

MEDICAL *express* REPORTS

ISSN 0956-8298
VOLUME 15 ISSUE 6

19th Annual CMSC
1-5 June 2005

15th Meeting of the ENS
18-22 June 2005

Two major conferences in June 2005 examined recent advances in the treatment of patients with multiple sclerosis (MS). These were the Annual Meeting of the Consortium for Multiple Sclerosis Centers (CMSC) in Orlando, USA, and the Meeting of the European Neurological Society (ENS) in Vienna, Austria.

This time attracting over 1000 healthcare professionals and others specialising in the care of people with MS, the CMSC meeting is now an important event for the communication of study results in the field. The ENS meeting devotes a large portion of the scientific programme to MS, and approximately 1600 delegates were in attendance. Both meetings had large symposia programmes and, in total, almost 200 posters detailing results from MS studies were presented. Exhibition halls filled with major pharmaceutical companies were also features of both meetings.

This issue of *Medical Express Reports* discusses highlights from both meetings, including the Schering AG-supported symposium at the ENS meeting entitled '*Betaferon® at 16 Years: Pioneering Long-term Experience*', and the CME-accredited 3rd Annual Symposium '*Early Start, Long-term Results: Optimising Treatment Options for Patients with Multiple Sclerosis*'. In addition to focusing on early and long-term treatment, new data on cognitive outcomes, therapies in development, comparative studies and increased interferon beta dosing are presented.



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St Stephen's Cathedral is an impressive landmark of the Austrian capital, Vienna – host of the 15th Meeting of the ENS.

Betaferon® at 16 years

Delaying Betaferon® therapy could have an adverse effect on long-term outcomes, suggest data presented by Professor George Ebers at the ENS meeting 2005.

Patients initially enrolled in the 250 µg Betaferon® group in the 1990 original pivotal trial have better outcomes in terms of ambulation and survival than those enrolled in the placebo group, the preliminary data indicate. The results also show that Betaferon® is safe and well tolerated over the long term, as indicated respectively by survival data and adherence to therapy. The 16-year long-term follow-up (LTF) study provides a

clinical assessment of patients who first enrolled in the Betaferon® pivotal trial. Analyses are currently intention to treat, meaning that once the patient left the double-blind phase of the pivotal trial, they could have received any, or none, of the available disease-modifying therapies. The Betaferon® 16-year LTF study is expected to provide landmark long-term safety, tolerability and efficacy data for patients initiated on Betaferon® therapy compared with control populations. No other immunomodulatory treatment has been available for this length of time.

For a discussion of the preliminary data please turn to page 3. ■

Design of 16-year LTF study

The 16-year long-term follow-up (LTF) study is an exploratory multi-centre, open-label, observational study of patients with relapsing-remitting (RR) multiple sclerosis (MS) who participated in the pivotal North American randomised, placebo-controlled study of Betaferon® (1988–1990). The study's objective is to evaluate the impact of Betaferon® treatment on long-term outcomes in these patients, reported Professor George Ebers, Oxford, UK (Poster 499, ENS meeting 2005).

Patients are contacted and invited to participate in the study. If they agree, some information is collected immediately, such as whether they are able to walk unaided, with aids or use a wheelchair, and a clinical visit is arranged so that a neurologist can thoroughly assess their current clinical status. There are also plans to identify and assess a never-treated control cohort. The information gathered will include:

- Medical history
- Medication history
- Adverse events associated with use of Betaferon®
- Neurological and functional scores
- Neuropsychological status
- Quality of life as determined using patient-reported measures
- An up-to-date magnetic resonance imaging scan
- Analysis of blood chemistry, blood cell counts, thyroid function and immunological parameters.

Analyses of these data will be exploratory and hypothesis generating. For outcome analyses, patients will be stratified by original dose group (250 µg Betaferon®, 50 µg Betaferon® or placebo subcutaneously every other day) and by overall exposure to Betaferon®. Outcomes of the treated population will also be compared with the outcomes of the untreated patients from the control cohort or natural history information derived from the London, Ontario Natural History Database. ■

Cognition and quality of life over 16 years of Betaferon®

Cognitive and health-related quality of life (HRQoL) evaluations are key objectives of the 16-year long-term follow-up (LTF) study, stated Dr Dawn Langdon, London, UK (Poster 234, ENS meeting 2005). The study is using a novel combination of HRQoL scales that will reveal multiple aspects of the disease, yielding a large amount of information that will go beyond the normal Expanded Disability Status Scale (EDSS) score measurements. Furthermore, measuring these outcomes is painless and inexpensive. The study is testing a possible methodological solution to evaluate long-term HRQoL and will increase understanding of HRQoL in more advanced MS disease and under long-term treatment with Betaferon®.

Patient-reported outcomes (PRO) incorporate responses to therapy which can evaluate patient satisfaction with treatment, performance measure for productivity assessment, discomfort, inconvenience and any other patient-based assessments of health status. HRQoL is a subcategory of PRO, and comprises physical, psychological and social components. HRQoL and patient well-being have become important factors in MS during the past decade, serving as significant measures of treatment efficacy additional to established clinical outcomes.

Cognitive impairment is experienced by 40–60% of patients with MS, said Dr Langdon. It affects HRQoL, disease management and adherence to treatment. The relationship between HRQoL and cognitive impairment is

complex and poorly understood, particularly in long-term disease.

There is some evidence that Betaferon® has beneficial effects on HRQoL (Table 1) and cognition in patients with MS, but there are currently no long-term data demonstrating a treatment effect. The 16-year LTF study of the original cohort of the Betaferon® pivotal trial is currently ongoing and will investigate HRQoL.

The HRQoL battery of tests used in the 16-year LTF study includes:

- Functional Assessment of Multiple Sclerosis (FAMS)
- EuroQoL 5-dimension (EQ-5D) questionnaire
- Multiple Sclerosis Standard Health Care Survey (MS-SHCS)
- Hospital Anxiety and Depression Scale (HADS)

Continued on page 10

Study	n	Follow-up	PRO	Outcome
Betaferon® RRMS	117	~5 years of treatment	SF-36	Improvement compared with controls
Betaferon® SPMS	718	Up to 3 years	SIP	Beneficial effect (lessening of deterioration compared with placebo)
Avonex® RRMS	172 (137)	Up to 8 years	SIP	All objective indicators worsened by follow-up
Avonex® SPMS	327	2 years	SF-36	Possible effect on mental but no effect on physical outcomes compared with placebo
Avonex® RRMS	121	1 year	SF-36	No negative effect on MS patient's QoL
Rebif® RRMS	576	1 year	SF-36	Improvement for therapy-responders compared with controls or non-responders

PRO, patient-reported outcomes; RR, relapsing-remitting; SP, secondary progressive; SF-36, 36-item Short Form Health Survey Questionnaire; SIP, Sickness Impact Profile; QoL, quality of life.

