LETTER TO THE EDITOR

Guidelines on use of anti-IFN-B antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-B antibodies in multiple sclerosis

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Neutralizing antibodies letter

We applaud the efforts of the European Federation of Neurological Society (EFNS) committee to help provide guidance in the neutralizing antibody issues with interferons [1]. However, their consensus-based recommendation for mass neutralizing antibodies (NAb) screenings (at least twice) for each interferon treated patient is questionable on both scientific and economic grounds. The considerable confusing and conflicting clinical data on NAb effects have not been resolved. The committee focused much of their attention on data that supported their opinion, whilst minimizing data that conflicted with their opinions. They even misstated some relevant data, which did not support their opinion.

In addition to the scientific issues, the cost of multiple tests of (potentially) hundreds of thousands of interferon treated patients worldwide might be enormous. Their vague guidelines for additional NAb testing after 2 years [if increased multiple sclerosis (MS) disease activity] might include a minor relapse, vague new symptoms, or a single new magnetic resonance imaging (MRI) lesion, which would further increase the number of NAb tests.

The committee opined that high titered (1:100), persistent NAbs (positive NAbs on two consecutive tests) are causing current or will cause future suboptimal treatment responses (SORs).

They lumped the NAb data from all interferons. Are all NAb titers the same? Much of the current data indicates differences in frequency, persistence, and titer amongst the various interferons NAbs. For example, does a NAb titer of 1:100 for Betaferon have the same clinical relevance as the same titer for Rebif or Avonex?

They also lumped data 'trends' ($P > 0.05$) with scientific data ($P < 0.05$). For example, Table 4 lists 24 outcomes, where statistical significance had been measured related to NAbs. Of these 24 outcomes, 14 were not statistically significant. Only four outcomes had $P < 0.05$ and only six outcomes had $P < 0.01$. In other words, $< 50\%$ of the outcomes they relied upon showed a statistical impact of NAbs on clinical or MRI activities. In fact, some of the data 'trends' contradicted the committee's opinion. For example, the committee misstated that NAbs had a deleterious effect on disability progression in the Betaferon pivotal trial. In fact, the data showed a positive trend ($P = 0.08$). This paucity of statistically significant outcomes and conflicting data does not support mass NAb testing at this time.

We agree with the committee that considerable NAb data indicates an association of NAbs with increased clinical activity, especially on the MRI. However, Cutter [2] and Petkau and White [3], in separate articles have emphasized that 'associations' of NAbs to clinical parameters do not necessarily mean 'causation'.

What is the magnitude of the NAb issue? What percent of interferon patients are at risk for high titered, persistent NAbs that cause SORs? These risks have not been identified using their recommended NAb test, which has only Class IV data for validation.

What is the magnitude of the NAb issue for the specific interferons? Avonex was reformulated several years ago with the resulting reduction of risk of NAbs from 22% to $< 5\%$ at a 1:20 titer (not 1:100). We suggest the Avonex patients' risk for high titered, persistent NAbs on consecutive tests is inconsequential. Why test Avonex patients?

Rebif, which currently may have the highest risk for persistent, high titered NAbs, has recently been reformulated. The 48-week NAb titers of the reformulated drug at 1:20 (not 1:100) show a decrease in titer and frequency compared with the EVIDENCE Trial Rebif data (Rebif vs. Avonex Trial). NAb data at 18 and 24-month are still awaited but may help better define the prevalence of NAbs to the reformulated Rebif.

Betaferon has the highest percentage of patients with NAbs from many, but not all, data sets (Sorensen). The alleged 'culprit' for SORs is high titered, persistence NAbs, but most Betaferon patients have low titered NAbs that are often transient. For example, Rice *et al.* [4] showed a reversion of NAbs to $< 10\%$ of patients after 8 years of Betaferon therapy. Polman *et al.* [5] showed a substantial reversion of NAbs from positive to negative in patients in the secondary progressive multiple sclerosis (SPMS) Betaferon Trial. Using the committee recommended 1:100 titer on two consecutive tests, the percentage of positive patients will undoubtedly be even lower. Hillert *et al.* [6] reported at the American Academy of Neurology (AAN) (2005) that only 9% of Betaferon patients had high titers of NAbs . Further, Hurwitz and Polman [7] reported that only 7% of patients with increased clinical activity (SORs?) on Betaferon had high titers of NAbs (1:400). These data indicate that SORs are related to other factors in most Betaferon patients. These data also suggest that NAbs may be less prevalent in SORs than the general Betaferon treated population [8].

