

Routine interferon-neutralising antibody testing in patients with relapsing-remitting multiple sclerosis

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ABSTRACT Multiple sclerosis is a leading cause of disability in young adults, with the Scottish population suffering the highest prevalence in Europe. Disease-modifying therapies, including beta-interferon (IFN- β), are increasingly used to minimise relapse frequency in the majority of patients who present with a relapsing-remitting disease pattern. Unfortunately, neutralising antibodies (NABs) may develop against IFN- β and are associated with reduced efficacy. These antibodies may be detected using a serum sample. Despite the importance of this problem, from both a patient's perspective and a wider community and economic standpoint, there is no universally agreed protocol for the use of NAB testing. Authorities variously suggest routine 'screening' testing or, conversely, testing only in specific situations. In Scotland, routine testing is seldom used. We report our experience of routine NAB testing in 105 patients (of whom 35 were NAB-positive) over two years in NHS Tayside and comment on its cost and implications.

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KEYWORDS Interferon, multiple sclerosis, neutralising antibody

DECLARATION OF INTERESTS Dr O'Riordan has been a principal investigator in clinical trials sponsored by Merck Serono, Teva and Bayer Schering. He has also been a consultant to, or lectured at meetings sponsored by, Merck Serono, Teva, Bayer Schering and Biogen Idec. NHS Tayside is currently participating in the Department of Health's Risk Sharing Scheme on Disease Modifying Therapies in Multiple Sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is a leading cause of disability in young adults in the Western world. It places an appreciable burden on the individual, as well as on families, carers and the health services. Prevalence in Scotland is high, and is thought to vary between 150 per 100,000 population in the west of Scotland to more than 250 per 100,000 in Orkney. In 80–85% of individuals with MS, the disease first presents in a relapsing-remitting pattern, with periods of neurological symptoms or disability interspersed with periods of relative normality.¹

Disease-modifying therapies (DMTs) are increasingly widely used in an effort to reduce the frequency of MS relapses in the relapsing-remitting stage of the disease. These agents act to reduce the severity and frequency of relapses by around one third.¹

Our practice is to use either beta-interferon (of which four preparations were available at the time of our study) or glatiramer acetate as first-line therapy, with natalizumab and mitoxantrone considered as potential second-line therapies for aggressive relapsing-remitting MS and relapsing-progressive MS, respectively.

Interferon therapies are, however, potentially immunogenic, and host antibodies may arise against the agent. These are known to be associated with reduced in-vivo efficacy of interferon, and are termed neutralising antibodies (NABs). Neutralising antibodies bind to the beta-interferon (IFN- β) molecule and cause disruption of the normal biological action of the drug by affecting binding to its receptor.² Antibodies against glatiramer acetate are not felt to be of clinical relevance and are not further considered here.³

There is no universally agreed standard method for NAB testing. However, in general, the first step is to screen for antibodies binding to IFN- β , generally by enzyme-linked immunosorbent assay (ELISA). A further assay, specifically for neutralising activity, is then carried out, seeking suppression of the in-vivo action of IFN- β . The most commonly used assay is the cytopathic effect assay in which the ability of IFN- β to inhibit viral replication in culture cells is measured.^{2,4}

A variable proportion of patients may become NAB-positive. Neutralising antibodies are not thought to be associated with systemic side effects; however, there is robust data to suggest that the development of NAB positivity is associated with the decreased clinical

effectiveness of IFN- β , both in decreasing relapse rate and modifying brain magnetic resonance imaging (MRI) outcomes.