Table 1: Influence of therapy on quality of life in MS.

High patient identification for the ongoing 16-year LTF study

Recruitment to the 16-year long-term follow-up (LTF) study began in January 2005 and all 11 original North American sites are participating. Even after 16 years, by 14 June 2005, 299 (80.4%) of the original 372 patients had been identified, reported Professor George Ebers, Oxford, UK (Poster 499, ENS meeting 2005). 'All sites except one have identified more than 65% of their patients and two sites have identified 100%', he said. The high number of patients identified gives confidence that the population evaluated is likely to be representative of the overall cohort.

The percentage of patients identified to date is similar for the three original treatment allocation groups: Betaferon® 250 µg subcutaneously (sc) every other day (eod) (102 patients); Betaferon® 50 µg sc eod (98 patients); and placebo (99 patients).

Survival in the Betaferon®-treated groups is greater than in the placebo group when looking at the intent-to-treat population (Figure 1). Steps are currently being taken to identify the cause of death for all deceased patients.

More patients treated with Betaferon® in the pivotal trial have also reported continued ability to walk than those patients receiving placebo (Figure 2).

Betaferon® therapy is also well tolerated over the long term. Case report forms (CRFs) for 135 patients have been

reviewed so far. Almost half of these patients are currently taking Betaferon® at the licensed dose of 250 µg sc eod. Furthermore, 58/135 (43%) patients have been taking 250 µg Betaferon® for more than 80% of the time during the past 16 years. The median exposure to Betaferon® in those 135 patients has been almost 12 years (4286 days). These data indicate that Betaferon® is safe over the long term.

These preliminary data suggest that Betaferon® treatment initiated sooner rather than later has a long-lasting beneficial impact. Final conclusions on this question wait for more patients to be identified. Analysis of the outcomes will then be carried out, and comparisons with natural history cohorts made. 'The London, Ontario database is the gold standard to which results will be compared', said Professor Ebers. ■

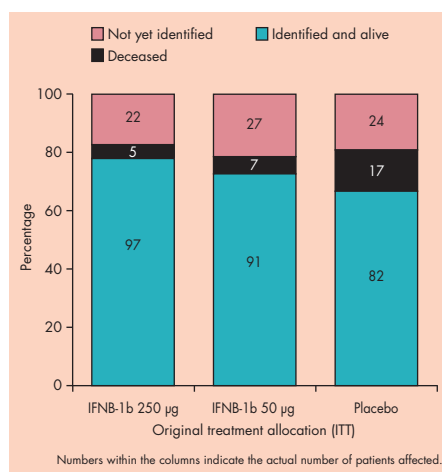


Figure 1: Patient disposition of the 16-year LTF study according to original treatment allocation (n=372). ITT, intent-to-treat.

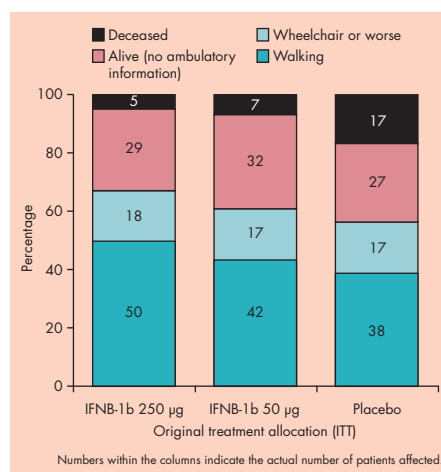


Figure 2: Ambulatory status of patients according to original treatment allocation (n=299). ITT, intent-to-treat.

Background

As MS is a chronic, long-term disease, it would be ideal to inform treatment decisions with data from long-term, randomised, double-blind, placebo-controlled clinical trials. However, inclusion of a placebo-control group in a long-term study is unethical – it is not in the best interests of the patients given placebo to be denied an efficacious therapy for so long. Also, patients taking placebo for long periods of time are likely to receive no benefit and choose not to stay in the study. Furthermore, the definition of 'best practice' evolves over time as data on new therapies or dosing regimens become available. Thus, if a trial continues for a sufficient period of time, even the 'on-treatment' group may be inadequately treated according to best practice guidelines.

An alternative to a randomised, placebo-controlled, long-term study is an open-label, non-randomised, long-term study that recruits consenting patients for the non-treated arm (for example, those with personal reasons to refuse treatment, although this is also problematical as this patient group may, for example, have more severe disease activity at baseline) and includes a process for periodically revising the on-treatment protocol. Although less rigorous, this type of study satisfies ethical concerns. However, practical problems are encountered. The likelihood of patients discontinuing participation in the study increases with time, and makes the results difficult to interpret – perhaps data are skewed by loss of the sickest patients, who wish to change therapy, or by loss of the healthiest patients, who are busy and inconvenienced by the study demands. Continuous long-term trials are also expensive to support, and clinical trials of new drugs are given a higher priority. Creative approaches are required to obtain data on the benefits of long-term, disease-modifying therapy for MS patients. Two valuable methods are the use of natural history control groups, and a cross-sectional review of all patients at a time point distant to the end of the trial. These are both being used in the 16-year long-term follow-up study.

Cognitive dysfunction in CIS and early MS – CogniCIS/CogniMS study

Cognitive deficits can be a significant problem for people with clinically isolated syndrome (CIS) and in early MS, but few data are available for this patient group. CogniCIS/CogniMS aims to obtain data on cognitive functioning and investigate its interaction with clinical outcome and health-related quality of life (HRQoL) measures.

Cognitive deficits can undermine the skills necessary for everyday activities and, therefore, have a significant influence on quality of life. While such problems are acknowledged in patients diagnosed with MS, little is known about the influence that cognitive deficits have on patients with CIS and early MS and whether it can be used to predict prognosis of the disease.

