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**22nd Congress
of The European
Committee for
Treatment and
Research in
Multiple Sclerosis
Madrid, Spain,
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2006**



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The Palacio de Comunicaciones, Plaza de Cibeles, Madrid – host city for the 22nd ECTRIMS meeting

Betaferon® licensed for early MS treatment in EU

Based on the positive results of the Betaferon® In Newly Emerging Multiple Sclerosis For Initial Treatment (BENEFIT) study, the European Union (EU) authorities have granted an extension of the label for Betaferon® (interferon beta-1b; IFNB-1b) to include patients with a first event suggestive of multiple sclerosis (MS), who are considered to be at high risk of conversion to clinically definite (CD) MS.

This decision represents an opportunity for European patients to receive treatment that could significantly reduce their risk of, and delay the onset of, CDMS, with its attendant disability. The BENEFIT study found that risk of conversion from clinically isolated syndrome (CIS) to CDMS was

significantly higher in patients with multifocal onset, that is, those whose clinical symptoms show at least two underlying lesions of the central nervous system (CNS). Monofocal patients, whose symptoms and signs were caused by one CNS lesion, were also at particularly high risk if they had high disease dissemination or activity, as shown by magnetic resonance imaging (MRI) scans.

IFNB-1b is now licensed in the EU for treatment of CIS patients who have an active inflammatory process warranting treatment with corticosteroids, for whom alternative diagnoses have been ruled out, and who are determined to be at high risk of CDMS. 'High risk' is defined as multifocal onset, regardless of MRI findings, or monofocal onset with at least nine T2 lesions, or at least one gadolinium-enhancing lesion. ■

Almost 5000 international physicians and researchers gathered in Madrid, Spain for Europe's most important event of the year concerning the research and treatment of multiple sclerosis (MS). This is an increase in attendance of over 30% compared with previous years.

A broad variety of topics was covered in the 4-day scientific programme, which included seven satellite symposia, as well as 38 oral presentations and almost 700 posters. The top floor of the impressive Palacio Municipal de Congresos hosted a wide range of exhibits from the pharmaceutical industry.

Recently, a number of advances in research in the field of MS have led to changes in our approach to treatment with disease-modifying therapies. This issue of *Medical Express Reports* outlines highlights of the topics discussed at ECTRIMS 2006, including presentations at a well-attended Schering AG-supported satellite symposium, and several important poster and oral presentations. ■

Early treatment can slow nerve destruction

Multiple sclerosis (MS) is especially destructive to the central nervous system (CNS) in its early stages, and early intervention can slow this process. Professor Giancarlo Comi, San Raffaele Scientific Institute, Milan, Italy, chaired a discussion of the rationale for early treatment by a trio of leading researchers at an informative symposium:

Maximising the benefits of MS treatment: Early intervention with high efficacy interferon beta therapy.

'In treating MS, we are dealing with a severe disease,' said Professor Comi, 'but we have the advantage of being in a position to detect the disease in its earliest biological stage.' Clinicians can make use of this advantage by using appropriate therapy early, when it will be most beneficial to the patient.

To prevent the accumulation of disability, we must target the disease at the time the most damage is occurring

A number of magnetic resonance imaging studies, using various techniques, show that most of the permanent damage to the CNS caused by MS happens early in the disease course. This damage is at least partly related to inflammation, which is predominant in early stages of the disease. Professor Comi pointed out that brain atrophy also occurs at this time, is correlated with the amount of inflammation, and can be slowed by immunomodulatory therapy.

'To prevent the accumulation of disability, we must target the disease at the time the most damage is occurring,' said Professor Comi, who then stated that

immunomodulatory therapies, which target inflammation, elicit a good response in the initial stages of disease, but have reduced efficacy at later stages when there are lower levels of inflammation (Figure 1). 'The CHAMPS, ETOMS and BENEFIT studies show that immunomodulatory therapies are more effective when given very early, compared to delayed treatment,' he said.

The results of the BENEFIT study have now shown a strong treatment effect in clinically isolated syndrome (CIS)

patients, stated Professor Mark Freedman, The Ottawa Hospital, Ottawa, Canada. He added that the effect of a high-dose, frequently administered interferon beta (IFNB) treatment in CIS was, until recently, unknown. For example, Betaferon® (IFNB-1b) treatment can reduce the risk of conversion to clinically definite MS by 50% over 2 years in comparison with placebo ($P < 0.0001$). 'By starting treatment at the CIS stage, we would hope to delay the point at which progression ensues,' he concluded. ■

