HIGH LIGHT

Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing–remitting MS

J.A. Cohen, MD; M. Rovaris, MD; A.D. Goodman, MD; D. Ladkani, PhD; D. Wynn, MD; and M. Filippi, MD; for the 9006 Study Group

Abstract—*Objective:* To evaluate the safety, tolerability, and efficacy of glatiramer acetate (GA) 40 mg daily vs the approved 20-mg formulation in relapsing–remitting multiple sclerosis. *Methods:* Eligibility criteria included clinically definite multiple sclerosis, Expanded Disability Status Scale score 0 to 5.0, no previous use of GA, at least one relapse in the previous year, and 1 to 15 gadolinium-enhancing (GdE) lesions on a screening MRI. MRI was repeated at months 3, 7, 8, and 9, and neurologic examinations were performed at baseline and months 3, 6, and 9. *Results:* Of 229 subjects screened, 90 were randomly assigned to GA 20 mg (n = 44) or 40 mg (n = 46). The groups were well matched at baseline for demographic, clinical, and MRI characteristics. The primary efficacy endpoint, total number of GdE lesions at months 7, 8, and 9, showed a trend favoring the 40-mg group (38% relative reduction, $p = 0.0898$). A difference between the two dose groups emerged as early as month 3 (52% reduction; $p = 0.0051$). There was a trend favoring the 40-mg group for relapse rate with benefit on proportion of relapse-free subjects ($p = 0.0183$) and time to first relapse ($p = 0.0367$). GA 40 mg was well tolerated, with an overall safety profile similar to that of 20 mg. Some features of injection site reactions and immediate postinjection reactions were more common and severe with the higher dose. *Conclusions:* Glatiramer acetate (GA) 40 mg was safe and well tolerated. The overall efficacy results suggested that a 40-mg dose of GA may be more effective than the currently approved 20-mg daily dose in reducing MRI activity and clinical relapses.

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Three pivotal trials[1-4] and a meta-analysis of those studies[5] support the benefit of glatiramer acetate (GA) 20 mg by daily subcutaneous injection on relapse rate, accumulation of disability, and MRI lesion activity in relapsing–remitting multiple sclerosis (RRMS). In addition, a long-term open-label study[6] and use for more than a decade in clinical practice also demonstrate the safety and tolerability of GA.

There are few published data regarding other doses of GA. In an early study,[7] three patients with acute disseminated encephalomyelitis were treated with GA 2 to 3 mg by daily IM injection for 2 weeks. In the same study, four patients with terminal multiple sclerosis (MS) were treated with 2 to 3 mg every 2 to 3 days for three weeks and then 2 to 3 mg weekly over 2 to 5 months. No adverse effects were seen in this small pilot study, but no definite conclusions regarding efficacy could be drawn. In a second preliminary open-label study,[8] 12 patients with chronic progressive MS and 4 with RRMS were treated with GA 5 mg by IM injection five times per week for 3 weeks, three times per week for 3 weeks, twice per week for 3 weeks, and then once per week for the remainder of a 6-month period. Many of the patients demonstrated initial improvement, but over time and as the dose was reduced, the response disappeared. Over the next year, the dose was gradually increased to 20 mg per day. Among the 15 subjects who completed the study, 2 of 3 patients with RRMS and 3 of 12 with chronic progressive MS were described as improved. GA was well tolerated in this study. The randomized controlled trial of 50 subjects with RRMS by Bornstein et al.[1] tested 20 mg by daily subcutaneous injection and demonstrated a beneficial treatment effect on relapses and disability progression with good tolerability. In a

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From the Mellen Center for MS Treatment and Research (J.A.C.), Cleveland Clinic Foundation, Cleveland, OH; Neuroimaging Research Unit (M.R., M.F.), Department of Neurology, San Raffaele Scientific Institute, Milan, Italy; Department of Neurology (A.D.G.), University of Rochester, Rochester, NY; Teva Pharmaceuticals (D.L.), Petach Tiqva, Israel; and Consultants in Neurology (D.W.), Northbrook, IL.

