

New Guidelines for MS Treatment - no cause for celebration

In February, the Association of British Neurologists endorsed and released the 2007 ABN Guidelines for Treatment of Multiple Sclerosis with β -interferon and Glatiramer Acetate,¹ an update of the 2001 Guidelines. We and others however view the new document with concern and dismay.

What are the changes? The first is a recommendation for starting treatment in patients with Clinically Isolated Syndromes (CIS) if accompanied by certain MR scanning changes (according to the revised McDonald criteria²). The second is a recommendation for starting treatment in both relapsing-remitting (RR) and secondary progressive MS after "one disabling relapse in the last year" (previously, two clinically significant relapses in the past two years were required). Additionally, there is also a recommendation that patients with RR disease may be started on therapy even if they have suffered no recent relapses at all, but if an MRI scan appears active.

Our concerns focus on the lack of clinical evidence of patient benefit for these treatment recommendations, and the cost implications to PCTs.

CIS Guidelines

The evidence for treatment in patients with CIS is based upon the ETOMS, CHAMPS and BENEFIT studies.^{3,5} Each trial randomised MRI-positive patients to either placebo or β -interferon at varying doses. BENEFIT acknowledges that blinding was unsuccessful (67% of patients correctly guessing they were taking the active drug); ETOMS acknowledged the surprisingly low annual relapse rate in this selected group (placebo arm 0.43 / year). These studies reported that over a 2 to 3 year period on treatment approximately 15% of patients avoided a relapse.

It is also the case, however, that 50% of these patients would not have had a relapse whether treated or not. Indeed it is well documented that patients with CIS MRI positive or negative have a reasonably good chance of not developing further clinical symptoms of MS over a 10 year period of follow up⁶ and pre-MRI natural history suggests that 1 in 5 will have no further symptoms after 25 years.⁷

These ETOMS, CHAMPS and BENEFIT data suggest that ~85% of patients starting treatment will experience no benefit (BENEFIT indicates that the "patient number needed to be treated in order to prevent one case of CDMS (ie one relapse) within the study period of 2 years is estimated to be 5.9"³). This equates to ~12 years of treatment (2190 injections at a drug cost alone of ~£90 000) to stop 1 relapse in 12 patients over a 2 year period. The other 11 patients experience no benefit – but will often experience unpleasant side effects and the accompanying 'medicalisation' that starting treatment with β -interferon entails.

In any case, the point has been well made that interferons even in responding patients do not 'prevent multiple sclerosis' "except with reference to a restricted window of time, which is clinically not a very meaningful way to think of therapy for a chronic, relapsing disease. As for delay, surely the CIS must be regarded as the onset of the disease in these patients, so there can be no delay."⁸

Longitudinal MRI studies clearly show that the disease process starts some while – months or years – before clinical neurological presentation. Therefore, to propose (as in these Guidelines) that the biologically rather arbitrary moment of the first clinical event has huge therapeutic significance is not rational. More than this, to recommend that we should treat six or seven patients immediately following this event, so as (in effect) to delay one relapse in

one patient by perhaps six months, during a 40-50 year illness, by the introduction of a treatment that appears to have no impact on long term disability, is unsustainable. Waiting a few months for the next attack in that individual, and treating her or him alone, is surely more sensible.

After all, "people with clinically isolated syndromes, just as those with multiple sclerosis, fear future disability, not a change in diagnostic label".⁹ And while we of course acknowledge the intuitive and attractive hypothetical link between early treatment and delay in long-term disability, this pre-supposes the treatment to be effective in preventing disability. Sadly, there is no clinical or trial evidence yet to support early treatment on grounds of preventing disability. ETOMS reported interferon to have no significant effect on the accumulation of disability,⁴ and the 5 year open-label extension study of the CHAMPS cohort likewise showed a lack of effect on disability.¹⁰ We eagerly await the results from the DoH risk-sharing scheme for patients treated as per the last ABN criteria – the UK is perhaps the last available place to test this essential hypothesis for CIS patients – but until evidence is in place it is surely incorrect to make new recommendations.

