Glatiramer Acetate in Primary Progressive Multiple Sclerosis: Results of a Multinational, Multicenter, Double-Blind, Placebo-Controlled Trial

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Objective: To determine whether glatiramer acetate (GA) slows accumulation of disability in primary progressive multiple sclerosis.

Methods: A total of 943 patients with primary progressive multiple sclerosis were randomized to GA or placebo (PBO) in this 3-year, double-blind trial. The primary end point was an intention-to-treat analysis of time to 1- (entry expanded disability status scale, 3.0–5.0) or 0.5-point expanded disability status scale change (entry expanded disability status scale, 5.5–6.5) sustained for 3 months. The trial was stopped after an interim analysis by an independent data safety monitoring board indicated no discernible treatment effect on the primary outcome. Intention-to-treat analyses of disability and magnetic resonance imaging end points were performed.

Results: There was a nonsignificant delay in time to sustained accumulated disability in GA- versus PBO-treated patients (hazard ratio, 0.87 [95% confidence interval, 0.71–1.07]; $p = 0.1753$), with significant decreases in enhancing lesions in year 1 and smaller increases in T2 lesion volumes in years 2 and 3 versus PBO. Post hoc analysis showed that survival curves for GA-treated male patients diverged early from PBO-treated male subjects (hazard ratio, 0.71 [95% confidence interval, 0.53–0.95]; $p = 0.0193$).

Interpretation: The trial failed to demonstrate a treatment effect of GA on primary progressive multiple sclerosis. Both the unanticipated low event rate and premature discontinuation of study medication decreased the power to detect a treatment effect. Post hoc analysis suggests GA may have slowed clinical progression in male patients who showed more rapid progression when untreated.

Ann Neurol 2007;61:14–24

Multiple sclerosis (MS) is a condition with considerable clinical, radiological, and pathological heterogeneity.[1] Several clinical forms of MS have been recognized, and the course of individual patients is highly variable. Relapsing-remitting MS (RRMS) is the most common clinical type and is the presenting form of the disease for more than 80% of patients.[2] Primary progressive MS (PPMS) is the least common phenotype, affecting only about 10% of all MS patients.[2,3] PPMS affects a greater proportion of male patients, and patients tend to be older at onset and diagnosis compared with relapsing forms of MS.[3] Strictly defined, patients with PPMS have progressive disease from onset and a lifelong clinical course that is without discernible relapses or attacks of well-defined neurological dysfunction that may completely or partially remit. Relapse does occur in two other forms of progressive MS, secondary progressive and progressive relapsing MS; these diagnoses depend on whether the first attack occurred before (secondary progress) or after (progressive relapsing) the onset of progressive neurological dysfunction.[1]

Evidence from magnetic resonance imaging (MRI)

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Received Aug 19, 2006, and in revised form Dec 11. Accepted for publication Dec 11, 2006.

Members of the PROMiSe Trial Study Group are listed in the Appendix on page xx.

Published online Jan 29, 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21079

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and histopathology suggests that progressive axonal degeneration and neuronal loss, rather than the dramatic active and recurrent inflammation observed with RRMS, are the hallmarks of the pathology that underlies progressive phases of MS,[4] but a component of chronic inflammation remains. Because neurological disability can accumulate with relapses, then incompletely remit, it has been difficult or impossible to distinguish the effects of therapy on suppression of attacks from effects on disease progression in cohorts of patients with continued relapses. Patients with PPMS, therefore, present a unique study population with which to investigate the effects of a therapeutic agent on clinical disease progression in the absence of the confounding influence of clinical relapses.

There have been few treatment trials in PPMS patients, in part due to the relative availability of PPMS patients compared with RRMS patients.[5,6] When disease progression is the outcome under study, trial durations must be sufficiently long and sample populations sufficiently large to avoid type 2 statistical errors (no finding of treatment effect when one exists).[7] Prior studies in PPMS patients have included small patient cohorts; a placebo (PBO)-controlled 2-year exploratory trial was conducted with 50 PPMS patients who received intramuscular interferon-β-1a,[8] and a 2-year pilot study of interferon-β-1b included both patients with PPMS (n = 49) and transitional MS (n = 24).[9] These studies failed to show significant treatment effects of the respective interferon-β drugs on the primary end point, accumulation of disability. Another small pilot trial (N = 14) evaluated the effects of riluzole on MRI parameters; results suggest it may have a neuroprotective effect in PPMS patients, but larger studies are needed to verify these initial findings.[10]

Clinical treatment studies are urgently needed, because there is no evidence that any therapeutic agent can delay the accumulation of disability in PPMS patients. Glatiramer acetate (GA; Copaxone; TEVA Pharmaceutical Industries, Petach Tikva, Israel) was shown to be effective in reducing the number of relapses, reducing accumulating disability as measured by Expanded Disability Status Scale (EDSS) scores, and decreasing MRI activity and lesion burden in patients with RRMS.[11,12] In a 2-year, phase II clinical trial, Bornstein and colleagues[13] studied the effects of subcutaneous GA 15mg twice daily over 2 years in patients with "chronic progressive" MS (N = 106). A review of case report forms from that study identified 31 patients either with PPMS (n = 23) or whose disease was characterized by the onset of progressive gait disturbance more than 10 years after a single attack ("transitional progressive" MS; n = 8). Post hoc analyses of data from these 31 patients supported the assumption of a delay in the time to progression of disability and an increase in the proportion of progression-free patients among the patients randomized to GA compared with those randomized to PBO.[7]

This study was conducted to determine whether the approved 20mg GA subcutaneous daily dose and formulation could slow progression of accumulated disability in a larger, prospectively followed sample of patients meeting strict criteria for PPMS.