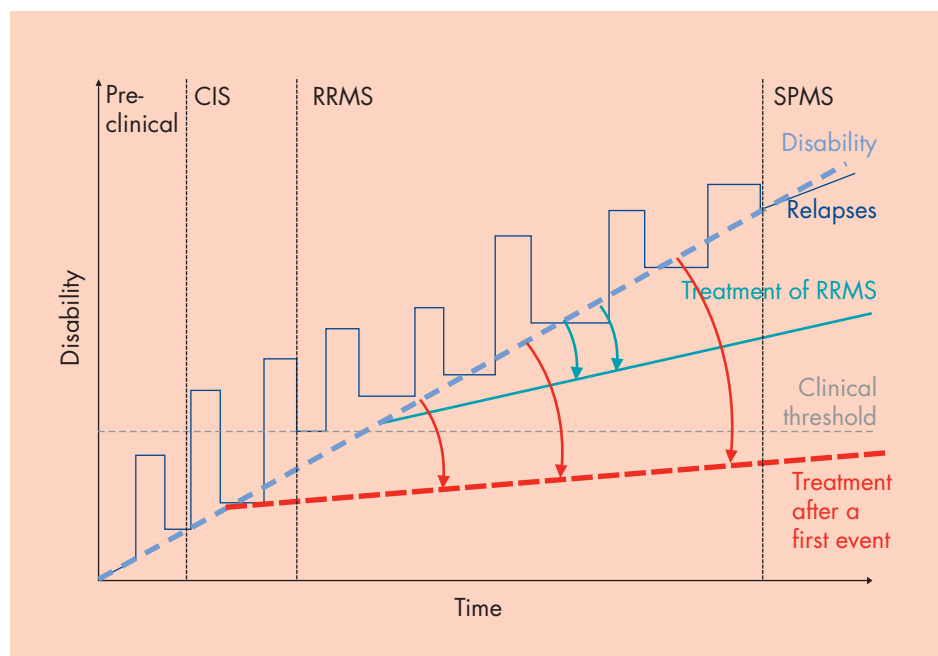


Figure 1: Hypothetical expectations of response to early treatment. RRMS, relapsing-remitting MS; SPMS, secondary progressive MS. Figure presented by Giancarlo Comi at ECTRIMS 2006

BENEFIT subgroups analysis supports early treatment

Patients with a clinically isolated syndrome (CIS) have a high risk of progression to clinically definite (CD) multiple sclerosis

(MS) within 2 years if they are not treated. A subgroup analysis of data from the BENEFIT study, presented by Professor Chris

Polman, Vrije University Medical Centre, Amsterdam, the Netherlands (Abstract 688), showed that certain patients run a particularly high risk of disease progression if they are not treated at an early stage.

All patients in the placebo group of the BENEFIT study were found to be at high

risk of CDMS. When they were subdivided according to mono- or multifocal onset, patients with monofocal disease were found to be at especially high risk of CDMS if they had a higher level of disease activity or dissemination as determined by magnetic resonance imaging (MRI) (≥ 9 T2 lesions or ≥ 1 gadolinium-enhancing lesion). For example, mono-focal patients with ≥ 9 T2 lesions had a 55% risk of CDMS at 2 years, compared with 31% in those with < 9 T2 lesions. This correlation between MRI findings and risk of CDMS was not found in multifocal patients, who were at high risk regardless of lesion burden (Figure 2). Betaferon® (IFNB-1b) had a more pronounced treatment effect in monofocal patients with disease activity or dissemination at onset; for example, in patients with ≥ 9 T2 lesions, treatment effect was 61%, whereas it was only 41% in patients with < 9 T2 lesions. These results led the European Union authorities to grant a new label for IFNB-1b in the treatment of certain patients with CIS suggestive of MS, as described on page 1. ■

