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Editorial

Neutralizing anti-IFN-β antibodies

How much more evidence do we need to use them in practice?

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Neutralizing antibodies (NAbs) are a major hurdle to the successful use of biologics in clinical practice. The impact of NAbs is obvious in biologic systems with no redundancy. NAbs induced in response to treatment with recombinant erythropoietin or thrombopoietin cause life-threatening complications of pure red cell aplasia and thrombocytopenia as a direct result of inhibiting the activity of the endogenous hormones. For the type 1 interferons (α and β), NAbs have not yet been shown to have untoward biologic effects. This may relate to the fact that IFNα and IFNβ have overlapping biologic activities or that they are produced locally as autocrine or paracrine mediators and are therefore less likely to be exposed to NAbs. In comparison, the evidence that NAbs interfere with the therapeutic effect of type 1 interferons is much clearer. In subjects with multiple sclerosis (MS), NAbs inhibit the induction of IFNβ-specific gene products and lessen the benefit of IFNβ on both MRI activity and relapse rate. Furthermore, three articles in this issue of *Neurology* show that NAbs[1,2] impact negatively on disease progression and are likely to persist.[3]

NAbs do not appear until 6 to 24 months after IFNβ is initiated and do not have consistently measurable effects in trials of less than 2 years' duration. In the pivotal IFNβ-1b study (Betaseron/Betaferon), the clinical impact of NAbs on MS relapse rate only became apparent after 18 months of therapy.[4] In the subcutaneous IFNβ-1a PRISMS study (Rebif) there were no reported differences in the clinical and MRI endpoints between NAb+ and NAb− patients at 2 years.[5] However, in the 4-year extension phase of PRISMS, the relapse rate was 60% greater (0.81 vs 0.50, $p = 0.002$), the median number of T2 active lesions was five times greater (1.4 vs 0.3, $p < 0.01$), and the median change from baseline in the MRI burden of disease was three times greater (+17.6% vs −8.5%, $p < 0.001$) in NAb+ compared with NAb− subjects.[6] In the pivotal once-weekly IM IFNβ-1a (Avonex) trial, which was terminated early, a strong trend toward reduced treatment benefit on MRI, but not clinical disease activity, was seen in NAb+ patients.[7]

Data on the impact of NAbs on MS disease progression have been less clear. In fact, none of the phase III IFNβ trials was powered to detect an effect of NAbs on disease progression. Despite this, data have now demonstrated an impact of NAbs on disease progression. In a recently published open-label study of 78 IFNβ-treated MS subjects followed for a median of 3 years, a higher percentage of NAb+ patients vs NAb− patients had worsening of Expanded Disability Status Scale (EDSS) scores during the period of follow-up ($p = 0.013$).[8] Similarly, in a second open-label study of 65 subjects followed for up to 4 years, the mean EDSS score increased from 2.2 ± 0.8 at baseline to 3.6 ± 1.2 at year 2 in the 10 subjects with high-titer NAbs compared with NAb− subjects in whom there was no significant change in their EDSS scores ($p < 0.01$).[9]

A re-analysis of the impact of NAbs in the PRISMS study, published in this issue of the *Journal*,[1] shows that over the entire 4 years of study, relapse and disability measures were similar between NAb+ and NAb− patients. However, once NAbs developed, significant differences were noted between NAb+ and NAb− groups on MRI, relapse, and disability outcome measures. As expected, the impact on disability was less predictable than on the other outcomes. In fact, it was only significant in the "interval-positive analysis," in which subjects provide data to both the NAb+ and NAb– groups depending on their status at the time data were collected. Using this method, the difference between NAb+ and NAb– groups in the rate of confirmed 1-point EDSS change was significant over the 4 years of the study (NAb+/NAb− rate ratio = 1.50,

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95% CI 1.03–2.17, $p = 0.03$). Also in this issue, Kappos et al.[2] report that in the European IFNβ-1a (Avonex) dose-comparison study in which patients were randomized to treatment with IFNβ-1a 30-μg or 60-μg IM once weekly for up to 4 years, NAb+ subjects had a higher rate of mean change or worsening in the EDSS score from baseline to month 48 compared with NAb− subjects ($p = 0.01$).

