

MEDICAL *express* REPORTS

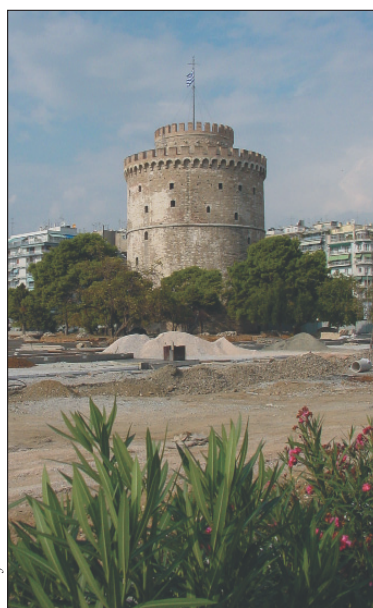
ISSN 0956-8298
VOLUME 15 ISSUE 8

**Joint 21st ECTRIMS
Congress and
10th Annual
ACTRIMS Meeting
28 September–
1 October 2005**

The BENEFITs of early intervention

The BENEFIT (Betaferon®/ Betaseron®, interferon beta-1b, for Newly Emerging multiple sclerosis For Initial Treatment) study reveals a highly significant and clinically meaningful effect of therapy in the treatment of patients with a first clinically demyelinating event and an MRI scan indicative of multiple sclerosis (MS).

'Interferon beta-1b demonstrated robust and compelling effects on the progression to MS in patients with a first clinically demyelinating event suggestive of MS,' said Professor Ludwig Kappos, Basel, Switzerland. With Betaferon® treatment the onset of clinically definite (CD) MS was delayed by 1 year at the 25th percentile compared with placebo, and there was a risk reduction of 50% over 2 years from the development of CDMS in the Betaferon® group. Supportive MRI outcomes data demonstrated that the median cumulative number of newly active lesions and the change in T2 lesion volume are reduced by Betaferon® treatment compared with placebo. The implementation of a titration scheme for the first 19 days of therapy helped patients attain the 250 µg dose of Betaferon®. In addition, patients were recommended to use concomitant



White Tower, Thessaloniki, Greece.

medication and autoinjectors to reduce the incidence of flu-like symptoms and optimize injection technique, respectively. Adherence was high, with 93% of patients from the Betaferon®-treated group reaching the scheduled end of the study.

In-depth results from the BENEFIT study are reported on pages 2–5. ■

Treatment optimization with current therapies to improve patient outcomes was the main focus of discussion at the recent joint meeting of the European Committee for Treatment and Research in Multiple Sclerosis and the American Committee for Treatment and Research in Multiple Sclerosis in Thessaloniki, Greece.

The biannual joint meeting alternates between a European and a US venue and on this occasion it was Greece's second largest city, Thessaloniki, that welcomed over 3500 physicians and researchers, and representatives from major pharmaceutical companies exhibiting at the congress. There was a broad selection of topics covered in the symposium programme, and almost 700 posters were on display over the course of the 4-day meeting.

This issue of *Medical Express Reports* describes topics discussed at the ECTRIMS/ACTRIMS Congress, including highlights from the Schering AG-supported symposium *The BENEFIT of Early Treatment*. In addition, new data describing the beneficial effects of very long-term treatment (16 years) are detailed, as well as reports on new therapies on the horizon.

NOVEMBER 2005

MRI outcomes support role for early treatment intervention

Data from the double-blind part of the BENEFIT study show that Betaferon® treatment had a favourable effect on the two secondary MRI efficacy variables, median cumulative number of newly active (new gadolinium [Gd]-enhancing or new/enlarging T2) lesions and the median absolute change in T2 lesions volume. Supportive MRI evaluations also favoured Betaferon® treatment. These results add to the clinical evidence and provide backing for the role of early treatment intervention in patients with a first clinically demyelinating event and MRI scan suggestive of MS.

