"Interferon β-1b-neutralizing antibodies 5 years after clinically isolated syndrome."

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ABSTRACT

Although NAb positivity was associated with increased brain MRI activity, no discernible effects on clinical outcomes were found. This finding may reflect the greater power of MRI compared with clinical outcomes to detect the treatment effects of IFNβ-1b and may also result from temporal changes in NAb titers and biology.

CITE THIS VERSION

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Interferon β-1b–neutralizing antibodies 5 years after clinically isolated syndrome

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For the BENEFIT Study Group

ABSTRACT

Objective: To determine the frequency and consequences of neutralizing antibodies (NAbs) in patients with a first event suggestive of multiple sclerosis (MS) treated with interferon β-1b (IFNβ-1b).

Methods: In the Betaseron/Betaferon in Newly Emerging MS For Initial Treatment (BENEFIT) study, patients were randomly assigned to 250 µg IFNβ-1b (Betaferon) or placebo subcutaneously every other day for 2 years or until diagnosis of clinically definite MS (CDMS). Patients were then offered open-label IFNβ-1b for up to 5 years. NAb status was assessed every 6 months by the myxovirus protein A induction assay. A titer >20 NU/mL was considered NAb-positive, with low (≥20–100 NU/mL), medium (≥100–400 NU/mL), and high (≥400 NU/mL) titer categories. Here we examine early-treated patients, who received IFNβ-1b for up to 5 years.

Results: NAbs were measured in 277 of 292 early-treated patients and detected at least once in 88 (31.8%) patients, with 53 (60.2%) reverting to NAb negativity by year 5. Time to CDMS, time to confirmed disability progression, and annualized relapse rate did not differ between NAb-positive and NAb-negative patients or between periods of NAb positivity vs NAb negativity within patients. Increases in newly active lesion number and T2 lesion volume and conversion to McDonald MS were associated with NAb positivity and were more pronounced with higher titers.

Conclusions: Although NAb positivity was associated with increased brain MRI activity, no discernible effects on clinical outcomes were found. This finding may reflect the greater power of MRI compared with clinical outcomes to detect the treatment effects of IFNβ-1b and may also result from temporal changes in NAb titers and biology. Neurology® 2011;77:835–843

GLOSSARY

BENEFIT = Betaseron/Betaferon in Newly Emerging MS For Initial Treatment; CDMS = clinically definite multiple sclerosis; CI = confidence interval; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IFNβ = interferon β; MS = multiple sclerosis; NAB = neutralizing antibody.

Neutralizing antibodies (NAbs) can develop during interferon β (IFNβ) treatment, as with other injected protein therapies, and reduce or abrogate normal biologic and treatment effects by preventing IFNβ binding to its receptor, thereby blocking receptor activation and expression of IFN-inducible genes. NABs against IFNβ usually develop 3–18 months after treatment initiation and may disappear with continued therapy. The effects of NAbs on clinical outcomes in IFNβ-treated patients are inconsistent. Some studies show that clinical outcomes are the same for NAb-negative and NAb-positive patients, and others report differences. Failure to detect consistent NAb effects on clinical outcomes may be a result of most prospective studies being relatively short.

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The Betaseron/Betaferon in Newly Emerging MS For Initial Treatment (BENEFIT) study assessed IFNβ-1b (Betaferon, Bayer HealthCare Pharmaceuticals, Wayne, NJ) in patients with a first event suggestive of multiple sclerosis (MS) over 5 years. It provided a unique opportunity to prospectively assess the frequency/dynamics of NAb evolution and their long-term consequences.

**METHODS**

**Study design.** Patients were randomly assigned to 250 µg IFNβ-1b subcutaneously every other day or placebo (5:3), within 60 days after onset of the first clinical event, for ≤2 years or until clinically definite MS (CDMS) was diagnosed.” Patients were then offered IFNβ-1b for up to 5 years. Neurologic assessments were undertaken at least every 6 months. Up to 10 MRI scans were obtained (screening, annually during years 1–5, and months 3, 6, 9, and 18 in the placebo-controlled phase only). Anti-IFNβ antibodies were evaluated every 6 months using the myxovirus protein A induction assay with IFNβ-1b.

**Statistical analyses.** Analyses were limited to patients initially randomized to IFNβ-1b, to provide a longer, more homogeneous observation period than delayed treatment in patients initially randomized to placebo. p Values are for 2-sided tests.

