Treatment of multiple sclerosis with newer immune-modulating drugs

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SYNOPSIS

Multiple sclerosis can be a severely disabling disease. Recently introduced immunomodulatory drugs (interferon beta or glatiramer acetate) should be considered for the treatment of patients in the earlier stages of the disease, if they have a relapsing-remitting course. These therapies have replaced older immunosuppressants such as methotrexate, at this stage of the disease. On average, immunomodulatory drugs reduce relapse rates by about 30% and retard the progression of disability by about 12–18 months. Whilst these benefits are relatively modest, they offer for the first time a means to alter the natural history of the disease. Several studies suggest that the positive effects of these drugs on the rate of progression of disability and relapse frequency are maintained over time. They all need to be given by frequent injections, and regular monitoring of their adverse effects is a necessary part of management. Immunomodulatory drugs have been used in multiple sclerosis patients intensively for at least 10 years without any apparent long-term adverse effects.

Index words: interferon beta, glatiramer acetate.

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Introduction

Multiple sclerosis is a chronic inflammatory, demyelinating disease of the central nervous system and is the commonest cause of neurological disability in young adults. In most patients it initially follows a relapsing-remitting course and in the early stages there is often complete recovery between attacks. With time, there is less recovery and finally most patients enter a secondary progressive phase. About 10% of patients have a primary progressive course with deterioration from the outset without relapses and remissions.

Multiple sclerosis should be managed with education and counselling as well as medications. Acute attacks can be treated with intravenous methylprednisolone. This shortens the duration of symptoms associated with a relapse, although it probably does not alter the ultimate recovery following an attack.[1]

New immune-modulating therapies (drugs which adjust the activity of the immune response to a desired level), interferon beta-1b (Betaferon), interferon beta-1a (Avonex and Rebif) and glatiramer acetate are now available. These drugs are of value in the relapsing-remitting phase of the disease[2,3,4,5] and appear to alter the natural history of multiple sclerosis. They have not been compared with other treatments, such as methotrexate.

Rationale for therapy with immunomodulatory drugs

The rate and extent of axonal loss during the relapsing-remitting phase of the disease is thought to determine when a patient enters the secondary progressive phase. Beyond a certain threshold, further axonal loss leads to more rapid disablement.[6] In double-blind, placebo-controlled trials, immunomodulatory drugs have reduced the frequency of relapses and the volume of the lesions seen with MRI. We hope that this will also reduce the rate of axonal loss over time and hence delay entry into the secondary progressive phase. While this concept is difficult to prove *in vivo*, one placebo-controlled study of interferon beta-1a (Avonex) found a reduction in the rate of brain atrophy, used as a marker of axonal loss, in the second year of treatment.[7] A number of studies have also shown treatment has a positive effect on the rate of disability progression in patients in the early phases of multiple sclerosis (Table 1).[3,4,5]

There have been two placebo-controlled studies of interferon beta (1a or 1b) in secondary progressive multiple sclerosis.[8,9] The first study showed a positive effect on delaying progression. (Proportion of patients with confirmed progression over three years: 49.7% placebo versus 38.9% for interferon beta-1b, $p < 0.005$).[8] The second study found no difference between interferon beta-1a (Rebif) and placebo on the progression of disability over three years.[9] One explanation for this discrepancy may be that some of the patients in the initial study were still in the relapsing-remitting phase rather than a secondary progressive phase because they had a higher relapse rate than expected.

The evidence of efficacy of immunomodulatory drugs in the secondary progressive phase of multiple sclerosis is therefore not established.

Subsidy of immunomodulatory therapy

Treatment costs more than $1000 per month. The Pharmaceutical Benefits Scheme subsidises immunomodulatory drugs for the treatment of patients with relapsing-remitting multiple sclerosis who:

- have had two attacks in the preceding two years with partial or complete recovery

Table 1

A comparison of the results of pivotal double-blind controlled trials of immunomodulatory drugs in the treatment of patients in the relapsing-remitting phase of multiple sclerosis

	Interferon beta-1a (Rebif)[4]		*Interferon beta-1a (Avonex)*[3]		*Interferon beta-1b (Betaferon)*[2]		*Glatiramer acetate*[5,16]	
	Placebo	44 microgram interferon beta-1a three times weekly	Placebo	30 microgram (6 million units) interferon beta -1a weekly	Placebo	0.25 mg (8 million units) interferon beta -1b (alternate days)	Placebo	20 mg glatiramer acetate (daily)
Mean relapse rate after 12 months	1.08	0.87	NR		1.43	0.97	1.02	0.81
Mean relapse rate after 24 months	2.56	1.73**	0.90	0.61**	1.27	0.84***	1.68	1.19**
Probability of sustained disability progression by >1 on EDSS† scale (sustained at two years)	48%	24%*	33.3%	21.1%*	NA		28.8%	20.8%*
Mean change in MRI lesion load (over 12 months) compared with baseline MRI scans performed at trial entry	10.9% (area)	–3.8%*** (area)	–3.3% (volume)	–13.1%* (volume)	12.2% (area)	–1.1% *** (area)	4.7 mL (volume)	3.0 mL** (volume)