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Address correspondence and reprint requests to Dr. Jeffrey A. Cohen, Mellen Center U-10, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: cohenj@ccf.org

subsequent study of 106 subjects with chronic progressive MS,[9] GA was administered subcutaneously at a dose of 15 mg twice per day for 2 years. This dose was well tolerated and demonstrated benefit on some disability endpoints. All subsequent studies of GA administered by injection used a 20-mg daily dose, the currently approved regimen. No dose comparison study has been published. In this study, we sought to evaluate the efficacy, tolerability, and safety of GA at a dose of 40 mg by daily subcutaneous injection in RRMS.

Methods. *Subjects.* Eighteen centers in the United States participated in this study (see appendix E-1 on the *Neurology* Web site at www.neurology.org for investigators and study committees). Enrollment started in October 2003 and was completed in January 2005. The inclusion and exclusion criteria were nearly identical to those in the European/Canadian MRI trial.[4] Key inclusion criteria included clinically definite MS,[10] age 18 to 50 years inclusive, Expanded Disability Status Scale (EDSS) score 0 to 5.0, at least one clinical relapse in the previous year, and 1 to 15 gadolinium-enhancing (GdE) lesions on an MRI scan obtained at screening. Key exclusion criteria included relapse or steroid treatment within 30 days of the screening visit or between the screening and baseline visits, previous GA therapy, interferon therapy within 60 days, immunosuppressant therapy within 6 months, previous use of cladribine or total lymphoid irradiation, investigational therapy within 6 months, known sensitivity to mannitol, and inability to undergo MRI with paramagnetic contrast agents. The protocol and consent documents were approved by the institutional review boards of the participating centers. Subjects provided written informed consent before undergoing any study-related procedures.

Treatment. Eligible subjects were equally randomized to receive GA (Copaxone®) 20 mg or 40 mg by a single daily subcutaneous injection for 9 months. The randomization list, stratified by study center, was computer generated by the Teva Statistical Data Management Department. The drug preparations were identical except for GA concentration. Subjects and all personnel involved in the study were blinded to treatment assignment. Subject and investigator blinding were not formally assessed.

Design. The trial was a multicenter, randomized, double-blind, parallel-group, dose-comparison study lasting 9 months. For trial purposes, a month was defined as 28 ± 4 days. At each study site, a treating neurologist was responsible for the overall medical management of subjects including safety monitoring. An examining neurologist performed a standardized neurologic examination, Timed 25-Foot Walk (T25FW), and calculated Functional System scores and EDSS score (Neurostatus, L. Kappos, MD, Department of Neurology, University Hospital, Basel, Switzerland) at scheduled and unscheduled visits.

At the screening visit, potential subjects were informed about all aspects of the study, gave written informed consent, and then underwent physical and neurologic examinations including EDSS and T25FW, laboratory studies, and brain MRI. The MRI analysis center reviewed the results of the MRI and notified the site whether the subject qualified based on MRI criteria. Subjects returned for the baseline visit within 14 days of the screening MRI and were randomized to one of two doses of GA using an interactive voice response system. MRI obtained at screening also served as the pretreatment baseline MRI. MRI was repeated at months 3, 7, 8, and 9 or at early termination (if the subject had been in the trial at least 3 months). Scheduled MRI scans were not delayed because of steroid treatment for a confirmed relapse. Neurologic evaluations were performed at baseline and then every 3 months. Vital signs (blood pressure, pulse, and temperature), adverse events, and concomitant medications were assessed at baseline and then at months 1, 3, 6, 7, 8, and 9 or early termination. Height and weight were measured at screening, and weight was measured at month 9 or early termination. Laboratory safety assessments (hematology, serum chemistries, and urinalysis) and EKG were performed at baseline and then at months 1, 3, 6, and 9 or early termination. Blood samples for anti-GA antibodies were collected at baseline and then at every 3 months or early termination.

