Immunomodulatory Agents for the Treatment of Relapsing Multiple Sclerosis

A Systematic Review

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Background: Within the past 10 years, several immunomodulatory agents (IMAs) have become available for the treatment of relapsing multiple sclerosis (MS), making therapeutic decisions more complex. We performed a systematic review of the literature to assess the efficacy and safety of these agents on physical, inflammatory, and cognitive measures of disease activity.

Methods: We identified relevant studies by searching electronic databases (MEDLINE and Current Contents) from January 1, 1993, through August 31, 2001. We included English-language reports of data from phase 3 trials of interferon beta-1b (Betaseron), 2 preparations of interferon beta-1a (Avonex and Rebif), or glatiramer acetate (Copaxone) for the treatment of relapsing MS.

Results: Twenty-one studies met explicit inclusion criteria. Comparison of study results indicated no differences among IMAs regarding their efficacy on relapse-related measures. Interferon beta-1a significantly reduced disability progression, whereas no significant effect of glatiramer acetate or interferon beta-1b on disability progression was seen. On inflammatory measures, all of the IMAs showed reductions in the burden of disease (T2-weighted lesions) to varying degrees. Interferon beta and glatiramer acetate reduced new lesion activity; however, interferon beta had a more profound effect. One interferon beta-1a preparation (Avonex) appeared to reduce brain atrophy, whereas glatiramer acetate showed an effect in 1 of 2 studies. Only Avonex demonstrated efficacy in slowing progression of cognitive dysfunction.

Conclusions: Data show that the IMAs have similar effects on several physical and inflammatory measures. In addition, Avonex has demonstrated efficacy in slowing cognitive progression in relapsing MS. One disadvantage of interferon beta is the possibility of immunogenicity, which may occur more often with subcutaneous administration. The IMAs have similar safety and tolerability profiles.

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MULTIPLE SCLEROSIS (MS) is a multifocal, demyelinating disease of the central nervous system (CNS) that is characterized by recurrent or chronically progressive neurologic dysfunction. Multiple sclerosis is first recognized by clinicians as relapsing-remitting MS (RRMS) in most patients.1 Relapsing-remitting MS is characterized by well-defined disease relapses followed by periods of full recovery or with residual deficit on recovery. Although a lack of disease progression between relapses is seen, RRMS may be ongoing subclinically before clinical manifestations. Secondary-progressive MS starts as RRMS and is characterized by gradual disease progression with or without relapses, minor remissions, and plateaus.2 Natural history data suggest that of patients with RRMS at onset, the disease will transform to progressive MS after 10 years in more than 50% and after 25 years in approximately 90%.1

Multiple sclerosis is a heterogeneous disease, with high intrapatient and interpatient variability in the clinical course and manifestations. The disease is manifested in physical symptoms (relapses and disability progression), CNS inflammation, brain atrophy, and cognitive dysfunction. Hence, the ideal therapy for MS would be effective against multiple aspects of the disease (ie, physical, inflammatory, and cognitive). Since 1993, the following 2 types of immunomodulatory agents (IMAs) have been available as first-line therapies for the treatment of relapsing MS in the United States: interferon beta-1b (Betaseron; Berlex Laboratories, Montville, NJ), interferon beta-1a (Avonex; Biogen, Inc, Cambridge, Mass), and synthetic glatiramer acetate (Copaxone; Teva Neuroscience, Kansas City, Mo). Another form of interferon beta-1a (Rebif; Serono, Inc, Norwell, Mass) is available in
Europe, Canada, and Australia, and recently in the United States. In 1998, a consensus statement issued by the National Multiple Sclerosis Society recommended that therapy with an approved disease-modifying agent should be initiated as soon as possible after a definite diagnosis of MS and determination of a relapsing course.

Although clinicians have effective agents to choose from, selecting the appropriate treatment can be challenging because of the wide intratreatment and interpatient variability observed in the clinical course and symptoms of MS. In addition, differences in study design, patient population, and clinical end points make it difficult to compare trials. The purpose of this report is to summarize data regarding the efficacy and safety of each IMA from phase 3 clinical trials. Since no single outcome measure captures all aspects of the disease, MS therapies are evaluated according to their efficacy on physical, inflammatory, and cognitive measures of disease activity.

