Neurology Research Review™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

Issue 55 – 2019

In this issue:

Abbreviations used in this issue
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
HR = hazard ratio
HSCT = hematopoietic stem cell transplantation
MRI = magnetic resonance imaging
MS = multiple sclerosis
RRMS = relapsing-remitting MS
PPMS = primary progressive MS

Welcome to this special issue of Neurology Research Review, focusing specifically on MS.

In this issue, an analysis of MSBase data shows that initial treatment with fingolimod, alemtuzumab, or natalizumab is associated with a lower risk of conversion to secondary progressive MS than initial treatment with glatiramer acetate or beta-interferon in patients with RRMS. A preliminary study of patients with RRMS shows that HSCT prolongs the time to disease progression compared with DMT, and another MSBase analysis reports that DMTs have no substantial effect on disability outcomes in patients with PPMS. A Canadian study reports that approximately 10% of individuals discontinue their first oral DMT within 6 months and 20% do so within one year, and a UK study suggests that a personalised protocol of subcutaneous cladribine may be a viable therapeutic option in MS patients who are ineligible for treatment with oral DMTs.

We hope you find these and the other selected studies interesting, and welcome your feedback.

Kind regards,

Dr Jennifer Pereira
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Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis

Authors: Brown J et al., for the MSBase Study Group

Summary: This analysis of MSBase data investigated the association between initial DMT and conversion to secondary progressive MS. 1555 patients with RRMS who started treatment with a DMT in 1988–2012 at 68 neurology centres in 21 countries were included. Patients were followed up for a minimum 4 years. Compared with propensity score-matched untreated patients, patients initially treated with glatiramer acetate or beta-interferon had a significantly lower risk of conversion to secondary progressive MS (HR, 0.71), as did patients initially treated with fingolimod (HR, 0.37), natalizumab (HR, 0.61) and alemtuzumab (HR, 0.52). Initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a significantly lower risk of conversion than initial treatment with glatiramer acetate or beta-interferon (HR, 0.66). The probability of conversion was lower when glatiramer acetate or beta-interferon were started within 5 years of disease onset vs later (HR, 0.77), or when glatiramer acetate or beta-interferon were escalated to fingolimod, alemtuzumab, or natalizumab within 5 years vs later (HR, 0.76).

Comment: This study from MSBase uses propensity matching to look at time to convert to secondary progressive MS by treatment regimen and early or late start of DMT. Epidemiological studies from the pretreatment era show that 80% of patients with RRMS will develop secondary progressive disease within 20 years. This study shows that in a large cohort of 1555 patients, there was a reduction in the 5-year risk of conversion to secondary progression in those on fingolimod, natalizumab and alemtuzumab compared to glatiramer and beta-interferon and in both groups compared to no treatment. This study also showed that those who started earlier on treatment (within 5 years) were less likely to convert to secondary progressive disease. This further supports our current treatment paradigm – early treatment with effective immunotherapy.

Reference: JAMA 2019;321(2):175-87
Abstract

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Independent commentary by Dr Jennifer Pereira BHB, MBChB, FRACP, MD

After undergraduate training in medicine at the University of Auckland, Jennifer trained in neurology at Auckland City Hospital. Postgraduate training consisted of an MS research fellowship, with the Therapeutic Immunology Group in the Department of Clinical Neurosciences, University of Cambridge (UK). **For full bio CLICK HERE**

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis

Authors: Burt R et al.

Summary: This preliminary study compared nonmyeloablative autologous HSCT vs DMT in patients with highly active RRMS. 110 patients with at least 2 relapses while receiving DMT in the previous year and an EDSS score of 2–6 were randomised to receive HSCT (plus cyclophosphamide 200 mg/kg and antithymocyte globulin [ATG] 6 mg/kg) or DMT of higher efficacy or a different class than that taken previously. 98 patients were evaluated at 1 year and 23 were evaluated yearly for 5 years (median follow-up, 2 years). Disease progression had occurred in 3 patients in the HSCT group and 34 patients in the DMT group at 1 year. During the first year, mean EDSS scores improved from 3.38 to 2.36 in the HSCT group but worsened from 3.31 to 3.98 in the DMT group (between-group mean difference, –1.7; p<0.001).