NA Not assessed NR Not reported *** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$ † Expanded disability status score

Table 2

Currently available newer immunomodulators for the treatment of multiple sclerosis in Australia

Drug	*Route*	*Dose*	*Adverse effects*
Interferon beta-1a (Rebif)	Subcutaneous (single-dose pre-filled syringe) Auto-injector available	44 microgram three times a week (e.g. Monday, Wednesday, Friday)	Injection site reactions occur with subcutaneous injections in 100% of patients, severe with skin ulceration in 10%
Interferon beta-1a (Avonex)	Intramuscular (reconstituted) Not suitable for auto-injector	30 microgram (6 million units) weekly	No reactions with intramuscular injections Flu-like symptom complex (fever, chills, malaise, myalgia, sweating) after injections: up to 76%
Interferon beta-1b (Betaferon)	Subcutaneous (reconstituted) Auto-injector available	0.25 mg (8 million units) on alternate days	Elevated liver enzymes, alteration in blood count, hypersensitivity reactions, neutralising antibodies Depression, may aggravate spasticity
Glatiramer acetate	Subcutaneous (reconstituted) Auto-injector available	20 mg daily	Injection site reactions in 100%. Severe with skin ulceration: rare Immediate post-injection reaction (10%) occurs straight after injection and consists of transient flushing, chest tightness, dyspnoea, palpitations

- remain ambulant
- have their diagnosis confirmed by MRI of the brain or spinal cord.

These criteria mirror those used for patient selection in most of the clinical trials. Patients who have progression of disability despite treatment are not eligible for repeat prescription of subsidised drugs.

Interferon beta

Interferon beta is a normal constituent of the human immune system. It is produced by immunologically active cells in response to inflammation or infection and seems to dampen inflammatory reactions by directly inhibiting the proliferation, migration and activation of immune cells through various mechanisms.[10] The Avonex and Rebif preparations have an identical protein structure to the human molecule while Betaferon differs by one amino acid. These preparations are produced in large quantities by genetically modified bacteria or cells (*E. coli* or hamster ovary). The contraindications and adverse reactions of all the beta interferons are similar. They are reasonably well tolerated, but patients should be educated regarding potential adverse effects (Table 2).

Contraindications

Interferons are contraindicated in women who are trying to conceive and during pregnancy (category D) and lactation.

They should be ceased three months before planned conception, but may be resumed immediately after delivery or when breastfeeding stops. If a woman taking interferon becomes pregnant, termination of pregnancy is not advised; the potential risks (as shown by animal models) to the fetus should be discussed with the patient. These risks appear to be low and a number of successful pregnancies have occurred in such a situation.

Beta interferons are contraindicated in decompensated hepatic disease and in patients with refractory epilepsy.[11] The use of interferon beta preparations in patients with a history of **severe** depression and/or suicidal ideation is also contraindicated. They should be used with caution in patients with anaemia, thrombocytopenia or monoclonal gammopathies.

Adverse reactions

The commonest adverse reaction is a flu-like symptom complex.[11] Symptoms commence 2–6 hours after injection and resolve within 24 hours. They can be managed by taking paracetamol or ibuprofen just before the injection and again four hours afterwards. Evening injections are advised so patients sleep through their symptoms. This reaction is usually only a significant problem for the first 3–6 months after starting therapy.

Injection site reactions commonly occur 24–48 hours after subcutaneous (not intramuscular) injection, but rarely progress to skin necrosis. To minimise these reactions education about aseptic injection technique and rotating injection sites is essential. The injections are usually given in the lower abdomen, buttocks or anterior thighs.

Halving the dose of the first few injections may reduce the severity of flu-like symptoms and injection site reactions. Ensuring the solution is not cold (i.e. at body temperature) or applying ice to the injection site before injection will minimise discomfort. Subcutaneous injections are better tolerated if given with an automated self-injecting device.

Depression can occur but beta interferons may be given to patients with depression if it is being treated. Prophylactic antidepressants are not indicated in those with a past history of depression. These patients should be informed that symptoms of depression might be aggravated by beta interferon treatment, particularly if the drug is injected more than once a week. This association is a weak one but patients with a history of depression should be closely monitored.[11]

Serious hypersensitivity reactions (bronchospasm, anaphylaxis) may occur infrequently. Betaferon and Rebif may exacerbate spasticity in some patients.

