Neurology Research Review™

SUPPLEMENT: MULTIPLE SCLEROSIS

Making Education Easy

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In this issue:

Abbreviations used in this issue

AHSCT = autologous haematopoietic stem cell transplantation
DMT = disease-modifying therapy
EDSS = Expanded Disability Status Scale
JCV = John Cunningham virus
MRI = magnetic resonance imaging
MS = multiple sclerosis
PML = progressive multifocal leucoencephalopathy
RRMS = relapsing-remitting MS
SPMS = secondary-progressive MS

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

In this issue, a NZ report finds a potential missed opportunity to decrease the cost of MS treatment, a US survey evaluates risk tolerance associated with current MS therapies, and Italian investigators review outcomes after AHSCT following natalizumab discontinuation in patients with aggressive MS. A subgroup analysis of the OPERA I and II studies reports that the efficacy benefits of ocrelizumab over interferon beta-1a in RRMS are maintained across different demographic, treatment and MS-related subgroups, and an Italian cohort study gives insight into the longitudinal course of natalizumab-related PML.

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

Kind regards,

Dr Jennifer Pereira
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The cost of teriflunomide in the treatment of relapsing-remitting multiple sclerosis

Authors: Millar J et al.

Summary: Teriflunomide is the active metabolite of leflunomide, an older immunosuppressant drug that was registered in 1998 for use in rheumatoid and psoriatic arthritis. 70% of an oral dose of leflunomide is metabolised to teriflunomide, but it costs considerably less (30 leflunomide tablets cost $2.90 in NZ whereas 28 teriflunomide tablets cost $1,582.62). This study determined whether any of the international drug regulatory bodies that considered the registration and subsidy of teriflunomide for MS discussed the idea that leflunomide might be more cost effective. The minutes of 8 international regulatory bodies that approved teriflunomide were reviewed. Only 3 of the 8 agencies (Food and Drug Administration, European Medicines Agency, and the Canadian Agency for Drugs and Technology in Health) considered the relationship between the two drugs and their relative efficacy in MS. The remaining agencies accepted the teriflunomide application at face value and compared its cost-effectiveness with existing MS drugs. They did not discuss the potential role of leflunomide as a therapy for MS.

Comment: In NZ we have two main groups of individuals with active MS that are ineligible for funded DMT. Those with a single relapse, and those who meet relapse criteria but who cannot walk 500m. In the majority of cases, those who cannot walk 500m are never going to meet criteria for funding, unless PHARMAC extend the EDSS score beyond 4.0. The costs, as described in this paper for teriflunomide (Aubagio®; $NZ1,582.62 for 28 tablets or $NZ56.52 per tablet) are not affordable for individuals over many years. If patients cannot walk 500m but are having relapses and have new or enhancing lesions on scan, leflunomide (the prodrug of teriflunomide) although "unproven" could be considered.

Reference: NZ Med J 2019;132(1490):36-41

Abstract

A survey of risk tolerance to multiple sclerosis therapies

Authors: Fox R et al.

Summary: This US study determined patient tolerance to various risk scenarios associated with current MS therapies. Patients with MS from the North American Research Committee on Multiple Sclerosis Registry's online cohort and the National Multiple Sclerosis Society completed a questionnaire on tolerance to real-world risks associated with a hypothetical therapy. Risks included skin rash, infection, kidney injury, thyroid injury, PML and liver injury. PML and kidney injury had the lowest risk tolerance (1:1,000,000) whereas thyroid injury and infection risks had the highest tolerance (1:1000). Men, younger patients, and patients with greater disability had a higher tolerance to all risk scenarios. Risk tolerance was also higher in patients currently taking an MS therapy vs those not taking any therapy, and in patients taking infusion therapies. Patients taking injectables had a lower risk tolerance.

Comment: The commitment to a medication with the potential for significant side effects requires in-depth discussions between patient and neurologist. It is helpful to understand what the risk tolerance is for your individual patient. This paper identifies some factors that influence this. It certainly holds true in my clinical practice that those who have had their independence and function impacted by severe MS and are established on natalizumab will tolerate a 1:100 risk of PML while awaiting PHARMAC funding of ocrelizumab.

