The New England Journal of Medicine

VOLUME 343 SEPTEMBER 28, 2000 NUMBER 13

INTRAMUSCULAR INTERFERON BETA-1a THERAPY INITIATED DURING A FIRST DEMYELINATING EVENT IN MULTIPLE SCLEROSIS

LAWRENCE D. JACOBS, M.D., ROY W. BECK, M.D., PH.D., JACK H. SIMON, M.D., PH.D., R. PHILLIP KINKEL, M.D., CAROL M. BROWNSCHEIDLE, PH.D., THOMAS J. MURRAY, M.D., NANCY A. SIMONIAN, M.D., PETER J. SLASOR, SC.D., ALFRED W. SANDROCK, M.D., PH.D., AND THE CHAMPS STUDY GROUP*

ABSTRACT

Background Treatment with interferon beta has been shown to help patients with established multiple sclerosis, but it is not known whether initiating treatment at the time of a first clinical demyelinating event is of value.

Methods We conducted a randomized, double-blind trial of 383 patients who had a first acute clinical demyelinating event (optic neuritis, incomplete transverse myelitis, or a brain-stem or cerebellar syndrome) and evidence of prior subclinical demyelination on magnetic resonance imaging (MRI) of the brain. After initial treatment with corticosteroids, 193 patients were randomly assigned to receive weekly intramuscular injections of 30 μg of interferon beta-1a and 190 were assigned to receive weekly injections of placebo. The study end points were the development of clinically definite multiple sclerosis and changes in findings on MRI of the brain. The trial was stopped after a preplanned interim efficacy analysis.

Results During three years of follow-up, the cumulative probability of the development of clinically definite multiple sclerosis was significantly lower in the interferon beta-1a group than in the placebo group (rate ratio, 0.56; 95 percent confidence interval, 0.38 to 0.81; $P=0.002$). As compared with the patients in the placebo group, patients in the interferon beta-1a group had a relative reduction in the volume of brain lesions ($P<0.001$), fewer new or enlarging lesions ($P<0.001$), and fewer gadolinium-enhancing lesions ($P<0.001$) at 18 months.

Conclusions Initiating treatment with interferon beta-1a at the time of a first demyelinating event is beneficial for patients with brain lesions on MRI that indicate a high risk of clinically definite multiple sclerosis. (N Engl J Med 2000;343:898-904.)

MULTIPLE sclerosis is a chronic, inflammatory, demyelinating disease of the central nervous system that most commonly affects women, with an onset typically between 20 and 40 years of age. A diagnosis of clinically definite multiple sclerosis requires the occurrence of at least two neurologic events consistent with demyelination that are separated both anatomically in the central nervous system and temporally.[1] Magnetic resonance imaging (MRI) of the brain, by identifying lesions consistent with the occurrence of demyelination, can add certainty to the diagnosis.[2,3] The presence of such MRI-identified lesions in a patient with an isolated syndrome of the optic nerve (optic neuritis), spinal cord (incomplete transverse myelitis), or brain stem or cerebellum of recent onset is associated with a high risk of clinically definite multiple sclerosis.[4-8] When the cause is demyelination, all three syndromes are presumed to have a common pathogenesis.

Interferon-beta has demonstrated benefits in the treatment of patients with established multiple sclerosis, including slowing the progression of physical disability,[9,10] reducing the rate of clinical relapses,[9-11] and reducing the development of brain lesions, as assessed by MRI,[9-12] and brain atrophy.[13] However, it is not known whether treatment of patients earlier in the course of multiple sclerosis is of value. Therefore, we designed a randomized, double-blind, placebo-con-

From the Department of Neurology, State University of New York School of Medicine at Buffalo and Buffalo General Hospital, Buffalo (L.D.J., C.M.B.); the Jaeb Center for Health Research, Tampa, Fla. (R.W.B.); the Department of Radiology–MRI, University of Colorado Health Sciences Center, Denver (J.H.S.); the Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation, Cleveland (R.P.K.); the Multiple Sclerosis Research Unit, Centre for Clinical Research, Victoria General Hospital, Queen Elizabeth II Health Sciences Centre, Halifax, N.S., Canada (T.J.M.); and Biogen, Cambridge, Mass. (N.A.S., P.J.S., A.W.S.). Address reprint requests to Dr. Jacobs at the Department of Neurology, Buffalo General Hospital, 100 High St., Buffalo, NY 14203, or at ljacobs@kaleidahealth.org.

