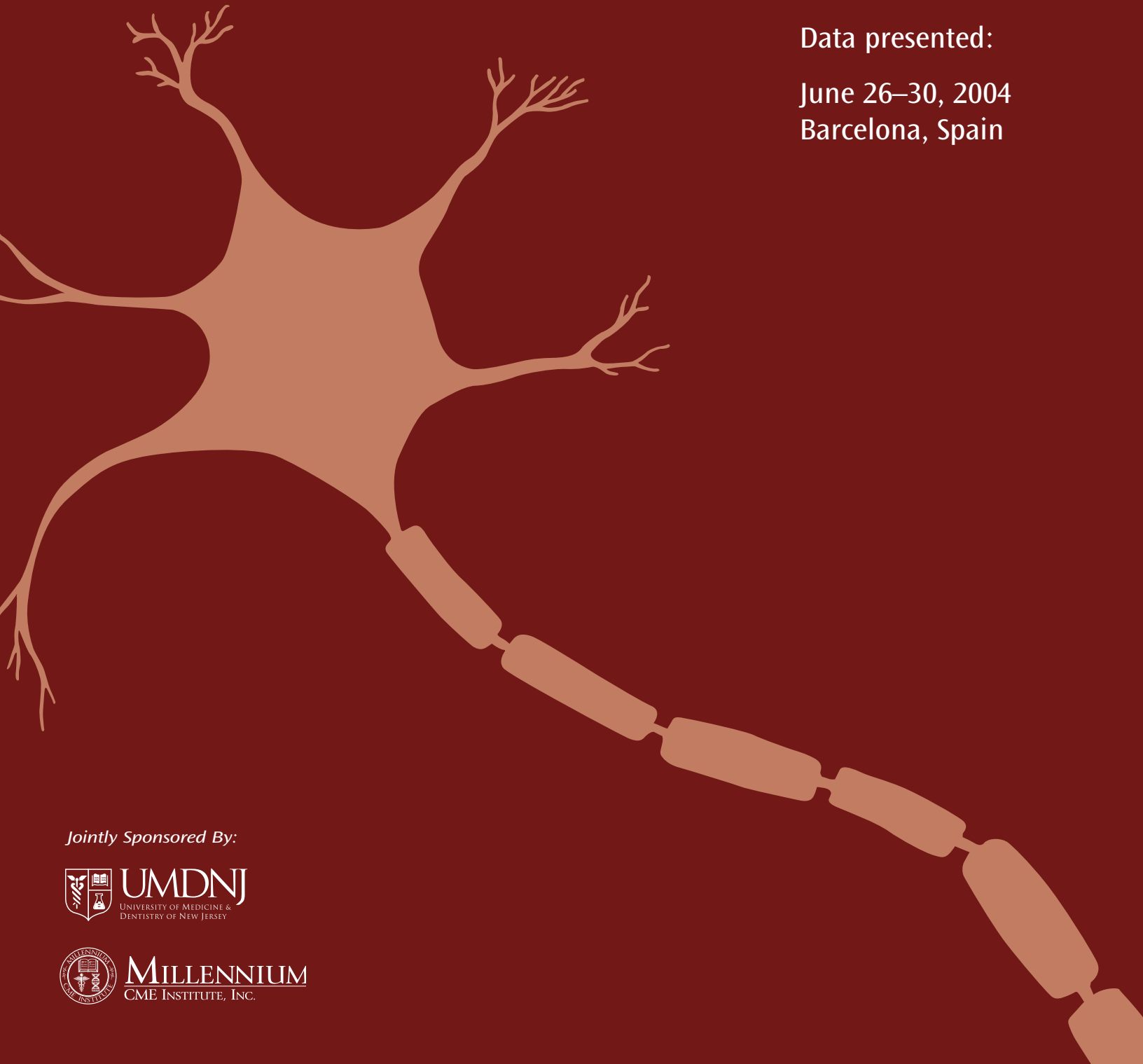


MULTIPLE SCLEROSIS FORUM REPORT™

From the 14th Meeting of the European Neurological Society -
Perspectives in the Optimal Management of Multiple Sclerosis

Data presented:

June 26–30, 2004
Barcelona, Spain



Jointly Sponsored By:



This report was reviewed for medical and scientific accuracy by Andrew R. Pachner, MD, Professor, Department of Neurology and Neurosciences, University of Medicine & Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey.

Expert Commentary

Andrew R. Pachner, MD, Professor, Department of Neurology and Neurosciences, University of Medicine & Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey

Data presented at the 14th Meeting of the European Neurological Society provide further insight into current issues surrounding the optimal treatment and management of multiple sclerosis (MS). The topics discussed at this year's meeting included selection criteria for determining the optimal immunomodulatory agent in treating MS, how to interpret and clinically manage the development of neutralizing antibodies induced by interferon beta therapy, and potential treatment options for those patients who experience disease progression despite best treatment practices.