Comment: With increasing evidence from cohort studies and meta-analyses that autologous HSCT is an effective treatment for active MS, the publication of this phase 2 randomised controlled trial of HSCT was much awaited. 110 patients were randomised to HSCT (using a low intensity conditioning regimen of cyclophosphamide and ATG) versus a higher efficacy or different class of MS treatment as determined by the patient's neurologist. Those who received HSCT showed an improvement in the primary outcome measure of disability progression at 1 year (3 patients in the HSCT group versus 34 in the DMT group showed an increase in EDSS score by 1 point at 1 year). It is important to carefully look at the inclusion criteria. The patients in this study had active disease and were failing effective medical treatment – 2 relapses on DMT in the year prior with an EDSS of 2.0–6.0. The study did not include treatment-naïve patients or those whose disease was effectively controlled on available DMTs.

Reference: JAMA 2019;321(2):165-74
Abstract

Anti-inflammatory disease-modifying treatment and disability progression in primary progressive multiple sclerosis

Authors: Lorscheider J et al., for the MSBase Study Group

Summary: This analysis of MSBase data investigated the impact of anti-inflammatory DMTs on disability outcomes in patients with PPMS. 195 patients with PPMS who had never been treated with a DMT were propensity score matched with 338 patients who were receiving a DMT. Pairs were followed up for a median 3.4 years. No between-group differences were seen for 3-month EDSS progression events, EDSS improvement, or reaching an EDSS score ≥7.

Comment: This study again uses MSBase to evaluate whether the currently available treatments proven in RRMS are of benefit to those with primary progressive disease. In 533 matched patients (195 on treatment) over a 1.2- to 5.5-year follow-up there was no evidence that those treated with DMTs had an improved outcome. However, of the 195 matched patients only 5 were on rituximab and 2 on alemtuzumab whereas the majority of patients were on beta-interferon and glatiramer acetate. The conclusion from this study that "these therapies have no substantial effect on short- to medium-term disability outcomes in PPMS" is correct in this cohort, but the majority of those included were on low efficacy agents.

Reference: Eur J Neurol 2019;26(2):363-70
Abstract

Association of inflammation and disability accrual in patients with progressive-onset multiple sclerosis

Authors: Hughes J et al., for the MSBase Study Group

Summary: This longitudinal prospective study from the MSBase group examined the role of inflammatory disease activity as a determinant of disability accrual in patients with progressive-onset MS. 1419 patients with adult-onset PPMS or progressive-relapsing MS were included. During follow-up, the likelihood of confirmed disability progression was lower in patients with vs without superimposed relapses (HR, 0.83; p=0.003). The proportion of follow-up time spent on DMT significantly reduced the risk of confirmed disability progression in patients with relapse (HR, 0.96; p=0.01) but not in those without relapse.

Comment: This study investigates the response to DMTs in those patients with primary progressive disease versus progressive relapsing MS (or active progressive disease). It tells us that patients with active disease have a less severe phenotype and likely benefit from available DMTs. Fortunately, current PHARMAC criteria allow us to treat individuals with underlying progression providing they are having relapses, have new lesion formation on scan, and can walk 500m.

Reference: JAMA Neurol 2018;75(11):1407-15
Abstract

Efficacy and safety of alemtuzumab versus fingolimod in RRMS after natalizumab cessation

Authors: Pfeuffer S et al.

Summary: This study evaluated efficacy and safety outcomes in patients who switched to alemtuzumab or fingolimod after cessation of natalizumab treatment. Outcomes for 144 patients at 12 German neurology centres were reviewed. The risks of clinical relapses, adverse events and MRI progression were higher in patients who switched to fingolimod vs alemtuzumab (HRs: 2.24, 7.78 and 2.41, respectively). The odds ratio for disability progression at 12 months was 4.84 (p=0.003).

