Neuropsychologic Status in Multiple Sclerosis After Treatment With Glatiramer

Amy Weinstein, PhD; Steven I. L. Schwid, MD; Randolph B. Schiffer, MD; Michael P. McDermott, PhD; Daniel W. Giang, MD; Andrew D. Goodman, MD

Background: Glatiramer acetate (Copaxone) therapy reduces clinical disease activity in relapsing-remitting multiple sclerosis (MS).

Objective: To study the effect of glatiramer therapy on neuropsychologic function as part of a randomized, placebo-controlled, multicenter trial.

Methods: Two hundred forty-eight patients with relapsing-remitting MS and mild to moderate disability (Expanded Disability Status Scale score, <5.0) were tested before and 12 and 24 months after randomization to administration of glatiramer acetate, 20 mg/d, or matching placebo. Neuropsychologic tests examined 5 cognitive domains most often disrupted in patients with MS: sustained attention, perceptual processing, verbal and visuospatial memory, and semantic retrieval.

Results: Baseline neuropsychologic test performance was similar in both treatment groups and was within normal range, except for impaired semantic retrieval. Mean neuropsychologic test scores were higher at 12 and 24 months than at baseline, and no differences were detected between treatment groups over time. No significant interactions were detected between treatment and either time or baseline impairment.

Conclusions: Our 2-year longitudinal study showed no effect of glatiramer therapy on cognitive function in relapsing-remitting MS. Although it is possible that glatiramer therapy has no effect on cognitive function, the lack of measurable decline in cognitive function in both patient groups for 2 years limits the opportunity for glatiramer to demonstrate a therapeutic effect by minimizing such decline. Emerging treatments for MS should continue to be examined for their effect on cognitive impairment because it can be a critical determinant of disability. A greater understanding of the natural history of cognitive decline in MS is essential for a rational design of these drug trials.

Arch Neurol. 1999;56:319-324

Results of numerous neuropsychologic studies demonstrate that up to 65% of patients with MS show impairment in cognitive function during their illness. The most frequently occurring changes in cognitive function are found in measures of recent memory, sustained attention, perceptual processing, verbal and visuospatial memory, and semantic retrieval. Immediate and remote memory and language skills are the least-disrupted aspects of cognitive functioning.

Cognitive changes in MS are not necessarily associated with changes in measures of physical impairment or disease duration. For example, results of numerous studies demonstrate that memory impairment may be observed early in the disease process in the presence of minimal physical disability. Traditional measures of overall neurologic impairment in MS, such as the Expanded Disability Status Scale, are insensitive to the presence of cognitive defi-
PATIENTS AND METHODS

STUDY DESIGN

A randomized, double-blind, placebo-controlled, multicenter phase 3 trial studying the effects of glatiramer therapy on MS was conducted at 11 centers in the United States. Two hundred fifty-one patients with relapsing-remitting MS were randomly assigned to receive a regimen of daily subcutaneous injections of glatiramer acetate, 20 mg, or matching placebo and were followed up systematically for 2 years. The primary results of this trial have been published previously.1 Effects on neuropsychologic outcomes from this study are presented.

PATIENTS

Patients aged 18 to 45 years with clinically definite MS or laboratory-supported MS who had at least 2 relapses in the 2 years before entry into the study were included. All patients had mild to moderate disability at baseline as defined by an Expanded Disability Status Scale score between 0 and 5.0. As reported previously, the distributions of age, sex, race, duration of disease, mean relapse rate in the previous 2 years, and Expanded Disability Status Scale score were similar in the treatment groups at baseline (Table 1). Nineteen patients (15.2%) withdrew from the glatiramer-treated group and 17 patients (13.5%) withdrew from the placebo-treated group.

PROCEDURE

Neuropsychologic tests were administered to all patients by trained research coordinators at each of the 11 study sites. Neuropsychologic testing occurred at a screening visit within 1 month before drug initiation and after 12 and 24 months of masked treatment. Tests were presented in the same order at each visit to standardize possible effects of fatigue, with alternate forms used to minimize practice effects.

NEUROPSYCHOLOGIC EVALUATION

The Brief Repeatable Battery of Neuropsychological Tests was chosen as the measure of cognitive functioning. This battery was developed by the Cognitive Functions Study Group of the National Multiple Sclerosis Society specifically for use in clinical trials of potential MS treatments, with tests chosen because they are sensitive to neuropsychologic deficits common in patients with MS.4,30 The Brief Repeatable Battery of Neuropsychological Tests requires 20 minutes to administer and can be presented by nonpsychologists after training. It consists of 5 tests, including measures of sustained attention and concentration (Paced Auditory Serial Addition Test and Symbol Digit Modalities Test), verbal learning and delayed recall (Buschke Selective Reminding Test), visuospatial learning and delayed recall (10/36 Spatial Recall Test), and semantic retrieval (Word List Generation Test).