Reference: Neurology 2019;92(14):e1634-42

Abstract

Safety and efficacy of autologous hematopoietic stem-cell transplantation following natalizumab discontinuation in aggressive multiple sclerosis

Authors: Mariottini A et al.

Summary: This retrospective Italian study reviewed the safety and efficacy of AHSCT compared with conventional DMTs after natalizumab discontinuation. 52 patients with aggressive RRMS who discontinued natalizumab after at least 6 doses and who had ≥6 months of follow-up were included. 11 patients underwent AHSCT (plus cyclophosphamide or corticosteroids) a minimum of 6 months after natalizumab withdrawal, and 41 patients received other DMTs approved for MS after an adequate wash-out period (controls). Baseline clinical and demographic characteristics did not differ significantly between groups. No fatality or life-threatening complications (including PML) were observed. After 3 years, 54.5% of patients in the AHSCT group compared with 11.5% in the DMT group had no evidence of disease activity (p=0.0212).

Comment: In the future AHSCT will increasingly be used as a treatment strategy for individuals with MS. Just like any switch between therapies there are a number of important considerations and the appropriate duration of a "washout period" is one of these. In this article 11 patients switched from natalizumab to AHSCT either due to treatment failure or high PML risk with aggressive disease pre-natalizumab. There was a median washout period of 8 months. Even with bridging cyclophosphamide or methylprednisolone in the intervening months the annualised relapse rate went from 0.28 to 1.29. The ideal wash-out time pre-HSCT should be shorter than this, but will likely need to be determined individually according to factors such as risk of disease reactivation, JCV status and what DMT the patient is on.

Reference: Eur J Neurol 2019;26(4):624-30
Abstract

Association of rituximab treatment with disability progression among patients with secondary progressive multiple sclerosis

Authors: Naegelin Y et al.

Summary: This retrospective cohort study evaluated disability progression in SPMS patients treated with rituximab. Patients at 3 MS centres in Basel, Lugano, and Amsterdam who were being treated with rituximab (rituximab group) or had never been treated with rituximab (controls) were included. Patients were followed for up to 10 years. Covariate-adjusted analysis of a propensity score matched set (44 pairs) found that SPMS patients who were treated with rituximab had a significantly lower EDSS score during a mean follow-up of 3.5 years (mean difference, –0.52; p<0.001). Time to confirmed disability progression was significantly delayed in the rituximab group (hazard ratio, 0.49; p=0.03).

Comment: In a large phase III randomised controlled trial, siponimod (a selective sphingosine-1-phosphate receptor modulator like fingolimod) has recently been shown to improve disability outcomes in patients with SPMS. Comparatively, this retrospective study of 44 patients treated with rituximab is small and non-randomised. Using 44 propensity matched controls (patients with SPMS who had never been treated with rituximab) and followed for a duration of up to 10 years (mean of 3.5), the authors showed an improvement in the EDSS by 0.5. This suggests rituximab may be of benefit but compared to that seen in siponimod (EDSS improved by 26% with average EDSS of 6.0) we are not seeing the same level of benefit.

Reference: JAMA Neurol 2019;76(3):274-81
Abstract

Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis

Authors: Turner B et al.

Summary: This study reported subgroup analyses of the OPERA I and OPERA II studies that compared the efficacies of ocrelizumab and interferon beta-1a in patients with RRMS. In the 2 studies, patients with RRMS were randomised to receive either ocrelizumab (600mg given by intravenous infusion every 24 weeks) or subcutaneous interferon beta-1a (44µg three times per week throughout the 96-week treatment period). Subgroups were based on demographic and disease characteristics, as well as prior treatment. The significant treatment benefit of ocrelizumab over interferon beta-1a seen in the OPERA I and OPERA II populations was maintained across most subgroup strata for all end-points (including annualised relapse rate, disability progression, and MRI outputs).