CogniCIS/CogniMS comprises two complementary, observational, international, multicentre, 2-year, longitudinal studies of cognitive impairment. In a poster at the CMSC meeting 2005 (W13), Dr Dawn Langdon,

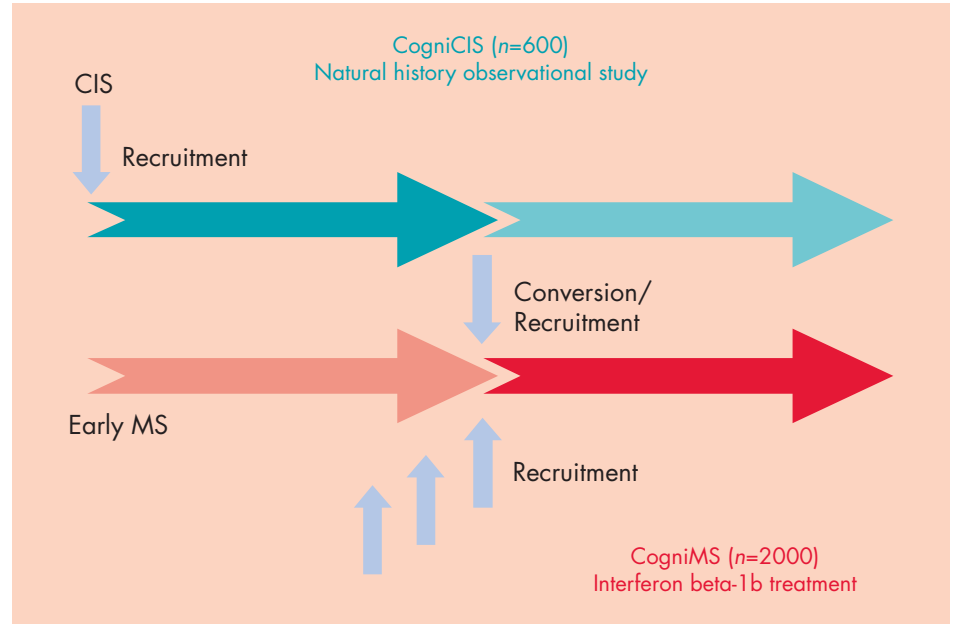


Figure 3: CogniCIS/CogniMS study design.

London, UK, presented the study design (Figure 3). The aim is to recruit 2000 patients who have been diagnosed with MS and have started treatment with Betaferon® to the CogniMS arm, and 600 patients with CIS suggestive of MS to the CogniCIS arm, stated Dr Langdon.

The study has been designed to characterise the profile and time dynamics of cognitive impairment in CIS and early MS patients and will examine how subjective cognitive status, depression, fatigue and HRQoL relate to cognition in these populations. ■

BEST – Improvement in quality of life for Betaferon® patients

Quality of life interim data from the Betaferon® in Early RRMS Surveillance Trial (BEST) indicate that patients treated with Betaferon® and not experiencing progression show an improved Functional Assessment of Multiple Sclerosis (FAMS) Trial Outcome Index (TOI) compared with Betaferon® patients demonstrating disease progression. FAMS is simple to use in a routine manner, and these early results indicate that it can discriminate between different courses of MS as well as between different levels of disability.

BEST is a prospective, international, 5-year, observational study to assess the safety, tolerability and long-term effect of Betaferon® on early disease progression, reported Dr David Cella, Evanston, IL, USA, in his presentation at the ENS meeting 2005 (Abstract O136). More details about the BEST study and the clinical 2-year analyses can be found on page 11.

Interim, 2-year, health-related quality of life (HRQoL) data are available for 292 patients from nine countries. Overall physical health as reported by patients was analysed using the FAMS-TOI. The median score from baseline to the individual's last visit remained stable. In those patients who remained stable ($n=188$), the median change in FAMS-TOI was +2.4, indicating an

improvement in HRQoL. In patients whose EDSS score improved ($n=39$), the median change in FAMS-TOI was +4.0, whereas in those patients who experienced progression ($n=46$), the FAMS-TOI reduced by 11.3 points, indicating a worsening in HRQoL. ■

Anticipating benefits – Betaferon® in early MS

The last of the 468 patients who started therapy have completed the 2-year investigational treatment with Betaferon® in the BENEFIT (BEtaferon®/Betaseron® in Newly Emerging multiple sclerosis For Initial Treatment) study. Initial analyses show high adherence (93%) to Betaferon® 250 µg subcutaneously (sc) every other day (eod) in patients with the first clinical signs of MS, reported Professor Chris Polman, Amsterdam, The Netherlands. ‘The dropout rate after 2 years is low even if all of these patients came from the Betaferon® group’, he said. Furthermore, over 90% of all patients completing the study have decided to continue treatment with Betaferon® in an open-label, follow-up study. BENEFIT is the first study providing valuable data on the effects of Betaferon® on conversion to clinically definite (CD) MS.

BENEFIT, a multicentre, randomised, double-blind, placebo-controlled, Phase III study, was designed to investigate the safety, tolerability and efficacy of Betaferon® in patients with the first clinical

symptoms indicative of MS. It will evaluate the effect of early treatment with Betaferon® initiated after the first clinically demyelinating event on the development of a second attack, and the impact of early treatment on the formation of new brain lesions (measured by MRI).

The BENEFIT study has been conducted at 98 centres in 20 countries and has included 487 patients. Of these, 468 received at least one dose of study medication (250 µg Betaferon® sc eod or placebo) and, in all cases, treatment began within 60 days after symptoms were assessed, reported Professor Polman. Patients continued in the study for 24 months unless they experienced a second attack and were diagnosed with CDMS. At this point patients were given the opportunity to participate in the open-label, follow-up study. The overall design of the BENEFIT study is shown in Figure 4.



Professor Chris Polman speaking at the Schering symposium during the 15th ENS meeting in Vienna, Austria.

Reliable and precise tools for identifying patients at risk of developing CDMS are vital, especially when early treatment is an option. In addition, providing evidence for dissemination in time and space of central nervous system involvement is a key issue in diagnosing MS. For these reasons, and to reduce an unwanted source of variation, both the local BENEFIT study investigator and a central assessment committee classified each patient’s first event. Local investigators characterised events as ‘monosymptomatic’ or ‘polysymptomatic’, while the committee assessed whether the event was ‘monofocal’ or ‘multifocal’. The main outcome of the study will be to determine if early treatment can affect disease course, and results from the double-blind phase of the BENEFIT study will be presented for the first time atECTRIMS 2005 (28 September–1 October). ■

High reliability of FAMS

Interim analyses in 235 patients have demonstrated that the Functional Assessment of Multiple Sclerosis (FAMS) questionnaire is a highly reliable instrument which has a strong association with patient disability (Poster 237, ENS meeting 2005).