Buschke Selective Reminding Test

The version of the Selective Reminding Test37,38 chosen for this study is a 6-trial verbal list–learning test designed to measure verbal learning and recall from memory over time. The procedure involves reading the patient a list of 12 words and having the patient recall as many words as possible in any order. In each of the following learning trials, only words not recalled on the preceding trial are presented. The patient is then instructed to continue to recall all words from the list, including those not repeated. After 6 list presentations, delayed recall is tested after an 11-minute delay. Scores are based on consistent long-term retrieval, the number of words recalled consistently on all subsequent trials without reminding; delayed recall, the number of items recalled from the complete list after an 11-minute delay; and long-term storage, the sum of words recalled after 6 repeated trials.

cits and to changes in cognition over time.1 In fact, the natural history of cognitive changes in MS is largely unknown.

Cognitive impairment in MS may have a negative impact on vocational and social roles beyond that related to physical disability.29 Despite equivalent physical disability, patients with MS with cognitive impairment have lower rates of employment, greater withdrawal from social activities, and more extensive need for personal assistance at home because of greater difficulty performing routine household tasks than patients without cognitive impairment.9,30 Activities of daily living and quality of life are more impaired than predicted by physical disability alone.8,26,31

Two previous studies32,33 attempted to determine the effects of drug treatment on neuropsychologic deficits in patients with MS. Pliskin et al32 examined neuropsychologic function in a randomized trial involving 30 patients with MS after 2 and 4 years of high- or low-dose treatment with interferon beta-1b or placebo. Although there was significant improvement in delayed visual memory between years 2 and 4 of the trial in patients receiving high-dose interferon beta-1b relative to nonsignificant changes in the placebo group, the results are difficult to interpret because baseline assessments were not performed, the sample size was small, and only 1 of several tests performed showed any effect of treatment.

Smits et al33 examined neuropsychologic function in a randomized, double-blind, placebo-controlled, crossover design clinical trial of patients with MS treated with 4-aminopyridine, a potassium channel blocker with the potential to improve conduction through demyelinated pathways. No effect of treatment was detected, but only 20 patients were included, with treatment for only 2 weeks, providing limited power to detect modest effects. Interpretation of this study was also complicated by the use of a crossover design without a washout period.

The present investigation is the first large-scale study to determine whether a treatment used to alter the course of MS affects cognitive function. We postulated that cognitive function would measurably decline during the trial and that treatment with glatiramer might minimize that decline.
RESULTS

BASELINE NEUROPSYCHOLOGIC TEST RESULTS

At baseline testing, neuropsychologic test performance was similar in both treatment groups (Table 2). Mean scores were lower than established norms but not greater than 2 SDs below the mean and therefore were considered to be within the range of normal performance. The exception was Word List Generation Test scores, which showed impairment (>2 SDs below the mean) in both treatment groups (Table 2).

RESPONSE TO TREATMENT

Mean neuropsychologic test scores were improved at 12 and 24 months compared with baseline for the placebo and glatiramer groups (Table 2). The improvement over time was statistically significant (P < .002) for the consistent long-term retrieval, delayed recall, and long-term storage components of the Buschke Selective Reminding Test; the 10/36 Spatial Recall Test; and the Paced Auditory Serial Addition Test. The Symbol Digit Modalities Test (P = .04) and the Word List Generation Test (P = .08) showed trends toward improvement over time. Table 3 presents the estimated treatment effects and associated 95% confidence intervals. No differences were detected between the treatment groups for any of the neuropsychologic test results. No significant interactions were detected between the effects of glatiramer therapy and either time or baseline level of impairment.

COMMENT

This is the first large-scale study to determine whether a treatment used to alter the course of MS affects cognitive function. Despite clear evidence of improvement in other measures of disease activity, such as relapse rate and neurologic disability, we found no effect of glatiramer therapy on the course of cognitive impairment in relapsing-remitting MS.
Neurologic and cognitive deficits are not strongly associated with each other in patients with MS, and outcome measures for these features have different degrees of sensitivity for impairment and therapeutic effects. Thus, it is possible that use of glatiramer truly had an effect on neurologic function but not on cognitive function, but the data do not support definitive conclusions.

First, without a measurable decline in cognitive function in patients treated with placebo, there was no opportunity for glatiramer to demonstrate a therapeutic effect by minimizing that decline. Instead, both groups demonstrated improvement over time, with significant changes on measures of memory and attention. Although alternate test forms were used in an attempt to minimize practice effects, procedural learning, familiarity, and comfort with the testing procedure may explain improved performance. Also, a beneficial effect from the extra care, attention, and supportive social contact incurred during this study may have improved the overall performance in both groups.

