A new era in the treatment of multiple sclerosis

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Multiple sclerosis (MS) is an immune-mediated disorder of the central nervous system.[1] Untreated MS results in significant disability during the prime of life for many with the disease.[2] The aetiology of MS remains to be fully elucidated, but the Epstein-Barr virus,[3] relative vitamin D deficiency[4] and smoking[5] have been identified as environmental risk factors that interact with the more than 100 genetic loci associated with susceptibility for the disease.[6,7]

The past 20 years has seen considerable progress in understanding the pathophysiology and advancing the treatment of MS.[8] A number of moderately effective and, more recently, highly effective therapies have been licensed and funded in Australia and other parts of the world. We have recently reviewed in the *Journal of Clinical Neuroscience* the practicalities of using these therapies and their place in the treatment of individual patients in the Australian and New Zealand context.[9-11] The purpose of this article is to highlight some recent developments in MS treatment, with a particular emphasis on the wider implications of the newer agents for health care providers.

Summary

- Multiple sclerosis (MS) is an autoimmune disease of the central nervous system with a multifactorial aetiology and highly variable natural history.
- A growing understanding of the immunopathogenesis of the condition has led to an expanding array of therapies for this previously untreatable disease.
- While a cure for MS remains elusive, the potential to reduce inflammatory disease activity by preventing relapses and minimising disease progression is achievable.
- The importance of early treatment in minimising long-term disability is increasingly recognised.
- Most of the newer, more effective therapies are associated with risks and practical problems that necessitate an active management strategy and continuous vigilance.
- While the initiation of these therapies is likely to remain the responsibility of neurologists, other specialist physicians and general practitioners will be involved in the identification and management of adverse effects.

Methods

This review represents the consensus reached by experts in MS treatment from across Australia and New Zealand. Our findings are based on a critical review of pivotal Phase III clinical trials, and of Cochrane reviews and other systematic reviews of particular themes. Recommendations are made according to the National Health and Medical Research Council levels of evidence scale.[12]

The current landscape of MS therapy

The choice of therapy for a person with MS will depend on the phase and clinical activity of the disease, individual patient considerations, and the practicalities of drug administration. Appendix 1 summarises data on the dose, route of administration, efficacy, practicalities of use and adverse effect profiles of the 13 MS therapies that are currently licensed in Australia or New Zealand, have completed Phase III clinical trials, or for which a Cochrane meta-analysis is available. The various therapies have differing levels of efficacy, but the impact of even the most effective agents over the short-to-medium term on disease progression and brain atrophy is modest. Conversion to or continuation of progressive disease can still occur while using the most effective therapies, although evidence of new inflammatory disease activity, such as clinical relapses and new lesions identified by magnetic resonance imaging (MRI), may have been almost completely abolished.[13]

The two agents with the greatest efficacy are both administered as intravenous infusions. Each is associated with significant risks, either in the form of progressive multifocal leukoencephalopathy (PML) for natalizumab,[14] or the development of other autoimmune diseases, most commonly Graves' disease, with alemtuzumab.[15]

The safety of the long-established injectable therapies (β-interferons and glatiramer acetate) has been confirmed over two decades of use, but these medications have minor side effects and require self-administered subcutaneous or intramuscular injections.[16,17] Their efficacy in preventing relapses is modest, but their longer-term benefit in reducing rates of secondary progression is encouraging.[16] Preparations of these two agents that require less frequent administration may improve their tolerability.[18,19]

The oral agents fingolimod and dimethyl fumarate have intermediate efficacy, appear to be safe, and are well tolerated; they have relatively minor adverse effects that need to be monitored and managed.[20,21]

The efficacy of the oral agent teriflunomide appears to lie somewhere between that of the other two orally administered drugs and the injectable therapies (β-interferons and glatiramer acetate), and its safety profile is also reassuring.[22]

Practicalities

Disease-modifying therapy should be considered in any patient with a first episode of demyelination where supporting evidence in the form of MRI and cerebrospinal fluid (CSF) findings strongly support a diagnosis of MS, or when relapsing-remitting MS has been diagnosed. Those patients

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who elect not to commence treatment — because of personal preference or because they regard the disease course as mild — should be carefully monitored for evidence of further disease activity, to ensure that this decision can be reviewed when necessary.

