

Evaluation of Beta Interferons for Multiple Sclerosis

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Multiple sclerosis (MS) is thought to be an immune-mediated inflammatory disease that results in demyelination in the white matter (the brain and spinal cord) of the central nervous system. It affects more than 400,000 people in the U.S. The disease is most often diagnosed between the ages of 20 and 40, and it affects more women than men.

Because no cure for MS exists at this time, the goals of therapy are to modify the course of the disease and to delay the progression of symptoms.¹ This article presents an evaluation and comparison of three available disease-modifying drugs (DMDs) used in the treatment of *relapsing–remitting* MS (RRMS):

- interferon β -1a (Rebif®, Serono)
- interferon β -1a (Avonex®, Biogen)
- interferon β -1b (Betaseron®, Berlex)

MECHANISM OF ACTION

Natural interferons help to modulate the immune system so that the body can fight disease, but the specific interferon-induced proteins and the exact mechanism by which recombinant interferons act in patients with MS are not completely understood. Interferon β mediates its biological response by binding to specific surface receptors in response to viral infections and other biological inducers. When this occurs, interferon β can alter the expression and response to surface antigens and can enhance immune cell response.

Interferon β -1a can induce expression of the following markers: 2',5'-oligoadenylate synthetase, β_2 -microglobulin, and neopterin.

Interferon β -1b can induce the expression of the following markers: 2',5'-oligoadenylate synthetase, protein kinase, and indoleamine 2,3-dioxygenase. The exact role of these markers in MS is unknown.²⁻⁴

DOSING

Rebif 44 mcg is given three times a week as a subcutaneous (SQ) injection; dose titration is required (Table 1).²

Avonex 30 mcg is given once a week as an intramuscular (IM) injection.³

Betaseron 250 mcg is given every other day by SQ injection.⁴

PHARMACOKINETICS

The pharmacokinetic information available is somewhat limited (see Table 1).

MONITORING PARAMETERS

The following monitoring parameters are required in addition to those parameters that are normally monitored in patients with MS:

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Rebif®

A complete blood count (CBC) and liver-function test should be monitored at one, three, and six months after initiation of therapy, then periodically thereafter. Thyroid function tests should be monitored every six months in patients with a history of thyroid dysfunction.²

Avonex®

A CBC with differential white blood cell (WBC) count and a platelet count should be monitored every six months, and blood chemistry profiles with liver-function tests should also be monitored every six months during therapy. No difference was noted between placebo and Avonex in clinical trials with regard to elevations in liver enzymes. During initiation of therapy, patients should be monitored if they have a history of congestive heart failure or cardiac disease, as recommended in postmarketing reports.³

Betaseron®

A CBC with a differential WBC count, along with hemoglobin and platelet counts, should be monitored before initiation of therapy and periodically thereafter (every three months). Blood chemistry profiles, including liver-function tests before initiation of therapy and periodically thereafter (three months), should also be monitored. If the absolute neutrophil count (ANC) drops below 750/mm³, therapy should be discontinued (although this decline did not occur in clinical studies). If the ANC does fall below 750/mm³, therapy should be restarted at 50% of the original dose after the ANC rises above 750/mm³.⁴

INDICATIONS

Indications are similar for the three agents. Rebif and Avonex are indicated for the treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and to delay the accumulation of physical disability. Their efficacy in chronic progressive MS has not been established.

Betaseron is indicated for ambulatory patients with RRMS to reduce the frequency of clinical exacerbations. Its safety and efficacy in chronic-progressive MS has not been evaluated.

CONTRAINDICATIONS AND WARNINGS

All three agents are contraindicated in patients with a history of hypersensitivity reactions to natural or recombinant interferon β , Albumin Human USP, or any other component of the formulation. Table 2 summarizes drug-specific warnings; Table 3 lists other precautions.

IMMUNOGENICITY

Rebif®

In the Prevention of Relapses and Disability by Interferon β -1a Subcutaneously in MS (PRISMS) trial, 23.8% of patients receiving 22 mcg and 12.5% of patients receiving 44 mcg developed neutralizing antibodies (NAbs) by the end of the study, which took place over two years.⁵

Beta Interferons for MS

Table 1 Pharmacokinetic Parameters of Interferons for Multiple Sclerosis

Parameter	Interferon β -1a (Rebif®, Serono)	Interferon β -1a (Avonex®, Biogen)	Interferon β -1b (Betaseron®, Berlex)
Dose	<ul style="list-style-type: none"> • Weeks 1–2: 8.8 mcg (20% target dose) • Weeks 3–4: 22 mcg (50% target dose) • Week 5+: 44 mcg • SQ injection three times a week 	30 mcg once-weekly intramuscular injection	250 mcg (8 million units) every other day by subcutaneous injection
Time to peak (hr)	14 hr	3–15 hr	1–8 hr
Half-life (hr)	69 hr	10 hr	8 min –4.3 hr

Data from Rebif®, Avonex®, and Betaseron® package inserts.