The FAMS and its translations are validated instruments measuring health-related quality of life in MS. Some of the items deal with culture-specific concepts, which may lead to different responses beyond appropriate translation. The data presented revealed some differences in the way patients in Austria, Germany and Poland interpret culture-specific FAMS items. The final evaluation of all 546 patients will add to these findings. ■

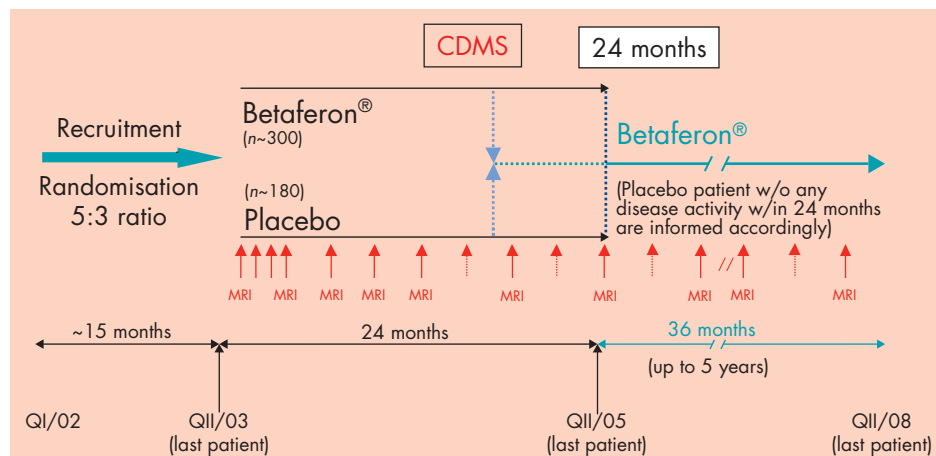


Figure 4: Design of the BENEFIT study and follow-up.

Early treatment in MS is important

Even between relapses, MS is an active and destructive disease, and axonal injury occurs early and continuously. Importantly, early treatment may delay or prevent this damage, explained Avertano Noronha, Chicago, IL, USA, in the CME-accredited symposium 'Early Start, Long-term Results: Optimising Treatment Options for Patients with Multiple Sclerosis' at the CMSC meeting 2005.

Axons are damaged early in MS because demyelination by inflammatory mediators leaves them vulnerable to transection. Once an axon has been cut, the remaining axon swells and neuronal function is lost. This type of injury is most pronounced in early MS, when inflammatory cell numbers are highest, but it may be silent because the brain compensates for neuronal loss. Both demyelination and axonal loss correlate with brain atrophy, which also occurs early in MS. The rate of brain atrophy in some regions of the central nervous system correlates with the extent of disability.

The efficacy of interferon beta in preventing early neural damage has been examined in several studies. One study showed that Betaferon® reduced brain N-acetyl aspartate (NAA) levels, believed to indicate neural dysfunction, in MS patients. Another study demonstrated

that the rate of brain volume loss in MS patients was reduced during treatment with Betaferon®. There is also evidence that progression from clinically isolated syndrome (CIS, early MS) to clinically definite (CD) MS is less likely with interferon beta treatment. More evidence on the value of early treatment for CIS patients will be provided by the BENEFIT study (see page 5).

Despite evidence that patients with CIS and an abnormal MRI are likely to develop CDMS and that disease-modifying treatment can be beneficial, early treatment of minimally or non-symptomatic patients is controversial. The major concern is that patients who will never develop CDMS or who will experience benign (minimally disabling, minimally progressive) MS will receive unnecessary treatment. This concern must be balanced against evidence that

neuronal damage can only be prevented before injury to the axon, and that the long-term consequences of neuronal damage profoundly impact patients' lives. With current evidence, treatment is recommended for CIS patients with characteristics of a poor prognosis (Table 2). Early treatment is the best option available for CIS patients who want to preserve long-term function and quality of life. ■

- Multiple MRI lesions disseminated in space and time
- Initial episode of moderate or substantial severity
- Efferent (not just sensory) systems affected
- Persistent impairment after the initial episode

Table 2: Characteristics of CIS patients with a poor prognosis.

Evidence-based MS treatment

Disease-modifying therapies with a variety of mechanisms of action are available to treat MS. Evidence from clinical trials has been analysed to develop recommendations for treating patients with different subtypes and stages of MS.

Although our understanding of the pathogenesis of MS is incomplete, therapies have been developed that suppress immune cell activity in the periphery, prevent entry of immune cells across the blood-brain barrier (BBB) and suppress immune cell activity in the central nervous system (CNS), reported Barrie Hurwitz, Durham, NC, USA. Interferon beta is believed to affect the periphery, BBB and, possibly, the CNS. In contrast, glatiramer acetate works in the periphery and possibly in the CNS, but does not affect the BBB. Results indicate that natalizumab appears to work at the BBB only, although the availability of this treatment has been

suspended due to several related deaths from the rare disease progressive multifocal leucoencephalopathy (PML). Differences in site of action probably account for differences in the clinical and MRI outcomes of these therapies.

Numerous clinical trials performed to test MS therapies provide class I evidence of efficacy. According to the American Academy of Neurology, a class I trial is prospectively designed (with defined inclusion/exclusion criteria and primary outcomes), enrolls a representative patient population, includes an appropriate control group, randomly assigns patients to treatment groups that are substantially

equivalent, performs blinded independent assessments of outcome, and accounts for all patients who drop out of the study. Based on class I data showing a reduced attack rate, interferon beta is considered appropriate therapy for patients who are at high risk of developing clinically definite MS or who already have RRMS or secondary progressive MS and are still experiencing relapses. In contrast, glatiramer acetate is recommended in patients with RRMS, but it is unclear whether glatiramer acetate is helpful in patients with progressive disease.

Interferon beta and glatiramer acetate are currently approved or recommended for the treatment of relapsing forms of MS, but natalizumab is not. Although recent class I data from AFFIRM and SENTINEL support a decreased rate of relapses and reduced progression of disability in RRMS patients, several cases of a severe, potentially fatal adverse event – PML – have been

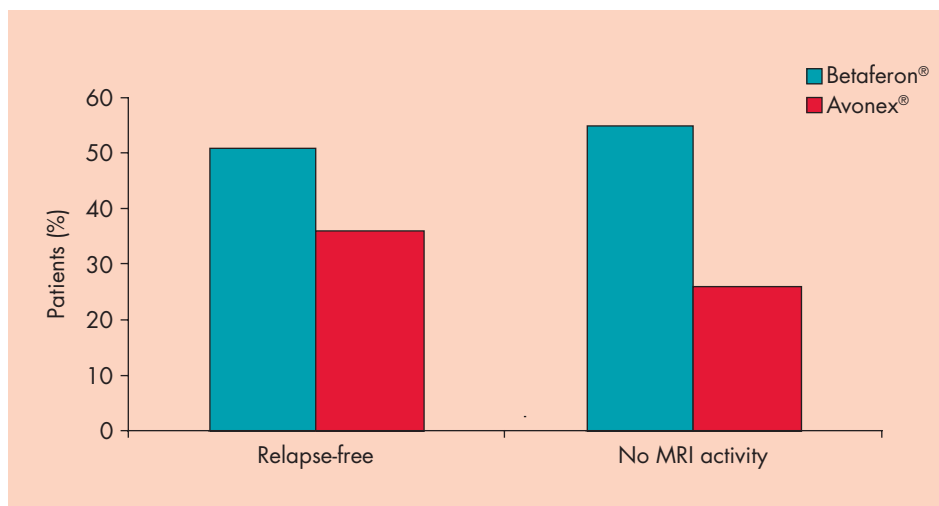


Figure 5: High-dose (250 µg) Betaferon® every other day is superior to low-dose, low-frequency Avonex®: INCOMIN 2-year results.

identified. The safety of natalizumab is currently under intense scrutiny.