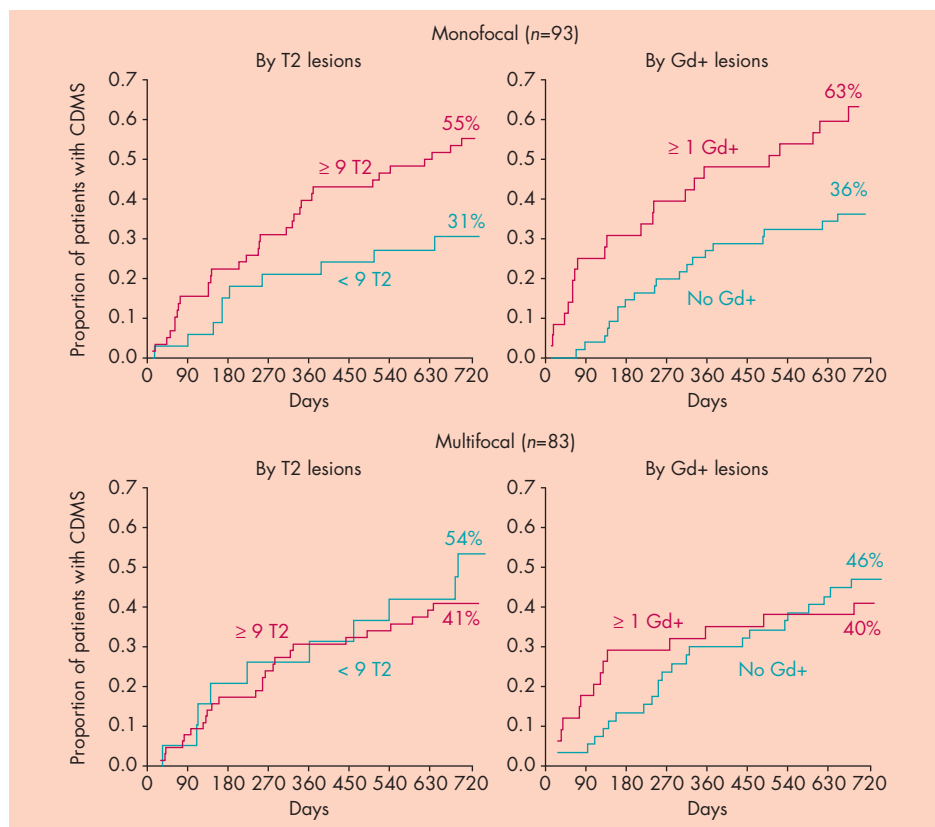


Figure 2: Impact of disease dissemination on the risk of conversion to CDMS over 2 years in placebo group. Gd+, gadolinium-enhancing

Baseline characteristics can predict long-term outcomes in MS

Several features of a first clinical event can help a clinician predict the risk for each patient, explained Professor Giancarlo Comi, San Raffaele Scientific Institute, Milan, Italy. These include symptoms and magnetic resonance imaging (MRI) lesion load at onset, relapse rate over the first 2 years, and the progression of disability over the first 5 years.

The number of relapses a patient has in the first 2 years of multiple sclerosis (MS) is an important predictor of future disability. Patients who relapse five times or more in this period can progress to a high level of disability as much as four times faster than those who suffer only a single relapse (Figure 3). Multifocal onset, a high initial lesion load, and progression to substantial

disability within 5 years also indicate a poor prognosis.

Testing for presence of antimyelin antibodies has previously been proposed as a predictor of the risk of disease progression. However, results from the BENEFIT study, presented by Dr Jens Kuhle from University Hospital, Basel,

Switzerland (Abstract 83), showed that tests for antimyelin antibodies have little or no prognostic value. Patients who tested positive for antibodies against myelin oligodendrocyte glycoprotein and myelin basic protein after a first clinical event did not have a heightened risk of clinically definite MS, or McDonald MS. ■

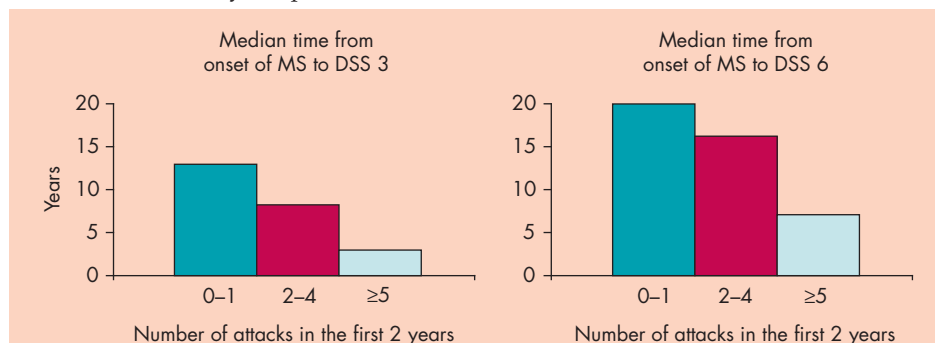


Figure 3: Number of attacks in first 2 years can predict future disability levels (based on a 25-year follow-up with a total of 25 000 patient-years of observation). DSS, Disability Status Scale. Figure presented by Giancarlo Comi at ECTRIMS 2006. Adapted from Ebers et al. JNNP 2001;71 (Suppl 2):16

Optimising adherence to therapy

Adherence to therapy is crucial in giving multiple sclerosis (MS) patients the best chance for the future. Frequent and open communication between the patient and healthcare professionals, adequate patient education and minimization of adverse events are all key factors in achieving the best possible adherence, said Professor Mark Freedman, The Ottawa Hospital, Ottawa, Canada.

