ABN Guidelines for Treatment of Multiple Sclerosis with ß-interferon and Glatiramer Acetate

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Background

The last ABN guidelines for use of the licensed MS disease modifying treatments – ß-interferon and glatiramer acetate - were published in January 2001. An evaluation in 2002 by the National Institute of Clinical Excellence (NICE) concluded that ß-interferon and glatiramer acetate are 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 are eligible by the ABN guidelines are provided with treatment in the NHS and monitored annually for up to 10 years. Although recruitment to the cohort for follow-up within the Risk Sharing Scheme is now complete, the Department of Heath has instructed NHS funders that new patients with MS who fulfil the ABN criteria should continue to be eligible for treatment in the NHS.

Since 2001, a number of additional randomised clinical trials have been reported and use of these agents has increased markedly in the UK. New diagnostic criteria for MS, incorporating MRI and CSF findings, have also been developed that allow MS to be diagnosed after one clinical episode (clinically isolated syndrome [CIS]). With this in mind the ABN has felt it timely to update its own guidelines. It is hoped that NHS commissioners and NICE will give the revised guidelines appropriate consideration. In the meantime, it should be noted that the funding commitment under the Risk Sharing Scheme applies to patients eligible for treatment under the ABN's 2001 guidelines not the revised 2007 version.

Most randomised, placebo-controlled trials have been of 2 or 3 years duration. After considering the results of these trials overall, the following observations can be made:

1 In patients with CIS and abnormal MRI, relapsing remitting MS and secondary progressive MS with superimposed relapses, beta interferon has a consistent effect in reducing relapses (by about one third over two years)[1-10]
2 In patients with relapsing remitting MS, glatiramer acetate reduces relapse rate by about one third over two years[11,12]
3 Disease modifying treatments may reduce the development of disability through prevention of relapses that would otherwise have resulted in residual dysfunction, although the effect appears modest over the trial study periods[1-3]
4 The disease modifying treatments do not appear to modify progressively increasing disability that is unrelated to relapses[8-10,13,14,15]

When patients with relapsing MS are treated with disease modifying treatments, it is not known whether the long term course of MS, e.g. 5 or more years, is altered. Long term treatment effects are being studied in the Department of Health's Risk Sharing Scheme, which started in 2002 and is scheduled to run for 10 years.

There are significant though modest relationships of MRI lesion load and activity in CIS and relapsing MS with relapses and disability[16-18]. Beta interferon and glatiramer acetate reduce MRI lesion activity[1-10,12]. Although unproven, it seems plausible that reduced MRI activity in relapsing remitting MS has potential to favourably influence the prognosis.

With the larger body of evidence and continued clinical experience, it is now considered appropriate to revise the ABN guidelines. The present guidance concerns only beta interferon and glatiramer acetate: it is recognised that future guidance for other disease modifying therapies such as mitoxantrone and natalizumab might be helpful.

2
Guidelines

General

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 by their neurologist before making a decision. Disease modifying treatment should be started and supervised by a consultant neurologist; preferably one with an interest in MS. MS nurses provide very valuable support to patients who receive disease modifying treatments.

Recommendations for starting treatment

All eligible patients should be ambulant (maximum EDSS 6.5) and have a diagnosis of MS established by the McDonald criteria with relapsing onset.They will normally be aged 18 or more years, although treatment at a younger age may be warranted in some circumstances.

A Diagnosis of MS by the McDonald criteria[19] within one year of presentation with a clinically isolated syndrome (CIS) typical for MS* (ß-interferon only)

*e.g., unilateral optic neuritis, isolated brain stem syndrome such as internuclear ophthalmoplegia, or partial spinal cord syndromes

Rationale: Although ß-interferon delays the time to second relapse in CIS patients with a single, abnormal MRI scan at presentation[4-6], many such patients will not have new relapses in the early years (e.g. 50% of placebo patients in the CHAMPS trial did not have further relapses during the 3 years of follow up[4]) and not all will develop clinically definite MS even with prolonged follow up[17,20]. On the other hand, CIS patients developing MS by the McDonald criteria after 3 months and one year of follow up have a high (75-85%) probability of having further relapses and developing clinically definite MS within 3 years[21-23]. It is therefore recommended that treatment is initiated after the diagnosis of MS is made but only if this is within one year of the CIS when a high rate of further clinical relapses has been reported[21-23]. Two MRI scans may be required during the first year in order to detect dissemination in space and time and diagnose MS[19]. See Appendix for recommendations for use of MRI during the first year from CIS onset in patients who do not have further clinical symptoms.

