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CONFERENCE REVIEW

ECTRIMS 2018

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In this review:

Abbreviations used in this review
CIS = clinically isolated syndrome
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
JCV = John Cunningham virus
MRI = magnetic resonance imaging
MS = multiple sclerosis
ORS = overall response score
PML = progressive multifocal leukoencephalopathy
SF-36 = 36-item Short Form survey

Welcome to our review of the 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held recently in Berlin.

The programme covered new developments in all areas of MS, including treatment, genetics, pathology, imaging, immunology and epidemiology. Although I was unable to attend the conference in person, I've reviewed the meeting abstracts and consider the following 10 reports to be particularly interesting. Links have been provided to the abstracts, and more information about the meeting can be found online at https://www.ectrims-congress.eu/2018.html.

I hope you find the Conference Review interesting and look forward to receiving any feedback you may have.Kind regards

Dr John Mottershead
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Prediction of conversion to multiple sclerosis using the 2017 McDonald and 2016 MAGNIMS criteria in patients with clinically isolated syndrome

Authors: Miclea A et al.

Summary: This retrospective analysis performed at the Bern University Hospital in Switzerland compared the accuracy of 2016 MAGNIMS and 2017 McDonald criteria for predicting the conversion to MS in patients diagnosed with CIS according to 2010 McDonald criteria. Of 127 patients included in the analysis, 67 (52.8%) converted clinically and/or radiologically to MS after a median duration of 1.1 years. Retrospectively applying the 2017 McDonald and 2016 MAGNIMS criteria to patients with CIS and investigating the conversion to MS resulted in a mean sensitivity of 0.89 and 0.6, respectively, and a specificity of 0.31 and 0.5, respectively.

Comment: The 2017 McDonald criteria were developed in the light of empirical data, with the aim being to allow earlier diagnosis of MS in people who have only had a single event, without sacrificing specificity. The results of this retrospective study are in line with the results of other larger studies and suggest that the 2017 criteria work reasonably well. In NZ, disease-modifying treatments are only funded for people who have had at least 2 clinical attacks. This stance by Pharmac reflects the finding from many studies that using baseline clinical and laboratory findings at the stage of a single attack to predict whether there will be at least one more attack (clinically definite MS) is only around 85% accurate – 15% of patients who fulfil McDonald 2017 or other similar criteria will never have a second attack.

Poster P970; Oct 12
Abstract

The review of systems questionnaire discriminates medically unexplained neurologic symptoms from neurologic disease in a multiple sclerosis referral clinic

Authors: Jones B et al.

Summary: The review of systems (ROS) questionnaire is used to collect information about symptoms affecting a range of organ systems. Patients responding "yes" to a high percentage of ROS items have been shown to correlate with medically unexplained symptoms in various specialty clinics. This retrospective review from a specialty MS clinic examined the utility of the ROS questionnaire for distinguishing MS from medically unexplained symptoms. 166 new patients seen in the University of Alabama MS Clinic in 2017/2018 were evaluated, and 27 (16.2%) of them had medically unexplained symptoms. These patients gave more positive responses to the ROS questions (mean 38.7%) than the other patients (mean 23.8%). When patients responded "yes" to >45% of items, the ROS questionnaire predicted medically unexplained symptoms with 52% sensitivity and 94% specificity.

Comment: This study found that patients judged to have medically unexplained symptoms gave, on average, more positive answers to the ROS questions than did the other patients in an MS clinic. The difference of 39% versus 24% was statistically significant, but would be difficult to use in clinical practice. The results would need to be backed up by longer term confirmation of diagnosis in the patients studied, but do sit nicely with the idea that patients with functional presentations are often polysymptomatic.

Poster P976; Oct 12
Abstract

Late clinical activity in long-standing non-active multiple sclerosis patients

Authors: Corti L et al.

