Intramuscular Interferon Beta-1a for Disease Progression in Relapsing Multiple Sclerosis

Lawrence D. Jacobs, MD,* Diane L. Cookfair, PhD,† Richard A. Rudick, MD,‡ Robert M. Herndon, MD,§ John R. Richert, MD,¶ Andres M. Salazar, MD,** Jill S. Fischer, PhD,‡ Donald E. Goodkin, MD,†† Carl V. Granger, MD,‡‡ Jack H. Simon, MD, PhD,§§ John J. Alam, MD,¶¶ David M. Bartoszak, MD,** Dennis N. Bourdette, MD,*** Jonathan Braiman, MD,** Carol M. Brownscheidle, PhD,* Michael E. Coats, MD,** Stanley L. Cohan, MD,¶ David S. Dougherty, MD,** Revere P. Kinkel, MD,‡ Michele K. Mass, MD,§ Frederick E. Munschauer, III, MD,* Roger L. Priore, ScD,† Patrick M. Pullicino, MD, PhD,* Barbara J. Scherokman, MD,††† Bianca Weinstock-Guttman, MD,‡ Ruth H. Whitham, MD,*** and The Multiple Sclerosis Collaborative Research Group (MSCRG)

The accepted standard treatment of relapsing multiple sclerosis consists of medications for disease symptoms, including treatment for acute exacerbations. However, currently there is no therapy that alters the progression of physical disability associated with this disease. The purpose of this study was to determine whether interferon beta-1a could slow the progressive, irreversible, neurological disability of relapsing multiple sclerosis. Three hundred one patients with relapsing multiple sclerosis were randomized into a double-blinded, placebo-controlled, multicenter phase III trial of interferon beta-1a. Interferon beta-1a, 6.0 million units (30 μg), was administered by intramuscular injection weekly. The primary outcome variable was time to sustained disability progression of at least 1.0 point on the Kurtzke Expanded Disability Status Scale (EDSS). Interferon beta-1a treatment produced a significant delay in time to sustained EDSS progression ($p = 0.02$). The Kaplan-Meier estimate of the proportion of patients progressing by the end of 104 weeks was 34.9% in the placebo group and 21.9% in the interferon beta-1a–treated group. Patients treated with interferon beta-1a also had significantly fewer exacerbations ($p = 0.03$) and a significantly lower number and volume of gadolinium-enhanced brain lesions on magnetic resonance images (p-values ranging between 0.02 and 0.05). Over 2 years, the annual exacerbation rate was 0.90 in placebo-treated patients versus 0.61 in interferon beta-1a–treated patients. There were no major adverse events related to treatment. Interferon beta-1a had a significant beneficial impact in relapsing multiple sclerosis patients by reducing the accumulation of permanent physical disability, exacerbation frequency, and disease activity measured by gadolinium-enhanced lesions on brain magnetic resonance images. This treatment may alter the fundamental course of relapsing multiple sclerosis.

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The standard treatment of relapsing multiple sclerosis consists of symptomatic therapy and corticosteroid therapy for exacerbations. Intrathecal natural beta interferon [1–4] and systematically administered recombinant interferon beta-1b [5] have been shown to decrease the frequency of exacerbations, but not the accumulation of physical disability, the most important factor affecting the lives of individual multiple sclerosis

From the *William C. Baird Multiple Sclerosis Research Center, Millard Fillmore Health System, and the Department of Neurology, The Buffalo General Hospital, Buffalo; †MSCRG Data Management and Statistical Center, Department of Neurology, The Buffalo General Hospital, Buffalo; ‡Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation, Cleveland, OH; §Department of Neurology, Good Samaritan Hospital and Medical Center, Portland, OR; ¶Department of Neurology, Georgetown University Medical Center, Washington, DC; **Department of Neurology, Walter Reed Army Medical Center, Washington, DC; ††University of California at San Francisco/Mount Zion Multiple Sclerosis Center, San Francisco, CA; ‡‡Department of Rehabilitation Medicine, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY; §§Department of Radiology-MRI, University of Colorado Health Sciences Center, Denver, CO; ¶¶Biogen, Inc, Cambridge, MA; ***Department of Neurology, Oregon Health Sciences University, Portland, OR; and †††Department of Neurology, Kaiser Permanente Medical Center, Springfield, VA.

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Address correspondence to Dr Jacobs, Department of Neurology, The Buffalo General Hospital, 100 High Street, Buffalo, NY 14203.

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patients. Currently there is no therapy available that alters progression of disability. This study was designed to determine whether systemically administered interferon beta-1a could slow the progression of irreversible neurological disability associated with relapsing multiple sclerosis.