Comment: Ocrelizumab will likely soon be funded for RRMS in NZ. This paper serves to remind us of the efficacy of this agent. It sits alongside the high efficacy agents (rituximab, mitoxantrone, alemtuzumab and natalizumab). Compared to interferon beta-1a the annualised relapse rate was reduced by 44%, there was 40% reduction in disability progression, and a 94% reduction in new gadolinium-enhancing T1 lesions on MRI. A subgroup analysis which assessed different demographic, treatment and MS-related variables (EDSS above and below 4 and 2.5, MRI activity and brain volumes) showed that the efficacy was maintained across the subgroups.

Reference: J Neurol 2019;266(5):1182-93
Abstract

Early diagnosis of progressive multifocal leucoencephalopathy

Authors: Scarpazza C et al., for the Italian PML Group

Summary: This longitudinal study evaluated the development of natalizumab-related PML. Clinical and neuroradiological information was analysed for 41 Italian patients who developed natalizumab-PML between 2009 and 2018. PML lesions were detectable in the presymptomatic phase in 78% of patients, and lesion volume increased by 62.8% for each month spent in the presymptomatic phase. PML features were detectable on MRI before the 24th month of therapy in 31.7% of patients.

Comment: Natalizumab reduces new MS lesion formation on scan by 91%. In practice, most patients on natalizumab have stable MRI scans therefore if a new lesion is detected this must be carefully assessed to determine if the lesion is an MS lesion or a PML lesion. Notably if the lesion is small the cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for JCV DNA may well be negative even if the lesion is in fact due to PML – in this series 2 asymptomatic patients were JCV -ve. If a presymptomatic possible PML lesion is seen on MRI, natalizumab should be discontinued and the individual monitored for signs of immune-reconstitution inflammatory syndrome (IRIS). This paper contributes to the literature by identifying that 78% of patients who are diagnosed with PML have prediagnostic evidence of PML infection on MRI. On average there is radiological evidence of PML for 5 months prior to symptom onset – justifying the 3- to 4-monthly MRI scans performed on high risk individuals. This paper again confirms the correlation of low lesion volume at diagnosis with improved clinical outcome at 12 months.

Reference: J Neurol Neurosurg Psychiatry 2019;90:261-67
Abstract

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**

Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis

Authors: Moore J et al.

Summary: This single-centre, phase II trial in Australia investigated the efficacy and safety of AHSCT for patients with RRMS and SPMS. Patients underwent AHSCT using BEAM (carmustine, etoposide, cytarabine, melphalan) + antithymocyte globulin chemotherapeutic regimen. 35 patients (20 RRMS and 15 SPMS) completed AHSCT, with a median follow-up of 36 months. Median EDSS at baseline was 6 and patients had failed a median of 4 DMTs (66% failed treatment with natalizumab). Event-free survival at 3 years was 60% overall, and 70% in patients with RRMS. 44% of patients had a sustained improvement in EDSS, and there was no treatment-related mortality.

Comment: This single-centre, prospective study details the outcomes of 35 patients who have had AHSCT at St Vincent's Hospital in Sydney. The selection criteria for transplant included those aged 18–60 years with an EDSS of 2–7. To undergo transplant patients needed to demonstrate active disease despite treatment with a DMT with a clinical relapse or gadolinium lesions on MRI. These criteria are similar to the Neurological Association of NZ (NANZ)-ratified NZ AHSCT selection criteria. St Vincent's use the moderate conditioning regimen (versus the mild regimen used in the recently published phase II randomised controlled trial by Burt et al.) which is also most likely to be the strategy that will be used if AHSCT is funded in NZ. Funding is currently under consideration by the Ministry of Health.

Reference: J Neurol Neurosurg Psychiatry 2019;90(5):514-21
Abstract

Prediction of natalizumab anti-drug antibodies persistency

Authors: Deisenhammer F et al., on behalf of the ABIRISK Consortium

Summary: This study evaluated the magnitude of natalizumab anti-drug antibodies (ADA) response and persistency in MS patients. 43 patients with a positive enzyme-linked immunosorbent assay (ELISA)-ADA result within 6 months of treatment initiation (baseline) who had a follow-up serum sample available 12–30 months later were included. Meso Scale Discovery (MSD)-ADA titres and drug levels were also measured. Median MSD-ADA titre was 4881 at baseline and 303 at follow-up. Natalizumab ADA titres >400 at baseline had a 94% sensitivity and 89% specificity to predict ADA persistency. Despite continuous treatment, most patients with persistent ADA had no detectable drug levels.