Summary: This observational study evaluated patients with long-standing non-active remitting MS who suddenly had an acute disease exacerbation. 28 patients in the European Database for Multiple Sclerosis (EDMUS) who were aged ≥50 years and had a new relapse after at least 10 years of relapse-free disease were included. At the time of the new relapse, mean disease duration was 27.6 years, the mean relapse-free period was 21 years, and mean EDSS was 3.3. All 9 patients (31%) who underwent an MRI because of the new relapse were found to have at least 1 gadolinium-enhancing T1 lesion. During a mean 5-year follow-up after the relapse, 8 patients (28%) had further clinical activity with a mean of 1.9 more relapses, but mean EDSS was stable.

Comment: This study confirms that it is possible to have a relapse in older patients after many years of clinical stability. Furthermore, a relapse in this context was often followed by further relapses in the next 5 years. The results from this database analysis suggest that late reactivation of MS is rare, but that when it happens, disease-modifying treatments may be appropriate. The relapses were confirmed to be inflammatory events and not pseudo relapses in those patients who underwent contemporaneous MRI.

Poster P672; Oct 11
Abstract

Independent commentary by 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.

This publication has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for CME for the General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes. Please **click here** to download your CPD MOPS Learning Reflection Form.

Did risk stratification modify the incidence of PML in natalizumab-treated MS patients in France?

Authors: Vukusic S et al., on behalf of the OFSEP Investigators

Summary: In 2012, three factors were determined to be associated with an increased risk of PML in natalizumab recipients: exposure to natalizumab for >24 months, previous use of immunosuppressants, and a positive JCV serology. Since then it has been possible to stratify MS according to risk of developing PML during treatment with natalizumab. This analysis of data from the OFSEP cohort evaluated the impact of risk stratification on the incidence of PML in natalizumab recipients in France. 6318 patients in the OFSEP cohort were exposed to natalizumab in 2007–2016, and 45 cases of PML were diagnosed. A Poisson regression model showed a 45.3% increase in natalizumab-associated PML each year from 2007 to 2013, but a significant 23.0% decrease per year after 2013 when risk stratification became possible.

Comment: PML in MS patients exposed to natalizumab is the most significant clinical risk associated with this highly efficacious treatment. There has now been one confirmed case of PML due to natalizumab in NZ. This study follows the rate of PML in France before and after 2013. Since 2013, neurologists have been able to test JCV serology titre at baseline and make decisions on whether or not to use natalizumab – and how closely to monitor treated patients – according to the risk of PML. Generally, patients with high titres of JCV are not treated with natalizumab or are treated for less than 2 years. The French data, where PML rates have been falling every year since 2013, suggest that this strategy works well.

Poster P1746; Oct 12
Abstract

Extended interval dosing of natalizumab shows comparable efficacy to standard interval dosing starting from the second year of treatment

Authors: Ruggieri S et al.

Summary: It has been suggested that moving from standard interval dosing to extended interval dosing (≥35 days) of natalizumab will minimise the risk of PML. This Italian study compared the efficacy of standard interval vs extended interval dosing of natalizumab in terms of ''no evidence of disease activity-3" (NEDA) in 270 patients with MS who completed 4 years of follow-up. NEDA rates were better in the standard interval group than the extended interval group after 1 year (84.9% vs 73.6%; p=0.018) but did not differ significantly between groups after 2, 3 or 4 years.

Comment: One strategy to reduce the risk of PML in patients with positive JCV serology exposed to natalizumab is to increase the dosage interval from the standard 4 weeks. In NZ, many centres now dose at 5- or 6-week intervals. Previous studies have shown that PML incidence is lower with extended interval dosing and that efficacy seems not to be greatly affected. This study largely confirms that efficacy is maintained with extended interval dosing, but did show that there were higher rates of MS activity (disability, relapses and/or MRI lesions) during the first year with extended interval dosing. An obvious thought is that patients could be treated for a year with dosing every 4 weeks, then might be switched to extended interval dosing. Many neurologists will still be reluctant to use natalizumab at all in high titre JCV positive patients.