Betaferon® treatment had a favourable effect on two secondary MRI efficacy variables

The median cumulative number of newly active lesions was significantly lower in Betaferon®-treated patients compared with placebo patients at Months 12 and 24 ($P < 0.0001$, adjusted for number of Gd-enhancing lesions at screening; Figure 1A), reported Professor Frederik Barkhof, Amsterdam, The Netherlands (Poster 583 ECTRIMS/ACTRIMS 2005). The median absolute change in T2 lesion volume from screening to Month 12 ($P = 0.026$) and Month 24 ($P = 0.026$) was also reduced by Betaferon® treatment compared with placebo (Figure 1B). All other supportive MRI variables of the secondary endpoints of the BENEFIT study showed statistically significant and profound effects of Betaferon® treatment on lesion development. ■

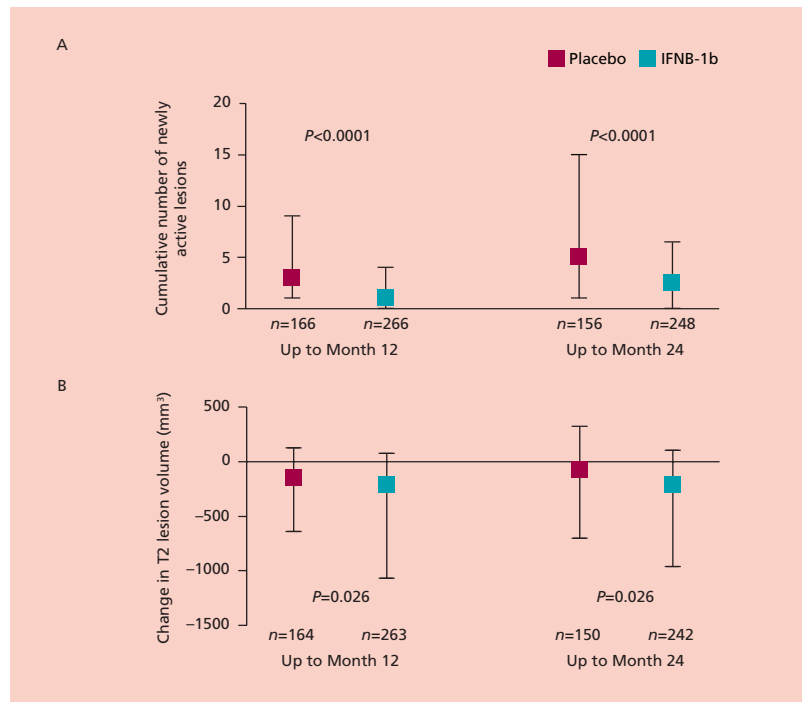


Figure 1: Secondary MRI endpoints, cumulative number of newly active lesions (A) and change in T2 lesion volume (B) were improved by Betaferon® treatment.

Validation of the BENEFIT standardization scheme

During the BENEFIT study, neurologists determined whether patients presenting with a first clinical event had one (monofocal) or more (multifocal) lesions in the central nervous system. Monofocal patients have less disseminated disease. Results presented at ECTRIMS/ACTRIMS 2005 by Dr J? Nielson (Poster 102) demonstrated that the classification scheme was valid by comparing the results of the application of the scheme with the MRI data obtained in the patients.

Patients classified as multifocal had more T2 lesions (median 20) than monofocal patients (median 15.5) and more T1 hypointense lesions (median 2 versus

median 1). Furthermore, the more MRI criteria for MS that were fulfilled, the more likely it was that a patient was classified as multifocal. The clinical

classification scheme was therefore deemed meaningful. The prognostic value of monofocal or multifocal classification will be evaluated in a follow-up study. ■

Time to diagnosis of MS is delayed by Betaferon®

Betaferon® 250 µg subcutaneously every other day reduced the risk of developing clinically definite (CD) MS, according to the Poser diagnostic criteria, by 50% in patients with a first clinical demyelinating event and MRI scan suggestive of MS. With Betaferon® treatment, the onset of CDMS was delayed by 1 year at the 25th percentile ($P < 0.0001$; Figure 2). At Day 255, 25% of patients treated with placebo had reached CDMS, while this event occurred at Day 618 in Betaferon® patients.

When comparing Betaferon® treatment with placebo, the risk ratio was 0.53 without adjustment and 0.50 when adjusted for key disease prediction factors. Betaferon® therapy, therefore, reduced the risk of progression to CDMS according to the Poser criteria by 50% over 2 years compared with placebo.

