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## 17th World Congress of Neurology 5-11 November 2005

Multiple sclerosis was a key theme at the World Congress of Neurology (WCN) held recently in Sydney, Australia. This major gathering of neurologists from around the world occurs every 4 years. The Congress creates a unique opportunity for physicians to update their knowledge in cutting-edge areas of neurology and the neurosciences from international leaders in these fields.

The city of Sydney welcomed over 5000 physicians and researchers, and representatives from major pharmaceutical companies showed their commitment to clinical research and development at the Congress by participating in the large exhibition. Presentations covered recent advances, emerging trends and prospects for future developments. The MS symposium programme covered a wide selection of topics and almost 150 posters detailing MS research results were on display.

This issue of *Medical Express Reports* describes a selection of topics discussed at the WCN, including highlights from the Schering AG-supported symposium *Betaferon®: Early and Lasting Benefit*. New data from the 16-Year Long-term Follow-up study are presented, as well as highlights from the BENEFIT (BETAferon®/Betaseron® in Newly Emerging multiple sclerosis For Initial Treatment) Study. ■



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Sydney Harbour Bridge, Sydney, Australia – host city to the 17th World Congress of Neurology.

## Betaferon®: clinical impact of 16 years' treatment

**Data from the 16-Year Long-term Follow-up (LTF) Study indicate that Betaferon® has a good safety profile and is well tolerated in the long term, reported Professor George Ebers, University of Oxford, UK. He added that preliminary data from the study also suggest that long-term treatment may slow the time to expanded disability status scale 6 (EDSS 6) progression and are consistent with the hypothesis that beginning treatment early has long-lasting clinical impact.**

The aim of the LTF study is to allow clinicians to assess the long-term safety and efficacy of Betaferon®, explained Professor Ebers during his presentation at the Schering AG-supported symposium

*Betaferon®: Early and Lasting Benefit*. He said that so far almost 90% of patients have been identified from the original 372 enrolled in the pivotal Betaferon® trial. As of 23 September 2005, case report forms for 210 patients have been reviewed. All 11 of the original trial sites are participating in the study.

The data indicate good adherence to therapy and minimal adverse events. The time to reach an EDSS score of 6 was greater in patients who had been receiving Betaferon® for more than 80% of the period between starting treatment in the pivotal trial through to 2005 compared with those patients receiving Betaferon® for less than 10% of this period.

Further results from the 16-Year LTF Study are reported on page 3. ■

## BRIGHT study indicates less injection site pain with Betaferon<sup>®</sup> compared with Rebif<sup>®</sup>

Latest data from the Betaferon<sup>®</sup> versus Rebif<sup>®</sup> Investigating Higher Tolerability (BRIGHT) study shows that Betaferon<sup>®</sup> 250 µg administered every other day causes less injection site pain (ISP) than Rebif<sup>®</sup> 44 µg three times weekly regardless of the autoinjector type or needle size used. Dr Karl Baum, Hennigsdorf Clinic, Germany, presented these results from data obtained in July 2005 including 221 patients (Betaferon<sup>®</sup>: 156; Rebif<sup>®</sup>: 65) with relapsing-remitting (RR) MS (Poster P480, WCN 2005).

The ongoing BRIGHT study aims to determine the influence of ISP on patient satisfaction by comparing ISP following subcutaneous administration of Betaferon<sup>®</sup> 250 µg with Rebif<sup>®</sup> 44 µg in patients with RRMS.

**Betaferon<sup>®</sup> 250 µg administered every other day causes less ISP than Rebif<sup>®</sup> 44 µg**

Patients self-assessed their ISP over a period of 15 consecutive injections using a 10 mm visual analogue score.