Research Patients and Methods

Research Patients

Three hundred one patients with relapsing multiple sclerosis were enrolled at four clinical centers [6]. Inclusion criteria were definite multiple sclerosis [7] for at least 1 year, baseline Expanded Disability Status Score (EDSS) [8] of 1.0 to 3.5 inclusive, at least 2 documented exacerbations in the prior 3 years, no exacerbations for at least 2 months at study entry, and age 18 to 55 years. Our definition of relapsing multiple sclerosis included patients with complete remissions (returned to baseline preexacerbation disability status) and patients with incomplete remissions (did not return to their baseline preexacerbation disability status because of new residua) [9]. Patients were excluded because of prior immunosuppressant or interferon therapy, adrenocorticotropic hormone or corticosteroid treatment within 2 months of study entry, pregnancy or nursing, an unwillingness to practice contraception, the presence of chronic-progressive multiple sclerosis, or any disease other than multiple sclerosis compromising organ function. The protocol was approved by the respective institutional review boards and patients signed informed consent forms. A National Institutes of Health (NIH) Safety and Monitoring Committee monitored the study and evaluated interim safety analyses throughout.

Study Design

This was a double-blinded, placebo-controlled, randomized trial [6]. Efron's biased coin method was used for randomization [10]. Sample size calculation was based on a Kaplan-Meier analysis and an intent-to-treat design. We assumed that 50% of placebo recipients and 33% of interferon beta-1a recipients would worsen by at least 1.0 EDSS point within 104 weeks. The expected placebo progression rate was based on the median time to progression (104 weeks) in the placebo arm of another clinical trial [11]. The study was designed to have a statistical power of 80% to detect a group difference of this magnitude with an α level of 0.05. Sample size estimates also assumed that 25% of interferon beta-1a recipients would discontinue treatment prematurely but would still be followed and that 10% of patients would be lost to follow-up.

The study was initiated in November of 1990. In early 1993, the study statistician reported that the patient dropout rate was less than 3%, substantially lower than the originally estimated dropout rate of 10%. Therefore, the sample size could be reduced slightly, and the study could be ended earlier without sacrificing statistical power. Based on this information, the study investigators decided that enrollment could be stopped at 288 patients, and the study could end approximately 1 year earlier than originally planned. At the time of this decision, 301 patients had already been enrolled. Therefore, no further patients were enrolled. The decision to end the study early was made without knowledge of any interim efficacy results, and was reviewed and agreed on by the NIH Safety and Monitoring Committee.

All personnel and patients were blinded to treatment status. Study visits were scheduled at baseline and every 6 months. Treating physicians reviewed toxicity test results, examined patients, and made all medical decisions. Independent examining physicians determined the EDSS score. Patients did not discuss medical issues with the examining physician.

Intervention

Interferon beta-1a (Avonex, Biogen, Inc), a natural sequence, glycosylated, recombinant Chinese hamster ovary product, was administered intramuscularly at a dosage of 6.0 million units (30 μg) weekly for up to 104 weeks. Dose and interval were determined by a pilot study [12]. Injections were performed by study nurses or by local health professionals under the supervision of study personnel. Acetaminophen, 650 mg, was given prior to and for 24 hours after each injection to decrease interferon-related side effects. Patients received appropriate standard medical care (anticholinergics, antidepressants, antispastic drugs, physical therapy, psychological counseling). At the discretion of the treating physician, patients in exacerbation received intramuscular adrenocorticotropic hormone gel, 80 units daily for 10 days, or intravenous methylprednisolone 1,000 mg daily for 4 days, followed by a brief course of oral prednisone.

Primary Outcome Variable

The primary outcome variable was time to onset of sustained worsening in disability, defined as deterioration from baseline by at least 1.0 point on the EDSS persisting for at least 6 months. The EDSS is a quantitative clinical rating scale of neurological impairment with scores ranging from 0 to 10; increasing numbers reflect increasing disability. Worsening on the EDSS could begin on a scheduled or unscheduled visit, but had to persist for at least two scheduled visits 6 months apart to exclude transient fluctuations in clinical status. Examining physicians underwent prestudy training sessions to standardize scoring procedures [13].

Exacerbations

On-study exacerbations were defined by the appearance of new neurological symptoms or worsening of preexisting neurological symptoms lasting at least 48 hours in a patient who had been neurologically stable or improving for the previous 30 days accompanied by objective change on neurological examination (worsening of 0.5 point on the EDSS or a worsening by $\geq$1.0 point on the pyramidal, cerebellar, brainstem, or visual functional system scores) [6]. Symptoms reported between scheduled visits were reviewed by the treating physician; patients were examined immediately if symptoms suggested exacerbation. When it was not possible for the Center examining physician to examine the patient at the time of an exacerbation, the examination was videotaped according to a standardized script and subsequently scored by the examining physician.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was performed yearly using a standardized protocol [6]. Ninety-eight percent of

the MRI studies were acquired at 1.5 T, the remainder at 1.0 T. MRIs were analyzed by one neuroradiologist and one technician (both blinded to treatment). The number and volume of discrete gadolinium-enhanced lesions were determined by the neuroradiologist. T2 lesion volume measurements were based on a modification of a thresholding approach [14] using the long–repetition time (TR)/short–echo time (TE) images.

Statistical Analyses

Two-tailed tests were used for all statistical analyses. Time to onset of sustained progression (our primary outcome measure) and time to first exacerbation were analyzed using the Kaplan-Meier method, with significance determined by a log-rank test, stratified by clinical center [15]. Since the study was designed on an intent-to-treat basis, patients who discontinued treatment continued to be followed until the end of the study whenever possible and were included in the analyses.