With Betaferon® treatment, the onset of CDMS was delayed by 1 year

Similarly, the proportion of patients reaching MS according to the McDonald criteria was lower in the Betaferon® group ($P < 0.0001$). 'The relative reduction is clearly significant, with a value of 46%,' said Professor Ludwig Kappos, Basel, Switzerland, in his presentation as part of the scientific programme of ECTRIMS/ACTRIMS 2005 (Abstract O50). The proportion of placebo patients reaching MS according to the McDonald criteria was 85%, while only 69% of Betaferon® patients were diagnosed with MS (Figure 3). Therefore, the cumulative probability over 2 years of not developing MS according to the McDonald criteria was twice as high in the Betaferon® group as in the placebo group.

Betaferon® therapy reduced the risk of progression to CDMS by 50%

The high proportion of patients treated with placebo reaching MS according to the McDonald criteria indicates a high probability that patients presenting with a first clinical demyelinating event and MRI suggestive of MS will progress to MS. Therefore, there is an important need for early intervention in this patient population to delay progression to CDMS.

Betaferon® also had a robust effect in patients with less disseminated and less active disease at the time of the first event. Betaferon® reduced the risk of progression to CDMS by 55% ($P < 0.00001$) in patients with monofocal disease onset (i.e. signs and symptoms explained by a single demyelinating lesion). ■

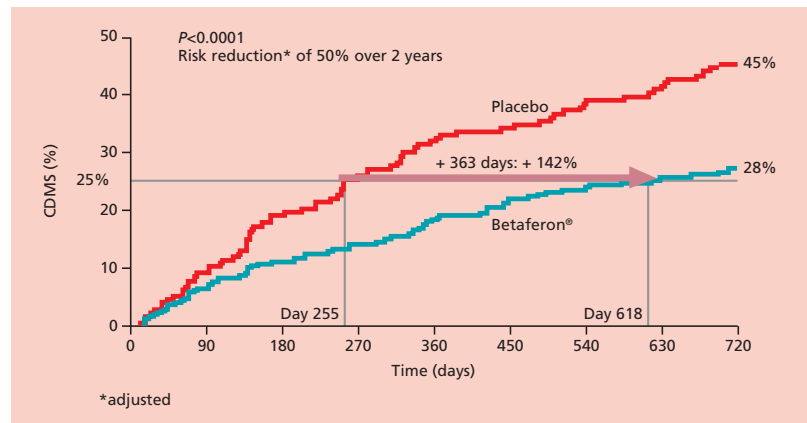


Figure 2: Proportion of patients developing CDMS according to the Poser criteria was reduced by Betaferon® treatment compared with placebo.

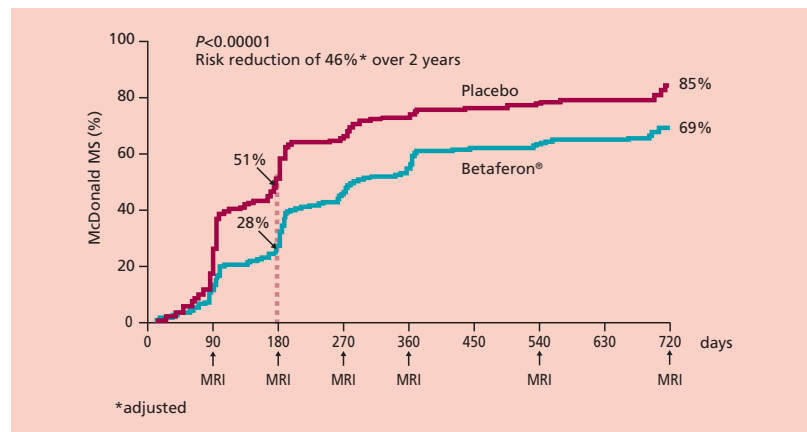


Figure 3: Proportion of patients developing MS according to the McDonald criteria was reduced by Betaferon® treatment compared with placebo.

Clinical implications of the BENEFIT study

Clinicians are currently faced with a dilemma regarding treatment with immunomodulatory therapy when a patient comes to them with a first clinical event. Clinical studies have shown that Betaferon® is highly effective in relapsing forms of MS, providing reassurance to clinicians. The results of the BENEFIT study of patients with a first clinical event ‘reiterate that these patients are at a high risk of having greater disease activity,’ explained Professor Mark Freedman, Ottawa, Canada, in his presentation at the Schering AG-supported symposium at ECTRIMS/ACTRIMS 2005. These patients require a treatment that is highly effective and also well tolerated.