Comparative data ( $n=221$ ) demonstrated that significantly more patients treated with Betaferon<sup>®</sup> 250 µg remained pain-free over all 15 injections at all three timepoints compared with those on Rebif<sup>®</sup> 44 µg (Figure 1). Injection site reactions were also significantly less frequent with Betaferon<sup>®</sup> 250 µg compared with Rebif<sup>®</sup> 44 µg. These beneficial effects with Betaferon<sup>®</sup> 250 µg did not depend on either the type of autoinjector (Betaject Light vs Rebiject II) or the needle gauge (26/27G vs 29/30G). Overall, 78.8% of Betaferon<sup>®</sup> 250 µg-treated patients either had no pain or were satisfied with their treatment compared with just 49.3% of those given Rebif<sup>®</sup> 44 µg. ■

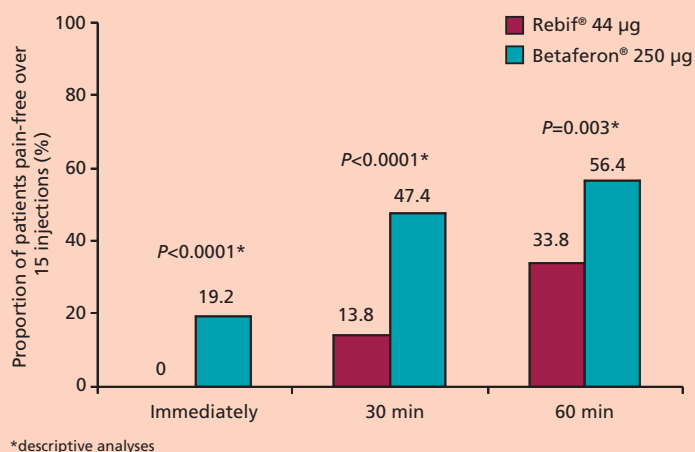


Figure 1: Significantly more patients treated with Betaferon<sup>®</sup> 250 µg remained pain-free over all 15 injections at all three timepoints compared with those on Rebif<sup>®</sup> 44 µg.

## FAMS – validated for use in 12 languages for 15 countries

Translations of the Functional Assessment of Multiple Sclerosis (FAMS) health-related quality of life (HRQOL) questionnaire in 12 languages are now ready for use in clinical trials and other research studies. A poster presented by Dr Joao de Sa, Santa Maria Hospital, Lisbon, Portugal (Poster 0521, WCN 2005) gave validation data from a study in 272 patients with MS and explained that cross-cultural evaluation of the translations has been successfully completed.

FAMS is a 58-item multidimensional HRQOL instrument that assesses six MS subscales and is suitable for all types of MS. Validation in these 12 languages mean that it can now be used in 15 countries.

The study evaluated the linguistic validity, acceptability and preliminary psychometric performance of the 12 translations. All subscales demonstrated significant differences depending upon the Performance Status Rating (PSR). The total mean FAMS score correlated well with EDSS scores (EDSS <2: 135.1; EDSS 2–4: 113.7; EDSS >4: 88.5). Revisions were only needed to the Hebrew, Traditional Chinese, Farsi and Ukrainian translations.

As the patient's experiences of MS and its treatment do not necessarily reflect disease severity, information provided by the FAMS questionnaire translations should be very useful for understanding treatment outcomes in both clinical trials and everyday practice. ■

# Betaferon® 250 µg – efficacy, safety and patient satisfaction over 16 years

'A remarkable achievement,' is how Professor George Ebers from the University of Oxford, UK, described the current identification status of the 16-Year Long-term Follow-up (LTF) Study. Almost 90% of the 372 patients from the original Betaferon® pivotal trial have been identified so far. No other immunomodulatory therapy can provide treatment data for this length of time in such high patient numbers. All 11 of the original trial sites are participating in the study, with several sites already reporting 100% ascertainment. Summarising, he said that Betaferon® 250 µg has been shown to be safe and well tolerated over this 16-year period. Preliminary results from the LTF study also indicate that Betaferon® may delay the time to expanded disability status scale 6 (EDSS 6) progression. Furthermore, fewer patients assigned to Betaferon® 250 µg during the pivotal study have died compared with those patients receiving placebo, and this unexpected result has initiated further investigation.

