 countries, 1131 patients with SPMS (aged 18–60 years, EDSS score 3.0–6.5) who had no clinical relapses in the past 24 months were randomised 2:1 to receive oral tolebrutinib (60mg once daily) or matching placebo. Most participants (77%) had previously received at least one DMT. Tolebrutinib delayed the time to onset of 6-month confirmed disability progression by 31% compared with placebo (hazard ratio 0.69, 95% CI 0.55–0.88; p=0.0026).

Comment: Bruton tyrosine kinase (BTK) inhibitors are being heavily studied in MS, as their effects on B cell and microglial activity inside the blood-brain barrier suggest potential efficacy against the smouldering inflammation seen in chronic progressive MS. Results of trials in RMS have been a little mixed so far. This trial looked at non-relapsing SPMS, with average age 49 and only low levels of baseline MRI inflammatory activity. The results look pretty good. There was a 31% reduction in the primary outcome, confirmed 6-month disability progression. This is better than the result for siponimod, the only drug to have shown significant benefit previously in SPMS (26% reduction in disability progression). The siponimod SPMS trial population contained relatively high numbers of patients with MRI or relapse activity, who are more responsive to immunomodulation. Safety of tolebrutinib was reasonable – there were modestly higher rates of upper respiratory tract infections, and 4% of patients had liver enzyme elevation of 3x upper limit of normal or greater. One patient died of complications after liver transplantation performed because of presumed tolebrutinib-induced liver failure. Overall, this looks like the most positive study to date in SPMS, although 26.9% of patients still progressed over the approximate 4-year trial period despite tolebrutinib treatment (versus 37.2% on placebo).

Late Breaking Oral Presentations; abstract no. 4027/0136
Abstract

New clinical subtypes of MS identified in big data predict disability progression and response to DMT treatment

Presenter: Vicky Leavitt (US)

Summary: This large real-world study applied unsupervised machine learning to clinical data from a cohort of 6362 MS patients at ten centres in three countries, and identified three clinical subtypes. The subtypes were based on first clinical symptom to emerge: cognition-first (subtype 1; 38% of sample), motor-first (subtype 2; 31%), and fatigue-anxiety-depression first (subtype 3; 31%), and differed in age, sex, whole brain atrophy, T2 lesion volume, current DMT status, and DMT type. Cox regression revealed that subtypes 1 and 2 had slower decline than subtype 3 based on age, and subtype 2 had slower decline than subtypes 1 and 3 based on months on DMT.

Comment: Machine learning approaches are increasingly being used to try and make sense of large data sets, or to find things in the data which are not apparent using other techniques. This study found that patients could be separated according to onset with cognitive, motor or fatigue/affective symptoms. The authors suggest that cognitive and motor onset patients progressed more slowly for their age than fatigue/affective onset patients, and that motor onset patients progressed more slowly when months on treatment were controlled for. It is difficult to know how much these findings are influenced by the relative responsiveness of rating scales used for the different clinical domains.

Clinical aspects of MS – diagnosis and differential diagnosis; abstract no. 213/P001
Abstract

Unveiling MS specialists' views on multiple sclerosis prognostication

Presenter: Sofie Aerts (Belgium)

Summary: This qualitative study examined how MS specialists perceive and apply the concept of prognosis in MS management. Semi-structured interviews were undertaken with 13 MS specialists (ParadigMS Foundation) across 12 Eurasian and Middle Eastern countries. The interviews covered current prognostication practices and the role of prognosis in decision-making. Preliminary analysis of the interviews revealed substantial divergence in MS prognostication practices, with MS prognosis estimation currently lacking a standardised scientific-based approach. Most practices currently classify patients solely based on visible disease activity, although the specialists considered quality of life to be a central outcome measure.

Comment: This study looked at how (and how much) specialists assessed prognosis when looking at individuals with MS. Unsurprisingly, visible disease activity (accumulated disability, relapses and MRI changes) were the main factors considered. The other side of this scenario, when considering which (if any) disease-modifying treatment to use for an individual, is the effect of individual patient characteristics on likely treatment response. Although some information is available on this (e.g. people with recent inflammatory changes on MRI typically benefit more from aggressive treatment), we are a long way from a truly individualised approach to MS therapy.

Clinical aspects of MS – diagnosis and differential diagnosis; abstract no. 867/P004
Abstract

Misdiagnosis of multiple sclerosis in an adult neurogenetics clinic: Characterising historical and radiographic red flag features

Presenter: Leah Zuroff (US)

Summary: This study assessed the rate of MS misdiagnosis in patients with atypical MS who were referred to an adult neurogenetics clinic for testing for genetic leucoencephalopathies. The medical records of 61 patients with atypical MS were reviewed to determine whether they actually met 2017 McDonald criteria for relapsing-remitting MS (RRMS) or PPMS, and whether they had any historical or radiographic 'red flag' features of MS. Twenty-five (41.0%) patients were diagnosed with RRMS, 35 (57.4%) with PPMS, and one with RIS, but only 28% of patients with RRMS and 21% with PPMS met 2017 McDonald criteria. The most common radiographic red flags were lesion confluence, corpus callosal thinning, lesion symmetry, and anterior temporal lobe and external capsule T2 hyperintensities. Most patients (78.7%) had historical red flags, including positive family history, onset after age 50, extrapyramidal signs, and isolated progressive myelopathy. Only five patients were found to have genetic leucoencephalopathies.