Patients and Methods

Study Design

The protocol for this 3-year, multinational, multicenter, randomized, double-blind, PBO-controlled study was approved by regulatory agencies and the local institutional review boards of all participating centers. An approved amendment to the original protocol allowed all reconsenting subjects who completed the 3-year, double-blind treatment period to continue in a blinded extension trial whereas remaining on their assigned treatment with GA 20mg or PBO (2:1 assignment ratio) until the last enrolled patient had completed 3 years of daily subcutaneous treatment (up to 53 months for the first patient enrolled). Concomitant treatment with corticosteroids was discouraged, but if required in the investigator's judgment, therapy was limited to 5 days of intravenous treatment with methylprednisolone. Concomitant use of immunosuppressive, immunomodulating, antineoplastic, or investigational drugs was not permitted.

Two interim data analyses were planned. An independent group of neurologists, MS experts, and a statistician comprised a data safety monitoring board (DSMB). The DSMB reviewed unblinded data from the interim analyses and could recommend discontinuation of the study based on safety and efficacy results. The first interim analysis was conducted after 600 or more patients had completed at least 1 year of treatment (or terminated early), and the second interim analysis occurred when 600 or more patients completed at least 2 years of treatment (or terminated).

Patients

All patients gave written informed consent before participating in the trial. Eligible patients were between 30 and 65 years of age with an entry EDSS[14] score of 3.0 to 6.5 inclusive. The diagnosis of PPMS was confirmed by the principal investigator at each study site, and those with a history of any relapses were specifically excluded. All patients were required to have progressive neurological symptoms including evidence of myelopathy for at least 6 months before the screening visit, with objective evidence of pyramidal damage on neurological examination, including a Functional System (FS) score for the pyramidal system of 2 or greater. All patients were to have evidence of multilevel (disseminated) central nervous system disease based on objective evidence from neurological examination alone or supplemented by findings on MRI or visual- or auditory-evoked responses. Cervical spondylitic myelopathy must have been excluded by evidence of previous cervical imaging, preferably cervical MRI. Major competing causes of progressive neurological disease, such as thyroid dysfunction, amyotrophic lateral sclerosis, alterations of vitamin B_{12} metabolism, neurosyphilis, human T-cell

lymphoma virus-1 seropositivity, and Lyme disease were excluded as appropriate for each patient.

All patients were required to have undergone lumbar puncture for assay of cerebrospinal fluid to determine the presence of oligoclonal bands, increased IgG synthesis, or both. However, abnormalities of IgG synthesis were not a requirement for study entry. The patient eligibility committee critically reviewed all patients lacking evidence of intrathecal synthesis of immunoglobulins for consistency with a diagnosis of PPMS. If otherwise consistent with the diagnosis of PPMS, they were allowed entrance into the trial.

Patients were ineligible if they had lymphopenia level less than 3,000 cells/ml; had used an interferon-β drug, immunosuppressant, immunomodulating agent, corticosteroid, or investigational drug within 3 months of study entry; had any other known life-threatening, clinically significant, or uncontrolled illness; were allergic to gadolinium or had any condition that would preclude MRI; or if they were pregnant or lactating.

Assessments

All patients were attended by a treating neurologist and an examining neurologist who were blinded to treatment. The treating neurologist supervised drug administration, recorded and treated adverse events, and coordinated MRI testing. The examining neurologist was responsible for all neurological testing, including Ambulation Index and FS scoring. Neurological examinations were supplemented by MS Functional Composite (MSFC) testing, which included a timed 25-foot walk test, cognitive function test (Paced Auditory Serial Addition Test [PASAT]), and 9-hole peg test (9-HPT). The MSFC was performed three times in screening evaluations before baseline assessment. A baseline and annual cerebral MRI evaluation was done to assess T1-weighted and fluid-attenuated inverse recovery (FLAIR)–based quantitative MRI images. Neurological, laboratory, and vital sign evaluations were conducted during on-site visits at months 1 and 3 and every 3 months thereafter until month 36, and continued every 3 months for patients in the double-blind extension trial. At site visits, patients returned any unused study medication and received another 3-month supply.

The primary end point was an intention-to-treat analysis of the time to confirmed disease progression, defined as an EDSS change of 1 point or more sustained for 3 months in patients with an EDSS score at baseline of 3.0 to 5.0 (hereafter referred to as 1-step sustained progression), or 0.5 or greater EDSS point sustained for 3 months in patients with a baseline EDSS score of 5.5 to 6.5 (referred to as 0.5-step sustained progression) over the 36-month study. Secondary and exploratory end points included proportion of progression-free patients, changes from baseline in mean EDSS scores and mean MSFC scores, number and volume of brain lesions defined by FLAIR on MRI, number of gadopentetate dimeglumine (Gd)–enhanced lesions, volume of T1-hypointense lesions (black holes) as a percentage of FLAIR-defined lesion burden, and brain volume loss. Safety was assessed by adverse event reporting, vital signs, electrocardiograms, and laboratory tests.

Magnetic Resonance Imaging Protocol and Image Analysis

A uniform imaging protocol required that 1.5-Tesla scanners (General Electric, Milwaukee, WI) with EchoSpeed version 5.4 or better operating system were used at all participating centers. Baseline brain MRI was performed using a specialized pulse acquisition sequence provided to each site: Attenuation of Fluid by Inversion Recovery with Magnetization Transfer Imaging with Variable Echoes (AFFIRMATIVE).[15] AFFIRMATIVE images included simultaneously acquired transaxial spin density, T2-weighted, and FLAIR images at two echo times with magnetization transfer pulses. Contiguous T1-weighted transaxial images using the same spin-echo pulse sequence with magnetization transfer were obtained before and 5 minutes after the intravenous administration of Gd contrast agent at a dose of 0.2ml/kg. All images were obtained at 3mm slice thickness without gaps.