STUDY SELECTION AND INCLUSION CRITERIA

Data were obtained from published clinical trials of IMAs (interferon beta products and glatiramer acetate) as first-line therapy for the treatment of RRMS or other relapsing forms of MS. Relevant studies were identified by searching electronic databases (MEDLINE and Current Contents) from January 1, 1993, through August 31, 2001, using the terms multiple sclerosis, interferon beta, and glatiramer acetate. To be included in this review, reports were required to be written in English, and the data had to be from (or part of) a phase 3 trial of an IMA used as first-line therapy for the treatment of relapsing MS. Phase 3 trials were defined as large (≥100 patients per treatment arm), randomized, double-blind studies designed to evaluate the efficacy and safety of a drug on the basis of clinical outcomes; small open-label trials were not included. In addition, trials were excluded if they pertained to MS treatments for more progressive forms of relapsing disease or secondary progressive MS (e.g., mitoxantrone hydrochloride therapy).

We assessed the study design, clinical characteristics of the patients, outcome measures, comparison groups, and drug doses. Efficacy data were summarized according to physical (relapse-related measures and disability), inflammatory (magnetic resonance imaging [MRI] measures of disease activity and brain atrophy), or cognitive measures of disease activity. Safety outcomes assessed included the severity and incidence of treatment-related adverse events and the development of neutralizing antibodies (NABs) to interferon beta.

PHASE 3 TRIALS IN RRMS

We identified a total of 45 articles. We included 21 in the review of efficacy after initial screening of the abstracts. Four of the 21 selected articles reported the primary clinical results of the pivotal phase 3 trials for each agent. The remaining 17 articles reported the results of secondary outcomes (e.g., MRI results) or post hoc analyses of the pivotal phase 3 trials or of additional phase 3 studies. Studies were excluded if they were small-scale (n<100 patients per treatment group), nonrandomized, nonmasked, or non–phase 3 clinical trials.

Study Design and Patients

The study designs and patients in each phase 3 trial are summarized in Table 1. All phase 3 trials were randomized, placebo-controlled, double-blind, multicenter, 2-year studies. The interferon beta-1b phase 3 trial included 372 patients with baseline Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5.5 (mean, 2.9) and at least 2 relapses during the 2 years before enrollment. Patients were randomized to receive subcutaneous (SC) interferon beta-1b, 8 miU (250 µg) or 1.6 miU (50 µg), or placebo every other day for 2 years. The primary end points were the annual relapse rate and the proportion of relapse-free patients. Secondary end points included the number of days to first relapse, relapse duration and severity, change from the baseline EDSS and Scripps Neurologic Rating Scale scores, and quantitative disease burden as measured by means of T2 lesion activity on annual MRI scans.

In the phase 3 trial of Avonex, 301 patients with relapsing MS were randomized to receive 30 µg of the study drug (n=158) or placebo (n=143) intramuscularly once weekly for 2 years. Patients with a baseline EDSS score of 1.0 to 3.5 (mean, 2.4) who experienced at least 2 relapses during the 3 years before enrollment (mean, 1.2) were enrolled in the study. The primary outcome variable was time to onset of sustained worsening in disability, defined as deterioration from baseline by at least 1.0 point on the EDSS that was sustained for at least 6 months. Secondary outcome variables included relapse rate, the number and volume of lesions with contrast enhancement on T1-weighted MRI after administration of gado-}

In the phase 3 trial of Rebif, the Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in Multiple Sclerosis (PRISMS) study, 560 patients with RRMS were randomized to receive SC interferon beta-1a, 22 or 44 µg, or placebo 3 times weekly for 2 years. Patients were included in the study if they had had at least 2 relapses during the 2 years before enrollment and an EDSS score of 0 to 5.0 (mean, 2.5). The primary outcome measure was the relapse rate. Secondary outcome measures included the proportion of relapse-free patients, times to first and second relapses, time to sustained disability progression, findings on an ambulation index and an arm function index, need for corticosteroids and hospitalization due to MS, and MRI measures of disease burden and T2 active lesions.

In the phase 3 trial of glatiramer acetate, 251 patients with RRMS were randomized to receive 20 mg of the study drug or placebo SC once daily for 2 years. Patients who had had at least 2 relapses during the 2 years before enrollment and an EDSS score of 0 to 5.0 (mean, 2.6) were enrolled in the study. The primary outcome variable was the mean number of relapses during 2 years. Secondary outcome variables included the proportion of relapse-free patients, time to first relapse, pro-
portion of patients with sustained disease progression, and mean change in the EDSS score and an ambulation index.

All of these phase 3 trials were randomized, placebo-controlled, double-blind multicenter studies with similar patient populations. The mean baseline EDSS score was slightly higher in the interferon beta-1b trial (mean, 2.9) compared with the other trials (mean EDSS scores, 2.4-2.6). Three of 4 studies used the relapse rate as the primary outcome measure in the Avonex trial, the time to sustained progression in disability was the primary end point.

