expedited publication

Interferon beta-1b is effective in relapsing-remitting multiple sclerosis.

I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial

The IFNB Multiple Sclerosis Study Group*

Article abstract—We report a multicenter, randomized, double-blind, placebo-controlled trial of interferon beta-1b (IFNB) in 372 ambulatory patients with relapsing-remitting multiple sclerosis (MS). Entry criteria included an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 and at least two exacerbations in the previous 2 years. One-third of the patients received placebo, one-third 1.6 million international units (MIU) of IFNB, and one-third 8 MIU of IFNB, self-administered by subcutaneous injections every other day. The primary end points were differences in exacerbation rates and proportion of patients remaining exacerbation-free. The annual exacerbation rate for patients receiving placebo was 1.27; for 1.6 MIU IFNB, 1.17; and for 8 MIU IFNB, 0.84 after 2 years. Exacerbation rates were significantly lower in both treatment groups compared with the placebo group (8 MIU versus placebo, $p = 0.0001$; 1.6 MIU versus placebo, $p = 0.0101$; and 8 MIU versus 1.6 MIU, $p = 0.0086$), suggesting a dosage effect. The reduction in exacerbation severity in the 8 MIU group was attributable to a twofold reduction in the frequency of moderate and severe attacks. More patients in the 8 MIU group (n = 36) were exacerbation-free at 2 years compared with the placebo group (n = 18; $p = 0.007$). EDSS scores changed little from baseline in both the placebo and treatment arms. Accordingly, a significant change in disability could not be discerned in this trial. Finally, in serial MRIs, MS activity was significantly less in the high-dose IFNB group. IFNB treatment was well tolerated: the significant reductions in exacerbation rates, severity of exacerbations, and accumulation of MRI abnormalities occurred in the absence of serious side effects. IFNB is the only treatment that has substantially altered the natural history of MS in a properly controlled clinical trial.

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Multiple sclerosis (MS) is a common neurologic disease that is a major cause of disability and economic loss, especially in young adults. Extensive research has failed to identify the cause of MS, but present consensus is that damage to the nervous system results from immunologic processes.[1,2] Although many therapies have been used, none has significantly reduced exacerbation rates, the accumulation of disability, and the increase in MS lesion burden as judged by cranial MRI.[3] The advent of MRI has facilitated diagnosis and provided a sensitive index of disease activity and extent of disease burden.[4,5] Evaluation of treatment has remained difficult because of the well-known tendency for natural remission of symptoms; even MRI lesions frequently regress without treatment. There have been no previous reports of any treatment capable of preventing both exacerbations and new MRI lesions.

Three rationales existed for trials of interferon beta in MS. Jacobs et al,[6] suspecting that MS was due to a virus, injected natural interferon beta intrathecally and reported a significant reduction in exacerbations. Earlier studies used both natural and recombinant alpha and beta interferons because of their immunomodulatory functions. These studies were encouraging but inconclusive.[7,8] A third rationale for trial of interferon beta in MS is provided by two prospective studies[9,10] showing that intercurrent clinical viral infections trigger new attacks and may be the most powerful environmental influence on the MS process.[11]

A double-blinded, dose-finding pilot study[12] in subjects with relapsing-remitting MS showed that

See also pages 641 and 662

* See page 660 for the IFNB Multiple Sclerosis Study Group participants.

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recombinant interferon beta-1b (IFNB) could be administered safely at a dose of 8 million international units (MIU) every other day, and suggested that treatment decreased the risk of exacerbations.

This report presents pooled results from two identically designed, 2-year, multicenter, double-blind, placebo-controlled studies, each with three parallel treatment groups (placebo, and 1.6 MIU and 8 MIU IFNB). One study was conducted in the United States and one in Canada. Enrollment began in June 1988 and continued to May 1990. Data on the first 338 enrollees were subjected to an intent-to-treat analysis after 2 years. All subjects still in the study were given the option of continuing treatment in a double-blinded fashion, extending the total treatment period to 5½ years for some patients. The safety and efficacy results for the first year of these extension studies are also included and discussed as 3-year data.