The ABN MS panel attempts to reduce mis-treating potentially benign patients by using serial MRI imaging. The Guidelines' Appendix outlines the suggested use of MRI in CIS patients. However, there is again no good clinical evidence to suggest that treating patients who have serial MRI changes rather than relapses will have any impact on future relapses or disability. Again, hypothetically this is an attractive idea but one that needs to be tested in a phase III study before, not after, becoming incorporated into Guidelines.

Another issue is that the McDonald MRI criteria are (appropriately, of course) very clearly defined and highly stringent. Properly interpreting brain lesions in this context requires close familiarity with and adhesion to the Tintore revision of the Barkhoff criteria. The Revised Guidelines manuscript indicates that "determination that a T2 lesion is indeed new can be challenging. A new T2 lesion must be of sufficient size and location to reflect one that could not have been missed previously for technical reasons of slice orientation, thickness or spacing, tissue contrast, patient motion, or other artifacts. This requires standardised scanning procedures with emphasis on careful repositioning, as well as input from qualified evaluators". At a practical level, we do not believe this is realistic outside (literally) one or two MRI-super-specialised units.

We believe that clinical outcomes (relapses) are more reliable and more relevant than MRI. Patients with more aggressive disease declare themselves early and receive treatment; those with quiet disease do not. This is currently established practice, and any significant alteration of this should be predicated upon clear evidence of benefit.

Single Relapse Guidelines

Many centres run relapse clinics. It is not infrequent to see a patient sustaining a relapse (often 'disabling') many years or even decades after their last event. The new criteria now recommended treatment be initiated – this despite natural history data clearly showing that the annual relapse rate on average tends to reduce over time. This raises the distinct possibility that many patients who have a very low risk of having further relapses for many years could now be started on β -interferon.

Again the rule that a significant change in practice requires an evidence base appears to have been entirely ignored.



Prof Neil J Scolding is the Burden Professor of Clinical Neurosciences at the University of Bristol. He has an interest in clinical and biological aspects of inflammatory brain disease, in particular, multiple sclerosis.



Mr Alastair Wilkins is Consultant and Senior Lecturer in Neurology at the University of Bristol, Frenchay Hospital. He has a clinical and research interest in multiple sclerosis – specifically, in the cause and prevention of axon degeneration.



Mr David Cottrell is a Consultant Neurologist and Senior Clinical Lecturer at Frenchay Hospital and the University of Bristol. He has a specialist interest in multiple sclerosis and in particular primary progressive MS.

Correspondence to:

Neil Scolding
E. n.j.scolding@bristol.ac.uk

Costs

Our last concern relates to the added burden of cost that these guidelines, if implemented, will impose. It is important to recall that these are agents not approved initially by NICE (for use in patients with a much higher annual relapse rate). Now, the ABN proposes, on the basis of no cost-efficiency data and no evidence of long term disability benefit, a substantial increase in the number of patients receiving β -interferon (in particular from the new single relapse guideline).

These added costs relate to pharmaceutical, neuroimaging and staffing and are difficult to estimate. But if one does attempt to estimate QALY values, in drug costs alone for CIS patients, assuming the average time of disability from relapse is two months, it would be in the region of £540,000. We fear that our PCTs may react to this by increasing, rather than decreasing, their stringency and vigilance concerning funding for treating MS patients as a whole. Where they do fund treatments, then it may surely be the case that, within a fixed budget, adverse consequences must result for other patients.

Summary

The more general problem we perceive is that this document lacks balance. It concentrates exclusively on 'earlier and more' interferon treatment, while failing to acknowledge less 'positive' new information. We now have, for example, a far clearer picture since the 2001 Guidelines concerning the absence of any useful impact of IFN or glatiramer on progressive disability. But no mention is made in the current Guidelines, let alone any attempt to address, the rigorous systematic meta-analysis of the pivotal studies of interferon beta in relapsing-remitting multiple sclerosis pointing out the absence of any detectable significant effect of the interferons on the accumulation of disability,¹¹ or the negative Cochrane Review of glatiramer in RR-MS concluding that there was insufficient proof of any beneficial effect on relapse rate or on disability progression¹². These surely merit attention.