Over the past decade, the development of biologic therapies has had a dramatic effect on the treatment of MS. Results of the Quality Assessment in Multiple Sclerosis Therapy Study (QUASIMS), a large, retrospective, comparative study reported at this meeting, indicate that the available interferon beta agents (intramuscular interferon beta-1a [Avonex], subcutaneous interferon beta-1a [Rebif], and subcutaneous interferon beta-1b [Betaferon in the US and Betaferon outside the US]) offer comparable efficacy in preventing relapse and delaying disease progression.¹

Recently, neutralizing antibodies have become recognized as a potential confounding factor to achieving successful long-term outcomes in patients with MS. The development of neutralizing antibodies to interferon beta may severely negate the therapeutic benefits of interferon beta. This *Multiple Sclerosis Forum Report™* contains important information regarding the development of neutralizing antibodies and identifies potential clinical strategies for management of this problem.

Additionally, new data were presented on the chemotherapeutic agent mitoxantrone (Novantrone). For patients with difficult-to-treat or challenging MS, mitoxantrone has shown promising activity that may result in stabilization of MS disease. However, this potential is offset by the dose-limiting cardiotoxicity of mitoxantrone. Nonetheless, several investigators reported their experience in using mitoxantrone safely and effectively in patients with MS.

These issues constitute the focus of this *Multiple Sclerosis Forum Report™*. I hope you find this information useful and beneficial for your patients in developing long-term management strategies for MS.

Comparable Efficacy of Interferon Beta Agents

Direct Comparison Study of the Effect of Beta-interferons in Iranian Patients with Multiple Sclerosis: Results of a 6-year Therapy.

Hossein Pakdaman, MD, Professor of Neurology, Shahid Beheshti University, Tehran, Iran and President of the Iranian Neurological Association

According to Hossein Pakdaman, MD, Professor of Neurology, Shahid Beheshti University, Tehran, Iran, and President of the Iranian Neurological Association, the incidence of MS in Iran has been rapidly increasing. Current estimates place the number of individuals with MS at 40,000 – among a population of 75 million. Dr. Pakdaman reported the results of a long-term study evaluating Avonex, Rebif, and Betaseron in the treatment of clinically definite MS.

This single-blind (physician), direct comparison study evaluated 214 patients with clinically definite MS who received treatment with intramuscular Avonex 30 mg once weekly (n = 72), subcutaneous Rebif 22 mcg three times weekly (n = 83), or subcutaneous Betaseron 8 MIU every other day (n = 59).² The three treatment arms were matched according to age, gender, age at diagnosis, and mean Expanded Disability Status Scale (EDSS) score. The primary outcomes of the study were relapse rate, disability progression, mean number of T2 active lesions, mean number of T1 lesions, and adverse events from treatment.

At the end of the first year of treatment, 76.3% of patients treated with Avonex were relapse-free, compared with 73.5% for Rebif 22 mcg and 71.2% for Betaseron (Table 1). Mean changes in EDSS (mean baseline EDSS 2.1) at the end of the first year of treatment were 0.6, 0.5, and 0.6 for Avonex, Rebif, and Betaseron, respectively. Mean changes in EDSS at the end of the second year were 1.3, 1.2, and 1.2, respectively, and at the end of the fifth year were 2.2, 2.0, and 2.35, respectively.

Throughout the study, patients were evaluated by magnetic resonance imaging (MRI). At the end of the first year of treatment, 79.0% of patients treated with Avonex were free from new T2 lesions, compared with 91.5% for Rebif 22 mcg, and 88.3% with Betaseron. After 5 years of treatment with Avonex, Rebif, and Betaseron, the percentage of patients free from new T2 lesions was 45.3%, 40.2%, and 41.4%, respectively.

Table 1. Results at 1 Year for Patients Treated with Avonex, Rebif, and Betaseron.

	Avonex	Rebif	Betaseron
Relapse Free	76.3%	73.5%	71.2%
Mean Change in EDSS	0.6	0.5	0.6
Free From New T2 Lesions	79.0%	91.5%	88.3%

EDSS = Expanded Disability Status Scale.

“For years, the efficacy of disease-modifying agents used in treating multiple sclerosis was questioned by many physicians. Now, there is no question they are effective, and this study shows that the agents we are using [interferon beta] offer comparable efficacy. The highlight of our study is that we have followed these patients for six years. This is not simply a matter of a one-year comparison,” advised Dr. Pakdaman.

The major adverse event associated with treatment as described by the investigators was skin rash, which was observed in 56.2% of patients taking Betaseron, 45.4% taking Rebif, and 21.1% taking Avonex. Commenting on patient preferences, Dr. Pakdaman noted, “Although the long-term efficacy of these agents is comparable, I find that many patients prefer Avonex because fewer injections are required.”

