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**New Perspectives  
on Neutralizing  
Antibodies against  
Interferon Beta  
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Each year, neurologists gather at the *Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)*, last held in Madrid, Spain, to update their knowledge on key issues related to the treatment of multiple sclerosis (MS) patients. This year, the relevance of neutralizing antibodies (NAbs) against interferon beta (IFN $\beta$ ) was explored.

This issue of *Medical Express Reports* focuses on the Bayer Schering Pharma AG-sponsored Educational Workshop: *New Perspectives on Neutralizing Antibodies against Interferon Beta*, held prior to ECTRIMS. A panel of international speakers, Chaired by Professor Douglas Goodin (University of California at San Francisco, USA), included the eminent researchers: Per Soelberg Sørensen (University of Copenhagen, Denmark), Jan Hillert (Karolinska Institute, Sweden), Gavin Giovannoni (University College London, UK), and Anthony Reder (University of Chicago, USA). They reviewed their recent data and discussed the controversial issue of NAb development against IFN $\beta$ , during MS treatment from a variety of perspectives, including:

- Differences between NAbs directed at different forms of IFN $\beta$
- Key characteristics of NAbs that affect their clinical impact
- Methods to prevent or decrease NAbs
- Selected studies on the clinical importance of NAbs for MS patient. ■



Madrid, Spain – venue for the ECTRIMS congress

## The NAbs controversy: shades of grey

**There is considerable debate over the clinical significance of neutralizing antibodies (NAbs) that sometimes develop following MS treatment with interferon beta (IFN $\beta$ ). Data addressing the relevance of NAbs against IFN $\beta$  was reviewed by experts.**

Sensitive assays for NAbs have been developed, which means that a patient may test positive for low-titre or fluctuating NAbs but still have a physiological response to IFN $\beta$  when tested for activity. Characteristics of NAbs, such as their concentration and their persistence, affect their relevance to patient outcome. Therefore, the relevance of NAbs to IFN $\beta$  can be viewed as a 'grey zone' and not a 'black and white' issue.

Controversy often emerges from complex issues that require extensive research. During this NAbs workshop, more questions than answers emerged. Questions included: What is the best method for measuring NAbs? What

concentration of NAbs is 'high'? What is the evidence that 'high' concentrations of NAbs reduce the effectiveness of therapy? How do NAbs directed against IFN $\beta$ -1a and IFN $\beta$ -1b differ from each other? Does the severity of a patient's MS affect NAb formation? Are NAbs predictive? Should therapy only be changed when a patient is failing treatment? Are other reasons for poor response to IFN $\beta$  therapy more common and more important than NAbs? Can the impact of NAbs be observed in a large registry study? Does the outcome of a patient with NAbs improve after switching to a non-IFN $\beta$  therapy?

The answers to some of these questions are reported in the following pages, and the answers to others remain open. During lively discussions, some participants expressed reservations about making treatment choices based on NAb testing when so much uncertainty remained. ■

*Note: Due to the controversial nature of this topic, opinions or conclusions expressed by individuals should not be interpreted as reflecting the opinions or conclusions of other faculty members or as a group consensus.*

# Antibodies against interferons differ

Antibodies recognize specific molecular epitopes, which are unique structural domains within proteins.

Dr Anthony Reder of the University of Chicago, IL, USA, emphasized that the protein sequences and the 3-dimensional structures of the currently available interferon beta (IFN $\beta$ ) products (Betaferon<sup>®</sup>, Rebif<sup>®</sup> and Avonex<sup>®</sup>) differ (Figure 1). As a consequence, the molecular epitopes recognized by neutralizing antibodies (NAbs) against the three products also differ. For example, the binding of NAbs to residues 1–12 is lower in patients treated with IFN $\beta$ -1b (Betaferon<sup>®</sup>).

