A RESEARCH REVIEW™
CONFERENCE REVIEW

MSMilan 2023 Conference Review

9th Joint ECTRIMS-ACTRIMS Meeting

Making Education Easy

11-13 October, 2023

In this review:

Abbreviations used in this review:
BTK = Bruton's tyrosine kinase
CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts & leukoencephalopathy
CIS = clinically isolated syndrome
CNS = central nervous system
CSF = cerebrospinal fluid
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
MOG(AD) = myelin oligodendrocyte glycoprotein antibody (-associated disease)
NGD = neurogenetic disease
RCT = randomised controlled trial
RR = rate ratio

Welcome to our review of the 2023 ECTRIMS-ACTRIMS Meeting held in Milan, Italy.

I was delighted to virtually attend this year's conference. With the theme *'Every person. Every pathway'*, the presentations focused on how we as physicians can improve the care and the lives of all patients with multiple sclerosis (MS), through exploring every possible approach. Here I discuss eleven sessions which were particularly interesting and relevant to local practice. Some of the highlights include data which shows that many patients with neurogenetic diseases such as CADASIL are misdiagnosed with MS, and an extension study demonstrates that tolebrutinib has a favourable long-term safety profile and encouraging efficacy signals in relapsing MS. Another paper of interest provides evidence that sub-cutaneous natalizumab every 6 weeks is likely to be as effective as IV administration in the management of relapsing-remitting MS, and it is largely preferred by patients as it calls for less time in the clinic. Detailed abstracts for the presentations are published online here.

I trust you find this conference review interesting and informative, and I look forward to reading your thoughts and comments.

Kind regards,
Dr John Mottershead
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Clinical and radiological phenotype of adult-onset neurogenetic diseases mimicking multiple sclerosis

Speaker: Gabrielle Macaron (Montreal, Canada)

Summary: In this observational study, researchers carried out a multinational data search to identify and describe patients who had either been diagnosed with MS alone but who actually also had a neurogenetic disease (NGD-MS), and patients with a NGD who had been misdiagnosed as having MS (Mis-MS). Among a total of 46 patients, nine were classified as NGD-MS and 38 as Mis-MS. All patients in the NGD-MS cohort had initially been diagnosed with CIS or relapsing-remitting MS, and most had an overlapping mitochondrial disorder. Among those in the Mis-MS cohort, 67% had been misdiagnosed with primary progressive MS. The most common NGD was CADASIL (n=9); other NGDs included hereditary diffuse leukoencephalopathy with spheroids and leber hereditary optic neuropathy, Alexander disease, Krabbe disease, PolG disease and spastic paraplegia 2/5/6/7. CSF oligoclonal bands were identified in 2/24 patients in the Mis-MS cohort and 5/6 in the NGD-MS cohort. Mis-MS patients typically received steroid therapy (48.6%) and platform and high-efficacy MS-specific DMTs (24.3% and 10.8%, respectively).

Comment: This study from France, Italy and Canada looked at genetic diagnoses in people originally diagnosed with MS. In most cases, the genetic diagnosis replaced the diagnosis of MS, although around 20% of patients were felt to have both MS and a genetic neurological condition. Two-thirds of the patients misdiagnosed with MS had been thought to have primary progressive MS, which accounts for only around 10 to 20% of all people with MS. Some of the genetic disorders identified were conditions like CADASIL which don't resemble MS closely clinically, but have MRI findings that can look like MS. Others were conditions like hereditary spastic paraparesis that have progressive CNS degeneration and can be confused with primary progressive MS. NZ neurologist Ian McDonald, after whom the modern MS diagnostic criteria are named, once said that he always worried about the security of an MS diagnosis if oligoclonal bands were negative. This study vindicates his concern, as only two out of 24 cases misdiagnosed with MS had positive bands.

Abstract number 1577/P003
Abstract

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How well do junior neurology residents recognize multiple sclerosis?