Second, patients were generally unimpaired at baseline in terms of overall cognitive performance. It could be that the effects of glatiramer administration are apparent only in patients who have a certain degree of initial baseline impairment. Our analyses of the interaction between treatment and baseline status did not reveal a dependence of the effect of glatiramer therapy on baseline performance. The subgroup of patients with impaired performance at baseline, however, was relatively small, thus limiting the power to detect differential treatment effects.

Third, it could be that the effects of glatiramer therapy are not discernible during 24 months with this testing battery in this patient population. Little is known about the natural history of cognitive changes in MS. Only a few longitudinal investigations have been undertaken to address this question. Findings have been mixed, with some results showing cognitive decline and others showing no progressive worsening. Mariani et al46 followed up 19 patients with relapsing-remitting MS for 2 years and found no progressive worsening of cognitive function and no association between cognitive and magnetic resonance imaging (MRI) changes. Another study by Amato et al,47 following up patients with relapsing-remitting MS for 4 years, did not show worsening on measures of verbal memory and abstract reasoning measures beyond the initial baseline deficits. By the end of the study, however, new semantic retrieval deficits emerged.

### Table 1. Baseline Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glatiramer (n = 125)</th>
<th>Placebo (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34.6 ± 6.0</td>
<td>34.3 ± 6.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>88 (70.4)</td>
<td>96 (76.2)</td>
</tr>
<tr>
<td>Men</td>
<td>37 (29.6)</td>
<td>30 (23.8)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>118 (94.4)</td>
<td>118 (93.6)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (5.6)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>Previous 2-y relapse rate</td>
<td>2.9 ± 1.3</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
<td>EDSS score</td>
<td>2.8 ± 1.2</td>
<td>2.4 ± 1.3</td>
</tr>
<tr>
<td>Ambulation Index</td>
<td>1.2 ± 1.0</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>Duration of MS, y</td>
<td>7.3 ± 4.9</td>
<td>6.6 ± 5.1</td>
</tr>
</tbody>
</table>

*EDSS indicates Expanded Disability Status Scale; MS, multiple sclerosis. Values are expressed as either mean ± SD or number (percentage).

### Table 2. Cognitive Test Results by Treatment Group and Visit

<table>
<thead>
<tr>
<th>Test</th>
<th>Treatment Group</th>
<th>Visit</th>
<th>Reference Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/36 Spatial Recall</td>
<td>Treatment Group</td>
<td>Baseline</td>
<td>12 mo</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>Glatiramer</td>
<td>20.43 ± 4.90</td>
<td>22.11 ± 5.04</td>
</tr>
<tr>
<td>Placebo</td>
<td>19.85 ± 4.50</td>
<td>21.19 ± 5.74</td>
<td>22.60 ± 5.49</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>Glatiramer</td>
<td>7.32 ± 2.13</td>
<td>7.69 ± 2.32</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.11 ± 2.16</td>
<td>7.21 ± 2.54</td>
<td>7.94 ± 2.34</td>
</tr>
<tr>
<td>Paced Auditory Serial Addition</td>
<td>Treatment Group</td>
<td>Baseline</td>
<td>12 mo</td>
</tr>
<tr>
<td>3 s</td>
<td>Glatiramer</td>
<td>46.63 ± 10.20</td>
<td>48.44 ± 10.33</td>
</tr>
<tr>
<td>Placebo</td>
<td>45.10 ± 10.49</td>
<td>47.88 ± 10.40</td>
<td>48.18 ± 10.85</td>
</tr>
<tr>
<td>2 s</td>
<td>Glatiramer</td>
<td>35.79 ± 11.31</td>
<td>38.98 ± 10.70</td>
</tr>
<tr>
<td>Placebo</td>
<td>35.68 ± 10.15</td>
<td>38.26 ± 10.66</td>
<td>38.67 ± 10.89</td>
</tr>
<tr>
<td>Symbol Digit Modalities</td>
<td>Treatment Group</td>
<td>Baseline</td>
<td>12 mo</td>
</tr>
<tr>
<td>Glatiramer</td>
<td>51.73 ± 13.46</td>
<td>52.42 ± 13.94</td>
<td>53.78 ± 14.66</td>
</tr>
<tr>
<td>Placebo</td>
<td>52.28 ± 13.00</td>
<td>54.18 ± 13.60</td>
<td>53.92 ± 13.62</td>
</tr>
<tr>
<td>Word List Generation</td>
<td>Treatment Group</td>
<td>Baseline</td>
<td>12 mo</td>
</tr>
<tr>
<td>Glatiramer</td>
<td>30.29 ± 10.50</td>
<td>31.07 ± 10.10</td>
<td>31.53 ± 10.12</td>
</tr>
<tr>
<td>Placebo</td>
<td>30.40 ± 8.71</td>
<td>30.67 ± 9.60</td>
<td>31.58 ± 9.98</td>
</tr>
<tr>
<td>Buschke Selective Reminding</td>
<td>Treatment Group</td>
<td>Baseline</td>
<td>12 mo</td>
</tr>
<tr>
<td>Consistent long-term retrieval</td>
<td>Glatiramer</td>
<td>34.97 ± 15.00</td>
<td>39.57 ± 14.29</td>
</tr>
<tr>
<td>Placebo</td>
<td>34.70 ± 15.57</td>
<td>40.65 ± 16.62</td>
<td>38.57 ± 15.56</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>Glatiramer</td>
<td>8.46 ± 2.78</td>
<td>9.02 ± 2.83</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.46 ± 2.62</td>
<td>9.08 ± 2.78</td>
<td>8.89 ± 2.74</td>
</tr>
<tr>
<td>Long-term storage</td>
<td>Glatiramer</td>
<td>46.97 ± 13.82</td>
<td>49.64 ± 12.30</td>
</tr>
<tr>
<td>Placebo</td>
<td>46.18 ± 13.57</td>
<td>50.44 ± 13.44</td>
<td>48.75 ± 13.41</td>
</tr>
</tbody>
</table>