Initially, images were centrally processed using previously defined automated segmentation strategies.[16,17] However, during patient enrollment, the image analysis program underwent an upgrade to incorporate several revisions in the image analysis strategy and segmentation algorithms. The results using the new segmentation program were strongly correlated with those of the original segmentation system, and all results reported here are from an analysis of the entire image data set with the advanced image analysis package.[7]

Statistical Analyses

SAMPLE SIZE. Sample size projections were constructed to achieve an experiment-wise $\alpha = 0.05$ for analysis of time to disease progression sustained for 3 months using the Cox proportional hazards regression. Simulations were performed under the assumption, based on natural history data current at the time,[18] that 40% of the enrolled patients would have an entry EDSS score of 3.0 to 5.0 (stratum I) and 60% would enroll with EDSS scores of 5.5 to 6.5 (stratum II). Underlying assumptions were that 50% of the PBO-treated patients in stratum I and 20% of the PBO-treated patients in stratum II would progress each year.[19] Assuming exponentiality, the expected mean time to progression of PBO patients was 1.44 and 4.48 years for stratum I and stratum II, respectively. The joint weighted mean time to progression, therefore, was 3.26 years, which is equivalent to a yearly hazard ratio for survival of 0.307. GA was projected to prolong the time to clinical progression by 40% compared with PBO treatment. A uniform drop-out rate of 40% was projected for the study. Using a 2:1 randomization to active drug or PBO, these assumptions led to a target sample of 900 patients. The estimated power of the study under these assumptions, based on 5,000 simulation runs, was 84.5%.

PATIENT CHARACTERISTICS AT BASELINE. Comparability of study groups at baseline (demographic characteristics, medical history, disease measures) was assessed using one-way analysis of variance or Kruskal–Wallis test for continuous variables and χ^2 or Fisher's exact test for categorical variables.

PRIMARY OUTCOME AND PRINCIPAL ANALYSIS. The intention-to-treat data set included all EDSS data collected during the 36-month study, plus data collected during the

double-blind extension study at scheduled visits (eg, months 39 and 42) and at unscheduled visits conducted after 36 months from the first treatment dose. Survival distributions of the primary outcome measure, time to sustained 1-step progression of accumulated disability for patients with entry EDSS less than 5.0, or 0.5-step for patients with baseline EDSS of 5.5 or more were computed for each treatment group using Kaplan–Meier methods. The principal analysis compared the two treatment arms using the baseline-adjusted Cox proportional hazards model, with baseline EDSS, pyramidal FS score, age, and sex included as covariates in the model.

For the first interim analysis, a treatment effect was to be considered statistically significant at the level of $\alpha = 0.00045$, and for the second interim analysis, $\alpha = 0.00543$. The final study analysis used a two-sided significance level of $\alpha = 0.04818$, representing the use of the Lan–DeMets correction to type I error to account for the rate of information accumulated.

SECONDARY AND EXPLORATORY END POINTS. The proportions of progression-free patients in the GA and the PBO groups were compared using baseline-adjusted logistic regression with baseline EDSS, pyramidal FS score, age, and sex as covariates. Changes from baseline values in mean EDSS scores were analyzed using a baseline-adjusted repeated-measures analysis of covariance strategy. Baseline timed 25-foot walk test, pyramidal FS score, age, and sex were included in the model as covariates. Changes from baseline in cerebral lesion volume defined by FLAIR and in the number of Gd-enhanced lesions were calculated yearly; only baseline cerebral lesion volume or Gd-enhanced lesion number was used as a covariate in these analyses.

Post Hoc Sensitivity Analyses

Post hoc analyses were performed to evaluate efficacy in subpopulations of patients. Factors considered included sex, age, study duration, patients with no relapses or Gd-enhanced lesions on study, and alternative definitions of progression.

Results

Patient Characteristics at Baseline

A total of 943 patients were randomized to the trial and received at least one dose of study medication (Fig 1). Approximately half (49%) of all enrolled patients were male, and the majority of patients (78%) tested positive for the presence of oligoclonal bands in cerebrospinal fluid, and/or increased IgG index, and/or increased IgG synthesis (Table 1).[7]There were no significant differences between the GA (n = 627) and PBO (n = 316) groups in clinical or demographic characteristics at baseline.

Table 2 shows baseline clinical characteristics by EDSS stratum and treatment randomization. Patients in EDSS stratum II tended to be older, have longer duration of disease, and more impaired function, as measured by components of the MSFC score. Baseline MRI characteristics are shown in Table 3. With the exception of Gd-enhancing-based MRI markers of inflammatory activity, MRI measures were worse in patients in EDSS stratum II.

