Annals of Neurology
Supplement to Volume 36, 1994

# Multiple Sclerosis: Approaches to Management



*Proceedings of a Symposium Sponsored by*
*Associazione Italiana Sclerosi Multipla*
*Association of Universities and Colleges of Canada*
*Autoimmune Inc*
*Berlex*
*French Foreign Affairs Travel Grant*
*International Federation of Multiple Sclerosis Societies*
*Ligue Française Contre La Sclérose en Plaques*
*Merck & Co Inc, Rahway, NJ, U.S.A.—Research Laboratories*
*Minister of Health—Canada (N.H.R.D.P.)*
*Multiple Sclerosis National Society—Canada*
*National Institutes of Health (NINDS)*
*National Multiple Sclerosis Society—U.S.A.*
*Schering*
*Serono*
*Vancouver Island Multiple Sclerosis Society*

Victoria, B.C., Canada
September 10–13, 1993

**Supplement Editor**

**Donald H. Silberberg, MD**
*Professor and Chairman*
*Department of Neurology*
*University of Pennsylvania Medical Center*
*Philadelphia, PA*

This supplement, under the direction of Donald H. Silberberg, MD, was made possible by a generous grant from Berlex Laboratories.

# The Interferon-β1b Clinical Trial and Its Implications for Other Trials

Donald W. Paty, MD, FRCP

This trial was monitored by both clinical and magnetic resonance imaging (MRI) methods. Clinical effect was a 30% reduction in relapse rate in the group treated with a high dose. The MRI activity rate was reduced by a median of 70% in both treatment groups. The burden of disease measure showed a clear-cut dose effect in the 2-year analysis. Future trials must be monitored by MRI. In addition, placebo controls will continue to be necessary in most trials, especially if long-term effects are to be measured.

Paty DW. The interferon-β1b clinical trial and its implications for other trials.
Ann Neurol 1994;36:S113–S114

The interferon-β1b trial involved both clinical and magnetic resonance imaging (MRI) monitoring of disease activity [1, 2]. There are a few principles learned from that trial that must be practiced in future studies using MRI monitoring. First, there must be a centrally quantified and interpreted system for handling the MRI data. A study like this one produces an enormous problem in data handling that requires a very sophisticated data base. There also must be a standardized scanning protocol that is required to be followed in a very rigid way.

We assumed that we could quantify the pathology of the disease by MRI and we have called that measure the burden of disease (BOD). We do not know the precise tissue changes that are present within the pathology detected as abnormal areas seen on the MRI scan. Determining that in vivo pathology will be a very exciting area for research in the future [3–8].

As part of the study we did a frequent MRI substudy in the 52 patients from Vancouver [2]. New, enlarging, and recurring lesions were identified. There were 17 or 18 patients per treatment group. The most conservative way of interpreting the MRI data was to calculate the mean percentage of active scans per patient. That measure was 35% in the placebo group and one-half of that (approximately 17%) in both treatment groups. We do not know why a dose effect was not seen on the MRI activity measure. It may be that MRI is such a sensitive measure that one would have to go to a very low dose of drug to detect the threshold.

In counting active lesions, the numbers can be very high, particularly in a few patients. Therefore, the results were expressed as medians rather than means. There was quite a striking difference in the medians, showing a treatment effect looking at all active lesions, new lesions, or percent active lesions. However, the most conservative way to interpret the data (percent active scans) was consistent with all of the other MRI and clinical measures. In fact, one of the most striking features of this trial was the internal consistency of the results.

The most sensitive measure early in the trial was the percent active scans per group. The percent active scans per group was the measure in which a change could be seen from baseline to the first scan at 6 weeks. That treatment difference continued for the entire 2 years of the study. However, the difference between the two groups was not statistically significant until the 1-year point. The lack of statistical significance early on was due to the small number of patients in the cohort.

Using the BOD measure, both the Vancouver cohort and the total multisite cohort were used. However, separate technicians were used for measuring the Vancouver frequent scans and the yearly multisite scans. The overlap scans were quantitated by both technicians so that there was consistency in the data within each study.

Comparing all cases in the multisite study, a dose effect can be seen. However, we are still not comfortable with the slope of the curve in the BOD measure. In the third year, there was a falloff in all three groups. A reevaluation of the third year drop-off phenomenon is underway.

There was a positive correlation between the MRI area and the baseline Expanded Disability Status Scale (EDSS) ($r = 3.5$) ($p = 0.001$). This correlation was statistically significant but not clinically impressive.

