

**2nd MS Forum
Pan-Asian
Conference
19-20 November 2004**

Consensus achieved on regional management of MS

After extensive debate, delegates reached consensus on the majority of a series of statements relating to the classification and the diagnosis of multiple sclerosis (MS), particularly with emphasis on presentations of MS seen in Asia and the Middle East.

Multiple sclerosis in Asia and the Middle East shares many similarities with Western MS as seen in the Caucasian population, but there are notable and important differences that must be considered by physicians in these regions. To explore these differences, an expert group of 12 neurologists from the regions, together with four international advisors, met in Tokyo, Japan, in February 2004, in order to reach initial consensus. Known as the Tokyo Consensus Group, the experts considered such questions as: whether or not classical MS in the Western and Asian populations is the same; whether the clinical and MRI features, and the underlying pathologies, of optic spinal MS (OSMS) are the same as those of neuromyelitis optica (NMO); whether classical MS, OSMS and NMO represent a spectrum of the same disease; what specific limitations the McDonald criteria have in the region; whether or not the Poser criteria are adequate for a diagnosis of MS in Asia; and what, therefore, is needed for diagnostic



The City Hall, Ho Chi Minh City, Vietnam.

criteria in Asia. The Tokyo Consensus Group drafted a series of 17 statements, and sought endorsement in Vietnam, where they were reviewed and discussed. The two chairmen ultimately put the consensus statements up for vote among all delegates present at the conference.

Further details of the consensus discussions are reported on pages 2-5. ■

The challenges of classifying MS, with particular emphasis on Asian and Middle Eastern presentations, and its diagnosis in these regions, provided the focus for lively discussion at this year's MS Forum Pan-Asian Conference, held in Ho Chi Minh City, Vietnam.

Under the chairmanship of Drs Kazuo Fujihara of the Tohoku University School of Medicine, Japan, and Benjamin KC Ong, of the National University of Singapore, over 110 neurologists from 16 countries sought endorsement of a series of regional consensus statements on the issues of classification and diagnosis of MS, and actively debated current 'hot topics' in Asia and the Middle East.

This issue of *Medical Express Reports* considers highlights from the conference, entitled *MS Across Continents: Challenging the Knowledge of MS in Asia and the Middle East*, and includes coverage of presentations given on long-term therapy with disease-modifying agents and recent therapeutic advances.

Cooperative efforts advance the management of MS

Through organised cooperative efforts, such as the *MS Forum Pan-Asian Conference*, real progress is being made in the management of MS in Asia and the Middle East, Professor Duc Hinh Le told delegates in his honourable welcome address.

As discussed at length during the 1st *MS Forum Pan-Asian Conference*, held in Bangkok, Thailand in 2003, MS is a multi-faceted disease, with differences in presentation, changing patterns of disease and incidence across the regions (Figures 1 and 2). In Asia and the Middle East (compared with the Caucasian world) there is a lower overall prevalence of the disease, a relatively lower proportion of the progressive forms of MS and a greater presence of the optic spinal form of MS (OSMS), noted Dr Ho Jin Kim, Boramae Sungmo Hospital, Seoul, Korea. There is also a higher female to male ratio, cerebellar presentations are rare and there is a lower positive rate of oligoclonal bands. Despite this heterogeneity, however, a consensus among neurologists is essential in order to characterise and treat MS confidently in Asia and the Middle East.

In Japan, at least evidence now suggests that MS has entered the age of being considered a 'treatable disease'

The traditional view that MS is a disease of 'the West' is no longer true, noted Professor Saida, chair of the inaugural *MS Forum Pan-Asian Conference*, held in 2003. In Japan, the incidence has risen considerably over the past 50 years, but at least evidence now suggests that MS has entered the age of being considered a 'treatable disease'. 'The introduction of Betaferon[®]', he commented, 'continues to have considerable impact on the prognosis for those with MS'. ■



Professor Duc Hinh Le, Vice-President of the Vietnamese Association of Neurology and President of the Hanoi Society of Neurology, and Professor Takahiko Saida, Director of the Utano National Hospital, Japan, and member of the MS Forum Executive Committee, welcome delegates to Ho Chi Minh City.