Comment: This study examined people with MS on natalizumab who switched treatment for either breakthrough disease or high risk of progressive multifocal leukoencephalopathy. Reactivation of background MS disease (and possibly rebound) occurs after switching from natalizumab to an alternative DMT. This is more likely when a long washout is used, the patient is switched to a less efficacious agent, and in those with more aggressive disease pre natalizumab. This study shows that those switching from natalizumab to alemtuzumab experienced fewer relapses compared to those who switched to fingolimod. This occurred even though a higher proportion of patients (55.8% vs 2%) were switched to alemtuzumab for ongoing disease activity on natalizumab.

Reference: J Neurol 2019;266(1):165-73
Abstract

The disease burden of multiple sclerosis from the individual and population perspective: which symptoms matter most?

Authors: Barin L et al.

Summary: This analysis of data from the Swiss MS Registry investigated which MS symptoms contribute most to disease burden in individuals and from a population perspective. 855 patients with RRMS or progressive MS (PMS) had health-related quality of life (HRQoL) measured using the EuroQol 5-Dimension (EQ-5D) index and the EQ-Visual Analogue Scale (EQ-VAS). In patients with RRMS, gait and balance problems caused the greatest individual burden, and were also important at the population level (frequencies of 45% and 52%, respectively). Fatigue, depression, and spasticity also contributed to the population disease burden in RRMS patients (frequencies of 74.1%, 31%, and 38%, respectively). In PMS, spasticity, paralysis, pain and bowel problems had the largest impact on HRQoL, both at individual and population levels.

Comment: In our RRMS population much of clinic time is allocated to prescribing and monitoring the safety of DMTs. Time to address symptoms management is limited. This paper highlights those symptoms in the RRMS population that impact most on quality of life and should be prioritised – balance, spasticity and depression. In the PMS group, spasticity and pain have the biggest impact.

Reference: Mult Scler Relat Disord 2018;25:112-21
Abstract

Comparative effectiveness of dimethyl fumarate versus fingolimod and teriflunomide among MS patients switching from first-generation platform therapies in the US

Authors: Ontaneda D et al.

Summary: This US study compared relapse rates in MS patients after switching from a platform therapy to dimethyl fumarate versus fingolimod or teriflunomide. Dimethyl fumarate patients were propensity-score matched 3:1 to fingolimod patients and 3:1 to teriflunomide patients based on age, gender, region, MS severity, annualised relapse rate (ARR), and number of hospitalisations during the pre-index period. 2136 switch patients were included in the dimethyl fumarate-fingolimod cohort, and 1112 switch patients in the dimethyl fumarate-teriflunomide cohort. Analysis of the cohorts showed that patients who switched to dimethyl fumarate had post-index ARRs and risk of relapse comparable to those who switched to fingolimod, but significantly lower ARR (rate ratio, 0.667) and risk of relapse (HR, 0.679) than those who switched to teriflunomide.

Comment: We have fingolimod, dimethyl fumarate and teriflunomide available in NZ. They are all moderate efficacy oral agents. Relative efficacy is important but is always weighed up against the side-effect profile which must be matched to the individual. For an example, in a woman of childbearing age, dimethyl fumarate is a safer option (category B1) than teriflunomide which is teratogenic and fingolimod which has a category D rating.

Reference: Mult Scler Relat Disord 2019;27:101-11
Abstract

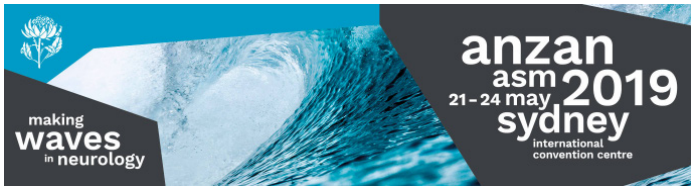
Persistence and adherence to the new oral disease-modifying therapies for multiple sclerosis

Authors: Setayeshgar S et al.

