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CONFERENCE REVIEW

Making Education Easy

11-13 September 2019, Stockholm, Sweden

In this review:

Abbreviations used in this review
ARR = annualised relapse rate
CI = confidence interval
CDP = confirmed disability progression
EDSS = Expanded Disability Status Scale
HR = hazard ratio
IRR = incidence rate ratio
MRI = magnetic resonance imaging
MS = multiple sclerosis
RoMS = relapsing at onset multiple sclerosis
RRMS = relapsing-remitting multiple sclerosis
SPMS = secondary progressive multiple sclerosis

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Welcome

to our review of the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), held recently in Stockholm, Sweden. This year's programme represented the many new developments in all areas of MS, including epidemiology, genetics, pathology, biomarkers, imaging, immunology and treatment. Special attention was also given to one of the major remaining unmet needs in MS – to fill the void of efficient treatments for progressive MS. I have reviewed the meeting abstracts and found the following 10 reports to be particularly interesting.

I hope you find this conference review stimulating, and I look forward to your feedback.

Kind regards

Dr John Mottershead
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Physicians' perspectives on the identification and diagnosis of secondary progressive multiple sclerosis during the clinical encounter

Authors: Vollmer T et al.

Summary: This cross-sectional survey of 300 board-certified general and MS-focused academic and community neurologists in the US was undertaken to investigate clinical indicators that are important to neurologists in diagnosing secondary progressive multiple sclerosis (SPMS). The physician's, 63% of whom were general neurologists (59% worked in private practice), were queried on how they had diagnosed SPMS in patients who had transitioned to SPMS in the past year, the importance of specific clinical indicators, and other factors influencing the treatment approach. Two-thirds of respondents considered SPMS to be a distinct phenotype and MS-focused neurologists reported treating three times as many SPMS patients as general neurologists (mean 76 vs 26). The most important clinical factor in diagnosing SPMS was clinical history in the prior year (45% of respondents), with MRI findings ranked least important by 56% and most important by 15% of respondents. Additional criteria in the diagnosis were worsening daily function, patient-reported worsening functions/symptoms and worsening gait (53%, 21%, and 20%, respectively). Most of the respondents specified a 3- to 6-month interval during which a patient should demonstrate change to make the diagnosis. Over one-third of physicians reported declining ambulation among the top five indicators for SPMS and more than half always used neurological exams, patient history in the prior year, patient self-report of symptoms/decline, MRI, and gait assessments to confirm the diagnosis of SPMS.

Comment: This study from the United States asked neurologists how they diagnose secondary progressive MS. In contrast to diagnosing a clinically isolated syndrome, MS by McDonald criteria or clinically definite relapsing-remitting MS, there is no discrete clinical or radiological event that defines the transition to secondary progression. It is no surprise that declining ambulation was held to be the most influential factor in diagnosing progression, but it is surprising that some respondents felt that they could diagnose progression based on changes happening over only a 3- to 6-month period. Modern diagnostic criteria separate progressive MS patients into active (those with relapses and/or MRI activity as well as a progressive course) and inactive groups. It is not yet clear how much this classification will help in predicting response to disease-modifying agents such as siponimod, which has clinical trial evidence of efficacy in secondary progressive MS, although one of the other presentations reviewed in this report suggests that this may be important.

Poster P1090
Abstract

Misdiagnosis of multiple sclerosis

Authors: Midaglia L et al.

Summary: These authors investigated the magnitude of MS misdiagnosis in 352 patients referred to the Multiple Sclerosis Centre of Catalonia (Cemcat) between July 2017 and June 2018, and assessed the impact of the presence of comorbidities and of wrong interpretation of MRI findings on the chances of a misdiagnosis. An established diagnosis of MS had been made prior to referral to the Cemcat in 112 (31.8%) patients, while 76 (21.6%) were referred with 'suspected' MS. In 47 (13.4%) patients the term 'demyelinating' alone appeared on the referral form, and only neurological signs or symptoms were described as the reason for referral in 104 (29.5%) patients. Disease-modifying treatment was being taken by 46.7% of patients at the time of first assessment. An MRI had been performed in 86.6% (85% in external MRI facilities) and in 72% of cases the MRI result was known by the referring physician. Findings revealed an MS misdiagnosis in 12.6% of (14/112) of patients and in 92.8% (13/14) of those patients MRI had identified multifocal white matter lesions; these lesions were non-specific and not suggestive of MS in more than half (57.1%) of the patients. Comorbidities including cardiovascular risk factors, psychiatric disorders, and other neurological diseases were more prevalent in patients with a misdiagnosis of MS than patients with MS ($p = 0.02$). Cerebrovascular disease (3), migraine (3) and conversion disorders (3) were most frequently misinterpreted as MS.