Expanding on these areas, Professor Ebers explained that preliminary results from the LTF study show that long-term treatment with Betaferon® may slow the time to reach an EDSS score of 6 in those patients who received Betaferon® for over 80% of the period between starting treatment in the pivotal trial and 2005 compared with those patients who received Betaferon® for less than 10% of this period: the median times to an EDSS of 6 being 17 years and 7 years, respectively. In patients receiving Betaferon® for the period between these two extremes, i.e. for 10–80% of the time, the median time to an EDSS score of 6 was 10 years.

**Long-term treatment with Betaferon® may slow the time to EDSS 6**

Correlation has also been found between length of exposure to Betaferon® and the extent of T2 burden of disease, and this is not dependent upon EDSS score. Hence, patients treated for longer with Betaferon® had a lower median T2 burden of disease (mm<sup>2</sup>) and this was as true for patients with an EDSS score <3,

as it was for an EDSS score ≥3 to <6 and an EDSS score ≥6, explained Professor Ebers.

**The median time of exposure to 250 µg Betaferon® has been 3644 days, i.e. 10 years**

The latest results from the LTF study show that 34 of the identified patients are deceased. However, in those patients originally assigned to placebo, 19/110 (17%) identified patients are deceased, compared with 6/112 (5%) of those assigned to Betaferon® 250 µg.

**The study results also highlight high patient satisfaction with Betaferon®**

The study results also highlight high patient satisfaction with Betaferon®. Of the 210 case report forms reviewed so far from patients enrolled in the Betaferon® pivotal trial over 16 years ago, 41% have been taking Betaferon® for more than 80% of the time between the end of the pivotal trial and 23 September 2005. In these 210 patients, the median time of exposure to 250 µg Betaferon® has been 3644 days (i.e. 10 years). In patients originally assigned to 250 µg Betaferon®, the median length of treatment is 5014 days – almost 14 years. Even after 16 years, Betaferon® remains a therapy with a high level of patient acceptance. ■

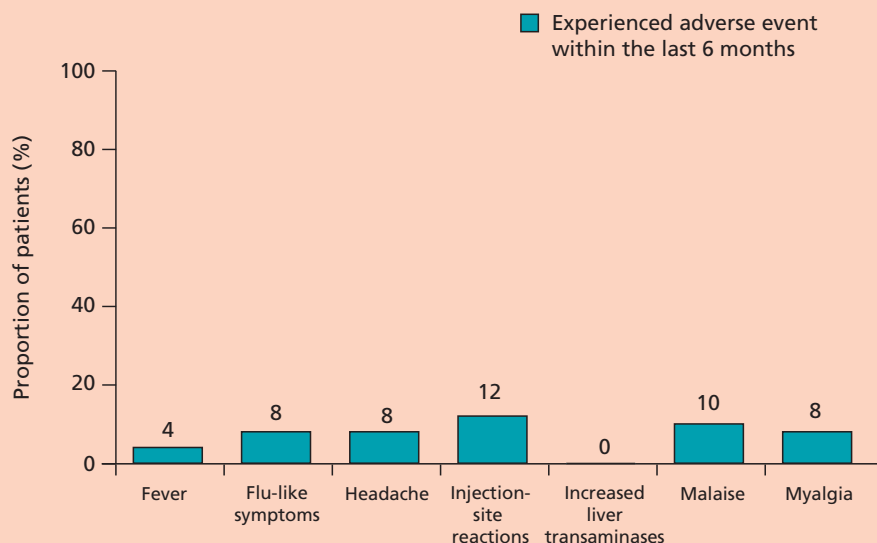


Figure 2: Adverse events to Betaferon® in patients on treatment in the last 6 months.