A relapse was defined as the appearance of one or more new neurologic symptoms, or the reappearance of one or more previously experienced symptoms lasting at least 48 hours, not accompanied by fever or infection, and preceded by a stable or improving neurologic state over the previous 30 days. Subjects were instructed to notify the study center of a potential change in neurologic status immediately, and an unscheduled visit was conducted within 7 days of notification. An event was counted as a relapse only when the subject's symptoms were accompanied by objective changes in the examining neurologist's examination corresponding to an increase of at least 0.5 steps on the EDSS, one grade in two or more Functional System scores, or two grades in one Functional System score. Isolated changes in bowel, bladder, and cognitive function did not qualify as relapses. The treating neurologist determined whether the change in symptoms qualified as an on-study relapse, which could be treated at the discretion of the treating neurologist with a standard 1,000-mg dose of IV methylprednisolone for 3 consecutive days without an oral taper.

The Steering Committee supervised the conduct of the study. An independent Data Safety Monitoring Board met five times via teleconference during the trial to review study conduct and blinded safety data and a sixth time after completion of the trial to review unblinded safety results. They had the authority to recommend discontinuation of the trial for safety concerns.

MRI scanning and analysis. The MRI Analysis Center in the Neuroimaging Research Unit, San Raffaele Scientific Institute, Milan, Italy, served as the MRI analysis center. Participating centers submitted a test scan of a volunteer with clinically definite MS for approval before enrolling subjects. All sites had 1.0- or 1.5-T scanners. Dual-echo spin-echo sequences (repetition time [TR] 2,200 to 3,000, echo time (TE) 15 to 50/80 to 100, echo train length 4 to 6, 3-mm slice thickness, and 44 contiguous axial slices) were used to obtain proton density and T2-weighted images. T1-weighted images (TR 450 to 650, TE 10 to 20) with the same scan geometry were obtained 5 minutes after injection of 0.1 mmol/kg of Gd. Slices were positioned to run parallel to a line joining the most inferoanterior and inferoposterior parts of the corpus callosum. Subjects were carefully repositioned at follow-up according to published guidelines.[11]

Image quality was reviewed at the MRI analysis center using predetermined criteria. Unsatisfactory images were rejected, but not repeated. Identification of GdE, T2-hyperintense, and T1-hypointense lesions was performed by consensus of two experienced observers, as previously described.[12,13] Trained technicians then outlined the lesions using a semiautomated segmentation technique based on local thresholding,[14] with reference to marked hard copies. Lesion volumes were calculated automatically. In a previous study using the same measurement technique, the median intraobserver coefficients of variation were 1.6% (range 1.8% to 6.2%) for T2 and 4.0% (range 2.2% to 8.4%) for T1 lesion loads.[14] Treating and examining neurologists at the sites were blinded to MRI results during the study.

Outcome measures. The primary efficacy outcome measure was total number of GdE MRI lesions at months 7, 8, and 9. Secondary outcome measures included total number of new GdE lesions at months 8 and 9, total number of new T2-hyperintense lesions at months 8 and 9, change from baseline to termination in T2-hyperintense lesion volume, relapse rate, and change from baseline to each visit in the T25FW. Prespecified exploratory endpoints included change from baseline to termination in total GdE lesion volume, change from baseline to termination in total T1-hypointense lesion volume, MRI metrics at month 3, and change from baseline to each visit in EDSS. Post hoc analyses included time to first relapse, proportion of relapse-free subjects, and responder analyses.

Statistical analysis. All efficacy and safety analyses were performed on the intent-to-treat (ITT) cohort, defined as all randomized subjects. For analysis of the primary efficacy endpoint, the additional condition of having at least one MRI scan at month 7, 8, or 9 was required to permit statistical analysis, resulting in 39 subjects on GA 20 mg and 42 subjects on GA 40 mg. Analysis of the primary efficacy outcome and other analyses of GdE or new T2-hyperintense lesions used quasi-likelihood (overdispersed) Poisson regression (SAS PROC GENMOD) employing DIST = POI and DSCALE in the options of the MODEL statement with