We acknowledge that there is a significant discrepancy between prescribing rates in the UK (perhaps 11%) and those in the US and continental Europe (25-30%). However, to assume that this discrepancy reflects poor practice in the UK, and to generate guidelines encouraging neurologists to conform in the treatment of MS is surely a hasty conclusion. The UK has a strong ethos of practising rigorous evidence-based medicine, and this may well provide an alternative explanation for the discrepancy. If the relatively low prescribing rate is perceived as problematic, then the first step should be to gather evidence concerning the numbers of patients who meet the 2001 ABN Guidelines but who have not been offered treatment. Attempting to increase numbers of patients

treated with unproven therapies may be popular but is surely not good medicine.

In summary, we would find it difficult to improve upon a recent position statement from the Mayo Clinic Neurology team – that it is best to “avoid treating those with a greater chance of benign course ..., a low chance of benefit, ... and those with an indeterminate prognosis (e.g. CIS...)”; and that “pronouncements and guidelines based on unproven surrogates that are weakly correlated with disability and for which long-term predictive value is unknown and not helpful.”¹³

References

1. *ABN Guidelines for Treatment of Multiple Sclerosis with β -interferon and Glatiramer Acetate*, Association of British Neurologists, (2007).
2. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. *Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria"*. Ann Neurol 2005 Dec;58(6):840-6.
3. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, et al. *Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes*. Neurology 2006 Oct 10;67(7):1242-9.
4. Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O, et al. *Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study*. Lancet 2001 May 19;357(9268):1576-82.
5. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownschield CM, Murray TJ, et al. *Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis*. CHAMPS Study Group. N Engl J Med 2000 Sep 28;343(13):898-904.
6. O'Riordan JI, Thompson AJ, Kingsley D, MacManus DG, Kendall BE, Rudge P, et al. *The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up study*. Brain 1998;121:495-503.
7. Eriksson M, Andersen O, Runmarker B. *Long-term follow up of patients with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis*. Mult Scler 2003 Jun;9(3):260-74.
8. Dorfman L, Balcer LJ. *Optic Neuritis*. N Engl J Med 2006 Jul 13;355(2):212.
9. Coles A. *The curious incident of disability in multiple sclerosis trials*. Lancet Neurol 2006 Nov;5(11):899-900.
10. Kinkel RP, Kollman C, O'Connor P, Murray TJ, Simon J, Arnold D, et al. *IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event*. Neurology 2006 Mar 14;66(5):678-84.
11. Filippini G, Munari L, Incorvaia B, EBERS GC, Polman C, D'Amico R, et al. *Interferons in relapsing remitting multiple sclerosis: a systematic review*. Lancet 2003 Feb 15;361(9357):545-52.
12. Munari L, Lovati R, Boiko A. *Therapy with glatiramer acetate for multiple sclerosis*. Cochrane Database Syst Rev 2004;(1):CD004678.
13. Pittcock SJ, Weinschenker BG, Noseworthy JH, Lucchinetti CF, Keegan M, Wingerchuk DM, et al. *Not Every Patient With Multiple Sclerosis Should Be Treated at Time of Diagnosis*. Arch Neurol 2006 Apr 1;63(4):611-4.

Read ACNR free on-line

You can read every issue of ACNR free of charge by downloading PDFs from our website at www.acnr.com

Simply register by sending an email to Rachael@acnr.co.uk, and we will notify you every two months when new issues are uploaded to the site.

Do you have an idea for an article?

Are you organising an event, can we help with publicity?

Would you like to review a book, perhaps you're writing one?

Please contact

Rachael Hansford, Publisher
 ACNR (Advances in Clinical Neuroscience & Rehabilitation)
 1 The Lynch, Mere, Wiltshire, BA12 6DQ, UK
 Tel/Fax. 01747 860168, Mobile. 07989 470278
 E. Rachael@acnr.co.uk

www.acnr.com