He went on to detail how we can optimise patient adherence. 'We need to keep both the patient and the physician enthusiastic about maintaining the treatment,' Professor Freedman said. Patients need to have adequate contact with healthcare professionals, who can answer their questions and reassure them. 'Making use of patient support programmes is very important,' he advised. Patient adherence in trials of high-dose, high-frequency treatments is encouragingly high; for example, adherence was over 90% in the BENEFIT study. Indeed, it appears that patients in this study had a lower incidence of 'flu'-like symptoms, perhaps indicating that they got used to the drug quickly. Tolerability can be enhanced by the dose titration technique used when starting Betaferon® (interferon beta 1b; IFNB-1b) treatment, and by using autoinjectors and pain-relieving drugs. ■

BRIGHT study indicates that Betaferon® causes less injection site pain than Rebif®

The results of a recent study, presented at ECTRIMS by Dr Karl Baum, Hennigsdorf Clinic, Hennigsdorf, Germany, show that Betaferon® (interferon beta 1b; IFNB-1b) causes less injection site pain (ISP) and fewer injection site reactions (ISRs) than Rebif® (IFNB-1a).

The Betaferon® versus Rebif® Investigating Higher Tolerability (BRIGHT) study recorded the frequency and severity of ISP in patients treated with the full dose of IFNB-1b (250 µg subcutaneously every other day) or the full dose of IFNB-1a (44 µg subcutaneously three times weekly). Patients rated the severity of pain immediately, 30 minutes and 60 minutes after 15 consecutive injections. Significantly more IFNB-1b patients than IFNB-1a patients were pain-free at all three time-points over the 15 injections (Figure 4). This was true regardless of the size of needle used. The proportion of pain-free injections per patient was also significantly higher with IFNB-1b ($P < 0.0001$ in all cases). The proportion of patients who had no

Significantly more IFNB-1b patients than IFNB-1a patients were pain-free at all three time-points over the 15 injections

ISRs was significantly higher with IFNB-1b than with IFNB-1a, and significantly more IFNB-1b than IFNB-1a patients either had no pain, or were satisfied with their treatment ($P = 0.006$). ■

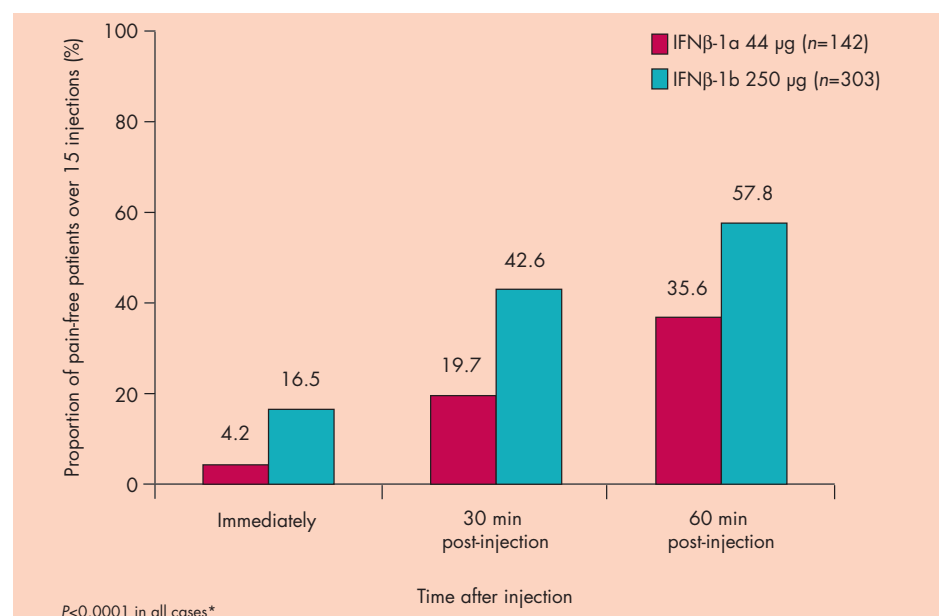


Figure 4: A higher proportion of IFNB-1b patients were pain-free over all injections

Smaller needles cause less injection site pain

Patients injecting Betaferon® (interferon beta-1b; IFNB-1b) experience less injection site pain when they use a smaller-sized needle, a subgroup analysis of the BRIGHT study has revealed. A new application system for IFNB-1b is being introduced, which will contain a finer needle. This may mean lower levels of injection site pain for IFNB-1b patients in future.

