Interferon β-1a in the Treatment of Multiple Sclerosis
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Multiple sclerosis (MS) is a progressive, debilitating illness that affects the nerve cells in the brain and spinal cord. It is presumed to be an autoimmune disorder of the central nervous system (CNS) that results in acute focal inflammatory demyelination and axonal loss with limited remyelination, culminating in chronic multifocal sclerotic plaques. This leads to a disruption of nerve signals within the CNS, causing symptoms that may affect vision, sensation, and body movements.

The disease affects twice as many women as men, with an estimated incidence of seven people per 100,000 annually. The prevalence is approximately 120 people per 100,000, and the lifetime risk is one person in 400. It is the most common nerve disorder in young people and affects more than one million young adults worldwide. The familial recurrence rate is approximately 15%. MS seems to be genuinely polygenic; however, the distribution of MS cannot be explained on the basis of population genetics alone. Although there appears to be a genetic predisposition, no single MS gene has been identified.

In about 25% of patients, MS does not affect activities of daily living; conversely, up to 15% of patients become severely disabled within a short time. The life expectancy varies according to the degree of disease progression and the individual. Overall life expectancy is usually at least 25 years from disease onset.

MS is difficult to diagnose and poses a challenge to many physicians. The symptoms of MS are similar to those of other autoimmune disorders and include blurred vision, slurred speech, trembling of the hands, muscle weakness, and unsteady gait, among others. In addition to the many different clinical symptoms experienced by patients, the course of MS can follow several different patterns throughout a patient’s life. The three most common patterns are as follows:

- Relapsing-remitting MS (RRMS). Relapses are followed by periods of recovery. For most patients with this form of MS, this phase evolves into the secondary, or progressive, stage of the disease.
- Primary-progressive MS (PPMS). Patients experience steady deterioration with no episodes of relapses or remissions. This form of MS affects approximately 10% of patients.
- Secondary-progressive MS (SPMS). Patients experience continuous neurological worsening, with or without superimposed relapses.

Although there is no cure for MS, there are treatment options to alleviate symptoms, to prevent relapses, and to reduce the severity of relapses. Antidepressants are used to improve the mental health of MS patients; diazepam (Valium®, Roche) and baclofen are commonly used to relieve muscle tightness and spasms. Corticosteroids and interferons are used to treat relapses. Interferons are the first-line drugs of choice for RRMS.

**CLINICAL PHARMACOLOGY**

Interferons are naturally occurring proteins that demonstrate immunomodulatory, antiviral, and antiproliferative biological activities. They exert their biological effects by binding to specific receptors on the surface of cells. The binding of interferon beta to its receptors initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers, including 2,5'-oligoadenylate synthetase, β₂ microglobulin, and neopterin, which may mediate some of the biological activities. The specific interferon-induced proteins and the mechanisms by which interferon β-1a exerts its effects in MS have not been fully defined.

**PHARMACOKINETICS**

In healthy volunteer subjects, a single subcutaneous injection of 60 mcg of interferon resulted in a peak serum concentration (Cₚ) of 5.1 ± 1.7 International Units (IU)/ml (mean ± SD), with a median time of peak serum concentration (Tₚ) of 16 hours. The serum elimination half-life (tₑ) was 69 ± 37 hours, and the area under the serum concentration versus the time curve (AUC), from zero to 96 hours, was 294 ± 81 IU·hours/ml. Following subcutaneous injections in healthy volunteer subjects every other day, an increase of approximately 240% in the AUC was observed, suggesting that accumulation of interferon β-1a occurs via genetically engineered Chinese hamster ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of interferon β-1a is identical to that of natural fibroblast-derived human interferon beta. Natural interferon beta and interferon β-1a are glycosylated, with each one containing a single N-linked complex carbohydrate moiety.

