

Future therapies in multiple sclerosis

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Abstract

It is now 15 years since the first disease modifying therapy was licensed for use in people with multiple sclerosis. During those 15 years four therapies have become established for treatment of early relapsing remitting disease and two others have entered the field for treatment of more aggressive disease, or in those patients who are perceived to have failed therapy. Current therapies impact beneficially on the disease process, especially on the number and severity of relapses. The future should bring more effective, tolerable and convenient therapies, and include oral therapies and monoclonal antibodies. The ultimate goal of neuro-protection and repair of damaged areas of the neuraxis may be more distant. It is inevitable when new therapies become available their short term effects and safety will be ensured, but physicians will have to be careful to inform patients fully about risk to benefit ratios and the relative uncertainties of long-term effects of major immunomodulation. This review considers some of the most promising agents now in phase III trials.

Multiple sclerosis (MS) is a chronic disease of the central nervous system which is believed to be auto-immune and inflammatory. The cause is unknown, but almost certainly represents the loss of immune tolerance to tissues within the central nervous system and is related to genetic and environmental factors predisposing and then triggering immunological damage. One of the cardinal features of MS is its variability. In the great majority of people with MS an acute and presumed inflammatory series of relapses and remissions is followed by a more gradual deterioration in function, the accumulation of disability, and ultimately a slow progression, implying a degenerative process. It is easy to understand the role of acute inflammation with spread systemically of foci into the central nervous system as the cause of the acute relapsing and remitting phase¹, but the role of inflammatory and immune factors in the more degenerative phase of the disease, either as secondary progressive (SPMS) or primary progressive MS (PPMS) is less certain.²

EXISTING DISEASE MODIFYING THERAPY

Throughout most of the world there are four agents available as disease modifying therapy (DMT) for RRMS and two for more severe disease, or as rescue therapy. There are three interferon β preparations and glatiramer acetate, all have been used for more than a decade, have a good safety record, are reasonably tolerable to the patient and modestly effective in reducing the number and

severity of relapses. There is some evidence that their short-term effect upon disability is continued into the long term and they remain the standard initial therapy for people with MS.³⁻⁵

All of the agents have been shown to be more effective when given early in the course of the disease and phase III trials of three of the four agents have demonstrated benefit when given after a first clinical episode of MS-like symptoms in people with an abnormal cerebral MRI scan, the condition termed clinically isolated syndrome (CIS). The fourth agent has been shown to have an effect in a very low dose and is currently being studied in a phase III trial.⁶⁻⁸

Concern is sometimes expressed about the early initiation of DMT in people who may not have MS and those who might have a “benign” form of the disease. There is, however, increasing evidence that the great majority of people with MS-like symptoms, diagnosed by neurologists expert in the field and associated with two or more T2 weighted lesions on cerebral MRI are extremely likely to progress to develop MS; there is further evidence that the prediction of benign disease is difficult and most people identified with benign disease at 10 or 15 years develop increasing problems later in life.⁹ There is therefore evidence based indication to treat people with CIS and an abnormal MRI scan, though many neurologists would perform a second MRI scan after three months to try to achieve the International Criteria for the definition of MS before beginning treatment.

In the near future, bio-similar preparations of the currently available interferons β and glatiramer

acetate may become available. Their registration and licensing will be problematic and it is possible that one or more of the agents will be marketed as a bio-identical product.

For those patients who are thought to have particularly severe or rapidly evolving disease, and for those who are perceived to have failed treatment with interferon β and glatiramer acetate the two common options are the use of the monoclonal antibody natalizumab or the cytotoxic agent mitoxantrone. The former is shown to be very effective in reducing relapses and to show an impact on disability within two years.¹⁰ It is given as a monthly injection and is more tolerable to most patients than more frequently injected agents, but it carries a potential risk, presently estimated at less than 1:1000, for the development of the opportunistic infection progressive multifocal leukoencephalopathy (PML), a condition seen in immunosuppressed patients and due to the activation of the JC virus within glial cells. There are well defined algorithms available for the monitoring and investigation of people with MS who are given natalizumab and during the next 12-18 months two major studies, TOUCH and TYGRIS, will provide better evidence of the proportionate risk of such therapy.¹¹ Mitoxantrone, an older drug, and an immunosuppressant carries potential risks of cardiotoxicity and, perhaps more significantly, acute leukaemia. The risk of the latter is of the order of 0.5-1% and the risk of the former prevents patients being given more than about 240 mg in total.

Both of these more aggressive therapies provide models for the way in which physicians in future will discuss with people with MS the potential benefits and the possible dangers of the more aggressive immunomodulating regimes.