# The McDonald Criteria 2005 revisions

**Further guidance on magnetic resonance imaging (MRI) evidence for dissemination in time, the use of spinal cord imaging and simplified diagnostic criteria for primary progressive (PP) MS are key areas in the 2005 revised McDonald Diagnostic Criteria aimed at simplifying and speeding up diagnosis while maintaining adequate sensitivity and specificity, explained Professor Alan Thompson, University College London, UK. Speaking during his presentation, 'New criteria for the diagnosis of MS', Professor Thompson reminded delegates that high specificity is even more important than high sensitivity when diagnosing a lifelong condition like MS in order to avoid false-positive diagnoses. He also stated that diagnostic criteria must be simple or they will be ignored.**

In a review of the development of diagnostic criteria for MS and summary of the 2005 revisions to the McDonald Diagnostic Criteria, Professor Thompson explained that dissemination of disease course in time and space, along with the exclusion of all other differential diagnoses, are essential for an accurate clinical diagnosis of MS.

An international panel produced the original McDonald criteria for MS in 2001, and since then they have been widely used, evaluated and discussed.

Professor Thompson described how the overall aim of the expert panel, which met early in 2005 in Amsterdam to review these criteria, was to produce a set of clinically useful, simple diagnostic criteria for MS that could be readily used by clinicians in everyday practice. They re-assessed existing diagnostic criteria for MS with a view to retaining all the useful features whilst recommending any appropriate changes, and they also clarified definitions and simplified the disease categories.

The panel was also charged with integrating MRI into the diagnostic criteria to demonstrate dissemination of lesions in time, clarifying the use of spinal cord imaging and simplifying the diagnostic criteria for PPMS. Professor Thompson said that MRI is the most sensitive paraclinical test for MS, with around 95% of patients with clinically definite MS having MRI abnormalities, and its

importance in MS diagnosis has been acknowledged for some time. It was Barkhof et al. in 1997 who first suggested that four dichotomous MRI variables should be used, and showed that the risk of MS increased as each additional MRI criteria was fulfilled (e.g. enhancing lesion, juxta cortical lesion, infratentorial lesion).

To achieve its aims, the expert panel included literature searches for relevant

data and their recommendations were evidence-based wherever possible. Input from the MS clinical community was also reviewed by the panel and incorporated into the revisions. The 2005 Revisions to the McDonald Diagnostic Criteria for MS are shown in Table 1 (Polman CH *et al. Ann Neurol* 2005;58:840). Professor Thompson recommended that, as for all new criteria, they should be validated in new cohorts of unselected patients.

In explaining the historical development of the diagnostic criteria for MS over the past 50 years, Professor Thompson said that it has been an evolutionary process and several criteria are in use today, including the Poser (Poser CM *et al. Ann Neurol* 1983;13:227), Barkhof (Barkhof F *et al. Brain* 1997;120:2059) and McDonald criteria (McDonald WI *et al. Ann Neurol* 2001;50:121). Studies evaluating the 2001 McDonald criteria suggest that they permit earlier diagnosis of MS than the Poser criteria and that a T2 lesion at 3 months provides adequate evidence of dissemination in time, although these studies have limitations. ■

## Demonstration of dissemination in time

- Gd-enhancement at least 3 months after onset of the initial clinical event, if not at site of event
- New T2 lesion at any time compared with a reference scan done at least 30 days after onset of the initial clinical event

## Spinal cord imaging

- Exclusion of alternative diagnosis
- Useful in showing dissemination in space if brain lesions are not informative:
- No cord swelling; unequivocal hyperintense T2 or Gd-enhancing; focal lesions (not diffuse)
- $\geq 3$  mm in size;  $< 2$  vertebral segments long
- Occupying only part of the cord cross-section
- Equivalent to a brain infratentorial lesion
- Can contribute along with individual brain lesions to reach required lesion number

## Diagnosing primary progressive MS

- 1 year of disease progression (retrospective or prospective)
- Plus two or three of the following:
  - + Brain MRI (9 T2 lesions or  $\geq 4$  lesions with +VEP)
  - + Spinal cord MRI ( $\geq 2$  focal T2 lesions)+ CSF by oligoclonal bands using isoelectric focusing and/or elevated IgG index

Gd, gadolinium; MRI, magnetic resonance imaging; VEP, visual evoked potential; CSF, cerebrospinal fluid; IgG, immunoglobulin G.

