



Revised (2009) Association of British Neurologists' guidelines for prescribing in multiple sclerosis

INTRODUCTION

In January 2001, the Association of British Neurologists (ABN) first published guidelines for the use of licensed disease modifying treatments (β -interferon and glatiramer acetate) in multiple sclerosis. In 2002, the National Institute of Clinical Excellence (NICE) concluded that treatments with β -interferon and glatiramer acetate were not cost effective but asked the parties involved '*to consider what action could be taken so that the NHS could obtain these drugs in a way that would be cost effective*'. Therefore, a Risk Sharing Scheme was started in 2002 in which patients who meet the ABN guidelines are provided with treatment funded through the NHS and monitored annually for up to 10 years at which point the intention is to assess efficacy and amend expenditure if this is shown not to match NICE requirements for cost-efficacy¹. Recruitment to the cohort for follow-up within the Risk Sharing Scheme is now complete and – pending evaluation at or beyond 10 years - the Department of Health has instructed NHS funders that new patients with multiple sclerosis who fulfil the ABN criteria should continue to be eligible for treatment with funding provided through the NHS.

Revised guidelines for the use of interferon and glatiramer acetate in multiple sclerosis, published in 2007, were designed to supplement rather than supplant the 2001 guidelines taking into account the revised McDonald criteria for the diagnosis of multiple sclerosis to include patients with clinically isolated syndromes subsequently showing evidence for disease activity.

Since the 2007 guidelines, further drugs has been licensed for use in the treatment of patients suffering from rapidly evolving multiple sclerosis, namely Natalizumab and Mitoxantrone. There are a number of other drugs in various phases of clinical development, appraisal and licensing including orally active treatments (Cladribine and Fingolimod), and the monoclonal antibody Alemtuzumab.

This further revision of the ABN guidelines takes account of studies on treatments for multiple sclerosis published since the 2007 revision and aims to represent a national consensus concerning the use of currently approved disease modifying drugs in multiple sclerosis. These may require revision as other treatments receive approval for use in this indication.

These guidelines are not designed to replace clinical judgement but represent a consensus of British neurologists concerning the appropriate use of disease modifying drugs in multiple sclerosis. As with the use of any form of treatment, physicians must make themselves aware of safety issues, long term complications and any pre-treatment assessments that are required, as well as forming a view on efficacy. Treating neurologists should be prepared to discuss these issues fully and frankly with their patients before and during any course of treatment.

BACKGROUND

Beta interferon and glatiramer acetate reduce relapse rates and MRI lesion activity in multiple sclerosis^{2,3,4}. It seems plausible that reducing MRI activity in relapsing remitting multiple sclerosis might also prove a reliable surrogate for favourably influencing the clinical course of disability and

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November 2009

longer term prognosis. However, the relationships between MRI lesion load and activity, and relapse frequency and disability in individuals with a Clinically Isolated Syndrome and relapsing multiple sclerosis are surprisingly imprecise. Furthermore the evidence suggests that these drugs have a much diminished effect on disease activity beyond the first year of treatment^{5,6,7}.

After considering the evidence, the following summary statements can be made concerning the use of disease modifying drugs in the treatment of multiple sclerosis:

1. In patients with relapsing remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis with superimposed relapses, Beta interferon has a consistent effect in reducing relapses (by about one third over two years)^{2,8-16}. This may also apply to patients with a clinically isolated syndrome in whom abnormal MRI indicates a high probability of subsequent conversion to clinically definite multiple sclerosis and those who subsequently meet the revised McDonald criteria for multiple sclerosis¹⁷.
2. In patients with relapsing remitting multiple sclerosis, Glatiramer Acetate reduces relapse rate by about one third over two years^{18,19}.
3. Beta-Interferon and Glatiramer Acetate may reduce the development of disability through prevention of relapses that would otherwise have resulted in residual dysfunction, although the effect appears modest at best, and some trials have not shown any benefit^{2,8,9}.
4. Beta-Interferon and Glatiramer Acetate do not appear to modify progressively increasing disability that is unrelated to relapses^{3,14,15,20-22}. When patients with relapsing multiple sclerosis are treated with Beta-Interferon and Glatiramer Acetate, it is not known whether the long term course of multiple sclerosis, e.g. at and beyond 5 years, is altered. Specifically, it is not established reliably that long-term interferon: (a) reduces the accumulation of disability by whatever mechanism or; (b) prevents or slows entry to the secondary progressive stage of the disease.
5. In clinically isolated syndromes the interferons reduce the conversion rate to multiple sclerosis from 45–50% in untreated patients to 28–35% over 2–3 years²³⁻²⁵. and glatiramer acetate probably has a similar effect²⁶⁻²⁹. However, at best, only a marginally significant gain in terms of disability with interferon treatment has been demonstrated over 3 to 5 years³⁰.
6. In patients with rapidly evolving aggressive relapsing-remitting multiple sclerosis, consideration should be given to the use of Natalizumab in accordance with NICE guidelines. In expert centres, various other treatments may also be considered, including Mitoxantrone.
7. No treatments are yet available that convincingly alter the course of progressive multiple sclerosis in the absence of relapses once this stage of the disease has been reached.
8. As newer treatments emerge and clinical equipoise is agreed between the clinician and patient, participation should be encouraged in clinical trials, rather than open label prescribing.