During the past 13 years the advent of DMT has given rise to the possibility of combination therapy or the use of induction therapy with one agent then maintenance with another DMT. There are currently studies of combinations of interferon β and glatiramer acetate¹² and of each of those agents together with mitoxantrone or azathioprine. It is improbable that there will be further studies of combinations of therapy with natalizumab and interferon β since the initial reports of progressive multifocal leukoencephalopathy with natalizumab occurred in patients taking both treatments.

ORAL THERAPY

It is generally assumed that the compliance of patients, or their adherence to therapy, will be

better when oral agents replace those that require parenteral injection. It is difficult to be certain of the benefits of a daily tablet compared to a once monthly or once yearly infusion, but this is the target of most of those agents being used orally.

Cladribine

This adenosine deaminase-resistant purine nucleoside analogue preferentially depletes sub-populations of lymphocytes. It is already used in treatment of people with haematological malignancy and it was originally used parenterally in people with MS almost 20 years ago. There are two phase III studies currently underway, using doses between 0.7-2.0 mg/kg, the first is a two year randomised, placebo controlled trial of cladribine mono-therapy in people with relapsing remitting multiple sclerosis (RRMS) and the second is a combination study involving induction with oral cladribine and maintenance therapy with interferon β -1a 44 μ g given thrice weekly.¹³ In the first study the primary outcome measure is relapse rate during the two years of the trial, and in the latter is the number of new gadolinium enhancing lesions on MRI scan.

Cladribine has been awarded "fast-track" status by the FDA and it is probable that the results of these studies will be available early in 2009.

Teriflunomide

This is a dihydro-orotate dehydrogenase inhibitor which has been shown to affect favourably the experimental allergic encephalomyelitis model of inflammatory demyelination. In a short phase II trial it was shown to impact significantly and beneficially on MRI scan unique active lesions and there was a trend in the higher treatment group towards a lower annualised relapse rate with fewer patients demonstrating an increase in disability even though the trial lasted only 36 weeks.¹⁴ This, rather surprising effect upon clinical parameters, led to phase III studies, two of which are looking at the effect of teriflunomide in RRMS, one in Europe and one in North America, and a third examining its effect in CIS.

Fingolimod

Fingolimod (FTY720) is an analogue of sphingosine-1-phosphate which modulates S1P receptors and entraps lymphocytes in secondary lymphoid organs inhibiting their ability to enter the central nervous system. The drug is already

used in transplant management and in an initial phase II trial showed a significant and rapid reduction in MRI measures of inflammation and in clinical relapses. There was an extension phase of the initial 6 month trial and the difference in MRI and clinical relapses has continued to three years.¹⁵

There are two phase III trials underway, one against placebo and one in comparison with an approved DMT.

The diffuse effects of the S1P analogue result in changes in pulse rate, blood pressure and symptoms of breathlessness, headache and nausea. There is a significant lymphopaenia in the peripheral blood and in the phase II study there was a single case of posterior reversible leukoencephalopathy syndrome (PRES) with a persistent neurological abnormality. In the phase III trials there have been two fatalities due to Herpes infection. In future it is possible that more specific S1P molecules will become available and lessen side-effects. There is some suggestion in vitro that fingolimod (FTY720) can increase mature and immature oligodendrocyte populations and therefore might have a potential effect on remyelination.

Fumaric acid

Fumaric acid (BG12) was developed for the treatment of psoriasis in the belief that the dermatological problem was caused by an abnormality on the Krebs cycle. It appears to inhibit the expression of pro-inflammatory adhesion molecules on endothelium and reduce cytokine production, and it may have novel neuroprotective effects by an action on oxidative metabolism. A phase II trial showed a significant reduction of gadolinium enhancing lesions on MRI and a reduction in T1 weighted black holes.¹⁶ It is now in phase III studies where minor problems include headache, nasopharyngitis and flushing which, in some patients, is so severe as to preclude continued use of the agent.

MONOCLONAL ANTIBODIES

Monoclonal antibodies are selective immunoglobulins which bind to specific molecules of the surface of targeted cells. In MS agents acting against both T and B cells have been considered and are being studied in phase III trials. They are very effective immunomodulating therapies and therefore have potential toxicity, including infusion related reactions, the development of neutralising antibodies and the occurrence of

opportunistic infections or neoplasia.

Natalizumab

The first monoclonal to be licensed for use in MS is natalizumab (Tysabri) which targets alpha-4 integrin, an adhesion molecule on the surface on T-lymphocytes. By blocking this molecule it prevents the lymphocyte interaction with surface adhesion molecules on the endothelium of the cerebral vessels and the ingress of such activated T-cells to the central nervous system.

Two major phase III trials were performed and the agent was licensed in 2004. It was withdrawn from the market in 2005 after 2 patients, who had completed one of the phase III trials in which they took natalizumab together with interferon β -1a, developed PML.¹⁷ In another trial in patients with Crohn's disease a further case was identified retrospectively.

