Interferon beta-1b is effective in relapsing-remitting multiple sclerosis.
II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial

D.W. Paty, MD; D.K.B. Li, MD; the UBC MS/MRI Study Group*;
and the IFNB Multiple Sclerosis Study Group*

Article abstract—We performed yearly MRI analyses on 327 of the total 372 patients in a multicenter, randomized, double-blind, placebo-controlled trial of interferon beta-1b (IFNB). Clinical results are presented in the preceding companion paper. Baseline MRI characteristics were the same in all treatment groups. Fifty-two patients at one center formed a cohort for frequent MRIs (one every 6 weeks) for analysis of disease activity. The MRI results support the clinical results in showing a significant reduction in disease activity as measured by numbers of active scans (median 80% reduction, $p = 0.0082$) and appearance of new lesions. In addition, there was an equally significant reduction in MRI-detected burden of disease in the treatment as compared with placebo groups (mean group difference of 23%, $p = 0.001$). These results demonstrate that IFNB has made a significant impact on the natural history of MS in these patients.

NEUROLOGY 1993;43:662-667

Cranial magnetic resonance imaging (MRI) is a powerful procedure for diagnosing multiple sclerosis (MS), for delineating its natural history and, potentially, as an objective quantitative outcome measure for assessing the response of MS patients to experimental therapy. Clinical MS is characterized by the presence of symptomatic lesions in the CNS and by progressive neurologic impairment. In relapsing-remitting MS (RRMS), there are unpredictable attacks resulting in neurologic deficits separated by periods of variable duration of remission, ie, apparent quiescence or stability of disease. Serial cranial MRI studies[1,2] have revealed that, in contrast to its clinical profile, RRMS is almost always active, with new and recurrent MRI lesions appearing and disappearing during periods of clinical remission. The majority of new lesions detected by serial cranial MRI are neurologically silent. The lack of clinical expression of new lesions places severe constraints on the use of clinical assessment alone to determine disease activity, disease progression, and disease modification by therapy. In addition to the number of exacerbations and their

degree of severity, the clinical standard for determining neurologic impairment in MS is the Expanded Disability Status Scale (EDSS),[3] which is somewhat insensitive, is heavily weighted toward motor disturbances and ambulatory deficits,[4] and has a considerable intra- and inter-rater variability.[5]

In contrast, currently used MRI techniques that are appropriately T_2-weighted can precisely define the location and extent of MS lesions above the level of the midcervical cord. However, individual cranial MRIs do not correlate well with clinical status as measured by standard impairment scales.[6] Prospective systematic serial cranial MRIs not only reveal changes that are more frequent and dynamic than are clinical manifestations but also show that most new lesions are asymptomatic.[7-12] The positive effect of beta interferon-1b on reducing relapse rates in MS is documented in the preceding companion article.[13] In the present investigation, we used MRIs in parallel with clinical assessment to monitor a randomized, placebo-controlled clinical trial of recombinant interferon beta-1b (IFNB) in

RRMS. Interferon beta-1b (Betaseron) is manufactured by Chiron and supplied by Berlex Laboratories.

The MRI studies carried out in parallel involved (1) quantitation of disease burden on a yearly basis by measurement of the extent of all cranial lesions slice by slice, and (2) frequent MRIs done every 6 weeks to study the dynamics of mostly asymptomatic new and active lesions.

Methods. *Study design.* A randomized, placebo-controlled trial was conducted at 11 sites in the United States and Canada. Project enrollment was 372 patients. Patients with clinically definite or laboratory-supported definite RRMS were centrally randomized between three treatment arms: placebo, 1.6 MIU IFNB*, and 8 MIU* IFNB, self-administered subcutaneously on alternate days. Inclusion and exclusion criteria and other clinical information is given in the companion paper.[13] All patients had baseline and annual cranial MRIs at the end of the first, second, and third years. MRIs from 327 patients were available for quantitation and met the standards for inclusion in the study. A 52-patient cohort at the University of British Columbia (UBC) had MRIs every 6 weeks for the initial 2 years.