Evidence indicates that irreversible axonal injury occurs early in the MS disease course, even before clinical symptoms are detected. This early inflammatory damage may not be lethal to axons at the time of the insult, but may predispose them to death. Furthermore, as the disease progresses it may be more difficult to control this immune-mediated destruction. The results of the BENEFIT study showed that, without treatment, most placebo patients (85%) presenting with a first clinical event and MRI scan suggestive of MS will develop MS according to the McDonald criteria within 2 years. ‘Therapy aimed at reducing inflammation needs to be in place when inflammation is occurring,’ said Professor Freedman. ‘If we wait until a patient has two clinical attacks, there is a lot of disease activity that has occurred sub-clinically.’ Both the CHAMPS (Jacobs CD *et al. N Engl J Med* 2000;18: 898–904) and ETOMS (Comi G *et al. Lancet* 2001;357:1576–1582) studies examined the efficacy of once weekly, low-dose interferon beta-1a (30 µg intramuscularly or 22 µg subcutaneously, respectively) in patients who experienced a first clinical event. However, unlike the BENEFIT follow-up study, neither study included a pre-planned, long-term analysis of the effects of early intervention.

The BENEFIT study was designed to include a population representative of real-life clinical practice. Specifically, the study included patients with monofocal and multifocal presentation.

Betaferon® reduced the risk of progression to CDMS by 55% ($P < 0.00001$) in patients with monofocal disease onset (i.e. signs and symptoms that are explained by a single demyelinating lesion). ‘The treatment effect is even stronger in this patient group,’ said

Monofocal onset

- Clinical symptoms are explained by one single central nervous system (CNS) lesion, e.g. blurred vision in the left eye
- Less disseminated onset of disease

Multifocal onset

- Clinical symptoms are explained by at least two underlying CNS lesions, e.g. blurred vision of the right eye and brisk quadriceps reflex on the left
- More disseminated onset of disease

Professor Freedman. Essentially, similar patient groups were enrolled in the BENEFIT and ETOMS studies, whereas the CHAMPS study was different – only patients with a monofocal presentation were included (i.e. less severe disease). It is interesting to see the differences in the results of the respective trials (Table 1).

Given that there is firm evidence to support the dose–response relationship of interferon beta in relapsing forms of MS (Durelli L *et al. Lancet* 2002;359:1453–1460; Panitch H *et al. Neurology* 2002;59: 1496–1506), it is of considerable interest to examine whether increased benefits can be obtained in patients with a first event suggestive of MS if higher doses and frequent administration are used. The

Betaferon® reduced the risk of progression to CDMS by 55% in patients with monofocal disease onset

BENEFIT study is the first trial to show a significant and clinically meaningful effect of Betaferon® 250 µg every other day in patients with a first clinical event and MRI indicative of MS. The pre-planned long-term follow-up period (at least 3 years) will reveal further valuable long-term data in 2008. ■

	BENEFIT Mono-/multifocal	ETOMS Mono-/multifocal	BENEFIT Monofocal subgroup only	CHAMPS Monofocal only
Patients (n)	468	309	246	383
Risk reduction for conversion to CDMS (Poser criteria)	50% ^a	35% ^a	55% ^b	44% ^b
Premature discontinuation of study in interferon beta group	7.2%	10%	15.1%	16%

^aAdjusted.
^bUnadjusted.

Table 1: A comparison of BENEFIT, ETOMS and CHAMPS results.

High adherence to Betaferon® in BENEFIT

Patient adherence was high in the BENEFIT study, indicating that frequently administered subcutaneous Betaferon® 250 µg is well tolerated by patients presenting with a first clinical event suggestive of MS, reported Professor Chris Polman, Amsterdam, The Netherlands, during the Schering AG-supported satellite symposium.