Several analyses were conducted on the subset of patients who were accrued early enough to complete 104 weeks of follow-up by the end of the study. This included the proportion progressing (χ^2 test), the within-person change in EDSS (Mann-Whitney test [16]), and the number of exacerbations per patient (Mann-Whitney test). Annual exacerbation rates were calculated for this subset in the usual way, dividing the total number of exacerbations during the first 104 weeks by the total person-years of exposure. The annual exacerbation rate has been widely reported by many other authors. Although this is a standard in the field, this approach is dependent on the assumption that the time to a patient's first exacerbation is independent of the time from a patient's first exacerbation to their second exacerbation (i.e., that there are not some patients with inherently higher exacerbation rates than other patients). However, since this approach has been so widely used in the literature, it was necessary to include the annual exacerbation rate for comparability to data in other publications. We used the usual method for determining significance rates (i.e., the likelihood ratio test). Annual exacerbation rates also were calculated for all patients, using all-time on-study, in the same manner as above.

MRI analyses included comparisons at each time point of the number and volume of gadolinium-enhanced lesions (Mann-Whitney test), the proportion of enhanced scans (χ^2 test), and the percentage change in T2 volume from baseline (Mann-Whitney test).

Results

Baseline Characteristics by Study Arm

The 301 patients were randomly assigned to receive placebo (N = 143) or interferon beta-1a (N = 158). There were no significant group differences in baseline demographic, clinical disease, or MRI characteristics (Table 1; also see Table 6). The subset of patients accrued early enough to accumulate at least 104 weeks of follow-up (87 placebo recipients, 85 interferon beta-1a recipients) also showed no significant group differences in baseline characteristics, including the number and volume of gadolinium-enhanced lesions at study entry. Accrual of patients continued for more than 2 years. To determine whether the baseline characteristics of patients differed by accrual date, possible associations between baseline demographic, clinical disease, and MRI characteristics and accrual period were studied using the Kruskal-Wallis statistic [17]. Accrual periods were categorized into four intervals of approximately 6½ months each. No associations were found between any of the baseline characteristics and accrual period (all p values > 0.37).

Table 1. Demographic and Baseline Disease Characteristics for Total Study Population by Treatment Arm

	Placebo	Interferon Beta-1a
Accrual by site		
Buffalo	38 (27%)	48 (30%)
Cleveland	39 (27%)	41 (26%)
Portland	37 (26%)	42 (27%)
Washington, DC	29 (20%)	27 (17%)
Total accrual	143 (100%)	158 (100%)
Sex		
Male	40 (28%)	40 (25%)
Female	103 (72%)	118 (75%)
Race		
White	131 (92%)	147 (93%)
Black	9 (6%)	11 (7%)
Other	3 (2%)	0 (0%)
Age (yr)		
Mean (SEM)	36.9 (0.64)	36.7 (0.57)
Range	16–54	18–55
Prestudy disease duration (yr)		
Mean (SEM)	6.4 (0.49)	6.6 (0.46)
Range	1.0–31.0	1.0–30.7
Prestudy exacerbation rate		
Mean (SEM)	1.2 (0.05)	1.2 (0.05)
Range	0.67–3.20	0.67–3.70
Baseline EDSS score		
Mean (SEM)	2.3 (0.07)	2.4 (0.06)
Range	1.0–3.5	1.0–3.5

EDSS = Expanded Disability Status Scale; SEM = standard error of mean.

Follow-up

In accordance with the study design, patients were treated and followed for variable lengths of time (Table 2). All patients, regardless of duration of follow-up, were included in the failure-time analyses. To allow confirmatory evaluations for patients in whom EDSS score worsening was identified on their last visit before the final censor date, the final censor date for the primary outcome variable (sustained progression) was 6 months before the end of the study. Only 5 patients were lost to follow-up before their primary end point was definitively determined. In accordance with the study design, these 5 patients were included in the failure-time analysis for the duration of their observation periods.

Table 2. Number of Patients Followed to Each Scheduled Visit

Week of Visit[a]	Placebo (N = 143)	Interferon Beta-1a (N = 158)
26	142	157
52	136	151
78	111	123
104	87	85
130	56	55
156	16	15

[a]While enrollment date varied, the end-of-study date was the same for all patients. Thus, there are variable lengths of follow-up. All patients, regardless of duration of follow-up, were included in the failure-time analysis.