*Other participants in the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) are listed in the Appendix.

trolled clinical trial to determine whether weekly intramuscular injections of interferon beta-1a (Avonex) in patients with a first demyelinating event and with MRI evidence of prior subclinical demyelination in the brain reduced the incidence of clinically definite multiple sclerosis.

METHODS

Patients

The study was conducted at 50 clinical centers in the United States and Canada from April 1996 until March 2000. The protocol and informed-consent forms were approved by the institutional review board at each site, and all patients gave written informed consent. Study oversight was provided by an independent data and safety monitoring committee.

Eligible subjects were patients between the ages of 18 and 50 who had a first isolated, well-defined neurologic event consistent with demyelination and involving the optic nerve (unilateral optic neuritis), spinal cord (incomplete transverse myelitis), or brain stem or cerebellum (brain-stem or cerebellar syndrome) that was confirmed on ophthalmologic or neurologic examination. Patients also had to have two or more clinically silent lesions of the brain that were at least 3 mm in diameter on MRI scans and were characteristic of multiple sclerosis (at least one lesion had to be periventricular or ovoid). The onset of the visual or neurologic symptoms had to have been no more than 14 days before intravenous corticosteroid therapy was started (as described below) and no more than 27 days before randomization. Patients with a prior neurologic or visual event consistent with the occurrence of demyelination that lasted longer than 48 hours were excluded.

Treatment Assignment and Monitoring

All patients received 1 g of methylprednisolone per day intravenously for 3 days, followed by 1 mg of prednisone per kilogram of body weight per day orally for 11 days and a 4-day period of tapering in which 20 mg was given on the first day, 10 mg on the second, 0 mg on the third, and 10 mg on the fourth. In order to achieve balance with respect to the number of lesions on T_2-weighted MRI scans (two, three or four, five to seven, and eight or more) and the type of initial clinical event (optic neuritis, spinal cord syndrome, or brain-stem or cerebellar syndrome), we used a minimization procedure[14] to assign patients randomly in approximately equal numbers to the two treatment groups. The distribution of the treatment groups according to study site was what would be expected by chance ($P=0.88$). One group received 30 μg of interferon beta-1a (Avonex, Biogen) weekly by intramuscular injection, whereas the other group received a matching placebo. The treatment period was planned to be three years. Patients and site personnel were unaware of the treatment assignments.

Treatment began after the course of intravenous methylprednisolone was completed while the patient was still receiving oral prednisone. To minimize the symptoms of the interferon-related influenza-like syndrome, patients were instructed to take 650 mg of acetaminophen before each injection and then every 6 hours after each injection for 24 hours during the first six months of treatment.

We assessed compliance with the protocol by reviewing the patients' diaries and counting the number of empty vials that were returned. Each center was instructed to report all adverse events during the first six months of treatment, but thereafter to report only serious adverse events, as well as depression, seizures, cardiac events, and injection-site reactions, whether or not they were serious. An influenza-like syndrome was defined as the presence of influenza-like symptoms, fever, or chills. Every six months, blood was obtained for hematologic and serum chemical tests and physical examinations were performed. Laboratory values that exceeded prespecified ranges were considered abnormal. Serum was assayed for the presence of neutralizing antibodies every six months; we report the incidence of titers greater than or equal to 1:20 — the level that has been associated with reduced biologic activity of interferon beta-1a.[15]

Study Procedures and End Points

At the end of the first month (and again at the end of the second month, if the patient's condition was not considered to be stable or improving at month 1), each patient was examined by a treating and an examining neurologist, both of whom were unaware of the patient's treatment assignment. Subsequent examinations were scheduled at month 6 and every six months thereafter; additional examinations were performed within seven days after a patient reported new visual or neurologic symptoms. The treating neurologist was responsible for asking the patient about adverse events and visual or neurologic symptoms, whereas the examining neurologist performed a structured neurologic examination without knowledge of the patient's history during or before the study.