The implementation of a titration scheme (Figure 4) helped patients to initiate Betaferon® therapy and may have contributed to the notable tolerability of Betaferon®. In addition, patients were advised to use an autoinjector to reduce the incidence of injection-site reactions, and concomitant medication with non-steroidal anti-inflammatory drugs (NSAIDs) to diminish the occurrence of flu-like symptoms. ‘The titration scheme, and other factors, such as autoinjectors and use of NSAIDs, contributed to the good adherence,’ said Professor Polman. In total, 93% of patients enrolled in the Betaferon® treatment arm reached the end of the study, compared with 94% of placebo patients (Figure 5). Only 2.1% of Betaferon® patients discontinued the study due to adverse events, while 3.8% withdrew consent (4.0% in the placebo group), 1.0% were lost to follow-up (1.1% in the placebo group) and 0.3% gave ‘other’ reasons (0.6% in the placebo group). The excellent retention rate in the BENEFIT study also compares favourably with other studies in early MS since the results from the CHAMPS and ETOMS studies show retention rates of 85% and 90%, respectively. The percentage of patients adhering to study medication in the BENEFIT trial was 90% for the placebo group and 85% for patients taking Betaferon®. Reasons for why patients stop taking the medication were withdrawal of consent, adverse events, lost to follow-up, planned pregnancy and ‘other’.

A titration scheme helped patients to initiate Betaferon® therapy

Once the double-blind portion of the study ended, 95% of patients chose to enter the open-label, follow-up study on Betaferon® therapy. This indicates a high level of patient satisfaction with Betaferon®. Furthermore, with such a high proportion of patients entering the follow-up, ‘this puts us in a good position to study the long-term impact of this treatment,’ said Professor Polman.

Importantly, quality of life was maintained on treatment, showing that any adverse events noted had no impact on this measure. Betaferon® was very well tolerated and had an excellent

95% of patients chose to enter the open-label, follow-up study on Betaferon® therapy

safety profile in this study. Furthermore, with regard to injection-site reactions and flu-like symptoms, ‘there was a decrease, as we would expect, in these adverse events over time,’ commented Professor Polman. ■

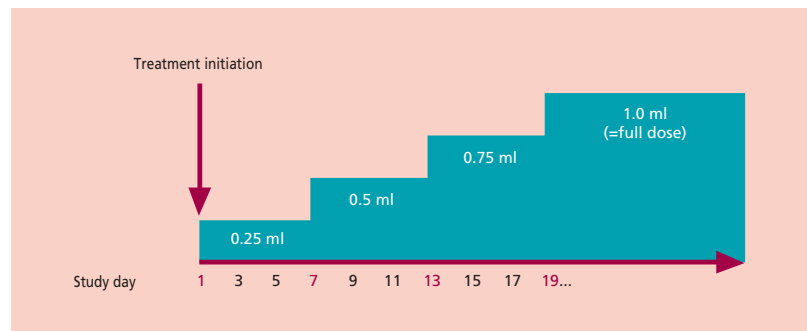


Figure 4: Dose titration aids the tolerability of Betaferon®.

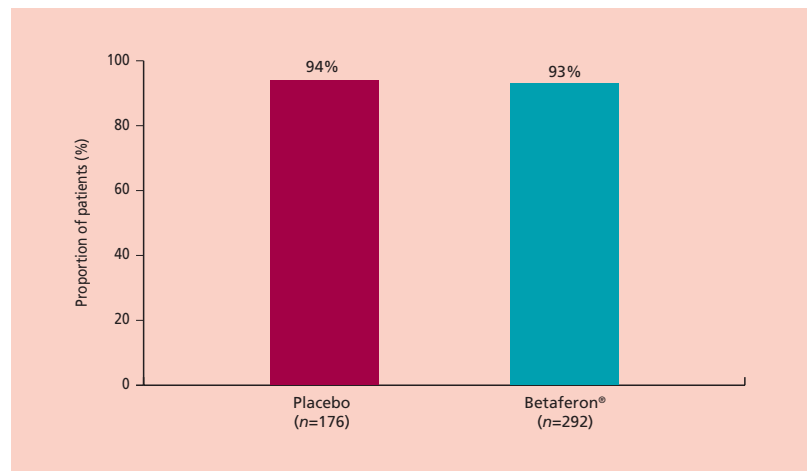


Figure 5: A high proportion of patients with a first event suggestive of MS adhered to Betaferon® therapy.

The total cost of MS in the USA

The total cost of MS in the USA is \$39 500 per patient per year and the main overall cost driver is early retirement, reported Dr Gisela Kobelt, Karolinska Institute, Stockholm, Sweden (Poster P148, ECTRIMS/ACTRIMS 2005). Dr Kobelt presented important new data from the first complete bottom-up study to investigate the cost of MS in the USA since the introduction of disease-modifying therapies (DMTs).