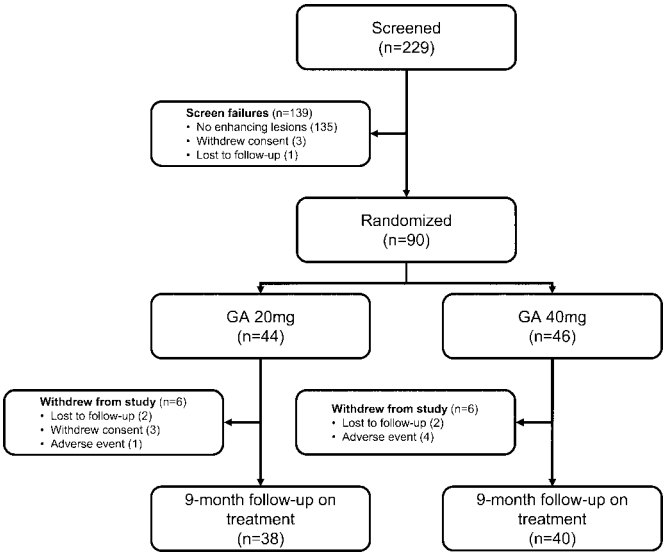

Figure 1. Trial profile. GA = glatiramer acetate.

an offset based on the log of proportion of available scans (1/3, 2/3, or 3/3). Baseline GdE lesion count and center effects were used as covariates in the model in addition to the treatment effect. The numbers of subjects withdrawing early due to adverse events were compared using the Fisher exact test, and time to withdrawal was analyzed by log-rank test. Relapse rates were analyzed using Poisson regression with relapse rate in the year before entry and baseline EDSS as covariates. Analysis of proportion of relapse-free subjects used the χ^2 test. Time to first confirmed relapse was displayed graphically by Kaplan–Meier curves and analyzed by log-rank test. In post hoc analyses, subjects were classified as responders or nonresponders based on the occurrence of relapses, EDSS progression, and the presence of GdE or new T2-hyperintense lesions at months 7, 8, and 9. Analyses based on two definitions were performed using logistic regression adjusted for site and baseline GdE lesion number. All reported p values were two-tailed. Data analysis was performed by Teva Pharmaceutical Industries, Israel. The authors had independent access to the data.

Sample size was based on the results of the European/Canadian MRI Study.[4] It was estimated that 50 evaluable subjects per group would provide 90% power to detect a 60% treatment effect between the groups in the total number of GdE lesions at months 7, 8, and 9 with two-sided $\alpha = 0.05$.

Results. *Follow-up.* Subject accrual and follow-up are summarized in figure 1. The most common reason for screen failure was lack of GdE lesions on screening MRI. Three subjects withdrew consent, and one subject did not return for the baseline visit. Because of slow accrual, recruitment was discontinued when 90 subjects were enrolled, 44 on GA 20 mg and 46 on GA 40 mg. Thirty-nine subjects on GA 20 mg and 42 subjects on GA 40 mg had at least one MRI scan at month 7, 8, or 9 required for inclusion in the ITT cohort for the primary efficacy endpoint. Thirty-eight subjects completed 9 months of double-blind treatment on GA 20 mg, and 40 on GA 40 mg. Early withdrawal due to adverse events was uncommon and occurred in 1 subject (2.3%) on GA 20 mg vs 4 subjects (8.7%) on GA 40 mg ($p = 0.36$). The subject on 20 mg withdrew from the study after experiencing severe dyspnea, speech disorder, and panic reaction immediately after injection, assessed as related to study medication by the investigator. The adverse events leading to early termination of 4 subjects on 40 mg included immediate postinjection reaction (IPIR; n = 2), injection site reaction, (n = 1), and increased fatigue (n = 1). There was no difference in time to withdrawal due to adverse events ($p = 0.95$).

Demographic and baseline disease characteristics. Demographic, clinical, and MRI characteristics of the two treatment groups were well matched at baseline (table 1). The overall study population had active disease with an average of 1.5 relapses in the previous year and 3.4 GdE lesions at entry.