A Comparison of the Efficacy and Tolerability of Interferon Beta Products Used as Initial or Follow-up Therapy for the Treatment of Relapsing Multiple Sclerosis: Results from the QUASIMS Study.

Volker Limmroth, MD, PhD, University Hospital Essen, Essen, Germany

Similar efficacy results emerged from a much larger retrospective, controlled, observational study reported by Volker Limmroth, MD, PhD, University Hospital Essen, Essen, Germany. The QUASIMS study involved 4,754 patients with clinically definite relapsing-remitting MS from 510 sites in Germany, Austria, and Switzerland, who received 2 years of uninterrupted therapy with intramuscular Avonex 30 mcg once weekly (36.3%), subcutaneous Betaseron 8 MIU every other day (35.9%), subcutaneous Rebif 22 mcg three times weekly (19.6%), or subcutaneous Rebif 44 mcg three times weekly (8.2%).¹ The QUASIMS database contains the largest cohort of MS patients ever assembled to compare the effectiveness of interferon beta agents.

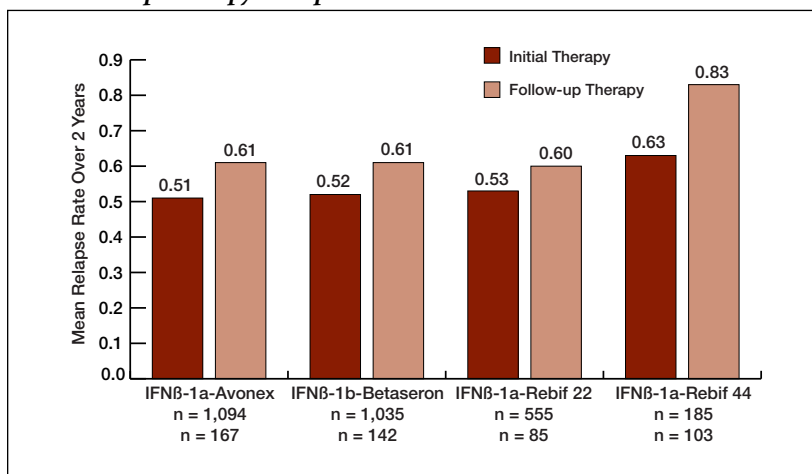
“We believe this is the largest head-to-head study of treatment in multiple sclerosis patients,” remarked Dr. Limmroth, “and the first to address the question of whether patients benefit after being switched from one interferon beta agent to another.”

QUASIMS divided patients into two categories: those who received immediate and sustained treatment (uninterrupted for 2 years) with interferon beta as initial therapy (initial therapy group), and those who received interferon beta for *less than* 2 years before switching to another interferon beta agent and continuing that agent for at least 2 years without interruption (follow-up therapy group). The initial therapy group consisted of 3,991 patients while the follow-up therapy group consisted of 662 patients. The majority of patients received interferon beta treatment for 3 to 4 years.

The results of this study revealed two key findings: interferon beta agents are essentially equivalent in their clinical efficacy (judged by relapse rates and disease progression), and patients in the follow-up therapy group (who had switched agents prior to 2 years of uninterrupted treatment) fared significantly worse than patients receiving interferon beta for 2 uninterrupted years as their initial strategy. According to Dr. Limmroth, these findings suggest that interferon beta agents are equally efficacious and that there is no additional clinical benefit from switching from one interferon beta agent to another.

Annualized relapse rates over 2 years of treatment were similar among the interferon beta agents (with the exception of Rebif 44 mcg, which was higher), and were more favorable in the initial therapy group than in the follow-up therapy group (Figure 1).

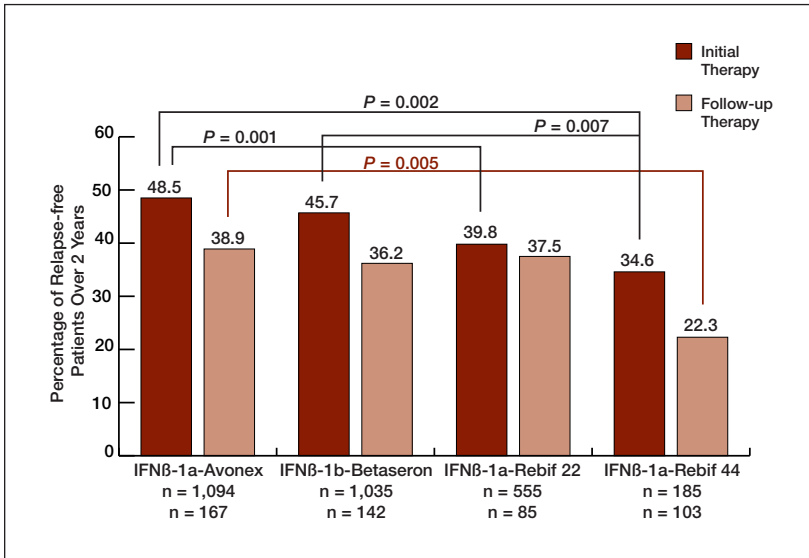
Figure 1. Annualized Relapse Rate Over 2 Years in the Initial Therapy and the Follow-up Therapy Groups.



