Neutralising antibodies to interferon β during the treatment of multiple sclerosis

Giovannoni and colleagues are to be commended for their detailed analysis of the impact of neutralising antibodies (NAB) to interferon β (IFNβ) during the treatment of multiple sclerosis. We are in general agreement with many of their statements and conclusions, but a few points should be discussed in a wider context.

With respect to the clinical significance of neutralising antibodies to IFNβ, the authors state that “IFNβ has little if any clinical and MRI efficacy in the presence of neutralising antibodies.” We think it is appropriate to be more circumspect, as most published studies suggest that in NAB positive patients, clinical (and MRI) efficacy of interferon treatment is present when compared to placebo, and that there is some evidence that more immunogenic higher dose treatment can be more effective than less immunogenic lower dose treatment. Giovannoni et al appear to base their statement on the increase in T2 burden of disease in the NAB positive group in the PRISMS extension study, but they do not mention similar comparisons which, if interpreted in the same way, would indicate that the NAB positive group does better than the placebo group. For example, the relapse rate in placebo patients was 1.3/year in years one to two, whereas it was 0.81 and 0.50 in NAB positive and NAB negative high dose patients in years three to four. We recognise that this specific comparison is fraught with difficulties owing to time trends in the relapse data, but these potential difficulties are present in all such comparisons. In a recent paper we report—in probably the largest study of neutralising antibodies in multiple sclerosis—describing 100 NAB positive patients in the European SPMS study—that high titres of neutralising antibodies do have a clinical impact, but that this impact is rather limited, and that on both clinical and MRI measures patients on active treatment who develop neutralising antibodies continue to do consistently better than those on placebo. The main conclusions of this paper are based on longitudinal analyses of the data on those patients who switched from NAB negative to NAB positive status; this is the only statistical approach that allows a direct assessment of whether the change from NAB negative to NAB positive status is associated with diminished efficacy of a treatment. Cross sectional comparisons are not fully reliable for establishing the impact of neutralising antibody positivity, as NAB positive and negative subgroups may differ on baseline variables (maybe unobserved) that are predictive of both neutralising antibody formation and diminished clinical response.

Giovannoni et al also state that during continued treatment “in the case of IFNβ-1b some NAB positive patients revert to NAB negative status over two to five years of follow up” and that “patients with high titres of neutralising antibodies seldom revert to being negative.” In the European study of IFNβ-1b in secondary progressive multiple sclerosis the proportion of treated patients who have been NAB positive and subsequently revert back to being NAB negative is about 40% after a treatment duration up to three years (without convincing evidence that patients with higher titres revert less frequently), whereas in the study by Rice et al this percentage is close to 80% after a mean treatment duration of more than eight years.

In our opinion, these data suggest that the clinical impact of neutralising antibodies to IFNβ during the treatment of multiple sclerosis may be more limited and more transient than suggested in the editorial, and that the development of neutralising antibodies in itself does not provide justification for switching treatments or for considering (aggressive) strategies to reduce or revert the development of neutralising antibodies. Given the current rather uncertain state of knowledge concerning the impact of neutralising antibodies, we advocate that treatment decisions should be based on clinical grounds rather than on neutralising antibody titres.

Neutralising antibodies to interferon β

I read the editorial by Dr G Giovannoni and colleagues’ with great interest. I have, however, to report a minor error concerning the list of the excipients of the Rebif reported in their table 1. In the table the authors reported the following excipients: mannitol, HSA, sodium acetate, acetic acid, sodium chloride. Actually, as you can check in the summary of product characteristics published from EMEA (www.emea.eu.int) on 29 March 1999, in the list of excipients sodium chloride is absent, whereas sodium hydroxide is present.

C Ortenzi
Department of Molecular, Cellular and Animal Biology, University of Camerino, 62032 Camerino, Italy; claudio.ortenzi@tin.it

Authors’ reply

We would like to thank Dr Ortenzi for pointing out our transcription error in relation to the excipients of Rebif® in table 1 of our editorial.

We agree with Polman and colleagues that recent comparisons show that the more immunogenic higher dose interferon β (IFNβ) preparations are more efficacious than the lower dose less immunogenic preparations over 24 month1 and six month2 periods of observation. However, as discussed in our editorial, the development of neutralising antibodies and their effects on the clinical efficacy of IFNβ are delayed. In the PRISMS study the effect of neutralising antibodies on clinical efficacy only became apparent after years 3–4.3 In the pivotal IFNβ-1b study an effect on relapse rate was only observed in the 19–24 and 25–30 month epochs.4 Hence we would argue that these comparative studies1 are simply too short, and in the case of the INCOMIN trial underpowered (n = 188),4 to demonstrate an effect of neutralising antibodies on clinical efficacy. It is therefore impossible to extrapolate the significant short term difference shown in these studies beyond the periods of observation reported.