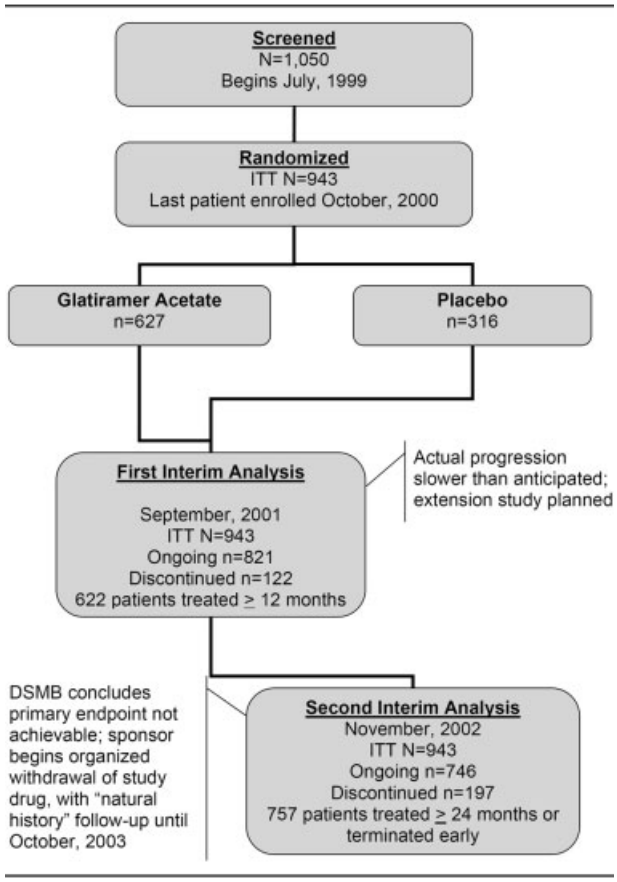

Fig 1. Patient disposition. ITT = intention to treat.

Early Study Termination

The first interim analysis showed that progression in EDSS stratum I was much lower than anticipated by the study design. Progression rates in the 662 patients with at least 12 months of study exposure were 16.1% in EDSS stratum I (predicted value 50%) and 19.3% in EDSS stratum II (predicted value 20%). No treatment effect on the primary outcome measure was detected at this analysis, and the DSMB recommended the study continue.

The second interim analysis included 935 patients with postbaseline EDSS data, 757 of whom had completed 2 or more years in the study or had terminated prematurely. No treatment effect on the primary outcome measure was detected. Futility analyses, suggested slim conditional probability for detecting a statistically significant treatment effect if the study was to proceed to its planned conclusion, and the DMSB recommended that the study be terminated. The possible effects of sex were not considered in the futility analysis. Following these recommendations, the sponsor ceased treatments with study medication for all patients. Specifically, at their next regularly scheduled visit, unused

Table 1. Patient Characteristics at Entry

Characteristics	GA (n = 627)	PBO (n = 316)	All (N = 943)
Male sex, n (%)	296 (47.2)	164 (51.9)	460 (48.8)
White, n (%)	561 (89.5)	286 (90.5)	747 (89.8)
Mean age, yr (range)	50.4 ± 8.4 (24-66)	50.2 ± 8.1 (23-66)	50.4 ± 8.3 (23-66)
Mean time from first symptom ± SD,. yr	11.0 ± 7.3	10.7 ± 7.7	10.9 ± 7.5
Mean time from diagnosis ± SD, yr	5.0 ± 4.9	5.1 ± 5.4	5.0 ± 5.1
Mean EDSS score ± SD	4.9 ± 1.2	4.9 ± 1.2	4.9 ± 1.2
Pyramidal FSS	3.0 ± 0.6	3.0 ± 0.6	3.0 ± 0.6
Cerebellar FSS	2.0 ± 1.2	2.0 ± 1.3	2.0 ± 1.3
Brainstem FSS	0.9 ± 0.9	0.9 ± 1.0	0.9 ± 1.0
Sensory FSS	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.1
Bowel/Bladder FSS	1.5 ± 0.9	1.6 ± 1.0	1.6 ± 1.0
Visual FSS	1.1 ± 1.1	1.1 ± 1.2	1.1 ± 1.1
Mental FSS	0.7 ± 1.0	0.7 ± 1.0	0.7 ± 1.0
Mean Ambulation Index ± SD	3.2 ± 1.5	3.1 ± 1.4	3.1 ± 1.5
Mean timed 25-foot walk ± SD, sec	12.9 ± 15.0	11.4 ± 11.0	12.4 ± 13.8
Mean 9-hole peg test ± SD, sec[a]	29.1 ± 20.7	28.9 ± 16.3	29.1 ± 19.3
Mean PASAT 2 ± SD	39.3 ± 12.9	38.1 ± 12.4	38.9 ± 12.8
Mean PASAT 3 ± SD	48.6 ± 11.9	47.9 ± 11.8	48.4 ± 11.9
CSF-positive, n (%)	493 (78.6)	246 (77.8)	739 (78.4)

[a]Dominant hand.

SD = standard deviation; EDSS = Expanded Disability Status Scale; FSS = Functional System Score; PASAT 2 = 2-minute Paced Auditory Serial Addition Test; PASAT 3 = 3-minute Paced Auditory Serial Addition Test.

study medications were collected and a study termination visit performed that was identical to that planned for the original study. All patients were invited to formally consent to continue participation after they stopped taking the study drug as part of a "natural history extension" to capture additional information until the originally projected conclusion of the trial. After they ceased taking the study drug, patients could use any medication (or none) during the natural history extension period. When the decision was made to discontinue treatment, 60% of GA and 59% of PBO patients had received study drug for 24 months, and 18 and 15%, respectively, had received study medication for 36 months. Cerebral MRIs were obtained for any patients attending a 36-month visit, whether they had completed the study per protocol or were part of the natural history extension (ie, not receiving study medication). Table 4 lists reasons for discontinuing study drug for all patients up to the time of the DSMB decision to terminate the study.