### Physical Measures

The physical category includes measures of relapse (eg, annual relapse rate and proportion of relapse-free patients) and progression in neurologic disability. Relapses are defined as the appearance of new neurologic symptoms or the worsening of a preexisting neurologic symptom in a patient who had been stable or improving for a period (eg, 30 days) before the relapse. Studies differ in the amount of time the symptoms are required to last (24 vs 48 hours) and the amount of time allowed for the examining neurologist (masked to treatment assignments) to verify the relapse. Progression in neurologic disability is most often assessed using the EDSS. The EDSS assesses cerebellar, pyramidal, brainstem, sensory, bowel, bladder, visual, and mental functional systems on an ordinal scale, with scores ranging from 0 (normal neurologic examination findings) to 10 (death due to MS) in half-point increments. Scores that range from 0 to 3.5 indicate the number of functional symptom scores and the severity of dysfunction for each functional system, whereas scores of greater than 4.0 are based primarily on the effect of the disease on ambulation.

A summary of the effects of each agent on relapses and disability progression is shown in Table 2. A significant effect of interferon beta-1b was observed on the primary outcome variable, the annual relapse rate. The annual relapse rate was 1.17 (95% confidence interval, 1.03-1.33) in patients treated with 1.6 mL of the study drug, 0.84 (95% confidence interval, 0.72-0.97) in patients treated with 8 mL of the study drug.

### Table 1. Study Designs of Pivotal Phase 3 Trials*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Patient Population</th>
<th>Treatment Groups</th>
<th>Efficacy End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b (Betaseron)*</td>
<td>Randomized, double-blind, placebo-controlled, multicenter, 2-year study</td>
<td>N = 372 with RRMS; EDSS scores, 0-5.5</td>
<td>1.6 mL SC every other day (n = 125); 8 mL SC every other day (n = 124); and placebo (n = 123)</td>
<td>Primary: relapse rate; proportion of relapse-free patients; secondary: time to first relapse, relapse duration and severity, change in EDSS and NRS scores, T2 lesion burden and activity</td>
</tr>
<tr>
<td>Interferon beta-1a (Avonex)*</td>
<td>Randomized, double-blind, placebo-controlled, multicenter, 2-year study</td>
<td>N = 301 with relapsing MS; EDSS scores, 1.0-3.5</td>
<td>30 µg IM once weekly (n = 158); and placebo (n = 143)</td>
<td>Primary: sustained disability progression; secondary: relapse rate, number and volume of Gd-positive lesions, number and volume of T2 lesions</td>
</tr>
<tr>
<td>Interferon beta-1a (Rebif)*</td>
<td>Randomized, double-blind, placebo-controlled, multicenter, 2-year study</td>
<td>N = 560 with RRMS; EDSS scores, 0-5.0</td>
<td>22 µg SC 3 times weekly (n = 189); 44 µg SC 3 times weekly (n = 184); and placebo (n = 187)</td>
<td>Primary: relapse rate; secondary: proportion of relapse-free patients, time to relapses, time to progression in disability, ambulation index, arm-function index, steroid use, hospital admissions, MRI disease burden, and T2 active lesions</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)*</td>
<td>Randomized, double-blind, placebo-controlled, multicenter, 2-year study</td>
<td>N = 251 with RRMS; EDSS scores, 0-5.0</td>
<td>20 mg SC once daily (n = 125); and placebo (n = 126)</td>
<td>Primary: mean number of relapses over 2 years; secondary: proportion of relapse-free patients, time to first relapse, proportion of patients with sustained disease progression; and mean change in EDSS score and ambulation index</td>
</tr>
</tbody>
</table>

*RRMS indicates relapsing-remitting multiple sclerosis (MS); EDSS, Expanded Disability Status Scale; SC, subcutaneous injection; NRS, Scripps Neurologic Rating Scale; IM, intramuscular injection; Gd, gadolinium; and MRI, magnetic resonance imaging.

**Defined as a >1.0-point worsening of the EDSS score for ≥6 months.

†Defined as a >1.0-point worsening of the EDSS score for ≥3 months.