According to Dr Reder, antibodies against IFN $\beta$ s may also differ in function. While NAbs reduce the binding of IFN $\beta$  to its receptor, binding antibodies may produce positive effects. For example, antibody binding may modify IFN $\beta$  in a manner that enhances its affinity for its own receptor, or protects IFN $\beta$  from degradation and increases the effective half-life of IFN $\beta$  in the body. Alternatively, antibodies may bind to Fc receptors on monocytes and dendritic cells, and thereby inhibit immune responses. Dr Reder suggested that alternative antibody functions may contribute to the trend towards initial improvement in relapse rate in NAb-positive patients observed in clinical trials such as PRISMS (Figure 2). ■

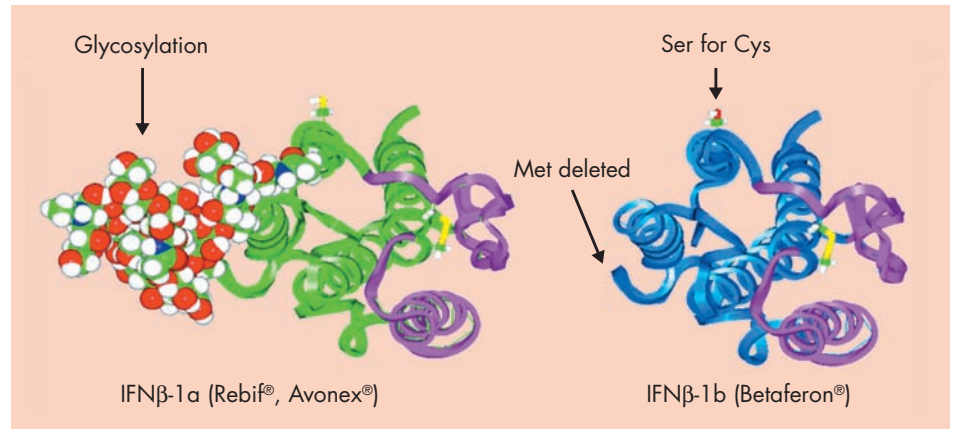


Figure 1: Structural differences between IFN $\beta$ -1a and IFN $\beta$ -1b that influence NAb formation

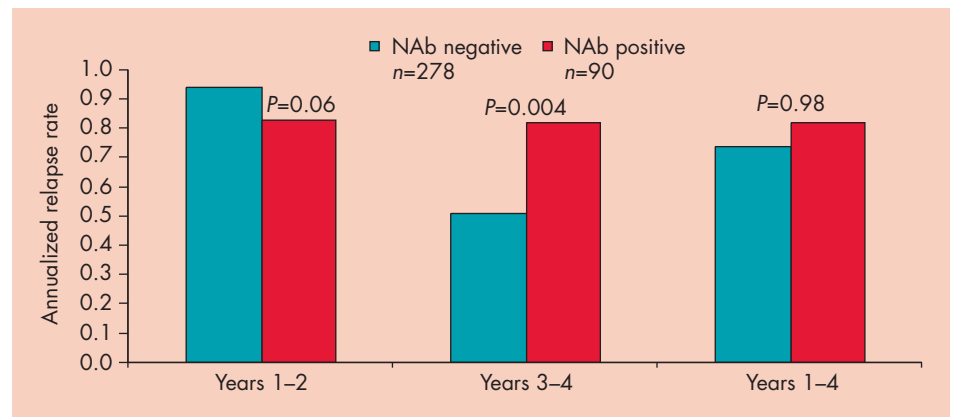


Figure 2: PRISMS: annualized relapse rates in patients positive for NAbs to IFN $\beta$ -1a at any time during the study. Adapted from Francis et al. *Neurology* 2005;65:48–55

## NAb production is a complex and dynamic process

Neutralizing antibodies (NAbs) are produced against all three interferon beta (IFN $\beta$ ) products, but distinct properties of these products affect the overall impact of the NAbs produced. For example, seroprevalence is higher with IFN $\beta$ -1b (Betaferon<sup>®</sup>) than IFN $\beta$ -1a (Rebif<sup>®</sup>), but IFN $\beta$ -1b is less immunogenic. Patients treated with IFN $\beta$ -1b are also more likely to revert to a NAb-negative status.

Four key characteristics may impact the overall effect of NAbs, explained Professor Per Soelberg Sørensen, from the University of Copenhagen, Denmark: immunogenicity (mean NAb titre in NAb-positive patients); seroprevalence (percentage of NAb-positive patients in a

patient population); the affinity of NAbs for IFN $\beta$ ; and the time course of the appearance and disappearance of NAbs.

NAb titre is the most important factor because it determines the physiological and clinical significance of NAbs.

Studies measuring IFN $\beta$ -induced MxA expression demonstrate that high titres of NAbs block the *in vivo* bioactivity of IFN $\beta$ , whereas low titres may not. Professor Jan Hillert, from Karolinska Institute, Huddinge, Sweden showed that patients with titres between 11 and 150 often retained their response to IFN $\beta$ , and reduced but measurable responses to IFN $\beta$  could be observed in patients with titres between 150 and 600.