Of interest in both the PRISMS-4[1] and pivotal IFNβ-1b[4] studies, subjects who were destined to develop NAbs had a greater reduction in relapse rate in the first 6 months of therapy compared with subjects who did not go on to develop NAbs. This not only dilutes the negative impact of NAbs on relapse rates when using data averaged across the whole study period, but suggests a difference in the biologic response of these subjects to IFNβ therapy. This observation deserves further study. At present it is not possible to predict which subjects will develop NAbs. The majority of subjects who develop binding antibodies early after initiating IFNβ therapy will go on to develop NAbs. It may therefore be possible to treat binding-positive patients early, using various strategies, to prevent NAb+ seroconversion.[10]

Approximately 30% of NAb+ subjects become NAb− spontaneously over a period of several years; subjects treated with IFNβ-1b[11] and with low NAb titers (<75–100 NU) are more likely to revert to NAb−.[12,13] Additional data on reversion rates are presented in this issue from the large Danish population-based study.[3] Of 455 subjects with MS treated for at least 24 months on IFNβ, 52% were classified as persistently NAb−, 41% as persistently NAb-positive (at least two consecutive positive samples 6 months apart), and the remaining 7% fluctuated between being NAb+ and NAb−. Subjects who remained NAb− after 24 months of therapy rarely developed NAbs. The majority of subjects, who had been NAb+ from 12 through 30 months after the start of IFNβ therapy, remained NAb+. Reversion to NAb− was more common with IFNβ-1b than IFNβ-1a; 52% of NAb+ subjects on IFNβ-1b reverted to NAb− after 36 months compared with only 19% of subjects receiving IFNβ-1a. The finding that reversion to being NAb− is more frequent with IFNβ-1b than with IFNβ-1a may be because tolerance is more likely to occur with ongoing administration of larger protein loads during IFNβ-1b treatment. The ongoing trial studying the standard dose and double-dose IFNβ-1b (BEYOND) will help elucidate whether this strategy could help reduce further the occurrence and persistence of NAbs.

Incorporating NAbs and NAb testing into clinical practice. Despite the increasing evidence that NAbs abrogate or reduce the clinical efficacy of IFNβ on MRI outcomes, on relapse rate, and now on disability progression, NAb testing has not been part of routine clinical practice. Avoiding NAbs by opting for a low immunogenic preparation from the outset, e.g., IM IFNβ-1a, is a reasonable strategy. However, this strategy may compromise clinical efficacy: weekly IM IFNβ-1a is less efficacious in short-term studies than both IFNβ-1a 44 μg SC three times weekly[14] and IFNβ-1b 250 μg SC every other day.[15] The superior efficacy of high-frequency IFNβ preparations needs to be weighed against the greater risk of developing NAbs with these preparations.

Once a person with MS is in treatment, it seems reasonable to screen for NAbs at 12 and 24 months or at the time of a relapse. If a subject has not seroconverted after 24 months of therapy, he or she is unlikely to do so; therefore, further routine testing is not recommended.

At present there is little evidence to guide clinicians on how to manage persistently NAb+ subjects who are doing well clinically. Ideally, these subjects should be studied to determine how to manage them appropriately. Currently, the NAb test should be viewed as predictive; NAb+ subjects are more likely to fail IFNβ therapy in the future compared with NAb− subjects; the odds of having a relapse in a NAb+ period compared with a NAb− period is between 1.51 and 1.58 ($p < 0.03$), and the time to first relapse is prolonged on average by 244 days in subjects who are NAb− at 12 months after the start of IFNβ treatment compared with those who are NAb+ ($p = 0.009$).[11]

It has been argued that is unnecessary to test for NAbs in subjects who have had a relapse as clinicians would be inclined to stop or switch treatment in these patients regardless of their NAb status. As IFNβ is only partially effective, the majority of patients would be expected to have a breakthrough in disease activity at some stage, but this does not necessarily imply the subject is an IFNβ nonresponder. However, if this subject were persistently NAb+, one would classify him or her as being a nonresponder and would have a good reason to switch therapy. Some have proposed switching to a less immunogenic IFNβ preparation. In one report, switching NAb+ IFNβ-1b-treated patients to the less immunogenic IM IFNβ-1a resulted in 53% reverting to NAb− after 1 year and 75% reverting to NAb− after 2 years.[16] Randomized clinical studies are currently being undertaken to evaluate this strategy. As NAbs to IFNβ-1b and IFNβ-1a are cross-reactive, we do not recommend switching within the IFNβ class at present.

In conclusion, it is well established that NAbs reduce the biologic and clinical efficacy of IFNβ. The efficacy of IFNβ and hence the cost-effectiveness of treatment will be improved if the development of NAbs can be prevented or reversed. Subjects with MS who develop NAbs are likely to become IFNβ nonresponders. They are by definition at higher risk of having relapses in the future (if they have not already had them) and can now be considered to be at increased risk of disease progression. The rationale for incorporating NAb testing into clinical practice and for doing appropriately powered switching studies to establish how to manage NAb+ subjects

who are "doing well" on IFNβ is compelling. In addition, strategies to prevent or reverse the development of NAbs need to be explored. The overall efficacy of IFNβ therapy as a class of MS disease-modifying therapies can be improved if the problem of NAbs can be overcome.

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