**Definitions of NAb status.** A titer of 20 NU/mL was the cutoff between NAb negativity (<20 NU/mL) and positivity (≥20 NU/mL). NAb-positive titers were further categorized into low (≥20–100 NU/mL), medium (≥100–400 NU/mL), medium-high (≥100–400 NU/mL), and high (>400 NU/mL) titers. Two definitions for eventually NAb-positive patients were evaluated: at least one NAb-positive titer or 2 consecutive (confirmed) positive measurements. Reversion to persistent NAb negativity was assumed if a patient had at least one NAb-negative titer at a subsequent timepoint and no additional NAb-positive titers after reversion. NAbs measured >30 days after the end of study medication were excluded.

**Effect of NAbs on outcomes.** Differences between “never NAb-positive” and “eventually NAb-positive” subgroups were evaluated cross-sectionally. Because results from unconfirmed and confirmed definitions of NAb positivity were very similar, findings using the confirmed definition are presented in the supplementary material on the Neurology® Web site at www.neurology.org.

Because NAb status may have changed over time, further analyses compared NAb-negative with NAb-positive time periods by time-to-event analyses, considering NAb status as a time-dependent covariate, and by longitudinal analyses for repeated outcome measures. All switches between titer levels (dynamic switching) were considered. The effect of NAbs on outcomes was analyzed for NAb positivity ≥20 NU/mL and with respect to different titer categories.

**RESULTS**

**NAb characteristics.** NAbs were measured in 277 of 292 early-treatment patients. Over 5 years, 31.8% (88 of 277) were NAb-positive at least once; of these, 15.2% had low (42 or 277), 7.2% medium (20 of 277), and 9.4% (26 of 277) high peak titers. By year 5, 60.2% (53 of 88) with ≥1 NAb-positive titer reverted to NAb negativity: –85.7% (36 of 42) with low, 65.0% (13 of 20) with medium, and 15.4% (4 of 26) with high NAb titers. NAbs were measured consecutively at least twice in 26.7% (74 of 277) of patients, with 12.3% (34 of 277), 6.9% (19 of 277), and 7.6% (21 of 277) achieving low, medium, and high titers, respectively. By year 5, 54.1% (40 of 74) of patients with at least 2 consecutive NAb-positive titers reverted to NAb negativity, with 76.5% (26 of 34), 68.4% (13 of 19), and 4.8% (1 of 21) of those with low, medium, and high titers, respectively, reverting. There was a stronger tendency in NAb-negative vs eventually NAb-positive patients to prematurely terminate study medication (34.4% vs 19.3%) or leave the study (14.8% vs 11.4%). NAb-negative compared with NAb-positive patients were more likely to terminate study medication (36.9% vs 11.8%) and the study (21.4% vs 10.0%) because of adverse events.
Of 88 eventually NAb-positive patients, 48 (54.5%) had a monophasic increase in NAb burden with reversion to NAb negativity by study end; 29 (33.0%) experienced a persisting increase in NAb positivity; and 11 (12.5%) fluctuated between NAb positivity and NAb negativity. In 48 patients with a monophasic increase in NAb positivity, 32 reached low, 13 medium, and 3 high peak titers. Duration of NAb positivity was comparatively short in the low-titer group and increased in a stepwise manner from medium to high titers (mean numbers of consecutively positive NAb measurements in monophasic patients with low, medium, and high peak titers were 2.2, 5.3, and 6.7, respectively). In 29 patients with persisting NAb positivity, 2 achieved low, 6 medium, and 21 high peak titers (5 of them had a <3-year observation period because of premature study termination). Patients with persisting NAb positivity and high peak titers showed declining titers over time.

Effect of NAbs on clinical outcomes. No significantly increased hazard in time to CDMS and time to EDSS score progression occurred in eventually NAb-positive patients for any titer (figure 1). Notably, patients with low peak NAb titers exhibited a significantly reduced hazard in time to CDMS relative to that of never NAb-positive patients (HR 0.536; \( p = 0.037 \)) (figure 1). Similar results for eventually NAb-positive patients with at least 2 consecutively positive NAb measurements are shown in table e-1.

When NAb status was used as a time-dependent covariate, there was no increased risk for CDMS or EDSS score progression during NAb-positive periods (table 1). There was also no measurable increased risk for CDMS or EDSS score progression during low, medium, and high NAb titer periods (table 1). Similar results were obtained when medium to high NAb titer levels were combined in a single category (table e-2).

