

19th Congress of the European Committee for Treatment and Research in Multiple Sclerosis

17-20 September, 2003; Milan, Italy

The management of multiple sclerosis (MS) has shown dramatic improvements during the past decade moving towards earlier diagnosis and more aggressive treatment, suggested Professor David Bates, professor of clinical neurology, Royal Victoria Hospital, Newcastle, UK, opening the congress.

The diagnosis of MS was generally imprecise and drawn out ten years ago, Professor Bates explained. However, several developments, including the publication of the McDonald criteria in 2001, have facilitated earlier diagnosis. Improved diagnostic techniques – including greater availability of MRI – means that the diagnosis of MS is now becoming more streamlined than in the past. The treatment of MS has also progressed, from use of palliative therapies to widespread use of targeted, disease-modifying therapies. “The first real breakthrough in MS therapy occurred in 1993, with the introduction of beta-interferon – the first agent to effectively alter the course of MS,” he noted.

The last decade has also seen major progress in understanding of the natural history of MS. “Understanding of the pathology of MS has shifted from focusing entirely on demyelination, to include inflammation and axonal loss as well,” Professor Bates told delegates. For the future, he predicted the development of a wider range of therapies targeting different processes underlying MS, in addition to optimisation of current treatment options and improved tailoring of treatment and monitoring of disease status in individual patients. “Head to head trials are now showing superior efficacy for high dose and higher frequency of interferon treatment,” he reported, adding, “Studies are also indicating that Betaferon may slow primary progressive MS.”

Higher doses of interferon improve outcomes

Promising results from the first stage of a major trial designed to investigate higher doses of interferon showed good short-term tolerability and safety.

The BEYOND (Betaferon Efficacy Yielding Outcomes of a New Dose) study was designed to clarify findings from clinical practice that higher and more frequent dosing of interferon beta improves outcomes in patients with relapsing-remitting MS. The study will compare interferon beta-1b at a daily dose of 250mcg with the higher dose of 500mcg, self-administered by subcutaneous injection every other day for two years, and with glatiramer acetate in patients with relapsing-remitting multiple sclerosis.

Preliminary results from 71 patients randomised so far to one of the two doses of interferon showed that the higher dose (500mcg) was well tolerated. Dose escalation had been successful, with 90% of patients in the 500mcg group and 80% of the 250mcg group reaching the target dose. A dose-response effect was observed in side-effects including flu-like symptoms, which affected 48% of the 500mcg interferon group compared to 34% of patients given the lower dose.

“The 500mcg dose of interferon beta-1b was well tolerated. Some adverse events observed tended to be more frequent in the 500mcg treatment arm, but the majority of cases were mild,” reported one of the research group, Dr Barrie Hurwitz, Duke University Medical Center, Durham, USA. “The higher incidence of events may be indicative of an increased systemic biological activity of the 500mcg dose,” he suggested.

Exploring the reasons for investigating higher doses of interferon, Professor Giancarlo Comi, director of neurology,

University Vita-Salute San Raffaele, Italy, said, “Both clinical and pharmacological studies support a dose- and frequency-dependent response to interferon-beta in the treatment of MS. The original pilot study of Betaferon offered hints that the 500mcg dose could have even greater effects on clinical and biological response markers than the currently used 250mcg dose.”

Clinical practice suggests no association between neutralising antibodies to interferon and lack of efficacy

Relatively few patients develop neutralising antibodies when treated with interferon beta-1b and their appearance seems to be unrelated to lack of efficacy, according to clinical data from more than 13,000 patients with MS.

The study analysed the development of neutralising antibodies in samples from 4687 patients in Europe and Australasia and from 1975 patients in the USA and Canada, using a standard MxA assay at centralised testing laboratories. The patients in the study had been diagnosed with MS for more than five years and had been treated with interferon beta-1b for one to four years. More than two-thirds (67.8%) of the patients from Europe and Australasia tested antibody-negative, while only 32.2% were positive. In the North American patients, 79% were antibody-negative. Only 7.9% of the European and Australian group and 7% of patients from the USA and Canada had antibody titres > 500.

It has previously been suggested that development of neutralising antibodies to interferon beta might affect treatment outcomes but studies have been inconclusive, using different antibody tests and patient populations. The American Association of Neurology guidelines (1996) suggested testing patients for antibodies who are on treatment for at least 12 months and who do not respond fully. This meant that this study probably included a high proportion of patients whose doctors were concerned about suboptimal response.

“The incidence of high neutralising antibody titres was low even though the study group might have been enriched for patients failing to respond optimally to interferon beta-1b,” the researchers, from Duke University Medical Center, Durham, USA, reported. “It appears likely, therefore, that neutralising antibodies are not the cause of suboptimal response to treatment in the majority of cases.”

Randomised study shows significant reductions in pain with cannabis-based medicinal extract

Cannabis-based medicinal extract achieves significant reductions in neuropathic pain and pain-related sleep disturbance, according to the first study of this compound.

The UK-based study randomised 66 patients with MS and central pain (59 dysaesthetic, seven painful spasms) to a whole plant extract oromucosal spray of tetrahydrocannabinol (THC):cannabidiol (CBD). Patients gradually titrated their dose up to a maximum of 48 sprays over 24 hours (each spray delivered 2.7mg THC and 2.5mg CBD).

