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Review

Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: An Australian and New Zealand perspective Part 3 Treatment practicalities and recommendations

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ABSTRACT

In this third and final part of our review of multiple sclerosis (MS) treatment we look at the practical day-to-day management issues that are likely to influence individual treatment decisions. Whilst efficacy is clearly of considerable importance, tolerability and the potential for adverse effects often play a significant role in informing individual patient decisions. Here we review the issues surrounding switching between therapies, and the evidence to assist guiding the choice of therapy to change to and when to change. We review the current level of evidence with regards to the management of women in their child-bearing years with regards to recommendations about treatment during pregnancy and whilst breast feeding. We provide a summary of recommended pre- and post-treatment monitoring for the available therapies and review the evidence with regards to the value of testing for antibodies which are known to be neutralising for some therapies. We review the occurrence of adverse events, both the more common and troublesome effects and those that are less common but have potentially much more serious outcomes. Ways of mitigating these risks and managing the more troublesome adverse effects are also reviewed. Finally, we make specific recommendations with regards to the treatment of MS. It is an exciting time in the world of MS neurology and the prospects for further advances in coming years are high.

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1. Introduction

In this third and final part of our review we look at the many factors that can influence the choice of treatment for individual people with multiple sclerosis (MS). These include specific matters relating to women with MS and adverse effect profiles. We provide practical advice on how to manage the common and rarer, but important, adverse effects that are seen with these therapies. We then go on to make specific recommendations with regards to the use of disease modifying therapy (DMT) in MS.

2. Breakthrough disease and switching therapy

Studies of outcome in patients on therapy clearly indicate a worse prognosis for patients experiencing further disease activity in the form of clinical relapses [1,2], worsening disability [3] or new MRI activity [2,4]. This has led to the concepts of "freedom from disease activity" [5] and "breakthrough disease" [6] or "suboptimal response" [7] whilst on therapy. The degree to which new disease activity should prompt a reconsideration of treatment is far from black and white, but an abridged version of the Canadian guidelines on management of new disease activity on therapy is given in Table 1 [8]. New disease activity within the first 3 months of therapy is of less significance due to the delay in onset of effect for some therapies [9] and also the latency in the emergence of disease activity, which may have commenced prior to any change in therapy, being up to 3 months [10]. After this period any new disease activity should certainly be reviewed carefully and consideration given to an appropriate change [11].

Long term cohort studies have demonstrated that approximately 20% of patients commenced on DMT will have continuing high disease activity necessitating treatment escalation early on [12]. Furthermore, Australian data have shown that more than half of patients will discontinue their first therapy over a 2 year time frame due to a combination of inadequate efficacy and more commonly, poor tolerability [13]. One fifth of patients will switch therapy more than once [14]. There are no controlled, blinded studies of the outcome of switching therapies and evidence principally comes from well-conducted, retrospective, open-label, observational studies comparing "before" and "after" relapse rates. These studies are therefore prone to reporting bias and problems of regression to the mean. Results have demonstrated that switching between injectable DMT is safe and will generally result in improved disease control [15,16]. Switching from a β-interferon to glatiramer acetate [17], particularly when persistent antibodies to β-interferon are present [18,19], can be associated with a significant reduction in relapse rates.

Escalating therapy in response to continuing disease activity with either natalizumab or immunosuppressive treatment has been shown to improve clinical and MRI measures of disease activity [20–22]. Comparative studies suggest that these therapies can provide better disease control than switching to another injectable DMT [16,23].

With the development of a seemingly sensitive test for carriers of the John Cunningham (JC) virus, the issue of needing to discontinue natalizumab therapy has emerged. Studies have demonstrated that switching to glatiramer acetate is better than switching to no therapy, but still gives less than ideal disease control [24]. Studies of switching from natalizumab to fingolimod have shown mixed results [25–27], but anecdotally the majority of patients do well with this change. One specific issue regarding the discontinuation of natalizumab, particularly as this is often done in the setting of a positive JC virus antibody test, is the emergence of immune reconstitution inflammatory syndrome (IRIS – see below) after 4–12 weeks (often after a new therapy has commenced) [28,29]. This syndrome could be the explanation for some of the cases of "rebound disease" [30,31] and examples of tumefactive MS [32] that have been described following the discontinuation of natalizumab. In many cases, JC virus polymerase chain reaction (PCR) in cerebrospinal fluid was not performed, and even when this test has been reported as negative this may be because of a DNA copy number that is below the threshold for detection in the laboratory used. The role that subsequent fingolimod treatment might play in the development of progressive multifocal leukoencephalopathy (PML) or IRIS is uncertain at this point in time, but these are rare events and the potential hazards of leaving patients with highly active disease on no therapy for 3 months or more are not inconsiderable [33]. There are currently limited data to guide appropriate washout periods for switching between therapies but, except where the clinical situation is greatly concerning, a washout period that is at least equivalent to the normal inter-dose interval for the drug being discontinued would seem to be appropriate. Pharmacokinetic and pharmacodynamic data for available therapies together with dosage frequency are summarised in Table 2.

3. Pregnancy and breast feeding

No treatment for MS is currently listed as being safe for use in pregnancy or breast feeding (Table 2 in *Part 1 Historical and established therapies* of this review) and the general recommendation for all is that treatment should be discontinued prior to conception or when a woman unexpectedly discovers that she is pregnant. A recent systematic review of reproductive issues in MS treatment came to the same conclusion based on currently available published data [34]. However, as summarised in Table 3, a number of agents have been studied in large pregnancy registries with no apparent problems emerging in the babies born to mothers who were exposed. Similarly, several agents either are not excreted in breast milk or are destroyed when taken by the oral route and should therefore be safe whilst breast feeding. Given the well described potential for relapse in the 3 months post-partum and for relapses to occasionally occur in pregnancy it is important for all women with MS contemplating having a child to consult with their neurologist to consider their individual risks with regards to the severity of their disease, any previous occurrence of

Table 1
Levels of concern warranted for multiple sclerosis breakthrough disease on treatment

Feature	Level of concern		
	Low	Medium	High
Relapses	<1/year 1 functional system only Prompt, full recovery	1/year EDSS change (IVMP) Incomplete recovery	>1/year Hospitalisation (IVMP) Little/no recovery
Disability increase (EDSS)	<1 point	1 point	>1 point
MRI activity (T2 or GE)	1 lesion	2 lesions	>2 lesions

Adapted from Freedman et al. [8].
EDSS = Expanded Disability Status Scale, GE = gadolinium enhancing, IVMP = intravenous methylprednisolone, T2 = T2-wighted.