Few trials have directly compared the recommended MS therapies, but different formulations and dosing schedules of interferon beta therapies were compared in the INCOMIN (Figure 5) and EVIDENCE studies. To date, higher and more frequent doses of interferon beta are associated with greater efficacy in RRMS patients. The BEYOND study, which compares the efficacy of two doses of Betaferon® and one dose of Copaxone®, will provide more data on the relative magnitude of patient responses to specific therapeutic regimens (see page 12). ■

Long-term data support beneficial effect of therapy

Long-term evidence of the efficacy of immunomodulatory therapy currently supports the value of continuing treatment for MS. In fact, ongoing disease-modifying therapy may protect the brain from damage, said Samuel Hunter, Nashville, TN, USA.

Multiple sclerosis is a long-term disease and its treatment should be guided by long-term studies. However, clinical experience has shown that it is difficult to retain patients continuously in long-term trials. Results from the Betaferon® 16-year long-term follow-up (LTF) study were presented, and these are highlighted on pages 1 and 3. Furthermore, 8-year follow-up of the PRISMS trial showed lesser MRI lesion burden in patients initially treated with a standard dose (44 µg) of interferon beta-1a subcutaneously compared with those initially treated with placebo or a lower dose (22 µg). In addition, less disability progression was seen 8 years later in SPMS patients initially treated with Betaferon® than in those given placebo.

An alternative to the long-term placebo-controlled trial is comparison of treated patients with a natural history control. Patients enrolled in epidemiological/natural history studies are usually similar to those enrolled in clinical trials, with the exception that clinical trials generally exclude patients with very

mild or extremely aggressive disease. To date, comparisons between interferon beta-treated patients and natural history controls support the efficacy of long-term treatment with interferon beta. Twelve-year data measuring T2 burden of disease over time found improvement in patients treated with Betaferon®, but marked worsening of disease in never-treated patients (Figure 6). The 12-year data also revealed that neutralising antibodies against Betaferon® all but

disappeared in all patients, suggesting that tolerance develops. The ongoing 16-year LTF study will provide additional data on long-term MRI changes, progression of disability, antibody status, cognitive changes, quality of life and resource utilisation.

While the evidence supporting use of long-term therapy is growing, there is no evidence that stopping therapy benefits patients. Indeed, it is possible that failing to initiate therapy, or discontinuing it, has a negative impact on long-term outcome. A study has also shown that later reductions in the dose of interferon beta can lead to re-activation of the disease. Early and continued immunomodulatory therapy with high-dose, frequently administered interferon beta may prevent axonal loss that cannot be reversed once it has occurred. ■

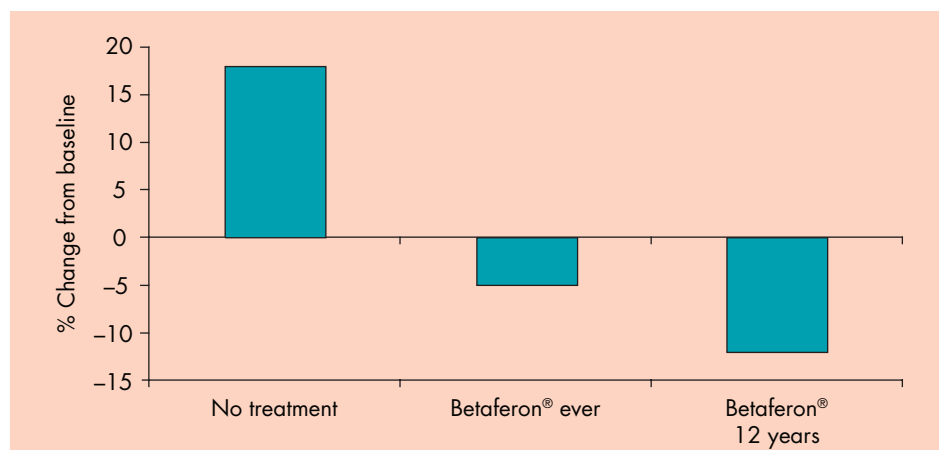


Figure 6: Change in T2 burden of disease over 12 years.

Brain adaptation hides early neural damage

The hypothesis that progressive brain damage is hidden by neuroplasticity supports the need for early and continuing treatment of RRMS. Dr Robert Shin, Baltimore, MD, USA, speaking at the symposium, 'Neuroprotection and Neuroregeneration', proposed that MS causes progressive, continuous damage. However, this is hidden by brain reorganisation until adaptive mechanisms fail years later, leading to visible, rapid deterioration.

Functional MRI (fMRI) data show that the brain adapts to damage, hiding the effects of injury. For example, patients with clinically isolated syndrome (early MS) compensate by using larger areas of their motor cortex for movement than normal subjects.

Neuroplasticity is the ability of the brain to reorganise after injury. The effects of neuroplasticity are most apparent after focal brain injuries, such as ischaemic strokes or relapsing MS. Because other parts of the brain acquire new functions,

patients with significant brain damage may be able to function normally. Although neuroplasticity is a positive adaptation, the absence of symptoms may lead patients and physicians falsely to conclude that there is no damage.

Functional MRI identifies brain regions that are active during performance of specific functions, such as finger motion, interpretation of visual input or retrieval of memories. BOLD contrast analysis detects more oxygenated haemoglobin in active areas, whereas

deoxyhaemoglobin is detected in less active areas. The responsible areas are most clearly defined when the scan is taken during alternating 30-second periods of rest and activity.

Neuroplasticity is the ability of the brain to reorganise after injury

Patients with RRMS have been followed with fMRI for months after attacks. One patient with weakness on the right side of her body showed activity in both the right and left sides of her brain when asked to move her right thumb. Over time, the areas of activation were reduced in size, but did not normalise. Patients recovered from optic neuritis were also studied with fMRI during photic stimulation, in which it was demonstrated that multimodal sensory cortex, not the occipital region, was activated by visual stimuli. ■

Immunomodulatory therapy reduces death rate

The death rate for MS patients receiving disease-modifying therapy (DMT) was halved, according to a recent retrospective survey described by Amy Poel, Seattle, WA, USA (Poster S50, CMSC 2005). In those receiving no DMT, the death rate was slightly raised over the overall population death rate of 13% for the 7 years studied.