Methods. *Patients.* Three hundred seventy-two patients, all of whom had had clinically definite or laboratory-supported definite MS[13] for more than 1 year, were entered into the study in 11 different medical centers in the United States and Canada. The studies were approved by the institutional review boards of the participating centers, and all subjects gave informed consent. The distribution among centers and results of randomization into the three treatment arms of the study are shown in table 1. All patients were between the ages of 18 and 50 years, were ambulatory with Kurtzke Expanded Disability Status Scale (EDSS)[14] scores of 5.5 or less, and had had at least two acute exacerbations during the previous 2 years. All had been clinically stable for at least 30 days before entry and had received no ACTH or prednisone during this period. Prior treatment with azathioprine or cyclophosphamide excluded patients from the study.

Exacerbations. An exacerbation was defined as the appearance of a new symptom or worsening of an old symptom, attributable to MS; accompanied by an appropriate new neurologic abnormality; lasting at least 24 hours in the absence of fever; and preceded by stability or improvement for at least 30 days. Documentation of an exacerbation implied that the investigator thought there was at least one new MS lesion or enlargement of an old one.

Study medication. IFNB was manufactured by Chiron Corporation, Emeryville, CA, and supplied to the investigators as Betaseron by Berlex Laboratories, Richmond, CA. Betaseron is a 165-amino acid, 18,500-dalton, type I interferon made in *Escherichia coli*, using recombinant technology. Each milligram of IFNB contained 32 MIU of IFNB as measured in an assay on human fibroblast monolayers, using a vesicular stomatitis virus challenge. Identical vials containing lyophilized IFNB (either 1.6 MIU or 8 MIU)* and placebo were prepared. Each IFNB vial contained 15 mg USP human albumin and 15 mg dextrose in addition to the IFNB content, and each placebo vial contained only a similar quantity of albumin and dextrose.

Table 1. Enrollment of patients by study center

Site	Placebo	IFNB 1.6 MIU	IFNB 8 MIU	Total
Temple U	10	10	10	30
Thomas Jefferson	10	10	10	30
UCSF	10	10	10	30
U Alabama	4	4	4	12
U Arizona	12	12	11	35
U Chicago	16	16	16	48
U Maryland	10	10	10	30
Hôpital de Notre Dame	12	12	12	36
Montreal Neurologic Inst.	8	8	8	24
U British Columbia	17	18	17	52
U Hospital, London, Ont.	14	15	16	45
Totals	123	125	124	372

Withdrawal criteria. These were (1) steady progression of disability for 6 months, (2) treatment with more than three courses of ACTH or prednisone (each 28 days or less) during a 1-year period, (3) failure to take scheduled doses of trial medication for more than 2 consecutive weeks, and (4) moderate or severe drug toxicity persisting on rechallenge.

Study design. After randomization, each patient was instructed in self-administration of study medication. The first three injections were given at the study center under observation; thereafter, patients injected themselves subcutaneously every other day.

All personnel at each study site were blinded to treatment categories. Two physicians at each site were designated: one neurologist who was not aware of drug side effects to do the periodic examinations, and another "treating" neurologist who knew about side effects and injection site reactions, reviewed laboratory findings for toxicity, and was responsible for overall care. When significant toxicity occurred, study medication was stopped, and resumed at one-half dose when manifestations subsided. If toxicity recurred, the patient was dropped from the study; if not, the one-half dosage was continued for the balance of the trial.

After the first few months of more frequent visits, patients were evaluated every 12 weeks, or more often if symptoms occurred suggesting the possibility of MS exacerbation. Each evaluation included a standard neurologic examination, and a Scripps Neurologic Rating Scale (NRS)[15] score and a Kurtzke EDSS score were determined.

Each patient had a baseline cranial MRI, and this was repeated yearly. A cohort of 52 patients at the University of British Columbia also had head MRIs repeated at 6-week intervals for 2 years. Techniques for measurement of the total area of MS involvement by MRI as well as details of the care taken to ensure consistent scans at all study sites are presented in a separate publication.[16] All MRIs were interpreted by the Radiology Department of the University of British Columbia in a blinded fashion.

Efficacy criteria. The primary end points of the studies were annual exacerbation rate and proportion of exacerbation-free patients. Secondary end points included time to first exacerbation (days); exacerbation duration and severity (as defined by quantitative change in NRS score: 0 to 7 = mild; 8 to 14 = moderate; and >15 = severe), change in EDSS and NRS scores from those at

* Subsequent to the conduct of this study, the standard for potency of the international units of IFN beta have been changed. The previous reference standard (native IFNB, National Institutes of Health) indicated the dosages to be 9 million IU (9 MIU) and 45 million IU (45 MIU). The new international reference standard (recombinant IFNB, World Health Organization) translates the dosages to 1.6 MIU and 8 MIU, respectively. This publication uses the latter standard.