Annualized relapse rate did not increase in eventually NAb-positive patients, regardless of whether data were analyzed for the entire study period or after year 1 (tables 2 and e-3). A significantly lower annualized relapse rate over the entire study period occurred among eventually NAb-positive individuals, specifically in patients developing low peak NAb titers. There was also no increase in relapse rates in persistently NAb-positive patients (table 2), and there were no systematic differences for NAb-negative vs NAb-positive patients in study years 1–5 with the exception of high NAb titers in year 2 (negative vs high titer 0.18 vs 0.41; \( p = 0.03 \)) and low NAb titers in year 5 (negative vs low titer 0.17 vs 0.46; \( p = 0.01 \)). Notably, patients with medium to high NAb titers in year 4–5 showed low relapse rates (≤0.13; table e-4).

Longitudinal analyses showed that the switch from NAb negativity to positivity at any titer level did not increase relapse risk and EDSS score (table 3). Notably, in NAb-positive periods, estimated ef-
Persistently positive patients were defined as patients with at least one positive NAb titer (≥20 NU/mL) not reverting to NAb negativity up to the end of the study. Persistently positive patients are defined as patients with at least one positive NAb titer (≥20 NU/mL) not reverting to NAb negativity up to the end of the study.

Persistently positive patients defined as patients with at least one positive NAb titer (≥20 NU/mL) not reverting to NAb negativity up to the end of the study.

Because of the relatively low clinical disease activity, the power to detect the effects of NAb on clinical outcomes was limited. For example, in the cross-sectional analysis comparing eventually NAb-positive (n = 88) vs NAb-negative patients, estimated power (of a 2-sided test at α = 0.05) to detect a 50% increase in relapse rate was approximately 62% (this drops to 32% if only the 26 patients with high peak titers are considered; the power for longitudinal analysis is similar).

Cross-sectional analyses showed that eventual NAb positivity in patients with high peak titers was associated with increased risk of McDonald MS (figure 1, table e-1). Progression to McDonald MS was driven primarily by MRI events. NAb-positive periods at each titer level were associated with an increased risk of McDonald MS (tables 1 and e-2), particularly during medium (p < 0.001) and high NAb titer periods (p < 0.001).

Effect of NAbs on MRI outcomes. Eventually NAb-positive patients had an increased mean number of newly active lesions (12.2 vs 8.6, p < 0.001) and change in T2 lesion volume (+82 vs −289 mm³, p < 0.001) over 5 years. Compared with never NAb-positive patients, increases in the mean number of newly active lesions were significant for patients with low (9.3 vs 8.6, p = 0.048), medium (15.9 vs 8.6, p < 0.001), or high NAb titers (13.6 vs 8.6, p < 0.001). For median change in T2 lesion volume, increases relative to those in never NAb-positive patients were significantly greater only for patients with medium (+271 vs −289 mm³, p = 0.018) and high titers (+210 vs −289 mm³, p < 0.001).

Longitudinal analyses showed a significant increase in newly active lesions in NAb-positive vs NAb-negative time periods (table 3). There were no significant increases in T2 lesion volume during NAb-positive time periods (table 3).
**Table 3** Effects of NAb switching on clinical and MRI disease parameters over 5 years*  

<table>
<thead>
<tr>
<th></th>
<th>Estimates (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse risk, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (≥20 NU/mL) vs negative</td>
<td>15.3 (20.1 to 66.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Single model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (20–100 NU/mL) vs negative</td>
<td>30.5 (11.8 to 93.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Medium (100–400 NU/mL) vs negative</td>
<td>17.4 (45.0 to 150.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>High (≥400 NU/mL) vs negative</td>
<td>-31.1 (66.3 to 41.0)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>EDSS change</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (≥20 NU/mL) vs negative</td>
<td>-0.09 (0.18 to 0.00)</td>
<td>0.055</td>
</tr>
<tr>
<td>Single model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (20–100 NU/mL) vs negative</td>
<td>-0.10 (0.19 to -0.01)</td>
<td>0.032</td>
</tr>
<tr>
<td>Medium (100–400 NU/mL) vs negative</td>
<td>-0.04 (0.20 to 0.13)</td>
<td>0.66</td>
</tr>
<tr>
<td>High (≥400 NU/mL) vs negative</td>
<td>-0.10 (0.32 to 0.12)</td>
<td>0.31</td>
</tr>
<tr>
<td>** Newly active lesion rate, %**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (≥20 NU/mL) vs negative</td>
<td>107.6 (70.5 to 152.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (20–100 NU/mL) vs negative</td>
<td>93.6 (54.5 to 142.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medium (100–400 NU/mL) vs negative</td>
<td>130.5 (77.6 to 199.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High (≥400 NU/mL) vs negative</td>
<td>139.8 (76.3 to 226.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>** T2 lesion volume change, mm³**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (≥20 NU/mL) vs negative</td>
<td>80 (26 to 226)</td>
<td>0.28</td>
</tr>
<tr>
<td>Single model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (20–100 NU/mL) vs negative</td>
<td>65 (82 to 212)</td>
<td>0.39</td>
</tr>
<tr>
<td>Medium (100–400 NU/mL) vs negative</td>
<td>73 (120 to 267)</td>
<td>0.46</td>
</tr>
<tr>
<td>High (≥400 NU/mL) vs negative</td>
<td>181 (140 to 503)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; NAb = neutralizing antibody.  
* Results are based on the unconfirmed definition of NAb status and the dynamic switching model.  