### Table 2. Summary of Results on Physical Measures of Disease Activity From Pivotal Phase 3 Trials*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Reduction in Relapses, %†</th>
<th>Relapse-Free Patients, %†</th>
<th>Median Time to First Relapse, d†</th>
<th>Reduction in Disease Progression, %†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b (Betaseron)*</td>
<td>8 mL (250 µg) SC every other day</td>
<td>34</td>
<td>31</td>
<td>295</td>
<td>29</td>
</tr>
<tr>
<td>Interferon beta-1a (Avonex)*</td>
<td>30 µg IM once weekly</td>
<td>32</td>
<td>38</td>
<td>331</td>
<td>37</td>
</tr>
<tr>
<td>Interferon beta-1a (Rebif)*</td>
<td>22 µg SC 3 times weekly</td>
<td>29</td>
<td>27</td>
<td>228</td>
<td>23</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)*</td>
<td>20 mg SC once daily</td>
<td>29</td>
<td>34</td>
<td>287</td>
<td>12</td>
</tr>
</tbody>
</table>

*Abbreviations are explained in the first footnote to Table 1.

†Defined as a >1.0-point worsening of the EDSS score for ≥6 months.

‡The Avonex trial required sustained progression for 6 months; the Rebif trial, for 3 months; and the glatiramer trial, for 3 months.
drug, and 1.27 (95% confidence interval, 1.12-1.43) in patients treated with placebo (P=.01 for 1.6 mIU; P<.001 for 8 mIU), representing a 34% reduction in relapses with 8 mIU of interferon beta-1b (Table 2). The number of relapse-free patients after 2 years was not significantly different between the group receiving 1.6 mIU of interferon beta-1b and the placebo group (P=.07), but it was significantly higher in the group receiving 8 mIU of interferon beta-1b compared with the placebo group (36 vs 18; P=.007). Treatment with 8 mIU of interferon beta-1b significantly prolonged the median time to first relapse (295 days) compared with placebo (P=.02). No statistically significant treatment effect on confirmed disability progression was observed (defined as a ≥1.0-point increase in EDSS score) in any of the 3 study years with either dose of interferon beta-1b. The 8-mIU dose, but not the 1.6-mIU dose, was approved for the treatment of RRMS on the basis of the results of this trial. The findings of this study suggest that a dose-response curve for interferon beta-1b exists.

In the phase 3 trial of Avonex, time to sustained progression of disability, the primary outcome variable, was significantly greater in patients treated with interferon beta-1a compared with placebo (P=.02). The proportion of patients with progression of disability by 2 years based on results of Kaplan-Meier analysis was 21.9% for interferon beta-1a and 34.9% for placebo, representing a 37% reduction in the risk for disability progression with interferon beta-1a. Annual relapse rates for patients who completed 2 years of treatment were 0.90 for placebo-treated patients and 0.61 for interferon beta-1a–treated patients (P=.002), representing a 32% reduction in relapse rate with interferon beta-1a (Table 2). The reduction in the relapse rate was 18% for all patients, regardless of time in the study. Analysis of all patients using all time in the study also showed that interferon beta-1a significantly reduced the annual relapse rate compared with placebo (0.67 vs 0.82; P=.04). Patients treated with interferon beta-1a were significantly less likely than those treated with placebo to experience multiple relapses (P=.03); 38% of the interferon beta-1a–treated patients were relapse free compared with 26% of the placebo-treated patients. Interferon beta-1a increased the median time to first relapse (331 days) compared with placebo; however, the between-group difference failed to reach statistical significance.

The mean number of relapses was significantly lower during the 2 years of treatment with both doses of Rebif compared with placebo (P<.005); the mean number of relapses was 1.82 for the 22-µg group, 1.73 for the 44-µg group, and 2.56 for the placebo group. The reductions in the relapse rate were 29% for the 22- and 32% for the 44-µg groups (Table 2). In addition, the proportion of relapse-free patients was significantly higher (P<.003), and the mean number of moderate-to-severe relapses was significantly lower (P<.005) in the 2 interferon beta-1a groups compared with the placebo group; no significant differences were observed between the 2 interferon beta-1a doses. The time to sustained disability progression was significantly longer (P<.05) in both interferon beta-1a treatment groups compared with the placebo group. Based on estimations of published Kaplan-Meier curves, reductions in disease progression were 23% for the group receiving 22 µg of the study drug and 31% for the group receiving 44 µg.