Performance of MRIs and analysis of MRI data. MRIs were performed at each site in accordance with a scanning protocol designed to standardize procedures among sites. This protocol described strict positioning techniques and scanning standards as well as the precise information and content of the film and computer tapes to be sent to the UBC MRI Analysis Group.

Scans were obtained in the transverse plane from the level of the foramen magnum to the vertex. Each site used external and internal landmarks specific to its scanner to duplicate the same imaging plane and patient position for each subsequent study. A double echo spin-echo sequence was used, with the echo times appropriate to each scanner chosen so that CSF was low intensity (dark) on the first echo and high intensity (bright) on the second echo. These sequences were chosen to maximize lesion detection and facilitate lesion tracing. Exactly the same positioning and imaging sequences were used on subsequent studies.

All scans were critically interpreted and quantitated at UBC. The MRI Analysis Group at UBC had no clinical knowledge of any of the patients analyzed. The analysis computer at UBC was programmed to read, convert, and display the data from the various instruments, which ranged in field strength from 0.15 to 1.5 T (General Electric, Fonar, Philips, Picker, and Siemens). All films and tapes were checked for consistency, completeness, and compliance with the MRI scanning protocol. Scans were rejected if they did not meet the standards set in the protocol.

The presence, location, and extent of MS lesions were marked on the films by two radiologists, by consensus. Where there was a disagreement, a third senior radiologist also reviewed the films, and a final consensus was reached. The MRI data were then displayed directly from computer tapes on a high-resolution graphics monitor,

and regions of interest of the previously marked lesions were outlined by the analysis technician. Quality control was verified through reproducibility studies, which showed a coefficient of variation of 6% for a single observer.[14] Multiple observers had a high interobserver variation; therefore, one technician alone traced the lesions for the multisite quantitative studies and a separate technician alone traced the lesions for the UBC cohort.[15,16] The areas of the lesions were summed slice by slice for a total lesion area and recorded as mm². As an additional check for consistency, at the end of the study each technician was given randomly selected baseline and interim scans to requantitate without knowledge of the initial analytic results.

Lesion activity was analyzed in a different fashion in the subgroup that had scans every 6 weeks, using previously described and established methodology[17] according to the following definitions. *New lesions* were those that had never been seen before, *recurrent lesions* were those reappearing at the same site at which an earlier lesion had disappeared, and *enlarging lesions* were those showing a significant increase in size from a previously stable-appearing lesion. (Significant change in size was >70% for small [<1 cm] lesions and >10% for large [>1 cm] lesions). An *activity event* was any new, recurrent, or enlarging lesion. Any continuously changing activity through several scans was designated an activity event only once. An active scan was defined as any scan showing an activity event.

Statistics and data analysis. Treatment group differences based on the annual MRI data were analyzed using an analysis of variance (ANOVA) model. Total change in lesion area and percentage change in lesion area for individual subjects were ranked and used in the ANOVA. The model accounted for the effects of treatment group, study site, and treatment group by study site. The mean percent change in lesion area was sensitive to outliers. Therefore, for each treatment group, the percent change in total lesion area for the entire group was displayed. This is also why the median percent change within each treatment group was used.

The 6-weekly serial MRI data were collected at the UBC site only. The percent of scans active and annual lesion rates for individual subjects were ranked and then analyzed using an ANOVA model that had treatment group as its only effect. A two-sided Fisher's exact test was used to compare treatment groups on the number of subjects with active lesions.

An intent-to-treat analysis was used for data presented in this report. SAS software was used for all analyses.

Evaluation of annual MRIs. Change in MRI lesion area was ranked as analyzed for treatment group differences using the ANOVA of ranks model. The comparability of baseline lesion areas across treatment groups at entry to the study was determined. Change in lesion area and percentage change in lesion area from baseline to 1 year, 2 years, and end point (3 years) were compared across treatment groups. Correlation of the MRI change from baseline to end point was analyzed in regard to treatment group effects within each protocol. Disease burden (total lesion area) and neurologic impairment were correlated.