GENERAL MANAGEMENT ADVICE

Disease modifying treatments should be started and supervised by a consultant neurologist; preferably one with special expertise in multiple sclerosis. When considering potential disease modifying treatment options in relapsing-remitting multiple sclerosis and clinically isolated syndromes, it is important that risk and benefit are fully appreciated by patients and neurologists. In rapidly evolving aggressive relapsing-remitting multiple sclerosis, the risks of potentially more toxic treatments such as Natalizumab or Mitoxantrone may be outweighed by the potential benefits. Conversely, in milder disease these risks may not be justified and other treatment options remain more appropriate.

Prior to starting treatment with any disease modifying agent patients should have appropriate pre-treatment investigations and monitoring during treatment for relevant complications of the particular

therapy being used. This would include a full blood count, liver function tests, urea and electrolytes and protein electrophoresis. The latter is to ensure that the patient does not have a monoclonal gammopathy, since the administration of cytokines, including beta interferon, to patients with a pre-existing monoclonal gammopathy has been associated with the systemic capillary leak syndrome, shock-like symptoms and occasional fatal outcome.

Other specific pre-treatment investigations and monitoring investigations apply to Natalizumab³¹ and Mitoxantrone³². Physicians prescribing these drugs must take account of these before and during a patient's course of treatment.

Regular follow-up is essential, to monitor and manage adverse effects, and any other problems related to the disease or its treatment. It is suggested that follow-up is performed at months 1 and 3, and then three monthly until the end of the first year after which six monthly intervals are sufficient.

There appears to be little consensus concerning whether and when anti-beta-interferon antibodies should be measured routinely and how the results should be used. However the presence of such antibodies, especially when sustained high titres are detected may be useful in the decision to terminate interferon treatment when there is evidence that it is ineffective in a particular patient (see recommendations for termination of treatment, below).

In the USA and parts of continental Europe, physicians frequently use MRI to follow up disease activity in patients on disease modifying agents. This has not been part of regular practice in the UK, but may be occasionally be useful when decisions need to be made concerning the termination of treatments.

MS specialist nurses play an important role in managing symptoms as well as providing information and reassurance to patients on treatment during and between clinic attendances.

It is important from the outset to give patients accurate information on the expectations of treatment including the evidence that efficacy of beta interferons is only partial, usually modest in magnitude and certainly not curative. Patients can also obtain information from the Multiple Sclerosis Society and other lay organisations that have jointly produced information written in lay language, as well as a range of leaflets on other symptomatic, psychological and social aspects of living with multiple sclerosis. A freephone helpline is provided by the Multiple Sclerosis Society on 0800 800 8000. The MS Trust (01462 476700) also provides information to patients concerning the use of disease modifying drugs in multiple sclerosis.

ABN GUIDANCE FOR STARTING DISEASE MODIFYING TREATMENT

All eligible patients will normally be ambulant (maximum EDSS 6.5) and aged 18 or more years. No treatments are licensed for use during pregnancy.

A. Relapsing remitting multiple sclerosis. (β -interferon or glatiramer acetate). Patients with a diagnosis of active multiple sclerosis with relapsing onset; active disease is defined by two clinically significant relapses in the previous two years.

Neurologists may, in certain other circumstances where the evidence for efficacy is less secure, also consider advising treatment after discussion with the patient concerning the risks and benefits. For example;

- (i) patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (i.e. development of multiple sclerosis).

- (ii) patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity (i.e meet the revised McDonald criteria for MS)
- (iii) individuals aged less than 18 with relapsing remitting multiple sclerosis.

B. Aggressive multiple sclerosis. Patients with relapsing and remitting multiple sclerosis that is considered to be rapidly evolving and likely to prove severe in due course should be considered for treatment with Natalizumab or Mitoxantrone by specialist neurologists. Rapidly evolving and severe multiple sclerosis is defined by two or more disabling relapses in 1 year, with one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

C. Secondary progressive multiple sclerosis. Treatment is not recommended in non-relapsing secondary progressive multiple sclerosis and only in relapsing secondary progressive multiple sclerosis when relapses are the predominant cause of increasing disability.

D. Primary progressive multiple sclerosis

No disease modifying treatment is indicated.

RECOMMENDATIONS FOR DISCONTINUATION OF TREATMENT

Decisions to start or stop treatment, or to perform MRI for diagnosis and management, should recognise the central importance of patient choice; patients should be fully informed of relevant facts and uncertainties before making a decision in discussion with their treating neurologist.

It is almost impossible to conclude in individual patients that treatment is providing no benefit and the problem of discontinuation is compounded by the fact that there are few alternative options for disease modification. Therefore, it is not feasible to have mandatory stopping criteria that apply in all cases. The following scenarios are suggestive of loss of or limited benefit from treatment and should be taken into account when deciding whether treatment should be discontinued:

1. The development of more aggressive clinical relapses with increased frequency compared to pre-treatment levels, especially if MRI shows new or enhancing lesions, should prompt neurologists to discuss more powerful treatment options particularly, at present, with Natalizumab although the options are expected to change over the next few years. Where the disease has not become rapidly evolving, or relapses have continued to occur at similar frequency to pre-treatment levels, it would seem sensible to review and consider stopping treatment.
2. The development of non-relapsing secondary progressive multiple sclerosis with loss of ability to ambulate (EDSS 7 or more),
3. Positive tests for neutralising antibodies to beta interferon (NAB), especially if sustained and in high titre, strengthen the case for discontinuation when the above clinical or MRI features are also present²⁴. Neutralising antibody testing should use a reliable assay provided by a competent laboratory.

NOTE. The Association of British Neurologists receives donations for educational support of the annual scientific symposium from Pharmaceutical Companies that market treatments for multiple sclerosis.

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