Speaker: Claudia Zbrzeski (New York, USA)

Summary: The objective of this 'close the loop' resident clinical acumen project was to explore the diagnostic patterns and errors made by junior neurology residents in recognising MS and other demyelinating diseases (MS/DD). Over 6 years, junior residents believed that 66 of 1472 'uncertain' cases were MS/DD, however only 44 of these (66%) were actually MS/DD. Among the 'over-called' cases, 41% were non-neurologic, 41% CNS (including stroke) and 18% peripheral nervous system. Junior residents initially 'missed' 23% of the cases which had a final diagnosis of MD/DD (n=57), misdiagnosing them as either non-neurologic (23%), CNS neoplastic (31%), stroke (23%) or CNS infection (15%). Residents correctly recognised 44 cases as MS/DD. The specificity of resident accuracy in identifying MS/DD was 66.7%, and the accuracy in the entire cohort of 1472 cases was 64.0%.

Comment: This is an interesting study from New York, looking at diagnostic errors made by neurology trainees. In this sample at least, trainees were more likely to over-call MS diagnoses than to miss them. Stroke, neoplasia and peripheral nervous system disorders made up the majority of conditions initially wrongly diagnosed as MS, whereas neoplasia, stroke and CNS infection were the three most likely diagnoses in people where an MS diagnosis was initially missed. I think these will have been cases deliberately selected to be challenging, as neoplasia (presumably CNS lymphoma, brain metastases or primary brain tumour) is not often confused with MS in routine clinical practice.

Abstract number 1048/P002
Abstract

Uncovering alternative diagnoses in patients with suspected multiple sclerosis

Speaker: Andreu Vilaseca (Barcelona, Spain)

Summary: This session shared longitudinal data from the Barcelona CIS cohort collected between 1994 and 2023. From a total of 1468 patients initially thought to have CIS, 1368 were diagnosed with MS according to the 2017 McDonald criteria, however an alternative diagnosis was made in 100 patients (6.8%). Among this sub-set of patients, diagnostic work-ups revealed neurological syndromes including optic neuropathy (37.0%), spinal cord syndrome (16.0%) and functional syndrome (15.0%). Immune-mediated diseases were the most common aetiology (41.0%), followed by functional disorders (15.0%) and vascular disease (10.0%). Of the 26 misdiagnosed patients who had at least one suggestive inflammatory-demyelinating lesion on baseline MRI, 16 (61.5%) had other immune-mediated neurologic diseases (including MOGAD) and five (19.2%) had vascular disease. The 2017 McDonald criteria were not met for any of the misdiagnosed patients.

Comment: These are very interesting data from a large Barcelona cohort of CIS patients collected over a 29-year period. One hundred out of 1468 patients (6.8%) were misdiagnosed with MS. Of those with a baseline brain MRI, only 26/90 of people misdiagnosed with MS had an inflammatory lesion at baseline, underlining the caution that should be used in diagnosing MS in someone without supportive MRI findings. It is encouraging that none of the patients who were misdiagnosed would have met 2017 McDonald diagnostic criteria. The most frequent revised diagnoses were other inflammatory disorders such as MOGAD (testing for MOG antibodies only became available towards the end of this cohort period), functional disorder and cerebrovascular disease.

Abstract number 2247/P404
Abstract

Effectiveness of oral prednisone tapering following intravenous methylprednisolone for acute optic neuritis in multiple sclerosis

Speaker: Adi Wilf-Yarkoni (Petah-Tikva, Israel)

Summary: These researchers investigated whether a tapering of oral prednisone following intravenous methylprednisolone affected the visual outcomes of optic neuritis in 51 patients (25% male; mean age 33.9 years) with MS. A total of 26 patients (51%) received tapering of oral prednisone following intravenous methylprednisolone, and 25 (49%) received intravenous methylprednisolone alone. Patients with recurrent optic neuritis and ophthalmological comorbidities were excluded. At follow-up, there were no significant between-group differences in retinal nerve fibre layer loss or high-contrast best-corrected visual acuity. A larger, prospective study (ACON) is underway to further validate these findings.