Comment: The diagnosis of MS includes the concept of "no better explanation", because the MRI findings and clinical features of MS may be seen in other conditions. The diagnostic criteria for relapse-onset MS also stress the importance of objective findings to back up the patient-reported description of an event. For example, a history of possible optic neuritis should be backed up by objective clinical findings such as a swollen or pale optic disc, or objective investigational features such as an abnormal optic nerve on MRI or a delayed visual evoked potential. This study suggests that over-reliance on the presence of white matter abnormalities on MRI, which are increasingly common in older people due to vascular disease, may result in misdiagnosis, especially if there is a history of cerebrovascular disease or psychiatric disorders.

Poster P715
Abstract

Introduction of new diagnostic criteria for multiple sclerosis and time interval between disease onset and MS diagnosis

Authors: Stawiarz L et al.

Summary: The interval from first symptom of MS to the date of diagnosis in relation to the introduction of upgraded MS diagnostic criteria from conservative to more liberal ones was evaluated in this study of 19,600 MS patients from the Swedish MS registry collected between 1996 and 2019. The probability of survival was evaluated for 5 diagnosis epoch groups according to the diagnostic criteria advised at the time: 1965-1982 Schumacher, 1983-2000 Poser, 2001-2004 McDonald's first version, 2005-2009 revisions of 2005, 2010-2016 revisions of 2010 and 2017-2019 revisions of 2017. Using Poser criteria, half of all the patients received a MS diagnosis within 6.1 years, and this time was shortened to 1.4 years in the epoch of the first McDonald's criteria, and by a further reduction to 4 months for the third set of McDonald's criteria. During the Poser epoch, only 20% of patients got a diagnosis in the first year after onset compared with 45% during the epoch of the first McDonald criteria and almost 90% during the epoch of the last McDonald revision criteria.

Comment: Prior to the adoption of McDonald diagnostic criteria for MS in 2001, a diagnosis of relapse-onset MS could only be made after there had been at least 2 clinical events. McDonald criteria recognised that MRI could be used to anticipate further clinical activity, provided that certain criteria – new or enhancing lesions – were satisfied. This study illustrates the difference this change in diagnostic criteria makes to the time taken to make a diagnosis of MS following an initial symptomatic presentation. The findings were that 90% of patients received their MS diagnosis within 12 months under new criteria, compared to 20% when the oldest criteria were operational.

Abstract 99
Abstract

Thirty years outcomes of 2295 patients with relapsing at onset multiple sclerosis and low disability ten years after diagnosis: a population-based observational study

Authors: Mathey G et al.

Summary: This study using data from ReLSEP (Registre Lorrain des Scléroses en Plaques), a regional exhaustive French registry, aimed to describe the probability of further expanded disability status scale (EDSS) worsening in patients with relapsing at onset multiple sclerosis (RoMS) and an EDSS score ≤2.0 10 years after disease onset. The study also illustrated the shape of EDSS evolution in these patients from year 10 to year 30 and identified factors associated with not having worsened after 10 years. Among 2295 patients with an EDSS score ≤2.0 at year 10, 50% worsened before 22.6 years of disease duration. Of 562 uncensored patients at year 30, an EDSS score of ≤2.0 was present in 159 (28.3%) patients. The slopes of worsening of EDSS in groups of patients with worsening of disability at different time points seemed to be parallel between 10 and 30 years and the longer a patient remained with low disability, the older they were when the worsening of EDSS occurred. Remaining with an EDSS score ≤2.0 during follow-up was associated with a good recovery after the first relapse ($p < 0.05$) and a young age at onset ($p < 0.05$). At approximately 55 years of age, there was a slowing in the evolution of EDSS and the EDSS scores at advanced ages were finally lower in those with longer initial phases with an EDSS score ≤2.0.