Evaluation of MRIs performed every 6 weeks. The percent active scans per patient was calculated by dividing the number of observed scans with activity by the total number of scans (excluding baseline) in each treatment arm. In addition, for each patient, an annual rate of lesion activity was calculated by dividing the number

Table 1. Number of MRIs available and mean and median percent change from baseline in total disease burden (mm²) as measured by MRI in each treatment group

Time point	Measurement	Placebo	Treatment group 1.6 MIU	8 MIU	Placebo vs 8 MIU p value*
1 year	N	110	110	107	
	Mean group change	12.2%	4.1%	−1.1%	
	Median change	10.9%	3.0%	−6.2%	<0.001
2 years	N	98	100	96	
	Mean group change	20.0%	10.5%	−0.1%	
	Median change	16.5%	11.4%	−0.8%	<0.001
3 years (end point)	N	111	112	109	
	Mean group change	17.1%	1.1%	−6.2%	
	Median change	15.0%	0.2%	−9.3%	0.002

* The p values were calculated from an analysis based upon individual patient data. This table expresses the mean changes based on group means because the % change based upon individual data was heavily influenced by the very large percentage changes in patients with very low disease burden at baseline.

Table 2. Status of percentage change in MRI area at end point

Status	Placebo	IFNB 1.6 MIU	8 MIU
>10% increase	63 (52%)	46 (37%)	35 (29%)
Stable (+10%)	22 (18%)	23 (18%)	21 (17%)
>10% decrease	37 (30%)	56 (45%)	66 (54%)

Placebo vs 8 MIU: p = 0.001

Table 3. Number of MRIs available and median change in total lesion area by MRI (mm²) by treatment group

Time point	Measurement	Placebo	IFNB 1.6 MIU	8 MIU
Baseline	Area	2,611	2,750	2,392
1 year	N	111	113	107
	Median change	152.5	45.2	−72.0
2 years	N	99	103	96
	Median change	305.1	142.0	−13.0
3 years (end point)	N	112	115	109
	Median change	198.7	0.0	−118.9

of active lesions by the number of years the patient had been in the study. The annual rate of new, enlarging, and recurrent lesions was similarly determined.

Results. *Patient characteristics.* The companion paper[13] gives the detailed clinical characteristics for all patients. MRI data were available for 327 of the 372 patients enrolled in the clinical study. Of these 327 patients, 70% were women and 94% were white. Extensive statistical analyses for differences between the three treatment groups showed that they were comparable for basic demographic factors and key disease characteristics. No significant interaction between treatment group and study site was seen for any baseline characteristic.

Findings for MRIs performed annually. Despite a standardized MRI protocol, unavoidable changes in software and hardware resulted in some differences among sites. Although these alterations did not affect the relative changes between treatment groups, they may have affected the absolute numbers reported as total lesion area. Therefore, the percentage change in lesion area (table 1) was selected as the most appropriate analysis of the multicenter data from yearly scans. The mean increase at 1 year in lesion area for the placebo group was 12.2% compared with a mean decrease of 1.1% in the 8 MIU group (p = 0.001). As treatment continued, the difference between treatment groups for percentage change at both annual scans remained highly significant. The placebo group had a mean increase of 17.1% whereas the 8 MIU group showed a mean decrease of 6.2% at the third year (p = 0.002). Table 1 shows the mean and median percent changes for each group. Note that the median percent changes and the mean group changes were very similar.

Significant site-by-treatment-group interaction effects were evident in the ANOVA of ranks model for percentage change in MRI area at end point (p = 0.040) and change in total MRI area at end point

(p = 0.037). To determine the cause of the interactions, the same ANOVA model was applied to three data sets: the placebo and 8 MIU groups, the placebo and 1.6 MIU groups, and the 1.6 MIU and 8 MIU groups. This subset analysis revealed that only the placebo group to 8 MIU group comparison had a significant treatment group-by-site interaction. However, in examining the mean ranks from that ANOVA, the mean rank for the 8 MIU group was lower than that of the placebo group at every site. Therefore, the significant interaction term was due to a differing degree of effect rather than conflicting effects among sites.