Primary Outcome

The tendency for delay in the time to sustained progression of accumulated disability in GA-treated patients compared with PBO-treated patients did not achieve statistical significance (hazard ratio, 0.87 [95%

Table 2. Clinical Characteristics at Entry by Extended Disability Status Scale Stratum

	Stratum I[a]		Stratum II[b]	
Characteristics	GA (n = 341)	PBO (n = 169)	GA (n = 286)	PBO (n = 147)
Mean age ± SD, yr	49.8 ± 8.2	50.0 ± 8.2	51.3 ± 8.5	50.5 ± 8.1
Mean time from first symptom ± SD, yr	10.1 ± 7.6	9.2 ± 7.5	12.0 ± 6.9	12.4 ± 7.7
Mean time from diagnosis ± SD, yr	3.8 ± 4.4	3.7 ± 4.7	6.5 ± 5.1	6.6 ± 5.9
Mean EDSS score ± SD	3.9 ± 0.6	3.9 ± 0.5	6.2 ± 0.4	6.1 ± 0.3
Mean Ambulation Index ± SD	2.1 ± 0.7	2.0 ± 0.5	4.5 ± 1.0	4.3 ± 1.1
Mean timed 25-foot walk ± SD, sec	6.7 ± 2.7	6.6 ± 2.2	20.2 ± 19.6	17.0 ± 14.1
Mean 9-hole peg test ± SD, sec[c]	24.7 ± 8.7	24.5 ± 7.0	34.5 ± 28.4	34.0 ± 21.7
Mean PASAT 2 ± SD	40.3 ± 12.7	39.7 ± 12.3	38.2 ± 13.2	36.2 ± 12.2
Mean PASAT 3 ± SD	49.9 ± 11.2	49.4 ± 11.0	47.1 ± 12.5	46.2 ± 12.5

[a]Stratum I = baseline Extended Disability Status Scale (EDSS) score of 3.0 to 5.0.
[b]Stratum II = baseline EDSS score of 5.5 to 6.5.
[c]Dominant hand.

GA = glatiramer acetate; PBO = placebo; SD = standard deviation; PASAT 2 = 2-minute Paced Auditory Serial Addition Test; PASAT 3 = 3-minute Paced Auditory Serial Addition Test.

Table 3. Magnetic Resonance Imaging Characteristics at Entry by Extended Disability Status Scale Stratum

Characteristics	All Patients	Stratum I[a] (n = 507)	Stratum II[b] (n = 431)	*p* (Stratum I vs II)
Patients with any Gd enhancements, n (%)	14.1	13.1	15.0	0.4084
Mean number of Gd enhancements (SD)[c]	0.45 (2.7)	0.32 (1.32)	0.59 (3.71)	0.3771
Mean Gd-enhanced lesion volumes, μl (SD)[c]	35 (193)	26 (113)	45 (256)	0.3762
Mean number of FLAIR lesions (SD)[c]	134 (63)	130 (61)	138 (65)	0.05
Mean BOD1 (SD), ml[c]	7.25 (9.08)	6.28 (7.32)	8.40 (10.69)	0.001
Mean BOD2 (SD), ml[c]	1.13 (1.64)	1.01 (1.53)	1.27 (1.76)	0.02
Total BOD (SD), ml[c]	8.38 (10.14)	7.28 (9.67)	8.26 (11.87)	<0.001
Mean CSF (SD), ml[c]	202 (61)	195 (56)	209 (66)	0.001
Mean nCSF (%)[c]	14.5 (4.0)	14.0 (3.8)	15.0 (4.2)	<0.001
Mean brain fraction (SD)	0.86 (0.04)	0.86 (0.04)	0.85 (0.04)	<0.001

[a]Stratum I = baseline Extended Disability Status Scale (EDSS) score of 3.0 to 5.0.
[b]Stratum II = baseline EDSS score of 5.5 to 6.5.

SD = standard deviation; Gd = gadolinium; FLAIR = fluid-attenuated inversion recovery; BOD1 = volume of lesions on the AFFIRMATIVE images segmented as high signal intensity on the long-echo FLAIR magnetization transfer contrast (MTC) and normal or high signal on the short-echo FLAIR MTC images; BOD2 = volume of lesions on the AFFIRMATIVE images segmented as high signal intensity on the long echo FLAIR MTC and low signal on the short echo FLAIR MTC images; Total BOD = BOD1 + BOD2; nCSF = cerebrospinal fluid volume normalized to total segmented intracranial contents.

confidence interval (CI), 0.71–1.07]; $p = 0.1753$). The Kaplan–Meier survival distributions for the two treatment groups are displayed in Figure 2.

The yearly hazard ratios (± standard error) of progression of accumulated disability in the PBO group were 0.21 ± 0.03, 0.22 ± 0.03, and 0.31 ± 0.05 for the first, second, and third year of the study, respectively, which were slower overall than had been anticipated during study design (0.307).

Secondary and Exploratory Outcomes

Smaller proportions of GA patients experienced sustained progression of accumulated disability compared with PBO-treated patients (39.6 vs 45.2%, respectively), but the differences were not statistically significant. Mean EDSS scores increased from baseline by 0.61 ± 1.13 points in the PBO group and by 0.58 ± 1.00 point in the GA group (not statistically different). Similarly, changes from baseline MSFC scores were not significantly different between GA and PBO groups.