Because of regression to mean and the well documented tendency for the relapse rate to decrease with disease duration, it is not possible to draw any meaningful conclusions from a comparison of the relapse rate in years 1–2 and years 3–4 from the PRISMS extension study.4 In addition to the impact of neutralising antibodies on relapse rate, the PRISMS extension study clearly shows—the more objective T2 lesion volume or burden of disease—that the average annualised increase in lesion volume over four years in the neutralising antibody positive (NAB+) patients is similar to the increase in the annualised lesion volume in the placebo treated patients in the first two years of the study (NAB+ 4.4% v placebo 5.4%).5 Similarly, in the IFNβ-1b study5 the annualised relapse rate of NAB+ patients is identical to patients on placebo (1.08 v 1.06). In the IFNβ-1a (Avonex®) trial,6 the impact of neutralising antibodies was limited to MRI outcomes. The failure of neutralising antibodies to have an effect on disease progression and relapse rate in this study probably reflects the size and duration of follow up, as the study was terminated prematurely. It is these data from the pivotal relapsing multiple sclerosis clinical
trials, and other studies on in vivo markers of IFNB activity discussed in our editorial, that we use to support our statement that “interferon β has little if any clinical and MRI efficacy in the presence of neutralising antibodies.”

Data on the impact of neutralising antibodies in secondary progressive multiple sclerosis (SPMS) trials is less clear. This is to be expected, however, as the efficacy of IFNB on disease progression—the primary outcome measure in SPMS trials—is limited and hence it would be difficult to demonstrate a significant impact on neutralising antibodies on the primary outcome measure when the actual therapeutic intervention itself is only marginally effective. It would be very surprising if neutralising antibodies had a significant impact on disease progression, as none of the trials is powered to detect an effect of neutralising antibodies on this outcome. For example, in the European SPMS study, 100/360 (28%) of IFNB-1b treated patients became NAB+ (titre > 20) over the course of the trial.24 This is not a conservative approach by applying the results from the trial,20 and assuming that NAB+ patients behave like those on placebo and NAB− patients behave like the IFNB-1b-treated cohort, one would expect 49.8% of the 100 NAB+ patients to progress over three years, compared with 38.9% of the 260 NAB− patients. At the same level of significance (0.029) from the original study, it would only have a 35% chance of detecting a significant difference between NAB+ and NAB− patients (Fishier’s exact test). Compare this to a power of 80% used in the design of the original study. This power calculation is an overestimate as it ignores the therapeutic effect observed before the development of neutralising antibodies, as evidenced in this study,25 which if taken into account would seem reasonable if there are no carryover therapeutic effects of IFNB-1b treatment from the NAB− to NAB+ phase and if the follow up in the NAB+ phase is of sufficient duration to account for the delayed effects (24 to 48 months) of neutralising antibodies on clinical efficacy. In this study the mean follow up in the NAB+ phase would be on average too short (less than 24 months) for one to be confident of excluding a delayed effect of neutralising antibodies on disease progression.

Despite the lack of power of these subanalyses, they produce some surprising results. In the cross sectional study there was a trend towards greater disease activity in patients in the NAB+ group in the third year, and a significant percentage T2 volume change from baseline to year 1, year 2, and the last visit21; in the underpowered and potentially flawed longitudinal analysis there was no indication of an attenuation of treatment effects on disability progression but, surprisingly considering the lower relapse rate in secondary progressive multiple sclerosis there was a robust effect on relapse rate.26

Another way of interpreting the European SPMS NAB data as presented by Polman and colleagues is that the much higher dose of IFNB-1b (875 µg/week) given in that study, in comparison with the lower licensed doses of IFNB-1a (30–132 µg/week), acted to quench some of the neutralising activity of the antibodies. Similarly, the higher doses may be responsible for inducing high dose tolerance in a subset of the patients. These phenomena are well observed with other biologicals in which the read-outs are more objective than in multiple sclerosis—for example, coagulation in anti-factor VIII and glucose levels in anti-insulin antibody positive patients.