Once a risk management plan had been devised and two monitoring studies (TOUCH in the USA and TYGRIS in the rest of the world) had been implemented, the drug was allowed to be used again from 2007. There have subsequently been three further reports of PML, two in July of 2008 and one in October, two of the patients had taken other cytotoxic preparations, azathioprine and methotrexate, but one had taken no other immunomodulating therapy and the opportunistic infection occurred after 17 months treatment. There are now more than 30,000 patients worldwide taking natalizumab, but the great majority have not yet taken the drug for more than 2 years. In MS, PML has only been seen in people who have taken the agent for more than 14 months.

There are inevitable problems in relation to hypersensitivity reactions, which tend to occur with the second infusion, about 6% of patients are shown to develop antibodies which reduce the efficacy of the treatment, and a greater proportion have infusion related reactions which can usually be managed symptomatically.

Natalizumab provides the best current example for discussions between physician and patient prior to the initiation of therapy, and the recognition of the benefit to risk ratio. It also provides an example of a treatment algorithm which provides careful monitoring of unexpected or usual symptoms, the subsequent cessation of therapy, and the elimination of the agent from the body to allow the reconstitution of the immune system, which seems likely to promote recovery from PML.

Daclizumab

Daclizumab is an anti-CD25 humanised monoclonal antibody. It binds to the interleukin (IL) 2 receptor and it decreases T cell stimulation. It was initially evaluated in people who were perceived to be failing on interferon β therapy and showed a benefit in reducing MRI activity. In a larger phase II trial, again used as add-on therapy, there was a significant reduction in new and enlarging gadolinium enhancing lesions and a non-significant reduction of about one-third in relapse rate over the six months of the trial.¹⁸ The drug is likely to begin phase III studies in the near future, though whether in its add-on or as sole therapy compared to placebo or to another DMT is not yet decided.

Rituximab.

The anti-CD20 monoclonal rituximab has been used in MS because of the belief that B cells are involved in the immunopathogenesis. It has been shown, in a large phase II trial, to provide a significant reduction in mean total gadolinium enhancing lesions on MRI scan and there was a trend towards lower annualised relapse rates in the study which was performed for a year.¹⁹ It was well tolerated, but it seems likely that more humanised versions of the anti-CD20 monoclonal will be studied in future.

It is evident that an anti-CD20 agent is likely to be beneficial in the humorally mediated demyelinating disease, neuromyelitis optica (NMO), in which the presence of the aquaporin 4 antibody indicates the higher probability of a B-cell involvement. There have been small studies of rituximab in people with NMO and the treatment effect seems impressive.²⁰

There have been reported cases of PML in people with non-malignant disease treated with rituximab, though in each instance other immunomodulating therapies had been used.

Alemtuzumab

This is a humanised monoclonal antibody binding to CD-52 on the surface of T and B cells. It is already used in haematological malignancy and the profound depression in T cells lasts for more than 12 months.

The drug has been tried in the past in people with progressing MS but shown to be ineffective, though to reduce greatly the number of T2 weighted MRI lesions.

A recent phase II study in RRMS compared two doses of alemtuzumab with interferon β -1a and showed significant benefit in reduction in relapses and in EDSS of the monoclonal over the interferon β .²¹ The trial was interrupted during its planned 3 year course due to 6 patients who developed idiopathic thrombocytopenic purpura, one of whom died.²² There has also been recognition of autoimmune thyroiditis occurring in patients treated with alemtuzumab. There are now two phase III trials of the agent underway, one as comparison against placebo and one in comparison to interferon β -1a in patients who have failed earlier DMT.

THE CURRENT POSITION

At present we have available four DMT which have stood the test of time. They have been used for more than a decade, they include three interferons β and glatiramer acetate, they appear safe in the long-term, effective in the short-term and reasonably tolerated. There is some evidence that their short-term efficacy is translated into long-term benefit. Their effects are modest.

For rescue medication we can use the monoclonal antibody natalizumab or cytotoxic therapies, such as mitoxantrone. They both have increased risks, but also appear to have increased efficacy compared to the interferons, but we are still limited in our understanding of the long-term safety of these agents.

In the near future we shall be offered the first of the oral medications and within 5 years other monoclonal antibodies. We will begin to use these agents without long-term plans for their use, or evidence of their effect in combination. We will therefore need to explain very carefully to our patients the potential risks and benefits and only when the patient agrees to accept the risk can we reasonably introduce the novel therapy. We shall need very careful monitoring of the longer-term effects of the more effective immunomodulating agents as we begin to use them. In the near future the tailoring of individual regimes will be possible; we need measures and algorithms to help define the best therapy with the most acceptable risks for each individual patient and situation.²³

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