An alternative method of examining change in cranial MRI area was to categorize the patients according to the level of percentage change from baseline (table 2). This method corrects for some of the noise due to methodologic variation. Comparing the number of patients whose cranial MRIs showed >10% *increase*, those with >10% *decrease*, and those within 10% of baseline, the results obtained were similar to those detected by analyzing the median percent changes in MRI area and are statistically significant (p = 0.001) for the comparison of placebo and 8 MIU groups. Also, the change at 1 year, 2 years, and end point in total lesion area (expressed as mm²) showed a significantly larger increase in the placebo group as compared with the 8 MIU group (p = 0.0010, p = 0.0001, and p = 0.0012, respectively) (table 3). The decrease in area measurement in the third year detected during the end-of-study consistency check was due to a step reduction during the third year in the measurement of lesion size by the technician. This change

Table 4. Percent of scans with activity

Measurement	Statistic	Placebo	IFNB 1.6 MIU	IFNB 8 MIU
Percent of scans active	Median	29.4	11.8	5.9
	Mean	34.6	17.0	15.4
	SE	6.0	3.8	4.5
Overall:		$p = 0.0170$		
Placebo vs 8 MIU:		$p = 0.0062$		
Placebo vs 1.6 MIU:		$p = 0.0349$		
1.6 vs 8 MIU:		$p = 0.4692$		

Table 5. Active lesion rate

Measurement	Statistic	Placebo	IFNB 1.6 MIU	IFNB 8 MIU
Active lesions per year	Median	3.0	1.0	0.5
	Mean	4.9	1.8	2.0
	SE	1.3	0.4	0.7
Overall:		$p = 0.0234$		
Placebo vs 8 MIU:		$p = 0.0089$		
Placebo vs 1.6 MIU:		$p = 0.0412$		
1.6 vs 8 MIU:		$p = 0.5070$		

Table 6. New lesion rate

Measurement	Statistic	Placebo	IFNB 1.6 MIU	IFNB 8 MIU
New lesions per year	Median	2.0	0.5	0.5
	Mean	3.2	1.1	1.2
	SE	0.9	0.2	0.5
Overall:		$p = 0.0085$		
Placebo vs 8 MIU:		$p = 0.0026$		
Placebo vs 1.6 MIU:		$p = 0.0317$		
1.6 vs 8 MIU:		$p = 0.3207$		

affected all scans similarly and did not affect the intertreatment group comparisons, which remained highly significant. The reduction in area in the third year was probably due to an unconscious effort on the part of the technician to be conservative as she became more confident in determining the margin of the lesions. A detailed analysis of this phenomenon will be the subject of a separate publication.

The association of disease burden (lesion area) with neurologic impairment was determined. Baseline and end point EDSS scores were significantly correlated with baseline (R = 0.231) and end point (R = 0.262) lesion area, showing that there is a connection between MRI burden of disease and neurologic impairment.

Findings on serial cranial MRIs performed at 6-week intervals. A total of 881 cranial MRIs were performed and evaluated on 52 patients. An average of 17 scans was performed on each patient (17 on placebo, 18 on 1.6 MIU, and 17 on 8 MIU). The total number of scans on treatment were placebo, 282; 1.6 MIU, 283; and 8 MIU, 264. Significant treatment group differences were detected between the placebo and both treatment groups for the percent of scans that were active (table 4), the annual rate of active lesions (table 5), and the annual rate of new lesions (table 6). The 8 MIU group had a median of 80% fewer active scans than were present in the placebo arm. The 8 MIU group had a median reduction of 83% in the rate of active lesions compared with that of the placebo group (table 5). Significantly more 8-MIU-group patients were free of active lesions over the course of the study than were placebo patients (seven high-dose patients versus one placebo, Fisher's exact test, $p = 0.039$). The annual rate of new lesions was also significantly lower for both the 8 MIU and 1.6 MIU treatment groups than for the placebo group. The 8 MIU group showed a median reduction of 75% in the rate of new lesion formation (table 6).

