Regular review

Drug treatment of multiple sclerosis

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Multiple sclerosis is the most common cause of chronic neurological disability in young adults, with a prevalence of about 1 in 1000. About 50% of patients are unable to walk without assistance 15 years after onset. As yet, no treatment can halt the accumulation of disability. In recent years, however, there has been substantial progress in understanding the pathogenetic mechanisms of the disease and in developing techniques to monitor treatment. Based on this progress treatments were developed that have a favourable impact on the natural course of the disease (disease modifying drugs). We discuss the evidence available from large randomised, placebo controlled studies, and we address several questions that still generate wide interest in relation to treatment with disease modifying drugs. Treatment of symptoms and rehabilitation, which still remain the mainstay of treatment for most patients with multiple sclerosis, are not reviewed here.

Summary points

- Disease modifying treatment should be considered early in the course of multiple sclerosis for patients with an unfavourable prognosis
- Considerable dispute still exists among experts about the optimal time to start treatment
- Interferon beta is the first line treatment for relapsing-remitting multiple sclerosis
- Glatiramer acetate—although not yet available in several European countries—has comparable efficacy in relapsing-remitting multiple sclerosis
- Future trial results are crucial to assess the role of interferon beta in secondary progressive multiple sclerosis
- Magnetic resonance imaging has an important role in better understanding the treatment response in multiple sclerosis

Methods

We have concentrated mainly on drugs that have been specifically approved for use in multiple sclerosis. Our sources included papers from Medline, information from international meetings on multiple sclerosis, and ongoing discussions with colleagues.

Multiple sclerosis

Clinical course

Multiple sclerosis usually manifests clinically in the third or fourth decade, typically presenting with a relapsing-remitting course which, after a period of time (average 5-15 years), in most patients is followed by the onset of the so called secondary progressive phase. Secondary progression can occur in the presence or absence of superimposed relapses. A subgroup of patients labelled with relapsing-remitting disease show a relatively benign course with little or no disability after 10 or more years. About 10% of patients have a primary progressive course from onset, without clinical relapses. Rarely, patients have malignant multiple sclerosis with a rapidly progressive course. The ability to predict the development of disability in a disease as variable as multiple sclerosis is a major challenge. Although unfavourable prognostic features have been recognised (box), their power to give an accurate prognosis for individual patients is modest at best.[1]

Factors associated with unfavourable prognosis in multiple sclerosis

- Male sex
- Older age at onset
- Motor or cerebellar signs at onset
- Short interval between initial and second attack
- High relapse rate in early years
- Incomplete remission after first relapses
- Early disability
- High lesion load detected by early magnetic resonance imaging of the brain

Cause

Epidemiological evidence has long suggested that two factors are involved in causing multiple sclerosis: exposure to an environmental agent and genetically determined susceptibility. The environmental agent is widely assumed to be infective, most likely viral, but all evidence is indirect and inconclusive, and few people believe that there is a single virus that causes multiple

sclerosis. Genetic studies have convincingly shown that there is not a single gene for multiple sclerosis: multiple genes are involved,[2] but how the genetic factors operate and how they interact with the environmental agents in establishing the disease is largely unknown.

Pathogenesis

The widespread belief, although unproved, is that multiple sclerosis is an organ specific autoimmune disease orchestrated by autoreactive T cells. Activation of these autoreactive T lymphocytes in the systemic circulation may enhance their movement through the blood-brain barrier, which then leads to multifocal sites of perivascular cuffing of lymphocytes and destruction of myelin sheath within the central nervous system. To date, however, evidence of a unique immunological abnormality in patients with multiple sclerosis is lacking. In particular, T cells that recognise myelin can be isolated with similar frequency from patients with and without multiple sclerosis.