Table 2. Demographic and baseline disease characteristics of all enrollees (372 subjects)

Variable	Placebo (n = 123)	IFNB 1.6 MIU (n = 125)	IFNB 8 MIU (n = 124)
Sex			
Female	88	85	86
Male	35	40	38
Race			
White	116	116	116
Other	7	9	8
Age (yr)			
Mean	36.0	35.3	35.2
SEM	0.6	0.7	0.6
Age at diagnosis (yr)			
Mean	32.1	30.6	30.5
SEM	0.6	0.7	0.6
MS duration from diagnosis (yr)			
Mean	3.9	4.7	4.7
SEM	0.3	0.4	0.4
Baseline EDSS			
Mean	2.8	2.9	3.0
SEM	0.1	0.1	0.1
Baseline NRS			
Mean	81.1	80.8	80.6
SEM	1.0	1.1	1.0
Exacerbations in prior 2 years			
Mean	3.6	3.3	3.4
SEM	0.1	0.1	0.2
Last exacerbation before entry (days)			
Mean	134.9	140.8	157.9
SEM	10.3	10.2	10.8

MIU Million international units.

There were no significant differences between any of these groups.

baseline; quantitative disease burden as measured by annual MRI; and disease activity as measured by MRI in a frequent-scanning substudy.

Statistical methods. As specified in the study protocols, the data from the two studies were combined and analyses were based on an intent-to-treat data set. The analyses for the extension studies covered the full 3 years of available data. SAS software was used for all analyses.

For continuous variables, treatment-group differences were analyzed using an analysis of variance (ANOVA) based on ranked data. This model accounted for the following effects: treatment group, study site, and treatment group by study site. Categorical variables, such as sex and race, were tested for general association by use of the Cochran-Mantel-Haenszel (CMH) chi-square test stratified for site. Similarly, categorical variables with an ordinal scale, such as exacerbation count per patient, were tested for treatment group differences using the CMH ANOVA statistic. This statistic corresponds to a site-adjusted ANOVA. A two-tailed Fisher's exact test was used for categorical data that were sparse. In the display of group exacerbation rates, the 95% confidence intervals were calculated using a Poisson distribution based on the number of observed exacerbations in each treatment group.

Survival curves were calculated with life-table methods for the length of time before the onset of the first and second exacerbations. Data on patients were censored at the time of withdrawal. The log-rank statistic was used to test for comparability of the survival curves for each treatment arm.

Table 3. Effect of IFNB on exacerbations: Summary of 2- and 3-year data

Two-year data	Placebo (n = 112)	IFNB 1.6 MIU (n = 111)	IFNB 8 MIU (n = 115)	*p* value‡
Exacerbation rate	1.27	1.17	0.84*	0.0001
Exacerbation-free subjects	18	23	36	0.007
Median time to first exacerbation (days)	153	180	295†	0.015

Three-year data	Placebo (n = 123)	IFNB 1.6 MIU (n = 125)	IFNB 8 MIU (n = 124)	*p* value‡
Exacerbation rate	1.21	1.05	0.84	0.0004
Exacerbation-free subjects	17	23	27	0.097 NS
Median time to first exacerbation (days)	147	199	264	0.028

MIU Million international units.
* $p < 0.01$, 8 MIU vs 1.6 MIU.
† $p < 0.05$, 8 MIU vs 1.6 MIU.
‡ *p* value for 8 MIU vs placebo.

Results. *Demographic and baseline characteristics in the three treatment arms after randomization.* The three groups were comparable (table 2). In each there was an approximate 2:1 female-to-male preponderance and nearly the same mean age, disease duration, and baseline EDSS. Moreover, all three groups had had roughly the same number of exacerbations in the 2 years before the study.

Effect of IFNB on primary outcome measures. The primary and secondary efficacy results at 2 years (table 3) revealed that the exacerbation rate was 1.27 per year in the placebo group, 1.17 for the 1.6 MIU group, and 0.84 for the 8 MIU group (placebo versus 8 MIU, $p = 0.0001$; 1.6 MIU versus 8 MIU, $p = 0.0086$, and 1.6 MIU versus placebo, $p = 0.01$) (figure 1). The number of patients exacerbation-free was 18, 23, and 36, respectively, at 2 years (placebo versus 8 MIU, $p = 0.007$; 1.6 MIU versus 8 MIU, p = 0.076, NS) (figure 2).