A total of 4000 patients treated with DMTs at the last follow-up were randomly selected from the North American Committee on MS (NARCOMS) Patient Registry. Patient-reported demographic and prescription drug data were collected, along with patient-reported functional disability using Patient Determined Disease Steps, which correlates well with the Expanded Disability Status Scale (EDSS) score.

A total of 1909 (47.4%) questionnaires were suitable for analysis; and 98% of the respondents were receiving treatment with an MS-specific therapy (interferon beta: 59.5%; glatiramer acetate: 34%; mitoxantrone: 4.5%). The majority of patients (63.7%) had either

changed their work, reduced their working hours, or had stopped working completely due to MS, which had a considerable impact on the indirect costs. Early retirement due to MS

occurred in 31.4% of respondents. Disability increased the costs of MS. Figure 6 shows that the main cost driver was early retirement (34%) and DMTs accounted for 21% of the costs. ■

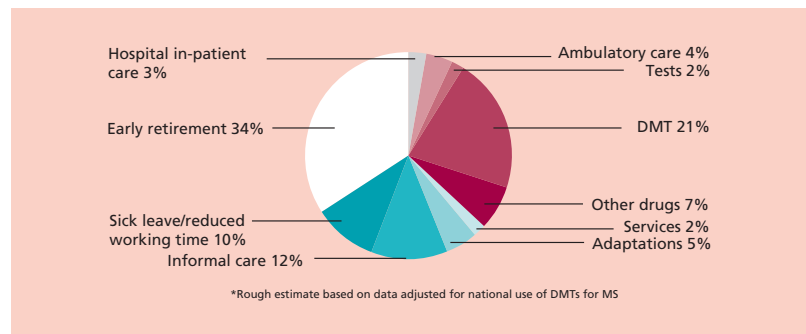


Figure 6: Distribution of the costs of MS in the USA (adjusted for DMT use).

BEST – ‘real-life’ treatment with Betaferon® in early RRMS

Analysis of interim data from the Betaferon® in Early RRMS Surveillance Trial (BEST) confirms that Betaferon® treatment reduces relapse rate and Expanded Disability Status Scale (EDSS) progression (Poster P584, ECTRIMS meeting 2005). Dr Ludwig Kappos, Basel, Switzerland, presented the latest data on 500 patients who have now completed 2 years of the study.

BEST is a prospective, 5-year, observational, international study of patients with early relapsing-remitting (RR) MS treated with 250 µg Betaferon® subcutaneously every other day in normal clinical practice. The decision to start therapy is separate from inclusion in the study, and patients should not have received previous interferon beta therapy. Data are collected every 6 months and the study is ongoing.

More than 3000 patients from 32 countries had enrolled in the study by April 2005, and 500 patients had attended a baseline visit and a follow-up visit after at least 2 years. Of these patients, 85% remained progression-free (Figure 7). Over the first 2 years of

treatment with Betaferon®, the mean annualized relapse rate decreased by 51%, from 0.90 pre-treatment to 0.44. Adverse events were reported in 9% of patients, but none was new or

unexpected. There was some correlation between early termination of treatment and a number of parameters, including female gender, higher pre-study relapse rates and greater pre-study disability. ■

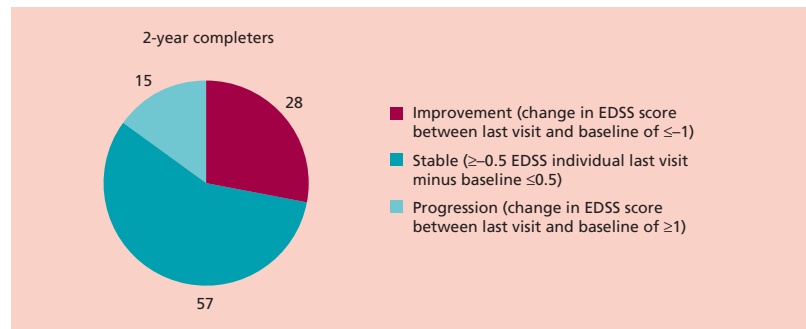


Figure 7: Disability status of the patients who have completed 2 years of the BEST study (%).