In spite of these unresolved inconsistencies, the committee recommended a change in therapy, if high titered NAbs persist, even if patients are clinically stable. Presumably, they hypothesize that NAbs will eventually cause SORs. If true, how long will it take to see the clinical effects of NAbs? Barbero *et al.* [9] showed that switching from a high-dose Betaferon to a low dose, but still active, interferon β-1a (Avonex) resulted in increased clinical disease activity within 1 year. Presumably, the clinical effects of NAbs, if they were to destroy the action of an interferon, would be seen sooner. Therefore, why not utilize the clinical neurological evaluation every 6 months to determine SORs? A thorough neurological evaluation, with the judicious use of MRI's, may be a less expensive option than mass, multiple NAb testing.

Our point is that most NAb data sets contain some controversial data, which can be used to support opposing points of view. Using the AAN Evidence Based Medicine (EBM) Guideline, no Class I

NAb data exists. Nonetheless, an association of NAbs to clinical outcomes in a small percent of patients is a feasible conclusion. At the same time, the short- and long-term data are consistent with the belief that interferons should remain a first line MS treatment.

However unintended, one possible consequence of mass NAb testing of interferon patients might be to discourage the overall use of interferons, even as an initial therapy. The 'hassle factor', the 'fear factor', and the extra expense of NAb testing may discourage some patients from considering these important treatment options. Another unintended outcome might be that SOR patients will continue therapy because they do not have NAbs. These potential problems would defeat the purpose of providing the best EBM care for our patients.

At present, we believe careful neurological evaluations may accomplish a similar result with less added expense or hassle. NAb testing has not yet been shown to be more cost effective than a rigorous neurological evaluation. Most current NAb studies are limited by small numbers. A large-scale effort to compare NAb data to clinical data would be a less expensive option than recommending mass NAb testing. If accepted, the committee's recommendations will affect patients and doctors worldwide before the recommended test at the recommended NAbs titers of 1:100 (repeated positive) are validated. The first issue should not be whether to test all interferon patients and change treatments if the tests are positive. Rather these questions should be asked first:

- In a large-scale population study on patients being treated with interferon for at least 18 months, 'What is the prevalence of NAb titers which are 1:100 and are repeated positive using the recommended test?
- What is the clinical outcome for those patients with this high titered, persistent NAb titers who continue on current therapy, versus those who stop therapy versus those who switch class of therapy? A 1-year study should answer these questions.

Until then, we recommend not spending our limited MS resources on routine, multiple NAb testing unless this testing program is first compared with robust clinical data to explore the valid impact, if any, of NAbs on the clinical outcome. In the meantime, neurologists should monitor all patients closely for indications of SORs, with or without NAb.

References

1. Sorensen P, Deisenhammer F, Duda R. Guidelines on use of anti-IFN-β antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-β antibodies in multiple sclerosis. *European Journal of Neurology* 2005; **12:** 817–827.
2. Cutter G. Statistical issues in neutralizing antibodies. *Neurology* 2003; **61**(9 Suppl. 5)**:** S38–S39.
3. Petkau AJ, White R. Statistical approaches to assessing the effects of neutralizing antibodies: IFNbeta-1b in the pivotal trial of relapsing-remitting multiple sclerosis. *Neurology* 2003; **61**(9 Suppl. 5)**:** S35–S37.
4. Rice GPA, Paszner B, Oger J, Lesaux J, Paty D, Ebers G. The evolution of neutralizing antibodies in multiple sclerosis patients treated with interferon ß-1b. *Neurology* 1999; **52:** 1277.
5. Polman C, Kappos L, White R. Neutralizing antibodies during treatment of secondary progressive MS with interferon beta-1b. *Neurology* 2003; **60:** 37–43.
6. Hillert J, Rot U, Sominada A, *et al.* Preparation, dose, and route of administration of interferon beta influences frequency and titre levels of neutralizing antibodies in MS patients. *Neurology* 2005; **64**(Suppl. 1)**:** a326 (Abstract P05.125).
7. Hurwitz B, Polman C. Neutralizing antibodies to interferon beta-1b: real world data. *Multiple Sclerosis* 2003; **9:** S40.
8. Goodin DS, Hurwitz B, Noronha A. Neutralizing antibodies to inferon B-1b are not associated with disease worsening in multiple sclerosis. *The Journal of International Medical Research* 2007; **35:** 173–187.
9. Barbero P, Verdun E, Bergui M, *et al.* High-dose, frequently administered IFN-B therapy for relapsing-remitting multiple sclerosis must be maintained over the long term: the IFN-B dose reduction study. *Journal of the Neurological Sciences* 2004; **222:** 13–19.