

Interferon beta in multiple sclerosis: how much BENEFIT?

Despite pivotal trials of the disease-modifying agents interferon beta and glatiramer acetate, worldwide approval by licensing agencies, and a growing trend to treat all patients with early multiple sclerosis, controversy still exists about who and when to treat.^{1,2}

When a person presents to a neurologist for evaluation of a first event (clinically isolated syndrome) suggestive of multiple sclerosis, the treating physician has a daunting task when making a rational therapeutic recommendation. He or she has to assimilate evidence-based medical facts, knowledge of the natural history of the disease, pharmaceutical promotional material, imperfect diagnostic criteria, and the patients' wishes. Does the evidence support the use of a disease-modifying agent without delay? For patients with limited clinical or radiographic disease dissemination, or when patients are reluctant to begin parenteral treatment, is a watchful waiting or delayed approach inappropriate?

The magnitude of clinical benefit in terms of disability prevention is an important consideration in the therapeutic decisionmaking process, in view of the financial cost, adverse effects, patients' reluctance to begin long-term parenteral therapy, and the fact that patients with multiple sclerosis might do well for decades without treatment.^{3,4} Trials have focused on accessible outcomes of relapse behaviour and MRI variables of disease activity, and have shown only partial benefit on disability progression over the short term.^{5,6} Objective interpretation of clinical effect is obscured when statistical analyses in large randomised trials emphasise relative risk reductions and their p values, rather than the magnitude of benefit (eg, numbers needed to treat, absolute risk reductions).

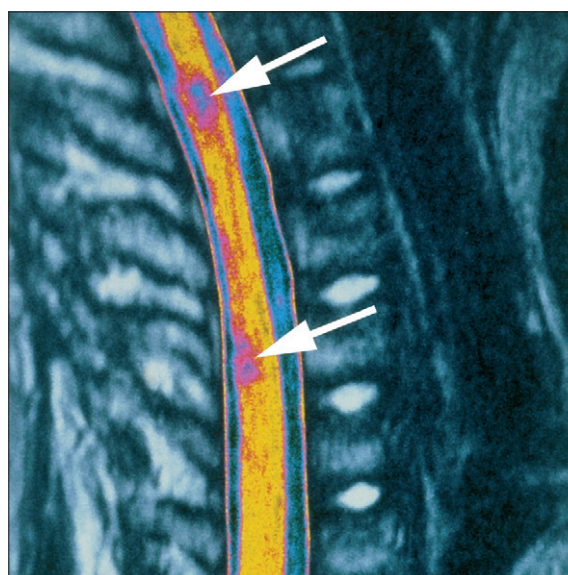
A key issue, for both multiple sclerosis and clinically isolated syndrome, is whether disease-modifying agents have any long-term benefit on accumulation of disability. The CHAMPS,⁷ ETOMS,⁸ and BENEFIT (2-year placebo-controlled phase)⁹ studies showed that treatment with interferon beta reduced the rate of conversion to clinically definite multiple sclerosis within 2 years of clinically isolated syndrome. The benefits, however, were modest. The number of patients needed to treat to prevent one from developing clinically definite multiple sclerosis at 2 years was six (BENEFIT) and at 3 years was seven (CHAMPS). Whether delaying

the second attack has any long-term effect on disability remains unclear.⁷⁻⁹

See [Articles](#) page 389

To answer the disability question, we must rely on extension trials which, although imperfect (unblinding of patients and evaluators, drop-outs, and assumptions from missing data), are the best we have.⁵ In today's *Lancet*, Ludwig Kappos and colleagues¹⁰ set a new benchmark in the presentation of results from BENEFIT, by providing measures of magnitude of clinical benefit (numbers needed to treat and absolute risk reductions) and subgroup analyses. Additionally, they have sought to address many concerns of previous trials by maintaining blinding for the initial randomisation for both patients and physicians, and had a lower drop-out rate (15% and 10% of interferon and placebo groups, respectively) than did other studies.¹¹

Kappos and colleagues report results of a 3-year follow-up of the BENEFIT trial, and provide data to support their conclusion that "early initiation of treatment with interferon beta-1b prevents the development of confirmed disability" and suggest that delaying treatment has "an effect on later accumulation of disability".¹⁰ At first look, one might surmise that this follow-up at last dispels controversy and provides the practising neurologist with the data needed to support early treatment for all patients with a clinically isolated syndrome and MRI findings suggestive of



Myelin damage (arrows) in multiple sclerosis

Science Photo Library

multiple sclerosis (at least two clinically silent lesions on T2-weighted scan). Unfortunately, caution is warranted and the general applicability of the findings to patients with clinically isolated syndrome is uncertain.