Comment: Studies like this one, which look at ultimate diagnosis in people originally diagnosed with MS, are useful as they tell us some of the conditions which can mimic MS, or can mimic the MRI appearances of MS to some extent. The findings show that PPMS is over-represented in misdiagnosed cases, one suspects partly because leucodystrophies and other mimics are more often progressive than episodic and partly because the clinical features of PPMS are less specific than those of RRMS. The authors imply that when McDonald diagnostic criteria are correctly applied, misdiagnosis is unlikely. In reality, a tentative diagnosis of MS will often be made where there is no better explanation and reasonable alternative diagnoses have been looked at, even if criteria for MS are not fully met.

Clinical aspects of MS – diagnosis and differential diagnosis; abstract no. 2005/P1012
Abstract

Safety and efficacy of frexalimab in the treatment of relapsing multiple sclerosis: 18-month results from the phase 2 open-label extension

Presenter: Gavin Giovannoni (UK)

Summary: This open-label extension (OLE) of a phase 2 trial evaluated the 18-month safety and efficacy of frexalimab in patients with RMS. In the initial double-blind trial, 129 patients were randomised 4:4:1:1 to receive frexalimab 1200mg IV every 4 weeks, frexalimab 300mg SC every 2 weeks, or matching placebos. After week 12, patients receiving placebo switched to the corresponding frexalimab arms and entered the OLE. At week 72, the number of gadolinium-enhancing T1 lesions remained low in patients who continued with frexalimab and in those who switched from placebo to frexalimab at week 12. New/enlarging T2 lesion count and change in T2 lesion volume remained low through week 72, and no new safety signals were observed.

Comment: There are currently two funded high efficacy treatments for MS in NZ – natalizumab and ocrelizumab. Both are given IV, but SC versions are likely to be funded in time. Frexalimab is potentially a good addition, as it does not reduce lymphocyte numbers (so might be expected to have a lower risk of opportunistic infections than established high efficacy treatments), acting via inhibition of the CD40L pathway which is involved in the inflammatory response seen in MS. Previous agents targeting this pathway have been associated with thromboembolic events, but these were not seen in this phase 2 study. Phase 3 studies of frexalimab have just begun, looking at patients with RMS and also, in a separate trial, at patients with non-relapsing SPMS. This latter group is especially important, as effective treatments for SPMS are currently limited.

Scientific Session 6: The future of new therapies in MS; abstract no. 242/0066
Abstract

Short-term B cell depletion results in medication-free, long-term freedom from disease activity and correction of immune tolerance defect in a subset of people with relapsing MS

Presenter: Bardia Nourbakhsh (US)

Summary: This proof-of-concept study investigated whether short-term use of a B cell-depleting medication (ocrelizumab) can correct B cell tolerance defects in people with MS and allow for medication-free prolonged freedom from disease activity. Nineteen patients with RMS received two courses of treatment with ocrelizumab and were then followed up with biannual clinical and radiological monitoring for at least 30 months. Five patients experienced MS reactivation 19–37 months after their last ocrelizumab treatment, but the remaining 14 patients had no clinical or radiological disease reactivation during 21–30 months of medication-free follow-up. Four out of seven patients who were tested had an impaired central B cell tolerance; all four of them had MS reactivation during the treatment-free period.

Comment: Ocrelizumab is an anti-CD20 monoclonal antibody that targets B-lymphocytes. It is a highly efficacious treatment for RMS and is modestly effective in PPMS. The pivotal studies used maintenance dosing every 6 months, which typically led to full suppression of peripheral CD19 cells (which are the ones most easily measured by our laboratories). There have also been studies looking at re-dosing with ocrelizumab only when CD19 counts start to return (one is presented in this review), and these generally show maintenance of control of MS activity. This study is different, and reframes ocrelizumab as an immune reconstitution therapy (like autologous haematopoietic stem cell transplantation, alemtuzumab or cladribine), at least for a subset of patients who had no re-emergence of MS activity after only two courses of treatment with ocrelizumab. The authors found that treatment failure was associated with failure to suppress autoreactive B cells.