The analysis, presented by Dr Karl Baum, Hennigsdorf Clinic, Hennigsdorf, Germany (Poster 692), identified a subgroup of 226 BRIGHT patients who used the Betaject Light® autoinjector with either a 27 G (n=186) or a 30 G (n=40) needle. Significantly more

respectively; $P=0.0086$; Figure 5). The mean proportion of pain-free injections per patient was also significantly higher with the 30 G needle at 60 minutes post-

injection ($P=0.0266$). More than 90% of patients reported that the Betaject Light® autoinjector was 'easy' or 'very easy' to use. ■

Significantly more patients using a 30 G needle reported being pain-free 60 minutes after all 15 injections than those using a 27 G needle

patients using a 30 G needle reported being pain-free 60 minutes after all 15 injections than those using a 27 G needle (75% versus 52.2%

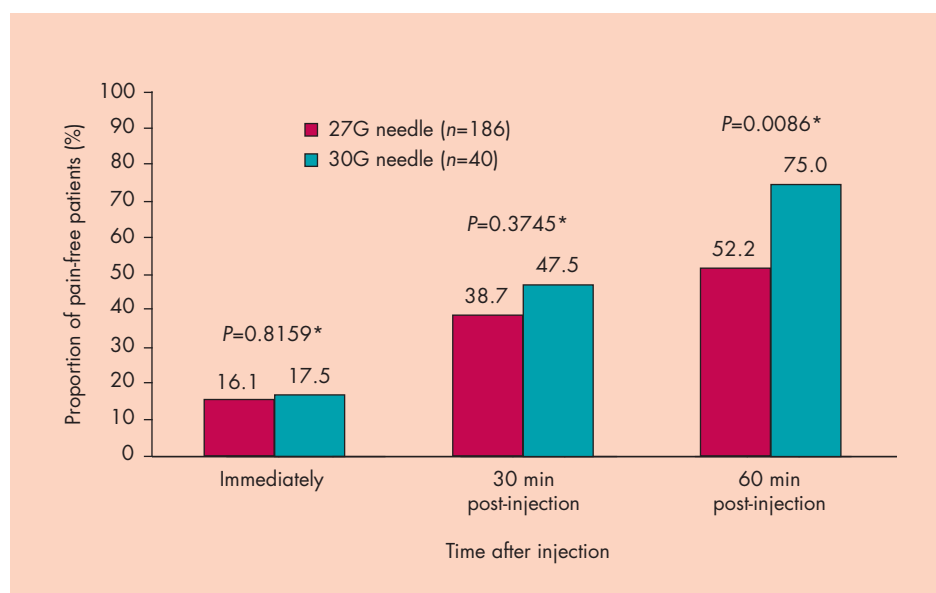


Figure 5: A significantly higher proportion of patients using a 30 G needle were pain-free 60 minutes after all injections. *Descriptive analysis

Autoinjectors reduce injection site pain

Betaferon® (interferon beta-1b; IFNB-1b) patients who use an autoinjector have fewer and less severe injection site reactions (ISRs) than those using a standard injection technique, reported Dr Bruno Brochet from Fédération des Neurosciences Cliniques du CHU de Bordeaux, Bordeaux, France (Abstract 690).

The EPICURE study, included 294 patients, and evaluated ISRs in 288 patients, using a crossover study design. The final results show that with a standard technique, 35.9% of injections resulted in a reaction. When either of two types of autoinjector (Betaject® or Betaject Light®) was used, reactions only occurred with 24.1% of injections ($P<0.0001$ in both cases). Reactions were also significantly more intense with a standard injection technique than with either of the autoinjectors ($P<0.0001$ in both cases; Figure 6). ■

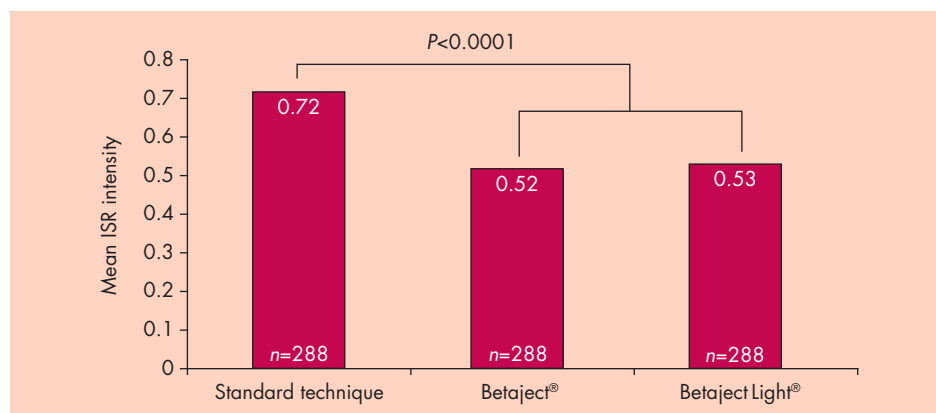


Figure 6: Mean intensity of ISRs

Early disability may predict long-term progression

Professor George Ebers, Oxford, UK, presented preliminary data from the longest-ever follow-up of multiple sclerosis (MS) patients on disease-modifying therapy.