Avonex®

In the phase III clinical study, 14% of patients receiving Avonex developed NABs by week 52, 21% by week 78, and 22% by week 104. NABs were detected in 4% of patients in the placebo group but always disappeared upon retesting. When a cut-off value was set so that no patients receiving placebo were included, 15% of patients receiving Avonex had NABs.⁶

Betaseron®

In the clinical study summarized in this article, NABs were detected in 11% of the patients receiving placebo, in 47% of the patients receiving 1.6 million units of Betaseron, and in 45% of the patients receiving 8 million units of Betaseron.⁷

ADVERSE DRUG REACTIONS

The most frequently occurring adverse drug reactions (ADRs) are listed next for each agent. A complete list of ADRs appears on the package insert.

Rebif®

The most common ADRs, when compared with those from placebo, include injection-site reactions, flu-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematological abnormalities, such as a decrease in WBC count, neutrophils, and lymphocytes. Psychiatric disorders were the most frequently reported serious ADRs.²

Avonex®

The most common ADRs, when compared with those from placebo, included flu-like symptoms, muscle aches, fever, chills, asthenia, and anemia. Although allergic reactions and liver abnormalities are not mentioned in the warnings, these reactions have been reported in association with similar interferon products and there is a possibility of their occurrence with Avonex.³

Betaseron®

The most common ADRs, when compared with those from placebo, include flu-like symptoms, injection-site reactions, injection-site necrosis, palpitations, hypertension, tachycardia,

peripheral vascular disorders, gastrointestinal disorders, an ANC below 1,500/mm³, a WBC count below 3,000/mm³, a baseline serum glutamate pyruvate transaminase (SGPT) level above 5, a total bilirubin concentration above 2.5 at baseline evaluation, somnolence, dyspnea, laryngitis, menstrual disorders, cystitis, breast pain, pelvic pain, myalgia, sweating, malaise, and menorrhagia.⁴

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with interferon β therapy. If beta interferons are given in combination with myelosuppressive agents, patients should be monitored appropriately to assess the possibility of additive effects on hematological abnormalities.

DRUG STORAGE AND ADMINISTRATION

Rebif®

Rebif is available in prefilled syringes. The needles are already attached to the syringe.

Rebif should be stored in the refrigerator, and the syringe should be removed from the refrigerator 30 minutes before injection to reduce injection-site reactions. The drug does not need to be mixed or prepared before injection. It can be self-administered by SQ injection or by using the autoinjector Rebiject®.

Injections should be given three times a week at least 48 hours apart and, if possible, at the same time of day. Rebif can be given in the thigh, hip, stomach, or upper arm. Sites should be rotated for each injection.⁸

Avonex®

Avonex is available as a powder for reconstitution. For every injection, a vial of Avonex powder, a vial of diluent (sterile water) for reconstitution, a syringe, a Micro Pin, a sterile needle, alcohol wipes, and a gauze pad are required.

The drug should be stored in the refrigerator, and the reconstituted product should be used within six hours. The syringe should be removed from the refrigerator 30 minutes before injection time.

Beta Interferons for MS

Table 2 Warnings Associated with Interferons β -1a and 1b

Warning	Rebif® (Serono)	Avonex® (Biogen)	Betaseron® (Berlex)
Depression*	✓ ¹	✓ ⁵	✓ ⁶
Hepatic toxicity	✓ ²		
Anaphylaxis	✓ ³		
Albumin (human)	✓ ⁴		
Injection-site necrosis			✓ ⁷

* An increased incidence of depression, suicidal ideation, and suicidal attempts has been reported in patients taking interferon agents. Prescribe with caution, because depression is common in patients with multiple sclerosis (MS).

¹ An increased incidence has been reported with Rebif.

² Rebif can cause symptomatic hepatic dysfunction (primarily jaundice) as a rare complication. Elevations in hepatic transaminases, especially serum glutamate pyruvate transaminase (SGPT), have been reported. Prescribe with caution in patients with active liver disease, alcohol abuse, and increased SGPT levels (above 2.5 times the upper limits of normal) or with a history of significant liver disease. The dose should be reduced if the SGPT is increased more than 5 times the upper limits of normal. Fulminant hepatic failure requiring liver transplantation has been reported from a non-U.S. postmarketing service in a patient who was also taking another potentially hepatotoxic agent.