Comment: If we could reliably select a group of patients who, on no treatment, would never become significantly disabled, we could spare them the risks and inconvenience of long-term treatment, and also save money from the health budget. This study looked at over 2000 patients who had minimal signs and little or no disability after 10 years with MS and found that 25% of these patients showed no progression between years 10 and 30. Unfortunately, this doesn't help very much, as the flip side is that nearly 75% of patients who had a benign course during their first 10 years subsequently went on to experience progression, and there did not seem to be a clear way to pick who would do well and who would not. The finding of slower rates of EDSS progression (in patients who were progressing) from 55 years onwards is intriguing, and fits with the clinical wisdom that sometimes MS may "burn out".

Poster P1119

Abstract

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Independent commentary by Dr John Mottershead

Dr John Mottershead is a Neurologist at SDHB. He trained at Oxford University as a medical student and was involved in research into uses of MRI in MS before completing his neurology training. From 2002 to 2009 he was a neurologist in Manchester working in both general neurology and a busy MS disease-modifying treatment clinic. In 2009 John 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.

Should I stay or should I go (on). Disease modifying therapies in patients with no evidence of disease activity for more than five years

Authors: Monschein T et al.

Summary: This study involving 49 patients who started interferon β or glatiramer acetate after the first clinical episode suggestive of MS, investigated the risk of MS disease recurrence after stopping these disease-modifying therapies. In all of the patients, the diagnosis of MS was supported by MRI, meeting Barkhof MRI criteria, and cerebrospinal fluid testing. Patients in the cohort were able to stop therapy if they had no evidence of disease activity (NEDA) for at least 5 years before they decided to stop therapy. Among the 49 patients discontinuing disease-modifying therapy, 26 experienced NEDA for at least 5 years of follow-up (range 5-8 years), while 23 exhibited either relapse (n = 7), MRI progression (n = 10), or both (n = 6). Age at disease-modifying therapy termination was the only predictive factor of ongoing freedom of disease activity (mean in the ongoing NEDA group 37.3 years versus 29.9 years in patients with recurrence of disease activity). The risk of recurrence of disease activity was 10% in patients aged >45 years at the time of disease-modifying therapy discontinuation and 56% in those <45 years of age. There was no significant difference in gender, type of disease-modifying therapy, treatment duration, and clinically isolated syndrome symptoms between those with ongoing NEDA and those experiencing a recurrence.

Comment: Do MS patients need lifelong disease-modifying treatment, even if they have been stable, with no relapse, MRI or disability activity for several years? This is a small study and cannot fully answer this important question. The finding that age at time of discontinuation was a strong predictor of continuing stability is interesting. The natural history of untreated MS includes a reduction in relapse rate and MRI activity over time. Without empirical studies like this one, we could not predict whether the period on disease-modifying treatments would "count" towards "MS age", or whether instead disease activity would pick up after discontinuation where it left off before the treatment was started. Larger studies that include patients on the newer agents will be required before neurologists and people with MS will feel confident in stopping treatment because of stable disease.

Poster P654
Abstract

Long-term reduction of relapse rate and confirmed disability progression after 6 years of ocrelizumab treatment in patients with relapsing multiple sclerosis

Authors: Giovannoni G et al.

Summary: This long-term open-label extension of the OPERA I and OPERA II phase III trials assessed the effects of switching from interferon β-1a to, or maintaining, ocrelizumab over 4 years of follow-up (82.3% completion) in patients with relapsing MS. Among those switching from interferon β-1a to ocrelizumab, the adjusted annualised relapse rate (ARR) decreased from 0.20 pre-switch to 0.10 after 1 year ($p < 0.001$), 0.08 after 2 years, 0.07 after 3 years and 0.04 after 4 years ($p = 0.05$). Ocrelizumab continuers maintained a low ARR through the 4-year period (ARR; baseline 0.13, 1 year 0.10, 2 years 0.08, 3 years 0.07, 4 years 0.05). The continuers group had fewer patients with 24-week confirmed disability progression (CDP) versus switchers in the pre-switch period (7.7% vs 12.0%), and at 1 year (10.1% vs 15.6%), 2 years (13.9% vs 18.1%), 3 years (16.2% vs 21.3%), and 4 years (19.2% vs 23.7%) (all $p < 0.05$).