While a start-slow-and-escalate approach has generally been advocated for patients with mild to moderate relapsing-remitting MS, most studies have highlighted the need to commence therapy early. There is insufficient evidence to support the concept of induction therapy (the use of higher-efficacy therapy initially followed by lower-efficacy therapy) for MS; optimal disease control generally requires continuation of an effective therapy.[11] Evidence of further disease activity (clinical or MRI findings) is generally regarded as indicating that escalation of therapy or a switch to an alternative should be considered.[11] The significance of new lesions in the first 6 months of therapy is uncertain, as they may reflect events that occurred before treatment started or a delay in response to treatment. For this reason, many neurologists advocate a repeat "baseline" MRI 6 months after commencing any new therapy.

There is currently little evidence for the utility of combination therapies, although relevant studies are being undertaken.[10] While concerns have been expressed about washout periods and the avoidance of overlaps when switching between therapeutic agents, no specific problems have been identified, with one exception: when treatment with natalizumab is initiated, there is an increased risk of PML in patients who are John Cunningham (JC) virus antibody-positive and have been exposed to immunosuppressive therapy.[23]

It is recommended that all MS therapies be withdrawn in women planning to become pregnant. There is, however, a risk that disease activity may re-emerge, particularly if there are delays in conceiving. This leads to difficult decisions about whether treatment should continue until it has been confirmed that the woman is pregnant, and whether therapy should be discontinued during the pregnancy itself.[11] The latter decision will often be guided by recent disease activity and any previous experience of MS attacks during pregnancy. The safest options for young women of childbearing age are glatiramer acetate and dimethyl fumarate (pregnancy category B1), while fingolimod (category D) and teriflunomide (category X) are the riskiest options. Pregnancy itself, particularly the second and third trimesters, is associated with a reduced risk of relapse, but this is balanced by an increased risk of disease activity in the first three months post-partum.[24,25]

All current treatments for MS have some minor side effects and several of the more potent agents are associated with specific risks that need to be managed.[11] These adverse effects and the recommended management strategies are summarised in Appendix 2. Three particular problems that need attention will be discussed here.

Progressive multifocal leukoencephalopathy

PML is caused by infection of the brain with the JC virus; it typically develops in the setting of immune deficiency or immunosuppressive therapy. PML has been extensively documented in patients with MS treated with natalizumab,[14] and there have been case reports associated with dimethyl fumarate[26] and fingolimod.[27] Lymphopenia was not present in two of the cases of PML with dimethyl fumarate and fingolimod, but further data are needed; caution is warranted when using these drugs in any patients who are JC virus antibody-positive. The JC virus is carried by 40%–50% of the general population, and carrier status can be tested with the Stratify JCV antibody test (Focus Diagnostics). After 4 years of exposure to natalizumab, patients who are positive for JC virus antibody have a 1 in 200 risk of developing PML; in patients who are JC virus antibody-negative, the risk is estimated to be less than 1 in 10 000.[23] The principal presenting symptoms are subacute onset hemiparesis, dysphasia, cognitive decline and seizures.[14] The onset of symptoms can be subtle, and may be further obscured by cognitive or dysphasic symptoms. If these or any other unexplained neurological signs develop in a patient taking natalizumab, they should be immediately referred to their neurologist, their treatment suspended, and urgent MRI and lumbar puncture assessments requested. The presence of JC virus DNA in the CSF should be tested by polymerase chain reaction (PCR), even when the results of serological testing for JC virus antibody are negative.

Autoimmune disease

Autoimmune thyroid disease (30%), idiopathic thrombocytopenic purpura (~ 1%), and, more rarely, anti-glomerular basement membrane (GBM) antibody glomerulonephritis can develop between 1 and 5 years after commencing treatment with alemtuzumab.[15] Continual vigilance for the symptoms of these complications is required and, perhaps more importantly, regular laboratory testing, including full blood counts each month for at least 5 years. If detected early, these conditions respond to standard therapies, but they can emerge quite precipitately and should be treated urgently by physicians with relevant expertise.[15]

Lymphopenia and deranged liver function test results

Almost all of the available therapies have been associated to varying degrees with lymphopenia or liver function derangement. These effects are likely to be part of the mechanisms of action for fingolimod, dimethyl fumarate, teriflunomide and alemtuzumab. Repeat testing and possibly the cessation of therapy are appropriate if significant deviations from normal values (Common Terminology Criteria for Adverse Events [version 3.0; CTCAE], grade 3: lymphocyte count $< 0.5 \times 10^9$/L, or greater than fivefold elevation of hepatic enzyme levels) or a persistent trend away from normal values do not resolve spontaneously. Therapy should be stopped immediately if a higher degree of abnormality (CTCAE, grade 4: lymphocyte count $< 0.2 \times 10^9$/L, or greater than 20-fold elevation of hepatic enzyme levels) is detected. In either situation, concomitant medications and the patient's medical background (recent infections, alcohol misuse, fatty liver disease) should be reviewed carefully before long-term decisions are made.