The survey involved a cohort of all US veterans who received health services for MS between 1 January 1995 and 31 December 2000, and had their status determined as of 31 December 2002. Approximately 20% of the patients received DMT during this period.

In those receiving no DMT, the death rate was slightly raised over the overall population death rate

Other predictors of death included increased age, male gender, and white race. Self-reported disease subtype was not predictive of mortality, but non-surviving patients reported greater mobility impairment prior to death than surviving patients.

The records of the United States Veterans Administration (VA) are a unique resource for retrospective outcome analysis. The population is large, heterogeneous, and thoroughly documented over a long time period. Furthermore, mortality reporting is virtually complete because death benefits are distributed when a report

is received. Results now emerging from the Betaferon® 16-year long-term follow-up study also suggest that treatment has a beneficial effect on survival (see page 3).

The results of this study were compared with those of several published studies. A previous study in US veterans also identified male gender as a risk factor for death in patients with MS. Furthermore, a separate study reported that mortality in MS patients increases with increasing disability. Compared with the general population of Canada, the risk of death was 1.6-fold higher in MS patients with minimal disability (EDSS 0–3.5) but 4.44-fold higher in patients with severe disability (EDSS ≥7.5). Death rates in Finland between 1964 and 1993 concluded that primary progressive MS conferred a 2.6-fold higher risk of death compared with RRMS. None of the studies cited looked for an influence of DMT on mortality. The final results of this analysis of US veterans are awaited with interest. ■

Holistic approaches to MS management

The management of MS patients has significantly improved over the past 10 years, and interferon beta is endorsed by the broadest dataset, stated Professor Peter Rieckmann, Würzburg, Germany, during the Schering AG-supported symposium at the ENS meeting 2005. The therapeutic efficacy of Betaferon® is supported by a broad mode of action, and its efficacy, safety and tolerability are fostered by more than 550 000 accumulated patient-years of experience.

Multiple sclerosis exhibits clinical activity that manifests as acute relapses, the accumulation of deficits and disease progression. However, much activity is also occurring under the surface (subclinical disease activity), such as demyelination, the development of inflammatory lesions, axonal/neural loss and functional plasticity. The goal of disease management is, therefore, to reduce the damage and enhance repair, Professor Rieckmann told the audience. He then advocated a multimodal approach to disease management that starts with diagnosis, and includes patient education, management of symptoms and prevention of progression.

Several disease-modifying therapies (DMTs) are now available for treating MS, and attention is turning to when therapy should be implemented to achieve the maximum benefit. Figure 7 shows disease activity according to time, and also the ongoing or completed trials looking at the merits of therapy at certain time points. Most DMTs delay progression rather than reverse damage already done, so early treatment is likely to be most beneficial. There are,

however, considerations as to how early treatment should be initiated, and these are discussed on page 6. Recommendations regarding therapy change with disease severity and escalation, as illustrated by the European MS Therapy Consensus Group guidelines. This group recommends treatment with interferon beta or glatiramer acetate when the disease course is less severe, with a move towards mitoxantrone therapy as the disease progresses. Relapse therapy, with corticosteroids, should be initiated when required.

Pre- and post-treatment and placebo-controlled trials can establish the efficacy of any one therapy, as shown by the pivotal trials, but how do we compare therapies? Direct comparisons can only be made with any certainty when the treatments are tested in head-to-head trials. Some comparative data do exist, such as for the different interferon beta dose and frequency regimens. The EVIDENCE trial comparing subcutaneous and intramuscular interferon beta-1a and the INCOMIN trial that compared subcutaneous Betaferon® and intramuscular interferon

beta-1a both found that high-dose, high-frequency therapies were more efficacious than low-dose, low-frequency interferon beta-1a. A proliferation of non-randomised, often retrospective, studies have sought to show comparative evidence for the available MS treatments. Owing to the non-randomised nature of these studies, however, inherent bias renders comparisons of efficacy meaningless. Nevertheless, these studies can provide useful information on safety and tolerability in real-world situations.

The goal of disease management is, therefore, to reduce the damage and enhance repair

In today's world, patients have access to many sources of information, not all of which are reliable, and they want to have a better understanding of the available therapies and a more active role in their disease management. The role of the health professional is, therefore, to give reliable information about the different therapies and their respective pros and cons. To do this, there is no substitute for practical experience of therapies within the clinic and the accumulated patient-years of data such treatment generates.

Management of MS, although much improved since the 1990s, needs to continue to advance to provide a positive future for patients with MS. To achieve this, we need to continue to improve the diagnostic criteria, determine when to start therapy for the best outcome and develop a better understanding of the pathology of the disease. ■

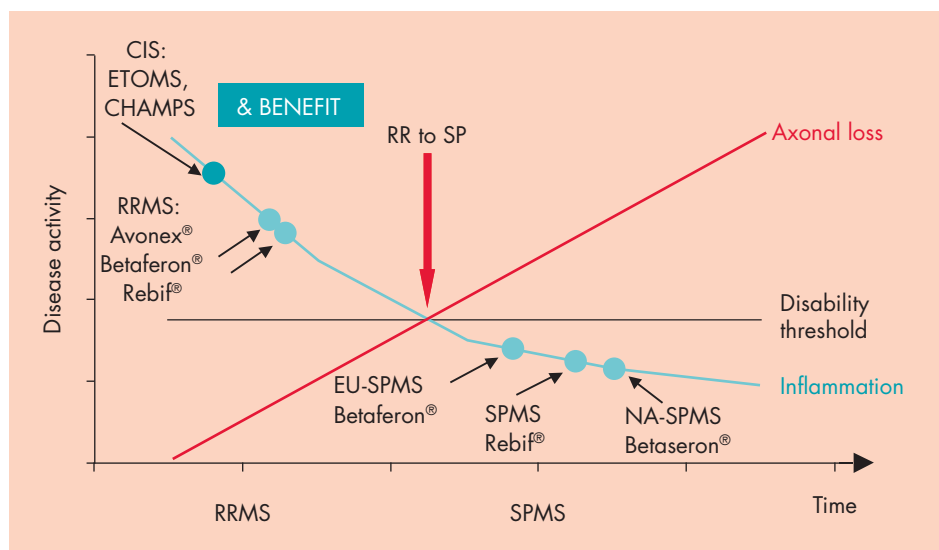


Figure 7: Therapy in MS. RR, relapsing-remitting; SP, secondary progressive.