Table 1: The 2005 Revisions to the McDonald Diagnostic Criteria for MS.

# BENEFIT study provides evidence for early intervention in MS

In the recent Betaferon®/Betaseron® in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) study, Betaferon® was found to be able to delay the development of MS when given at the first clinical event accompanied by an MRI scan suggestive of MS, explained Professor Mark Freedman from Ottawa University, Canada. He also showed that 85% of placebo patients in the study developed MS within 2 years according to the McDonald criteria. This means, he concluded, that the first clinical event must be taken seriously as an indicator of future MS disease. He hopes that this major and conclusive study, along with other evidence that is supportive of early intervention in MS, will remove the controversy over whether or not patients with a first clinical event and an abnormal magnetic resonance imaging (MRI) scan suggestive of MS could benefit from treatment.

Prior to the BENEFIT study, two previous studies, CHAMPS (Jacobs CD *et al. N Engl J Med* 2000;18:898) and ETOMS (Comi G *et al. Lancet* 2001;357:1576), had demonstrated that once weekly, low-dose interferon beta-1a (30 µg intramuscularly or 22 µg subcutaneously, respectively) delayed the time to clinically definite (CD) MS in patients who had experienced a first clinical event suggestive of MS.

**85% of placebo-treated patients developed MS within 2 years according to the McDonald criteria**

In the BENEFIT study, 468 patients started treatment with Betaferon® (n=292) 250 µg subcutaneously every other day or placebo (n=176) following a first clinical event accompanied by an MRI scan suggestive of MS; 93% completed the 2-year randomized, double-blind phase of the study. Professor Freedman highlighted the fact that Betaferon® significantly reduced (P<0.0001) the risk of developing CDMS by 50% in this study (Figure 3) and

delayed its onset by 1 year, a gain of 142% over placebo. A total of 85% of placebo-treated patients developed MS according to the McDonald criteria within 2 years, 51% developing it within 6 months. Overall, Betaferon® significantly reduced (P<0.00001) the risk of developing MS according to the McDonald criteria by 46% over the 2-year period of the study.

Professor Freedman also described a subgroup analyses which demonstrated

that the reduction in the risk of developing CDMS was even more pronounced in patients with less active, less disseminated disease compared with the whole study population and with those patients with more disseminated disease.

Patient satisfaction with Betaferon® treatment was high: 96% of all eligible Betaferon®-treated patients chose to enter the follow-up study, which will evaluate open-label Betaferon® 250 µg every other day (eod) until 2008.

**Patient satisfaction with Betaferon® treatment was high**

Patients entering the BENEFIT study had both monofocal (less disseminated) and multifocal (more disseminated) disease at presentation, thereby ensuring that the study population was representative of the general MS population. The double-blind treatment period lasted 2 years or until the patient was diagnosed with CDMS. The primary efficacy endpoints were time to CDMS based on relapse or Expanded Disability Status Scale (EDSS) progression ≥1.5 points and time to MS according to the McDonald criteria. ■