In the phase 3 trial, glatiramer acetate had a significant effect on the primary end point, relapse rate. The mean relapse rate at year 2 was 1.19 for glatiramer acetate–treated patients compared with 1.68 for placebo-treated patients (P=.007), representing a 29% reduction in favor of glatiramer acetate (Table 2). There were no significant effects of glatiramer acetate on the proportion of relapse-free patients or the median time to first relapse compared with placebo. Although there was a trend in slowing disability progression, glatiramer acetate had no effect on progression to sustained disability (defined as an increase of at least 1.0 points on the EDSS that was maintained for at least 3 months); 78% of patients receiving glatiramer acetate were free of progression compared with 75% of those receiving placebo. However, a higher proportion of glatiramer acetate–treated patients showed significant improvement on the EDSS, and a lower proportion of glatiramer acetate–treated patients showed worse EDSS scores compared with placebo-treated patients (P=.04).

As shown in Table 2, we found no major differences among IMAs with regard to their effects on relapse-related measures; all agents reduced the number of relapses by approximately 30%. Both preparations of interferon beta-1a (Avonex and Rebif) significantly reduced disability progression, whereas no significant effect of glatiramer acetate or interferon beta-1b (1.6 or 8 mIU) on disability progression was seen. However, neither study used disability progression as their primary end point.

Inflammatory Measures

Disease activity and inflammation in the CNS are assessed using MRI. Gadolinium-positive lesions indicate breakdown of the blood-brain barrier and acute inflammatory changes. New Gd-positive lesions are thought to have predictive value regarding the short-term course of MS, with a higher number of Gd-positive lesions associated with increased T2 lesion burden, relapse rate, and disability progression. Areas of high signal abnormality on T2-weighted MRI (eg, the number of new or enlarged T2 lesions [T2 lesion load]) are thought to provide a measure of past disease activity and are frequently referred to as the “burden of disease.” The T1 hypointense lesions (“black holes”) reflect axonal loss, gliosis, loss of the intracellular matrix, and demyelination and are thought to be markers for areas of more destructive focal CNS damage in patients with MS. Phase 3 trials of IMAs have evaluated the number and volume of Gd-positive lesions, the number and volume of T2 lesions, the number of new or enlarging T2 lesions, and the volume of T1 hypointense lesions. These imaging studies have limited intraobserver and in-
Placebo-treated patients showed a 29% increase from baseline in mean T1 lesion volume during the 2-year study (P=.001 vs baseline) compared with an 11.8% increase (not significant vs baseline) in interferon beta-1a-treated patients. The median increase in T1 lesion volume at 2 years was 124.5 mm³ in the placebo group and 40 mm³ in the interferon beta-1a group, which represented a 68% reduction in T1 lesion volume with interferon beta-1a treatment; the difference between groups was not statistically significant (P=.07).28 Analyses of MRI scans were conducted to determine the effects of interferon beta-1a on whole-brain atrophy as measured by brain parenchymal fraction (BPF).26 The BPF is defined as the ratio of brain parenchymal volume to the total volume within the brain surface contour. A total of 140 patients had MRI scans available from baseline, year 1, and year 2. Results showed that interferon beta-1a reduced the rate of brain atrophy by 55% compared with placebo during the second year of treatment (P=.03).29

The MRI data from the phase 3 trial of Rebif showed that interferon beta-1a produced a reduction in the burden of disease as measured by proton density on T2-weighted MRI.25 The T2 burden of disease showed a median decrease of 1.2% in the group receiving 22 µg of interferon beta-1a and a median decrease of 3.8% in the group receiving 44 µg of interferon beta-1a, but a median increase of 10.9% in the placebo group (P=.001 for both doses). Both interferon beta-1a doses also produced a significant reduction in the number of T2 active lesions compared with placebo (P<.001), with a significant dose effect in favor of the 44-µg dose (P=.001).6,20 In a cohort of 205 patients who underwent monthly scans, an analysis of combined unique lesions (Gd-enhanced T1/T2 lesions) showed significant reductions in the median number of combined unique active lesions and the percentage of combined unique active lesions on scans at 9 months in both interferon beta-1a treatment groups compared with the placebo group (P<.001). In addition, within the monthly MRI cohort, interferon beta-1a significantly reduced the median number of Gd-enhanced lesions at 9 months; an 82% reduction was observed in the 22-µg group and an 84% reduction was observed in the 44-µg group compared with the placebo group (P<.001).23 Data from the PRISMS study showed no effect of Rebif on brain atrophy.23

The effects of glatiramer acetate on MRI measures of disease activity were evaluated in a subset of patients (n=27) enrolled in the phase 3 study of glatiramer acetate.7,24 The primary outcome variables were the number and volume of Gd-positive lesions, the number and volume of T2 lesions, and brain atrophy as measured by BPF. Significant reductions from baseline in the number of Gd-positive lesions (P=.03) and in brain atrophy (P=.008) were observed in glatiramer acetate-treated patients compared with placebo-treated patients. Glatiramer acetate did not affect the number or the volume of T2 lesions. Some of these disparate findings may be explained by the number of patients studied (N=27).29