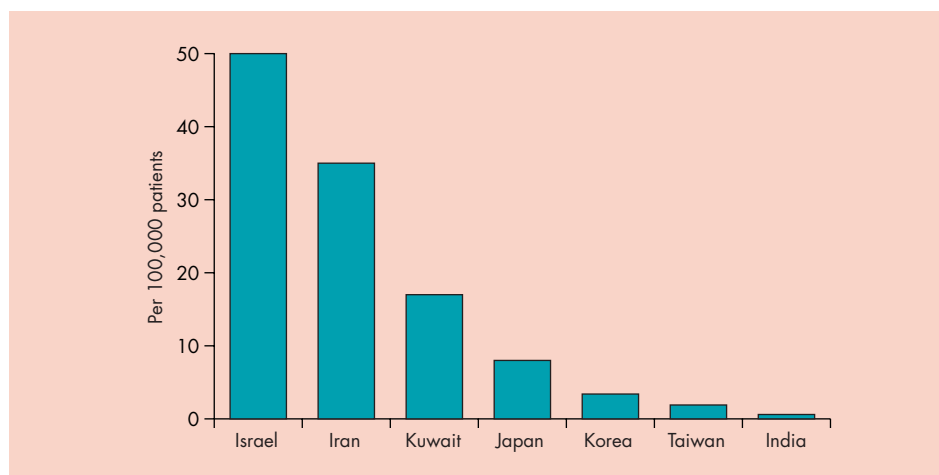


Figure 1: Prevalence of MS in selected countries in Asia and the Middle East.



Consensus Discussions: *A Step Forward*

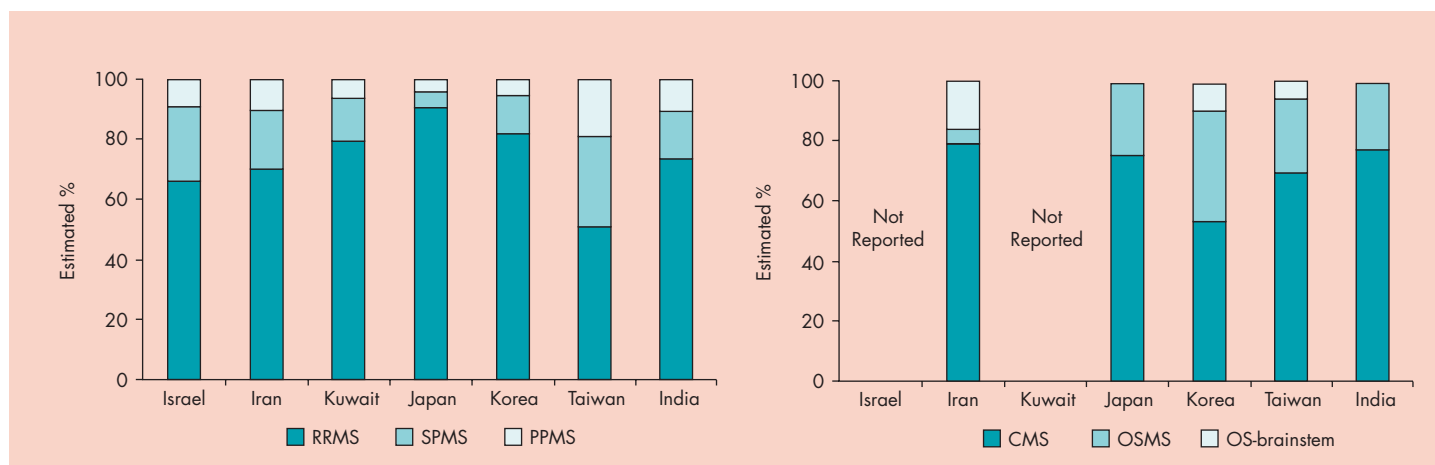


Figure 2: The classification of MS in selected countries in Asia and the Middle East.