Polman and colleagues have misinterpreted our recommendations. We do not recommend routine screening of neutralising antibodies at present, nor the switching of treatments in NAB+ patients unless clinically justified, nor aggressive strategies to reduce or reverse the development of neutralising antibodies. We simply state that further research is necessary to assess whether these strategies are appropriate. Polman and colleagues’ concluding statement that treatment decisions should be based on clinical grounds rather than on neutralising antibody titres is entirely in keeping with our recommendations.

We disagree with Polman and colleagues’ statement that “the clinical impact of neutralising antibodies to interferon β during treatment of multiple sclerosis may be more limited and neutralisation titres are suggested in the editorial.” Short to intermediate term data (< 4 years) from the relapsing multiple sclerosis studies discussed above do not support this claim, and long term clinical data (> 4 years) on the effects of transient neutralising antibodies on the therapeutic efficacy of IFNB-1b do not exist to support the latter half of their claim. In addition, evidence is needed to support whether or not the phenomenon of transient high titre neutralising antibodies occurs to a similar degree in patients treated with IFNB-1a; therefore the latter half of their statement, if true, may not be applicable to patients treated with IFNB-1a.

In conclusion, clinicians cannot ignore the issue of neutralising antibodies, particularly in view of the evidence from other fields of medicine in which neutralising antibodies reduce or inhibit the efficacy of a wide range of biologicals, including type I interferons. Why should interferon treatment in multiple sclerosis be any different?

G Giovannoni
Department of Neuroimmunology, Institute of Neurology, Queen Square, London WC1N 3BG, UK

F Deisenhammer
Department of Neurology, University of Innsbruck, Innsbruck, Austria

F E Munschauer
William C Baird Multiple Sclerosis Research Center, State University of New York, Buffalo, USA

Correspondence to: Dr Gavin Giovannoni; g.giovannoni@ion.ucl.ac.uk

References

A 1908 systematic review of the laterality of hysterical hemiplgia

Since the publication of our systematic review of the laterality of functional or medically unexplained weakness and sensory disturbance (1965–2000) we have come across a study from 1908 with a similar interest. Ernest Jones, later an eminent figure in the psychoanalytic movement, published his paper in French while working as an assistant physician at the London School of Medicine. He reported on the cumulative analysis of 277 cases of hysterical hemiplgia described by 146 authors in 164 articles published between 1880 and 1908. Most of this material is in French and German and includes cases mentioned in doctoral theses and books.

There was no excess of left sided hemiplegia compared with right in hysteria in his analysis—54% had paralysis on the right side and 46% on the left. This was contrary to the prevailing opinion of the time1 and also disagrees with another less systematic review of older studies (covering 100 subjects, 13 publications and 6 authors between 1885–1937). Jones’ conclusions—that the laterality of hysterical hemiplgia has no diagnostic value—were the same as ours. His study has not been cited for at least 40 years (and probably much longer even than that). It has been neglected, like many other negative studies before and since, but it deserves recognition on this subject.

J Stone, C Warlow
Division of Clinical Neurosciences, School of Molecular and Clinical Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XR, UK
Resolution of psychiatric symptoms secondary to herpes simplex encephalitis

We read with interest the editorial by Kennedy et al.,
detailing the short-term treat-
ment of herpes simplex encephalitis (HSE). We agree with the authors that we cannot overemphasise the seriousness of the neu-
ropsychiatric symptoms that a number of these patients display in the long term.

We report a 55 year old woman who was diagnosed with HSE; diagnosis was con-
firmed with a positive PCR test for herpes simplex in the CSF and acyclovir was started the following day after presentation. After a few weeks the patient's recovery was almost complete and she was discharged home. Six months later, there was an abrupt change when the patient developed insomnia and would sit up all night watching children's videos; she also became hostile and confused. She was admitted to a psychiatric unit where she continued to be confused and agitated with episodes of extreme behaviour such as undressing or trying to attack staff.

MRI showed appearances consistent with severe encephalomalacia of the right temporal lobe with evidence of gliosis in the frontal and temporal lobes consistent with previous HSE. It was surprising that the EEG tracing was normal with no focal or epileptiform features.