A European and Canadian placebo-controlled, double-blind phase 3 trial has been conducted to evaluate the effects of glatiramer acetate on MRI measures.25 This study included 239 patients with RRMS who had an EDSS score of 0 to 5.0 (mean, 2.4), at least 1 relapse in the 2 years before enrollment, and at least 1 Gd-positive lesion at the time of enrollment. Patients were randomized to receive SC glatiramer acetate, 20 mg (n=119), or placebo (n=120) once daily for 9 months. At 9 months, glatiramer acetate treatment produced a 29% to 35% reduction in the total number of enhancing lesions compared with placebo (P=.003).23 Significant reductions in the number of new Gd-positive lesions (P<.003), in the monthly change in Gd-positive lesion volume (P=.01), and in the volume and number of new T2 lesions (P=.006 and P<.003, respectively) were observed compared with placebo. Glatiramer acetate produced a 37% reduction in T1 hypointense lesion volume compared with placebo; however, this

The MRI scans of T1 hypointense lesions were examined in 80 patients treated with interferon beta-1a and 80 treated with placebo from the Avonex phase 3 trial.28
Table 3. Summary of Results on Inflammatory Measures of Disease Activity From Phase 3 Trials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>T2-Weighted Hyperintense Lesions</th>
<th>T1-Weighted Hyperintense Lesions</th>
<th>Gd-Positive Lesions</th>
<th>Brain Atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b</td>
<td>8 mlU (250 µg) SC every other day</td>
<td>++†</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>(Betaseron)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>30 µg IM once weekly</td>
<td>++‡</td>
<td>+§</td>
<td>++</td>
<td>++‡†</td>
</tr>
<tr>
<td>(Avonex)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>22 µg SC 3 times weekly;</td>
<td>++</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>(Rebif)</td>
<td>44 µg SC 3 times weekly</td>
<td>++</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>20 mg SC once daily</td>
<td>++‖§</td>
<td>+</td>
<td>+</td>
<td>d/−**</td>
</tr>
<tr>
<td>(Copaxone)</td>
<td></td>
<td></td>
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</tbody>
</table>

*NA indicates not applicable; minus sign, no treatment effect; and plus sign, treatment effect. Other abbreviations are explained in the first footnote to Table 1.
†Indicates significant reductions in yearly change in lesion area, rate of new lesions, and rate of active lesions compared with placebo; no effect was seen on enlarging or recurrent lesions.
‡Indicates significant reductions in new, enlarging, and new plus enlarging T2 lesions at 2 years compared with placebo.
§Indicates a near-significant reduction (68%) in T1 lesion volume at 2 years compared with placebo (P = .07).
‖Indicates a significant reduction (55%) in the rate of brain atrophy, as measured by brain parenchymal fraction, at year 2 compared with placebo.
¶Indicates significant reductions in the burden of disease (lesion area) and number of new, enlarging, and new plus enlarging T2 lesions at 2 years compared with placebo.
#Indicates significant reductions in the number of new T2 lesions and T2-lesion volume at 9 months compared with placebo; no effect was seen on the number and volume of T2 lesions in a smaller cohort from the phase 3 trial.
**A small cohort from the phase 3 trial showed benefit, but the 2 groups were not matched at baseline.

Tests cannot detect all of the cognitive deficits in MS. Hence, the best approach to measuring cognitive deficits in patients with MS is to select NP tests that measure information processing, verbal memory, and visual memory, which are the cognitive domains most affected by MS.36 For information processing, such tests include the following: the Paced Auditory Serial Addition Test, Trail-Making Tests A and B, Stroop test, Symbol-Digit Modalities Test, and the California Computerized Assessment Package. For verbal learning and memory, tests include the Buschke Selective Reminding Test, the Rey Auditory Verbal Learning Test, and the California Verbal Learning Test. For visual learning and memory, tests include the Wechsler Memory Scale–Revised Visual Reproduction, the 10/36 Spatial Learning Test, and the Ruff figurative Fluency Test.36

Neuropsychological function was assessed in 30 patients with MS who participated in the phase 3 trial of interferon beta-1b.37 These patients were administered a battery of tests that measured immediate and delayed memory recall, visual reproduction, attention/mental speed, and motor function and a depression inventory scale.37 Significant improvement was observed on 1 of 13 measures (delayed visual reproduction; P < .003 vs the placebo group) in patients who received the 8-mIU dose of interferon beta-1b. The clinical significance of this isolated improvement in 1 domain in the treated group remains uncertain, given the small number of patients studied.