The effect of treatment on enlarging and recurrent lesions was examined. No significant differences were observed among the three treatment groups in the rate of enlarging lesions (data not shown). There was an overall significant treatment-group difference in the recurrent lesion rate (data not shown). This difference was due to a significantly lower recurrent lesion rate observed in

the 1.6 MIU group. For this measurement, no significant difference between the placebo and 8 MIU groups was detected. The numbers of active lesions detected by this particular measurement were probably too low to give reliable results. However, in contrast to the clinical study, where the treatment effect was present primarily in the 8-MIU-dose group, the serial MRI studies clearly showed a significant treatment effect from both doses of IFNB.

Discussion. The results of this multicenter study provide confirmatory evidence supporting the clinical conclusion that recombinant IFNB reduces disease activity in RRMS.[13] It also reduces the expected increase in disease burden as measured by MRI. These results were achieved through the systematic analysis of serial MRIs performed by standardized methods at 11 centers. One center also performed frequent serial MRIs on 52 subjects once every 6 weeks. The annual studies provided a "snapshot in time" measure of disease burden as a sum of lesion area. The 6-week serial studies provided a dynamic measure of disease activity (analogous to relapses) reflected by new, recurrent, and enlarging lesions. Both methods confirmed the validity and usefulness of a quantitative approach to MRI analysis in MS and furnished two new and objective outcome measures devoid of the examiner bias present in clinical studies.

To establish maximum consistency among sites, we designed a protocol with standard MRI scanning procedures. Despite this standardization, modifications in software and hardware did occur at some sites, as might be anticipated in a field with rapidly changing technology. Recognition of this problem

led to the adoption of the method of median percentage change in total area of disease burden to display the data; this proved to be a valid measure and clearly showed the differences among the treatment groups. The quantitation of disease burden showed differences among the three treatment groups at 1 year, and the treatment differences increased in the second and third years of the study.

A consistently reproducible step change occurred in the areas measured during the third year. This reduction in area traced probably resulted from a conservative approach by the technician in tracing the margin of the lesions. Because the same step change occurred in all scans analyzed at the third year, it did not affect the intergroup differences, which continued to be highly significant statistically. This problem in consistency does, however, point out the difficulty of performing such a study over a number of years.

The serial MRI data obtained from the scans performed at 6-week intervals confirmed the clinical study[13] showing a significant reduction in disease activity. By using the frequent MRI method, future therapeutic trials in RRMS can be shorter in duration and less expensive, by using fewer patients. Serial and annual quantitative MRIs provide a powerful and objective adjunct to clinical measures and should be an integral part of future therapeutic trials. We believe that MRI is a predictor for future clinical outcome in MS. MRI methods can now be used as an initial indicator of possible treatment effects prior to the institution of long-term clinical trials. A European committee on the use of MRI in clinical trials[18] has reported statistical power calculations showing that monthly MRIs for activity in 150 patients in each arm of a treatment trial could show a statistically significant 50% reduction in disease activity in as little as 6 months. Our data support that concept while providing compelling evidence for interferon beta-1b having a significant impact on disease burden and disease activity over a 3-year study.

There is little antecedent information with which to compare the present study. However, where available, previous studies provide parallel information regarding the utility of cranial MRI as a monitor of disease activity. Kappos et al[19] used MRI as an outcome measure, with a visual assessment method, during the last 6 months of a treatment trial with cyclosporine, and were unable to show any treatment effect.

In a controlled trial of 100 patients treated with alpha-lymphoblastoid interferon,[20, 21] 80 patients had quantitative MRI evaluations at entry, at 6 months, and at 2 years of the trial. There was a quantitative increase in disease burden detected by MRI with a mean increase of 21% in extent of disease in the placebo group over 2 years. No MRI or clinical benefit was shown.

Quantitative annual MRIs performed on 157 chronic progressive MS patients in a cyclosporine treatment trial[22, 23] showed no significant clinical or MRI benefit from the cyclosporine. However, quantitative MRI provided a measure of burden of disease that showed a clear-cut increase in lesion area over time.