Neutralising antibody positivity is by no means the only factor associated with reduced clinical efficacy of interferon, and it is not certain that NAB positivity is a causative factor. Several randomised controlled trials of interferon (including major landmark trials of both IFN- β -1B and IFN- β -1A) have, however, demonstrated a reduction in efficacy on relapses in patients who developed NAB positivity.^{5,6} In a major phase three trial of IFN- β -1B, relapse rates in NAB-positive patients were equivalent to relapse rates in those given placebo.⁶ In a prospective Danish study, NAB-positive patients were found to have a significantly shorter time to first relapse, with the proportion of patients free of relapse being significantly lower.⁷

Similarly, MRI outcomes (such as the number of inflammatory lesions seen) are adversely affected by NAB positivity, with more active MRI lesions observed in patients who are NAB-positive.^{5,6} In one study NAB-positive patients had almost five times the median number of active lesions on T2 sequences compared with NAB-negative patients.⁵

There is, however, no universal agreement on the optimal system for NAB testing and, in particular, no agreement on whether NAB testing should be carried out routinely in all patients. Suggestions made by different authorities vary. The European Federation of Neurological Sciences (EFNS) consensus guidelines (2005) recommend routine NAB testing at 12 and 24 months after starting interferon therapy, with further action dictated by titre result (in other words the strength of NAB activity).⁸ It is suggested that a high titre which is sustained at repeated testing should prompt discontinuation of interferon therapy. The Association of British Neurologists (ABN), however, stop short of such a recommendation and suggest that, in the case of clinical or radiological deterioration, positive NABs, especially if at high titre and sustained, only strengthen a case for discontinuation of interferon therapy.⁹ Thus one authority suggests routine testing of NABs in all relevant patients, and another suggests only testing when clinical or radiological deterioration occurs. Usual practice in the UK in general, and Scotland specifically, favours the latter approach, with NABs only tested in the context of a clinical deterioration.

In contrast, our practice is to routinely screen for NAB positivity in all patients receiving interferon, following a local protocol based on current EFNS guidelines. We believe that routine NAB testing is a valuable adjunct to the decision-making process when deciding on appropriate DMT for any patient on interferon. We report here our experience of two years of routine NAB testing in NHS Tayside.

METHODS

All patients receiving IFN- β between April 2007 and April 2009 were enrolled in our audit. We recorded details of patients undergoing NAB testing, the preparation of interferon received, NAB titre results, results of repeat testing (where applicable) and treatment decisions made. Patients were receiving one of four IFN- β preparations: interferon β -1B ('Betaferon', Bayer) or interferon β -1A ('Rebif 22 μ g' dosing or 'Rebif 44 μ g' dosing, both Merck-Serono, or 'Avonex', Biogen). Our experience agrees with data accrued in major clinical trials (including those comparing glatiramer acetate with Rebif and with Betaferon) in suggesting that clinical and MRI efficacy of these agents is comparable.¹⁰ When using Rebif we generally use the 22 μ g preparation initially, with local experience suggesting that the 22 μ g preparation is better tolerated by patients with, in particular, less local cutaneous reactions. None of the patients at the time of audit were prescribed new formulation Rebif, which has since become available.

All patients were attending the NHS Tayside subspecialist DMT clinic at Ninewells Hospital, Dundee. Testing was performed at 12 and 24 months after starting therapy, or at 12 and 24 months after commencement of NAB testing in patients who had already been established on therapy. Patients were made aware of testing, which was carried out as part of routine clinical care. Venous blood samples were taken in a clotted tube at the time of the patient's routine clinic review (along with other routine monitoring). Blood samples were sent to the Neuro-immunology Unit, Institute of Neurology, Queen Square, London, for analysis. This unit provides centralised NAB analysis for centres throughout the UK.

In patients with a high positive titre (>100 neutralising units) or with a positive titre at a lower level, change in treatment was considered on an individual basis.

In patients taking any IFN- β , change of therapy to copaxone, natalizumab or mitoxantrone, as well as the cessation of therapy, were considered. We also considered changing patients from one interferon preparation to another. We took into account that NABs are felt to be cross-reactive and thus changing from one IFN- β preparation to another may not avoid clinically significant reduction of efficacy related to NABs. None of the patients included in this audit commenced natalizumab ('Tysabri') monoclonal antibody therapy.

Costs of NAB testing were provided by the NHS Tayside finance department. Costs of drug therapy were provided by the neurology pharmacist. Mathematical analyses of costs and savings were carried out using Microsoft Excel.