Secondary outcome measures. There was a significant prolongation of time to first and second exacerbations for the 8 MIU group compared with placebo after 2 years of treatment (table 3). This beneficial effect continued after 3 years of treatment, at which time the exacerbation rates remained significantly different for placebo versus 8 MIU ($p = 0.0004$), and the time to first and fifth exacerbations were also significantly prolonged. The number of patients exacerbation-free, however, which had been significantly different after 2 years of treatment with 8 MIU, was no longer significantly different after 3 years of treatment (placebo versus 8 MIU, $p = 0.097$, NS).

Exacerbations were rated as either mild, moderate, or severe according to changes in the NRS score. Table 4 shows that the combined annualized rates of moderate and severe exacerbations in the 8

MIU group at 2 years equaled 0.23, one-half the 0.45 rate for moderate and severe exacerbations in the placebo group (8 MIU versus placebo, p = 0.002). Sometimes patients were unable to visit the center promptly after exacerbations and had already improved to some extent when first examined; in such instances, the NRS score could not be calculated at the height of the attack (the "unknowns" in table 4).

One effect of the decreased number of severe exacerbations in the high-dose group was less need for hospitalization (table 5)

MRI lesion area. At the end of the first year, mean lesion area in relation to baseline, by MRI, increased by 12.2% in the placebo group and by

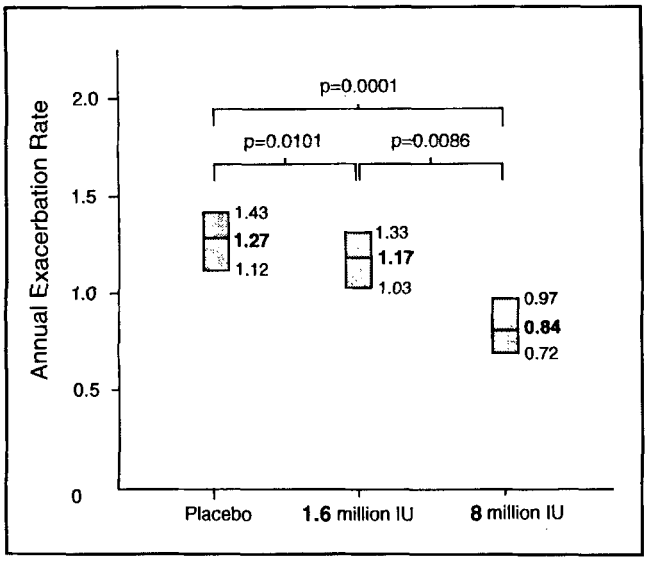


Figure 1. Exacerbation rates for the three treatment groups (boldface) in the first 2 years of the study, and 95% confidence intervals. The significance of the reduction in the 8 MIU group was essentially unchanged in the 3-year analysis. Overall, p = 0.0001.

Table 4. Severity of exacerbations by treatment group (2-year data)

	Placebo (n = 112)	IFNB 1.6 MIU (n = 111)	IFNB 8 MIU (n = 115)
Patients with exacerbations	94	88	79
Number of exacerbations	266	242	173
Total patient-years on study	209.2	207.0	207.0
Annual rate			
Mild	0.54	0.62	0.45
Moderate and severe	0.45	0.32	0.23
Unknown	0.28	0.22	0.15
Totals	1.27	1.17	0.84

Placebo vs 8 MIU for moderate/severe, p = 0.002.
Overall for moderate/severe, p = 0.007.