³ Anaphylaxis is a rare complication of Rebif therapy. Mild to severe skin rashes and urticaria have also occurred, without regard to dose or duration. Allergic reactions can occur after prolonged use.

⁴ Because Rebif contains human albumin, there is a remote risk of transmission of a viral disease.

⁵ Prescribe Avonex with caution, although no relationship has been established between the occurrence of depression and suicidal ideation in patients taking this drug. There was an equal incidence of depression in clinical trials with placebo and Avonex.

⁶ Prescribe Betaseron with caution; one suicide and four suicide attempts have been documented in patients taking this agent over three years.

⁷ Injection-site necrosis occurred in 5% of patients in clinical studies; it typically appears during the first four months of therapy but can also occur up to one year after initiation of therapy. If this reaction occurs and an open wound has developed, take precautions to prevent infection.

Data from Rebif®, Avonex®, and Betaseron® package inserts.

The drug can be self-administered once weekly by IM injection in the anterior or posterior thigh.⁹

Betaseron®

The drug is available as a powder for reconstitution. A vial of diluent (sodium chloride 0.54%), a vial of Betaseron powder, a syringe, a needle, and alcohol wipes are needed for every injection.

Betaseron can be stored at room temperature. The reconstituted product should be used immediately. If the drug is not used immediately, it should be refrigerated and used within three hours.

Betaseron can be self-administered every other day by SQ injection. It can be injected into the abdomen, the thighs, the back of the arms, and the buttocks.¹⁰

COST

Table 4 presents an example of comparison of costs of interferons used in the treatment of MS.¹¹

CLINICAL STUDIES

Rebif® (The PRISMS Study)⁵

Objective. To determine the safety and efficacy of Rebif versus placebo in patients with RRMS

Study Design/Patient Population. This randomized, double-blind, placebo-controlled study involved 560 patients from 22 centers with a clinically definitive or laboratory-supported diagnosis of MS for at least one year.

Inclusion Criteria

- At least two relapses in the preceding two years
- Expanded Disability Status Scale (EDSS) scores of 0 to 5.0
- Age of enrollees: 18 to 50 years

Exclusion Criteria

- Any previous systemic treatment with interferons, lymphoid irradiation, or cyclophosphamide (Cytosan®)
- Any previous treatment with other immunomodulatory or immunosuppressive treatment in the preceding 12 months

Endpoints

Primary efficacy endpoint. To determine the relapse count over the course of the study (the number of clinical exacerbations)

Other efficacy endpoints. The time to first and second relapse, the proportion of relapse-free patients, the progression in disability (an increase in EDSS scores by at least one point for three months), the ambulation index, the arm-function index, the need for steroid therapy and hospital admission, the extent of disease activity under magnetic resonance imaging (MRI), and the burden of disease.

Treatment Regimen. Patients were randomly assigned, in a 1:1:1 ratio, to receive placebo (187), Rebif 22 mcg (189), or Rebif 44 mcg (184) by SQ injection three times a week. Acetaminophen (Paracetamol) could be used prophylactically for flu-like symptoms, and relapses could be treated with steroids for three days.

Results. See Table 5.

Beta Interferons for MS

Table 3 Precautions in Prescribing Interferons

Precaution	Rebif® (Serono)*	Avonex® (Biogen)†	Betaseron® (Berlex)‡
Impairment of infertility	No changes observed in estradiol levels or menstrual cycle. No changes noted in sperm count, motility, morphology, or function in animal studies.	Only data from animal studies available. Menstrual irregularities, anovulation, and decreased serum progesterone levels noted in monkeys with doses 100 times the recommended human dose.	No data available in humans. No change in menstrual cycle or hormone levels observed in animals.
Pregnancy	Category C	Category C	Category C
Seizures	Use caution in patients with a pre-existing seizure disorder. Seizures associated with interferon therapy. No correlation between seizures and Rebif therapy.	Seizures in four patients in Avonex group but no seizures in patients in placebo group. Use caution in patients with a history of a seizure disorder.	—

* Data from Rebif® (interferon β -1a) package insert. Rockland, MA: Serono, Inc.; August 2002.

† Data from Avonex® (interferon β -1a) package insert. Cambridge, MA: Biogen, Inc.; April 2000.

‡ Data from Betaseron® (interferon β -1b) package insert. Richmond, CA: Berlex Laboratories; January 2002.

