PostScript

CORRESPONDENCE

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.[1] 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.[2] 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.[3] 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.[4] 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.[4 5]

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.

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Neutralising antibodies to interferon β

I read the editorial by Dr G Giovannoni and colleagues[1] 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.

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1 **Giovannoni G**, Munschauer FE, Deisenhammer F. Neutralising antibodies to interferon β during treatment of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2002;**73**:465–9.

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.[1]

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 month[2] and six month[3] 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 in years 3–4.[4] In the pivotal IFNβ-1b study an effect on relapse rate was only observed in the 19–24 and 25–30 month epochs.[5] Hence we would argue that these comparative studies[2 3] are simply too short, and in the case of the INCOMIN trial underpowered (n = 188),[2] to demonstrate an effect of neutralising antibodies on clinical efficacy. It is therefore impossible to extrapolate the significant short term differences 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 6] In addition to the impact of neutralising antibodies on relapse rate, the PRISMS extension study clearly shows—using 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 5.45%).[4 6] Similarly, in the IFNβ-1b study,[5] the annualised relapse rate of NAB+ patients is identical to patients on placebo (1.08 *v* 1.06). In the IFNβ-1a (Avonex®) trial,[7] 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 u, 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 IFNβ 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 IFNβ 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.[8 9] 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 IFNβ-1b treated patients became NAB+ (titre > 20) over the course of the trial.[10] Taking a conservative approach by applying the results from the trial,[8 10] and assuming that NAB+ patients behave as if they are on placebo and NAB– patients behave like the original IFNβ-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, a two sided test would only have a 35% chance of detecting a significant difference between NAB+ and NAB– patients (Fisher'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,[10] which if taken into account has the potential to further reduce the power of the subanalysis. Polman and colleagues further reduce the power of the subanalysis by limiting the longitudinal study to "switchers"—that is, clinical responses are compared within individual patients during NAB– and NAB+ periods.[10] This longitudinal approach reduces the number of patients available for analysis and potentially shortens the period of observation. A longitudinal approach would seem reasonable if there are no carryover therapeutic effects of IFNβ-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 the NAB+ group in the third year, and a significant percentage T2 volume change from baseline to year 1, year 2, and the last visit[10]; 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.[10]

Another way of interpreting the European SPMS NAB data as presented by Polman and colleagues is that the much higher dose of IFNβ-1b (875 μg/week) given in that study, in comparison with the lower licensed doses of IFNβ-1a (30–132 μg/week), acted to quench some of the neutralising activity of the antibodies.[10] 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.[1] 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.[1] 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.[1]

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 more transient than suggested in the editorial." Short to intermediate term data (< 4 years) from the relapsing multiple sclerosis studies discussed above[4 5 7] do not support this claim, and long term clinical data (> 4 years) on the effects of transient neutralising antibodies on the therapeutic efficacy of IFNβ-1b do not exist to support the latter half of their claim. In addition, evidence is yet to surface on whether or not the phenomenon of transient high titre neutralising antibodies occurs to a similar degree in patients treated with IFNβ-1a; therefore the latter half of their statement, if true, may not be applicable to patients treated with IFNβ-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?

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A 1908 systematic review of the laterality of hysterical hemiplegia

Since the publication of our systematic review of the laterality of functional or medically unexplained weakness and sensory disturbance (1965–2000)[1] we have come across a study from 1908 with a similar aim.

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.[2] He reported on the cumulative analysis of 277 cases of hysterical hemiplegia 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 time[3 4] and also disagrees with another less systematic review of older studies (covering 100 subjects, 13 publications and 6 authors between 1885–1937).[5]

Jones' conclusions—that the laterality of hysterical hemiplegia 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.

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Resolution of psychiatric symptoms secondary to herpes simplex encephalitis

We read with interest the editorial by Kennedy *et al*,[1] detailing the short-term treatment of herpes simplex encephalitis (HSE). We agree with the authors that we cannot overemphasise the seriousness of the neuropsychiatric 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 confirmed 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 nursing staff reported that the patient was generally confused but there were distinctive episodes where the patient would stare and then display abusive and disruptive behaviour for periods of up to an hour once or twice a day. Carbamezepine was started and when the patient reached a dose of 400 mg twice daily these episodes ceased completely and the patient's behaviour showed dramatic improvement. She continued to have mild cognitive impairment affecting mainly short-term memory.