Although statistically significant, the benefit of early compared with delayed treatment in terms of disability progression was small. The difference in mean scores on the expanded disability status scale (EDSS)¹² between first event and last follow-up were small in both the delayed treatment (a worsening of 0.15 steps) and the early-treatment groups (an improvement of 0.11 steps). To put this change in context, changes of less than 0.5 steps in EDSS have never been considered a validated outcome for individual patients. Furthermore, most patients in Kappos and colleagues' study had low EDSS scores (median 1.5, IQR 1.0–2.0), which are associated with lower reproducibility and higher inter-rater variability than higher EDSS scores.^{13,14}

Although the primary outcome in Kappos and colleagues' follow-up was based on the categorical measure time to confirmed worsening of EDSS by one or more steps, the additional presentation of EDSS data as a mean, whereby the EDSS is treated as a continuous variable even though it is a stepwise non-continuous scale (each step is assigned on the basis of a functional system score and ambulation), raises some concern. Some have argued that non-parametric distribution-free tests (eg, χ^2 or *U* tests) would be more appropriate.¹⁵

When patients in BENEFIT were stratified according to the extent of disability progression (steps of 0.5 or less, 1–2, and more than 2.0 by EDSS) within the 3-year follow-up, the differences for each of the three stratified groups between patients treated early and those whose treatment was delayed were small (2%, 1.0% and 2.8% respectively). Furthermore, 12 patients need to be treated early to avoid one additional patient developing a confirmed EDSS progression, defined as an increase in EDSS score of 1 or more steps.

A finding not to be overlooked in Kappos and colleagues' follow-up was the lack of a significant benefit of early compared with delayed treatment in patients with limited clinical signs or symptoms (53% of study patients) or limited MRI disease dissemination (29% of study patients with less than nine T2-weighted lesions) at baseline. In the post-hoc subgroup analysis, the limited sample size and the relatively low event rate of

“confirmed EDSS progressions” probably affects power for analysis, and the results of the final 5-year BENEFIT analysis will be important.

Kappos and colleagues have set a new standard against which future extension trials will be compared. They present the first evidence that interferon beta-1b treatment has a beneficial effect on accumulation of confirmed disability in patients with a first event suggestive of multiple sclerosis. The results should, however, be interpreted with care because the magnitude of benefit, although statistically significant, is clinically small. This follow-up should not be misconstrued as evidence for a treat-all approach.

Sean J Pittock

Departments of Neurology and Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN 55901, USA

Pittock.Sean@mayo.edu

I declare that I have no conflict of interest.

- 1 Pittock SJ, Weinschenker BG, Noseworthy JH, et al. Not every patient with multiple sclerosis should be treated at time of diagnosis. *Arch Neurol* 2006; **63**: 611–14.
- 2 Frohman EM, Havrdova E, Lublin F, et al. Most patients with multiple sclerosis or a clinically isolated demyelinating syndrome should be treated at the time of diagnosis. *Arch Neurol* 2006; **63**: 614–19.
- 3 Pittock SJ, Mayr WT, McClelland RL, Noseworthy JH, Rodriguez M. Clinical implications of benign MS: a 20 year population-based follow up study. *Ann Neurol* 2004, **56**: 303–06.
- 4 Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is slower than previously reported. *Neurology* 2006; **66**: 172–77.
- 5 Noseworthy JH. How much can we learn from long-term extension trials in multiple sclerosis? *Neurology* 2006; **67**: 930–31.
- 6 Noseworthy J, Miller D, Compston A. Disease-modifying treatments in multiple sclerosis. In: Compston A, Confavreux C, Lassmann H, et al, eds. *McAlpine's multiple sclerosis*, 4th edn. London: Churchill Livingstone, 2005: 729–802.
- 7 Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med* 2000; **343**: 898–904.
- 8 Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet* 2001; **357**: 1576–82.
- 9 Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006; **67**: 1242–49.
- 10 Kappos L, Freedman MS, Polman CH, for the BENEFIT Study Group. Effect of early versus delayed interferon beta 1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3 year follow-up analysis of the BENEFIT study. *Lancet* 2007; **370**: 389–97.
- 11 CHAMPIONS Study Group. IM interferon β -1a delays definite multiple sclerosis 5 years after a first demyelinating event. *Neurology* 2006; **66**: 678–84.
- 12 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; **33**: 1444–52.
- 13 Noseworthy JH, Vandervoort MK, Wong CJ, Ebers GC, and the Canadian Cooperative Multiple Sclerosis Study Group. Interrater variability with the Expanded Disability Status Scale (EDSS) and functional systems (FS) in a multiple sclerosis clinical trial. *Neurology* 1990; **40**: 971–75.
- 14 Goodkin DE, Cookfair D, Wende K, et al. Inter- and intrarater scoring agreement using grades 1.0 to 3.5 of the Kurtzke Expanded Disability Status Scale (EDSS). *Neurology* 1992; **42**: 859–63.
- 15 Kurtzke JF. Neuroepidemiology. Part II: assessment of therapeutic trials. *Ann Neurol* 1986; **19**: 311–19.