Poster P1770; Oct 12
Abstract

Impact of ozanimod on early and advanced relapsing multiple sclerosis: annualised relapse rate and MRI endpoints from two randomised, multicentre, double-blind, phase 3 studies (SUNBEAM and RADIANCE)

Author: Comi G et al., for the SUNBEAM and RADIANCE Study Groups

Summary: This post hoc analysis of data from the SUNBEAM and RADIANCE trials evaluated the use of the oral immunomodulator ozanimod in patients with early or advanced relapsing MS. 2659 patients were randomised in a double-blind design to receive daily oral ozanimod 1 or 0.5mg (equivalent to ozanimod 0.92 or 0.46mg, respectively) or weekly intramuscular beta-interferon 30µg for ≥12 (SUNBEAM) or 24 months (RADIANCE). The annualised relapse rate was lower with ozanimod compared with beta-interferon in patients with early or advanced relapsing MS. MRI showed that the number of gadolinium-enhancing lesions and the number of new/enlarging T2 lesions were also lower after 12 months with ozanimod vs beta-interferon in both early and advanced relapsing MS.

Comment: Ozanimod is a drug in the same class as fingolimod, a sphingosine-1-phosphate antagonist already funded for MS in NZ. This post hoc analysis showed that ozanimod was superior to beta-interferon in both short disease duration patients with low disability, and longer-duration patients with higher disability scores. Both groups were still in the relapsing-remitting phase of MS. Similar post hoc analyses of other trials in relapsing MS have generally found the same thing, suggesting that restricting use of DMTs to very early MS is not logical, as more established patients will be just as likely to benefit.

Poster P1191; Oct 12
Abstract

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Autologous stem cell transplantation in multiple sclerosis: the London experience

Authors: Rhone E et al., for the Pan-London AHSCT Group

Summary: This retrospective audit examined outcomes after autologous haematopoietic stem cell transplantation (AHSCT) for the treatment of MS in 3 London centres in 2012–2017. Of 54 patients with >6 months' follow-up, 55.6% had relapsing MS, 33.3% had secondary progressive MS and 11.1% had primary progressive MS. Median age at the time of AHSCT was 41.4 years. 75% of patients with relapsing MS had failed a high-efficacy DMT (the median number of previous DMTs was 2). Median baseline EDSS was 6, median time from diagnosis to AHSCT was 8 years, and median inpatient stay for transplant was 22 days. When assessed 36 months post-transplant, 88% of patients were free from disability worsening. 5 patients (9.3%) developed MRI lesions after AHSCT (median time to development: 21 months). Of the patients with relapsing MS, 5 (16.7%) had symptoms consistent with a clinical relapse after AHSCT, but only 1 of them had new lesions on MRI.

Comment: AHSCT has been demonstrated in numerous case series to be a highly effective treatment to suppress inflammatory activity in MS. These data from London add to the evidence that AHSCT works well in carefully selected patients and that modern regimens are associated with very low mortality. There is growing interest in this treatment from NZ neurologists, although at present logistic barriers mean that patients can only access AHSCT overseas.

Poster P567; Oct 10
Abstract

Oral drugs versus interferon-beta or glatiramer acetate as first-line disease modifying therapy in relapsing-remitting multiple sclerosis

Authors: Benkert P et al.

Summary: This registry study in Switzerland compared the efficacies of oral drugs versus platform injectables (beta-interferon or glatiramer acetate) as first-line DMTs in patients with relapsing-remitting MS. Data were retrieved from the Swiss MS treatment registry for 14,726 MS patients who started first-line DMT between January 1995 and September 2017. 2293 treatment-naïve patients with relapsing-remitting MS who initiated an oral DMT or platform injectable were included. Clinical outcomes were compared using propensity score matching. The matching procedure retained 1940 patients for the relapse end-point and 1348 patients for the disability progression end-point; median follow-up was 2.5 years. Patients who initiated an oral DMT were more likely to be relapse-free (hazard ratio, 0.67; p< 0.001) and free of 12-month confirmed disability progression (hazard ratio, 0.60; p=0.008) than patients who initiated platform injectables.