We could not show any effect of NAbs on key clinical outcomes (development of CDMS, relapses, and EDSS score progression). No differences in clinical outcomes were found for never NAb-positive and eventually NAb-positive patients or during NAb-positive and NAb-negative time periods within individual patients. In fact, neutralizing activity was associated with numerically better clinical outcomes. In many IFNβ-1b and -1a studies, it has been curiously noted that patients who were eventually NAb-positive experienced a greater reduction in relapses and EDSS score progression before NAb detectability. Once measurable, however, NAb positivity was shown to be associated with a higher relapse rate in several IFNβ trials. The observational Danish patient registry study, combining data from all 3 IFNβ treatments, showed that relapse rates were significantly higher during NAb-positive periods. These results differ from our findings in that over 5 years there was no apparent association with higher relapse rates. An obvious explanation could be that there were fewer overall relapses and little disability progression in BENEFIT, such that the power to detect significant differences between those with and without measurable NAbs was low, especially if the moderate treatment effect of IFNβ products on these clinical outcomes is considered: in the 88 eventually NAb-positive patients, the ability to detect a 50% increase in relapse rate/risk was approximately 60%. The power is further reduced to 32% when only the 26 patients who achieved high peak NAb titers (≥400 NU/mL) are considered.

Conversely, the absent effect of NAbs on clinical outcomes in BENEFIT agrees with several IFNβ-1b and IFNβ-1a prospective studies. The largest randomized, controlled study of IFNβ in patients with relapsing-remitting MS evaluated NAbs in 1,775 IFNβ-1b–treated patients for up to 3.5 years. This study had more power than BENEFIT to demonstrate the effect of NAbs on relapse rates, because of the higher clinical disease activity of participants and greater number of evaluable NAb-positive patients (n = 659). Increased relapse rates occurred during periods of high NAb titers only in patients receiving an experimental higher dose (500 µg subcutaneously every other day) rather than the approved dose in BENEFIT. Moreover, 2 large observational studies involving 10,000 patients did not demonstrate a relationship between NAb positivity and clinical worsening.

The 5-year observation period of our dataset provides insight into the complexity of IFNβ-1b–induced NAbs, because the heterogeneity in NAb evolution and persistence becomes more evident over this time: peak titer levels differed across patients and periods (table 3). This may be due to the resolution of T2 hyperintensity on the screening MRI originating from brain edema induced by the first clinical event leading to an apparent decrease in T2 lesion volume during the first trial year when neutralizing activity was just evolving or below detection.

On annual MRI scans, inflammatory activity indicated by the presence of at least one gadolinium-enhancing lesion was more frequent in NAb-positive patients than in NAb-negative patients (figure 2), with significant between-group differences at years 1 and 3. However, the percentage of NAb-positive patients with MRI activity decreased at years 4 and 5 and was not statistically different from that of NAb-negative patients.

**DISCUSSION** BENEFIT is the longest prospectively planned follow-up study of patients with a first event suggestive of MS and is thus suited to evaluate the long-term impact of IFNβ-1b–induced NAbs on clinical and MRI outcomes.
Time to event outcomes (time to CDMS, time to confirmed progression defined by an EDSS score increase of at least 1.0, and time to McDonald MS) were analyzed by Cox proportional hazards regression comparing the risk in neutralizing antibody (NAb)-negative patients vs that in eventually NAb-positive patients with low, medium, and high titers, while also adjusting for the covariates age, gender, number of T2/gadolinium-enhancing lesions, monofocal or multifocal presentation, and use of steroids at the time of a first clinical event suggestive of MS. Time to McDonald MS is a combined endpoint of clinical and MRI events. Arrows indicate when MRI was performed. Of note, the increase in risk in NAb-positive patients occurred at approximately the time of MRI, indicating that this risk increase was driven primarily by MRI events.
usually did not exceed low to moderate burdens, with a strong tendency for reversion to NAb negativity, particularly with peak low to moderate titers (85% and 65%). High titers occurred in approximately 10% of patients; the reversion rate was only 15% in those with at least 1 high titer and 5% with 2 consecutive high titers. Most IFNβ-1b–induced NAb titers are low and transient; IFNβ-1a is less likely to induce NAbs, but they are more persistent.15 The reason for more frequent NAb reversion among IFNβ-1b–treated patients is unclear but may involve the earlier induction of immunologic tolerance because of a higher protein load.

