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Review

Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: An Australian and New Zealand perspective Part 2 New and emerging therapies and their efficacy

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ABSTRACT

In Part 2 of this three part review of multiple sclerosis (MS) treatment with a particular focus on the Australian and New Zealand perspective, we review the newer therapies that have recently become available and emerging therapies that have now completed phase III clinical trial programs. We go on to compare the relative efficacies of these newer and emerging therapies alongside the existing therapies. The effectiveness of β-interferon in the treatment of different stages and the different disease courses of MS is critically reviewed with the conclusion that the absolute level of response in term of annualised relapse rates (where relapses occur) and MRI activity are similar, but are disappointing in terms of sustained disability progression for progressive forms of the disease. Finally we review the controversial area of combination therapy for MS. Whilst it remains the case that we have no cure or means of preventing MS, we do have a range of effective therapies that when used appropriately and early in the disease course can have a significant impact on short term and longer term outcomes.

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1. Introduction

In Part 2 of this review of disease modifying therapy (DMT) in multiple sclerosis (MS) we look at recently approved therapies

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and the emerging therapies that have recently completed phase III clinical trials or, as in the case of stem cell therapies, are already being used in selected patients. We then go on to review efficacy factors that influence treatment choice in individual patients and look at the initial trials of combination therapies.

2. Newly available therapies

2.1. Teriflunomide

Teriflunomide, a once-daily oral therapy, selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, which is required for *de novo* pyrimidine synthesis in proliferating lymphocytes [1]. Teriflunomide is a hepatic metabolite of leflunomide, an established therapy for rheumatoid arthritis [2]. In a phase III clinical trial, teriflunomide 14 mg reduced annualised relapse rate (ARR) by 32% *versus* placebo, and the risk of sustained (>12 weeks) disability progression by approximately 30% [3]. Teriflunomide also had positive effects on MRI outcomes, although it has not been shown to slow the rate of brain atrophy *versus* placebo over 2 years.

Common adverse events associated with teriflunomide include nausea, diarrhoea, hair thinning and elevation of alanine aminotransferase levels [3]. Less commonly, treatment can be complicated by peripheral nerve toxicity requiring drug discontinuation. Teriflunomide is a potential teratogen and is contraindicated in pregnancy and in women of child-bearing potential not using reliable contraception [4]. The drug has a long half-life (approximately 19 days), and in the case of inadvertent pregnancy (or plans to fall pregnant) on therapy, the drug must be rapidly "washed out" with cholestyramine or activated charcoal [4]. As a new agent the long term safety of teriflunomide is less certain than with injectable DMT, but the evidence for the medium to long term safety of leflunomide (a prodrug of teriflunomide) is well established [5].

2.2. Dimethyl fumarate

Dimethyl fumarate is thought to act through activation of the Nrf-2 pathway, an important protective pathway against oxidative stress [6]. It also produces a modest lymphopenia [7].

In a randomised placebo controlled phase IIb trial, gadolinium (Gad)-enhancing cerebral MRI lesions in the high dose treatment arm (240 mg three times daily) were reduced by 69%, compared with placebo [8]. These initial positive results have been supported by two phase III trials, DEFINE [9] (n = 1234) and CONFIRM [10] (n = 1430). Both were conducted with similar inclusion criteria, but CONFIRM included an active comparator, glatiramer acetate. DEFINE showed an approximate 53% reduction in ARR, a 90% reduction in Gad-enhancing lesions and a 72% reduction in new T1-weighted hypointense lesions for the twice daily dose. Dimethyl fumarate showed a 38% decrease in sustained disability progression in DEFINE, which was statistically significant for the primary endpoint of 3 month confirmation, but not 6 month confirmation. Dimethyl fumarate had better outcomes in all endpoints than glatiramer acetate in CONFRIM, but the study was not powered to prove superiority or non-inferiority.

No significant infections or malignancy have been noted. Long term safety data in MS are not available, but the related drug Fumaderm (Biogen Idec, Weston, MA, USA) has been approved for the treatment of psoriasis in Germany since 1994 [11]. Flushing (35%) and gastrointestinal (25%) side effects are common, but mostly settle after 1–3 months.

Three times a day dosing at 240 mg does not appear to offer much benefit over the twice daily regimen, which is the dose that has been approved by the Therapeutic Goods Administration in Australia. Just recently there have been several case reports of progressive multifocal leucoencephalopathy (PML) occurring in the setting of significant lymphopenia associated with treatment of psoriasis with fumarates where the drug was deemed highly likely to be of relevance in the causation of this adverse event [12,13].

2.3. Alemtuzumab

Alemtuzumab is a monoclonal antibody to CD52. It ablates circulating lymphocytes with B cells recovering fastest and $CD4^+$ T cells recovering more slowly, reaching ~200/ml at 6–9 months. It is given as an initial course with a slightly shorter course 12 months later and treatment is often not required again.

Alemtuzumab has been highly effective in MS trials compared to active therapy (subcutaneous β-interferon 1a). Three large trials studied patients with early aggressive treatment naive MS with relapses and active MRI lesions (CAMMS223) [14], treatment naive patients (CARE-MS I) [15] and patients relapsing on prior therapy (CARE-MS II) [16]. All trials demonstrated significant reductions in relapse rate (49–74%). In CAMMS223 and CARE-MS II there was a significant reduction in the rate of sustained disability progression (71% and 42%, respectively). The benefit of alemtuzumab compared to continued β-interferon in CAMMS223 was maintained to 5 years despite no further alemtuzumab treatment over this time [17].

There are significant risks with alemtuzumab, although surprisingly more from autoimmunity than infection. Infusion requires hospital supervision and reactions consisting of a mild recurrence of prior MS symptoms and inflammatory responses are almost universal, but can be ameliorated by the concomitant administration of steroids and anti-histamines. Early infections including herpes simplex, varicella zoster and pneumonia were increased, but were manageable with no deaths. PML has been noted in patients treated for lymphoproliferative disorders with alemtuzumab [18], but this complication has not been observed in MS. New non-MS autoimmunity peaking 2–3 years after treatment is common with thyroid disease (~20%) [19], immune thrombocytopenic purpura (~1–2%) and renal disease with anti-glomerular basement membrane (GBM) antibodies (~0.3%) being the most common [15,16]. The first idiopathic thrombocytopenic purpura patient on trial was not diagnosed and died [20]. One patient with anti-GBM disease required a renal transplant. Continued regular surveillance is likely to improve the outcome of these complications. Alemtuzumab treatment will require monthly pathology monitoring for at least 5 years. The long term risk of neoplasia is unknown.

Alemtuzumab offers superior MS control for actively relapsing MS patients compared to β-interferon, but with risks. It is probably not appropriate for milder new onset MS. In practice, like natalizumab, it is highly effective, with few patients having significant MS activity once treated.

3. Emerging therapies

3.1. Laquinimod

Laquinimod, or quinolone-3-carboxamide, attenuates disease in experimental autoimmune encephalomyelitis (EAE) with improvements in both central nervous system (CNS) demyelination and chronic axonal loss [21]. Several studies involving EAE models have shown that laquinimod decreases pro-inflammatory cytokines [21] and promotes a deviation from the pro-inflammatory T helper (Th)-1 pattern to the anti-inflammatory Th-2/Th-3 cytokine milieu [22]. A phase III study showed a non-significant 23% reduction in ARR together with a small, but statistically significant improvement in disease progression metrics in patients treated with laquinimod compared with placebo [23]. MRI lesions were significantly

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