Comment: For the last 4–5 years, Pharmac has funded the oral agents fingolimod, dimethyl fumarate and teriflunomide and has largely stopped funding new initiations of the older injectable treatments beta-interferon and glatiramer acetate. The reasoning behind this funding change was that clinical trial evidence largely suggested that the oral agents were more effective. This Swiss treatment registry study, which matched patients to try and reduce the effects of confounding factors, suggested that relapse and disability outcomes were indeed better with the oral agents.

Poster P1208; Oct 12
Abstract

Treatment escalation leads to fewer relapses compared with switching to another moderately effective therapy

Authors: Chalmer T et al.

Summary: This registry-based cohort study compared the effectiveness of switching to a highly effective DMT (HeDMT) or a different moderately effective DMT (MeDMT) after MS relapse. Data were retrieved from the Danish Multiple Sclerosis Registry for all adults with relapsing-remitting MS with EDSS <6 who experienced a relapse while being treated with a MeDMT, and subsequently switched to either a HeDMT or another MeDMT. The matched cohort comprised 814 patients (407 in each group) and median follow-up was 3.2 years. The group who switched to a HeDMT had a 39% lower risk of reaching first relapse than those who switched to a different MeDMT. Annualised relapse rates were 0.21 in patients who switched to a HeDMT and 0.34 in those who switched to a MeDMT.

Comment: Clinical trials are good at telling us whether drugs work, and head-to-head studies can tell us whether one drug is equivalent to or better than another. In real life, decisions also have to be made about whether to switch between agents. When switching, the choice will be whether to switch to a drug of equivalent efficacy or to try a higher efficacy agent that may come with higher risks. This Danish registry study found that switching to a higher efficacy agent (in NZ this would mean natalizumab) led to better relapse outcomes and possibly better disability outcomes. The results are not a huge surprise, but in the absence of prospective controlled comparative studies, these sorts of analyses add to the knowledge base and are important, especially when we consider that it will not be practical to do head-to-head comparisons of all potential treatment choices.

Abstract 263; Oct 12
Abstract

Relationship between overall response score of disability in MS with patient-reported outcome SF-36

Authors: Chang I et al.

Summary: The ORS is a composite of clinically relevant changes from baseline in EDSS, timed 25-foot walk, and 9-hole peg test. This study analysed data from the AFFIRM study (natalizumab vs placebo in patients with MS) to assess the relationship between ORS and patient-reported quality of life (assessed using the SF-36). Spearman correlation and linear regression models showed that the ORS had a linear correlation with change from baseline in both the SF-36 physical component summary (PCS) and the SF-36 mental component summary (MCS) at years 1 and 2. An ORS score of 3 (improvement from baseline) at year 2 was associated with mean increases in the SF-36 PCS and MCS of 8.9 and 9.1, respectively. An ORS of -3 (worsening from baseline) at year 2 was associated with mean decreases in the SF-36 PCS and MCS of -4.7 and -2.3, respectively.

Comment: Clinical studies in MS, including clinical trials, generally use the EDSS disability scale as a primary outcome measure. With very few exceptions, trials of new disease-modifying agents have failed to affect EDSS outcomes in secondary progressive or primary progressive MS. This could be because the drugs are genuinely ineffective in progressive disease, or it could be because EDSS, which in more disabled patients is essentially an ambulation index, is not very sensitive to, for example, changes in upper limb function. In more disabled patients, preservation of upper limb function is important, even if walking ability has already been compromised. This study showed a correlation between the SF-36 quality of life scale and a compound instrument that comprises EDSS, timed 25-foot walk and 9-hole peg test (a test of upper limb coordination). Funding agencies are often wary of compound outcome measures, but mapping of an instrument against a quality of life scale is a very important step towards validation.

Poster P942; Oct 11
Abstract

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