Recommendations

Recommendations for the treatment of MS are summarised in the Box. Key concepts that have emerged include

the importance of confidently establishing the diagnosis of MS early, with a view to considering therapy as soon as possible. Monitoring for and managing side effects is important from the perspective of maintaining compliance. Monitoring disease activity by regular clinical reviews and MRI scans during therapy is important, particularly over the first 1–2 years, with a relatively low threshold for escalating therapy in the event of new disease activity. In the case of interferon therapy, clinical relapses and radiological disease activity during the first year of therapy clearly identify patients who will develop more severe disease in subsequent years.[28]

All current MS treatments are envisaged as long-term therapies or, in the case of alemtuzumab, as requiring sustained monitoring after two or more courses of intravenous infusions. This gives rise to at least two significant problems. The first is maintaining compliance, which can become a significant challenge after several years of therapy, particularly, perhaps counterintuitively, in patients who remain healthy. The second is the need for ongoing monitoring. Several agents require intermittent haematological and liver function tests. Natalizumab therapy requires 6-monthly JC virus antibody testing in seronegative cases to ensure that the patient remains seronegative. Further, it is important to remain vigilant to potential late complications with some of the newer therapies. For patients treated with alemtuzumab, regular monitoring of haematological, renal and thyroid function parameters for at least 5 years and possibly longer is necessary.

Conclusions

We are in an exciting era for the treatment of MS. A number of effective therapies are available with a spectrum of efficacy and tolerability profiles that require careful tailoring to individual patients' needs, and we must weigh the pros and cons of the route and frequency of administration, together with the perceived potential benefits and risks for the individual patient. General practitioners and specialist physicians need to be aware of the potential complications and specific features of MS therapies, particularly in rural and remote settings where rapid access to specialist neurological services may not be available. Some complications (eg, anti-GBM antibody disease) are better treated by specialist physicians other than neurologists.

While considerable improvements in the treatment of the early inflammatory phase of MS have been achieved, the efficacy of these approaches in progressive disease has been disappointing, even with the more effective therapies.[13] Considerable effort is currently being invested in the investigation of the pathophysiology of progressive disease and of potential therapeutic targets by the International Progressive MS Alliance (in which Australian and New Zealand neurologists are participating).

It is evident that the indications for therapy in Appendix 1 and the recommendations listed in the Box are not entirely consistent with one another, and that there is an urgent need for the current restrictions on prescribing MS therapies to be adjusted in the light of new evidence. This will entail a rationalisation of the indications, which would assist neurologists to prescribe the most effective therapies at the appropriate time and in the appropriate setting for the patient, thereby improving their cost-effectiveness.

"The importance of early treatment in minimising long-term disability is increasingly recognised"

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References are available online at www.mja.com.au.

Recommendations for the therapy of multiple sclerosis*

Recommendation	NHMRC Level of evidence
1. In patients presenting with a clinically isolated syndrome, treatment with an injectable disease-modifying therapy should be considered.	I
2. Patients with active relapsing-remitting disease (2 relapses in 2 years) should be offered β-interferon, glatiramer acetate, natalizumab, fingolimod, teriflunomide, dimethyl fumarate or alemtuzumab.	I
3. Clinical progress should be monitored every 3–12 months, with repeat MRI after 3–12 months in the first instance and then every 12 months or less frequently, depending on the response to therapy. Clinical relapses or new MRI lesions should prompt consideration of escalation in therapy to fingolimod, dimethyl fumarate, natalizumab or alemtuzumab.	II-2
4. Where prognostic indicators in relapsing-remitting disease are poor from the outset, therapy with fingolimod, dimethyl fumarate, natalizumab or alemtuzumab should be considered.	I
5. In very rapidly progressive multiple sclerosis, or where disease fails to respond to standard therapies, the use of immunosuppressive therapy (mitoxantrone/cyclophosphamide), rituximab, autologous haematopoietic stem cell therapy or combination therapy should be considered carefully.	II-2
6. Where the level of disability becomes severe or disease continues to progress, therapy should be discontinued.	III
7. In clinical settings where requirements for government funding of approved therapies are not satisfied for technical reasons, and a significant inflammatory disease burden is suspected or standard therapies are contraindicated, the use of traditional immunosuppressive therapies (azathioprine/mycophenolate) should be considered after discussion of the potential benefits and risks with the patient.	II-1

MRI = magnetic resonance imaging. NHMRC = National Health and Medical Research Council.
* Adapted with permission from Broadley et al 2014.[11]

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