B Relapsing Remitting MS (ß-interferon or glatiramer acetate)

Active disease defined as one or more of:

1 Two clinically significant relapses in the last two years
2 One disabling relapse in the last year
3 Active MRI scan containing new or gadolinium enhancing lesions that have developed in the last year

Notes:

i *Criterion B1:* this is the same as the 2001 guideline.

ii *Criterion B2:* treatment may be considered appropriate for patients who have become disabled by a single relapse, especially if a recent or contemporaneous MRI also shows new or enhancing lesions. Treatment is not appropriate when the relapse is mild and remitting and there is no MRI activity

iii *Criterion B3:* when a recent MRI scan is active but the patient has not experienced recent relapses (i.e. B1 and B2 not fulfilled), it will not always be felt appropriate to commence treatment. Features that favour starting treatment include:
   a clinical evidence suggesting a poorer prognosis e.g. evidence for cognitive impairment, ataxia;
   b continued development of new and enhancing lesions on serial MRI scans.

C Secondary progressive MS (ß-interferon only)

Treatment is not recommended in non relapsing secondary progressive MS and only in relapsing secondary progressive MS when relapses are the predominant cause of increasing disability. This wording mirrors the intention as the 2001 guideline, but unlike the 2001 version it does not require two disabling relapses within two years since there may be one or more relapses of variable severity that cause a predominant relapse-related accumulation of disability.

D Primary progressive MS

Neither treatment is indicated.

Recommendations for discontinuation of treatment

It is almost impossible in individual patients to conclude 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. It is not feasible to have mandatory stopping criteria that apply in all cases. The following criteria are suggestive of loss of or limited benefit from treatment and should be taken in to account when deciding whether treatment should be discontinued:

1 Development of an increased number and severity of relapses or lack of relapse reduction compared with the pre-treatment 1 to 2 years, especially if MRI shows new or enhancing lesions. If relapses are severe and disabling, some neurologists will consider using more aggressive immunomodulation e.g., mitoxantrone.

2 Development of non-relapsing secondary progressive MS with loss of ability to ambulate (EDSS 7 or more),

Note:
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 present[24]. NAB testing should use a reliable assay provided by a competent laboratory.

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Appendix

Recommendations for use of MRI during the first year from CIS onset in the light of new ABN guidelines for disease modifying treatments for MS.

(NB: If CIS patients have a second clinical relapse within one year and are diagnosed with clinically definite MS, they are eligible for disease modifying treatment. The management algorithm below is for patients who have not had a second relapse during the year)

1 The decision to perform MRI in CIS patients should be jointly agreed by the doctor and patient after the patient has been informed of the potential implications of the investigation for diagnosis and management.

2 It is appropriate to offer to investigate CIS patients with conventional T2-weighted/FLAIR MRI of the brain at presentation as it gives predictive information on the risk for MS.
   i If feasible, additional gadolinium enhanced imaging may be useful because enhancing lesions are a component of both dissemination in space and time in the McDonald criteria
   ii Spinal cord MRI should also be performed when there is a spinal cord CIS with clinical concern that the cause may be other than demyelination.

3 If MRI shows no abnormalities suggestive of demyelination, the risk for MS is low (~20%) and repeat MRI is not required.

4 If MRI shows abnormalities that fulfil the McDonald criteria for MS, treatment with ß-interferon should be discussed.

5 If MRI shows abnormalities suggestive of demyelination but that do not fulfil the McDonald criteria, patients should be counselled about the diagnosis of MS and the treatment options available if further clinical, CSF or MRI evidence confirms the diagnosis. Some people may opt for a "wait and see" clinical follow-up period. If the neurologist and patient decide to proceed with using scanning, then repeat scanning should be performed within 12 months from CIS onset (in general an interval of 3-6 months between scans is recommended)
   i If repeat MRI shows abnormalities that fulfil the McDonald criteria for MS, treatment with ß-interferon should be discussed.
   ii If repeat MRI does not fulfil the McDonald criteria, treatment with ß-interferon is not recommended and further MRI scans are not recommended.

6 After more than one year from CIS onset, follow up and management should be determined by clinical symptoms.

7 Neurologists responsible for diagnosing MS and considering disease modifying treatments should be familiar with the McDonald criteria[19] – that incorporate clinical, MRI and CSF findings - and able to evaluate MRI scans with advice from a neuroradiologist as required.

8 It is estimated that about 5 extra scans will be required per 100,000 of the population per year.

Disclosure

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The current members of the ABN MS Guidelines Panel are:
Professor Alastair Compston, Dr Jeremy Dick, Professor Nigel Leigh, Professor Christopher Martyn, Professor David Miller, Dr Fred Schon, Professor Alan Thompson, Dr Carolyn Young and Professor John Zajicek. Their disclosures are available on the ABN website Register of Interests.

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Ormond House, 27 Boswell Street, London WC1N 3JZ
Email: info@theabn.org