In summary, the use of systematic and serial MRI in this study provided strong objective support for the clinical efficacy of interferon beta-1b in the treatment of RRMS both in decreasing disease activity and in reducing disease burden. The correlation between disease burden by MRI with the EDSS at entry and end point supports the conclusion that 8 MIU of IFNB given early in the disease altered the natural history of MS in these patients. The MRI showed more clearly than the clinical study[13] that a beneficial effect occurred at both doses of IFNB.

The University of British Columbia MS/MRI Study Group includes David K.B. Li, MD; Donald W. Paty, MD; E.L. Tanton, MD; Guo Jun Zhao, MD; Borys Flak, MD; Andrew Riddehough, BSc; Keith Cover, MSc; Brenda Rhodes, BSc; Andrea Cook, BSc; Karen Smith, RT; Lesley Costley, RT; Sylvia Renneberg, RT; Trudy Shaw, RT; and Monique Genton, RT, Vancouver, BC, Canada.

The IFNB Multiple Sclerosis Study Group comprises the following participating institutions, principal investigators (in italics), and investigative teams: Hôpital de Notre Dame (Montreal)—*Pierre Duquette, MD, Marc Girard, MD,* Liette Despault, RN, and Renee DuBois, RN; Jefferson Medical College—*Robert L. Knobler, MD, PhD, Fred D. Lublin, MD,* and Leith Kelley, RN; Montreal Neurological Institute—*Gordon S. Francis, MD, Y. Lapierre, MD, Jack Antel, MD,* Mark Freedman, MD, and Stanley Hum; Temple University Hospital—*Jeffrey I. Greenstein, MD, Bibhuti Mishra, MD,* and Joanne Muldoon, RN; University of Alabama School of Medicine—*John N. Whitaker, MD,* Bradley K. Evans, MD, and Beverly Layton, RN; University of Arizona—*William A. Sibley, MD,* Joan Laguna, and John Krikawa; University of British Columbia—*Donald W. Paty, MD, Joel J. Oger, MD, Lorne F. Kastrukoff, MD, PhD,* G.R. Wayne Moore, MD, Stanley A. Hashimoto, MD, Wendy Morrison, RN, and Jill Nelson, RN; University of California at San Francisco—*Douglas S. Goodin, MD,* Stephen M. Massa, MD, PhD, and Elena Gutteridge, RN; University of Chicago—*Barry G.W. Arnason, MD, Avertano Noronha, MD, Anthony T. Reder, MD,* and Roberta Martia, RN; University Hospital, London, Ontario—*George C. Ebers, MD, George P.A. Rice, MD,* and Jane Lesaux, RN; University of Maryland—*Kenneth P. Johnson, MD, Hillel S. Panitch, MD, Christopher T. Bever, MD,* and Kathleen Conway, RN. <u>Berlex Laboratories Inc.</u>—Joy Constine Wallenberg, MD, and Lisa Bedell, MS. <u>External Advisory Committee—</u> Chairman, Stanley van den Noort, MD, University of California, Irvine; Brian Weinshenker, MD, Mayo Clinic; William Weiss, PhD; Stephen Reingold, PhD, National Multiple Sclerosis Society; Andrew Pachner, MD, Georgetown University; and Wayne Taylor, PhD, McMaster University.

the manuscript, Dr. John Petkau for his statistical advice, and the many radiologists and technologists at the participating institutions for providing the MRI data for analysis. Last but not least, we wish to thank all the patients with MS who participated so willingly and made many personal sacrifices in order that this extraordinary study could be completed with excellent compliance.