RESULTS

A total of 105 patients were tested. In the two-year period of testing, 35 patients returned positive NAB titres on initial analysis, with a range of titres between 20 and 640 neutralising units (NU).

Patient demographics

Of the patients tested, duration of drug therapy at the time of testing was as follows:

- 1 year – 2 patients
- 2 years – 11 patients
- 3 years – 12 patients
- 4 years – 35 patients
- 5 years – 24 patients
- 6 years – 10 patients
- 7 years – 10 patients
- 9 years – 1 patient

Of the 105 patients tested, 84 had relapsing-remitting MS, and 21 had secondary progressive MS with relapses.

NAB titres

Of the 35 positive titres, 24 were at high positive levels (>100 NU, range 120–640) and 11 were at low positive levels (\leq 100 NU, range 20–100). The cut-off for defining high positive titres is generally considered to be 100 NU.⁸

Of those returning low positive titres, all were retested. Six of these reverted to negative titres (range of initial positive titre 20–100 NU). Repeat titres are awaited in one patient.

Of those patients demonstrating positive titres, very high titres (>100 NU) were not retested, and treatment was modified according to the judgement of the treating clinician. It is our experience – in keeping with other authors' findings – that in patients who manifest high titres, reversion to low titre status is uncommon.⁴

TABLE 1 Neutralising antibody test results and treatment decisions grouped by drug

	No. tested	Total NAB-positive	Of which >100 NU (% of tested)	Clinical decisions
Betaferon	28	17	10 (36)	1 changed to copaxone; 9 stopped therapy
Rebif 22	37	13	10 (27)	10 changed to copaxone
Rebif 44	8	2	1 (13)	1 changed to copaxone
Avonex	32	3	3 (9)	1 changed to copaxone; 1 changed to betaferon; 1 changed to mitoxantrone
Total	105	35	24	13 changed to copaxone; 1 changed to betaferon; 1 changed to mitoxantrone; 9 stopped therapy

Results obtained and clinical decisions made are outlined in Table 1. All low positive titres returned either low positive or negative results on repeat.

Frequency of NAB positivity at high titre

The frequency of NAB positivity at a high titre of >100 NU in our population (as a percentage of those tested) was compared with previously published rates.^{5,6,11–15} The frequency of NAB positivity previously reported varies between different studies and is affected by, among

TABLE 2 Costs of IFN therapy and NAB testing, 2007–09*

Drug	Cost per patient per year (£)	Number of patients tested	Total IFN cost per year (£)	Cost of testing per year (£)	Number changed or stopped	Financial implication per year after subtracting cost of testing (£)
Betaferon	7,231	28	202,468	3,194	10	63,317 (Net difference)
Rebif 22	7,501	37	277,537	4,221	10	12,808 (Net difference)
Rebif 44	8,931	8	71,448	912	1	2,220 (Net difference)
Avonex	8,502	32	272,064	3,650	3	8,324 (Net difference)
Total		105	823,517	11,977	24	86,669 (Net difference)

*All costs given in Pounds Sterling, 2009.