*Values are given as mean ± SD. No differences were detected between the glatiramer and placebo groups on any of the neuropsychological tests. Mean scores improved over time on all tests.

†Average performance in healthy adults. Ellipses indicate not established.
Measurable cognitive deterioration over time was found in patients with a different MS disease course (formally known as chronic-progressive MS) when followed up from initial diagnosis for 4.5 years. Feinstein et al\textsuperscript{45} further studied cognitive and MRI changes in 5 patients with relapsing-remitting MS and 5 patients with long-term benign MS for 6 months and found 3 patients with increased MRI lesions, 2 of whom showed cognitive decline.

Variable findings among these studies may be caused by differences in MS disease classification, length of follow-up, level of baseline impairment, and choice of cognitive test measures. The recent study by Hohol et al\textsuperscript{50} of 44 patients with MS (relapsing-remitting, relapsing-remitting-progressive, and chronic-progressive primary and secondary) attempted to account for some of these variables by studying the relationship between cognitive dysfunction and disease burden as measured by MRI for 1 year. The neuropsychologic test battery used in that study was the same battery used in our 2-year longitudinal investigation with glatiramer therapy. Their findings showed a similar pattern of long-term cognitive change, that is, during 1 year, cognitive performance did not worsen. Instead, verbal and nonverbal memory showed minor but significant improvement. They were able to show an association at 1 year between measures of attention of processing speed and MRI lesion burden, and the 4 patients who had cognitive worsening showed significant MRI changes.

It is possible that changes in the study design of clinical trials in MS might allow us to observe otherwise undetectable cognitive change, allowing clearer interpretation of treatment effects. Design features that could be altered include selection of patients with greater cognitive impairment at baseline, a longer treatment interval to allow a measurable decline to occur, inclusion of level of education to ensure no academic differences between groups, and choosing neuropsychologic tests that are more sensitive to within-patient longitudinal changes.

![Table 3. Effects of Glatiramer Treatment on Neuropsychologic Test Scores*](image)

* Treatment effects are estimated from repeated-measures analysis of variance models, which include treatment group, center, and baseline value of the neuropsychologic test of interest. See the text for details. Positive values indicate a beneficial effect of glatiramer acetate treatment relative to placebo treatment.

Despite the inconclusive results of this trial, emerging treatments for MS should continue to be examined for their effect on cognitive impairment because it can be a critical determinant of disability. Greater understanding of the natural history of cognitive decline in MS would be invaluable in the rational design of these trials.

Accepted for publication July 10, 1998.

This study was supported by Teva Pharmaceutical Industries Ltd, Petah Tiqva, Israel.


The following investigators participated at the 11 sites involved in this study: K. P. Johnson, MD, and H. S. Patchett, MD (University of Maryland, Baltimore); B. R. Brooks, MD (University of Wisconsin, Madison); J. A. Cohen, MD (University of Pennsylvania, Philadelphia); C. C. Ford, MD (University of New Mexico, Albuquerque); J. Goldstein, MD, and T. Vollmer, MD (Yale University, New Haven, Conn); R. P. Lisak, MD (Wayne State University, Detroit, Mich); L. W. Myers, MD (University of California, Los Angeles); J. W. Rose, MD (University of Utah and the Veterans Administration Medical Center, Salt Lake City); R. B. Schiffer (University of Rochester, Rochester, NY); L. P. Weiner, MD (University of Southern California, Los Angeles); and J. S. Wolinsky, MD (University of Texas, Houston).

Reprints: Amy Weinstein, PhD, Department of Neurology, University of Rochester Medical Center, PO Box 605, 601 Elmwood Ave, Rochester, NY 14642 (e-mail: aweinstein@mail.neurology.rochester.edu).

REFERENCES