The patient remained in the psychiatric unit for seven months during which time she failed to respond to different antipsychotic medications and she was heavily sedated. The patient reached a dose of 400 mg twice daily of bamazepine, which was started after his EEG showed seizure activity detected in temporal structures. Despite the absence of any EEG abnormalities in our case, it showed a similar favourable response to carbamazepine. We feel that any patient with prominent behav-

Our patient was an 18 year old boy who presented with violent outbursts. He was admitted to a psychiatric unit for seven months during which time he showed dramatic improvement in his psychiatric symptoms. He was moved to the psychiatric unit for further deterioration or relapse is uncommon.2 In our case the comparatively long period between recovery and onset of behavioural and psychiatric symptoms seemed to cast doubt about the association with the HSE and uncertainty regarding the appropriate treatment.

Vallini et al reported successful treatment of a HSE patient presenting with severe emo-
tional liability and explosive emotional outbursts.3 The patient responded to car-
bamazepine, which was started after his EEG showed seizure activity detected in temporal structures. Despite the absence of any EEG abnormalities in our case, it showed a similar favourable response to carbamazepine. We feel that any patient with prominent behavioural or psychiatric symptoms after HSE should have a therapeutic trial of car-
bamazepine, even in the absence of any clini-
cal or neurophysiological evidence of seizure activity.

References

Radiofrequency neurotomv

In reading the study by Govind and colleagues,1 in which they report the findings of an unblinded, uncontrolled, non-randomised trial of radiofrequency neu-
rotomy for the treatment of third occipital headache, we are surprised that the authors advocate this therapy.

The last statement of the abstract is: “No other form of treatment has been validated for this common form of headache”. This implies that Govind et al believe they have validated radiofrequency neurotomv for the treat-
ment of third occipital headache. Presumably they are prepared, given the apparently impressive numbers of respondents, to forego the usual practice of placebo controlled trial. We do not understand how the authors can expect this treatment to be realistically adopted in clinical practice with no attempt to validate it the way treatments are meant to be validated, through randomised, placebo con-
trolled trials. The statement in their final paragraph that “some practitioners may be averse to implementing a treatment that requires repetition” could perhaps more ap-
propriately state that “some practitioners may be averse to implementing a treatment that remains unvalidated”.

The authors state that one reason they did not do a placebo controlled study is that a previous study has already validated this technique in other patients.2 That a single trial of radiofrequency neurotomv in 24 so-called “whiplash patients” is sufficient basis for the current authors to abandon validation with a traditional method seems absurd, especially when closer inspection of that trial leaves it in a less positive light.3 We do not accept an argument that it was impossible to blind these subjects. It would be entirely reasonable to see just how often a placebo procedure alone indeed

References
we are aware that others are undertaking a prevalence estimate, being best described as an unusual, highly select, and heterogeneous group of subjects. It is of note that, in regard to validated therapies for whiplash patients, the current study would have been rejected by the criteria of the Quebec Task Force on Whiplash Associated Disorders. We suggest that an invasive procedure should not be advocated until it has been subjected to proper study. Fortunately, we are aware that others are undertaking a properly controlled trial of this form of therapy.

References

Authors’ reply

Our study reported an audit of outcomes for a treatment of a condition for which there is no other treatment available. It showed what proportion of patients obtained complete relief of pain, and for how long. We wish to adopt this treatment for their patients can do so. If not, they should explain to their patients that they, personally, cannot offer a better treatment for third occipital headache, we will adopt it. In the meantime we feel it would be dishonest of us to tell our patients there is nothing we can do for you.

N Bogduk, J Govind, W King
Royal Newcastle Hospital, Australia

Reference

CORRECTIONS

In the neurological picture of the June issue (Komotor JR, Clatterbuck RE. Coccidiodymomyces of the brain, mimicking en plaque meningioma. J Neurol Neurosurg Psychiatry 2003; 74:806) the initials of the first author were reversed; his name should read as Komotor RJ.


The ordering of the authors in the letter by De Tiège, Laureys, Goldman, et al in the July issue (Regional cerebral glucose metabolism inakinetic catatonia and after remission. J Neurol Neurosurg Psychiatry 2003; 74:1003-4) is incorrect, it should read as follows: X De Tiège, JC Bier, I Massat, S Laureys, F Lotstra, J Berré, J Mendlewicz, S Goldman.

In the June issue of JNPP fig 1 of the paper by Cagli S, Oktar N, Dalbasti T, et al (Failure to detect Chlamydia pneumoniae DNA in cerebral aneurysmal sac tissue with two different polymerase chain reaction methods. J Neurol Neurosurg Psychiatry 2003; 74:756-9) was incorrect. The following figure is the correct image that should have been published.