Comment: Ocrelizumab will be funded late in 2019 for patients with relapsing MS in NZ. This follow-up study shows that after 6 years on ocrelizumab, there is sustained and impressive suppression of relapse activity. By the end of year 6, around 1 in 5 patients will have experienced CDP despite treatment. This is a familiar disconnect between efficacy of drugs in suppressing relapses versus disability progression. Nevertheless, the patients treated with ocrelizumab from the beginning were still protected against disability progression when compared to patients who received lower efficacy interferon β-1a during years 1 and 2, and this latter group did not catch up over the next 4 years. It is encouraging that the authors report maintenance of the same relatively good safety findings compared to the double-blind phase. Some neurologists have been concerned about the potential risks of long-term B-cell suppression, and there were reports at this ECTRIMS meeting of an association between lower levels of immunoglobulin and infection in people treated with ocrelizumab, although the effect size looked small.

Poster P1015
Abstract

Comparative effectiveness of natalizumab and fingolimod in different subgroups of patients with relapsing-remitting multiple sclerosis

Authors: Sharmin S et al.

Summary: This analysis used data from 3 observational databases (Observatoire français de la sclérose en plaques, Danish Multiple Sclerosis Registry, global MSBase registry) to estimate the effect of natalizumab and fingolimod in RRMS patient subgroups. Natalizumab reduced the number of relapses versus fingolimod in females (IRR 0.76), those aged ≤37 years (IRR 0.64), with an EDSS score <4 (IRR 0.76) or <6 (IRR 0.80) or ≥6 (IRR 0.52), disease duration ≤7 years (IRR 0.63), patients with recent pre-baseline relapses (IRR 0.74), and in those with new MRI lesions <1 year prior to treatment (IRR 0.51). A higher probability of confirmed disability improvement was observed for natalizumab versus fingolimod among females (HR 1.36), those aged >37 years (HR 1.34), those with an EDSS score <6 (HR 1.21), those with recent pre-baseline relapses (HR 1.23) and those with no new MRI lesions <1 year prior to treatment (HR 4.35).

Comment: Post-hoc subgroup analyses from clinical trials can give useful pointers as to the relative efficacy of treatments in patients with different characteristics, but this is naturally limited to the interventions studied in the trial, usually one drug against placebo or against a lower efficacy comparator. In order to look at differences between two modern treatments, these investigators used a large database. The finding that natalizumab is more effective in females, younger patients and in patients with active disease is not surprising, although the gender difference is not immediately explicable. This study supports the general approach of neurologists in NZ, which is to offer higher efficacy treatment from the beginning where possible.

Poster P1418
Abstract

Five and seven-year prognostic value of new effectiveness measures (NEDA, MEDA, six-month delayed NEDA) in relapsing-remitting multiple sclerosis

Authors: Tsantes E et al.

Summary: This retrospective observational study assessed whether 'no evidence of disease activity' (NEDA), minimal evidence of disease activity (MEDA) and NEDA 6-months after treatment start (6md-NEDA) status at 2 years predicts disease course at 5 and 7 years in 165 patients with RRMS. At 2 years, 27% of patients maintained NEDA, 28% MEDA and 34% 6md-NEDA. All these groups had a lower risk of attaining all disability outcomes, compared to patients with evidence of disease activity (EDA). NEDA status patients had a lower risk of 3 month-confirmed disability progression after 5 years (OR 0.18; 95% CI 0.1-0.4; $p < 0.0001$) and 7 years (OR 0.16; 95% CI 0.05-0.4; $p = 0.001$) of disease, and a lower risk of converting to SPMS (OR 0.26; 95% CI 0.07-0.92; $p = 0.03$) and of having an EDSS score of 4.0 (OR 0.15; 95% CI 0.03-0.68, $p = 0.01$) after 7 years. 2-year NEDA had a high positive predictive (90%) and low negative predictive (42%) value, good specificity (92%) and low sensitivity (34%) for no progression at 7 years (accuracy 55%). A NEDA status also had a lower risk of CDP versus MEDA status after 7 years (OR 0.30; 95% CI 0.1-0.9; $p = 0.04$).

Comment: Our department, and several other centres in NZ, now requests annual MRI for patients on treatment. If there are new lesions on the annual scan, or if there has been relapse activity or disability progression, consideration is given to changing to a different drug, especially if there is a higher efficacy agent available. With the funding of a second high efficacy agent, ocrelizumab, as well as the longer established agent natalizumab, this practice will become more important. The findings from this study illustrate both the problems and the advantages of such an approach. The biggest problem is that even on high-efficacy treatments, MS activity is completely silenced in less than 50% of patients. On a mixture of agents in this study, only 27% of patients had no disease activity during the 2-year run-in. On the plus side, patients who had no disease activity during years 1 and 2 were more likely to have good outcomes over the next 4 years. This result provides support for a policy of monitoring and switching in the case of activity, although a trial of active management versus therapeutic inertia would be needed for full validation.