At the recommended doses, lymphopenia, neutropenia, thrombocytopenia, anaemia and elevated concentrations of liver enzymes can occur, particularly in the early phase of treatment.[11] As these adverse reactions are related to dose frequency, they are less likely to occur with weekly injections. Antimicrosomal antibodies may also be detected, but this rarely leads to clinically evident thyroid disease. Low calcium and high uric acid concentrations also appear to be associated with interferon beta-1b.

Neutralising antibodies develop in up to one third of patients. They are more frequent with the subcutaneously administered beta interferons. Further research is required to determine the clinical significance of these antibodies which may spontaneously lower in titre even if treatment continues. Testing for antibodies is not available in Australia.

Recommended monitoring

Regularly review the patient's injection technique and injection sites. Check liver function and the full blood count before starting therapy, then every three months. Monitor renal function if it is impaired.

Most mild laboratory abnormalities do not require treatment to be stopped. In the clinical trials of interferon beta-1b, treatment was stopped if hepatic transaminase concentrations exceeded ten times the upper limit of normal, or if bilirubin concentrations exceeded five times the upper limit of normal. In all instances, liver enzymes returned to normal on cessation of the drug and patients had no ill effects. If the drug is ceased, because of liver enzyme abnormalities, it may be resumed at 25% of the original dose and slowly increased with regular monitoring.[11]

Glatiramer acetate

Glatiramer acetate is a mixture of synthetic polypeptides designed to simulate myelin basic protein, a putative target antigen in multiple sclerosis. It interferes with MHC class II antigen binding on antigen presenting cells and induces antigen specific T suppressor cells.[12] Glatiramer acetate, in addition to being a first-line therapy, should also be considered in those who do not respond to or who do not tolerate interferon beta because of adverse effects. Monitoring of liver function and full blood count is not required.

Contraindications

Apart from hypersensitivity, there are no absolute contraindications to glatiramer acetate. It is not recommended when pregnancy is planned, during pregnancy (category B1) and lactation.

Adverse events

Occasionally a reaction occurs **immediately** after injection consisting of transient flushing, chest tightness, dyspnoea and palpitations. These self-limiting reactions tend to be isolated events which are unpredictable and infrequent.[5]

Injection site reactions commonly occur 24–48 hours after subcutaneous injection. To reduce these events the patients can take similar measures to those advised for beta interferon.

Comparing the preparations

In a recent unrandomised study over the first 18 months of therapy, frequent (daily or three times a week) subcutaneous injections (interferon beta-1a and -1b or glatiramer acetate) were more effective than weekly doses of intramuscular interferon beta-1a in reducing relapse frequency. There are no data to show if this finding affects the rate at which long-term disability develops.[13]

Betaferon, Avonex and glatiramer have to be reconstituted before injection. This can be difficult for patients with poor

dexterity, who may prefer Rebif which comes in a prepacked syringe.

Autoinjectors are available for subcutaneous injection of Betaferon, Rebif and glatiramer, but not Avonex as this requires an intramuscular injection and more detailed instructions.

Glatiramer is given as a daily injection, Avonex is a weekly injection, Rebif is injected three times a week and Betaferon is given every other day. The frequency of injections influences the incidence of flu-like adverse effects to the interferon beta preparations.

A higher dose of Avonex (60 microgram) has been compared to the currently available (30 microgram) dose. Both doses were equally effective in reducing disability progression, suggesting that the 30 microgram dose is around the dose ceiling for Avonex.[14]

There is a dose effect for subcutaneously administered beta interferon. Higher doses have a greater effect on relapse frequency and MRI lesion load.[15]

There is a comparative study of beta interferons and glatiramer acetate currently underway in the USA. This aims to compare the effectiveness of Avonex against glatiramer acetate. There are no data from this trial available as yet.

Large-scale double-blind placebo-controlled trials involving previously used treatments such as methotrexate and azathioprine have not been performed. It is therefore difficult to compare their efficacy with that of the new immunomodulating drugs. The newer drugs also have a different pattern of adverse effects from the older drugs.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 47)

3. Interferon beta significantly slows the deterioration of patients with progressive multiple sclerosis.
4. Patients whose disability increases while they are taking interferon beta should have their dose increased.

Multiple sclerosis: a patient's perspective

Laurel C. is a 48-year-old mother of two teenaged children. She has been taking an immunomodulating drug for five years.

AP: *When did you find out you had multiple sclerosis?*

LC: I woke up one morning in 1997 with numbness and tingling in my left foot. Over the next week, this spread to the whole left side of my body. I lost balance and was dragging my leg and bumping into things. My general practitioner organised an urgent appointment with a neurologist. An MRI scan showed I had multiple sclerosis.

Looking back I had probably had attacks before. In 1992 I developed Bell's palsy and I remember other