The 16-Year Long-term Follow-Up study is a multicentre, open-label observational study evaluating long-term outcomes in patients who participated in the Betaferon® (interferon beta-1b; IFNB-1b) pivotal clinical trial. It is the longest-ever follow up of any cohort treated with disease-modifying therapy for MS. The preliminary data (Poster 666), show that 329 (88.2%) of the original patients have been located, and that unidentified patients are distributed equally among the treatment groups. Overall survival in identified patients is 89% and tolerability appeared to be excellent over the 16 years of treatment. Figure 7 shows

current disability in surviving identified patients as measured by the Expanded Disability Status Scale (EDSS), in relation to EDSS scores at treatment initiation.

These data appear to show that disability progression can be predicted by patients' EDSS score at treatment initiation. ■

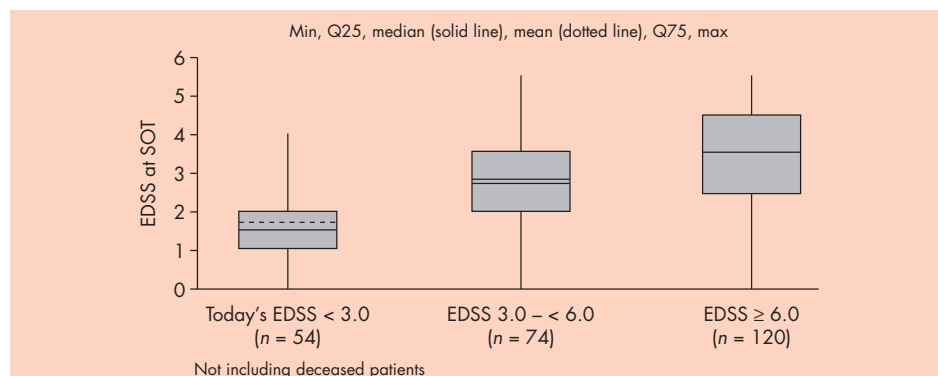


Figure 7. Correlation between current EDSS score with that at start of treatment (SOT)

Sustained effect of Betaferon® treatment

Magnetic resonance imaging (MRI) data suggest that Betaferon® (interferon beta-1b; IFNB-1b) has a sustained treatment benefit that is irrespective of the patient's disease duration.

MRI results from the 16-Year Long-Term Follow-up study, presented at ECTRIMS by Dr David Li, University of British Columbia, Vancouver, Canada, demonstrate that, as may be expected, patients who had not been treated with IFNB-1b for at least 90 days had a higher proportion of gadolinium-enhancing lesions than those discontinuing treatment more recently (Figure 8). This shows that IFNB-1b has an effect on gadolinium-enhancing lesions even after up to 16 years of treatment. ■

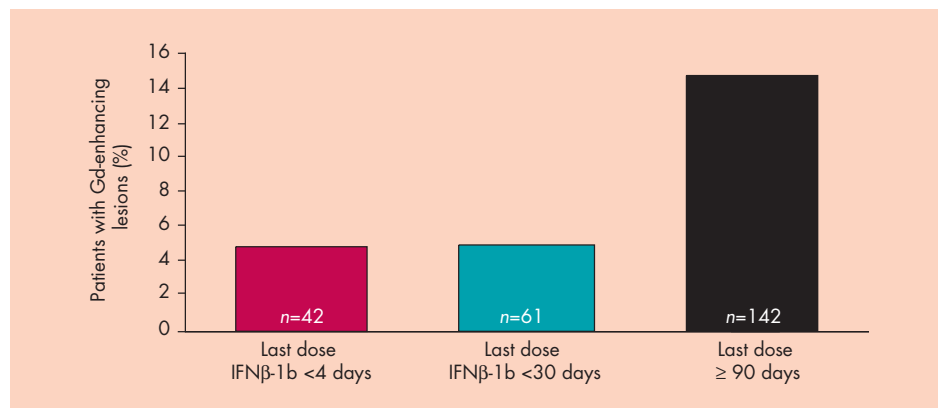


Figure 8: Patients with Gd-enhancing lesions stratified by treatment

Patients with a perceived poor response to Betaferon® found to have lower incidence of NABs

Two studies demonstrated that neutralising antibodies (NAB) to Betaferon® (interferon beta-1b; IFNB-1b) are transient, and may have little or no involvement in a poor response to treatment. This suggests that a patient's clinical course is a more useful basis for treatment decisions than their NAB status.