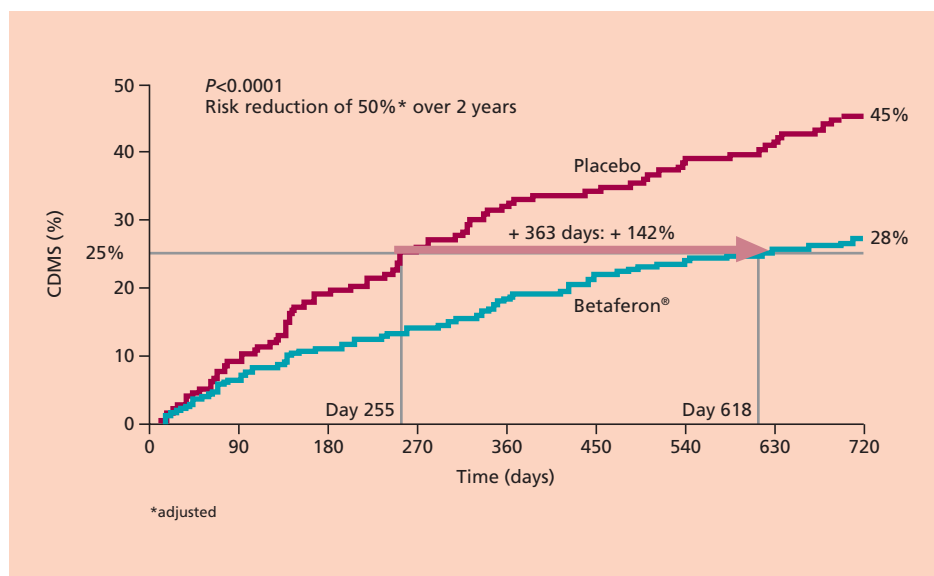


Figure 3: Reduction in the risk of developing clinically definite MS in patients who have had a first clinical event suggestive of MS and who subsequently received Betaferon® 250 µg every other day.

## Optimising interferon treatment in MS

Magnetic resonance imaging (MRI) activity in the first 6 months of interferon beta treatment is a reliable treatment response marker in patients with relapsing–remitting (RR) MS, explained Professor Luca Durelli from the University of Turin, Italy. This was established in the Optimization of Interferon dose for Multiple Sclerosis (OPTIMS) study and made it suitable in that study for reliably identifying 6-month suboptimal responders to Betaferon® 250 µg subcutaneously (sc) every other day (eod). These individuals were then randomized to receive either 375 µg or 250 µg Betaferon® for a further 6 months. Professor Durelli, said that those patients receiving the 375 µg dose demonstrated a significantly improved treatment effect. This led him to ask, ‘Have we reached the maximum therapeutic efficacy with interferon beta?’

Ideally, a treatment response marker should be easy to identify using routine clinical investigations and it should be identifiable early enough so that early treatment adjustments can be made. The OPTIMS study showed that the most sensitive indicator of a persistent suboptimal treatment response was to have two active scans during the first 6 months of treatment, and the most sensitive pairing always included an active scan at Month 6 (positive predictivity: 70–79%). Backward stepwise logistic regression confirmed that a single active scan at Month 6 was the strongest predictor of a persistent

**MRI activity in the first 6 months of interferon beta treatment is a reliable treatment response marker in patients with RRMS**

suboptimal MRI response ( $P=0.03$ ). The analyses also showed that a single active MRI scan during the first 6 months of treatment was a positive predictor for the presence of persistent disease activity as determined by the occurrence of relapses and/or expanded disability status scale (EDSS)-confirmed disease progression.

By the end of the 6-month randomized phase, the higher dose of Betaferon® (375 µg) had significantly reduced the risk of MRI disease activity by 72% ( $P<0.00011$ ) compared with the lower 250-µg dose (Figure 4). In addition, secondary efficacy variables significantly favoured the Betaferon® 375 µg dose. For example, only 14% of patients treated with Betaferon® 375 µg had new PD/T2 lesions compared with 55% of those given Betaferon® 250 µg ( $P<0.001$ ).

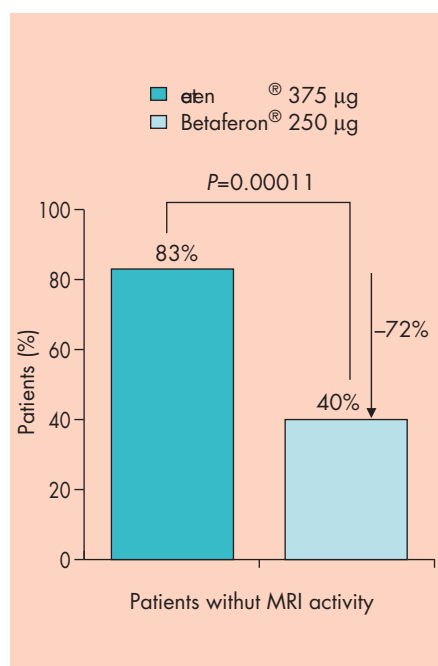


Figure 4. The OPTIMS dose (375 µg) of Betaferon® reduces the risk of MRI activity by 72% compared with the currently approved 250 µg dose.