Studies on the disease have suggested a noticeable heterogeneity in disease pathogenesis[3]; at least four different patterns of lesion pathology were shown. For example, in some cases the process seems to be directed primarily at the myelin sheath, with relative sparing of oligodendrocytes, whereas in other cases there is primary destruction of oligodendrocytes. Although the lesion of multiple sclerosis is primarily inflammatory and demyelinating, recent evidence re-emphasises that axonal loss may occur early in the disease course and that it is of critical importance in the development of irreversible disability.

Magnetic resonance imaging

Magnetic resonance imaging has both improved the diagnostic accuracy of multiple sclerosis and played an important part in better understanding the natural history of the disease. Patients with frequent relapses often exhibit new lesions after enhancement with gadolinium, indicating focal breakdown of the blood-brain barrier. Secondary or primary progression is associated with markers of tissue destruction as shown by magnetic resonance imaging (increased volume of T1 hypointense lesions, reduced magnetisation transfer ratio, progressive atrophy) rather than new activity of focal lesions.

In addition, magnetic resonance imaging has prognostic and therapeutic applications: the amount of lesions in the early phases of the disease predicts future disability, and quantification of disease activity (lesions shown after enhancement with gadolinium, new lesions) and lesion burden provides a powerful tool in therapeutic trials.[4 5]

Clinical trials

Advances in the treatment of multiple sclerosis depend on clinical trials because of the highly variable and unpredictable course of the disease and the difficulty in precisely measuring neurological disability. Because progression of the disease in general is slow, these clinical trials traditionally require relatively large numbers of patients and long periods of follow up.

The past decade has seen an increasing ability to perform preliminary examination of the effect of new treatments by using magnetic resonance imaging as an outcome measure. The advantage of magnetic resonance imaging is its high reproducibility as well as its high sensitivity in detecting disease activity, which is fivefold to 10-fold more frequent than clinical relapse.[5]

Treatment

The possibilities for treatment of multiple sclerosis depend on the clinical situation. We address separately treatment for a relapse and disease modifying treatment in the relapsing-remitting and the secondary progressive phase of the disease.

Treatment for relapses

Treatment for relapses is irrespective of whether they occur in the relapsing-remitting or the secondary progressive phase of the disease. Although almost all relapses show some degree of spontaneous recovery, most clinicians advise treatment for those relapses that have an important impact on function. For many years corticosteroids have been the first choice treatment. Corticosteroids shorten the duration of the relapse and accelerate recovery; however, there is no convincing evidence that the overall degree of recovery or the long term course of the disease is affected.

The most commonly applied regimen consists of a brief course of high dose methylprednisolone given intravenously (IVMP, 500-1000 mg per day for 3 to 5 days). Some clinicians substitute oral prednisone for intravenous methylprednisolone because it is easier to use and costs less. Data substantiating the comparable benefits of oral prednisone and intravenous methylprednisolone in acute relapses have been presented but are not definitive.[6] In various studies—all of them small—quite different dosage regimens of oral steroids have been applied.[7]

Disease modifying treatment for relapsing-remitting multiple sclerosis

The goal of treatment in patients with relapsing-remitting multiple sclerosis is to reduce the frequency and severity of relapses (and thereby prevent exacerbations) as well as to prevent or postpone the onset of the progressive phase of the disease. To achieve this goal, in the past especially, immunosuppressive drugs have been used, but they have never found widespread acceptance owing to limited efficacy and considerable toxicity.

More recently, large randomised controlled trials have been performed successfully with interferon beta-1a, interferon beta-1b, and glatiramer acetate.[8–11] These substances should be seen as immune modulators rather than immune suppressors. The trials have led to the regulatory approval of four agents (Avonex, Biogen, USA; Betaferon, Schering, Germany (Betaseron, Berlex, USA); Copaxone, TEVA, Israel; Rebif, Serono, Switzerland) for reducing the severity and frequency of relapses (table).