Dr Joel Oger from Neuroimmunology Laboratories and Multiple Sclerosis Clinic, Vancouver, Canada, presented the findings of a subgroup analysis of

IFNB-1b patients who tested NAB-positive at any point during the pivotal North American IFNB-1b trial (n=52; Abstract 803). The incidence of NAB

positivity peaked at around 18 months of treatment and then decreased thereafter. At 18 months, 83.7% of patients who were eventually NAB-

positive at some time during the study had a positive titre. However, by Month 39, 55.0% of this sub-group had reverted to NAb-negative status. This demonstrates that a large proportion of NAb-positive IFNB-1b-treated patients revert to NAb-negative status over a relatively short time (Figure 9).

Professor Douglas Goodin, University of California, San Francisco, USA, presented results of another NAb study, showing that two large cohorts of patients selected for a perceived poor response to IFNB-1b treatment had a significantly lower incidence of NAb than an unselected population. This suggests that NAb are not responsible for a poor clinical response to treatment. NAb were present in 21.3% of the North American cohort, and 27.6% of the European cohort, both of which comprised patients who were selected for a perceived poor response to IFNB-1b. These figures were significantly lower than that found in the unselected Australian cohort (37.0%), all of whom were tested regardless of response ($P < 1 \times 10^{-11}$ for both comparisons; Figure 10). ■

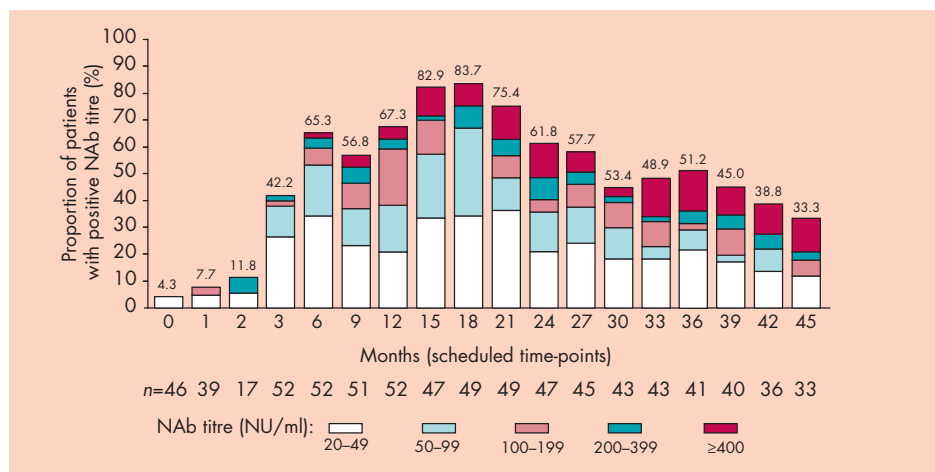


Figure 9: Proportion of patients from the eventually NAb-positive subgroup who were NAb-positive at each time-point

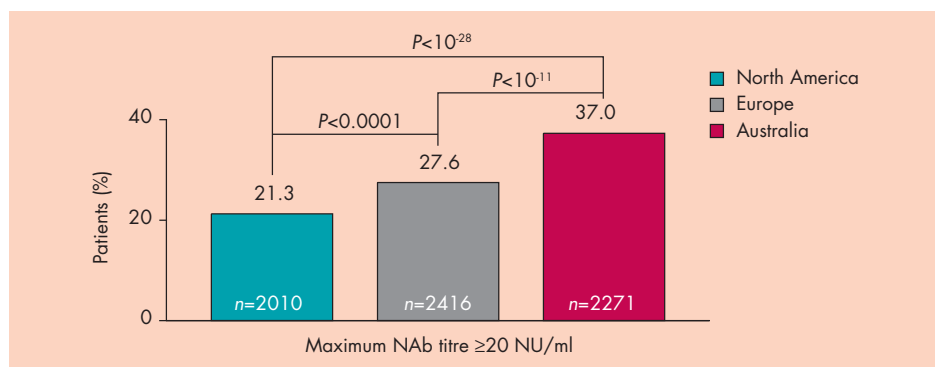


Figure 10: NAb were less prevalent in the selected cohorts (Europe and North America) than in the unselected cohort (Australia)

The 131st Annual Meeting of the American Neurological Association (ANA) took place in Chicago, USA, in October 2006. Among the highlights of the meeting were presentations of exciting new developments in two Betaferon® (interferon beta-1b; IFNB-1b) studies.

Long-term treatment improves clinical outcomes

Early-initiated, long-term IFNB-1b treatment can reduce relapse rates, delay conversion to secondary progressive (SP) multiple sclerosis (MS), and slow the progression of disability.