In the intention-to-treat analysis, significant GA treatment effects were demonstrated on MRI-monitored enhancement and plaque burden. During the first year of the study, the mean change from baseline number of Gd-enhancing lesions was significantly reduced in the GA group compared with the PBO group ($p = 0.0022$); a borderline significant trend was also observed at year 2 ($p = 0.0702$), but no differences were seen at year 3 (Fig 3). There were smaller increases in T2 lesion volume in the GA patients compared with PBO patients (Fig 4); the differences were statistically significant only in year 2 ($p = 0.0026$). There was no difference between treatment groups in

Table 4. Reasons for Stopping Study Drug up to and Including Trial Termination

	GA[a]		PBO[a]	
Reasons for Drug Cessation	n	%	n	%
All	627	100	316	100
Completed planned study course (3 years)	35	5.6	18	5.7
Death (not drug-related)	3	0.5	7	2.2
Death (relationship unknown)	1	0.2	—	—
Serious adverse event (not including deaths)	18	2.9	6	1.9
Patient decision, not otherwise specified	96	15.3	62	19.6
Patient declined extension	3	0.7	—	—
Lost to follow-up	18	2.9	7	2.2
Other (various reasons)	19	3.0	12	3.8
Adverse event (nonserious)	30	4.8	4	1.3
Sponsor's decision based on second interim analysis data safety monitoring board (DSMB) recommendation	404	64.4	200	63.3

[a]2:1 ratio in number of patients randomized to glatiramer acetate (GA) and placebo (PBO).

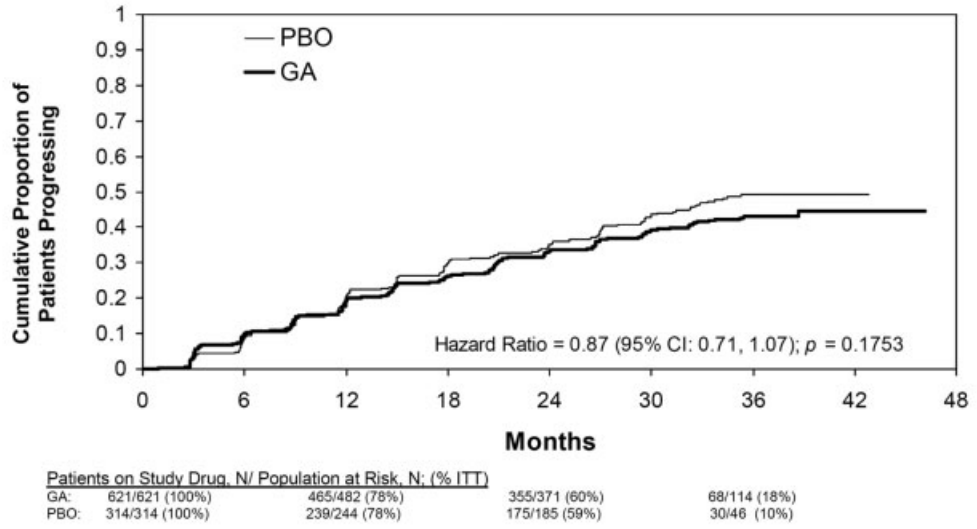

Fig 2. Onset of confirmed disease progression by time in study (Kaplan–Meier methodology). Thin line *denotes placebo (PBO);* thick line *denotes glatiramer acetate (GA). Hazard ratio = 0.87 (95% confidence interval, 0.71–1.07).* p = *0.1753.*

changes from baseline T1 hypointense lesion volume or in cerebral tissue volume loss (data not shown).

Post Hoc Sensitivity Analyses

Given the slow rate of progression in the PBO group and the truncated exposure to active therapy, post hoc analyses were performed to determine whether sensitivity could be improved enough to detect potential treatment differences.

Results in male patients (n = 455) demonstrated that GA significantly delayed time to sustained progression of accumulated disability compared with PBO treatment (hazard ratio, 0.71 [95% CI, 0.53–0.95]; $p = 0.0193$; Fig 5). Treatment differences emerged early and were maintained over time; 61.6% of male patients in the GA group versus 49.1% in the PBO group remained progression free. The results were similar (hazard ratio, 0.71 [95% CI, 0.51–0.98]; $p = 0.039$) using only the data available at the time of the second interim analysis. No significant differences between active treatment and PBO were detected in female patients (hazard ratio, 1.078 [95% CI, 0.794–1.464]; $p = 0.6304$; see Fig 5).

Post hoc analyses conducted using the variables age and varying study durations indicated nonsignificant differences in time to sustained progression of accumulated disability between the GA- and PBO-treated groups.

Altering the definition of disease progression (ie, increase of 2.0 EDSS points in stratum I and 0.5 EDSS point in stratum II, sustained for 3 months) indicated a trend toward a GA treatment effect. However, it was not statistically significant (hazard ratio, 0.803 [95% CI, 0.641–1.007]; $p = 0.0570$).

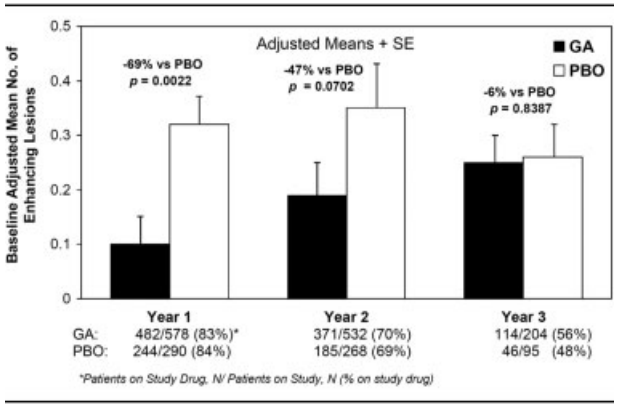

*Fig 3. Adjusted mean number of gadopentetate dimeglumine (Gd)–enhancing lesions. *Patients taking study drug (n)/patients in study (N) (% taking study drug).* Open bars *denote placebo (PBO);* solid bars *denote glatiramer acetate (GA).*

