Neutralizing anti-IFNβ antibodies: clarity and confusion

The article by Boz et al. [1] in this issue provides important data on the clinical effect of neutralizing antibodies (NAbs) to interferon beta (IFNβ) and stands in sharp contrast to the recently published ‘Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology’ on NAbs [2].

In their retrospective study of 262 patients predominantly on Rebif and Betaseron, Boz et al. demonstrate a substantial detrimental effect of NAbs on the therapeutic effect of IFNβ. Their study is the first postmarketing study in North America to evaluate the effect of NAbs on clinical outcomes, corroborating previous studies of effect of NAbs on IFNβ bioactivity which have demonstrated robust, titre-dependent suppression of IFNβ effect on biomarkers of IFNa/β receptor activation such as MxA, viperin and OAS gene expression [3,4]. This body of work from North America corroborates previous studies from Europe demonstrating marked diminution of IFNβ’s therapeutic effects by NAbs [5,6]. The studies showing clinical loss of efficacy in the presence of NAbs are even more impressive considering the deck is stacked against demonstrating such a clinical effect of NAbs on clinical measures, related to the ease of demonstrating suppression by NAbs of IFNβ biomarkers. There are three reasons for this. First, a substantial percentage of IFNβ-1b-treated patients can revert to NAb negativity after becoming NAb-positivity [7]. Secondly, the effect of bioactive IFNβ on central nervous system inflammation can be quite prolonged [8] which results in a delay between the onset of NAb-positivity and clinical effects [9]. Thirdly, the effect of IFNβ on clinical measures of multiple sclerosis (MS) is modest [10], so that demonstration of loss of clinical benefit requires large sample sizes. Given the power of the evidence which has overwhelmed the above hurdles, the recommendation of the Multiple Sclerosis Collaborative Research Group (MSCRG) almost a decade ago was that ‘patients should not be continued on therapy in the face of persisting NAB [11].’ Thus, it is not surprising that Serono, the company producing IFNβ-1a(Rebif), has created a new formulation intended to decrease immunogenicity and that Biogen Idec, the company producing IFNβ-1a(Avonex), spent considerable resources to lower the immunogenicity of their product when the initial formulation of their product had a NAb incidence of 22%. The EFNS, in the report of their Task Force of Anti-IFNβ antibodies in MS [12], recommended that testing for NAbs should be performed during the first 24 months of therapy and that therapy with IFNβ should be discontinued in patients with sustained high titres of NAbs.

In the face of all of this evidence over the last decade supporting the negative impact of NAbs on IFNβ therapy and the helpful recommendations of the EFNS group and the MSCRG before them, the conclusions of the Goodin report, published a few months ago [2], stand in stark contrast. The Goodin report concluded that ‘there is insufficient information on the utilization of NAb testing to provide specific recommendations regarding when to test, which test to use, how many tests are necessary or which cutoff titre to apply’. Is there any conceivable way one can reconcile these two apparently diametrically opposed positions?

The answer may lie in different perceptions of two issues: the burden of proof required for clinicians to utilize information obtained from diagnostic tests, and the fact that the NAb assay is an imperfect biomarker of the interference of anti-IFNβ antibodies with bioactivity, also called antibody-mediated decreased bioactivity (ADB) [3]. The authors of the EFNS and MSCRG reports accepted the inherent imperfections of the NAb assay, realized that it was not standardized and not completely correlated with absolute loss of bioactivity, but recognized that it is useful for patient management. The authors of the Goodin report held the NAb assay to an impossibly high standard and not surprisingly, found it wanting. Reconciliation may come in the fact that direct bioactivity measurements are available [3,4] and can be used in patients in whom the clinician may be hesitant to stop therapy, for example if NAbs are at low levels. However, under any circumstances it is hard to justify continued use of IFNβ therapy in patients who have NAB levels above 100 U.

Two other works have recently appeared in this journal addressing the IFNβ NAbs issue: a supplement edited by Dr Oger (2007) [13] labelled ‘Clarifying the Issues on Antibodies to Interferon in MS: Views from Industry and Four Academics’, and a review on NAbs by Farrell and Giovannoni [14]. The eight articles in the supplement, which are texts of
presentations of a symposium held at the Consortium of MS Centers meeting in Toronto in spring of 2004, review a number of different aspects of anti-IFNβ antibodies and provide an interesting spectrum of ideas and views. Not surprisingly, the industry representatives present viewpoints in line with the immunogenicity of their product. Drs Goelz and Walt, representing BiogenIdec, the maker of the IFNβ product with the lowest immunogenicity, Avonex, reviewed solid evidence of the importance of the problem of immunogenicity. Drs Cantillon and Antonijevic representing Schering AG, the maker of the IFNβ product with the highest immunogenicity, Betaseron, attempted, relatively unsuccessfully, to minimize the problem. Dr Al-Sabbagh, representing Serono, the maker of the IFNβ with a NAb rate of ~20%, on the one hand, downplayed the importance of NAbS, but, on the other hand, described how the company (at likely very great cost), was completely reformulating their product to reduce immunogenicity. Drs Oger, Deisenhammer, Pachner and Reder in the remainder of the supplement reviewed issues related, respectively, to binding antibodies (BABs), NAb assays [15], bioactivity markers and clinical outcomes of NAbS. Thus, the supplement represents a good reference for topics related to IFNβ immunogenicity; the two problems with the supplement are that much of the material is somewhat out-of-date, and there is no recommendation to practising clinicians about practically what needs to be done with MS patients. The latter problem is addressed by the excellent review by Farrell and Giovannoni, who not only summarize the wealth of data on the importance of NAbS, but also make concrete recommendations about anti-IFNβ antibody testing for the MS clinician.

Some of the above issues emerge in the study by Boz et al. in this volume. The manuscript confirms the findings from other studies that NAbS have an effect on relapse rate in the third and fourth year. However, because of lack of standardization of the assays used for NAb testing, the investigators used a capture ELISA methodology for BABs, which has not been proven to have adequate sensitivity to detect all NAb positives. As only binding antibody BAB-positive specimens were further tested in the NAb assay, an inadequately sensitive BAB assay would underestimate the incidence of NAb positivity. Indeed, the incidences of NAb positivity for each of the IFNβ preparations in the Boz study – 15% of Betaseron, 12% for Rebif and 0% for Avonex – was substantially lower than that found in other studies [7,11]. Also, the Boz study did not determine NAb titre, despite the fact that it is optimal in NAb studies to do so, as ADB is titre-dependent [4].

These problems with the Boz study do not detract from its findings, as well as those of many others, that are NAbS neutralize; they neutralize in vitro and they neutralize in vivo. The sooner that neurologists who prescribe IFNβ realize that, the better, whether those neurologists are in Europe, Canada or the USA.

References


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