According to Professor Hillert, NAb titres are more likely to be low after treatment with IFN $\beta$ -1b than after treatment with IFN $\beta$ -1a.

Professor Hillert also stated that patients with lower NAb titres are more likely to

regain IFN $\beta$  bioactivity over time than patients with high titres. NAb prevalence gradually increases over the first 6–24 months of treatment, then either remains stable or decreases depending on the IFN $\beta$  product. While patients may be NAb-positive for many years, Professor Sørensen showed that IFN $\beta$ -1b treatment is associated with a higher cumulative

probability of reverting to a NAb-negative status compared with IFN $\beta$ -1a (Figure 3). A study showed that after 12 years of IFN $\beta$ -1b therapy, only three of 59 (5%) patients had measurable NABs. Compared with NABs against IFN $\beta$ -1a, NABs against IFN $\beta$ -1b have a lower average titre and are more likely to disappear over time. ■

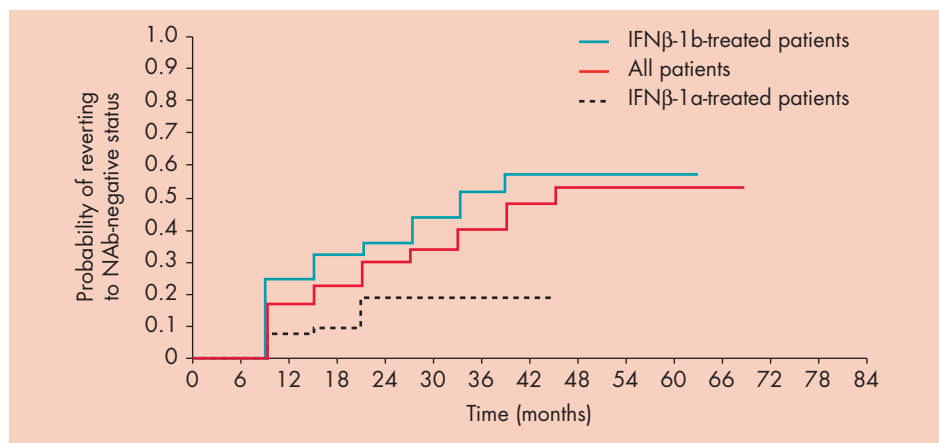


Figure 3: NAb-positive patients treated with IFN $\beta$ -1b are more likely to revert to a NAb-negative status than patients treated with IFN $\beta$ -1a. Reproduced with permission from Sørensen PS et al. Appearance and disappearance of neutralizing antibodies during interferon-beta therapy. *Neurology* 2005;65:33–39

## INCOMIN, EVIDENCE and a registry study

Despite neutralizing antibody (NAb) prevalence being higher in patients treated with IFN $\beta$ -1b (Betaferon<sup>®</sup>) or subcutaneous (s.c.) IFN $\beta$ -1a (Rebif<sup>®</sup>) compared with intramuscular (i.m.) IFN $\beta$ -1a (Avonex<sup>®</sup>), the high-dose and high-frequency patients experienced better outcomes in direct comparative trials than those treated with i.m. IFN $\beta$ -1a. Furthermore, recent results from a large registry study do not support the hypothesis that patients responding poorly to therapy are more likely to have NABs.

Professor Douglas Goodin of the University of California at San Francisco, CA, USA, presented data showing that the presence of NABs does not outweigh the enhanced efficacy of the higher dose/more frequently administered interferon betas (IFN $\beta$ s) during the first 2 years of treatment. Two comparative randomized clinical trials, EVIDENCE and INCOMIN, demonstrated that the proportion of relapse-free patients is higher with IFN $\beta$ -1b or s.c. IFN $\beta$ -1a treatment than with i.m. IFN $\beta$ -1a treatment despite greater NAB positivity.

**Data show that high-dose/frequently administered IFN $\beta$ s are more effective than low-dose IFN $\beta$  in the first 2 years of treatment**

In INCOMIN, IFN $\beta$ -1b-treated patients with NABs were more likely to be

*Continued on page 4*

## Induction of immune tolerance with higher-dose IFN $\beta$ -1b

The Optimization of Interferon dose for Multiple Sclerosis (OPTIMS) study demonstrated that a higher than standard dose of IFN $\beta$ -1b (Betaferon<sup>®</sup>, 375  $\mu$ g) reduced neutralizing antibody (NAB) seroprevalence over the 4-year study period more than the standard dose. These findings suggest that higher IFN $\beta$ -1b doses can induce immune tolerance, explained Dr Gavin Giovannoni from the Institute of Neurology, London, UK.