Professor Luca Durelli

Betaferon® 375 µg treatment was also associated with significantly fewer patients (16.7%) with new gadolinium-enhancing lesions compared with Betaferon® 250 µg (57.5%) ( $P<0.001$ ). The higher dose of Betaferon® (375 µg) also significantly ( $P<0.001$ ) increased the time to a first active lesion by 1 month compared with the 250-µg dose.

The OPTIMS study also clearly showed no significant differences in the adverse event profiles of the two doses of Betaferon®.

**“Have we reached the maximum therapeutic efficacy with interferon beta?”**

Finally, no significant association between suboptimal clinical response and NAb positivity was shown at any point during the study. Neither was there any correlation between the Betaferon® dose and NAb positivity, although patients treated with Betaferon® 375 µg had a 50% increased probability of their NAb titre decreasing or them returning to NAb-negative status ( $P=0.04$ ). Professor Durelli concluded that the higher dose of Betaferon® was associated with increased efficacy and earlier NAb disappearance. ■

# Consensus reached on MS in Asia and the Middle East – implications for diagnostic criteria

The unique clinical features of MS in Asian and Middle Eastern populations can make it difficult to reach a differential diagnosis and the diagnostic criteria commonly used in western populations to diagnose Asian MS patients may not be entirely suitable. As a result neurologists from Asia, together with international neurologists, agreed at The Third MS Forum Pan-Asian Conference that modified diagnostic criteria for Asian and Middle Eastern MS may be necessary.

A number of speakers described MS cases that they had observed in their clinics and a pattern of symptoms emerged that appear to distinguish Asian MS from western classical MS (CMS). Common symptoms in Asian patients include paroxysmal symptoms (e.g. painful tonic spasms), transverse myelitis, girdle sensations, dysphagia, and L'hermitte's signs and symptoms. Although these symptoms can also occur in western patients with CMS, they are relatively rare. For example, as many as 46% of Asian patients with optic-spinal MS (OSMS) and 16% of Asian CMS patients have tonic spasms, yet only 4% of western CMS patients show this symptom. Bilateral optic neuritis appears to be more common in Asian patients than in westerners, and the prevalence of oligoclonal bands is often lower in Asian patients, particularly in those patients with OSMS.



Jun-ichi Kira

Dr Allan Kermode from Sir Charles Gairdner Hospital, Perth, Australia, suggested that the McDonald criteria for MS (McDonald WI *et al. Ann Neurol* 2001;50:121) are applicable to most cases in the west, but are probably too restrictive for Asian cases, even CMS. In particular, he felt that the involvement of the spinal cord in Asian MS is not addressed by the McDonald criteria.

**The McDonald criteria for MS are applicable to most cases in the west, but they are probably too restrictive for Asian cases**

Professor Jun-ichi Kira from Kyushu University Hospital, Fukuoka, Japan, explained that there are three problems with applying the McDonald criteria to Asian patients with a clinically isolated syndrome (CIS). First, there has been no prospective study applying the McDonald criteria to Asian CIS patients for conversion to clinically definite (CD) MS. Secondly, there are few brain lesions in OSMS; and finally, long spinal cord lesions are a feature of Asian MS, especially those with OSMS. Professor Kira's own research suggests that the McDonald MRI criteria are not applicable to Asian patients with CIS suggestive of MS, and that the Poser criteria should be used instead (Poser CM *et al. Ann Neurol* 1983;13:227).