**DESCRIPTION**

Interferon β-1a (Rebif®, Serono) is a purified, 166-amino-acid glycoprotein with a molecular weight of approximately 22,500 daltons. The interferon is produced by recombinant DNA technology using genetically engineered Chinese hamster ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of interferon β-1a is identical to that of natural fibroblast-derived human interferon beta. Natural interferon beta and interferon β-1a are glycosylated, with each one containing a single N-linked complex carbohydrate moiety.

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after repeated administration. The total clearance is approximately 33 to 55 liters/hour.

The pharmacokinetic parameters of interferon β-1a in children, geriatric patients, and patients with renal or hepatic insufficiency have not been established.4

ADVERSE REACTIONS

The most commonly reported adverse reactions after administration of interferon were injection-site disorders; influenza-like symptoms such as headache, fatigue, fever, rigors, chest pain, back pain, myalgia, and abdominal pain; depression; elevation of liver enzymes; and hematological abnormalities.4

**DOSE AND ADMINISTRATION**

The recommended dosage of interferon β-1a is 44 mcg, injected subcutaneously three times per week. If possible, the drug should be administered at the same time on the same three days (i.e., Monday, Wednesday, Friday) at least 48 hours apart each week. Generally, the dose should be started at 8.8 mcg subcutaneously three times weekly and increased over a four-week period to 44 mcg three times weekly. Leukopenia or elevated liver-function test values may warrant dose reductions of 20% to 50% until toxicity is resolved.4

The drug is available as a sterile, preservative-free solution in prefilled syringes of 22 mcg and 44 mcg.

**CLINICAL TRIALS**

In a randomized, double-blind, placebo-controlled study (PRISM-2) of interferon β-1a in patients with RRMS, 560 participants were randomly assigned to receive subcutaneous interferon β-1a 22 mcg (n = 189), 44 mcg (n = 184), or placebo (n = 187) three times a week for two years.5 The mean number of relapses during the two years of the study was lower in both interferon β-1a groups than in the placebo group (P < .005). The percentage reduction for the patients receiving the 22-mcg dose, compared with those receiving placebo, was 27% (95% confidence interval [CI], range, 14%–39%), and the percentage reduction for patients receiving the 44-mcg dose, compared with those patients receiving placebo, was 33% (range, 21%–44%). The mean number of moderate and severe relapses during the two-year follow-up period was also lower in both interferon β-1a groups than in the placebo group (P < .005). The median time to first relapse was delayed by three and five months in the groups receiving 22 mcg and 44 mcg, respectively.

After the first year of treatment, relapse rates were lower for those receiving 22 mcg and 44 mcg of interferon β-1a than for those receiving placebo (P < .0001). The time to sustained progression in disability was significantly longer (P < .05) in both interferon β-1a treatment groups than in the placebo group (Table 1).

Magnetic resonance imaging (MRI) showed a progressive median increase of 10.9% in the number of lesions in placebo-treated patients but decreases of 1.2% and 3.8% in the groups receiving 22 mcg and 44 mcg of interferon β-1a, respectively (P < .0001), compared with those taking placebo for both doses. The number of active lesions was significantly lower in the patients receiving 22 and 44 mcg of interferon β-1a than in those receiving placebo (P < .0001). In patients receiving the 44-mcg dose, the number of lesions was significantly lower than in patients receiving 22 mcg (P = .0003).5

**PRISMS-4**, an extension of the PRISMS-2 study, was conducted to determine the long-term efficacy of interferon β-1a in patients with relapsing MS.6 Four years of treatment with interferon β-1a at doses of 22 mcg or 44 mcg significantly reduced the number of relapses per patient per year, compared with two years of placebo treatment followed by two years of interferon β-1a therapy. The smaller number of relapses per patient per year (over four years) in the 44-mcg group versus the 22-mcg group approached significance (P = .069).