Although the clinical impact of NABs is controversial in patients treated with the higher dose/frequently administered IFN $\beta$ s, such as IFN $\beta$ -1b reducing the immune response to IFN $\beta$  may maximize efficacy, 'If we can get patients onto high-dose/high-frequency IFN $\beta$  treatment without NAB development, I am sure that efficacy will be well above the 30% that we quote,' stated Dr Giovannoni.

Increasing the dose and frequency of therapy induces tolerance to other therapeutic proteins, such as factor VIII. Since the relative weekly protein load of IFN $\beta$ -1b is higher than that of the IFN $\beta$ -1a products, the more frequent reduction in NAB seroprevalence observed with IFN $\beta$ -1b may suggest that IFN $\beta$ -1b therapy induces immune tolerance during continuous treatment. Several studies including BEYOND are investigating the clinical advantages of higher doses of IFN $\beta$ . ■

Continued from page 3

relapse-free than i.m. IFNβ-1a -treated patients without NABs (Figure 4). A similar result was found in EVIDENCE. However, it is possible that longer-term studies are needed to observe a clinical effect of NABs.

Adding to the ongoing debate over the clinical significance of NABs are the recent findings of a large registry study of IFNβ-1b-treated patients. NAB testing was conducted in 6698 patients from 1996 to 2000, making this the largest and most statistically powerful dataset ever collected to evaluate the impact of NABs. In North America and Europe, primarily patients doing poorly on therapy were tested for NABs. In contrast, NABs were measured in all Australian patients because it was required for reimbursement.

A geographical subgroup analysis demonstrated a significantly lower NAB seroprevalence in patients responding poorly to therapy in North America and Europe than in all patients in Australia. The incidence of NABs in the unselected Australian cohort was almost twice that of the selected North American cohort (37% versus 21.3%, respectively;  $P < 10^{-28}$ ).

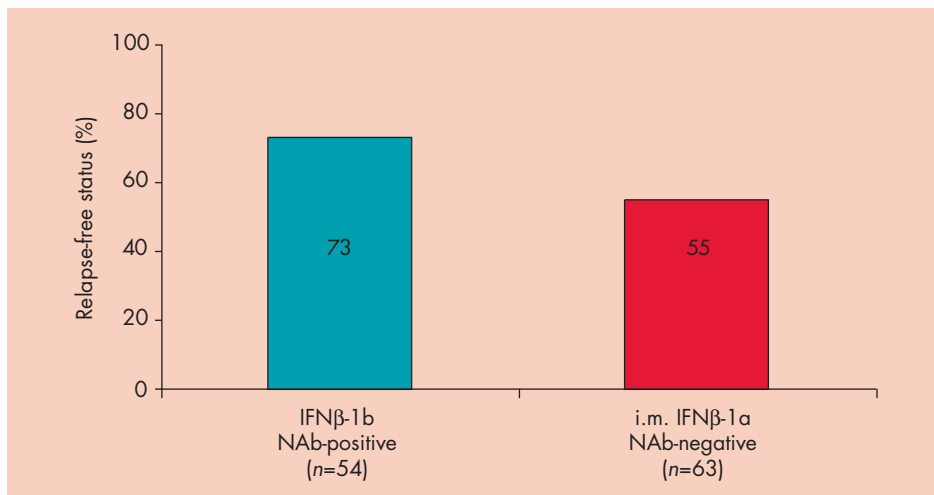


Figure 4: Results of the INCOMIN trial. More patients given IFNβ-1b were relapse-free compared with patients given i.m. IFNβ-1a, even when NAb-positive IFNβ-1b patients were compared with NAb-negative i.m. IFNβ-1a patients

**This registry trial has the largest and most statistically powerful dataset ever collected to evaluate the impact of NABs**

This observation is exactly the opposite of that expected if NABs are an important cause of poor response to

IFNβ therapy. The magnitude of the statistical significance of these differences excludes random variation as an explanation. At present, no satisfactory alternative explanation of these findings has been found.