Allan Kermode

As a result of the discussions at the last MS Forum Pan-Asian Conference held in Ho Chi Minh City, Vietnam, in 2004, the 2nd Consensus Group Meeting, which met in Tokyo, Japan in May 2005, discussed the issue of diagnostic criteria for Asian patients with suspected MS. The Consensus Group addressed a number of questions regarding Asian CMS and its relationship to western MS, neuromyelitis optica (NMO) and OSMS.

**A proposal of modified diagnostic criteria may be needed for Asian MS**

The Consensus Group concluded that the McDonald criteria need to be validated in the Asian population and that a proposal of modified diagnostic criteria may be needed for Asian MS, which would then form the basis of further research. ■

# Clinical implications of the BENEFIT and 16-Year LTF studies

Clinicians involved in managing MS patients must look at the findings of both the BENEFIT and 16-Year Long-term Follow-up (LTF) studies as both have important implications for patient welfare, explained Professor David Bates, University of Newcastle-upon-Tyne, UK. We now have evidence from three studies (BENEFIT, CHAMPS and ETOMS) clearly showing that interferon beta reduces the risk of clinically definite (CD) MS when given after the first clinical event suggestive of MS, explained Professor Bates. In addition, long-term therapy with Betaferon® is well tolerated and appears to have long-lasting beneficial effects.

It is now widely accepted that irreversible axonal injury caused by inflammation occurs early in MS. Hence, anti-inflammatory treatment applied early in the disease would appear to be the sensible approach, particularly as those patients with large numbers of early inflammatory events also experience early progression.

The BENEFIT study clearly demonstrated that most patients (85%) with a first clinical event and an abnormal magnetic resonance imaging (MRI) scan suggestive of MS will develop McDonald MS within 2 years, reported Professor Bates. The study also demonstrated that treatment with Betaferon® 250 µg every other day

(eod) provides benefits to patients presenting with a first clinical event, particularly in those with less active, less disseminated disease. Adherence to treatment was high and the majority of eligible Betaferon®-treated patients chose to enter the follow-up study.

Betaferon® has a well-known safety profile and side-effects are easily managed. Typical side-effects tend to diminish over time with long-term exposure to Betaferon®, as seen in the 16-Year LTF study. The interim results revealed that Betaferon® had long-lasting beneficial effects on a number of parameters, including an extended time to an expanded disability status scale (EDSS)

score of 6 (Figure 5), reduced T2 burden of disease and a greater proportion of ambulatory patients. There also appeared to be a positive effect on survival, which requires further investigation.

**Betaferon® should clearly be considered as first-line treatment for early cases of MS**

In general, therapy is not usually initiated until the patient has had at least three relapses, but results of the BENEFIT study show that patients would benefit from much earlier treatment initiation. The BENEFIT and 16-year LTF studies have clearly shown that long-term Betaferon® treatment over a wide spectrum of the disease course is advantageous.

Professor Bates concluded that Betaferon® should clearly be considered as first-line treatment for early cases of MS. ■

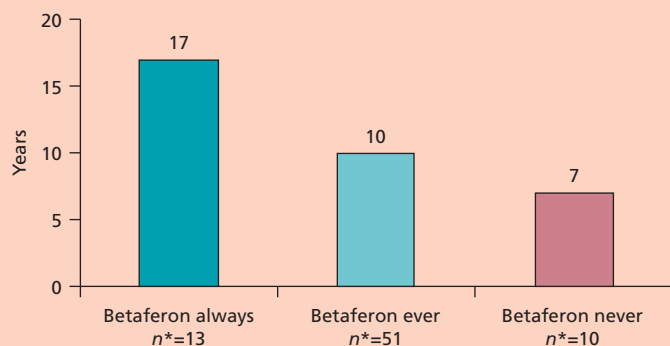


Figure 5: Median time to an EDSS score of 6 stratified according to exposure to Betaferon® (exposure calculated for the time between start of treatment in the pivotal trial and 2005 preliminary results).

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