IFNβ = Interferon beta.

In the initial therapy group, the percentages of relapse-free patients over 2 years were significantly higher for patients treated with Avonex (48.5%) and Betaseron (45.7%), than for those treated with Rebif 22 mcg (39.8%) and Rebif 44 mcg (34.6%) (Figure 2). In the follow-up therapy group, the 2-year relapse-free percentages were 38.9%, 36.2%, 37.5%, and 22.3%, respectively.

Figure 2. Percentage of Relapse-free Patients Over 2 Years in the Initial Therapy and the Follow-up Therapy Groups.



IFNβ = Interferon beta.

In the initial therapy group, the percentage of progression-free patients over 2 years was significantly greater in patients treated with Avonex ($P < 0.001$) and Rebif 22 mcg ($P = 0.001$) compared with Rebif 44 mcg, and significantly greater for Avonex than for Betaseron ($P = 0.001$).

Dr. Limmroth noted that although the interferon beta agents were comparable, there were subtle differences in favor of Avonex. These differences included patients treated with Avonex were more likely to remain relapse-free at 1 and 2 years, and progression-free at 2 years.

Approximately 19% of patients switched therapies: 18% changed from Avonex, 20% from Betaseron, 21% from Rebif 22 mcg, and 12% from Rebif 44 mcg. The predominant reason was a perceived lack of efficacy, which was reported more commonly for patients taking Rebif 22 mcg than for those taking Avonex or Betaseron. Therapy changes due to flu-like symptoms were reported significantly less often for Rebif 22 mcg than Betaseron, while changes due to injection-site reactions were reported significantly less often for Avonex than Rebif 22 mcg.

While the interferon beta agents were generally comparable in efficacy throughout the QUASIMS analyses, patients treated with Rebif 44 mcg performed significantly worse in most categories. The EDSS score and duration of disease in the Rebif 44 mcg group suggested there may have been higher disease activity in this group at baseline [at treatment initiation], according to Dr. Limmroth.

An analysis of patients who progressed ≥ 1 EDSS point during the study showed highly significant differences between Rebif 44 mcg and the average of Avonex, Betaseron, and Rebif 22 mcg for all baseline EDSS scores ($P > 0.0001$) (Table 2). For patients with baseline EDSS < 3 , an EDSS progression of at least 1 point was seen in 24.3% of patients treated with Rebif 44 mcg versus 19.9% of patients treated with Avonex, Betaseron, and Rebif 22 mcg; for baseline EDSS 3–4, progression was seen in 39.5% of patients treated with Rebif 44 mcg versus 23.0% of patients treated with Avonex, Betaseron, and Rebif 22 mcg; and for baseline EDSS > 4 , progression was seen in 51.9% of patients treated with Rebif 44 mcg versus 22.2% of patients treated with Avonex, Betaseron, and Rebif 22 mcg.

Table 2. Analysis of Patients Who Progressed ≥ 1 EDSS Point in QUASIMS.

	Rebif 44 mcg	Avonex, Betaseron, and Rebif 22 mcg (average)
Baseline EDSS < 3	24.3%	19.9%
Baseline EDSS 3–4	39.5%	23.0%
Baseline EDSS > 4	51.9%	22.2%

EDSS = Expanded Disability Status Scale.

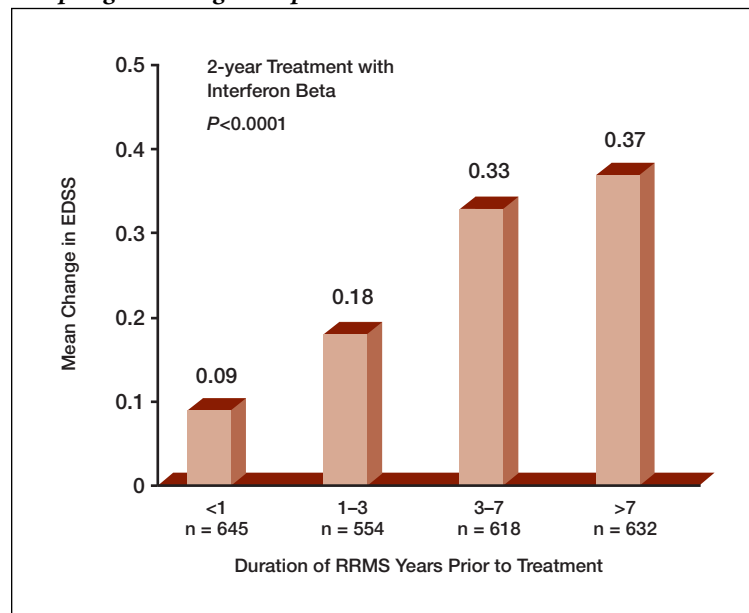
Dr. Limmroth stated that a significantly higher percentage of patients taking Rebif 44 mcg advanced at least one point in their EDSS score, compared with Avonex, Betaseron, and Rebif 22 mcg.