The process of reaching consensus in MS management

Collaboration of Asian and Middle Eastern neurologists, under the auspices of the MS Forum, ensured that this conference provided 'a positive step to move forward uniformly in the management of demyelinating disease in this part of the world', commented Dr Benjamin KC Ong, co-chairman of the meeting.

The first MS Forum Pan-Asian Conference held in Bangkok, Thailand, in 2003, presented a wealth of data on MS in Asia and the Middle East. Based on these findings, the Tokyo Consensus Group presented 17 draft consensus statements that reflected the regional issues to the MS Forum conference delegates in Vietnam. Finally, the consensus process required these delegates to vote to endorse the original consensus statements, or to propose their revision.

'The consensus discussions went very well,' said co-chairman Dr Kazuo Fujihara, 'although there is some divergence of views and obvious concerns.' What was nevertheless evident, observed Dr Fujihara, was the agreement by delegates that the criteria

from the Caucasian regions (Poser, McDonald, etc), as they currently stand, are not wholly applicable to the Asian population. Publication of the consensus statements in 2005 may contribute positively to the outcome of the forthcoming international diagnostic criteria

(known as the International Panel criteria). If so, this would be the first time that a truly international set of guidelines for the diagnosis of MS has been developed. More importantly, publication of the consensus statements will mean that neurologists across Asia and the Middle East will be armed with better guidance that will, ultimately, help in the treatment of their MS patients. Neurologists will also gain a solid foundation of knowledge from which their MS research can be furthered. ■



Participants at the Tokyo Consensus Workshop, February 2004:

D Bates (UK; Consultant)
K Fujihara (Japan; Co-Chairman)
BKC Ong (Singapore; Co-Chairman)
T Fukazawa (Japan)
Y Itoyama (Japan; Consultant)
A Kermode (Australia)
HJ Kim (Korea)
KK Kim (Korea)

J Kira (Japan)
LK Kwong (Hong Kong)
I Nakashima (Japan)
H Fukaura (Japan)
N Prayoonwiwat (Thailand)
T Saida (Japan; Consultant)
CP Tsai (Taiwan)
BG Weinschenker (USA; Consultant).

Classification of MS in Asia and the Middle East

The heterogeneity of MS lesions reflects their multi-factorial aetiology, explained Dr Ian Sutton of the Garven Institute of Medical Research in Sydney, Australia, to delegates at the *MS Forum Pan-Asian Conference in Vietnam*. The immunopathogenesis of the disease remains a hotly debated topic.

Inflammatory demyelinating diseases of the central nervous system could be assigned, for example, a diagnosis of classic MS, OSMS, NMO (Devic's disease), acute disseminated encephalomyelitis or experimental allergic encephalitis, he continued, although differences in NMO and classic MS are recognisable. Furthermore, inflammation can affect T-cells, plasma cells, macrophages or microglia, and environmental and immunogenetic factors may also influence the evolution of the MS plaque.

Given the diversity in presentation of MS, it is hardly surprising that, to date, there has been lack of agreement on classification across Asia and the Middle East.

Inflammation can affect T-cells, plasma cells, macrophages or microglia

Consensus discussions, such as took place in Ho Chi Minh City, seek to overcome the current lack of uniformity in classifying and diagnosing MS in these regions. Initial voting on the classification of MS, led by Dr Fujihara, showed consensus on some, but not all, of the issues raised. Delegates agreed on all three of the statements relating to whether or not classical MS in Western and Asian populations is the same disease. Two statements relating to the

question: 'Do classical MS, OSMS and NMO represent a spectrum of the same disease?' were also endorsed.

However, statements pertaining to the questions: 'Are the clinical and MRI features of OSMS the same as those of NMO?' and 'Is the pathology that underlies OSMS the same as that of NMO?' were not initially agreed and were hotly debated during focussed break-out sessions. Panel discussion subsequently brought a number of viewpoints to light, such as:

- The need to define categories of the disease better through a stronger evidence base

- The necessity for more pathological and long-term data in Caucasian and Asian MS to help decide if they are the same disease
- Requirement for more information on the clinical course of the disease
- The need to look into the logical MRI features of MS.