Comment: The literature regarding use of steroids for MS relapses is surprisingly sparse, although there is enough to confirm that steroids shorten the duration of maximal neurological deficit, without necessarily affecting the final outcome. My practice is only to use a steroid tail after 3 to 5 days of high-dose steroid if there is a special consideration, such as a history of rebounding after initial improvement with previous steroid courses. This small study in optic neuritis did not show a difference between patients receiving a tapering course and those who did not, suggesting that if there is a difference, it is likely to be small.

Abstract number 266/P1457
Abstract

Safety and clinical efficacy outcomes from the long-term extension study of tolebrutinib in participants with relapsing multiple sclerosis

Speaker: Jiwon Oh (Toronto, Canada)

Summary: In a phase 2b trial, the BTK inhibitor tolebrutinib was well-tolerated and showed a promising dose-dependent reduction in new gadolinium-enhancing lesions in patients with relapsing MS. This presentation shared the safety and efficacy data from week 144 in the long-term safety extension. Patients were initially blinded and continued their core tolebrutinib dose (5/15/30/60mg/day); following this, they received open-label tolebrutinib at 60mg/day. At data cut-off, most patients (82.4%) remained on treatment. The long-term and ongoing safety profile of tolebrutinib is favourable, and consistent with earlier data. The incidences of treatment-emergent and serious adverse events were similar across all doses. Among the 124 patients who received a dose of 60mg/day for ≥8 weeks, 68.5% remained relapse-free, with an annualised relapse rate of 0.23. Throughout the extension period to week 144, EDSS scores remained stable.

Comment: BTK inhibitors are arguably the next big hope in MS disease modification. Now that we know that drugs working on the peripheral immune response, such as natalizumab and ocrelizumab can be highly effective in early relapsing MS, but are disappointing in established progressive MS, attention has turned to drugs which cross the blood-brain barrier and act on microglia and/or B-lymphocytes. BTK inhibitors do all of these things. Phase 3 trials are ongoing, but these data from a phase 2b trial show encouraging signals for efficacy and safety. However, the patients in the trial had relapsing, rather than progressive MS, so it is too early to say whether these agents will be transformative.

Abstract number 1470/P278
Abstract

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Lymphopenia is not the primary mechanism by which diroximel fumarate exerts its therapeutic effects in patients with relapsing-remitting multiple sclerosis

Speaker: Barry Singer (St Louis, USA)

Summary: In the phase 3 EVOLVE-MS-1 study, patients with relapsing-remitting MS showed favourable outcomes with diroximel fumarate, however in the first year, lymphocyte counts dropped by ≈28% before stabilising. This subgroup analysis evaluated whether the efficacy of diroximel fumarate was mediated by lymphopaenia. When comparing patients with (n=452) and without lymphopaenia (n=593), researchers reported that there were no clinically meaningful differences in annualised relapse rate (0.12 vs. 0.14, respectively), confirmed disability progression at week 96 (9.3% vs. 10.2%) or number of gadolinium-enhancing lesions (0.1 vs. 0.6; 95.9% vs. 86.8% had no lesions).

Comment: Diroximel fumarate is very similar to dimethyl fumarate (Tecfidera®), with both drugs having the same active metabolite. Tecfidera® is funded in NZ and is a useful medium-efficacy disease-modifying drug. Diroximel fumarate has similar efficacy, but lower incidence of gastrointestinal side-effects. Lymphopaenia can occur with either drug. When using drugs like azathioprine, in some disorders it is possible that patients with moderate lymphopaenia may benefit more, because lymphopaenia is related to the mechanism of disease control. This study suggests that the disease-modifying effect of diroximel fumarate in MS is not mediated via lymphopaenia.

Abstract number 741/P287
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.