Compliance

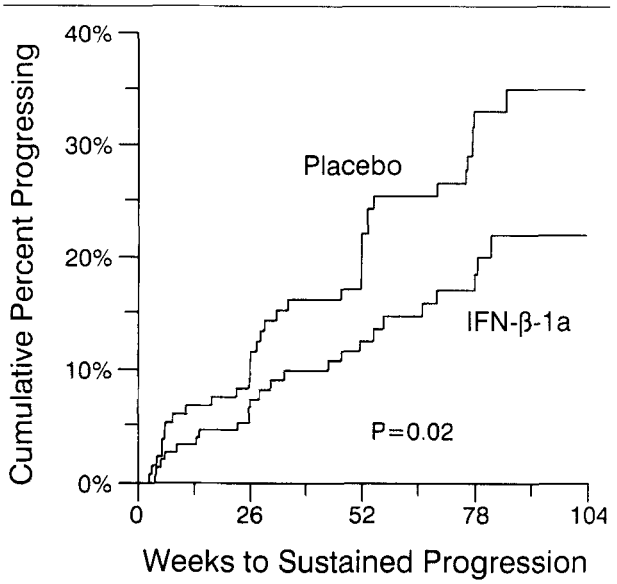
Twenty-three patients (9 placebo recipients, 14 interferon beta-1a recipients) discontinued injections early. As required by the intent-to-treat design, these patients continued to be followed and evaluated and their outcome data were included in the statistical analyses. Less than 1% of 1,416 scheduled visits were missed during the entire study.

Disability Progression

Time to sustained progression of disability, the primary outcome measure, was significantly greater in interferon beta-1a–treated patients than in placebo-treated patients ($p = 0.02$). The Kaplan-Meier failure-time curve illustrates the cumulative percentage of patients whose disability progressed at or before a given week while in the study (Fig). The proportion with progression of disability by 104 weeks estimated from Kaplan-Meier curves was 34.9% in placebo recipients and 21.9% in interferon beta-1a recipients. Of the patients accrued early enough to complete at least 104 weeks of the study, 29 (33.3%) of 87 placebo recipients and 18 (21.2%) of 85 interferon beta-1a recipients developed disability progression.

Timing of Sustained Progression Onset

The timing of beneficial effects of interferon beta-1a was explored by determining the probability of sustained progression onset occurring in year 1 and year 2 from the Kaplan-Meier model for all patients at risk during each time interval (Table 3). The probability of sustained progression onset was 22.0% in placebo-treated and 12.5% among interferon beta-1a–treated patients during year 1, and 16.5% (placebo) and 10.8% (interferon beta-1a) during year 2. To determine whether the timing of beneficial effects was similar in the 104-week patient subset, we computed the proportion of patients with sustained progression onset (e.g., treatment failures) occurring during year 1 and year 2 for patients in the study at least 104 weeks. In the subset of patients in the study for at least 104 weeks, 21.8% of placebo-treated patients and 12.9% of interferon beta-1a–treated patients became treatment failures in year 1. In year 2 the proportion of treatment failures was 14.7% (placebo) and 9.5% (interferon beta-1a) of at-risk patients.



Kaplan-Meier failure-time curve showing the cumulative percent progressing according to number of weeks to beginning of sustained disability progression.

Table 3. Probability of Onset of Sustained Progression[a]

	1st 52 Weeks	2nd 52 Weeks	104 Weeks
All patients using all data[b]			
Placebo	22.0%	16.5%	34.9%
Interferon beta-1a	12.5%	10.8%	21.9%
Patients in the study for at least 104 weeks[c]			
Placebo	21.8%	14.7%	33.3%
Interferon beta-1a	12.9%	9.5%	21.1%

[a]Probability of having the first onset of sustained progression in the time interval for the patients at risk in that interval.
[b]From Kaplan-Meier analysis.
[c]Using only the first 104 weeks of data for the subset of patients entered early enough to be followed 104 weeks. The numerators (number of treatment failures) and denominators (persons at risk in that time interval) that were used to derive these proportions were as follows: 19/87 (21.8%), 10/68 (14.7%), 29/87 (33.3%), 11/85 (12.9%), 7/74 (9.5%), and 18/85 (21.2%).

Change in Expanded Disability Status Scale Score

There was significantly greater change in both unconfirmed and sustained ($p = 0.02$) EDSS scores from baseline to week 104 in placebo compared with inter-

Table 4. Amount of Change in Expanded Disability Status Scale (EDSS) Scores to Week 104

		Placebo		Interferon Beta-1a	
		No.	%	No.	%
Unsustained change[a]		N = 87		N = 83	
Better	≥1.0	10	11.5	16	19.3
	0.5	10	11.5	13	15.7
Same	0.0	18	20.7	20	24.1
Worse	0.5	18	20.7	14	16.9
	1.0	3	3.4	5	6.0
	1.5	9	10.3	7	8.4
	2.0	4	4.6	4	4.8
	≥2.5	15	17.2	4	4.8[b]
Mean		0.74		0.25	
Standard error		0.16		0.14	
Sustained change[c]		N = 56		N = 55	
Better	≥1.0	5	8.9	10	18.2
	0.5	9	16.1	14	25.5
Same	0.0	14	25.0	13	23.6
Worse	0.5	11	19.6	8	14.5
	1.0	4	7.1	3	5.5
	1.5	2	3.6	3	5.5
	2.0	1	1.8	2	3.6
	≥2.5	10	17.9	2	3.6[b]
Mean		0.61		0.02	
Standard error		0.18		0.14	

[a]Within-person change in EDSS from baseline to week 104 for patients who completed a week 104 evaluation. (Two placebo patients who were followed for more than 104 weeks did not have a week 104 evaluation.)
[b]$p = 0.02$, Mann-Whitney rank sum test.
[c]Change from baseline to the lower of the scores at weeks 104 and 130. Therefore, only patients with data at both week 104 and week 130 are included.

feron beta-1a recipients (Table 4). Sustained change in EDSS score was calculated using the lower of the week 104 and week 130 EDSS scores, to ensure that any worsening was sustained for at least 6 months.