Conclusion. SQ interferon β -1a appeared to be effective in the treatment of RRMS by reducing exacerbations and by delaying the progression of disability over two years in a dose-related manner. Therapy was well tolerated.

Evaluation

Unlike the Avonex study,⁶ the Rebif trial resulted in a significant reduction in EDSS progression and in stage T2 lesion burden.

Overall, this was a well-designed study that maintained a good sample size because of a low dropout rate.

Avonex®: The IM Interferon β -1a Study⁶

Objective. To determine whether interferon β -1a could slow the progressive, irreversible, and neurological disability of RRMS

Study Design/Patient Population. This randomized, double-blinded, placebo-controlled study involved four clinical centers. The original number of patients required to meet an 80% power was calculated to be 301; because of the low dropout rate, however, it was determined that enrollment could be closed at 288 patients and the study could be ended approximately one year early. At the time, 301 patients had already been enrolled but the study was stopped early.

Inclusion Criteria

- A definitive diagnosis of MS for at least one year
- Baseline EDSS scores ranging from 1.0 to 3.5
- At least two documented exacerbations of MS in the previous three years
- No exacerbations for at least two months at enrollment
- Age of enrollees: 18 to 55 years

Exclusion Criteria

- Any prior immunosuppressant or interferon therapy, adrenocorticotrophic hormone (ACTH), or corticosteroid treatment within two months of screening
- Pregnant or nursing women; patients who were unwilling to practice contraception

- Presence of chronic-progressive MS or any other disease compromising organ function

Endpoints

Primary efficacy endpoints. To determine the time to onset of sustained disability progression, defined as deterioration from baseline evaluation by at least 1.0 point on the EDSS persisting for at least six months

Secondary efficacy endpoints. Frequency of exacerbations, results of MRI scans, two upper limb and three lower limb function tests

Treatment Regimen. Patients were randomly assigned, in a 1:1 ratio, to receive Avonex 30 mcg (n = 158) or placebo (n = 143) by IM injection once a week for up to two years. Acetaminophen 650 mg was given before and for 24 hours after each injection to decrease side effects. Steroids could be used for exacerbations.

Results. See Table 6.

Table 4 Typical Costs of Interferons

Product	Hospital Expense
Rebif® (Serono) One prefilled syringe, 44 mcg	\$86.58
Avonex® (Biogen) One vial, 33 mcg; one 10-ml vial of diluent, two alcohol wipes, one gauze pad, one 3-ml syringe, one Micro Pin, one needle, and one adhesive bandage	\$199.81
Betaseron® (Berlex) 0.3-mg/vial, including diluent	\$62.38
Data from Huntsville Hospital, Pharmacy Department, Huntsville, AL.	

Beta Interferons for MS

Table 5 Results of the PRISMS Study

Endpoints	Placebo	Interferon β -1a (Rebif® , Serono) (22 mcg)	Interferon β -1a (Rebif®, Serono) (44 mcg)
Primary efficacy endpoint			
Mean number of relapses per patient over two years	2.56	1.82*	1.73*
Secondary efficacy endpoints			
Median time to first relapse compared with placebo‡	—	Delayed 3 months	Delayed 5 months
Mean change in EDSS score	0.48	0.23†	0.24†
Proportion of relapse-free patients	16%	27%†	32%*
Mean time to sustained progression in disability for all patients Ψ	11.9 months	18.5 months§	21.3 months§
Mean number of steroid courses	1.39	0.97†	0.75*
Mean number of hospital admissions	0.48	0.38	0.25*
Burden of disease measured by T2 MRI (median)	10.9%	-1.2%¶	-3.8%¶
<p>* $P < .005$ compared to placebo. † $P < .05$ compared to placebo. ‡ After the first year of treatment, relapse rates were 33% and 37% lower in the 22-mcg and 44-mcg groups, respectively, with $P < .0001$. § $P < .05$ compared to placebo. ¶ $P < .0001$ compared to placebo. Ψ For the subset of patients with an EDSS score above 3.5, only the 44-mcg was significant compared with placebo; $P < .05$. EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; PRISMS = Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in MS. Data adapted from PRISMS Study Group. <i>Lancet</i> 1998;352:1498–1504.⁵</p>			

Conclusion. Interferon β -1a had a significant beneficial effect on RRMS by reducing the accumulation of permanent physical disability, the frequency of exacerbations, and the presence of disease activity.

Evaluation

The study was stopped approximately one year early; only a subset of patients (172) completed the full two years.