Ultimately consensus (i.e. >70% agreement) was achieved on all but two of the classification statements; both relating to the pathologies that underlie OSMS and NMO, because, noted Dr Fujihara, further data are needed to support them. ■



Panel discussion on the classification of MS in Asia and the Middle East. Left to right: Breakout discussion moderators: Ichiro Nakashima, Japan; Naraporn Prayoonwiwat, Thailand; Ho Jin Kim, Korea; Hikoaki Fukaura, Japan; Allan Kermode, Australia; Takahiko Saida, Japan; Chairman: Kazuo Fujihara (all discussants were part of the aforementioned Tokyo Consensus Group).

Diagnosis of MS in Asia and the Middle East

Although appropriate for diagnosing classical (Western) MS, the McDonald criteria are not as appropriate for MS in Asia, advised Dr Toshiyuki Fukazawa, Vice-President of Hokuyukai Neurology Hospital, Japan. MS in Asia should be diagnosed somewhat differently to that in the Caucasian countries.

The McDonald criteria – as recommended by an International Panel on the diagnosis of MS – state:

‘There should be little or no swelling of the cord, although exceptions occur, and such spinal lesions should be unequivocally hyperintense on T2-weighted image, be at least 3 mm but under 2 vertebral segments in length, and occupy only part of the cross-section of the cord. Lymphocytic pleocytosis should be less than 50/mm³.’

Based on these exclusion criteria, a considerable number of patients with MS in Asia and the Middle East would not be diagnosed with the disease. It would appear that the McDonald criteria, although developed by an International Panel, did not take into account the full spectrum of idiopathic inflammatory demyelinating disorders. ‘The McDonald criteria broadly banded patients and are not perfect’, agreed Professor Mark Freedman of the University of Ottawa, Canada. He concluded, however, that rather than creating a complete new set of criteria, the way forward may be to adapt what already exists. Professor Takahiko Saida, of the Utano National Hospital, Japan, agreed, saying that, as they currently stand, the McDonald statements are ‘too strong’. This point was further reinforced by Professor David Bates from the University of Newcastle-upon-Tyne, UK, and Chairman of the *MS Forum*.



Drs Benjamin KC Ong and Kazuo Fujihara, chairmen of the 2nd MS Forum Pan-Asian Conference, with Professor David Bates, UK, Chairman of the MS Forum.

Professor Bates noted that the recommended McDonald diagnostic criteria, published in 2001, allow few concessions to non-‘classic’ or ‘proteotypic’ MS. The only discussions of NMO and recurrent longitudinal extensive transverse myelitis are as possible variants of MS, with a failure to consider national and geographic variations in the character of inflammatory demyelination.

Neurologists at the 2nd *MS Forum Pan-Asian Conference* considered a number of questions on the diagnosis of MS, and were unanimous in their view of the need for diagnostic criteria that encompass the forms of MS seen in Asia and the Middle East. Although over 86% agreed that the Poser criteria are useful for diagnosing MS, delegates agreed that they do not facilitate early diagnosis. Integrating MRI scan criteria into the McDonald criteria was intended to facilitate early diagnosis, but in Asian and Middle Eastern populations, the criteria fail to fulfil the diagnostic needs of neurologists. Over 96% of delegates thought that, for MS patients in these regions, the issues with the current McDonald criteria include:

- Characterisation of spinal and brain lesions
- Classification of recurrent optic neuritis and/or recurrent myelitis

- Cerebrospinal fluid changes
- Serological status.

Further, almost 95% agreed that the McDonald criteria are unlikely to be widely used without evidence of their predictive value in Asian and Middle Eastern populations. Thus, it is timely to review and attempt to develop new, or modify existing, diagnostic criteria that might, therefore, be more applicable to people with MS in Asia and the Middle East, perhaps based on adaptation of the Wingerchuck criteria for NMO, which associate optic neuritis and myelitis without any other neurological signs, concluded Professor Bates. ■

Next Steps in the Consensus Process

- Drs Kazuo Fujihara and Benjamin KC Ong will incorporate the views of delegates at the *MS Forum Pan-Asian Conference*, Ho Chi Minh City, Vietnam, into the consensus statements
- The consensus statements will be submitted for publication to a peer-reviewed journal with the aim of publication in early 2005
- With publication of the consensus statements, neurologists across Asia and the Middle East will be better armed with further knowledge, which will ultimately help in the treatment of their MS patients.