Table 5. Hospitalizations for MS during 3 years of study

	Placebo	IFNB 1.6 MIU	IFNB 8 MIU	*p* value
Number of hospitalizations	65	53	37	0.046 (placebo vs 8 MIU)
Number of patients hospitalized	33	25	21	0.129 (overall) 0.05 (placebo vs 8 MIU)
Number of hospital stays	471	411	344	0.07 (overall) 0.023 (placebo vs 8 MIU)

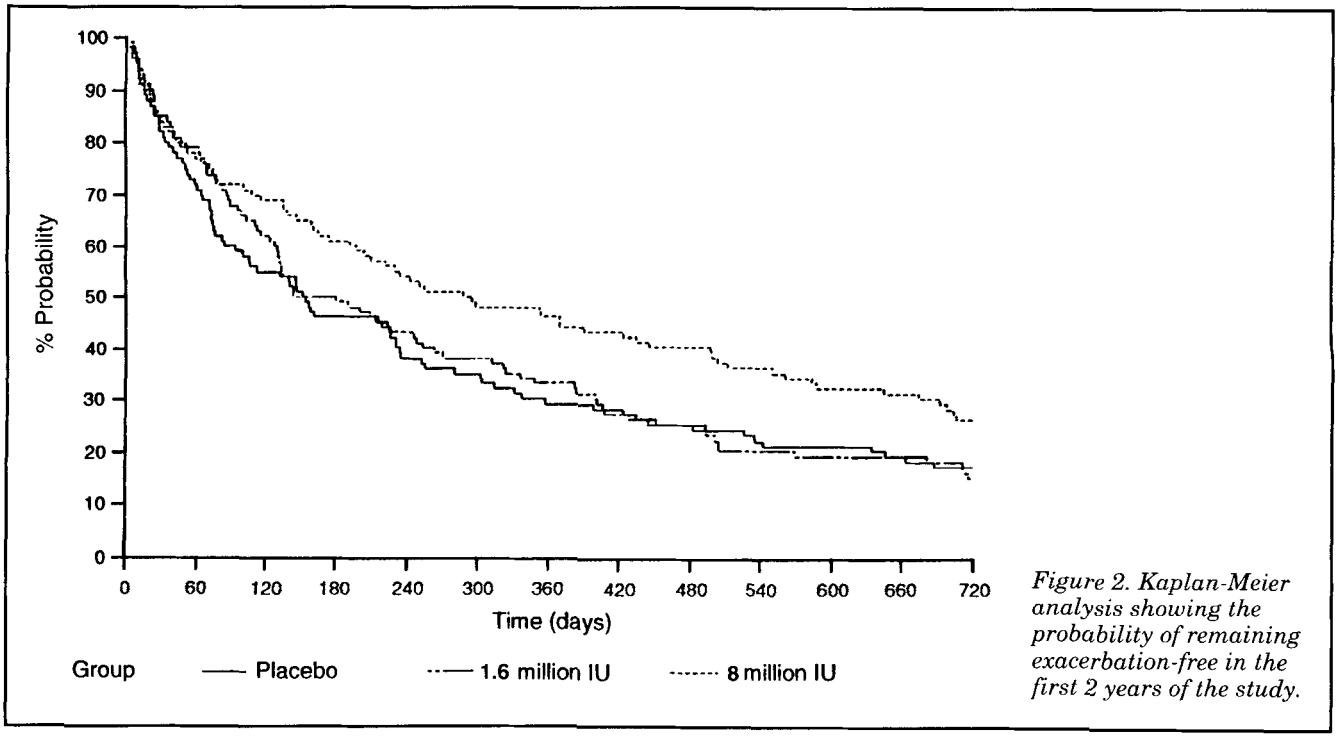


Figure 2. Kaplan-Meier analysis showing the probability of remaining exacerbation-free in the first 2 years of the study.

4.1% in the intermediate-dose IFNB group, and *decreased* by 1.1% in the high-dose group. At the end of the second year, the numbers were 20% increase (placebo group), 10.5% increase (1.6 MIU group), and 0.1% *decrease* in the high-dose group. At the end of 3 years the figures were 17.1% increase (placebo), 1.1% increase (1.6 MIU), and a 6.2% *decrease* in the high-dose group of patients. Additional MRI data are contained in a companion publication in this issue.[16]

EDSS and NRS. The NRS score, an attempt to express the neurologic examination as a single number, showed no material change in any of the treatment groups in any of the 3 study years. Likewise, there was no significant change in the mean EDSS score by treatment arm, although the numbers were all slightly higher in all three groups at 3 years compared with baseline. There was a trend suggesting lessened disability at the 3-year end point in the 8 MIU group ($p = 0.043$) (table 6). "End point" in table 6 denotes the EDSS score at the end of 3 years (or the EDSS at time of dropout); "confirmed end point" indicates two consecutive EDSS scores, separated by 90 days, that were identical, with both showing a 1.0 point increase over the baseline score. To calculate confirmed end point, use of early fourth-year examination data was necessary in most patients.