A statistical difference was not seen with regard to median time until the first exacerbations, as well as percentage change in T2 lesion volume, occurred at year two.

Because of the small number of patients, it is difficult to determine the true benefit in all endpoints.

Baseline EDSS scores, between 1.0 and 3.5, included patients with greater impairment than disability. Thus, even though there was a significant difference, it is unclear how to interpret this endpoint with regard to disability.^{12,13}

Betaseron®: The IFN- β (Interferon beta) MS Study⁷ and the Paty-MS/MRI Study¹⁴

Objective. To determine the safety and efficacy in patients with RRMS

Study Design/Patient Population. This randomized, double-blind, multicenter, placebo-controlled trial involved 372 patients in 11 centers. Two identical studies were conducted,

one in the U.S. and one in Canada.

Inclusion Criteria

- A clinical or laboratory definitive diagnosis of RRMS for at least one year
- EDSS scores between 0 and 5.5
- At least two exacerbations in the previous two years, with patients clinically stable for at least 30 days and with no steroid intake before enrollment in the study
- Age of enrollees: 18 to 50 years

Exclusion Criteria. Any previous treatment with azathioprine (Imuran®, Prometheus) or cyclophosphamide

Endpoints

Primary efficacy endpoints. To determine the rate of annual exacerbations as well as the proportion of patients who were exacerbation-free at the end of the study

Secondary efficacy endpoints. The number of days until the first exacerbation, duration and severity of exacerbations, changes in EDSS and Neurologic Rating Scale (NRS) scores from baseline values, the burden of disease as determined by annual MRI examinations, and extent of disease activity as measured by MRI in a substudy

Treatment Regimen. Patients were randomly assigned to receive placebo ($n = 123$), interferon β 1.6 million units ($n = 125$), or interferon β 8 million units ($n = 124$). Study drugs were

Beta Interferons for MS

given by SQ injection every other day.

Results. See Table 7.

Conclusion. Treatment with Betaseron resulted in significant reductions in the rate and severity of exacerbations and in the accumulation of MRI abnormalities. Betaseron was generally well tolerated. Its power to delay disability did not reach statistical significance.

Evaluation

The number of patients who were exacerbation-free at three years did not maintain statistical significance.

Because a change in EDSS scores did not reach statistical significance, a delay in progression could not be distinguished.

Although the exact significance of NABs is unknown, it is thought these antibodies might lessen the drug's action. The likelihood of developing NABs is higher with Betaseron than with the other two agents.

COMPARATIVE STUDIES

Evidence for Interferon Dose-Response:

European–North American Comparative Efficacy Trial (The EVIDENCE Study)

Because data from the trial are not yet available, the following information has been derived from Rebif full prescribing information and from Serono (www.rebif.com).^{15,16}

Objective. For Rebif to be marketed in the U.S., it had to show superiority over Avonex because of its orphan drug status; thus, the trial compared these two agents head to head.

Study Design/Patient Population. Serono sponsored this prospective, randomized, open-label, assessor-blinded study, which included 339 patients in the Rebif group and 338 patients in the Avonex group. The trial period was 48 weeks and involved 56 centers in the U.S.

Inclusion Criteria

- Patients who had not received earlier interferon therapy
- EDSS scores ranging from 0 to 5.5

Table 6 Study Results for Interferon β -1a (Avonex®)

Endpoints (All Patients Using All Data)	Placebo	Avonex® (Biogen) (30 mcg)
Primary efficacy endpoints		
Time to sustained progression of disability	—	Ψ ,*
Probability of the percentage of patients progressing at week 104	34.9%	21.9%
Secondary efficacy endpoints		
Mean change in EDSS score versus baseline score:		
• Unsustained (n = 87, n = 83)	0.74	0.25*
• Sustained (n = 56, n = 55)	0.61	0.02*
Frequency of exacerbations (annual exacerbation rate) for all patients	0.82	0.67†
Median time to first exacerbation	47.3 wk	36.1 wk $\Psi\Psi$
Results of MRI scan:		
• Mean number of lesions per patient		
▪ Year one (n = 123, 134)	1.59	1.04*
▪ Year two (n = 82, 83)	1.65	0.80‡
• Mean volume of lesions per patient		
▪ Year one	96.5	70.0*
▪ Year two	122.4	74.1§
• Percent change in T2 lesion volume		
▪ Year one (n = 116, 123)	−3.3%	−13.1%*
▪ Year two (n = 83, 81)	−6.5%	−13.2%◆◆

Ψ Treatment with Avonex significantly increased the time to sustained progression of disability compared with placebo.