Scientific Session 15: Discontinuation and de-escalation treatment in MS; abstract no. 324/0112
Abstract

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Alternate-day fingolimod tapering: Impact on rebound disease activity in patients with multiple sclerosis

Presenter: Tuncay Gündüz (Turkey)

Summary: This retrospective study investigated the impact of an alternate-day fingolimod tapering regimen on the severity of rebound disease activity (RDA) after drug cessation. 148 patients with MS who had ceased fingolimod treatment were classified into two groups based on the discontinuation approach: alternate-day tapering and abrupt cessation. Overall, 23 patients (15.5%) had RDA during the 6-month post-treatment period. The incidence of RDA was lower in those in the alternate-day tapering group (30.4%) compared with the abrupt cessation group (67.2%), but 6-month relapse-free survival rate did not differ significantly between groups.

Comment: Fingolimod is a medium efficacy oral treatment for RMS. Rebound severe inflammatory activity after discontinuation of fingolimod is a concern, and may occur in perhaps 10% of patients, although figures from different studies vary. It is tempting to think that gradual rather than abrupt discontinuation of fingolimod might reduce the rate of rebound activation, since fingolimod's mechanism of action involves sequestration of lymphocytes in lymph nodes, so a more gradual release of these cells into the circulation might result in a more controlled situation. This study is relatively small, retrospective and could suffer from indication bias and other confounders. Nevertheless, there is some support here for an alternate-day tapering regimen rather than abrupt discontinuation.

Scientific Session 15: Discontinuation and de-escalation treatment in MS; abstract no. 1089/0111

Abstract

B-cell tailored dosing versus standard interval dosing of ocrelizumab in relapsing-onset MS – interim analysis of a randomised controlled trial (BLOOMS trial)

Presenter: Laura Hogenboom (the Netherlands)

Summary: A randomised controlled trial is currently underway in the Netherlands comparing personalised interval dosing (PID) with standard interval dosing (SID) of ocrelizumab in patients with relapsing-remitting MS (RRMS). In the PID group, ocrelizumab infusions are extended as long as the CD19+ B cell count remains below 10 cells/μL (measured monthly after the standard interval of 6 months). At the time of this interim analysis, 119 patients had been randomised and followed up for 8.9 months. No radiological or clinical disease activity was observed in either group, and drop-out rate was low. Final results are expected in 2027.

Comment: The clinical trials of ocrelizumab in MS used maintenance treatment every 6 months. There are concerns that, over time, there may be increasing risks from a gradual decline in IgG levels on ocrelizumab. Consequently, there is interest in finding out whether re-dosing according to return of CD19 lymphocyte counts may be a useful alternative approach. The idea is that the brief re-emergence of B cell populations may be enough to provide protection against increasing infection risks, whilst not exposing patients to breakthrough MS activity. Several observational real-world studies have given encouraging findings. This prospective randomised controlled trial is only at an interim analysis stage, but the lack of any breakthrough MS activity in any patient, irrespective of whether they were receiving ocrelizumab every 6 months or according to CD19 repletion is certainly encouraging.

Scientific Session 15: Discontinuation and de-escalation treatment in MS; abstract no. 1288/0113

Abstract

Comparison of high efficacy treatment discontinuation and continuation among stable multiple sclerosis patients after 50

Presenter: Guillaume Jouvenot (France)

Summary: This retrospective, multicentre study compared discontinuation versus continuation of high efficacy treatment among patients older than 50 with stable MS (relapsing-remitting MS or SPMS). Data were extracted from the OFSEP database for 1620 patients aged >50 years, who were classified into two groups: discontinuation (n=1452) and continuation (n=168). For this analysis, 154 patients in each group were propensity score matched and compared. Mean age was 57.7 years and mean time since last clinical/radiological inflammatory activity was 5.6 years. The time to first relapse was significantly shorter in the discontinuation group than in the continuation group (hazard ratio 4.1, 95% CI 2.0–8.5; p<0.001). The risk of relapse differed according to the type of high efficacy treatment used: hazard ratios were 7.2 (95% CI 2.14–24.5; p=0.001) for natalizumab, 4.5 (95% CI 1.3–15.5; p=0.02) for fingolimod and 1.1 (95% CI 0.3–4.8; p=ns) for anti-CD20 drugs.

Comment: We have been treating people with MS in NZ for long enough now that there are considerable numbers of patients who have been treated for over 10 years, many of whom are aged over 50. It doesn't seem likely that everyone will benefit from being treated indefinitely. Previous studies have generally showed that stopping older, less effective treatments like beta-interferon is not especially problematic in stable patients over 50. This study reinforces the view that stopping natalizumab or fingolimod may be more difficult than stopping anti-CD20 drugs like ocrelizumab. This is likely to be due to the problem of rebound when stopping natalizumab or fingolimod, and the benefit of a longer duration of action from ocrelizumab, which suppresses B cell populations for 6 months or longer after each treatment. One approach may be to switch stable patients who are on natalizumab or fingolimod to an alternative agent as part of a de-escalation process, but we need more information on whether this would help.

Scientific Session 20: Aging with MS – implications for treatment; abstract no. 1633/0129

Abstract

INDEPENDENT COMMENTARY BY

Dr John Mottershead

Dr John Mottershead is a Neurologist at Te Whatu Ora Southern. 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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