As in previous studies, NAb evolution was associated with more inflammatory disease activity on cerebral MRI, which increased with peak titer level.7,11,13,20,22,29 This was reflected by increased conversion to McDonald MS, a phenomenon driven mainly by the appearance of new lesions over time. The dissociation between clinical and MRI outcomes is partly related to the detection of asymptomatic lesions, with a tendency to increase over time, because of the detection of asymptomatic lesions, mainly by the appearance of new lesions over time. The dissociation between clinical and MRI outcomes is partly related to the detection of asymptomatic lesions on brain MRI, which occur more frequently and at an earlier stage in the course of the disease. The reason for more frequent NAb reversion among IFNβ-1b–treated patients is unclear but may involve the earlier induction of immunologic tolerance because of a higher protein load.

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REFERENCES


CORRECTION

Interferon β-1b–neutralizing antibodies 5 years after clinically isolated syndrome

In the article “Interferon β-1b–neutralizing antibodies 5 years after clinically isolated syndrome” by H.-P. Hartung et al. (Neurology® 2011;77:835–843), the following errors occurred.

The authors did not plan to publish figure 1 and therefore did not reference it in the text. Moreover, this figure was published with an incorrect title and an incorrect legend. However, the figure presents correct data providing characteristic examples of the development and reversion of NAb positivity over time: (A) monophasic NAb course in 3 patients with peak low, medium, and high titers; (B) sustained NAb increase in a patient with peak high titers; and (C) fluctuating NAb course in 2 patients with peak low and high titers.

Figure 2 in the manuscript is also incorrect as it is an older version of similar analyses but provides less detailed information. See below for the new version of this figure, which should be figure 1 as referenced in the text of the manuscript. The correct version shows Kaplan-Meier curves in NAb-negative patients vs "eventually NAb-positive patients" with low, medium, and high titers for time to (A) CDMS, (B) confirmed EDSS progression, and (C) McDonald MS as presented below.

The figure referenced in the text as figure 2 is missing from the published article. This figure provides the percentage of patients with ≥ 1 gadolinium-enhancing lesion on brain MRI vs NAb positivity at annual timepoints as presented below.

The version of the paper that was peer-reviewed had the correct figures. Inadvertent substitution of the figures occurred later. The authors regret the errors.

Figure 1 Kaplan-Meier curves for time to (A) CDMS, (B) confirmed EDSS progression, and (C) McDonald MS

Figure 2 Percentage of patients with ≥1 gadolinium-enhancing lesion vs NAb positivity at annual timepoints

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg &gt; 20</td>
<td>141.3*</td>
<td>034.5*</td>
<td>1863.9*</td>
<td>1203.4*</td>
</tr>
</tbody>
</table>

NAb-positive n = 65
NAb-negative n = 193
Overall n = 258

Figure 2 *Mean NAb titers (NU/mL) in positive patients were lowest in year 1, increased until year 3, and then slightly decreased. Of note, due to reversion to stable NAB status in the majority of patients who eventually became NAb-positive, the number of NAb-positive patients decreased at later timepoints.

Figure 1 Time-to-event outcomes (time to CDMS, time to confirmed progression defined by an EDSS increase of at least 1.0, and time to McDonald MS) were analyzed by Cox proportional hazards regression comparing the risk in NAb-negative patients vs "eventually NAb-positive patients" with low, medium, and high titers, while also adjusting for the covariates age, gender, number of T2/ gadolinium-enhancing lesions, mono-/multifocal presentation, and use of steroids at the time of a first clinical event suggestive of MS. Time to McDonald MS is a combined endpoint of clinical and MRI events. Arrows indicate when an MRI was performed. Of note, increase in risk in NAb-positive patients occurred around the time of MRI, indicating that this risk increase was driven primarily by MRI events.
Interferon β-1b–neutralizing antibodies 5 years after clinically isolated syndrome
Neurology 2011;77:835; Published online before print August 17, 2011;
DOI 10.1212/WNL.0b013e318222e90d7

This information is current as of February 26, 2013