Exacerbations

Interferon beta-1a recipients who entered the study early enough to be followed for 104 weeks were less likely than placebo recipients to have experienced multiple exacerbations (Table 5). The number of exacerbations per patient was significantly higher in the placebo recipients than in the interferon beta-1a recipients ($p = 0.03$). More than twice as many placebo as interferon beta-1a patients had at least 3 exacerbations in 104 weeks. The annual exacerbation rate for patients accrued early enough to complete 104 weeks was 0.90 for placebo patients and 0.61 for interferon beta-1a patients ($p = 0.002$). The annual exacerbation rate for all patients using all time in the study was 0.82 for placebo patients and 0.67 for interferon beta-1a patients ($p = 0.04$). The Kaplan-Meier estimate of median time to first exacerbation was shorter for placebo

Table 5. Frequency of Exacerbations

Exacerbations for Patients with at Least 104 Weeks On-Study			
	Placebo (N = 87) Number (%)	Interferon Beta-1a (N = 85) Number (%)	*p* Value
No. of exacerbations[a]			
0	23 (26)	32 (38)	0.03[c]
1	26 (30)	26 (31)	
2	10 (11)	15 (18)	
3	12 (14)	6 (7)	
≥4	16 (17)	6 (7)	
Annual exacerbation rates (per patient-year)			
All patients[b]	0.82	0.67	0.04[d]
104-week patient subset[a]	0.90	0.61	0.002[d]

[a]Calculated using the first 104 weeks of data for patients accrued early enough to complete ≥104 weeks of follow-up.
[b]Calculated using all patients, all data, all-time on-study.
[c]Mann-Whitney rank sum test.
[d]Likelihood ratio test.

recipients (36.1 weeks) than for interferon beta-1a recipients (47.3 weeks). The difference in time to first exacerbation for the two treatment arms was not significant ($p = 0.34$).

Magnetic Resonance Imaging

The proportion of baseline MRI scans showing gadolinium-enhanced lesions did not differ by treatment group. By year 1 the proportion of positive scans among interferon beta-1a recipients had dropped to 29.9%, while the proportion of positive scans in placebo recipients was 42.3% ($p = 0.05$). This group difference persisted at year 2.

There were significant differences in favor of interferon beta-1a recipients at year 1, regarding the number ($p = 0.02$) and volume ($p = 0.02$) of gadolinium-enhanced lesions per patient (Table 6). These differences were maintained at year 2. There were large variations in the range of baseline, year 1, and year 2 T2 lesion volumes in both treatment groups (see Table 6). The median within-patient percent change in T2 lesion volume from baseline to year 1 was −3.3% in placebo recipients and −13.1% in interferon beta-1a recipients ($p = 0.02$). The median within-patient percent change in T2 lesion volume from baseline to year 2 was −6.5% in placebo recipients and −13.2% in the interferon beta-1a recipients (not significantly different).

Blinding Questionnaire

Blinding analyses were carried out at weeks 6, 52, and 104. Health care providers and patients were asked to

Table 6. Magnetic Resonance Imaging (MRI) Results

	Placebo		Interferon Beta-1a		
	No.	%	No.	%	*p* Value
No. of gadolinium-enhanced lesions					
Baseline	N = 132[a]		N = 141[a]		
0	61	46.2	67	47.5	
1	26	19.7	20	14.2	
2	11	8.3	14	9.9	
3	10	7.6	12	8.5	
≥4	24	18.2	28	19.9	$p = 0.82$[b]
Mean	2.32		3.17		
Standard error	0.37		0.62		
Year 1	N = 123[a]		N = 134[a]		
0	71	57.7	94	70.1	
1	17	13.8	17	12.7	
2	12	9.8	10	7.5	
3	9	7.3	4	3.0	
≥4	14	11.4	9	6.7	$p = 0.02$[b]
Mean	1.59		1.04		
Standard error	0.31		0.28		
Year 2	N = 82[a]		N = 83[a]		
0	47	57.3	59	71.1	
1	12	14.6	11	13.3	
2	12	14.6	6	7.2	
3	2	2.4	2	2.4	
≥4	9	11.0	5	6.0	$p = 0.05$[b]
Mean	1.65		0.80		
Standard error	0.48		0.22		
Lesion volume (mm^3)					
Baseline	N = 132[a]		N = 140[a]		
0	61	46.2	67	47.9	
1–100	20	15.2	21	15.0	
101–200	12	9.1	12	8.6	
201–500	18	13.6	18	12.9	
>500	21	15.9	22	15.7	$p = 0.97$[b]
Mean	219.0		255.0		
Standard error	36.2		45.1		
Year 1	N = 123[a]		N = 134[a]		
0	71	57.7	94	70.1	
1–100	25	20.3	21	15.7	
101–200	10	8.1	13	9.7	
201–500	10	8.1	1	0.7	
>500	7	5.7	5	3.7	$p = 0.02$[b]
Mean	96.5		70.0		
Standard error	21.2		24.9		
Year 2	N = 82[a]		N = 82[a]		
0	47	57.3	59	72.0	
1–100	18	22.0	16	19.5	
101–200	6	7.3	3	3.7	
201–500	5	6.1	2	2.4	
>500	6	7.3	2	2.4	$p = 0.03$[b]
Mean	122.4		74.1		
Standard error	48.5		38.3		
Percentage change in T2 lesion volume[c]					
Baseline to year 1	N = 116[d]		N = 123[d]		
Median baseline volume (mm^3)	8,365		6,478		
Median % change	−3.3%		−13.1%		$p = 0.02$[b]
Baseline to year 2	N = 83[d]		N = 81[d]		
Median baseline volume (mm^3)	8,510		5,520		
Median % change	−6.5%		−13.2%		$p = 0.36$[b]

