Effects of neutralizing antibodies to interferon beta in multiple sclerosis: a logical paradox

In this issue of the *Multiple Sclerosis Journal* Goodin et al. report the effects of neutralizing antibodies (NAbs) in the BEYOND study and conclude:

‘There was a notable dissociation between the impact of NAbs on MRI and clinical outcomes. On MRI measures, the impact was consistent and convincing, whereas on clinical measures the negative impact of NAbs was not apparent. The basis for this clinicoradiographic paradox is unknown but it suggests that the relationship between NAbs and the therapeutic effects of IFNβ-1b is complex.’

Already more than 20 years ago, in the pivotal trial of IFNβ-1b, it was shown that NAbs totally blocked the clinical effects of IFNβ-1b. In months 13–36, when NAbs had developed, the relapse rate in NAb-positive patients was reduced by 50% compared with that in NAb-negative patients and was similar to the relapse rate in placebo-treated patients.

Since then a large number of studies with an appropriate duration (>2 years) have demonstrated the detrimental effects of NAbs both on clinical and MRI outcomes (reviewed by Sorensen). Occasionally, there will be a single study like the BEYOND that does not show consistent NAb effects on clinical outcomes, i.e. only shows an effect in patients treated with IFNβ-1b 500 μg and not in patients treated with IFNβ-1b 250 μg, which can only be explained by a statistical type II error, and such observations should not muddle our understanding of the effects of NAbs.

After more than a decade of controversies joint transatlantic recommendations for clinical use of data on neutralizing antibodies to IFNβ therapy in multiple sclerosis were issued last year.

There are mainly two reasons why the authors have failed to show a consistent effect of NAbs on clinical outcomes, but only on MRI outcomes in the BEYOND study. One reason is that NAbs account for only a minor part of breakthrough disease. As IFNβ only reduces the relapse rate by approximately 30%, and as NAbs occur in less than 5% of patients treated with IM IFNβ 1a only a small proportion of relapses that occur during treatment with IM IFNβ 1a is a result of NAb formation. The majority of on-treatment disease activity is caused by the spontaneously occurring variation in underlying disease activity between patients with multiple sclerosis.

The other main reason is the problem that even in a study comprising a large number of patients the statistical power disappears when patients are split into subgroups and, hence, there is a strong possibility of type II errors. If, for example, 30% of the treated patients become NAb-positive in a trial, and the original design had a statistical power of 80% for showing an effect of NAbs on relapses, then the power will be reduced to 44% just by looking for the effect in NAb-positive and NAb-negative subgroups separately. In the BEYOND study the authors state an estimated power of 83% to detect a 50% increase in the relapse rate, but dividing the patients into groups with low, medium and high titres dilutes the statistical power considerably.

It is, however, mandatory to divide patients according to the NAb titres, at least into patients with low and patients with medium/high titres, because whereas IFNβ patients with high titre NAbs invariably have lost all bioactivity and therefore must be considered untreated, patients with low titres may have preserved some or full bioactivity and therapeutic effect of the administered IFNβ.

Further, the vast amount of knowledge about NAbs that has been collected during the last decade should be taken into consideration. Neglect of NAbs kinetic and pharmacodynamics, will make the study heavily biased and contribute to obscure the NAb effects on clinical outcomes. Several studies have shown that NAbs against IFNβ are characterized by low affinity antibodies in the first 6–12 months that have a protective effect on IFNβ and hence increase the effect of IFNβ. Further, 40% of patients treated with IFNβ-1b will revert to NAb-negative status within 4 years. Therefore, the once positive, always positive principle is not suitable for an evaluation of the effects of NAbs in patients treated with IFNβ-1b.

It is peculiar that NAbs in the patients treated with IFNβ-1b 500 μg caused a highly significant effect on relapses in both patients with moderate (63% increase) and high (78% increase) titres, whereas this could not be demonstrated in the patients treated with IFNβ-1b
250 μg. Only a lack of statistical power can explain this variability in the results. Regarding the effect on MRI outcomes, NAbs invariably and in a dose-dependent manner severely reduced or abolished the therapeutic effects of IFNβ-1b.

The authors find that these observations constitute a paradox. However, taking into consideration the different effects of IFNβ on MRI activity, relapse rate, and progression in Expanded Disability Status Scale (EDSS) score, the findings appear to be more logical than paradoxical. The different effect on clinical and radiological outcome measures in patients treated with IFNβ has by some been called a paradox, but the more pronounced effect on MRI, less pronounced on relapses, and no effect on disease progression in the pivotal trial of IFNβ-1b has never been claimed to indicate that the drug has no effect on clinical outcomes.

Regarding demonstration of the effect of NAbs on IFNβ-1b therapeutic efficacy, the pronounced therapeutic effect on MRI activity generates high power to the statistical analyses, whereas the modest effect on clinical measures provides much less power. In other words, it is difficult to show the disappearance of a weak therapeutic effect.

Niels Bohr, the Danish physicist, noted that a paradox could initiate progress. Let us hope that the solution of the clinico-radiographic NAb effect paradox could make progress in the understanding of the effects of NAbs on the therapeutic efficacy of IFNβ.

References