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.
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.1

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.34-36 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 test19 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.
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 treatment 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.

10/36 Spatial Recall Test

The 10/36 Spatial Recall Test, a more cognitively demanding version of the 7/24 test, assesses visuospatial learning and delayed recall. In the 10/36 test, patients are presented a random pattern of 10 circles displayed on a 6 × 6 checkerboard for 10 seconds. They must then remember and reproduce that display by placing checkers on a blank checkerboard. This process is repeated for 3 learning trials, with an additional recall after a 7-minute delay. Scores are the total number of correct immediate recall responses across the 3 trials and delayed recall.

Symbol Digit Modalities Test

The Symbol Digit Modalities Test is designed to measure perceptual processing and attention. The patient is presented a form with a symbol/digit key containing 9 different symbols in the upper boxes paired with numbers (1-9) in the lower boxes. Beneath the key, patients are presented only the symbols, to which they must match the numbers indicated in the key. The patient has 90 seconds to match as many digit/symbol pairs as possible. Scores are the number of correct responses in 90 seconds.

Paced Auditory Serial Addition Test

The Paced Auditory Serial Addition Test measures information processing speed and sustained attention. This serial addition task requires the patient to listen to a series of single-digit numbers presented on a prerecorded tape, 61 numbers total. Number presentation occurs at a rate of 1 number every 3 seconds. The patient is instructed to add the first 2 numbers, to report the answer, and then to add the following number to the previous number (ie, sum the 2 numbers spoken in a row). In the second part of the task, numbers are presented more rapidly, at the rate of 1 number every 2 seconds, increasing information processing demands. For both conditions, practice items are administered before formal test initiation to ensure that patients are familiar with and able to successfully perform task demands. Scores are the number of correct responses for each test condition, with a maximum of 60 correct answers at each presentation rate (2 seconds and 3 seconds).

Word List Generation Test

This test measures semantic retrieval and production. The patient is asked to produce, within 60 seconds, as many words as possible beginning with a specified letter, excluding proper names, numbers, and multiple forms of a word. Scores are the sum of admissible responses across 3 trials.

STATISTICAL ANALYSES

Of 251 randomized patients, 248 agreed to participate in the neuropsychologic testing protocol. Primary statistical analyses were performed according to the intention-to-treat principle and included all 248 patients. The last-observation-carried-forward imputation strategy was used for missing data. Secondary analyses were performed that included only patients having the response variable of interest at all 3 visits (baseline, 12 months, and 24 months). Results did not differ between the 2 analyses; therefore, only results of the intention-to-treat analyses are reported.

Repeated-measures analysis of covariance models were used to compare the placebo and glatiramer groups with regard to mean neuropsychologic test scores at 12 and 24 months. Separate analyses were performed for each neuropsychologic test. The models included treatment group, center, baseline neuropsychologic test score as a between-patient factor, and time as a within-patient factor. F tests were performed for significance of treatment effects, and 95% confidence intervals for these effects were computed using these models. In addition, F tests were performed for within-patient differences in mean performance over time in the combined cohort. Finally, exploratory analyses were performed to examine possible interactions between treatment and (1) time and (2) baseline neuropsychologic test scores, ie, to determine whether the effects of glatiramer therapy depended on either time or the severity of cognitive impairment at baseline.
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>
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<th>Table 1. Baseline Demographic Characteristics*</th>
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<td>Duration of MS, y</td>
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*EDSS indicates Expanded Disability Status Scale; MS, multiple sclerosis. Values are expressed as either mean ± SD or number (percentage).

<table>
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<th>Table 2. Cognitive Test Results by Treatment Group and Visit*</th>
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*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 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 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.

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.

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