The results of QUASIMS also found that early initiation of treatment with interferon beta is important; the longer the time between diagnosis and treatment initiation, the greater the mean change in EDSS during the 2 years of treatment (Figure 3).

“This finding reinforces the importance of early and sustained use of disease-modifying treatment,” advised Dr. Limmroth. “QUASIMS clearly showed that patients benefit from 2 years of treatment with interferon beta, regardless of the agent, and benefit most when started on treatment within the first year of diagnosis.”

The results of QUASIMS complement the results of other open-label comparisons,³⁻⁶ Dr. Limmroth noted, suggesting there are no real differences in clinical efficacy among interferon beta agents.

Figure 3. Correlation between Change in EDSS and Duration of Relapsing-remitting Multiple Sclerosis.*



* ≥ 2 relapses.

EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis.

Neutralizing Antibodies

Global Consensus on the Relevance of Neutralizing Antibodies.

Presented at the Biogen Idec™ Satellite Symposium, “Emerging Data in the Long-Term Treatment of Multiple Sclerosis.”

Andrew R. Pachner, MD, Professor, Department of Neurology and Neurosciences, University of Medicine & Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey

The use of interferon beta agents to treat patients with MS may result in the development of neutralizing antibodies against interferon beta. The level of neutralizing antibodies is initially low, and peaks 6 to 18 months after treatment initiation, after which the neutralizing antibodies either persist or disappear.

“It is generally agreed that the development of neutralizing antibodies results in decreased bioactivity, that interferon beta-1a is less immunogenic than interferon beta-1b, and that groups of patients in whom these levels persist for three to six months can be expected to have clinical consequences from decreased interferon beta effect,” explained Andrew R. Pachner, MD, Professor, Department of Neurology and Neurosciences, University of Medicine & Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey, at a satellite symposium on emerging data in the long-term treatment of MS.⁷

Dr. Pachner is an internationally recognized authority on neutralizing antibodies, and he recently chaired an international consensus conference on the topic in May 2003, held in London and sponsored by the Consortium of MS Centers.⁸

“There was general agreement at the consensus conference that practicing neurologists should be aware that persistent, high levels of anti-interferon beta antibodies are a significant problem and interfere with the therapeutic effect of interferon beta,” reported Dr. Pachner.

Dr. Pachner explained that antibody-mediated decreased bioactivity is a graded phenomenon that depends on the titer, avidity, and epitope-binding characteristics of the interferon beta antibody population. Decreased bioactivity of

injected interferon beta in patients with MS can be reliably detected by decreased levels of myxovirus protein A (MxA), an interferon-beta-induced gene product. The clinical sequelae of antibody-mediated decreased bioactivity depend on the duration and severity of decreased bioactivity and underlying MS activity. Persistence of high levels of anti-interferon-beta antibodies in patients with active MS will eventually lead to clinical evidence of loss of efficacy of interferon beta.

While knowledge regarding neutralizing antibodies is rapidly growing, there are still many areas in which more information is needed, including the management of patients who develop neutralizing antibodies. Several presentations at the 14th Meeting of the European Neurological Society provided additional insight on the subject of neutralizing antibodies.

The Persistence of Neutralizing Antibodies to Interferon Beta Over 6 Years of Treatment in MS Patients is Dependent on Titre and Interferon Beta Product.

Robert M. Herndon, MD, University of Mississippi, VA Medical Center, Jackson, Mississippi, and Susan E. Goelz, PhD, Biogen Idec™, Cambridge, Massachusetts

Neutralizing antibodies are considered to reduce the clinical efficacy of interferon beta in patients with relapsing MS.⁹⁻¹² An open-label safety extension study of the pivotal phase III Avonex trial¹³ suggests that clinicians should consider the specific interferon beta agent, as well as the titer of neutralizing antibodies, in managing patients with neutralizing antibodies.¹⁴

A total of 382 patients were enrolled in the extension study of which 218 patients participated in the original phase III trial. Of the original 218 patients, 103 patients had received placebo and 115 patients had received Avonex 30 mcg once weekly [Ed. patients in the original trial received the phase III formulation of Avonex, the manufacture of which was subsequently modified with resulting lower immunogenicity]. Of the remaining 164 patients, who were new to the study, 140 previously were treated with Betaseron and 24 had received no prior interferon beta treatment. At the initiation of the extension study, 108 patients (28%) were naïve to interferon beta treatment; 159 (42%) had received prior treatment with Betaseron only; 77 (20%) had been treated with Avonex only; and 38 (10%) had received both Avonex and Betaseron.¹⁵ Altogether, patients received Avonex treatment for 6 to 8 years.