Funding needs cooperation

In Caucasian populations, less than 20% of patients account for more than 50% of the costs, reported Dr Carolin Miltenburger, Head of Global Outcomes Research, Schering AG, Berlin.

The economic burden of MS increases as the disease advances, with most costs lying outside the healthcare budget, i.e. due to loss of productivity through early retirement or sick leave. Within 10 years of being diagnosed with MS, up to 80% of patients are unable to work and, as the disease progresses, caregiving with mobility help is required and personal and nursing care become increasingly costly (Figure 3). However, current therapies such as Betaferon® can delay disease progression, thus reducing long-term care costs.

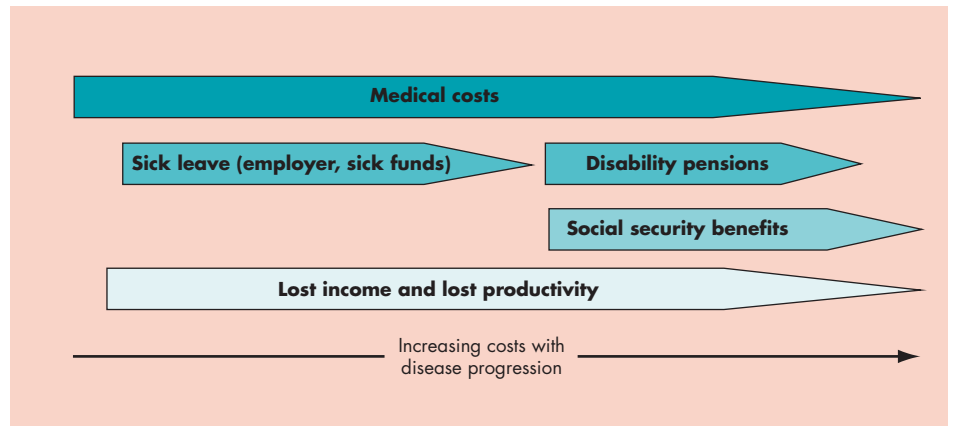


Figure 3: Lifelong costs of MS increase for all parties over time.

As decisions on approval of new therapies now take into account health economics and patient-reported outcomes, it is increasingly evident that the field of MS needs cooperation

between physicians, academic experts, patient groups and industry to ensure the successful introduction of new treatment options. ■

'Red flags' and pitfalls with diagnostic imaging

In 1986, Rudick *et al.* proposed various signs indicative of an inaccurate diagnosis of MS. In the era of routine MRI, additional 'red flags' must now be considered, advised Dr Makoto Matsui, of Utano National Hospital in Kyoto, Japan.

The classic 'red flags' proposed in 1986 include the absence of eye findings, i.e. optic nerve involvement; impaired extraocular movement; absence of clinical remission; lesions localised in the posterior fossa and spinal cord; atypical clinical features, i.e. absence of sensory findings, absence of bladder involvement; and absence of cerebrospinal abnormalities (although not necessarily a 'red flag' in Asia and the Middle East).

Additionally, we now know that we must also consider:

- Risk factors for cerebrovascular diseases, including hypertension,

diabetes mellitus and hyperlipidaemia

- Lack of optic neuritis
- Associated allergic diseases or eosinophils
- Associated pulmonary tuberculosis.

Further, with the advent of MRI, the following indicators must also be considered:

- The lack of lesions on MRI scans
- The possibility of over-interpreting MRI scans, especially of the brain.