Withdrawals, adverse events. and side effects. Sixty-five patients discontinued treatment during the first 2 years (23 in the placebo, 18 in the 1.6 MIU, and 24 in the 8 MIU groups). Although 122 patients did not finish the third year, that figure included 22 who chose not to continue when the study was extended. The overall dropout rate did not exceed that anticipated at the trial's inception. Moreover, the distribution of dropouts remained similar in the three treatment arms although the reasons were different. More placebo patients withdrew for lack of efficacy; there were 10 withdrawals in this group at 2 years for excessive use of steroids compared with only one withdrawal in each of the IFNB treatment arms for this reason. In contrast, more IFNB-treated patients discontinued because of toxicity. Among the 16 patients withdrawing for treatment side effects at 2 years, one was in the placebo group, five in the 1.6 MIU arm, and 10 in the high-dose group. Only one additional adverse-event withdrawal, a suicide, occurred in the third treatment year. The reasons for withdrawal due to treatment effects (patient numbers in parentheses) were abnormal liver enzymes (3), injection site pain (3), fatigue (3), and cardiac arrhythmia, allergic reaction, nausea, headache, "flu syndrome," confusion, and "felt sick" (1 each).

Other causes of withdrawal included unblinding events (9), excessive use of steroids (14), major noncompliance (2), exacerbation at baseline (1), and emotional instability (1). In addition, there was a wide variety of personal reasons, including dislike of injections, moving, and a desire to become pregnant.

Table 6. Effect of IFNB treatment on disability at 3-year end point

	End point*		Confirmed end point*	
	Stable	Worsened†	Stable	Worsened†
Placebo	74 (61%)	48 (39%)	88 (72%)	34 (28%)
IFNB				
1.6 MIU	81 (65%)	44 (35%)	90 (72%)	35 (28%)
8 MIU	89 (73%)	33 (27%)	97 (80%)	25 (20%)
Placebo vs 8 MIU	$p = 0.043$		$p = 0.161$	

* Defined in text.
† Worsened by at least one EDSS point.

The most common laboratory abnormality associated with IFNB treatment was a mild intermittent lymphopenia unassociated with significant changes in the total white blood cell count. Lymphopenia occurred at some time in 65% of placebo patients, 76% in the 1.6 MIU group, and 80% of the 8 MIU patients. Mild neutropenia occurred in 4% of the placebo, 6% of the 1.6 MIU, and 17% of the 8 MIU groups. There were no severe neutropenias.

Although mild neutropenia, anemia, and thrombocytopenia were present and statistically related to treatment group (being more common in the 8 MIU group), they were clinically insignificant and also sporadic. Mild or moderate SGPT changes occurred in five placebo patients, seven 1.6 MIU patients, and 14 high-dose patients at some time. Only four patients had elevations of SGOT.

Overall, incidence of notable side effects was low. Injection site reactions were seen in all treatment groups but more commonly in the 8 MIU group. Inflammation at injection site occurred at least once in 6% of placebo patients, 63% of 1.6 MIU patients, and 69% in the 8 MIU patients. Fever occurred in 34% of placebo patients, 40% of the 1.6 MIU group, and 58% of the high-dose group at some time. The incidence of myalgia was 24% for the placebo, 24% for the 1.6 MIU, and 41% for the high-dose groups. These side effects decreased after 3 months and approached the rate in placebo patients at 1 year, although injection site reactions always remained more common in IFNB-treated patients.

Except for flu-like symptoms and injection site reactions, the incidence of other adverse events was equally distributed across treatment groups. The only adverse events significantly associated ($p = 0.05$) with IFNB treatment at 8 MIU were fever, chills, myalgia, sweating, malaise, and injection site reactions.

Neutralizing antibodies. Screening for neutralizing antibodies was done in serum by ELISA on each visit. Positive serum from any patient led to additional testing of all sera from that patient in a bioassay for neutralizing activity. Eleven percent of placebo sera, 47% of the 1.6 MIU sera, and 45% of the 8 MIU sera had neutralizing activity at some time. There was no relationship between the pres-

ence of IFNB-neutralizing activity in the serum and exacerbation severity or time between exacerbations.