M E D I C A L ■ *express* ■ R E P O R T S

Treatment effect of Betaferon® at 16 years

A total of 331 (89%) patients from the original 372 enrolled in the pivotal Betaferon® trial have so far been identified, which is a tremendous achievement. Furthermore, of the investigated patients, 50% have been taking Betaferon® for more than 10 years, indicating a high patient satisfaction with their Betaferon® therapy. Some patients have been receiving Betaferon® for almost 14 years.

Case-report forms for 210 patients have been reviewed as of 15 September 2005. Of these, 70/210 (33%) are currently taking 250 µg Betaferon® and 86/210 (41%) have been taking Betaferon for more than 80% of the time span between the end of the pivotal trial and 15 September. The median exposure to 250 µg Betaferon® in the 210 patients has been 3644 days, or 10 years. For those patients investigated who were assigned to the 250 µg Betaferon® arm in the pivotal trial (n=78), the median length of treatment is 5014 days, i.e. almost 14 years.

Betaferon® has a good safety profile and is well tolerated in the long term, as indicated by the adherence to therapy and by the minimal adverse events. In the past 6 months, there were 93 patients taking Betaferon® 250 mg. In this group of patients, the proportion of patients experiencing explicitly queried adverse events was low (Figure 8).

Of the 297 patients identified who are alive, 175 (59%) are ambulatory and 76 (26%) require the use of a wheelchair or are bedridden. The status of the remaining patients is, as yet, unknown. Interestingly, 51% of the patients originally assigned to the Betaferon® 250 µg group in the pivotal trial report being able to walk with or without assistance, compared with 45% originally assigned to the placebo group. Furthermore, 95% of the patients originally assigned to the Betaferon® 250 µg group who have been identified are alive, compared with 83% from the placebo group. The greater number of deaths among the original members of the placebo group is a finding that warrants further attention.

Preliminary results from the 16-year long-term follow-up study of Betaferon® show that long-term treatment may slow the time to EDSS progression,

reported Professor George Ebers, Oxford, UK, in his poster presentation at ECTRIMS/ACTRIMS 2005 (Poster 296). The time for patients to reach an EDSS score of 6 was greater in patients who received Betaferon® for more than 80% of the time since the start of treatment in the pivotal trial and 2005 compared with those patients who were

treated for less than 10% of the time (Figure 9). These data are consistent with the hypothesis that early treatment initiation has a long-lasting beneficial impact. All analyses are strictly exploratory in nature and hypothesis generating, but results from the study allow clinicians to assess the long-term safety and efficacy of Betaferon®. ■

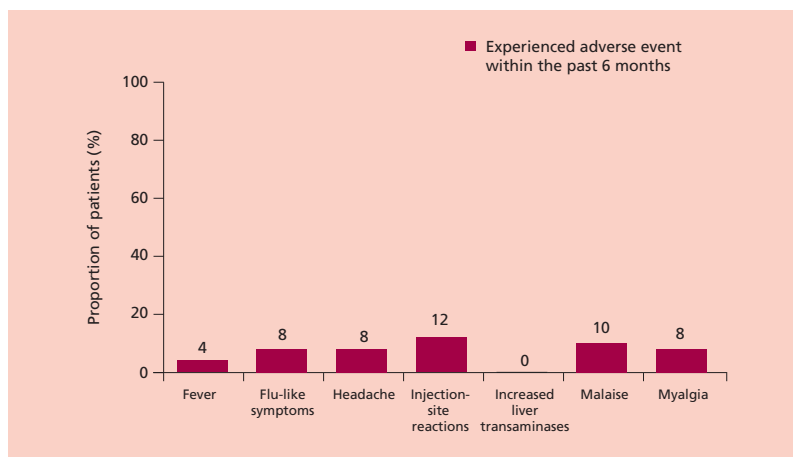


Figure 8: Adverse events to Betaferon® in patients on treatment in the past 6 months.