Approximately 3% of patients who had no neutralizing antibodies at baseline developed neutralizing antibodies (titer ≥ 20) during the first year of treatment with Avonex. Of the 281 patients who were neutralizing antibody-negative at baseline, 15 (5%) had at least one neutralizing antibody-positive sample over the 6-year extension. The neutralizing antibodies generally began to develop after approximately 6 months of treatment and reached a plateau at 12 to 18 months.

Of the 159 patients who received Betaseron prior to the extension study, 49 had detectable levels of neutralizing antibodies (titers ≥ 5) at baseline. Thirty-six of 39 Betaseron-treated patients became neutralizing antibody-negative, with median time to seroconversion of 6 months. Of the 77 patients who had received Avonex (phase III formulation), 11 had detectable levels of neutralizing antibodies (titers ≥ 5) at baseline.

Neutralizing antibodies were generally more persistent in patients with high titers than low titers. Among the 49 patients with low to medium titers (5–99), 44 patients (90%) seroconverted to neutralizing antibody-negative status over 6 years of treatment with Avonex. Of the 21 patients with high titers (≥ 100), only 7 patients (33%) became neutralizing antibody-negative. There were no seroconversions among the 6 patients with titers $> 1,000$. Patients who originally had low to medium titers of neutralizing antibodies to Avonex had generally more persistence of neutralizing antibodies, compared with neutralizing antibody-positive patients originally taking Betaseron and subsequently switching to Avonex. Four of five Avonex-treated neutralizing antibody-positive patients became neutralizing antibody-negative, but only after approximately 3 years.

The Role of Binding Antibodies

The Measurement of Antibodies Binding to Interferon Beta in Iranian Multiple Sclerosis Patients Treated with Interferon Beta.

Jamshid Lotfi, MD, Tehran University of Medical Sciences, Tehran, Iran and President of the Iranian Multiple Sclerosis Society

According to the preliminary results of an ongoing study, Avonex is considerably less immunogenic than Betaferon with respect to measurements of binding antibodies.¹⁶

The objective of the study was to determine the immunogenicity of interferon beta agents used in treating patients with MS. Sera were obtained from 60 patients treated with Avonex and 18 treated with Betaferon. Through enzyme-linked immunosorbent assay (ELISA) testing, binding antibodies were demonstrated in 22 of 60 patients (37%) treated with Avonex and 12 of 18 patients (67%) treated with Betaferon. Since the patients were tested only once for binding antibodies, and due to the limited sample size, the results could not be correlated with relapse rates; larger sample sizes would be required to demonstrate clinical correlation of binding antibodies.

“Some of these binding antibodies have a neutralizing characteristic. Our results show that Betaferon is more immunogenic than Avonex among Iranian multiple sclerosis patients, and this is compatible with prior studies in other countries,” advised co-investigator Farnaz Hooshmand, MD, Tehran University of Medical Sciences, Tehran, Iran.

Corroborating Comments from Dr. Pachner

In his satellite symposium presentation, Dr. Pachner discussed the issue of screening for binding antibodies in patients receiving interferon beta therapy. According to Dr. Pachner, binding antibody assays are an inexpensive screening modality that can, and probably should, be used for virtually all patients on interferon beta, since all are at risk for developing antibody-mediated decreased bioactivity. Avonex-treated patients, however, are of lesser priority in this regard because of their low incidence of neutralizing antibodies, Dr. Pachner added.

Dr. Pachner recommended screening patients with a binding assay at least twice, at 6 and 12 months after the first injection. Optimally, patients should also be screened at 3 months after initiation of therapy to identify, and potentially treat, patients who are rapidly developing high titers of antibodies. High binding antibody levels should be followed up by neutralizing antibody assays or bioactivity measurements. Those patients with neutralizing antibodies or reduced bioactivity should be retested in 3 months and if the pattern persists, treatment should be altered. On the other hand, in the majority of patients in whom the initial binding assays are below critical cutoffs, the patients and physicians can be confident that anti-interferon beta antibodies do not pose a problem.

Dr. Pachner concluded, “Immunogenicity of the interferon beta agent is one factor you should consider in selecting drugs for your patients.”