[a]N = number of evaluable MRIs available at each time point.
[b]Mann-Whitney rank sum test.
[c]Within-person change.
[d]Number of patients with T2 data at both time points. Within-person change was not calculated if T2 volume was zero at baseline.

indicate whether they knew which treatment the patient was receiving. Possible choices were "interferon beta," "placebo," or "don't know." Results indicate that the site personnel remained blinded throughout the study. At all time points at least 99% of examining physicians who completed a questionnaire said that they did not know the patient's treatment assignment. Patients, more often than health care providers, correctly guessed treatment assignment (32.2% of patients at week 104). Patients receiving interferon beta-1a were more likely to correctly guess their actual therapy assignment than were patients receiving placebo. However, more than half of those in the interferon beta-1a group guessed incorrectly or did not know over the three time points. Among the 68 interferon beta-1a–treated patients who guessed correctly on the week 6 questionnaire, 14 (21%) developed disability progression; 10 (11%) of the 87 interferon beta-1a–treated patients who answered either "don't know" or guessed incorrectly developed disability progression. This result argues against an effect of patients guessing correctly in biasing the results toward lowering the progression rate.

Safety

Interferon beta-1a was well tolerated, and 93% of patients completed treatment as scheduled. Two (1%) placebo and 7 (4%) interferon beta-1a recipients discontinued injections because of adverse events. One interferon beta-1a recipient died from pulmonary embolism and cardiac arrhythmia designated as unrelated to the study drug. Symptoms reported more frequently ($p < 0.1$) by interferon beta-1a recipients were restricted to flulike symptoms, muscle aches, asthenia, chills, and fever (Table 7); the median number of days on treatment with one or more of these symptoms was 7. Anemia, observed in 3% of interferon beta-1a–treated patients and 1% of placebo-treated patients, never required transfusion or discontinuation of the study drug. In both treatment arms, injection site reactions, depression, and menstrual disorders were each seen in 10 to 15% of patients. There was no evidence of liver enzyme elevation, leukopenia, or thrombocytopenia induced by interferon beta-1a. Serum neutralizing anti-interferon activity was observed in 14% of the interferon beta-1a recipients at week 52, in 21% at week 78, and in 22% at week 104. Neutralizing anti-interferon activity was also seen in 4% of the placebo patients, but always disappeared on repeat testing. Fifteen of the interferon beta-1a recipients tested positive for neutralizing activity when using a cutoff value at which no placebo patient tested positive.

Table 7. Adverse Events Seen More Frequently in Interferon Beta-1a–Treated Patients[a]

	Placebo (N = 143) No. (%)	Interferon Beta-1a (N = 158) No. (%)	p Value[b]
Headache	82 (57)	106 (67)	0.10
Flulike symptoms	57 (40)	96 (61)	<0.01
Muscle aches	21 (15)	53 (34)	<0.01
Nausea	32 (22)	49 (31)	0.12
Fever	18 (13)	37 (23)	0.02
Asthenia	18 (13)	33 (21)	0.07
Chills	10 (7)	33 (21)	<0.01
Diarrhea	15 (10)	25 (16)	0.23

[a]Symptoms reported by more than 10% of total population and at least 5% higher in treatment group than in placebo group.
[b]Fisher's exact test.

Mean scores on the Beck Depression Inventory [18] did not differ significantly between the two treatment arms at any time during the study, nor did they change significantly from baseline to year 2 in either group. One placebo recipient attempted suicide; there were no attempts in the interferon beta-1a group.

Discussion

Prior studies demonstrated the therapeutic activity of intrathecally administered natural interferon beta [1–4] and subcutaneous interferon beta-1b [5], a serine-substituted, nonglycosylated recombinant beta interferon produced in *Escherichia coli,* against multiple sclerosis. Both types of interferon beta reduced exacerbation rates in relapsing patients. However, the prior studies did not demonstrate a beneficial effect on physical disability, nor were they designed to do so [19].