From the Division of Neurology, The University of British Columbia, Vancouver, British Columbia, Canada.

Address correspondence to Dr Paty, Division of Neurology, Room 222, Vancouver General Hospital, 2775 Heather Street, Vancouver, British Columbia, Canada V5Z 3J5.

 

However, it was disappointing that the change in EDSS over the 2 years did not correlate with the change in MRI-detected BOD.

We were pleased to see that the change in MRI-detected BOD over time correlated with the exacerbation rate (DW Paty, unpublished results). The patients with the highest rate of exacerbation had the greatest change in MRI-detected BOD over time. Perhaps both the exacerbation rate and the quantitative MRI have the same prognostic implications.

What do these data mean for the future? First, the implication is that all future trials must be monitored by MRI. In addition, the MRI technique must be studied very carefully to determine what it is telling us about pathology.

There are also important implications for other trials, including other studies with interferon-β. For example, Copolymer-1 (Cop-1) is not toxic to patients. The Cop-1 study should be continued until such a time as interferon-β1b is freely available on the market. Other studies with nontoxic substances should be carried out with a placebo control as well. However, some toxic therapies such as inmmunosuppression are going to have to be carefully screened before they can be suggested for placebo-controlled studies.

If such substances show very strong trends toward statistical significance early in the study, perhaps these studies should be continued. They should be terminated early if they do not show an early highly suggestive trend toward therapeutic effect. MRI monitoring with frequent scans will allow early detection of treatment trends. Until such a time as interferon-β1b becomes freely available on the market it is appropriate to do placebo-controlled studies on relapsing and remitting patients, particularly if multiple doses in at least three arms are used. In such a study, patients would have a two-thirds chance of receiving either the previously shown effective drug dose or an even higher dose. For the time being, however, a placebo control will be necessary.

In addition, an important issue for future studies is whether or not the chronic–progressive phase of the disease can be affected by interferon-β1b. It is therefore appropriate that placebo-controlled studies continue to be done in that phase of the disease. It is only by placebo-controlled studies that we will determine whether these treatments have an effect on the chronic nature of the disease. It is appropriate to ask our patients to delay the treatment (which will reduce relapses by one-third) to find out if the drug influences the chronic nature of the disease. The importance of trying to answer that fundamental question is so great that placebo-controlled studies should be continued until that question has been answered.

It is widely assumed that it is the inflammatory aspect of the lesions that causes relapses. The interferon-β1b study showed very clearly that the inflammatory activity and most dynamic nature of the disease can be amenable to therapy. It is now vitally important that the chronic nature of the disease be studied with the same intensity.

In addition, comparative dose studies should also be done. Sensitive measures such as MRI should help us to see which doses are the most appropriate for specific indications.

In the future, it may be possible to dissect out some of the in vivo pathology using magnetic spectroscopy and T2-relaxation analysis [5–8]. In addition, an accurate determination of the slope of the curve in the BOD measure will also be useful in determining the persistence of treatment effect in open label studies.

## References


1. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:665–661
2. Paty DW, Li DK. Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Neurology 1993;43:662–667
3. McDonald WI, Miller DH, Barnes D. Annotation: the pathological evolution of multiple sclerosis. Neuropathol Appl Neurobiol 1992;18:319–334
4. Stewart WA, Hall LD, Berry K, Paty DW. Correlation between NMR scan and brain slice: data in multiple sclerosis. Lancet 1984; 2:412 (Letter)
5. Arnold DL, Matthews P, Francis G, Antel J. Proton magnetic resonance spectroscopy of multiple sclerosis: discrimination of acute and chronic lesions on the basis of metabolic characteristics. Neurology 1990;40(suppl 1):378 (Abstract)
6. Wolinsky JS, Narayana PA, Fenstermacher MJ. Proton magnetic resonance spectroscopy in multiple sclerosis. Neurology 1990;40: 1764–1769
7. Richards TL. Proton MR spectroscopy in multiple sclerosis: value in establishing diagnosis, monitoring progression, and evaluating therapy. AJR 1991;157:1073–1078
8. MacKay A, Whitall KP, Cover KS, et al. In vivo $T_2$ relaxation measurements of brain may provide myelin concentration. In: Balaban RS, ed. Book of abstracts. Society of Magnetic Resonance in Medicine, Tenth Annual Meeting, San Francisco, CA, August 10–16, 1991. Berkeley, CA: Society for Magnetic Resonance in Medicine, 1991