Treatment of Progressive Multiple Sclerosis with Mitoxantrone

Despite the use of disease-modifying therapies to treat MS, many patients will develop a progressive form of MS. Four years ago, the Food and Drug Administration (FDA) approved the chemotherapeutic agent mitoxantrone for the treatment of secondary-progressive MS,¹⁷ based on proven efficacy in reducing attack rates and delaying disease progression.¹⁸ Last year, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recommended the use of mitoxantrone for rapidly deteriorating MS patients.¹⁹

At the 14th Meeting of the European Neurological Society, several investigators reported encouraging results using

mitoxantrone as rescue therapy, and described various regimens with which this potent immunosuppressant can be safely and effectively used.

Effects of a Combined Mitoxantrone with Methylprednisolone Therapy on Primary and Secondary Progressive Multiple Sclerosis—an Interim Analysis.

Vera Carina Zingler, MD, Ludwig-Maximilians University, Munich, Germany

Vera Carina Zingler, MD, Ludwig-Maximilians University, Munich, Germany, reported on the clinical benefits of combining mitoxantrone with methylprednisolone for the treatment of MS,²⁰ a strategy that has been described previously as effective.²¹ Sixty-five patients with primary-progressive or secondary-progressive MS who had an EDSS of ≥ 0.5 on the Kurtzke scale (mean 0.7; range, 0.5–2.5) during the preceding 12 months participated in this prospective study. Treatment protocol consisted of 10 courses of intravenously administered methylprednisolone 500 mg on 5 successive days, plus mitoxantrone 10 mg/m² on Day 3 (using progressively longer treatment intervals for subsequent courses).

According to Dr. Zingler, 62 patients have been treated to date (18 with primary-progressive MS and 44 with secondary-progressive MS), having received between 4 and 10 courses of therapy. Overall, the EDSS has remained essentially unchanged in both patient groups. EDSS improved in 21 patients, remained unchanged in 30, and deteriorated in 11 patients by at least 0.5 points.

Dr. Zingler stated that most studies have been conducted in patients with secondary-progressive MS, but they observed patients with primary-progressive MS also respond to this therapy very well, and the addition of methylprednisolone appeared to help patients better tolerate mitoxantrone.

Mitoxantrone in Secondary Progressive Multiple Sclerosis: After or with Interferon Beta or Glatiramer Acetate.

Gulsen Akman-Demir, MD, Istanbul University, Istanbul, Turkey

Gulsen Akman-Demir, MD, Istanbul University, Istanbul, Turkey, reported on the use of mitoxantrone in 13 patients with secondary-progressive MS.²² Mitoxantrone was administered 8 to 12 mg/m² every 3 weeks for 6 cycles, then every 3 months for up to 28 months or to the maximum cumulative dose of 140 mg/m², after which there is a high risk of cardiotoxicity. All patients had exhibited disease progression despite previous disease-modifying therapy.

Alone or in combination with interferon beta or glatiramer acetate, mitoxantrone either stabilized or improved EDSS in most patients. Median EDSS was 6.25 pre-treatment and 6.0 post-treatment. All patients developed grade 1 hematologic toxicity, and in most cases grade 3 neutropenia (neutrophil count >500 to $<1,000/\text{mm}^3$) was observed (4 cases had grade 4 neutropenia, one with fever). Mitoxantrone was discontinued in one patient due to severe toxicity after one infusion and in another due to inconvenience (after 4 infusions), but most patients were able to remain on long-term treatment.

“To our knowledge, this is among the first studies in which mitoxantrone was combined with other immunomodulatory drugs. In most patients, treatment was well tolerated, with no increase in side effects with concomitant therapy,” remarked Dr. Akman-Demir. “At the recommended dose, mitoxantrone does not appear to produce cardiotoxicity.”

Mitoxantrone: Who to Treat with Which Dosage and Schedule.

Alessandra Lugaresi, MD, University of Chieti, Chieti, Italy

Italian investigators attempted to achieve higher response rates by modifying the mitoxantrone dosage in 51 patients with relapsing-remitting MS, secondary-progressive MS, and rapidly progressing primary-progressive MS.²³ Patients were initially treated with the FDA-approved dosing regimen of 12 mg/m² every 3 months. However, due to an

unsatisfactory early response, investigators modified the dosing regimen to 8 mg/m² once a month for 3 months, then 12 mg/m² every 3 months for 8 additional doses, for a cumulative mitoxantrone dose of 120 mg/m². After a severe relapse in one patient, investigators further modified the dosing regimen to 8 mg/m² every month for 3 months, then 8 mg/m² every 2 months for 14 total courses and a cumulative mitoxantrone dose of 112 mg/m². Intravenous methylprednisolone (1 gm) was added at every mitoxantrone infusion to reduce nausea and neutropenia and to enhance efficacy.

The final dosing schedule appeared to produce the most satisfactory results in terms of efficacy and toxicity, according to Alessandra Lugesesi, MD, University of Chieti, Chieti, Italy. “We recommend giving mitoxantrone 8 mg/m² every month for three months to stop the inflammation, then every two months to avoid neutropenia. In some very active patients, we titrate up to 140 mg/m², but we try to reserve a few courses in case we need to stop a significant exacerbation of the disease.”