The present study showed that treatment with interferon beta-1a significantly slowed the accumulation of physical disability that characterizes the natural course of relapsing multiple sclerosis. Time to sustained progression in EDSS score, the primary outcome measure, was significantly lengthened in patients treated with interferon beta-1a. Secondary disability analyses strongly supported those of the primary outcome. Increases in EDSS scores (sustained and unconfirmed) at week 104 compared to baseline were significantly less in interferon beta-1a recipients. While 11.4% of placebo patients experienced a sustained worsening in EDSS score of at least 2.5 points at 104 weeks, only 2.4% of interferon beta-1a–treated patients showed a sustained worsening of this magnitude. For patients accrued early enough to complete 104 weeks of follow-up, sustained progression occurred in percentages similar to those estimated by Kaplan-Meier methodology for the entire study population. There was a 43% reduction in the probability of beginning sustained progression among all interferon beta-1a recipients during year 1. The beneficial effect of interferon beta-1a remained evident during year 2. Similar reductions in risk were seen dur-

ing year 1 and year 2 in the subset of patients in the study for at least 104 weeks.

Other secondary efficacy analyses showed that interferon beta-1a was therapeutically active by reducing the frequency of exacerbations, and decreasing gadolinium enhancement on MRIs, compared with placebo. Autopsy correlations revealed that gadolinium enhancement occurs in acute parenchymal lesions characterized by blood-brain barrier disruption, inflammation, and edema [20]. By inference it is these acute lesions that are significantly reduced by interferon beta-1a treatment. Change in T2 lesion volume from baseline to year 1 was significantly different between the two groups, favoring patients treated with interferon. The between-group difference in percent change was approximately 3% less at year 2. The smaller number of patients with 104 weeks of follow-up and the large variability in T2 volumes observed at all three time points may have been responsible for the lack of significance observed at year 2. Because the difference in percent change of T2 lesion volume was not significant at year 2, the T2 findings must be interpreted with caution. The utility of annual T2 hyperintense lesion volumes as treatment metrics are now known to be complicated by additional factors, including large natural month-to-month fluctuations in T2 lesion load [21] and potential errors in measurement. Interval decreases in lesion load in placebo patients in this study, and in the year 2 to year 3 results in the interferon beta-1b trial results [22], are believed to be in part the result of measurement drift [22], probably exaggerated in this trial by the decision to evaluate each MRI without visual reference to an individual's prior or subsequent MRI (if available), with serial measurements in any given patient spread over a period of years. However, since T2 lesions are preceded by gadolinium-enhanced lesions [23], the gadolinium results suggest an effect of treatment on lesion formation at a relatively early stage.

It is possible that the pattern of steroid use contributed somewhat to the reduction in the percentage of gadolinium-enhanced lesions seen among placebo patients at year 1 and year 2. When we evaluated the number of patients in each treatment arm who received any steroids in the 60 days just prior to undergoing a year 1 or year 2 MRI, we found that at year 1, 12.2% of placebo-treated and 7.5% of interferon-treated patients received treatment within the 60 days prior to MRI. At year 2, 14.6% of placebo and 7.3% of interferon recipients received steroid therapy during the 60 days prior to MRI. However, steroid use cannot explain the greater reduction seen among interferon-treated patients, and the total number of patients receiving steroids just prior to an MRI was still relatively low in both treatment arms.

Progress in developing treatments to alter the natural history of multiple sclerosis has been slowed by difficulty quantifying disease progression [24]. We chose the EDSS as our principal measurement instrument because it is widely used and recognized as the best single disability measure in multiple sclerosis [25, 26]. To maximize its performance, the EDSS was carefully standardized and we required a single examining neurologist for each study center, prestudy training of examining physicians, and prestudy demonstration of EDSS reliability [13]. Examining physicians were unable to determine a patient's treatment status throughout the study. Because the end point measures were made by the examining physician and were objective and quantifiable, the possible impact of any unblinding on end point determination was minimal.

In relapsing patients, the precise measurement of disability is complicated by the unpredictable occurrence of exacerbations with variable recovery. To ensure that worsening in EDSS score represented permanent physical disability rather than an exacerbation-related temporary fluctuation in neurological status, a worsening EDSS score had to be sustained for at least 6 months for a patient to be considered a treatment failure. Previous studies showed that spontaneous recovery from sustained progression of 1.0 EDSS point of this duration is most unusual [27]. Finally, our patient population was relatively homogeneous with active relapsing disease and low EDSS scores in a range where disability changes occur more quickly than at higher scores [27].

The therapeutic activity of interferon beta-1a was observed without substantial toxicity. More than 90% of patients completed treatment as planned. Flulike symptoms were reported more frequently in interferon beta-1a recipients, but these were mild and transient. Lack of inflammation or pain at the injection sites was noteworthy and contributed to maintaining blinding. The rate of suicide in low-disability multiple sclerosis patients has been reported to be twice that of age-matched healthy control subjects [28], and a prior study of interferon beta-1b suggested an association with severe depression [5]. However, in the current study there was no evidence of increased depression in patients treated with interferon beta-1a.

The mechanisms of the therapeutic benefits of interferon beta-1a in relapsing multiple sclerosis are unknown, but undoubtedly involve its immunoregulatory actions. Type I interferon augments nonspecific suppressor T-cell function [29, 30], inhibits interferon gamma–induced class II major histocompatibility complex (MHC) expression by certain cell types [31], inhibits secretion of interferon gamma in some systems [32, 33], and induces interleukin-10 gene transcription in vivo (R. A. Rudick, personal communication, 1995). Interferon beta-1a inhibits mitogen or CD3 monoclonal antibody-driven T-cell activation [34]. These activities may benefit relapsing multiple sclerosis.