During years three and four, relapse rates were significantly lower for the group receiving 44 mcg than for the other groups. The relapse rate decreased progressively with each year of therapy, with values of 0.92, 0.82, 0.57, and 0.44 relapses per year for the 0.44-mcg group during years one through four. The relapse rates for placebo in the patients receiving 22 mcg were 1.3 during years one and two and 0.63 in years three and four (95% CI, 36%–63%; P < .001). Rates for

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**Table 1** Time (in Months) to Confirmed Progression* in Disability for Patients with Multiple Sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 187)</th>
<th>Interferon β-1a 22 mg (n = 189)</th>
<th>Interferon β-1a 44 mg (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile time to progression (months)</td>
<td>11.9</td>
<td>18.5†</td>
<td>21.3†</td>
</tr>
<tr>
<td>Risk ratio (95% CI)</td>
<td>1.00</td>
<td>0.58</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>(0.48–0.96)†</td>
<td>(0.43–0.91)†</td>
<td></td>
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<tr>
<td><strong>Group with high baseline EDSS (&gt;3.5)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile time to progression (months)</td>
<td>7.3</td>
<td>7.5</td>
<td>21.3</td>
</tr>
<tr>
<td>Risk ratio (95% CI)</td>
<td>1.00</td>
<td>0.75</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>(0.35–1.56)</td>
<td>(0.18–0.99)</td>
<td></td>
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</tbody>
</table>

* Progression = one or more steps in the Expanded Disability Status Scale (EDSS), sustained for at least three months.
† P < .05 compared with placebo.

placebo/44 mcg were 1.29 and 0.68 (95% CI, 31%–61%; \( P < .001 \)). In the three-group intent-to-treat analysis, the proportion of patients who were free from relapses after four years was greater in those taking 44 mcg (19%) and 22 mcg (14.4%) than in the crossover groups combined (6.7%; \( P < .001 \) crossover vs. 44 mcg; \( P = .016 \) crossover vs. 22 mcg).

The time to first confirmed progression did not differ significantly between the 22-mcg group (35.9 months) and the crossover group (\( P = .289 \)) or between the 44-mcg group and the 22-mcg group (\( P = .289 \)). In the PRISMS-2 trial, 61.7% of patients taking placebo were free from MS progression, compared with 70.3% for the patients receiving 22 mcg and 73.2% for the patients receiving 44 mcg. In the PRISMS-4 trial, 46% of the crossover group, 51% of the 22-mcg group, and 56% of the 44-mcg group remained free from progression (\( P = .070 \)). Patients receiving 22 mcg and 44 mcg had fewer new lesions than did the crossover group combined (\( P < .001 \) in each case), and the 44-mcg group had fewer new lesions than did the 22-mcg group (\( P < .001 \)).

The proportion of scans showing new lesions over four years was also lower in the patients receiving 44 mcg of interferon β-1a than in the patients receiving 22 mcg (\( P < .001 \)). The proportion of scans showing active lesions was lower for those receiving 44 mcg of interferon β-1a than for either the placebo/44 mcg or 22 mcg (\( P < .001 \) in each case). There were no significant differences between the 22-mcg and placebo/22-mcg groups.

Adverse events during the extension study were similar to those observed in the PRISMS-2 trial, and most of these were mild. The onset of adverse events during years three and four was higher in the crossover groups. During years three and four, 23% and 29% of patients, respectively, reported depression at least once. In PRISMS-2, patients receiving placebo reported depression more often than patients receiving interferon β-1a.6

Additional studies support the findings in this article and the positive effects of interferon β-1a in the treatment of MS.7–12

CONCLUSION

MS is a chronic, incapacitating illness that is difficult to diagnose. Neurological findings, clinical observation, examination of spinal fluid, MRI results, and sometimes tests of evoked potentials constitute the basis for diagnosis. No curative treatment is currently available for MS, but several medications can be used to treat the disease symptomatically. Interferon β-1b and β-1a have been used successfully to reduce the frequency and severity of relapses. MS research has evolved tremendously in the last decade, and our knowledge of this disease is increasing. This understanding will expedite the development of new treatments to improve the quality of life of patients with MS.

REFERENCES

4. Rebi® (interferon β-1a) package insert. Serono Pharmaceuticals, Randolph, MA.