Experience with cladribine tablets beyond year 4: the challenge of the long-term management

Speaker: Alex Torres Moral (Seville, Spain)

Summary: There is currently a paucity of data surrounding the use of cladribine beyond 4 years in patients with relapsing-remitting MS. This session described the experiences of 148 patients (72.8% female) who received cladribine for ≥4 years (mean time 35.2 months). At baseline and years 1, 2, 3, 4 and 5, the annualised relapse rates were 1.0, 0.03, 0.008, 0.06, 0.02 and 0.0, respectively. A total of 32 patients (80%) remained free of significant disease activity at 4 years. Across the study period, eight patients discontinued treatment; four of these were within the first year. Patients with significant disease activity were switched to anti-CD-20 therapies. Due to minimal disease activity at year 5, one patient was treated with a third cladribine cycle. Patients underwent yearly MRI and 6-monthly clinical follow-up if no disease activity or progression was detected.

Comment: Cladribine is an oral agent which is currently under consideration for funding by Pharmac. It is given as two short oral courses 1 year apart. It is thought to work by inducing immune reconstitution, in a similar way to bone marrow transplantation. The pivotal trial in relapsing-remitting MS showed good early efficacy, but less is known about the duration of these effects. This is important, because patients will be on no medication after they have received their two courses of cladribine, and some will be at risk of breakthrough disease activity. There is a published open-label extension of the pivotal CLARITY trail, which showed that around 75% of patients were relapse-free during years 3 and 4. This new study promises rather more than it delivers, as only a minority of patients have data beyond year 3. However, as far as it goes, it suggests that for most patients, relapse-free status is maintained in the medium term.

Abstract number 1417/P697
Abstract

Results from the NOVA extension study evaluating patient preference for subcutaneous versus intravenous administration with natalizumab Q6W dosing

Speaker: Heinz Wiendl (Münster, Germany)

Summary: The phase 3b NOVA indicated that most patients with relapsing-remitting MS who are stable on 4-weekly dosing of IV natalizumab can switch to 6-weekly dosing. In this extension phase, 141 patients received 6-weekly IV dosing for 36 weeks before being randomised to a 48-week crossover period (24 weeks subcutaneous 6-weekly dosing, 24 weeks IV 6-weekly dosing). The majority of patients (87.8%) preferred subcutaneous administration, with 82.9% describing that it "*requires less time in the clinic*". During the crossover period, disease activity was low overall. One patient missed one subcutaneous dose, with a subsequent relapse and new/newly enlarging T2 lesion. The safety signals of both administration methods were consistent with previous data, and with comparable rates of adverse events between routes. It was noted that the efficacy and safety data were limited by the short follow-up.

Comment: Sub-cutaneous rather than IV administration of biologics is attractive, because it may be possible at home - for example with infliximab; or if needing to be given in a healthcare facility, it will be quicker and more convenient. Natalizumab is currently usually given every 6 weeks via IV. This study provides some evidence that sub-cutaneous natalizumab every 6 weeks is likely to be as effective as IV, and is favoured by patients.

Abstract number 3114/P1657
Abstract

MS treatment start, continuation and discontinuation in the elderly

Speaker: Fredrik Piehl (Solna, Sweden)

Summary: The aim of this narrative review was to outline the current data surrounding treatment options for elderly patients with MS. It was concluded that there is less robust evidence for treatments in older age groups, and therefore it is recommended that physicians individualise treatment based on each person's course of MS disease and general health. Sub-group analyses of RCTs indicate that effective therapies have a greater effect versus placebo in younger patients aged <40 years. A limitation of many RCTs is that they tend to set age and comorbidity restrictions, making it difficult to generalise safety and efficacy findings to older patients, and potentially increasing the risk they face when undergoing treatment. It is difficult to make robust benefit-risk considerations for continuation versus stopping DMTs in older patients, given that the evidence base for ceasing therapy is substantially weaker than that for initiating therapy.