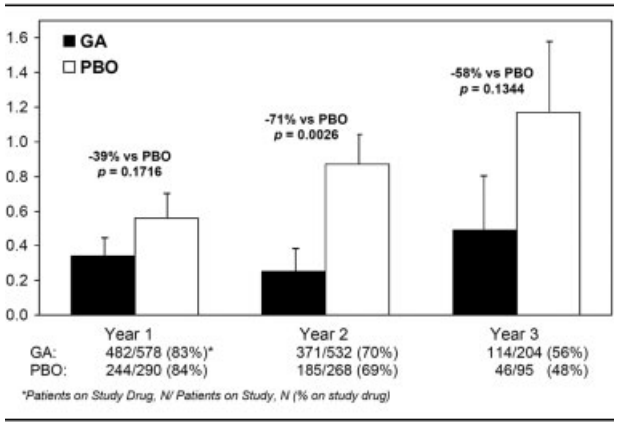

*Fig 4. Adjusted mean T2 lesion volume change. *Patients taking study drug (n)/patients in study (N) (% taking study drug).* Open bars *denote placebo (PBO);* solid bars *denote glatiramer acetate (GA).*

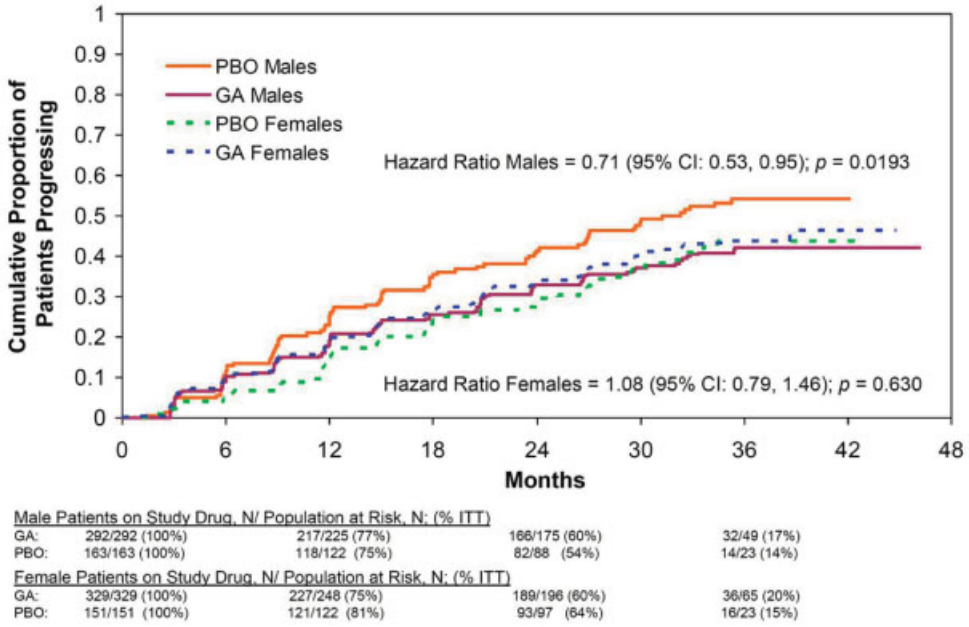

Fig 5. Onset of confirmed disease progression by time in study and sex (455 male and 480 female patients). Orange line *denotes male patients taking placebo (PBO);* purple line *denotes male patients taking glatiramer acetate (GA);* dashed green line *denotes female patients taking PBO;* dashed blue line *denotes female patients taking GA. Hazard ratio for male patients = 0.71 (95% confidence interval [CI], 0.53–0.95),* p = *0.0193; hazard ratio female patients = 1.08 (95% CI, 0.79–1.46),* p = *0.630.*

Safety

Table 5 shows the most commonly (≥5%) reported adverse events. The majority of reported adverse events were rated mild to moderate in severity. Local injection site reactions, with the exception of injection site hemorrhage, were reported more frequently in the GA group than in the PBO group. During the study, three (0.5%) GA-treated patients died (one case each of perforated duodenal ulcer, pneumonia with chronic obstructive pulmonary disease, and myocardial infarction) and seven (2.2%) PBO-treated patients died (two cases of sudden death otherwise unexplained, two cases of fatal myocardial infarction, and one case each of influenza, pneumonia, and stroke). None of the deaths in either treatment arm was attributed to study drug. Overall, 22.5% of patients taking PBO and 19.1% of patients randomized to GA took one or more courses of methylprednisolone during the study.

Discussion

This study is the largest double-blind, controlled treatment trial conducted in PPMS. Demographic characteristics of these PPMS patients were similar to those of PPMS patients in natural history cohorts and in other therapeutic trials.[6,8,20] For example, in a large (N = 216), geographically based cohort of PPMS patients in London, Ontario, Canada, mean age at disease onset was 38.5 years, and the ratio of male to female patients was 1:1.3.[20] Patient mean age at onset in a natural history cohort of PPMS patients (N = 352) in British Columbia, Canada, was 40.1 years, and ratio of male to female patients was again 1:1.3.[21] In our study, mean age at first symptom was approximately 39 years, and the male/female ratio was 1:1. Comparisons among PPMS cohorts for rates of progression are more difficult. In the Ontario cohort, median time to progression to EDSS score of 6 from disease onset was

Table 5. Most Common (≥5%) Adverse Events (Any Causality)