Summary: This population-based study examined persistence and adherence to oral DMTs for MS. Population-based health administrative databases in British Columbia, Canada were used to identify all MS patients who filled a prescription for an oral DMT (fingolimod, dimethyl fumarate, or teriflunomide) in 2011–2015. Of 858 individuals with ≥6 months of follow-up, 11.0% had discontinued their initial oral DMT by 6 months and 19.6% had discontinued their initial oral DMT by 12 months. Over 6 and 12 months, among those persisting with their oral DMT, 82.5% and 81.7% exhibited optimal adherence (≥80% of days). Age, sex, and comorbidity were not associated with persistence or adherence, but individuals with higher socioeconomic status were more likely to discontinue DMT within 6 months. Those who had previously used another DMT had higher odds of optimal adherence.

Comment: We spend a lot of time considering the best first DMT to prescribe to our patients. This is then supported with education and on-treatment support from our MS nurses. This study shows that this works, with 90% continuing their first agent for 6 months and 80% for 1 year, with over 80% adherence in those who persist on treatment. There are a minority of patients who develop side effects and require switching. Helping individuals stay on their current treatment is worthwhile as there is evidence that the more often you switch the less likely you are to persist on the next and subsequent treatments.

Reference: Mult Scler Relat Disord 2019;27:364-69
Abstract



Reduction in ocrelizumab-induced infusion reactions by a modified premedication protocol

Authors: Conte W et al.

Summary: This study examined whether a modified premedication protocol reduces the incidence of infusion-associated reactions (IARs) with ocrelizumab. Of 207 patients who were scheduled to receive ocrelizumab, 110 received modified premedication (cetirizine 10mg, ranitidine 75mg, and increased hydration the night before the ocrelizumab infusion; the regimen was repeated the next day prior to arrival). Just before the ocrelizumab infusion, all patients were pretreated with intravenous diphenhydramine 50mg, intravenous methylprednisolone 125mg, and oral paracetamol 650mg. The results showed a 10% overall prevalence of IARs in patients on the modified premedication protocol, compared to a 21.6% prevalence in those on the standard protocol (odds ratio, 0.40; p=0.024). The risk of IARs was lower in men and in older patients, and higher in patients with increased body mass index.

Comment: Ocrelizumab is administered as an intravenous infusion with patients receiving 300mg on day 1 and day 15 then 600mg 6-monthly ongoing. Prior to each dose patients are premedicated with methylprednisolone and an antihistamine. Infusion reactions occurred in 35% of patients in the phase III trials despite this and were managed by slowing or stopping the infusion. This study offers an alternative regimen which reduced the occurrence of infusion reactions from 21.6% with the standard premedication to 10% using the alternative regimen.

Reference: Mult Scler Relat Disord 2019;27:397-99
Abstract

Treating the ineligible: disease modification in people with multiple sclerosis beyond NHS England commissioning policies

Authors: Mao Z et al.

Summary: This UK study investigated the safety and efficacy of subcutaneous cladribine in MS patients ineligible for oral DMTs. 71 patients (36 with relapsing MS and 35 with progressive MS) received at least one treatment cycle of subcutaneous cladribine according to a personalised dosing scheme (30–40mg in week 1, and another 0–30mg in week 5 depending on total lymphocyte count at week 4). In 35 patients who were followed up for at least 20 weeks, median EDSS was 5.0 at baseline and 5.5 after a mean 11 months. Cladribine was well tolerated, with very few treatment-related adverse events observed. 50% of patients developed grade 1–2 lymphopenia, but only 1 developed transient grade 3 lymphopenia. No cases of varicella or other infections were observed. Four patients with relapsing MS had a total of 6 relapses during a mean 13 months of follow-up. In patients with progressive MS, 25% had active scans on MRI at baseline compared with none at follow-up.

Comment: The high cost of proven MS treatments means that access to them is restricted in NZ. Similar to the UK population described in this article, we too have a group of patients with active MS who are ineligible for funded treatment. This leads to off-label prescribing of treatments and in this article the authors detail their experience with subcutaneous cladribine – as opposed to oral cladribine (trade name Mavenclad®) proven in phase III trials. This was well tolerated with no new MS lesions seen on interval scans, however with only 71 patients included and a non-randomised sample conclusions on efficacy are not possible.

Reference: Mult Scler Relat Disord 2019;27:247-53
Abstract