Further findings of the ongoing analysis of data from the 16-Year Long-Term Follow-up study were presented at this year's ANA meeting by Professor Douglas Goodin, University of California, San Francisco, USA. The results show that long-term IFNB-1b treatment was correlated with a lower annual relapse rate. Treatment with IFNB-1b for 17 years was associated with a 6.6-year increase in time to SPMS compared with no treatment. Patients who received long-term IFNB-1b treatment took an average of 4.7 years longer than untreated patients to reach an Expanded Disability Status Scale (EDSS) score of 6. ■

Betaferon® has favourable effects on MSFC

Recently reported results of the BENEFIT study show that early IFNB-1b treatment can improve Multiple Sclerosis Functional Composite (MSFC) scores in comparison with placebo.

The median MSFC score of the IFNB-1b-treated group increased by 0.119 from baseline to study end, which was significantly higher than the 0.06 improvement in the placebo group ($P=0.0386$). Interestingly, this improvement was mainly driven by the cognitive function component of the test. As expected, no changes in ambulation were observed in this mild population, either on the MSFC or EDSS. These disability outcomes of the BENEFIT study, presented by Professor Hans-Peter Hartung, Düsseldorf, Germany, appear to support a potential cognitive benefit of early IFNB-1b treatment in patients with clinically isolated syndrome. ■

Treatment with Betaferon® controls disease progression

Interim results from the ongoing Betaferon® in Early relapsing-remitting multiple Sclerosis Surveillance Trial (BEST) observational study confirm that Betaferon® (interferon beta-1b; IFNB-1b) lowers relapse rates and stabilises or reduces disability over the first 3 years of relapsing-remitting MS.

Interim 2- and 3-year data from the BEST study were presented by Professor Ludwig Kappos, University Hospital, Basel, Switzerland, at this year'sECTRIMS meeting (Poster 694). They show that patients completing 2 and 3 years of IFNB-1b treatment have a marked reduction in their rate of relapse compared with pre-treatment rates. Patients completing 2 years of treatment showed a mean reduction in annual relapse rate of 53.7%, while those who completed 3 years showed a mean reduction of 38.9% (Figure 11). The good level of disease control over this period was also reflected by the proportion of patients whose disability level had not increased: 82.6% at 2 years, and 77.8% at 3 years.

Another poster presented by Professor Kappos announced that recruitment is complete for the BEST pharmaco-

genomic and pharmacogenetic study, which is expected to provide important

insights into the mechanism of action of IFNB-1b (Poster 695). ■

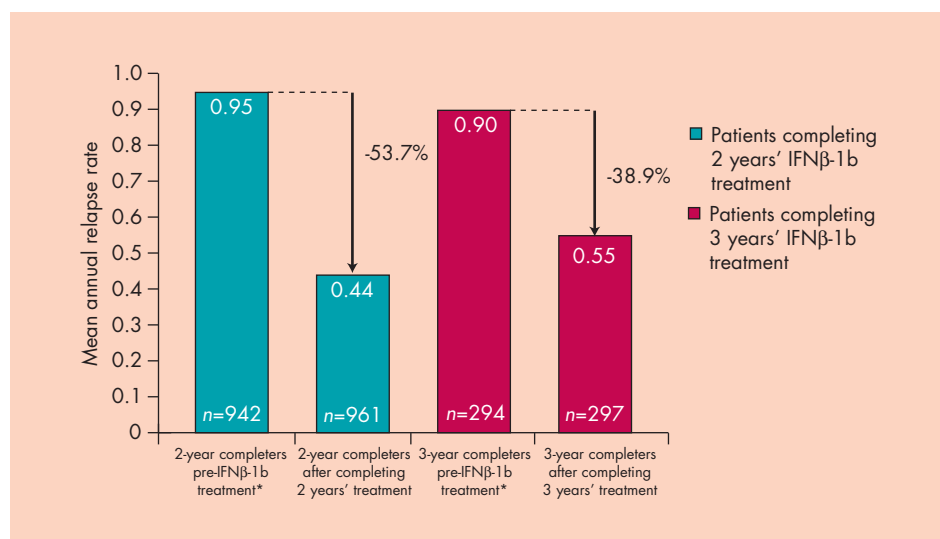


Figure 11: IFNB-1b treatment reduces mean annualized relapse rate. *, pre-treatment relapse rate was determined at baseline by the treating physician for the preceding 2 years

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Breaking news

In October 2006, the US Federal Drug Administration extended the license for Betaferon®/ Betaseron® (interferon beta; IFNB-1b) to include treatment of patients with a first event and magnetic resonance imaging features suggestive of multiple sclerosis (MS). IFNB-1b is the only high-dose, high-frequency IFNB approved in the USA for treatment of the earliest stage of MS. This follows a similar license extension in Canada in August. In November 2006, Australia became the latest country to expand its indication for IFNB-1b.