New treatment developments

The results of several trials testing new therapies for MS were presented during the ENS meeting 2005, with some proving to be more promising than others. Details of two therapies undergoing proof of concept studies are given below.

FTY720

The efficacy and safety evaluations of a Phase II study suggest that FTY720 has the potential to be a suitable disease-modifying therapy for relapsing forms of MS, stated Professor Ludwig Kappos, Basel, Switzerland at the ENS meeting 2005 (Oral O141).

The Phase II study being discussed involved 281 patients randomised to 1.25 mg or 5 mg FTY720 or placebo orally once daily. Two hundred and seventy-seven patients formed the intent-to-treat population and of these, 241 had had at least three post-randomised MRI scans.

The primary outcome measure was the mean number of gadolinium-enhanced T1 lesions in monthly post-baseline MRI scans. Significant reductions were seen in both the 1.25 and 5 mg groups compared with placebo, but discrepancies in the median values suggest the presence of outlying results.

The proportion of relapse-free patients was also significantly reduced in both FTY720 groups compared with placebo.

At least one adverse event occurred in more than 80% of patients in each treatment group, the most common being upper respiratory tract infections and headaches. Some mainly asymptomatic cardiovascular and pulmonary events were observed (reversible bradycardia and abnormal ECG), and the audience expressed concerns over these and other potential side effects given that FTY720 is a receptor modulator.

Temsirolimus

Temsirolimus had significant beneficial effects reported Professor Ludwig Kappos, Basel, Switzerland, when presenting the results of a multicentre, randomised, double-blind, placebo-controlled Phase 2 trial during an oral session on multiple sclerosis (Oral O158, ENS meeting 2005).

The trial was conducted in 296 patients who were randomised to 2 mg, 4 mg or 8 mg temsirolimus or placebo orally once daily. It comprised a 4-week run-in period, 36 weeks of therapy and a 4-week follow-up.

Therapy with 8 mg temsirolimus showed the greatest beneficial effect, with a 47.8% reduction in the number of cumulative gadolinium-enhanced T1 lesions (the primary endpoint) compared with placebo. Other endpoints also suggested a dose-dependent treatment effect, but not all parameters reached significance. The number of drop-outs and adverse events reported were both greater for the 4 and 8 mg groups compared with the 2 mg and placebo groups. While most adverse events were mild or moderate, they were most frequent in the higher dose group. Common adverse events were acne, hypercholesterolaemia, hyperlipidaemia and menstrual dysfunction.

Discussion of the trial results concluded that combination of temsirolimus with statins may be appropriate given the common side effects. There was also concern regarding steady-state dose achievement, and it is likely that the pharmacokinetics will need careful monitoring. ■

Continued from page 2

The cognitive tests selected are robust for sensory and motor deficits:

- Controlled Oral Word Association Test (COWAT)
- California Verbal Learning Test-II (CVLT-II)
- Symbol Digit Modality Task (SDMT)
- Delis-Kaplan Executive Function System (D-KEFS)
- Paced Auditory Serial Addition Task (PASAT)

Evaluating HRQoL and cognition in this study may add aspects of clinical effectiveness not usually covered by traditional clinical outcomes. Furthermore, cognitive skills will be evaluated in relation to clinical and MRI parameters, providing a validation of the cognitive tests. ■

Coping strategies in MS

The availability of a support network, including family, friends and professional care support (e.g. specialised MS nurses), contributes to help patients to cope with their MS, conclude data from Annett Apel, Rostock, Germany. The methods patients use to cope vary between patients with and without a support network.

The study evaluated 243 patients with clinically definite MS using the Trier Illness Coping Scale to assess coping behaviour. This scale has five subscales: rumination (RU), defence of threat (DT), search for social integration (SS), search for information and exchange of experience (SI), and search for support in religion (SR).

Multiple sclerosis patients who reported support through family ($n=220$), friends ($n=175$) or other MS patients ($n=163$) had higher scores on the subscales SS, SI and SR than patients without support in these categories. MS patients with an EDSS score of 3.0–6.0 had the highest scores for RU, DT and SI compared with patients who were less affected (EDSS <3.0). No connection was found between coping behaviour and age, duration of illness or course of disease. Women reported higher scores than men on the SI and SR subscales. ■

2-year BEST data on 'real-life' treatment with Betaferon® in early RRMS

Additional data from the Betaferon® in Early RRMS Surveillance Trial (BEST) confirms previous findings and continues to show that Betaferon® is an efficacious treatment for RRMS, reported Dr Stacy Wu, Basel, Switzerland (poster P504, ENS meeting 2005). She reported that 500 patients have now completed 2 years of the study and more than 3000 patients are participating in the trial.

BEST is an international, prospective, 5-year, observational study on patients with early stage RRMS. Patients were not treated with any interferon beta therapy before entering the trial and are all receiving 250 µg Betaferon® subcutaneously every other day.

By April 2005, 1248 patients had participated in the trial for 12 months, meaning that results of 1-year data analyses are available for a large cohort of patients. Ninety per cent of these patients were progression-free, 73% were relapse-free and 65% were progression- and relapse-free. The results from this larger cohort of 1248 patients confirm the finding of the 1-year interim data (591 patients).

In addition, 2-year data from 500 patients who have now completed 2 years of the study are available: 85% were progression-free (Figure 8), 55% were relapse-free and 50% were both relapse- and progression-free. The

mean annualised relapse rate also decreased by 51% in this cohort, from 0.90 pre-treatment to 0.44 after 2 years of Betaferon® therapy. Adverse events were reported in 9% of patients but were not new or unexpected. As well as clinical data, health-related quality of life data are being collected as part of this study,

and these 2-year results are discussed on page 4.