The primary prespecified end point was the development of clinically definite multiple sclerosis. For patients whose condition was neurologically stable or improving one month after the initiation of treatment with the study drug, the end point was defined as the occurrence of either a new visual or neurologic event or progressive neurologic deterioration. The former required documentation of a new clinical abnormality consistent with the patient's report of neurologic or visual symptoms that lasted more than 48 hours and that were attributable to a part of the central nervous system that differed from that of the initial episode at study entry. The latter was defined as an increase from month 1 of at least 1.5 points in the score on the Expanded Disability Status Scale.[16] On this scale, scores range from 0 to 10, with higher scores indicating more severe disability. A patient whose initial demyelinating event was clinically worse one month after the initiation of treatment was considered to have reached the primary end point if either further worsening was documented at two months or the patient withdrew from the study before completing two months of treatment. All end points were confirmed by a central end-point committee whose members were unaware of the patients' treatment assignments.

Patients in whom clinically definite multiple sclerosis developed discontinued treatment and were withdrawn from the study. Patients who discontinued treatment but who did not reach the end point were encouraged to return for follow-up assessments.

Findings on MRI of the brain served as a secondary prespecified end point. A screening MRI of the brain was performed to determine the patients' eligibility. Unenhanced T_2-weighted and enhanced T_1-weighted MRI scans of the brain were obtained with use of a standardized protocol at base line and at months 6, 12, and 18 in patients who were still in the study at those times. The baseline scan was obtained four or more days after the patient completed the course of intravenous methylprednisolone but while the patient was still receiving oral prednisone. MRI of the brain was not performed after 18 months because of the expectation that the rate of clinical outcomes would differ between treatment groups (since patients were withdrawn from the trial on receipt of a diagnosis of clinically definite multiple sclerosis) and could therefore skew the interpretation of the results. All scans that could be evaluated were graded at a central reading center without knowledge of the patients' treatment assignments. The number of new or enlarging lesions and the volume of lesions on T_2-weighted MRI scans and the number of gadolinium-enhancing lesions on T_1-weighted MRI scans were assessed according to a standardized method.

Statistical Analysis

We calculated that 380 patients would be needed for the study, given an estimated three-year rate of clinically definite multiple sclerosis in the placebo group of 50 percent, a relative effect of treatment of 33 percent, a 5 percent probability of a type I error (two-tailed), and a power of 80 percent. The calculation was adjusted to allow for 15 percent of the patients to be withdrawn or lost to follow-up before the development of clinically definite multiple sclerosis. Primary analyses included all randomized patients and followed the intention-to-treat principle. All reported P values are two-tailed.

The cumulative probability of clinically definite multiple sclerosis was calculated for each group according to the Kaplan–Meier product-limit method and compared with use of the Mantel log-rank test, beginning after one month of treatment (since by definition the end point could not be reached before one month). Data on patients in whom clinically definite multiple sclerosis did not develop were censored on the date they were last seen by the treating neurologist at either a scheduled or unscheduled visit. Unadjusted and adjusted rate ratios were determined from a proportional-hazards model. Differences in the size of effects in subgroups classified according to the initial clinical event and the number of brain lesions on T_2-weighted MRI scans at screening were assessed separately with use of interaction terms in the proportional-hazards model. The data on the volume of lesions and the number of lesions on MRI were evaluated with the use of the Mann–Whitney rank-sum test.

The trial was terminated in March 2000 at the recommendation of the data and safety monitoring committee after the single preplanned interim analysis of efficacy. This analysis revealed that treatment with interferon beta-1a was significantly better than treatment with placebo and met the stopping guidelines, which included a P value of 0.029.

RESULTS

Base-Line Characteristics

Between April 1996 and April 1998, 383 patients were enrolled in the trial: 193 were randomly assigned to the interferon beta-1a group and 190 to the placebo group. The base-line characteristics of the two groups were similar (Table 1).

Development of Clinically Definite Multiple Sclerosis and Brain Lesions on MRI

The cumulative probability of the development of clinically definite multiple sclerosis during the three-year follow-up period was significantly lower in the interferon beta-1a group than in the placebo group (rate ratio, 0.56; 95 percent confidence interval, 0.38 to 0.81; $P=0.002$) (Fig. 1). At three years, the cumulative probability was 35 percent in the interferon beta-1a group and 50 percent in the placebo group. After adjustment for age, type of initial event, the volume of lesions on T_2-weighted MRI scans, and the number of gadolinium-enhancing lesions on T_1-weighted scans, the effect of treatment with interferon beta-1a appeared to be stronger (adjusted rate ratio, 0.49; 95 percent confidence interval, 0.33 to 0.73; $P<0.001$). The effect of treatment was similar among subgroups classified according to the type of initial event ($P=0.49$ for the interaction) and the number of lesions on the T_2-weighted MRI scan at screening ($P=0.88$ for the interaction).