Results from the 64 patients who completed the study showed that the cannabis extract gave them significant reductions in the primary outcome of pain (-1.25 on a numerical rating scale; 95% CI -2.11, -0.39; p=0.005) and in sleep disturbance (p=0.003). The score on the neuropathic pain scale was also significantly reduced (-6.82 on the 100 point scale; p=0.039). While taking the extract, patients were 3.9 times more likely to feel ‘much’ or ‘very

much improved' than those on placebo. There were no significant differences between cannabis extract and placebo groups in secondary outcomes including neurological disability, anxiety, depression and measures of cognitive function, apart from a small reduction in a selective memory test with the active treatment.

The researchers, from the Walton Centre for Neurology

and Neurosurgery, Liverpool, commented, "This is the first study to show a significant reduction in neuropathic pain and pain-related sleep disturbance in people with MS treated with cannabis-based medicinal extract."

*Susan Mayor PhD,
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For an overview of the new guidelines for the management of MS, see page 26

Association of British Neurologists Autumn Meeting

1-3 October, 2003; Glasgow, UK

The educational symposium on 'neuroinflammation and neuroinfection' covered aspects of viral encephalitis, immunoglobulin therapy, immune-mediated neuropathy, and inflammatory markers in ischaemic stroke.

We were privileged to have Professor DH Miller speak on the contribution of MRI to the understanding and management of multiple sclerosis with particular reference to the McDonald criteria and potential use in monitoring of immunomodulatory treatment. Professor D Shaw delivered an outstanding lecture as ABN medallist.

A 'taster' of the conference is provided with the following short reports.

1. **PD LIFE - A prospective multi-centre longitudinal audit of quality of life in Parkinson's disease across the UK.** Chaudhuri, London and Newcastle. Preliminary results; In 95 patients with early disease after 10 months 65% are on monotherapy (58% L-dopa; 38% dopamine agonists), and dopamine agonists are rarely used in older patients. Using L-dopa or dopamine agonist made no change to the quality of life scores.
2. **Oligoclonal band negative MS – does it exist?** Joseph, Bristol. Nineteen oligoclonal band negative patients were identified from 539 cases over 6 years in this retrospective case-controlled study. Unusual features in this group included headaches, generalised seizures, depression, cognitive impairment and psychosis. A monophasic or relapsing remitting course was more likely and the majority had significant disability contrary to beliefs held that this was a benign illness.
3. **The presentation of adults with arteriovenous malformations (AVM's) of the brain: prospective, population based study.** Al-Shahi, Edinburgh, Glasgow, Aberdeen and Dundee. Ninety-two patients were diagnosed over 2 years. Incidental AVM's (21%) were found in population 2 years older than those who presented symptomatically. This group had prior history of intracranial haemorrhage in 21%, 21% had 1 seizure and 32% had epilepsy or haemorrhage.
4. **The MRC's Asymptomatic Carotid Surgery Trial (ACST) – results after 5 years follow up.** Thomas and Halliday, London. Most of the 3101 patients had over 80% carotid stenosis and were allocated to either immediate carotid endarterectomy (CEA) or deferred CEA (i.e. until patient became symptomatic). The early surgery group had a significant reduction in stroke risk. For any type of stroke the 5 year risk was 6.42% for immediate, compared to 11.75% for the deferred group. Risk of fatal or disabling stroke was 1.87% for immediate and 5.57% for deferred. Overall peri-operative risks were 2.6% (mostly strokes and cardiac prob-

lems). The benefit did not hold true for those over 75 where deaths removed the value of surgery.

5. **Abnormalities in cardiac rhythm revealed in patients with refractory epilepsy.** Simister, London. Cardiac rhythm monitoring devices were implanted into 19 patients with refractory focal epilepsy over a median 16 month period. Three of 19 patients had potentially life threatening heart rhythms including sino-atrial arrest and prolonged bradycardia requiring permanent pacemaker insertion.
6. **Functional paresis – paradoxes in illness beliefs and disability in 107 subjects.** Stone, Edinburgh. Patients with functional paresis (107), compared to those with neurologically defined paresis (46) of less than 2 years' duration were much less likely to blame stress and twice as likely to have given up work because of symptoms despite similar self-rated disability.
7. **Potassium channel antibody associated encephalitis: a potentially treatable non-paraneoplastic limbic encephalitis.** Schott, London, Oxford and Germany. Phenotypic features of 10 antibody positive patients were memory loss, confusion and seizures, with syndrome of inappropriate anti-diuretic hormone secretion in 8, and temporal lobe change on MRI in 8. Improvement with treatment varied (steroids, immunoglobulin and plasmapheresis), with definite improvement in 6, and thus mirrored a fall in antibody titres.
8. **Synthetic disialyl-galactose immunoabsorbents clear pathogenic anti-GQ 1 b ganglioside autoantibodies from serum in Guillain Barré syndromes.** Willison, Glasgow and Alberta, Canada. Development of a synthetic trisaccharide which can "wash out" the anti-GQ 1 b antibodies linked to Miller Fisher syndrome was described. Although not developed yet for patient treatment, the wider potential therapeutic applications of such a technique in antibody-mediated disease made this presentation the most exciting of the conference to these reviewers.

We were grateful to Dr R Thomas for a historical exposition in an expanded poster on Sir Robert Carswell, a Scottish pathologist responsible for the first description of the multiple sclerosis plaque. Original drawings kindly on loan from University College London were displayed. One mystery remains – the location of one of his original drawings – although a facsimile is available. If any reader can assist please contact Dr Thomas or one of the authors direct or c/o E-Mail. AdvancesinCNR@aol.com

*Vicky Marshall and Donald Grossett,
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Walking group at the summit of Ben Lomond after the conference, organised by Prof. Willison