Interferon beta

Currently two forms of recombinant interferon beta (interferon beta-1a and interferon beta-1b) have been

Clinical results of large randomised trials

Trial	Agent	Drug name	Disease type	Primary outcome	Result on primary outcome
Jacobs et al[8]	Interferon beta-1a	Avonex	Relapsing-remitting	Time to confirmed progression	Positive
	Interferon beta-1a	Avonex	Secondary progressive	Time to confirmed progression	Trial still ongoing
	Interferon beta-1a	Avonex	After first attack	Time to second attack	Presented as positive; not yet published
	Interferon beta-1a	Avonex	Primary progressive	Time to confirmed progression	Trial still ongoing
The PRISMS Study Group[9]	Interferon beta-1a	Rebif	Relapsing-remitting	Relapse rate	Positive
The SPECTRIMS study	Interferon beta-1a	Rebif	Secondary progressive	Time to confirmed progression	Presented as negative; not yet published
Comi et al[15]	Interferon beta-1a	Rebif	After first attack	Time to second attack	Trial terminated; not yet published
The INFB Multiple Sclerosis Study Group[10]	Interferon beta-1b	Betaferon*	Relapsing-remitting	Relapse rate	Positive
European Study Group[19]	Interferon beta-1b	Betaferon*	Secondary progressive	Time to confirmed progression	Positive
	Interferon beta-1b	Betaferon*	Secondary progressive	Time to confirmed progression	Presented as negative; not yet published
Johnson et al[11]	Glatiramer acetate	Copaxone	Relapsing-remitting	Relapse rate	Positive

*Betaseron in United States.

approved by US and European regulatory authorities for the treatment of relapsing-remitting multiple sclerosis. Interferon beta-1a (Avonex, Rebif) is a glycosylated, recombinant product from mammalian cells, with an amino acid sequence identical to that of natural interferon beta. Interferon beta-1b (Betaferon; USA: Betaseron) is a non-glycosylated recombinant product from bacterial cells in which serine is substituted for cysteine at position 17.

All three drugs have been studied in large double blind placebo controlled randomised clinical trials.[8–10] Inclusion in these studies was restricted to patients with clinically active disease in the years before entry to the study (two exacerbations in two years for Betaferon and Rebif; two in three years for Avonex) who had mild to moderate disability and essentially were fully ambulatory (expanded disability status scale 0-5.5 for Betaferon, 0-5 for Rebif, and 1-3.5 for Avonex). The most prominent clinical result of all trials was a clear reduction in both frequency (by about one third) and severity of exacerbations. These observations with regard to treatment effect were supported by convincing findings on magnetic resonance imaging both as a reduction of active lesions and as a positive effect on total lesion load in the brain.[12–14] Because of the robustness of the evidence, most experts consider interferon beta as first choice treatment in patients with relapsing-remitting multiple sclerosis. There are, however, still many unresolved issues related to treatment with interferon beta (box).

When to start and stop inteferon beta

In individual patients, decisions on initiation of treatment should be based on the course of the disease, but about 10-20% of patients have relatively benign disease so they may not require disease modifying treatment. Treatment should not, however, be postponed until after persistent neurological deficits have occurred, because interferon beta does not reverse fixed deficits. Disease modifying treatment should be considered early in the course of disease for patients with an unfavourable prognosis, but the rate and pattern of progression of disease cannot be reliably predicted at initial assessment. Whether long term treatment should start at the time of the first attack, which seems to be sensible for a preventive therapy, is currently under investigation in two placebo controlled studies.[15]

Unresolved issues in treatment with interferon beta

- Optimal moment of initiation of treatment
- Optimal dose, frequency, and route of administration
- Long term effects of treatment
- When to stop treatment
- Occurrence and relevance of neutralising antibodies
- Mechanism of action
- Cost utility

Most guidelines concerning treatment with interferon beta in relapsing-remitting multiple sclerosis are based on the inclusion criteria that have been used in the placebo controlled trials mentioned above. Patients with definite relapsing-remitting disease who have experienced at least two relapses in the past two or three years and who are still able to walk without support for at least 100 m are considered eligible for treatment. It is extremely important that before these long term treatments are implemented, counselling about realistic objectives, regarding both efficacy and side effects, takes place, as overly optimistic expectations may complicate treatment.