The diagnosis of clinically definite multiple sclerosis was the result of a second acute demyelinating event in all but five patients. One patient in each group had progressive neurologic worsening during the first two months of the study treatment, and one patient in the interferon beta-1a group and two patients in the placebo group had progressive neurologic disability without an acute exacerbation. Corticosteroids were prescribed for a neurologic event that did not qualify as clinically definite multiple sclerosis in the case of 9 patients in the interferon beta-1a group (3 of whom later met the criteria for clinically definite multiple sclerosis) and 22 patients in the placebo group (7 of whom later met the criteria).

The changes in the volume of brain lesions on T_2-weighted MRI scans differed significantly between the interferon beta-1a group and the placebo group at 6 months ($P<0.001$), 12 months ($P=0.004$), and 18 months ($P<0.001$) (Table 2). At 18 months, the median increase in lesion volume was 1 percent in the interferon beta-1a group, as compared with 16 percent in the placebo group. At 6, 12, and 18 months, there were also fewer new or enlarging lesions on T_2-weighted MRI scans ($P=0.001$, $P<0.001$, and $P<0.001$, respectively) and fewer gadolinium-enhancing lesions on T_1-weighted scans ($P=0.03$, $P=0.02$, and $P<0.001$, respectively) in the interferon beta-1a group than in the placebo group (Table 2). As compared with the placebo group, the interferon beta-1a group had 42 percent fewer gadolinium-enhancing lesions at 6 months, 55 percent fewer at 12 months, and 67 percent fewer at 18 months.

Completeness of Follow-up

Follow-up was discontinued early for a reason other than the development of clinically definite multiple sclerosis in 30 of the 193 patients in the interferon beta-1a group (16 percent) and in 27 of the 190 patients in the placebo group (14 percent). The mean (±SD) duration of follow-up for the remaining patients in whom clinically definite multiple sclerosis had not developed and who were still being followed when the trial was stopped or who had completed the 3-year final examination was 30.9±4.9 months in the interferon beta-1a group and 30.6±5.1 months in the placebo group, and the respective rates of completed visits were 99.4 percent and 99.5 percent. All of these patients completed at least 22 months of follow-up.

Adverse Events, Development of Neutralizing Antibodies, and Compliance

During the first six months, an influenza-like syndrome was reported by 54 percent of the patients in the interferon beta-1a group and by 26 percent of the patients in the placebo group ($P<0.001$). Depression was the only other adverse event whose incidence was at least 5 percentage points higher in the interferon beta-1a group than in the placebo group (incidence, 20 percent and 13 percent; $P=0.05$). Serious adverse events, none of which were attributed to treatment, occurred in 12 patients in the interferon beta-1a group and 19 patients in the placebo group. Neutralizing antibodies were detected in less than 1 percent of patients in the interferon beta-1a group at 12 and 18 months and in 2 percent at 24 and 30 months.

Treatment was discontinued because of an adverse

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ALL PATIENTS (N=383)	INTERFERON BETA-1a GROUP (N=193)	PLACEBO GROUP (N=190)
Female sex — no. (%)	289 (75)	141 (73)	148 (78)
Age — yr	33±7	33±8	33±7
Race or ethnic group — no. (%)			
White	330 (86)	166 (86)	164 (86)
Black	31 (8)	15 (8)	16 (8)
Hispanic	10 (3)	4 (2)	6 (3)
Asian	2 (1)	0	2 (1)
Other	10 (3)	8 (4)	2 (1)
Type of initial event — no. (%)			
Optic neuritis	192 (50)	95 (49)	97 (51)
Spinal cord syndrome	83 (22)	41 (21)	42 (22)
Brain-stem or cerebellar syndrome	108 (28)	57 (30)	51 (27)
Duration of symptoms before initiation of intravenous methylprednisolone — days			
Median	8	8	9
25th and 75th percentiles	5, 12	5, 12	5, 12
Duration of symptoms at initiation of study treatment — days			
Median	19	20	19
25th and 75th percentiles	16, 23	16, 23	16, 23
No. of brain lesions on T_2-weighted MRI screening — no. (%)			
2	66 (17)	33 (17)	33 (17)
3–4	125 (33)	64 (33)	61 (32)
5–7	81 (21)	41 (21)	40 (21)
≥8	111 (29)	55 (28)	56 (29)
Volume of lesions on base-line T_2-weighted MRI — mm^3†			
Median	2051	2279	1850
25th and 75th percentiles	1003, 4622	1247, 4719	860, 4064
No. of gadolinium-enhancing brain lesions on base-line T_1-weighted MRI — no. (%)†‡			
0	254 (70)	121 (66)	133 (74)
1	57 (16)	36 (20)	21 (12)
>1	51 (14)	26 (14)	25 (14)
Family history of multiple sclerosis — no. (%)	32 (8)	18 (9)	14 (7)