The effects of Avonex on cognitive function were evaluated in patients who participated in the phase 3 trial.38 Two hundred seventy-six patients were administered a comprehensive NP battery on study entry, and 166 patients also completed the comprehensive NP battery at year 2. The primary outcome measure was the 2-year change in performance on the comprehensive NP battery, grouped into domains of information processing and learning/memory (most often impaired in MS), visuospatial abilities and problem solving (moderately impaired), and verbal abilities and attention span (rarely impaired).
Results showed that interferon beta-1a significantly improved performance on measures of the cognitive domains most vulnerable to MS, ie, information processing and learning/memory (P = .01). In addition, interferon beta-1a slowed the progression of cognitive deterioration by 47% compared with placebo, based on a commonly used NP measure (the Paced Auditory Serial Addition Test processing rate) (P = .02).38

As part of the phase 3 trial of glatiramer acetate, 248 patients were randomized to receive SC glatiramer acetate, 20 mg, or placebo once daily.39 At baseline and after 12 and 24 months of treatment, patients were administered the Brief Repeatable Battery of Neuropsychological Tests, which includes measures of sustained attention and concentration, verbal learning and delayed recall, visuospatial learning and delayed recall, and semantic retrieval. No significant treatment effects were observed on any of the NP outcome measures.39 The active-treatment and placebo groups showed improvement in their cognitive function in this 2-year study.

To date, Avonex is the only treatment that has shown significant beneficial effects on the cognitive domains most affected by MS (Table 4). In their respective phase 3 trials, interferon beta-1b showed a significant effect on only 1 of 13 NP tests and glatiramer acetate demonstrated no effect. No reports on the effects of Rebif on cognitive function in MS have been made.

### Safety

Adverse events produced by interferon beta-1b were dose related, including injection-site reactions, fever, chills, myalgia, sweating, and malaise significantly associated with the 8-mIU dosage of interferon beta-1b (P = .05); injection-site reactions occurred in 69% of patients receiving 8 mIU compared with 6% of those receiving placebo. These adverse events decreased to placebo levels across the first year of treatment, although injection-site reactions remained common in the interferon beta-1b groups.

The incidence of flu-like symptoms, muscle aches, fever, and chills was significantly higher in the Avonex group compared with the placebo group (P < .05). Interferon beta-1a therapy was well tolerated, with 93% of patients completing treatment as scheduled. Injection-site reactions, depression, and menstrual disorders were reported by 10% to 15% of patients.5

In the phase 3 trial of Rebif, significantly higher incidences of injection-site reactions, lymphopenia, leukopenia, granulocytopenia, and increased alanine aminotransferase levels were observed in patients who received interferon beta-1a compared with placebo (P ≤ .05). All of these adverse events except injection-site reactions were observed more frequently with the 44-µg than the 22-µg dose. The most common adverse event associated with glatiramer acetate treatment was a localized injection-site reaction consisting of erythema and induration, which occurred at least once in 90% of glatiramer acetate–treated patients and 69% of placebo-treated patients. Another adverse event associated with glatiramer acetate treatment was a transient, unpredictable, systemic postinjection reaction, consisting of flushing, chest tightness, dyspnea, palpitations, and anxiety. This systemic reaction was reported in 15% of glatiramer acetate–treated patients and 3% of placebo-treated patients.7

### Neutralizing Antibodies

Neutralizing antibodies can develop during long-term administration of interferon beta products; however, there are differences in the incidence of NABs among the interferon beta products. The incidence of NABs reported for interferon beta-1b and Rebif has ranged from 38% to 47% and 12% to 24%, respectively,4,6,40 whereas the incidence of NABs to Avonex has ranged from 5% to 22%,5,41,42 The development of NABs has been shown to reduce the efficacy of interferon beta. In the phase 3 study of interferon beta-1b, patients with NAB-positive findings showed a significant increase in exacerbations (P < .05), a significant increase in enlarging lesions (P < .05), and an increase in new lesion formation (P = .07) after 18 months compared with patients with NAB-negative findings.43 Recent data from the 4-year extension phase of the PRISMS study showed that NABs were associated with significant reductions in the efficacy of Rebif.44