References

1. Paty DW. Multiple sclerosis: assessment of disease progression and effects of treatment. Can J Neurol Sci 1987;14:518-520.
2. Miller DH, Rudge P, Johnson G, et al. Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. Brain 1988;111:927-939.
3. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-1452.
4. Willoughby EW, Paty DW. Scales for rating impairment in multiple sclerosis: a critique. Neurology 1988;38:1793-1798.
5. Noseworthy JH, Vandervoort MK, Wong CJ, Ebers GC, Canadian Cooperative MS Study Group. Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) in a multiple sclerosis clinical trial. Neurology 1990;40:971-975.
6. Li DKB, Mayo J, Fache S, et al. Lack of correlation between clinical manifestations and lesions of MS as seen by NMR [abstract]. Neurology 1984;34(suppl 1):136.
7. Li DKB, Mayo J, Fache S, Robertson WD, Paty D, Genton M. Early experience in nuclear magnetic resonance imaging of multiple sclerosis. Ann NY Acad Sci 1984;436:483-486.
8. Isaac C, Li DKB, Genton M, et al. Multiple sclerosis: a serial study using MRI in relapsing patients. Neurology 1988;38:1511-1515.
9. Willoughby EW, Grochowski E, Li DKB, Oger JJF, Kastrukoff LF, Paty DW. Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. Ann Neurol 1989;25:43-49.
10. Koopmans RA, Li DKB, Oger JJF, et al. Chronic progressive multiple sclerosis: serial magnetic resonance brain imaging over six months. Ann Neurol 1989;26:248-256.
11. Thompson AJ, Kermode AG, MacManus DG, et al. Patterns of disease activity in multiple sclerosis: clinical and magnetic resonance imaging study. BMJ 1990;300:631-634.
12. Bastianello S, Pozzilli C, Bernardi S, et al. Serial study of gadolinium-DTPA MRI enhancement in multiple sclerosis. Neurology 1990;40:591-595.
13. The 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;43:655-661.
14. Paty DW, Isaac CD, Grochowski E, et al. Magnetic resonance imaging (MRI) in multiple sclerosis (MS): a serial study in relapsing and remitting patients with quantitative measurements of lesion size [abstract]. Neurology 1986;36(suppl 1):177.
15. Paty DW, Li DKB. Neuroimaging in multiple sclerosis. In: Theodore WH, ed. Clinical neuroimaging. New York: A R Liss, 1988:249-278.
16. Paty DW. Multiple sclerosis with an emphasis on MR imaging. Curr Neurol 1991;11:169-198.
17. Paty DW. Magnetic resonance imaging in the assessment of disease activity in multiple sclerosis. Can J Neurol Sci 1988;15:266-272.
18. Miller DH, Barkhof F, Berry I, Kappos L, Scotti G, Thompson AJ. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: concerted action guidelines. J Neurol Neurosurg Psychiatry 1991;54:683-688.
19. Kappos L, Städt D, Ratzka M, et al. Magnetic resonance imaging in the evaluation of treatment in multiple sclerosis. Neuroradiology 1988;30:299-302.
20. Kastrukoff LF, Oger JJ, Hashimoto SA, et al. Systemic lymphoblastoid interferon therapy in chronic progressive multiple sclerosis. I. Clinical and MRI evaluation. Neurology 1990;40:479-486.
21. Koopmans RA, Li DKB, Redekop WK, Zhao GJ, Palmer MR, Kastrukoff LF, Paty DW. The use of magnetic resonance imaging in monitoring a therapeutic trial with systemic lymphoblastoid interferon therapy of chronic progressive multiple sclerosis. J Neuroimaging (in press).
22. Multiple Sclerosis Study Group. Efficacy and toxicity of cyclosporine in chronic progressive multiple sclerosis: a randomized, double-blinded, placebo-controlled clinical trial. Ann Neurol 1990;27:591-605.
23. Koopmans RA, Li DKB, Zhao GJ, Redekop WK, Paty DW. MRI assessment of cyclosporine therapy of MS in a multicenter trial [abstract]. Neurology 1992;42 (suppl 3):210.

Neurology®

Interferon beta−1b is effective in relapsing−remitting multiple sclerosis: II. MRI analysis results of a multicenter, randomized, double−blind, placebo−controlled trial

D. W. Paty, D.K.B. Li, the UBC MS/MRI Study Group, et al.

This information is current as of April 1, 1993

AMERICAN ACADEMY OF NEUROLOGY®