Psychiatric problems after HSE are not uncommon; Hokkanen *et al* found that psychiatric problems are the main cause of long term disability in these patients.[2] Despite the fact that clinical relapse of HSE is well documented,[3] cognitive and psychiatric problems are usually already in place in the acute stage and 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 emotional liability and explosive emotional outbursts.[4] The patient responded to carbamezepine, 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 carbamezepine. We feel that any patient with intermittent behavioural or psychiatric symptoms after HSE should have a therapeutic trial of carbamazepine, even in the absence of any clinical or neurophysiological evidence of seizure activity.

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Authors' reply

Gaber and Eshiett report an interesting case of carbamazepine responsive neuropsychiatric syndrome after herpes simplex encephalitis (HSE). Neuropsychiatric symptoms after HSE are well recognised.[1] The frontotemporal and limbic lesions in HSE are particularly likely to cause behavioural and psychiatric symptoms. Retrospective studies have previously implicated HSE in the delayed syndromes of violent psychoses[2] and major depression.[3] However, psychiatric disorders are also common after non-herpes virus encephalitis. Hunter and others had emphasised the importance of considering encephalitic antecedents, even if clinically unapparent, in the differential diagnosis of psychiatric patients.[4] Long term follow up data from the National Childhood Encephalopathy study have shown more recently that 20% of the affected children developed epilepsy and a similar proportion had behavioural problems, hyperactivity or unsociable behaviour.[5]

Besides being a first line antiepileptic, carbamazepine is also recognised to possess considerable therapeutic value in certain psychoses and is an effective long term treatment for bipolar disorder in some cases.[6] Carbamazepine responsiveness in this particular case may not, therefore, imply that the psychiatric symptoms were epileptic in origin. However, EEG signatures of epilepsy are often absent interictally, and the presence of psychoses is known to normalise EEG changes ("forced normalisation") in epilepsy patients.[7] In this particular case, we certainly concur with the authors' use of carbamazepine and were delighted to learn of the favourable response.

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Radiofrequency neurotomy

In reading the study by Govind and colleagues,[1] in which they report the findings of an unblinded, uncontrolled, non-randomised trial of radiofrequency neurotomy 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 neurotomy as a form of treatment of third occipital headache. Presumably they are prepared, given the apparently impressive numbers of responders, 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 controlled trials. The statement in their final paragraph that "some practitioners may be averse to implementing a treatment that requires repetition" could perhaps more appropriately 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 neurotomy in 24 so-called "whiplash patients" is sufficient basis for the current authors to abandon validation with traditional methods seems absurd, especially when closer inspection of that trial lays 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 *does* indeed

"fool" the patient. Govind *et al* seem to have already decided that this is not possible, a convenient assumption.

Further, we are concerned that Govind *et al* state categorically that "among patients with whiplash injuries, third occipital headache is common". The study group from which they determine this prevalence has been reviewed elsewhere, and is wholly inappropriate for a prevalence estimate, being best described as an unusual, highly select, and heterogeneous group of subjects.[3]

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.[4] 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.

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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. Readers who wish to adopt this treatment for their patients can do so. If not, they should explain to their patients that they, personally, cannot offer them any treatment that is known to work; but they should not claim that there is no treatment. Our study shows that there is an option.

A placebo controlled trial would not prove that this treatment does not work. The outcomes should be the same as the benchmark established by our study, unless the operators perform the procedure poorly. A placebo controlled study could only show that all or part of the outcome is attributable to non-specific effects.

We consider this to be an unlikely outcome for we have never encountered in any of our own studies, nor in the literature, results showing that 86% of patients obtain complete relief of spinal pain following a sham procedure. Radiofrequency neurotomy has been shown to be associated with placebo responses in only a small proportion of patients, and for a limited duration.[1] They claim that responses to third occipital neurotomy is only a conjecture. In principle it is worthy of testing, but in practice it cannot be tested.