*Plus–minus values are means ±SD. There were no significant differences between groups. Seven patients (three in the interferon beta-1a group and four in the placebo group) did not meet all eligibility criteria: one patient began intravenous methylprednisolone 15 days after the onset of symptoms, two patients underwent randomization more than 27 days after the onset of symptoms, two patients were older than 50 years at the time of randomization, one patient had pale optic disks at base line, and one patient was found after randomization to have a vascular cause of the initial event rather than demyelination.

†MRI was performed at least four days after the patient completed the course of intravenous methylprednisolone, while the patient was receiving oral prednisone.

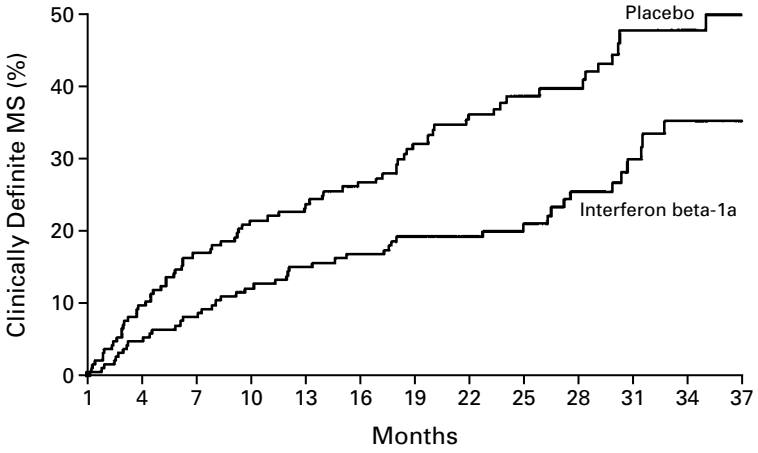
‡A total of 362 patients had MRI scans that could be evaluated (183 in the interferon beta-1a group and 179 in the placebo group).

event in one patient in the interferon beta-1a group (<1 percent) and in seven patients in the placebo group (4 percent). Treatment was stopped early for other reasons in 37 patients in the interferon beta-1a group (19 percent; 7 were lost to follow-up, 1 died in an automobile accident, 2 had disease activity, and 27 asked to withdraw or withdrew for other reasons) and in 28 patients in the placebo group (15 percent; 9 were lost to follow-up, 4 had disease activity, and 15 asked to withdraw or withdrew for other reasons). Treatment was not discontinued in any patient because of an abnormal laboratory value. The treatment assignment was revealed in the case of one patient who became pregnant.

Ninety-three percent of the patients in the interferon beta-1a group and 99.5 percent of the patients in the placebo group took the study medication at least 80 percent of the time; 88 percent and 94 percent, respectively, were at least 90 percent compliant.

DISCUSSION

The results of our trial add to the indications for interferon beta-1a in the treatment of multiple sclerosis. In addition to the previously demonstrated ben-



Interferon beta-1a group												
No. at risk	193	177	164	151	143	139	112	112	73	69	41	36
Clinically definite MS	9	6	7	5	3	4	0	2	4	3	3	0
Early withdrawal from study	7	7	6	3	1	4	0	1	0	0	0	1
Followed until end of study						19	0	36	0	25	2	1
Placebo group												
No. at risk	190	165	146	139	131	124	98	90	58	54	26	25
Clinically definite MS	18	13	7	4	6	8	6	3	1	6	0	1
Early withdrawal from study	7	6	0	4	1	1	1	5	0	2	0	0
Followed until end of study						17	1	24	3	20	1	0

Figure 1. Kaplan–Meier Estimates of the Cumulative Probability of the Development of Clinically Definite Multiple Sclerosis (MS) According to Treatment Group.