The results of this study clearly demonstrate that systemically administered interferon beta-1a significantly slows the progression of sustained neurological disability and is well tolerated in patients with relapsing multiple sclerosis. Furthermore, it reduces the frequency of exacerbations and disease activity as measured by serial gadolinium-enhanced MRI. These findings indicate that interferon beta-1a treatment alters the fundamental course of relapsing multiple sclerosis.

Appendix

The Multiple Sclerosis Collaborative Research Group (MSCRG) consists of the following sites and their respective study personnel in addition to the cited authors:

Buffalo, NY—*William C. Baird Multiple Sclerosis Research Center, Millard Fillmore Health System:* Lynne M. Bona, Mayra E. Colon-Ruiz, BS, Nadine A. Donovan, RN, Sandra Bennett Illig, RN, MS, NP, Yvonne M. Kieffer, RN, BSN, Margaret A. Umhauer, RN, MS, CNS; *Department of Neurology, The Buffalo General Hospital:* Colleen E. Miller, RN, MS, CNS; *Division of Developmental and Behavioral Neurosciences, Department of Neurology, The Buffalo General Hospital:* Ayda K. Kilic, MS, Erica L. Sargent, BS, Mark Schachter, PhD, David W. Shucard, PhD, Valerie Weider, PhD; *Physicians Imaging Center of Western New York:* Barbara A. Catalano, RT, Jeanne M. Cervi, RT, Colleen Czekay, RT, John L. Farrell, RT, Joseph S. Filippini, RT, Robert C. Matyas, RT, Kathleen E. Michienzi, RT; *Department of Microbiology, Roswell Park Cancer Institute:* Michio Ito, MD, Judith A. O'Malley, PhD; *Department of Social and Preventive Medicine, School of Medicine and Biomedical Sciences, State University of New York at Buffalo:* Maria A. Zielezny, PhD; *MSCRG Data Management and Statistical Center, Department of Neurology, The Buffalo General Hospital:* Jean M. Brun, BS, Anna L. Davidson, MPH, Lydia A. Green, RRA, BS, Kathleen M. O'Reilly, BS, James A. Shelton, MS, Karl E. Wende, PhD.

Cleveland, OH—*Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation:* Danielle Y. Barilla, MA, Sharon L. Boyle, BS, Katherine Kawczak Perkins, BA, Janet E. Perryman, Barbara G. Stiebeling, RN, MSN; *Department of Diagnostic Radiology, Cleveland Clinic Foundation:* Jan F. Konecsni, RT, Jeffrey S. Ross, MD.

Denver, CO—*Department of Radiology-MRI, University of Colorado Health Sciences Center:* Kim S. Choi, MS, Cathy J. Gustafson, RT, Bobbie J. Quandt, Ann L. Scherzinger, PhD.

Portland, OR—*Department of Neurology, Good Samaritan Hospital and Medical Center:* Debra A. Griffith, RN; *Department of Neurology, Oregon Health Sciences University:* Jeanne M. Harris, BS, Muriel D. Lezak, PhD, Ivan Mimica, PhD, Julie A. Saunders, RN, ANP; *Department of Radiology, Good Samaritan Hospital and Medical Center:* William E. Coit, MD, Carolyn R. Force, RTR, Frances J. Gilmore, RTR, Lisa B. Harris, RTR, McAndrew M. Jones, MD, Jeffery A. Kauffman, RTR, Karen E. Marberger, RTR, Jeff W. McBride, RTR, Lora L. Miller, RTR, Gail K. Wright, RTR.

Washington, DC—*Department of Neurology, Walter Reed Army Medical Center:* Judith A. Brooks, RN, MSN, Herbert R. Brown, Maria E. Graves, RN, Judith A. Schmidt, RN, DNSc; *Department of Neurology, Georgetown University Medical Center:* Jacqueline W. Mothena, BSN, RN; *Cognitive Neuroscience Unit, National Institute of Neurological Disorders and Stroke, NIH (Bethesda, MD):* Jordan H. Grafman, PhD, Mary K. Kenworthy, BA, Margaret M. Morton, BS, MEd; *Department of Radiology, Walter Reed Army Medical Center:* Denise M. Brown, RT, Douglas C. Brown, MD; *Department of Radiology, Georgetown University Medical Center:* Lucien M. Levy, MD, PhD.

The following scientific consultants were involved in the planning of this study: *University of Maryland Cancer Center (Baltimore, MD):* Ernest C. Borden, MD; *Research Institute, Cleveland Clinic Foundation (Cleveland, OH):* Richard M. Ransohoff, MD; *Department of Microbiology, New York University Medical Center (New York, NY):* Jan T. Vilcek, MD.

Kathleen McCarthy-Kirby, BS, and Marilyn Campion, MS, of Biogen were involved in the conduct and data analysis of the study, respectively.

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