### Table 4. Summary of Studies on Cognitive Measures of Disease Activity*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>No. of Patients</th>
<th>Measure(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1b</td>
<td>8 mIU (250 µg) SC every day</td>
<td>30</td>
<td>Immediate and delayed recall memory; attention/mental speed; DH and NDH</td>
<td>Significant improvement on 1 of 13 measures (P = .003), Wechsler Memory</td>
</tr>
<tr>
<td>(Betaseron)39</td>
<td></td>
<td></td>
<td>motor function; depression Information processing/learning memory (most</td>
<td>Scale–Visual Reproduction, Delayed Recall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>often impaired in MS); visuospatial abilities/problem-solving; verbal</td>
<td>Significant improvement on information processing/learning memory (P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>abilities/attention span</td>
<td>= .01); slowed progression of cognitive deterioration by 47% compared</td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>30 µg IM once weekly</td>
<td>166</td>
<td></td>
<td>with placebo based on the PASAT (P = .02)</td>
</tr>
<tr>
<td>(Avonex)38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>20 mg SC once daily</td>
<td>248</td>
<td>Sustained attention and concentration; verbal learning and delayed recall;</td>
<td>No effect on any of the NP tests</td>
</tr>
<tr>
<td>(Copaxone)39</td>
<td></td>
<td></td>
<td>visuospatial learning and delayed recall; semantic retrieval</td>
<td></td>
</tr>
</tbody>
</table>

*DH indicates dominant hand; NDH, nondominant hand; PASAT, Paced Auditory Serial Addition Test; NP, neuropsychological; SC, subcutaneously; and IM, intramuscularly.
Similar to findings with interferon beta-1b, patients in whom NABs developed during treatment with Rebif showed significantly higher relapse rates (P = .002), numbers of T2 active lesions, and burden of disease (P < .001) compared with patients with NAB-negative findings. In this study, the effects of NABs on efficacy were observed after 2 years of treatment. In the phase 3 trial of Avonex, no correlation was found between NAB status and disability progression or relapse rate. The lack of correlation is most likely due to the small number of patients who had NABs and the short 2-year follow-up.

Neutralizing antibodies can develop and significantly reduce the efficacy of interferon beta. The incidence of NABs is higher with interferon beta-1b than with the interferon beta-1a preparations. The clinical effects of NABs were observed after 18 to 24 months of administration, indicating that short-term studies cannot adequately assess the efficacy of interferon beta. The occurrence of NABs may relate to structural differences between interferon beta-1b and interferon beta-1a. Other important variables could include the frequency and route of administration of the interferon preparation.

**COMMENT**

To date, well-controlled head-to-head comparison studies to assess the relative efficacy of MS treatments have not been reported. Therefore, physicians must make treatment decisions based on a critical review of available data across clinical trials of each IMA. A major challenge in comparing the efficacy of MS agents is the variety of outcome measures used in clinical studies. The goal of the present review was to summarize data from randomized, double-blind, placebo-controlled, multicenter phase 3 trials to evaluate the efficacy of IMAs on physical, inflammatory, and cognitive measures of disease activity.

On physical measures of disease activity, no differences are found among the agents regarding their efficacy on relapse-related measures. However, only Avonex and Rebif have shown significant beneficial effects on disability progression. On inflammatory measures of disease activity, all IMAs have shown reductions in T2 hyperintense lesions to varying degrees. Interferon beta and glatiramer acetate reduce Gd-positive lesions; however, interferon beta products (82% to 89% reductions) appear to have a more profound effect than glatiramer acetate (29% to 35% reductions). Avonex has been shown to reduce brain atrophy as assessed by a 3-dimensional measure, BPF in year 2 of therapy; glatiramer acetate was shown to reduce brain atrophy in 1 of 2 studies. Regarding cognitive measures of disease activity, only Avonex has shown beneficial effects on the cognitive domains most affected by MS in a large, well-controlled clinical trial. Although more clinical trial evidence of the efficacy of interferon beta exists compared with glatiramer acetate, NABs to interferon beta can develop over time and potentially diminish their efficacy.

In general, interferon beta and glatiramer acetate are well tolerated. The most common adverse events associated with interferon beta treatment are flu-like symptoms, which decrease during the first year of treatment. Subcutaneous administration of interferon beta produces a higher incidence of injection-site reactions than does intramuscular administration; injection-site reactions are also commonly observed with glatiramer acetate treatment. The most common adverse event associated with glatiramer acetate treatment was a self-limited systemic reaction consisting of flushing, chest tightness, dyspnea, palpitations, and anxiety.

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