Event	GA, n (%)	PBO, n (%)
Abdominal pain	45 (7.2)	15 (4.7)
Accidental injury	228 (36.4)	103 (32.6)
Ambulation impaired	29 (4.6)	19 (6.0)
Asthenia	191 (30.5)	109 (34.5)
Back pain	124 (19.8)	82 (25.9)
Chest pain	78 (12.4)	34 (10.8)
Fever	30 (4.8)	17 (5.4)
Flu syndrome	71 (11.3)	30 (9.5)
Headache	114 (18.2)	65 (20.6)
Infection	209 (33.3)	124 (39.2)
Injection site edema	89 (14.2)	11 (3.5)
Injection site erythema	358 (57.1)	33 (10.4)
Injection site hemmorhage	130 (20.7)	90 (28.5)
Injection site inflammation	54 (8.6)	4 (1.3)
Injection site mass	223 (35.6)	15 (4.7)
Injection site pain	306 (48.8)	54 (17.1)
Injection site pruritus	126 (20.1)	6 (1.9)
Pain	168 (26.8)	91 (28.8)

GA = glatiramer acetate; PBO = placebo.

approximately 8.5 years.[20] In a cohort of 282 MS patients with a progressive course from onset in Lyon, France, median time to EDSS score of 6 was 7.1 years from diagnosis.[22] In contrast, the most recently reported natural history data in PPMS patients, those of the British Columbia cohort, indicated a slower rate of progression, with a median time to EDSS score of 6 of 13.3 years.[21] In our study, first MS symptoms occurred 9.8 and 12.1 years before study entry in strata I and II, respectively, and corresponding median baseline EDSS values were 3.9 and 6.2, respectively. Thus, our patients progressed at a rate fairly consistent with that of the British Columbia cohort but considerably slower than that of patients in the natural history cohort from London, Ontario.[18]

Power assumptions in our study were also based on findings from a subcohort of patients with "transitional" and primary progressive clinical courses who participated in a 2-year study of the effects of GA in chronic progressive MS patients.[13] Our assumptions regarding anticipated progression rate of untreated patients and expected therapeutic-effect size proved incorrect, and they appear to have contributed to a lack of statistical power to detect a treatment effect at 24 months, or the potential to detect one at 36 months. Post hoc sensitivity analysis, which was performed to determine whether different rates of progression occurred in subgroups of the overall population showed a significant GA treatment effect in the subgroup of male patients, who progressed at a greater rate in the PBO treatment group (50.9%) than did all patients receiving PBO (45.2%). No significant GA-treatment effect was observed in the subgroup of women in this study.

Several other post hoc analyses were performed that might have importance for future trial designs for PPMS. For example, an alternate definition of sustained progression of disability ($\geq$2 EDSS steps in stratum I and $\geq$0.5 in stratum II sustained for 3 months) was used in an analysis that showed a nonsignificant trend toward a treatment effect by GA (hazard ratio, 0.82 [95% CI, 0.62–1.09]; $p = 0.1796$). Another analyses used a 20% increase from baseline to termination in the timed 25-foot walk or in the 9-hole peg test in both hands as a measure of progression. Analysis showed a nonsignificant tendency in favor of GA (risk ratio, 0.91 [95% CI, 0.81–1.01]; $p = 0.0928$).

That the course of PPMS may progress faster in men than in women is somewhat supported by natural history data. In the London, Ontario natural history cohort mentioned earlier (N = 216), sex had no discernible effect on rate of disability progression during early levels of the Disability Status Scale, yet the time from onset of PPMS to Disability Status Scale score of 10 was significantly more rapid in men than in women ($p = 0.02$).[20] However, sex was not predictive of progression rate in the natural history cohorts that Ebers[6] and Tremlett[21] reported. Interestingly, meta-analysis of data from three PBO-controlled trials of GA in another phenotype of MS (RRMS) indicated that when stratified by sex, the risk for RRMS patients accumulating new disability was greater in male patients, regardless of treatment assignment.[23]

Despite the progressive disease course and presence of sometimes severe neurological impairment, the burden and activity of lesions on T2-weighted and Gd-enhanced brain MRI scans in PPMS are typically lower than those in other MS phenotypes.[24–26] Nevertheless, the effects of GA on these MRI indices were evident relatively early and were consistent with observed GA effects in RRMS patients.[12] Gd enhancement was significantly reduced within the first treatment year, and at year 2, there was a significantly lower rate of accumulation of T2 lesion burden with GA vs PBO. It may also be that the ease of demonstrating the effects of GA (or any other disease-modifying therapy) is highly interdependent on both the frequency of the disease-associated event and the magnitude of the drug effect on that marker of disease. MRI may be a more sensitive measure of near-term treatment effects in PPMS than of treatment effects on chronically evolving progression of accumulating disability. In Leary and colleagues'[8] 2-year study of IFN-β-1a (N = 50), there was no significant effect on the primary end point of time to progression of disability sustained for 3 months (defined as an increase of 1 step in patients with baseline EDSS $\leq$ 5 or an increase of 0.5 step in patients with EDSS $\geq$ 5.5 at baseline). However, there was a lower rate of accumulation of T2 lesion load with IFN-β-1a than with PBO. Similarly, in a 2-year study of IFN-β-1b that used the same definition of progression but sustained for 6 months, there was no significant effect of the drug on clinical progression, whereas there was a significant effect on changes in T2 and T1 lesion volumes and on the number of new T2 lesions at 24 months.[9]

The unanticipated low rate of disability progression and premature cessation of the study decreased the power to determine a treatment effect of GA. Nevertheless, it is hoped that the lessons learned in this study may inform future clinical therapy trials with PPMS patients, a group currently without proven effective therapeutic options.

We thank Dr P. Loupe and S. Owens for assistance with manuscript development.

Appendix

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