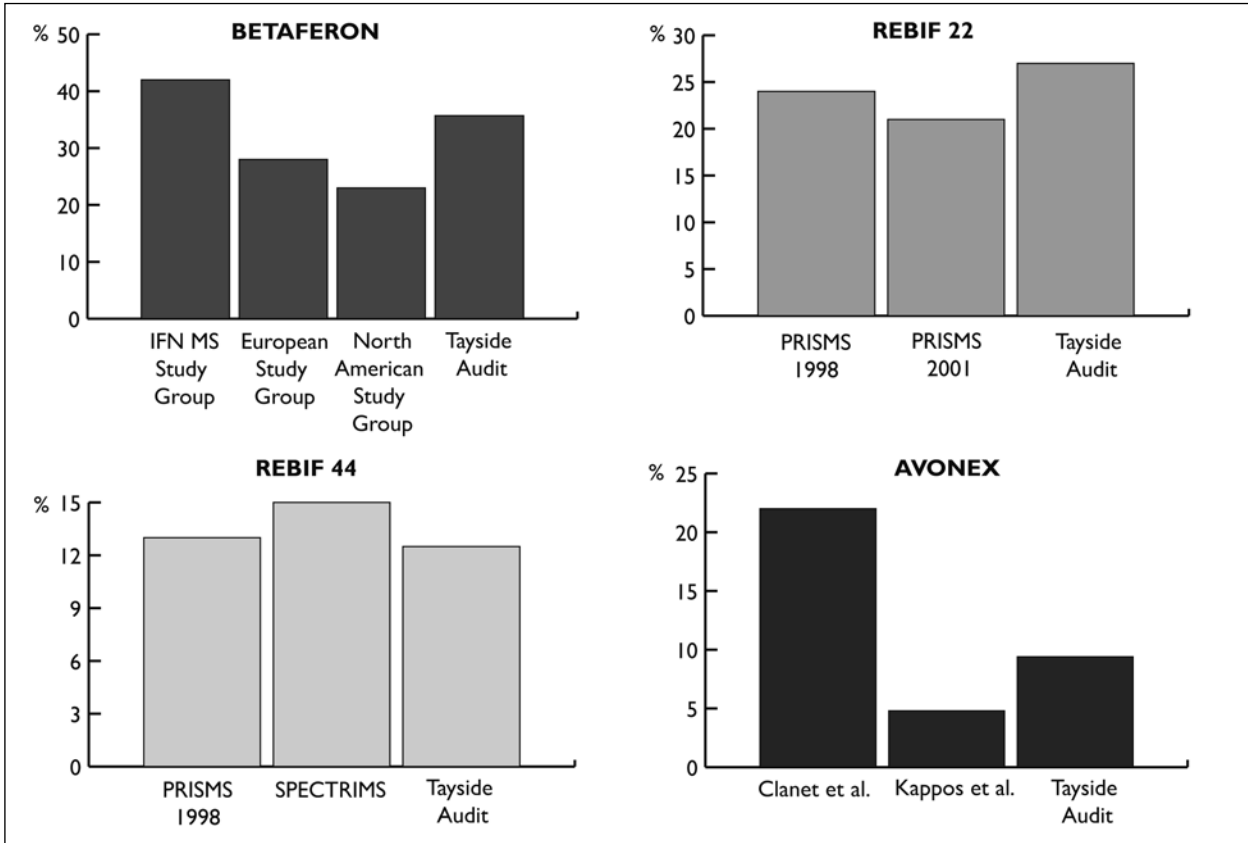


FIGURE 1 Frequency of high NAB positivity as a percentage of tests undertaken.

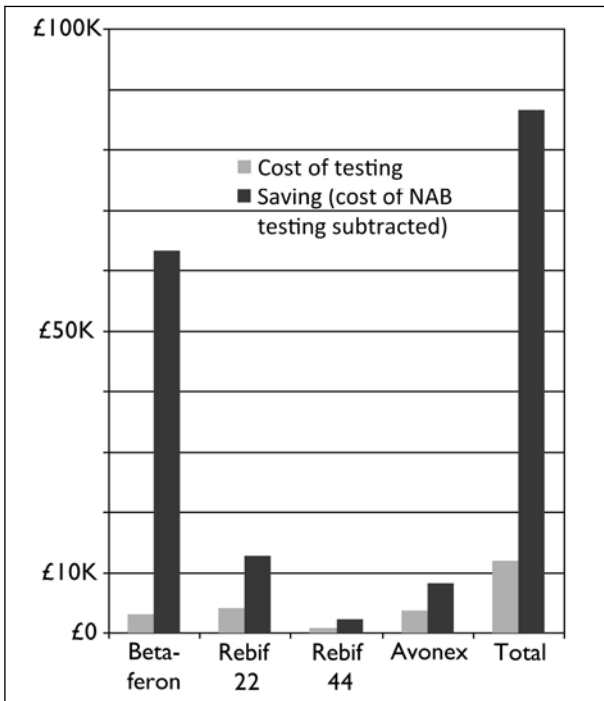


FIGURE 2 Cost of testing NAB titres compared with financial implications.

other factors, the agent itself (including any changes in formulation), the route of administration, assay (including interassay variability) and patient characteristics. Despite this, our rates of NAB positivity were comparable to those previously published (Figure 1).