* $P = .02$.

† $P = .04$.

‡ $P = .05$.

§ $P = .03$.

$\Psi\Psi$ $P = .34$.

◆◆ $P = .36$.

EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging.

Data adapted from Avonex® (interferon β -1a) package insert. Cambridge, MA: Biogen, Inc., April 2002.

Beta Interferons for MS

- At least two exacerbations of MS in the preceding two years
- Age of enrollees: 18 to 55 years

Endpoints

Primary efficacy endpoint. To compare the proportion of patients who were relapse-free at 24 and 48 weeks

Other efficacy endpoints. The rate of occurrence of first relapse along with several MRI measurements, including an assessment of brain lesions

Results. See Table 8.

Safety. According to the trial summary, the overall side-effect profile was similar for both groups of patients. Each group experienced common side effects, such as flu-like symptoms and muscle aches, with comparable frequency. Certain ADRs were significantly greater in the Rebif group, although they did not affect the number of patients who discontinued therapy because of the ADRs: injection-site reactions (80% vs. 24%), liver-function abnormalities (14% vs. 7%), and leukopenia (3% vs. less than 1%).²

Conclusion. Treatment with Rebif was superior to that with Avonex.

Evaluation

The study results are in abstract form only, and the information available for evaluation is limited.

On the basis of this study, the Food and Drug Administration (FDA) approved Rebif in March 2002.

Independent Comparison of Interferons (The INCOMIN Study)¹⁷

Objective. To compare the clinical and MRI benefits of alternate-day interferon β -1b (Betaseron) 250 mcg with once-weekly interferon β -1a (Avonex) 30 mcg.

Study Design/Patient Population. This two-year prospective, randomized, multicenter, open-label, parallel-group study involved 188 patients with RRMS at 15 centers. The Italian Ministry of Health and the Italian MS Society funded the study.

Inclusion Criteria

- A clinical definitive diagnosis of RRMS
- Baseline EDSS scores between 1 and 3.5
- Two documented relapses during the preceding two years
- No relapses or any corticosteroid treatment for at least 30 days before entry into the study
- Age of enrollees: 18 to 50 years

Exclusion Criteria

- Any previous systemic treatment with interferon β or therapy with other immunomodulatory drugs (except corticosteroids)
- Pregnant and lactating women; patients unwilling to practice acceptable birth control
- Patients with a diagnosis of Major Depression or a history of a suicide attempt
- Clinically significant heart, liver, renal, or bone marrow disease

Endpoints

Primary efficacy endpoints. The proportion of patients free from relapse and the proportion of patients without any new T2 lesions, as demonstrated by MRI

Secondary efficacy endpoints. Annual relapse rate, annual treated relapse rate, proportion of patients who were free from (and time until) sustained and confirmed progression in disability, and a change in EDSS scores

Treatment Regimen. Patients were randomly assigned to self-administer either Betaseron 250 mcg SQ every other day (n = 96) or Avonex 30 mcg IM once weekly (n = 92). Para-

Table 7 Data from a Two-Year Trial of Interferon β -1b (Betaseron®)

Endpoints	Placebo	Betaseron® (Berlex) (1.6 Million Units)	Betaseron® (Berlex) (8 Million Units)
Primary efficacy endpoints			
Annual exacerbation rate	1.27	1.17*†	0.84‡
Exacerbation-free patients	18	23§	36¶
Secondary efficacy endpoints			
Median time to first exacerbation (days)	153	153	295#
Change in EDSS score (confirmed)	NSC	180	NSC
Median number of active lesions per year	3.0	NSC	0.5Δ
Mean change in volume of T2 lesions at year oneΔΔ	12.2%↑		1.1%↓

*P = .01 compared with placebo.

†P = .0086 when comparing 1.6 million units (0.25 mg) with 8 million units (0.05 mg).

‡P = .0001 compared with placebo.

§P = .076 compared with 8 million units.

¶P = .007 compared with placebo at two years but not significant at three years.

#P = .015 compared with placebo.

ΔP < .009.

ΔΔP < .001.

EDSS = Expanded Disability Status Scale; NSC = no significant change compared with baseline at year three; P = .16.

Data adapted from Betaseron® (interferon β -1b) package insert. Richmond, CA: Berlex Laboratories; January 2002.