The cumulative probability of the development of clinically definite multiple sclerosis during the three-year follow-up period was significantly lower in the interferon beta-1a group than in the placebo group ($P=0.002$ by the Mantel log-rank test). The numbers of patients at risk are the numbers in whom clinically definite multiple sclerosis had not developed at the beginning of each three-month period. The end point was assessed beginning at one month, since according to the protocol that was the earliest possible time at which the end point could be reached. The "early-withdrawal" row indicates the number of patients in whom multiple sclerosis did not develop and whose follow-up ended before the study ended. Data were censored at the time of a patient's last completed neurologic examination.

efit of interferon beta in patients with established multiple sclerosis,[9-13] our results show that once-weekly intramuscular injections of interferon beta-1a, initiated at the time of a first clinical demyelinating event, are beneficial in patients who have MRI evidence of prior subclinical demyelination in the brain. In our study of 383 patients, interferon beta-1a reduced the rate of development of clinically definite multiple sclerosis within three years by about half. Findings on MRI scans of the brain provided additional objective support for the observation that the effects of treatment with interferon beta-1a were rapid and sustained. Interferon beta-1a was well tolerated, with no serious treatment-related adverse effects.

The base-line characteristics of the two groups were similar, and there was no evidence of confounding in the analyses. The percentage of patients who were withdrawn from the study for reasons other than the development of clinically definite multiple sclerosis was similar in the two groups. Most patients continued treatment until their protocol-specified follow-up concluded, and the rates of compliance were good in both groups. The occurrence of the influenza-like syndrome related to interferon beta-1a therapy could have provided some patients with a clue to the treatment assignment, but given that the examining neurologist was unaware of the patients' histories and that a separate, central end-point committee was used to verify all outcomes, this possibility should not have appreciably biased the results.

Because approved treatments for multiple sclerosis are available, we could not ethically keep patients in their assigned groups once clinically definite multiple sclerosis was diagnosed. Thus, the trial design could not provide any direct data on the long-term effect of interferon beta-1a on the rate of exacerbations or the progression of disability. However, the beneficial effects seen on MRI scans of the brain provide indirect evidence of a long-term benefit of treatment. A prior longitudinal study of patients with acute isolated demyelinating events found that the volume and number of brain lesions on T_2-weighted MRI scans

TABLE 2. FINDINGS ON T_1-WEIGHTED AND T_2-WEIGHTED MRI SCANS OF THE BRAIN, AFTER 6, 12, AND 18 MONTHS OF TREATMENT.*

VARIABLE	6 MONTHS		12 MONTHS		18 MONTHS	
	INTERFERON BETA-1a GROUP	PLACEBO GROUP	INTERFERON BETA-1a GROUP	PLACEBO GROUP	INTERFERON BETA-1a GROUP	PLACEBO GROUP
T_2-weighted MRI scans						
Change in volume of lesions — mm³						
Median	−123	40	102	214	28	313
25th and 75th percentiles	−653, 254	−175, 624	−375, 573	−45, 1238	−576, 397	5, 1140
No. of patients	145	145	134	120	119	109
P value	<0.001		0.004		<0.001	
No. of new or enlarging lesions — no. (%)						
0	82 (50)	63 (41)	65 (44)	32 (25)	62 (47)	22 (18)
1–3	60 (36)	46 (30)	56 (38)	47 (37)	41 (31)	47 (39)
≥4	23 (14)	43 (28)	28 (19)	47 (37)	29 (22)	50 (42)
No. of patients	165	152	149	126	132	119
Mean no. of lesions	1.5±2.7	2.8±4.3	2.1±3.3	4.0±5.0	2.1±3.2	5.0±7.7
P value	0.01		<0.001		<0.001	
T_1-weighted MRI scans						
No. of gadolinium-enhancing lesions — no. (%)						
0	115 (70)	93 (61)	100 (68)	71 (57)	109 (81)	66 (58)
1	27 (16)	16 (11)	28 (19)	20 (16)	13 (10)	23 (20)
>1	23 (14)	43 (28)	19 (13)	33 (27)	12 (9)	25 (22)
No. of patients	165	152	147	124	134	114
Mean no. of lesions	0.9±2.3	1.5±3.1	0.7±2.0	1.6±3.8	0.4±1.5	1.4±3.6
P value	0.03		0.02		<0.001	