MRI has become a major paraclinical tool in diagnosing MS and, in newly referred patients, it is important to analyse MRI data correctly to prevent

both false-positive and false-negative diagnostic errors. Dr Anat Achiron, Director of the Multiple Sclerosis Centre at the Sheba Medical Centre, Tel-Hashomer, Israel, described the development of the MS Analysis computerised, 3D, multispectral automatic software, based on the Bayesian classification of brain tissue

It is important to analyse MRI data correctly to prevent both false-positive and false-negative diagnostic errors

(white matter, grey matter, cerebrospinal fluid). This system enables quantitative volumetric measurement of demyelinating lesions and comparison of the change in MRI lesion load over time to assess disease activity and treatment effects. As such, it is anticipated to have significant clinical relevance. ■

Early MRI changes

MRI plays a fundamental role in the diagnosis of MS, explained Professor Takahiko Saida, of Utano National Hospital, Kyoto, Japan, and subclinical disease activity can be visualised by follow-up MRI studies. This is increasingly important in Japan, where the profile of MS disease over the past 50 years has moved towards that of classic (Caucasian) MS, i.e. with increased cerebral and cerebellar symptoms, particularly in younger patients.

Subclinical disease activity can be visualised by follow-up MRI studies

In MS patients with negative or equivocal brain MRI studies, however, MRI of the spinal cord can make a significant contribution. This is particularly important in non-Caucasian populations, where selective clinical involvement of the optic nerve, brainstem and/or spinal cord is relatively frequent. The presence of longitudinal spinal cord lesions extending three or more vertebral segments, for example, has been proposed as a hallmark finding of NMO. Extensively longitudinal spinal cord lesions are found in 20% of classic MS and 57% of optic-brainstem-spinal MS among Japanese patients, reported Dr Saida. ■

OSMS and classic MS in Japan

OSMS and classic MS do appear to be clinically distinct, and there are pathological features that are unique to OSMS, reported Dr Tatsuro Misu, of Tohoku University Hospital, Sendai, Japan.

Since autopsied cases of MS are limited in Asian countries, the pathological investigations provide precious information on what is happening in the central nervous system of patients with the disease. OSMS selectively targets the optic nerves and spinal cord, and is relatively common in Asia. Neuropathological studies in OSMS

frequently show tissue necrosis, cavity formation and grey matter involvement, as well as severe demyelination. Recent reports, however, suggest that infiltration of macrophages, neutrophils and eosinophils, and depositions of immunoglobulins and complement may be relatively unique to NMO. ■

A clear need for long-term outcome measures

There is a clear need for relevant long-term outcome measures in MS. Most clinical trials in MS are of 2 or 3 years' duration, despite the fact that disability in MS evolves slowly over several decades. Prevention or postponement of long-term disability is, clearly, the most important therapeutic aim of treatment. As such, we must take into account lessons from natural history to identify outcome measures relevant to MS therapy goals, advised Dr Bill Carroll, of the Sir Charles Gairdner Hospital, Perth, Australia.

The first truly long-term therapy data in MS to be reported (12-year data from the London, Ontario group) focused on tolerability and showed no unexpected late adverse events. Indeed, the study clearly demonstrated that, in an environment of improved education and comprehensive patient support, common adverse events of the flu-like syndrome largely disappeared over time. Many individuals maintained

Betaferon® therapy for more than a decade, thus deriving the benefit of delay in disease progression through long-term use of effective disease-modifying therapy.

To gain more insight, a 16-year follow-up study of patients who participated in the pivotal Betaferon® North American trial has been launched (Figure 4). This observational trial is the longest follow-up evaluation of any MS treatment. It will provide information on the 16-year effectiveness, safety and tolerability of Betaferon® in patients with relapsing-remitting MS, using a range of clinical, imaging, neurocognitive and quality-of-life outcomes compared to two different natural history cohorts. Results are expected in 2005 and will provide new data on long-term outcomes, thus giving clinicians further evidence to support their treatment decisions. ■

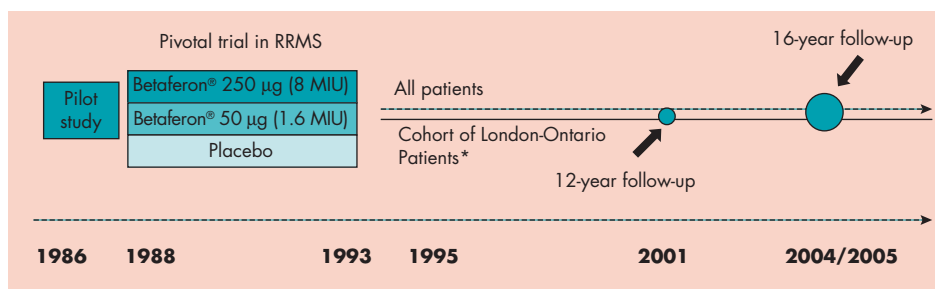


Figure 4: A 16-year follow-up investigation with Betaferon® in RRMS.