Beta Interferons for MS

Table 8 Results of the EVIDENCE Study

Endpoints	Rebif® (Serono) 44 mcg (Three Times Weekly)	Avonex® (Biogen) 30 mcg (Once Weekly)
Primary endpoints Proportion of patients who are relapse-free • 24 weeks (n =339, 338) • 48 weeks	75%* 62%†	63% 52%
Secondary endpoints Rate of first relapse Median number of MRI unique lesions per scan at 24 wk (n = 325, 325)	HR = 0.70‡ 0.17*	HR = 0.70 0.33
* $P < .001$. † $P = .009$. ‡ $P = .003$. EVIDENCE = Evidence for the Interferon Dose Response: European–North American Comparative Efficacy Study; HR = hazard ratio; MRI = magnetic resonance imaging. Data from Rebif® package insert, Rockland, MA: Serono; ² and www.noonanrusso.com/news/serono02/news/sero04.16.html . ¹⁵		

cetamol (four doses of 500 mg/day) was given as prophylactic therapy for fever or flu-like symptoms. Treatment with high-dose methylprednisolone (Medrol®, Pharmacia & Upjohn), 1 g/day for five to 10 days, was initiated during relapses.

Results. See Table 9.

Safety. More patients in the Betaseron group than in the Avonex group discontinued therapy because of ADRs ($P = .015$). Injection-site reactions were significantly more frequent in the Betaseron group than in the Avonex group ($P < .001$).

Conclusion. Every-other-day dosing with Betaseron was more effective than once-weekly dosing with Avonex.

Evaluation

Because the evaluating physician was not blinded for clinical outcomes, the possibility of bias existed; however, MRI findings were assessed in a blinded fashion.

Baseline EDSS scores, between 1 and 3.5, were more a measure of impairment than of disability.

A small number of patients participated in the study.

EVALUATION OF THE LITERATURE

The clinical trials summarized in this evaluation were chosen because they were the most reliable studies and involved direct comparisons that were presented to the FDA for drug approval. Several other articles were evaluated to suggest the most appropriate agent for inclusion on the hospital formulary.

The long-term efficacy of DMDs has become important because MS is a chronic disease. With most clinical trials evaluating patients for one to two years, follow-up of these trials was conducted to ensure that the efficacy of interferons was main-

tained in these patients. The PRISMS Rebif (PRISMS-4) Trial¹⁸ was continued for four years and showed a dose-related response to several of the endpoints. The clinical and MRI benefits with Rebif were maintained.

The development of persistent NABs in 14.3% of the patients in the 44-mcg group led to a decrease in drug efficacy in this subset of patients.¹⁸ Researchers have monitored patients taking Betaseron for 12 years, and efficacy has been maintained with a decrease in side effects. The incidence of NABs appears to be higher during the first year of therapy and tends to decrease with continued therapy.¹⁹ In clinical trials, both Avonex and Rebif have delayed the development of a definitive diagnosis of MS in high-risk patients.

One article that has addressed several topics, including NABs and bioavailability,²⁰ indicates that the risk for development of persistent NABs is 2% with Avonex, 15% with Rebif, and 31% with Betaseron. Because there is a concern that the development of NABs can reduce the long-term efficacy by blocking the drug's action, more long-term data should help to determine the significance of this finding.

Information on the bioavailability of the three interferons was limited until Bertolotto and colleagues developed a technique that measured myxovirus A (MxA) messenger ribo-

Table 9 Results of the INCOMIN Study

Endpoints	Betaseron (Berlex)® (250 mcg)	Avonex® (Biogen) (30 mcg)
Primary efficacy endpoints		
Proportion of patients who are relapse-free	49*	33
Proportion of patients without new T2 lesions	55%†	26%
Secondary efficacy endpoints		
Mean annual relapse rate	0.5*	0.7
Annual treated relapse rate	0.38‡	0.5
Number of progressed patients	13%§	30%
Time to sustained and con- firmed disability progression		$P < .01$
Mean EDSS score at 24 months	2.1¶	2.5
* $P = .03$ in favor of Betaseron. † $P < .001$. ‡ $P = .09$. § $P = .005$. ¶ $P = .004$. EDSS = Expanded Disability Status Scale; INCOMIN = Independent Comparison of Interferons. Data adapted from Durelli L, Verdun E, Barbero P, et al. <i>Lancet</i> 2002;359:1453–1460. ¹⁷		

Beta Interferons for MS

Table 10 Comparison of Interferons β -1a (Rebif® and Avonex®)