*Plus–minus values are means ±SD. The Mann–Whitney rank-sum test was used to calculate P values.

both at the time of the initial demyelinating event and subsequently were predictive of the degree of neurologic disability 10 years after the initial event.[7,8]

There has been controversy about the importance of performing MRI of the brain at the time of a first acute demyelinating event, particularly in patients who present with optic neuritis, since a clinical diagnosis of this syndrome generally can be established without ancillary testing.[17] The results of our study provide justification for obtaining MRI scans of the brain at the time of a first event to determine whether there is further evidence of multiple sclerosis. Our results indicate that once-weekly treatment with intramuscular interferon beta-1a is beneficial in patients who are deemed to be at high risk for clinically definite multiple sclerosis because they have subclinical demyelinating lesions on MRI of the brain. Our study does not provide the long-term follow-up data required to determine whether early initiation of treatment has long-term effects. However, the weight of current knowledge suggests that preventing or delaying a second attack of multiple sclerosis and reducing the progression of central nervous system demyelination as demonstrated on MRI scans of the brain will have long-term clinical benefits.

Supported by Biogen.

Drs. Jacobs, Beck, Simon, Kinkel, Brownscheidle, and Murray are paid consultants to Biogen.

APPENDIX

Other participants in the study were as follows: *Clinical Centers* — University of Toronto: P. O'Connor, P. Fleming, T. Gray; Buffalo General Hospital: C. Miller, R. Bakshi, F. Munschauer; Cleveland Clinic Foundation: D. Bolibrush, J. Cohen; Ottawa General Hospital: M. Freedman, U. Webb, H. Rabinowicz; Foothills Hospital: L. Metz, A. Davis, R. Ranawaya; Vancouver Hospital and Health Sciences Center: S. Hashimoto, W. Morrison, J. Oger; University of Maryland Hospital: H. Panitch, K. Costello, C. Bever; Multiple Sclerosis Center at Shepherd: W. Stuart, D. Court, D. Stuart; Georgetown University Hospital: C. Tornatore, D. Bartlett, J. Richert; Hôpital Notre Dame: P. Duquette, R. Dubois, G. Bernier; Allegheny Neurological Associates: T. Scott, L. Pappert, J. Brillman; Medical College of Virginia, Richmond Eye and Ear Hospital: W. Fenton, III, T. Anderson, J. Astruc; Salt Lake City Veterans Affairs Medical Center: J. Rose, J. Kline, J. Burns; Victoria General Hospital: P. Weldon, F. Bhan; University of Iowa College of Medicine: M. Wall, L. Vining, T. Grabowski; New York Hospital–Cornell Medical Center: B. Apatoff, K. Arapello, J. Friedman; University of Pennsylvania Medical Center: S. Galetta, D. Pfohl, G. Liu; London Health Sciences Centre University Hospital: G. Rice, T. Bental, P. Mandalfino; Michigan State University: E. Eggenberger, D. Snider, D. Kaufman; Yale School of Medicine: J. Guarnaccia, M. Shepard, J. Goldstein; Beta Research, Inc.: M. Reiss, E. Carter, G. Glista; Marshfield Clinic: L. Rolak, L. Scheller, D. Jacobson; University of Rochester: A. Goodman, M. Petrie, D. Mattson; Rush–Presbyterian–St. Luke's Medical Center: K. Karlin, A. Wallin, D. Stefoski; University of Texas Health Science Center: S. Brod, E. Cerretta, J. Wolinsky; Montreal Neurological Institute: D. Arnold, R. Arnoutelis, L. Durcan; Beth Israel Medical Center: M. Kupersmith, L. Cappolino, J. Herbert; Southern California Kaiser Permanente Medical Center: J. Rosenberg, D. McHugh, A. Blumenfeld; Swedish Medical Center: C. Smith, D. Kuder, S. Hamilton; Neurological Associates, Inc.: S. Thurston, J. McGee, J. O'Bannon; Carolinas Medical Center: M. Kaufman, M. Butler, S. Putnam; Ohio State University: K. Rammohan, A. Siffort, J. Lynn; St. Louis University Health Sciences Center: J. Selhourst, E. Holze-