Financial implications of NAB testing

Given that the direct cost of NAB testing has previously been felt to be a potential barrier to routine NAB testing, we were interested to estimate the financial implications of this approach. Financial costs of NAB testing (provided by NHS Tayside accountancy service) were £7,808 for the year April 2007–April 2008, and £4,171 for the year 2008–2009. The mean cost of testing each patient was therefore £114.09. The costs of interferon and copaxone treatment per patient year are given in Table 2.

We calculated for each drug the total cost of drug administration for all patients receiving the agent per year, the total cost of testing per year, and the number or patients in whom therapy was switched or stopped due to positive NAB titres. By comparing the cost of the previous and new agents and subtracting the cost of testing, we obtained estimated annual cost implications, which are summarised in Table 2. The net price difference per year directly compared with the cost of testing for each separate IFN drug is shown in Figure 2.

DISCUSSION

Disease-modifying therapies are becoming more frequently used in the management of MS – a disease which is a major cause of morbidity and disability in the UK in general and Scotland in particular. Beta-interferons and glatiramer acetate are used as first-line agents in an effort to decrease the frequency of MS relapses. Host NABs may arise against interferon and are associated with reduced efficacy; however, there is no universal agreement on the best strategy for testing NABs.

We feel that routine screening for NAB positivity may be a useful part of the assessment of MS patients in the UK, and can be used relatively easily with little inconvenience for the patient (particularly as blood tests are examined routinely at outpatient appointments). Weighed against this relatively minor burden is a potentially significant benefit.

Advocates of routine NAB testing suggest that, since NABs are associated with reduced biological and therapeutic activity of interferons, IFN- β should not be prescribed if NAB positivity develops.⁵ The patient may gain from this approach by avoiding unnecessary prolongation of interferon therapy and by expediting appropriate switching (or cessation) of therapy. This may confer benefits to the patient by minimising unnecessary pain and discomfort of drug therapy, minimising risk of side effects and, crucially, by ensuring that the patient is receiving the optimal therapy for his or her disease.

Possible burdens of routine NAB testing may include provoking anxiety in an otherwise stable patient if NABs are tested in the absence of clinical deterioration. Our experience has, however, been that patients are happy to proceed with routine NAB testing as long as the procedure is discussed before the time of testing.

The optimum strategy for use of NAB testing is complicated by questions including the extent of variability of NABs in a defined patient group, which may

be linked to interassay variability. Available data, however, suggest that rate of conversion from NAB-negative to NAB-positive status (or vice versa) in a selected patient is uncommon, particularly at very low or very high titres of NABs.⁴ The relative utility and reliability of differing methods of NAB estimation (for instance by measuring antiviral effect using the cytopathic effect assay, as in this study; or by measuring IFN- β -induced gene products using the myxovirus resistance protein A assay) also remain to be fully established.⁸

The expense of testing to the service concerned has been considered as a potential deterrent to routine testing.¹⁶ While, of course, we make the argument in favour of NAB testing on grounds of clinical utility and not of cost-effectiveness, our data suggest that the expense of testing should not represent a barrier to routine NAB testing. Further financial analysis is certainly warranted. The financial costs associated with routine NAB testing are, in our experience, offset by net savings attributable to appropriate changes in DMT (or cessation of therapy). Financial analysis (and in particular cost-effectiveness analysis) would further be strengthened by clinical outcome data for each patient group and quality-adjusted life-year analysis.