	Rebif® (Serono)	Avonex® (Biogen)
Administration • Frequency • Administration time	<ul style="list-style-type: none"> • Three times a week • Need not be prepared before administration 	<ul style="list-style-type: none"> • Once a week • Must be prepared before administration
Storage	Refrigerator	Refrigerator
EDSS scores used in placebo studies	1–5	1–3.5
Persistent NABs	15%	2%
ADRs • Injection-site reactions • Liver abnormalities • Leukopenia	Overall, ADRs were similar • 80% • 14% • 3%	Overall, ADRs were similar • 24% • 7% • <1%
Clinical superiority	See EVIDENCE study	See EVIDENCE study
Bioavailability	Interferon levels stayed above threshold longer than with Avonex	Interferon levels dropped below threshold value by the end of week
Costs for one injection	\$86.58	\$199.81
ADR = adverse drug reaction; EDSS = Expanded Disability Status Scale; EVIDENCE = Evidence for the Interferon Dose Response: European–North American Comparative Efficacy; NAB = neutralizing antibody.		

nucleic acid (mRNA). MxA mRNA represents the level of active interferon in the bloodstream, although a correlation between bioavailability and clinical response has not been established.

The Bertolotto study involved 115 patients with RRMS to determine the bioavailability of Avonex, Rebif, and Betaseron.²¹ Sixty-three percent of the patients were new to interferon therapy, so that the upper threshold MxA mRNA value could be determined to allow comparisons between treatment groups; this threshold value was measured to be 133. The remaining 37% included patients previously receiving interferon therapy with Avonex (n = 10%), Rebif (n = 17%), and Betaseron (n = 10%).

The patients in each interferon group received the standard FDA-approved dose, starting on a Monday. MxA mRNA levels were measured every 24 hours Monday through Friday. MxA mRNA levels increased in all three groups on Tuesdays and declined on Wednesdays. In the Rebif and Betaseron groups, levels rose again on Thursdays; in the Avonex group, the levels dropped below threshold (in NAB-negative patients). Both Rebif and Betaseron were administered multiple times during the week, and Avonex was administered once a week. At all times, MxA mRNA levels in the NAB-positive patients were consistently lower than in the NAB-negative patients. From these data, it was determined that bioavailability was higher in the interferons that were given more frequently (Rebif and Betaseron).

CONCLUSION

The three interferon agents described in this article have been efficacious in patients with RRMS. The interferons that are given more frequently (Rebif and Betaseron) produce higher MxA mRNA levels (correlates with interferon blood concentrations) in the body than the interferon that is given once a week. Although the ongoing study—which is expected to determine whether interferon bioavailability correlates with clinical response—has not been completed, the two agents that have higher bioavailability have demonstrated superior efficacy in comparative trials.

Rebif® vs. Betaseron®

In evaluations of efficacy for possible inclusion on the formulary, Rebif and Betaseron have demonstrated a higher efficacy rate than Avonex. Compared with Avonex and Rebif, Betaseron is associated with a higher rate of development of persistent NABs (31%), which can decrease long-term efficacy; dosing is also required most frequently for this drug (Table 10). The placebo-controlled study⁷ involving Betaseron did not meet clinical significance with regard to delaying disability; Betaseron also tended to produce more ADRs.

The Rebif PRISMS Trial (PRISMS-4)¹⁸ is the only study that has demonstrated a statistically significant reduction in EDSS scores and in T2 lesion volume. As a result of more convenient dosing and the other reasons discussed earlier, Rebif would be the most appropriate choice as the first-line therapy in this drug class.

Beta Interferons for MS

Avonex®

To determine the formulary status of Avonex, it is helpful to consider the drug's advantages and disadvantages. The drug's efficacy was established in a placebo-controlled trial in which Avonex was shown to reduce the accumulation of permanent physical disability, the frequency of exacerbations, and the presence of disease activity.⁶ In the EVIDENCE Study of Avonex and Rebif,^{2,15,16} several ADRs occurred at a higher rate (see Table 10) in the patients receiving Rebif than in those receiving Avonex, but this did not lead to a significant change in the dropout rate; 93% in the Rebif group and 94% in the Avonex group completed the trial. Outcomes from this head-to-head trial are reported from data after 48 weeks of therapy. Long-term data are essential to determine whether Rebif can maintain clinical superiority.

Recommendations

From an evaluation of the literature, it is recommended that Rebif be added to the hospital formulary as the agent of choice in this therapeutic class of interferons. Avonex should be available upon request for:

- patients who are at an increased risk for hepatic abnormalities or for psychiatric disorders
- patients who have developed persistent NABs while taking Rebif
- patients who cannot tolerate Rebif therapy

Betaseron should not be considered for inclusion on the formulary (see Rebif vs. Betaseron earlier).

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