mer, G. Hayat; Wayne State University School of Medicine: A. Tselis, C. Caon, R. Lisak: Massachusetts General Hospital: S. Wray, P. Sexton, J. Lehrich; University of Medicine and Dentistry of New Jersey Medical School: S. Cook, A. Jotkowitz, S. Bansil; Emory Clinic: N. Newman, J. Brown, P. Pennell; Mayo Clinic Arizona: J. Carter, J. Buckner, R. Caselli; Neurology Group: L. Kerson, M. Camasso, G. Donneief; East Bay Neurology, Inc.: J. Cooper, D. Salkovsky, H. Shale; University of Illinois Eye and Ear Infirmary: J. Goodwin, T. Johnson, A. Gulati; New England Medical Center: T. Hedges, C. Yardley, T. Tran; University of Missouri: S. Horowitz, A. Bonnett, R. Burger; Kaiser Permanente Medical Center: J. Javerbaum, C. Griffin, R.J. Whaley; Bowman Gray School of Medicine of Wake Forest University: D. Jeffery, S.E. Jackson, E. Bastings; Dartmouth–Hitchcock Medical Center: L. Kasper, K. Ryan, J. Bernat; Oregon Health Sciences University: M. Mass, S. Cooper Hanel, D. Bourdette; University of Florida: J. Guy, M. Wilson, M. Greer; Mayo Clinic: C. Lucchinetti, M. Botten, J. Noseworthy; Medical University of South Carolina: A. Walker, B. Muntz, W. Tyor; *MRI Reading Center*, University of Colorado Health Sciences Center — M. Meyer, R. Leek, C. Gustafson, D. Singel, B. Quandt, D.E. Miller, B. Coombs, A. Cajade-Law, M. Lajaunie; *End-Point Committee* — A. Miller (chair), J. Richert, J. Cohen, T. Vollmer, J. Oger; *Advisory Committee* — L. Jacobs (cochair), R. Beck (cochair), R.P. Kinkel, C. Brownscheidle, T.J. Murray, J. Simon; *Data and Safety Monitoring Committee* — J. Antel (chair), L. Myers, G. Birnbaum, S. Reingold, R. Burde, W. Sibley, J. Ware; *Biogen* — N. Blanchard, K. Lloyd, H. Park, F. Votruba, K. White.

REFERENCES

1. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227-31.

2. Fazekas F, Barkhof F, Filippi M, et al. The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. Neurology 1999;53:448-56.

3. Ormerod IE, Miller DH, McDonald WI, et al. The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study. Brain 1987;110:1579-616.

4. The Optic Neuritis Study Group. The 5-year risk of MS after optic neuritis: experience of the Optic Neuritis Treatment Trial. Neurology 1997;49:1404-13.

5. Jacobs LD, Kaba SE, Miller CM, Priore RL, Brownscheidle CM. Correlation of clinical, magnetic resonance imaging, and cerebrospinal fluid findings in optic neuritis. Ann Neurol 1997;41:392-8.

6. Morrissey SP, Miller DG, Kendall BE, et al. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis: a 5-year follow-up study. Brain 1993;116:135-46.

7. O'Riordan JI, Thompson AJ, Kingsley DPE, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS: a 10-year follow-up. Brain 1998;121:495-503.

8. Sailer M, O'Riordan JI, Thompson AJ, et al. Quantitative MRI in patients with clinically isolated syndromes suggestive of demyelination. Neurology 1999;52:599-606.

9. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996;39:285-94. [Erratum, Ann Neurol 1996;40:480.]

10. PRISMS (Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. Lancet 1998;352:1498-504. [Erratum, Lancet 1999;353:678.]

11. 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;43:655-61.

12. Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon β-1a for relapsing multiple sclerosis. Ann Neurol 1998;43:79-87.

13. Rudick RA, Fisher E, Lee JC, Simon J, Jacobs L, Multiple Sclerosis Collaborative Research Group. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Neurology 1999;53:1698-704.

14. Taves DR. Minimization: a new method of assigning patients to treatment and control groups. Clin Pharmacol Ther 1974;15:443-53.

15. Rudick R, Simonian NA, Alam JA, et al. Incidence and significance of neutralizing antibodies to interferon beta-1a in multiple sclerosis. Neurology 1998;50:1266-72.

16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444-52.

17. The Optic Neuritis Study Group. The clinical profile of optic neuritis: experience of the Optic Neuritis Treatment Trial. Arch Ophthalmol 1991;109:1673-8.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal*'s Editorial Offices.