Poster P1050
Abstract

Efficacy of siponimod in secondary progressive multiple sclerosis patients with active disease: the EXPAND study subgroup analysis

Authors: Gold R et al.

Summary: This *post-hoc* subgroup analysis of the phase III EXPAND study examined the effect of the selective sphingosine 1-phosphate receptor (S1P1,5) modulator siponimod 2 mg versus placebo in 779 active (76% with relapses in last 2 years and/or 45% with ≥1 T1 gadolinium-enhanced [Gd^+] lesions at baseline) SPMS patients. Siponimod reduced both 3-month (HR 0.69; 95% CI 00.53-0.91; $p = 0.0094$) and 6-month (HR 0.63; 95% CI 0.47-0.86; $p = 0.0040$) CDP risk versus placebo. The ARR was reduced in siponimod recipients by 46% ($p = 0.0005$), T1 Gd^+ lesion number by 85% ($p < 0.0001$), and new or enlarging T2 lesion number by 80% ($p < 0.0001$) versus placebo. Adjusted mean difference (siponimod vs placebo) over 12 months in T2 lesion volume was -1161.5 mm^3 ($p < 0.0001$).

Comment: Siponimod is a drug from the same class as fingolimod and is available in the USA for treatment of secondary progressive MS, but not in NZ. This sub-group analysis found that efficacy was greater in patients who had relapse activity or enhancing lesions on MRI prior to starting the trial when compared to the overall group. This is a similar result to that seen in the ocrelizumab primary progressive MS trial, where patients who had enhancing lesions at baseline had a greater slowing of disability progression than those who did not. It seems that even in progressive MS patients, efficacy of disease-modifying agents is at least partially related to their ability to reduce acute inflammation. Given that a single MRI will only capture a proportion of those patients who will have had enhancing lesions over, say, the previous 12 months, it is possible that the therapeutic response is in fact largely driven by the presence or absence of blood-brain barrier breakdown and inflammatory activity.

Poster P750
Abstract

Reduction of risk of secondary progressive multiple sclerosis within two years of treatment with cladribine tablets: an analysis of the CLARITY study

Authors: Vermersch P et al.

Summary: This *post hoc* analysis of the CLARITY study in 433 patients with relapsing multiple sclerosis receiving cladribine 3.5 mg/kg or placebo (n = 437), examined the association between baseline EDSS scores and progression to SPMS or to an EDSS score ≥6.0. Proxy SPMS progression occurred in 6.7% of cladribine recipients versus 13.5% of placebo recipients (OR 0.46; 95% CI 0.28-0.76; $p = 0.0024$). Among those with a baseline EDSS score ≤3.0, proxy SPMS progression occurred in 3.5% of cladribine versus 7.7% of placebo recipients (OR 0.44; 95% CI 0.19-0.99; $p = 0.0471$) while in those with an EDSS score ≥3.5 proxy SPMS progression occurred in 12.2% versus 22.4% (OR 0.48; 95% CI 0.26-0.9; $p = 0.0212$). Patients with at least one EDSS post-baseline score ≥6.0 were also less common amongst cladribine (6.4%) than placebo (14.5%) recipients (OR 0.4; 95% CI 0.24-0.66; $p = 0.0004$). Proportions among patients with 3-month CDP with EDSS ≥6.0 were 3.5% in those receiving cladribine versus 8.0% in those receiving placebo (OR 0.42; 95% CI 0.22-0.82; $p = 0.0114$).

Comment: Cladribine is an oral immunosuppressive treatment that is given in two short cycles over a 2-year period. There seems to be the potential for patients treated with cladribine to have a prolonged therapeutic response, possibly due to reconstitution of the immune system analogous to that which occurs after bone marrow transplantation. This study suggests that, in addition to cladribine's already known efficacy in suppressing relapses and early disability trajectories, there may be an important medium-term reduction in the transition to secondary progressive MS and to the hard disability milestone of EDSS ≥6.0, when patients begin to require wheelchair assistance. Cladribine is currently not funded in NZ.

Poster P385
Abstract