Discussion. The results of this study indicate that IFNB is well tolerated and has a beneficial effect on the course of relapsing-remitting MS. There were highly significant effects on most primary and secondary efficacy end points, including exacerbation rates, time to first and second exacerbations, severity of exacerbations, and MS activity and lesion burden as determined by MRI. There are no previous reports of any drug capable of producing all these treatment effects in MS. It is equally clear, however, that IFNB at 8 MIU every other day is only partially effective: patients in the high-dose group continued to have exacerbations, albeit at a reduced rate and of milder clinical severity.

Because study end points had been reached, the External Advisory Committee recommended that placebo and 1.6 MIU group patients be offered the option of changing to 8 MIU dosage in an orderly and expeditious manner.

While the data indicate a definite dose effect in favor of the 8 MIU treatment group, further clinical experience with IFNB will be necessary to determine whether different dosing schedules might produce more benefit. In an early pilot trial, 16 MIU three times weekly produced unacceptable toxicity (including chills, fever, and injection site reactions).[12] There is no experience with a daily dosing schedule in MS patients.

The mechanism of action of IFNB that is responsible for the the confirmed positive treatment effects remains unknown. Among the immunoregulatory properties of IFNB are its ability to inhibit interferon gamma (IFNG) synthesis,[17,18] to augment defective suppressor activity in MS patients,[19] and to inhibit class II major histocompatibility complex (MHC) antigen expression induced by IFNG on the surfaces of antigen-presenting cells.[20,21] In this respect it opposes IFNG, which has long been known to enhance antigen presentation by increasing class II MHC antigens. This ability to "neutralize" some of the biologic effects of IFNG during intercurrent viral infections could be an important mechanism of action in IFNB in MS.

An additional conceivable mechanism of IFNB benefit might be an elevated adrenal steroid level related to the injection site inflammatory response. This has been investigated, and does not occur with the dose and route of administration of IFNB used in this trial.[22] Another possible mechanism might include the effect of IFNB in downregulating tumor necrosis factor,[17] a molecule reported to be toxic to oligodendrocytes.[23]

Although IFNB has antiviral activity, there is little current support for the proposition that MS results from the direct effect of viral infection in the CNS. Attempts to culture viruses have been negative or inconsistent; transmission attempts in nonhuman primates have been unsuccessful; and earlier reports of retroviral sequences in MS patients have not been confirmed.[24,25]

The distinct possibility remains that IFNB modified the response to viral infections that trigger exacerbation of MS.[9,10] Although the incidence of banal virus-like infections was not reduced in IFNB-treated patients based on information in patient diaries, it is possible that the immune-modulating effect of IFNB altered the response to such infections. One center in this study has already found a strong temporal correlation between upper respiratory infections and exacerbations during the course of the blinded IFNB and placebo treatment,[10] confirming the results of an earlier 8-year prospective study showing that clinical viral infections are important triggers for exacerbations.[9] Since investigators remain blinded, it is impossible at this time to determine whether there was a differential effect related to the treatment arms in this study.

Because only a small number of patients entered the chronic progressive stage during this study, the trial gives us no indication of the effect IFNB might have on chronic progressive disease. Nevertheless, in a large population-based study,[26] a high exacerbation rate early in the course of MS predicted rapid subsequent progression. Thus, an agent that inhibits exacerbations may well have a long-term beneficial effect on disability. The MRI data, showing distinct reduction in lesion area in both the 8 MIU and 1.6 MIU groups, support this hypothesis. Further experience with IFNB will be necessary to definitely determine its effect on either primary or secondary chronic progression. The fact that exacerbation rates in the third year of the study remained suppressed compared with the placebo group suggests that there was not a decreasing clinical response with time. Additional information on disability will be available when data from the fourth and fifth years of the extended protocols are analyzed.

The efficiency of evaluating-neurologist blinding in the study was excellent, most admitting they have no knowledge as to the treatment arm of individual patients. This apparent good blinding effect was encouraged by the study design. However, since both investigators and patients are still blinded, the exact efficiency of investigator and patient blinding must be the subject of a later report. The fact that the absolutely blinded MRI data correspond with the clinical data is cause for optimism that efficient blinding occurred, however.

One effect of the efficacy of IFNB during this trial was a decreased number of hospitalizations and hospital days in the treated patients during the trial. There were significantly fewer hospitalizations and patients hospitalized in the 8 MIU group as well as significantly fewer hospital days for the treated group overall (table 5). This is likely to translate into a long-term reduction in overall health care costs for these patients.

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