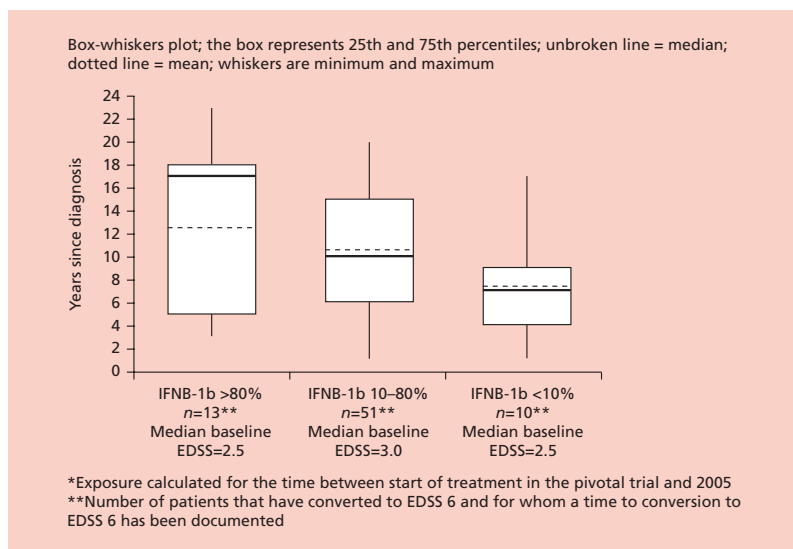


Figure 9: Time to an EDSS score of 6 stratified according to exposure to Betaferon®.*

The importance of early treatment

The evidence indicates that immunomodulatory therapy initiated early could be beneficial for patients, reported Professor Xavier Montalban, Barcelona, Spain, in his presentation at ECTRIMS/ACTRIMS 2005 (Oral presentation 49). Data from natural history studies indicate that early relapse rate may dictate progression, and irreversible axonal injury occurs early in MS. Furthermore, clinical trials with interferon beta have revealed a beneficial effect of therapy when started in patients with a first clinical event.

A study in patients with monosymptomatic disease has investigated the time to progression to an EDSS score of 6, and found that 90% of the impact on subsequent disability was related to the number of attacks in the first 2 years. The median time to reach an EDSS score of 6 was approximately 22 years in patients with one attack in the first year, compared with 13 years in those with 2–4 attacks and less than 7 years in those with ≥ 5 attacks (Weinshenker BG *et al. Brain* 1989;112:1419–1428). Therefore, disability appears to be correlated with attacks very early in the course of the disease.

Magnetic resonance imaging evidence also shows that axonal transection begins at disease onset, suggesting that cumulative axonal loss provides the pathological basis for progressive disability eventually encountered by most patients with MS. Examination of brain tissue obtained at autopsy from patients with MS showed that transected axons were a consistent feature of MS lesions and that their frequency was related to the degree of inflammation within the lesion (Figure 10).

Finally, clinical trials to evaluate the effect of early treatment in patients with

a first clinical event have demonstrated that such treatment is effective, but these studies have limitations. Long-term data are an important requirement to ascertain for certain whether long-term disability can be averted by early intervention. For many neurologists, the decision to initiate treatment is taken in expectation of long-term data becoming available. The BENEFIT study will address this important need by providing 5-year data on the treatment of patients presenting with a first clinical

event and MRI scan suggestive of MS with 250 μg Betaferon[®] subcutaneously every other day. ■

The BENEFIT study will address an important need by providing 5-year data

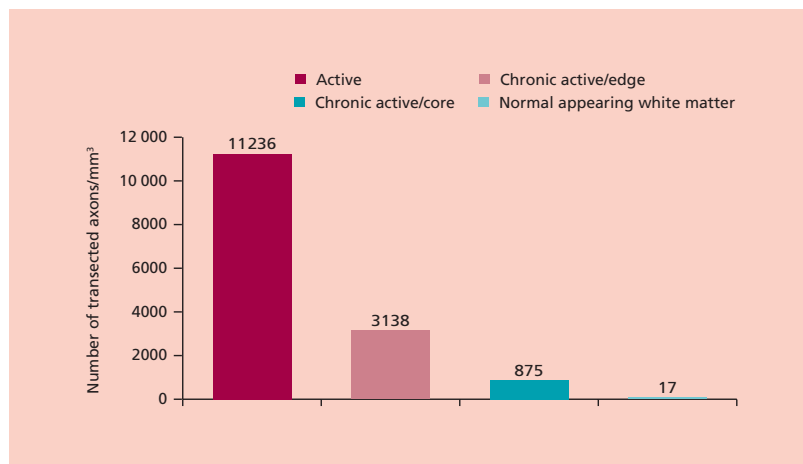


Figure 10: Axonal damage is associated with the amount of inflammation within the lesion. Reproduced with permission from Trapp BD *et al. N Engl J Med* 1998;338:278–285.



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