It is currently unknown whether treatment should be discontinued at some time as there is only limited information on the long term effects of interferon beta. Present guidelines on stopping treatment are related to side effects, desire to become pregnant, and perceived inefficacy as shown by frequent relapses or progression of disability during treatment.

Choice of drug

Direct comparisons between the different interferon beta preparations have not been made, and it is therefore impossible to draw definite conclusions from the published data about superiority of one preparation over another. The main differences between the registered drugs are the amount of interferon beta given and the route and frequency of administration: Avonex, 6 million units (30 μg) by intramuscular injection once weekly; Betaferon, 8 million units (250 μg) by subcutaneous injection every other day; and Rebif, 6 million units (22 μg) by subcutaneous injection three times a week. Treatment with any of these drugs is usually well tolerated.

One study compared three different dosages of interferon beta-1a given subcutaneously once weekly,

with placebo, showing increasing treatment effect with increasing dosage, thereby suggesting that some of the currently applied dose regimens might be suboptimal.[16]

Cost utility

Quality of life has been shown to be substantially reduced in patients with multiple sclerosis, and it would be important to know whether interferon beta has a favourable impact on quality of life. Although it is likely that a reduction in frequency and severity of attacks makes a difference to the quality of life of a patient with multiple sclerosis, studies have so far not provided firm evidence for this. Models based on assumptions (on costs and savings) and estimates of long term gains have been described, showing that treatment with interferon beta has a high cost per quality adjusted life years gained.[17]

Glatiramer acetate

Glatiramer acetate (Copaxone) is a synthetic copolymer with some immunological similarities to myelin basic protein, one of the major components of myelin. Daily treatment with subcutaneous injections of 20 mg of glatiramer acetate resulted in a 29% reduction of the annual relapse rate in a two year trial.[11] These clinical observations were later supported by findings on magnetic resonance imaging in a separate study.[18] Adverse effects of glatiramer acetate are usually mild. Definitive data on the effect of glatiramer acetate on disease progression are not available.

Glatiramer acetate was approved by the US authorities in 1996, but so far there is no pan-European licence. The indications for the use of glatiramer acetate are comparable to those for interferon beta, but most clinicians consider it to be a second line treatment for relapsing-remitting multiple sclerosis.

Disease modifying treatment for secondary progressive multiple sclerosis

The goal of treatment in patients with secondary progressive multiple sclerosis is to prevent progressive worsening of the disease. Until recently there was no agent that had a favourable impact on the disease once it had entered the secondary progressive phase.

Interferon beta

A randomised double blind placebo controlled multicentre trial of interferon beta-1b (8 million units subcutaneously every other day) was recently completed in Europe, including 718 patients with clinically active secondary progressive multiple sclerosis.[19] At the predetermined interim analysis, the study was stopped because of a significant difference in the time to confirmed neurological deterioration in favour of the treated group. The delay of progression was within a range of 9 to 12 months. Significant reductions were also observed in time to become wheelchair bound, number of steroid courses given, and number of admissions to hospital because of multiple sclerosis. Based on these results interferon beta-1b was approved for use in patients with secondary progressive multiple sclerosis in Europe.

Recently it was reported that in a large placebo controlled trial, interferon beta-1a (Rebif) failed to have a major effect on disease progression (the secondary progressive efficacy clinical trial of recombinant interferon beta-1a in multiple sclerosis (SPECTRIMS) study, 9th meeting of the European Neurological Society, Milan, 1999). So far, these results have only been published in abstract form. Full publication of the results is eagerly awaited, as are the detailed results of a second study of interferon beta-1b in patients with secondary progressive multiple sclerosis that was carried out in the United States.