The 2-year BEST data provide important information on 'real-life' application of Betaferon® as treatment for early RRMS for reducing the relapse rate and stabilising or improving disease progression. ■

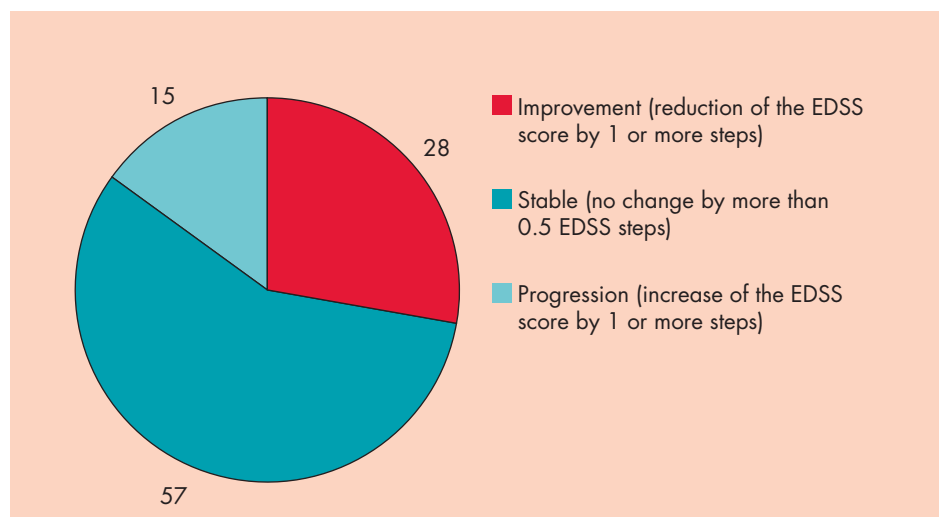


Figure 8: Disability status of the patients who have completed 2 years of the BEST study (%).

A BRIGHT future with MS therapy

Recruitment to the BRIGHT study is progressing well, reported Dr Colin O'Leary, Glasgow, UK. Already 226 patients have enrolled in this study to compare the frequency and severity of injection-site pain associated with Betaferon® and Rebif®.

Betaferon® versus Rebif® Investigating Higher Tolerability (BRIGHT) began in May 2004, and is a multicentre, international, observational, non-randomised, prospective study. Patients continue to administer their prescribed therapy, 250 µg Betaferon® or 44 µg Rebif®, throughout the trial, and assess

injection-site pain using a visual analogue scale diary. The study nurse or physician assesses injection-site reactions.

Figures reported during the ENS meeting 2005 show that 226 of the expected 300 patients (75%) have

already been recruited from 11 countries. Recruitment in Eastern Europe is going particularly well.

This study is due to be completed by autumn 2005 and the final results should be available by the end of the year. BRIGHT will detect any differences in the severity and quality of pain, and in the frequency and severity of injection-site reactions associated with the administration of Betaferon® compared with Rebif®. The ultimate aim of the BRIGHT study is to provide information to help determine the influence of injection-site pain on patient satisfaction with therapy and provide clinicians with data on patient comfort and convenience during interferon beta therapy. ■

BEYOND the current Betaferon[®] dose

Safety and tolerability data from the 1-year interim analysis of the BEYOND follow-up study suggest that 500 µg Betaferon[®] is well tolerated, reported Dr Barrie Hurwitz, Durham, NC, USA, at the ENS meeting 2005 (Poster P485).

The first phase of the BEYOND programme was designed to combine a pilot study with a maximum duration of 28 weeks, and a follow-up study of up to 2 years. The pilot study comprised a double-blind observation of at least 12 weeks (up to 28 weeks in some patients). Patients received either 250 µg or 500 µg Betaferon[®] subcutaneously every other day. Therapy was titrated up in steps of a quarter dose every 2 weeks, or as the patient could tolerate. The follow-up study began with 10 weeks of double-blind treatment, after which the study became open-label, with patients selecting a preferred dose (Figure 9).

During the pilot study, 38 patients were randomised to receive 250 µg Betaferon[®] and 33 to receive 500 µg. Over 90% of patients in each treatment arm attained the target dose within the required

timeframe and the number of patients who interrupted therapy was low and comparable between the two treatment arms. Flu-like reactions and associated adverse events were more common in the 500 µg treatment group, but there was no difference between injection-site reactions in the two groups and no new or unexpected adverse events.

Patients who completed the pilot study were eligible to participate in the follow-up and 63 of the original 71 patients enrolled. Of the 33 patients originally randomised to receive 500 µg Betaferon[®], 28 entered the follow-up study and 20 elected to remain on the 500 µg dose; these 20 patients remain on the 500 µg dose a year later. A total of 35/38 patients randomised to the 250 µg dose entered the follow-up study and, while 16 remained on the 250 µg dose,

19 chose to take the 500 µg dose. A year later, 11/16 are taking 250 µg Betaferon[®] and 12/19 are taking 500 µg (Figure 10).

One-year interim analyses show that patients taking 500 µg Betaferon[®] every other day for more than 12 months did not show clinical or laboratory side effects that exceeded the side effects seen during or shortly after initial dose escalation.

These data are based on an overall treatment duration of more than 1.5 years, and show that 500 µg Betaferon[®] is well tolerated. Final results for the second phase of the BEYOND programme (over 2100 patients) are expected in 2007, and will also show a comparison of 250 and 500 µg Betaferon[®], as well as a third group of patients who have been treated with glatiramer acetate. ■

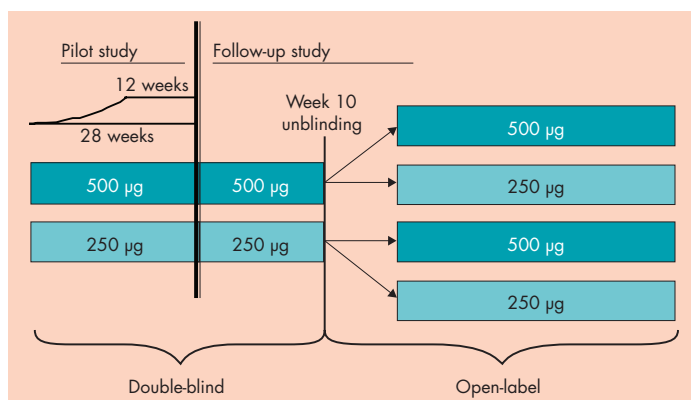


Figure 9: Design of the first phase of the BEYOND programme.

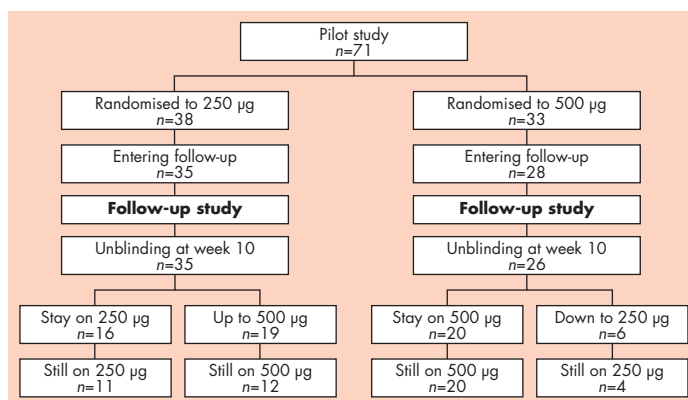


Figure 10: Patient flow during the first phase of the BEYOND programme.



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