Comment: There is a growing group of people with MS in NZ and around the world who have been on disease-modifying treatment for some time and are now aged 50 years or older. There are also people starting treatment who are aged over 50, although this is a smaller group. As this presentation argues, clinical trial evidence is mainly from younger people, and sub-group analyses generally show bigger treatment effects in younger patients. The first of several randomised discontinuation trials was published recently, and suggested that discontinuation of the older agents β-interferon and glatiramer acetate in older people with no recent relapse or MRI activity is likely to carry only a small risk of disease reactivation. We still need more evidence before we can give informed advice to people about the merits of stopping treatment.

Abstract number 4017/0015
Abstract

Ublituximab reduces thalamic volume loss and new lesion formation in participants of the ULTIMATE I & II phase 3 studies

Speaker: Douglas L Arnold (Montreal, Canada)

Summary: In the ULTIMATE I and II phase 3 trials, ublituximab significantly reduced the annualised relapse rate versus teriflunomide in patients with relapsing MS. It was suggested that thalamic injury may be an indicator of damage across the entire CNS. This post-hoc analysis assessed the impact that ublituximab had on thalamic volume and new lesion formation across these study periods. Over 2 years, ublituximab significantly decreased the loss of thalamic volume versus teriflunomide by 22% (p=0.0013). The increase in T1 hypointense lesion volume was also significantly reduced with ublituximab (6.32 vs. 24.87, p=0.0001), and this was more pronounced in year 2 of treatment. After year 1, the formation of new T1 and T2 lesions was almost entirely diminished with ublituximab.

Comment: There are now a range of anti-CD20 monoclonal antibodies with trial evidence in MS. Ocrelizumab is funded in NZ for both relapsing-onset and primary progressive MS. Rituximab has some evidence and is widely used in some other countries. Ofatumumab is a subcutaneous agent currently being considered by Pharmac. This study looks at ublituximab, which is not available in NZ, but has pivotal trial evidence showing strong efficacy in reducing relapses and MRI activity, but no significant reduction in disability progression compared to teriflunomide. This study looked at thalamic atrophy, which has growing support as a marker of disease progression. The findings are promising, and may suggest that the short-term measures of clinical disability used in the trial may underestimate differences between the treatments. This is an old problem - we know that disability scales used in trials are dominated by ambulation, which changes only slowly. Thalamic atrophy rates may be important, but are unlikely to convince funding bodies without a lot more evidence mapped against quality of life measures.

Abstract number 1262/P162
Abstract

The multiple sclerosis prodrome: Rates of physician visits were elevated in the 15 years before a first demyelinating event and differed by age and sex

Speaker: Helen Tremlett (Vancouver, Canada)

Summary: This international, population-based, matched cohort study analysed the rates of physician visits in the 15 years before a first demyelinating event in Canada and Sweden. A total of 46,727 patients with MS and 194,493 matched controls were included in the analysis (69% female; average age 43 years). The annual rates of visits by MS patients versus matched controls increased steadily from 15 years before disease onset (RR 1.18), and were highest in the final year before onset (RR 3.02). Males and younger patients had the highest relative rates of physician visits compared with matched controls. In the year prior to onset, the RRs (vs. controls) were 3.02 for males, 2.35 for females, 2.52 in patients aged <18 years and 2.24 in those aged ≥50 years.

Comment: There is emerging evidence that people with MS utilise certain aspects of healthcare more in the years leading up to clinical presentation. This is the prodrome, and is also seen in conditions like rheumatoid arthritis. This case-control study showed that physician consultation rates rose from a relative rate of 1.18 in the 15 years before presentation to 3.02 in the year before presentation. The prodromal differences were higher for males and higher for younger patients. The MS prodrome is fascinating, and may be related to subclinical MS lesions causing ill-defined symptoms like fatigue, and to immune system changes causing non-specific malaise.

Abstract number 144/P450
Abstract