The question as to when to start and stop interferon beta in secondary progressive disease is difficult to answer; evidence should be reviewed as the detailed results of further trials become available (table). It is likely that these results will also have an impact on the outcome of cost utility studies in secondary progressive multiple sclerosis.[20]

Reconsideration of traditional immunosuppressive regimens

Given the fact that both interferon beta and glatiramer acetate, although convincingly shown to be effective, have major limitations, including cost, inconvenience (given parenterally), and a relatively modest overall impact on disease course, several experts have urged reconsideration of the role of immunosuppressants such as azathioprine or methotrexate. Compared with inteferon and glatiramer acetate these drugs are much cheaper, are easier to give, and might also have a favourable effect on the natural course of the disease.[21 22] The lack of convincing data for immunosuppressants from magnetic resonance imaging—as opposed to interferon beta and glatiramer acetate—has probably contributed to their rather modest acceptance. This is especially important now that magnetic resonance imaging has achieved more widespread acceptance as a surrogate marker of disease progression owing to better understanding of its correlation with both clinical disability and underlying pathology of the disease.

New developments

On the basis of new technologies to manipulate the immune system, there is a whole range of new treatment strategies under investigation, varying from subtle immune interventions, such as induction of immune tolerance or administration of various monoclonal antibodies, to aggressive strategies such as bone marrow transplantation.[23] Recent observations of axonal damage early in the disease course and increasing disability despite optimal anti-inflammatory treatment emphasise the need for rigorous investigation of neuroprotective treatment.[24–26]

Many experts believe that various treatment strategies should be combined to be optimally effective. Alternatively, if preliminary neuropathological observations indicating that individual patients may have unique mechanisms underlying their disease process would be confirmed, it could be possible in the future to tailor treatment on the basis of individual patient characteristics.[27]

Conclusion

The introduction of interferon beta and glatiramer acetate as drugs effective in modifying the course of relapsing-remitting multiple sclerosis has had two benefits. Firstly, it has improved the treatment of multiple sclerosis, and, secondly, it has provided tools to unravel further the mechanisms of the disease and thereby justifies hope for further progress in the near future.

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A memorable patient

Looking at the evidence

He remained clinically depressed despite medication and took an overly negative view of every event in his life. Fresh from my training course in cognitive behaviour therapy, I felt sure I could help.

"Imagine you are in bed asleep one night and you are woken by a loud noise downstairs," I suggested. "What would you think, feel, and do?"

"It could be a burglar," he replied. "I'd be terrified—perhaps ring the police or hide." "What if you have a cat and remember that you left the window open by mistake?"

"I would feel OK, and just go downstairs to check and close the window."

From the discussion that followed, he began to realise that his low mood was kept going by a tendency to interpret everyday situations in a negative way. He faced metaphorical "burglars" around every corner. I suggested that challenging such pessimistic thoughts by coming up with alternative, more positive explanations could offer a route out of his depression. He agreed to test out this approach as homework, and we arranged to meet again one week later with some optimism.

When he returned for his next therapy session, I started by using an approach favoured by Socrates, who believed that the answers to important questions lie within ourselves. What had been the most important thing he had learnt from his recent experiences?

"Well doctor," he began. "Last night, I was lying in bed at 3 am and heard a noise downstairs. Remembering what we said about not jumping to conclusions, I thought perhaps it was the central heating, or perhaps the wind blowing. I went down to check, and found a burglar trying to get in through the kitchen window. He ran off before I managed to ring the police."

He sensed the irony in this outcome, one that I was clearly not expecting. "I'm feeling a lot better than last week," he announced. It was the first time I had seen him smile since we first met.

This patient taught me two valuable lessons. Firstly, as in so much of medicine, the patient is often proved right. Secondly, cognitive therapy is more than just positive thinking, which can sound simply like an instruction to "look on the bright side" to someone who is feeling depressed. It is about balanced thinking and basing our feelings on the evidence with which we are actually presented. The trouble with optimists is that they are sometimes afraid to face the truth.

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