Comment: Nine percent of individuals on natalizumab will develop ADA within the first 6 months of treatment; in 3% these are transient. The presence of ADA results in anaphylaxis and inefficacy. They can be tested for but this is expensive due to the shipping costs for a frozen serum sample. I test for the presence of antibodies to natalizumab in patients who have ongoing disease activity (relapses or new lesion formation on scan) or infusion reactions and discontinue the drug if these return positive.

Reference: Mult Scler 2019;25(3):392-98
Abstract

Safety of cladribine tablets in the treatment of patients with multiple sclerosis

Authors: Cook S et al.

Summary: This study reported safety data for oral cladribine tablets in patients with MS. Data for 923 patients treated with oral cladribine 10mg tablets (3.5 mg/kg cumulative dose over 2 years) or 641 placebo recipients were aggregated from 3 phase III clinical trials (CLARITY, CLARITY Extension and ORACLE-MS) and the PREMIERE registry. The incidence rate of treatment-emergent adverse events (TEAEs) in cladribine and placebo recipients was 103.29 and 94.26 per 100 patient-years, respectively. The increase in TEAEs with cladribine tablets was mainly driven by lymphopenia and a decreased lymphocyte count. An increase in TEAEs with cladribine was also seen for herpes zoster (0.83 vs 0.20 per 100 patient-years), but there were no cases of systemic, serious disseminated herpes zoster. There was no increase in the risk of any other infections (including opportunistic infections) with cladribine, and there was also no increase in malignancies.

Comment: Cladribine is currently funded in Australia, and is being considered by Medsafe in NZ. Cladribine is an oral reconstitutive therapy with an attractive dosing regimen. As a consequence of its mechanism of action, individuals are at risk of lymphopenia and related herpes zoster infection. Lymphocyte counts are monitored closely in the first few months after cladribine, and anti-viral prophylaxis is initiated if the lymphocyte count drops below 0.2.

Reference: Mult Scler Relat Disord 2019;29:157-67
Abstract

Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis

Authors: Mayer L et al.

Summary: This analysis of data from three phase III randomised trials (OPERA I, OPERA II, and ORATORIO) evaluated ocrelizumab infusion-related reactions (IRRs) in patients with RRMS or primary progressive MS (PPMS). 1651 patients with RRMS in OPERA I and OPERA II (825 ocrelizumab recipients and 826 interferon beta-1a recipients) and 725 patients with PPMS in ORATORIO (486 ocrelizumab recipients and 239 placebo recipients) were included. IRRs were reported in 34.3% of ocrelizumab recipients (vs 9.7% with interferon beta-1a) in the pooled OPERA studies and in 39.9% (vs 25.5% with placebo) in the ORATORIO study. Most of the IRRs were mild to moderate, and usually occurred after the first infusion. Severe IRRs were reported in 2.4% of ocrelizumab recipients in the OPERA studies and 1.2% in the ORATORIO study. Two serious IRRs occurred in the OPERA studies (both with the initial infusion).

Comment: Up to 40% of patients having ocrelizumab will experience an IRR. Ocrelizumab is given as an intravenous (IV) infusion at a dose of 300mg on day 1 and 15 and then 600mg every 6 months. The risk of IRR is highest with the first dose, reflecting the mechanism of action of ocrelizumab. It is cytotoxic, binding to CD20 on the surface of B cells leading to their destruction. The standard pretreatment regimen outlined in this paper is 100mg methylprednisolone, antihistamine and paracetamol. As detailed in our February 2019 *Neurology (MS) Research Review*, an alternate regimen reduced this risk to 10%. This alternate regimen is cetirizine 10mg, ranitidine 75mg and increased hydration the night before the ocrelizumab infusion and repeated the next day prior to arrival followed by pretreatment with IV diphenhydramine 50mg, IV methylprednisolone 125mg, and oral paracetamol 650mg.

Reference: Mult Scler Relat Disord 2019;30:236-43
Abstract

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