Effects of Therapy on Attention and Cognition

Positive Effects of Interferon Beta-1a Therapy on Attention and Cognition.

Pasquale Calabrese, MD, PhD, Head of the Department of Neurology/Neuropsychology, Ruhr-University Bochum, Bochum, Germany

Treatment with Avonex aided several measures of attention and cognition in a study of 12 MS patients reported by Pasquale Calabrese, MD, PhD, Head of the Department of Neurology/Neuropsychology, Ruhr-University Bochum, Bochum, Germany.²⁴ The cognitive performance of the patients was measured at baseline (before Avonex treatment), and after 12 and 52 weeks of Avonex treatment. Results were compared with those of healthy, education-matched controls. Examiners developed a brief screening tool for cognitive dysfunction (the Multiple Sclerosis Inventory of Cognition) to identify patients for study inclusion. After study enrollment, investigators used several measures for general intellectual abilities, attention, and memory to evaluate changes between baseline and post-treatment levels.

No significant difference emerged between patients and controls on measures of general intellectual performance. MS patients treated with Avonex improved slightly from baseline to 1 year in terms of reaction-time latencies, and improved significantly in terms of alertness response. The alertness test required subjects to press a button after detecting a target on the computer screen, and in half the tasks the target was announced by an acoustical warning to elicit a reaction. Patients displayed a slight decrease in motor speed over time, but an improvement in alertness. Significant differences were also found in total number of recalled items, as well as interference and delayed recall, between baseline and post-treatment ($P < 0.05$ for all measures).

“Attentional functions seem to reflect the earliest cognitive changes. On the basis of our results, we may hypothesize that interferon beta-1a treatment exerts a beneficial effect on attention. Since disturbances of attention and memory have a strong impact on activities of daily living, one might expect that the neuronal stabilization of these core functions induced by interferon beta-1a may also have an overall beneficial effect on quality of life in multiple sclerosis patients,” summarized Dr. Calabrese.

Expression of Interferon Type 1 Receptor

Expression of Type I Interferon Receptor in Multiple Sclerosis Patients Treated with Different Interferon Beta Molecules.

Oscar Fernandez, MD, PhD, Hospital Regional University Carlos Haya, Milaga, Spain

Preliminary research presented by Spanish investigators suggests that some patients fail to fully respond to interferon beta therapy because they have reduced expression of an important interferon type 1 receptor.²⁵

The biological activity of interferon beta is exerted through the interferon type 1 receptor (IFNAR), which is composed of two subunits, IFNAR1 and IFNAR2, which help activate the intracellular signaling cascade. Deficiency of one or both of these subunits may lead to loss of interferon activity. This study examined the expression of these receptors in 189 patients with MS, including 46 patients treated with Avonex, 45 patients treated with Betaferon, 68 patients treated with Rebif, and 30 patients with no treatment. The study also included 21 healthy controls.

mRNA expression of IFNAR1 and IFNAR2 was assessed by real-time RT-PCR quantification in peripheral blood mononuclear cells. Results were expressed as a ratio of each gene with a housekeeping mRNA expression gene as a reference to normalize mRNA levels.

Results of the study indicated that the level of expression of IFNAR2 was significantly decreased in MS patients treated with interferon beta, compared with non-treated MS patients ($P = 0.004$) and healthy controls ($P = 0.001$). There were no significant differences between non-treated MS patients and controls. There were no differences in IFNAR1 and IFNAR2 expression between any of the interferon beta therapies.

“We concluded that there is a decrease in both IFNAR1 and IFNAR2 expression in multiple sclerosis patients versus healthy controls, and this decrease is greater in patients receiving interferon beta treatment,” stated Oscar Fernandez, MD, PhD, Hospital Regional University Carlos Haya, Milaga, Spain. “All the decreases were more marked with regard to IFNAR2 (versus IFNAR1) expression, which is the more important subunit for interferon beta interactions. The reduction in the expression of levels of IFNAR1 and IFNAR2 was similar between the different interferon beta molecules.”

Although this is a potentially exciting finding, it will need to be confirmed in other laboratories. Previous studies of a number of bioactivity markers, such as MxA and oligoadenylate synthetase that are transduced through the IFNAR, have revealed no significant differences in the upregulation of these markers after interferon beta injection in MS patients versus controls.²⁶ Thus, IFNAR function does not appear to be clearly different between healthy controls and MS patients. However, if confirmed, Dr. Fernandez’s study could lead to an understanding of important differences between MS patients and controls.

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Disclosure

Andrew R. Pachner, MD
Grant/Research Support—Berlex Laboratories, Inc., Biogen IdecTM, National MS Society, NIH; *Consultant*—Berlex Laboratories, Inc., Biogen IdecTM, Schering

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