A strength of our study lies in demonstrating the clinical feasibility of routine NAB testing in an outpatient setting which is comparable to many in the UK. In addition, an preliminary cost analysis suggests that costs are, at the least, not prohibitive.

CONCLUSION

While further questions remain (including, for example, the use of NAB testing compared or combined with routine MRI imaging),^{17,18} we believe that routine NAB testing may be a valuable and cost-effective tool for neurology centres in the UK.

REFERENCES

- 1 Compston A, Confavreux C, Lassmann H, editors. *McAlpine's multiple sclerosis*. 4th ed. Edinburgh: Churchill Livingstone; 2006.
- 2 Farrell R, Giovannoni G. Measuring and management of anti-interferon beta antibodies in subjects with multiple sclerosis. *Mult Scler* 2007; 12:567–77. doi:10.1177/1352458506073522
- 3 Teitelbaum D, Brenner T, Abramsky O et al. Antibodies to glatiramer acetate do not interfere with its biological functions and therapeutic efficacy. *Mult Scler* 2003; 9:592–9. doi:10.1191/1352458503ms963oa
- 4 Sominanda A, Hillert J, Fogdell-Hahn A. Neutralizing antibodies against interferon beta: fluctuation is modest and titre dependent. *Eur J Neurol* 2009; 16:21–6. doi:10.1111/j.1468-1331.2008.02264.x
- 5 PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: long-term efficacy of interferon beta-1a in relapsing MS. *Neurology* 2001; 56:1628–36. Erratum in: *Neurology* 2001; 57:1146.
- 6 The IFNB Multiple Sclerosis Study Group. Interferon beta-1B is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993; 43:655–61.
- 7 Sorensen P, Ross C, Clemmensen KM et al. Clinical importance of neutralising antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. *Lancet* 2003; 362:1184–91. doi:10.1016/S0140-6736(03)14541-2
- 8 Sørensen PS, Deisenhammer F, Duda P et al. Guidelines on the use of anti-IFN-beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. *Eur J Neurol* 2005; 12:817–27. doi:10.1111/j.1468-1331.2005.01386.x
- 9 Association of British Neurologists (ABN). *ABN Guidelines for treatment of multiple sclerosis with β -interferon and glatiramer acetate*. London: ABN; 2007.

- 10 Mikol DD, Barkhof F, Chang P et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REBif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. *Lancet Neurol* 2008; 7:903–14. doi:10.1016/S1474-4422(08)70200-X
- 11 SPECTRIMS (Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS) study group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. *Neurology* 2001; 56:1496–504.
- 12 European Study Group on interferon beta-1b in secondary progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998; 352:1491–7.
- 13 The North American Study Group on interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology* 2004; 63:1788–95.
- 14 Clanet M, Kappos L, Hartung HP et al. Interferon beta 1-a in relapsing multiple sclerosis: four-year extension of the European IFN beta-1a dose-comparison study. *Mult Scler* 2004; 10:139–44. doi:10.1191/1352458504ms990oa
- 15 Kappos L, Clanet M, Sandberg-Wollheim M et al. Neutralizing antibodies and the efficacy of interferon beta-1a – a 4-year controlled study. *Neurology* 2005; 65:40–7. doi:10.1212/01.wnl.0000171747.59767.5c
- 16 Burks JS, Noronha A. Guidelines on the use of anti-IFN-B antibody measurements in multiple sclerosis: report of an EFNS Task force on IFN-B antibodies in multiple sclerosis. *Eur J Neurol* 2007; 14:e8–9. doi:10.1111/j.1468-1331.2007.01782.x
- 17 Durelli L, Barbero P, Bergui M. MRI activity and neutralising antibodies as predictors of response to interferon beta treatment in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2008; 79:646–51. doi:10.1136/jnnp.2007.130229
- 18 Deisenhammer F. Neutralizing antibodies to interferon-beta and other immunological treatments for multiple sclerosis: prevalence and impact on outcomes. *CNS Drugs* 2009; 23:379–96. doi:10.2165/00023210-200923050-00003

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