Improved outcomes for patients with MS

Active early demyelination, resulting in axonal loss, must be stopped, stressed Professor Mark Freedman of the University of Ottawa, Canada. Even in the very early stages of MS, when a patient has little disability, irreversible axonal damage has already occurred.

However, evidence from studies with Betaferon® suggests that early treatment to reduce inflammation may contribute to some degree of axonal recovery. We have been treating MS for over a decade with Betaferon®, which assures us of the continued long-term safety, tolerability and efficacy of this agent, Professor Freedman advised.

Recent studies have also confirmed that high-frequency interferon beta is superior to low-frequency (i.e. once-weekly) therapy in treating RRMS. For example:

- Twenty-four-month data from the INCOMIN study, comparing interferon beta-1a 30 µg (6 MIU) intramuscularly (im) once weekly with interferon beta-1b (Betaferon®) 250 µg (8 MIU) subcutaneously (sc) every other day, confirmed that higher and more frequent dosing improves outcome for MS patients

- A second directly comparative study, EVIDENCE, comparing interferon beta-1a 44 µg (12 MIU) sc three

times weekly with interferon beta-1a 30 µg (6 MIU) im once weekly, gave similar results to those of INCOMIN – favouring the high-frequency regimen

- A dose-reduction study, in which patients were switched from interferon beta-1b (Betaferon®) sc every other day to im interferon beta-1a once weekly, confirmed that reduction of interferon beta frequency and dose is not advisable, even in patients free from clinical and MRI disease activity for many years.

A review of all the clinical trials by the Therapeutics and Technology Assessment Committee of the American Academy of Neurology supports the view that interferon beta treatment is dependent on dose and frequency of administration (Figure 5).

Frequent administration of beta interferons maintains an increased level of biological response markers, which is not only advantageous to the overall

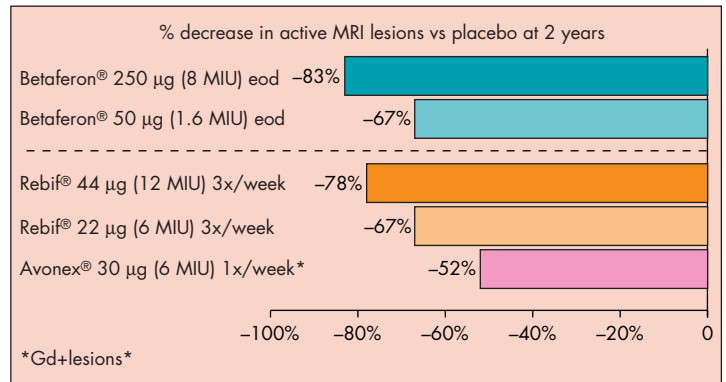


Figure 5: Evidence across controlled clinical trials shows dose- and frequency-dependent effects of the beta interferons.

efficacy of the drugs, but also to their tolerability. Flu-like symptoms tend to continue much longer with a low-frequency product, noted Professor Freedman, because the body has to get used to the therapy each and every week.

Ongoing studies, such as the second phase of the currently recruiting BEYOND programme, are investigating increased doses of Betaferon® (500 µg; 16 MIU) than is currently approved (250 µg; 8 MIU), and it is anticipated that this BEYOND dose will offer patients even greater benefits.

However, for the best outcome and to ensure full adherence to the regimen, patients need to be well educated about their medications. This requires reinforcement of the treatment goals and attention to side-effects, through regular clinic visits. This also serves as a way of monitoring treatment effects, and of providing patient support to ensure optimal response to therapy. ■



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