Professor Goodin concluded that these data seem incompatible with the view that NABs are responsible for the poor clinical response observed in the North American and European patients. Because of the unexpected nature of these results, they need to be replicated in another study. ■

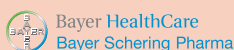


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## Product Information

**Betaferon® Composition:** Recombinant interferon  $\beta$ -1b 250  $\mu$ g (8.0 MIU) per ml when reconstituted. Betaferon contains 300  $\mu$ g (9.6 million IU) of recombinant IFNB-1b per vial.

**Indications:** Betaferon is indicated for the treatment of patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite MS. Patients with relapsing remitting MS and two or more relapses within the last two years, patients with secondary progressive MS with active disease, evidenced by relapses.

**Contraindications:** Initiation of treatment in pregnancy. Patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin or to any excipients. Patients with current severe depression and/or suicidal ideation. Patients with decompensated liver disease.

### Precautions:

- The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome.
- In rare cases, pancreatitis was observed with Betaferon use, often associated with hypertriglyceridaemia.
- Betaferon should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation. Depression and suicidal ideation are known to occur in increased frequency in the MS population and in association with interferon use. Patients treated with Betaferon should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Betaferon and treated appropriately. Cessation of therapy with Betaferon should be considered. Betaferon should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics.
- Thyroid function tests are recommended regularly in patients with a history of thyroid dysfunction or as clinically indicated. In addition to those laboratory tests normally required for monitoring patients with MS. Complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. AST (SGOT), ALT (SGPT) and  $\gamma$ -GT), are recommended prior to initiation and at regular intervals following introduction of Betaferon therapy, and then periodically thereafter in the absence of clinical symptoms.
- As for other beta interferons, severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking Betaferon. The most serious events often occurred in patients exposed to other drugs or substances known to be associated with hepatotoxicity or in the presence of comorbid medical conditions (e.g. metastasising malignant disease, severe infection and sepsis, alcohol abuse). Patients should be monitored for signs of hepatic injury. Withdrawal of Betaferon should be considered if the levels of serum transaminases significantly increase or if they are associated with clinical symptoms such as jaundice. In the absence of clinical evidence for liver damage and after normalisation of liver enzymes a reintroduction of therapy could be considered with appropriate follow-up of hepatic functions.

- Caution should be used and close monitoring considered when administering Interferon beta to patients with severe renal failure.
- It should also be used with caution in patients who suffer from pre-existing cardiac disorders. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia, should be monitored for worsening of their cardiac condition, particularly during initiation of treatment with Betaferon. Rare cases of cardiomyopathy have been reported: If this occurs and a relationship to Betaferon is suspected, treatment should be discontinued.
- Serious hypersensitivity reactions may occur. If reactions are severe, Betaferon should be discontinued and appropriate medical intervention instituted.
- Injection site necrosis has been reported in patients using Betaferon. It can be extensive and may result in scar formation. If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with his/her physician before continuing injections with Betaferon. If the patient has multiple lesions Betaferon should be discontinued until healing has occurred. Patients with single lesions may continue on Betaferon provided the necrosis is not too extensive, as some patients have experienced healing of injection site necrosis whilst on Betaferon.
- Neutralising activity was observed in patients in the different clinical trials. Between 23% and 41% of the patients developed serum interferon beta-1b neutralising activity; between 43% and 55% of these patients converted to a stable antibody negative status during the subsequent observational period of the respective study. The development of neutralising activity is associated with a reduction in clinical efficacy only with regard to relapse activity. The decision to continue or discontinue treatment should be based on clinical disease activity rather than on neutralising activity status.

**Side effects:** At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex and injection site reactions, which are mainly due to the pharmacological effects of the medicinal product. Injection site reactions occurred frequently after administration of Betaferon. The following side effect listing is based on reports from post marketing surveillance: Very common: Flu-like symptoms, chills, fever, injection site reaction, injection site inflammation, injection site pain; common: Injection site necrosis, uncommon: anemia, thrombocytopenia, leukopenia, depression, hypertension, vomiting, nausea, alanin aminotransferase increased, aspartate aminotransferase increased, urticaria, rash, pruritus, alopecia, myalgia, hypertonia; rare: skin discolouration, menstrual disorder, chest pain, malaise, sweating, weight decrease.

**Marketing Authorisation Holder and Numbers:** Schering AG, D-13342 Berlin, Germany, EU/1/95/003/003, EU/1/95/003/004,

**Preparation Date:** 06/06, Please refer to the Summary of Product Characteristics for further information.