The precepts of informed consent require that participants in a randomised controlled be informed of all the consequences and potential complications of a procedure. Numbness in the territory of the third occipital is an unavoidable side effect of third occipital neurotomy. It is a sign that the target nerve has been coagulated. It is an essential requirement for the procedure to work. The numbness lasts as long as the pain relief lasts. In a double blind trial this side effect cannot be masked. Therefore, patients who underwent a sham procedure would automatically know that they did not have the real treatment. Thereby the patients would be unblinded. Any placebo controlled trial which suffered unblinding would be fatally flawed and, therefore, unacceptable.

Any study that used a control short of a sham procedure would also be flawed, and would not escape criticism. Pundits would argue that patients would recognise that simply blocking the nerve, or simply inserting the electrode without mimicking the two hour procedure assiduously, is an obvious sham, and that any patient so treated would exhibit a nocebo effect.

For these reasons we did not venture to conduct a placebo controlled trial. If Dr Kwan and Dr Friel can show that a sham procedure on the third occipital nerve succeeds in achieving complete relief of pain in 86% of their patients we will gladly convert to their sham procedure.

We recognise it as a pity that our study would not be accepted by systematic reviews; but that is a problem for those who rely on reviews as the only source of evidence. In that regard we stand in good company. Were we to rely only on systematic reviews, radiofrequency neurotomy for trigeminal neuralgia would not be an accepted treatment; nor would we be allowed to perform appendicectomies.

While others are satisfied to deny care to patients while they engage in purist debates about levels of evidence, we are rewarded with patients grateful for the relief that they obtain, and who report: "you must repeat the procedure because I am never going back to suffering headaches again". If someone devises 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.

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1 **Lord SM**, Barnsley L, Wallis BM, *et al*. Percutaneous radio-frequency neurotomy for chronic cervical zygapophysial joint pain. *N Engl J Med* 1998;**335**:1721–6.

CORRECTIONS

In the neurological picture of the June issue (Komotar JR, Clatterbuck RE. Coccidiomycosis 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 Komotar RJ.

The ordering of the authors in the letter by Soragna D, Tupler R, Ratti *et al* in the June issue (An Italian family affected by Nasu-Hakola disease with a novel genetic mutation in the TREM2 gene. *J Neurol Neurosurg Psychiatry* 2003;**74**:825–6) is incorrect, it should be as follows: D Soragna, L Papi, MT Ratti, R Sestini, R Tupler, L Montalbetti.

The ordering of the authors in the letter by De Tiège, Laureys, Goldman, *et al* in the July issue (Regional cerebral glucose metabolism in akinetic 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 JNNP 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.

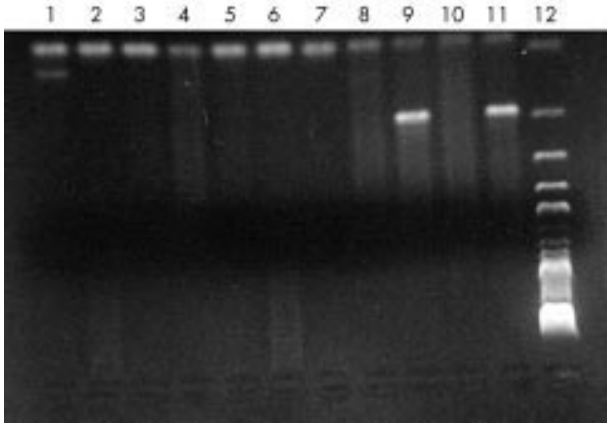

Figure 1 *C pneumoniae* TETR PCR of clinical samples. Lanes 1 to 3, 5 to 7 clinical samples. Lanes 4 and 8 negative control (water). Lanes 9 and 11 positive control (C pneumoniae 4×10^{-1} and 4×10^{-2} CFU). Lane 10 water. Lane 12 DNA molecular weight marker (XIV; 100 bp ladder, Roche Diagnostics). (Correction to *J Neuro Neurosurg Psychiatry* 2003;**74**:756–9.)