MRI outcomes. The results of clinical and MRI efficacy analyses are summarized in table 2. Mean total GdE lesion number at months 7, 8, and 9 showed a trend favoring GA 40 mg representing a 38% relative reduction vs GA 20 mg. Mean GdE lesions at months 7, 8, and 9 decreased in both groups compared with baseline, by 65% in the GA 20 mg

Table 1 *Baseline demographic and disease characteristics*

Characteristic	GA 20 mg (n = 44)	GA 40 mg (n = 46)	Total
Age, mean (SD), years	37.1 (7.0)	37.4 (6.5)	37.2 (6.7)
Female	31 (71%)	37 (80%)	68 (76%)
White	38 (86%)	44 (96%)	82 (91%)
Years since symptom onset, mean (SD)	7.4 (6.2)	6.7 (6.4)	7.1 (6.3)
Years since diagnosis, mean (SD)	3.2 (3.7)	3.8 (4.8)	3.5 (4.3)
Relapses in previous year, mean (SD)	1.5 (0.8)	1.5 (0.8)	1.5 (0.8)
Actual EDSS score, mean (SD)	2.0 (1.2)	2.1 (1.0)	2.0 (1.1)
Converted EDSS score, mean (SD)	2.0 (1.2)	2.0 (0.9)	2.0 (1.0)
T25FW, mean (SD), seconds	4.9 (1.3)	5.1 (1.3)	5.0 (1.2)
GdE lesion number, mean (SD)	3.4 (3.3)	3.4 (3.1)	3.4 (3.2)
GdE lesion number, median (range)	2.0 (1–15)	2.0 (1–14)	2.0 (1–15)
GdE lesion volume, mean (SD), mL	0.59 (0.686)	1.17 (3.74)	0.89 (2.73)
T2-hyperintense lesion volume, mean (SD), mL	16.97 (15.83)	18.89 (14.71)	17.96 (15.21)
T1-hypointense lesion volume, mean (SD), mL	3.65 (6.38)	4.39 (4.97)	4.03 (5.67)

GA = glatiramer acetate; EDSS = Expanded Disability Status Scale; T25FW = Timed 25-Foot Walk; GdE = gadolinium-enhancing.

Table 2 *Clinical and MRI efficacy results*

Endpoint	GA 20 mg (n = 44)	GA 40 mg (n = 46)	Effect size (95% CI)	*p* Value
Primary endpoint				
Total number of GdE lesions months 7, 8, 9; mean (SD)*	3.62 (4.06)	2.26 (4.06)	Rate ratio 0.62 (0.36, 1.08)	0.0898
Secondary endpoints				
Total number of new GdE lesions months 8, 9; mean (SD)	1.41 (1.86)	1.00 (1.91)	Rate ratio 0.73 (0.39, 1.35)	0.311
Total number of new T2-hyperintense lesions months 8, 9; mean (SD)	1.38 (1.76)	1.00 (2.00)	Rate ratio 0.70 (0.38, 1.30)	0.256
T2-hyperintense lesion volume change LOV vs baseline, mm^3, adjusted mean (SE)	800 (1,144)	1,516 (1,095)	Difference 715 (−3,678, 2,248)	0.631
Total number of confirmed relapses, mean (SD)	0.52 (0.59)	0.30 (0.59)	Rate ratio 0.59 (0.31, 1.16)	0.121
MSFC change at each visit vs baseline			No change or between-group difference	
Prespecified and post hoc exploratory endpoints				
GdE lesion volume change LOV vs baseline, mm^3, adjusted mean (SE)	−684 (50.81)	−801 (49.55)	Difference 117 (−16, 251)	0.0841
T1-hypointense lesion volume change LOV vs baseline, mm^3, adjusted mean (SE)	122.29 (115.71)	32.23 (109.72)	Difference 90.16 (−208.10, 388.42)	0.548
Number of GdE lesions month 3, mean (SD)	2.61 (4.22)	1.33 (1.58)	Rate ratio 0.48 (0.29, 0.82)	0.0051
Relapse-free subjects	23/44 (52.3%)	35/46 (76.1%)	Risk ratio 0.50 (0.27, 0.91)	0.0183
	NNT = 1.9	NNT = 1.3		
Time to first confirmed relapse (20th percentile), days	80	213		0.0367
EDSS change at each visit vs baseline			No change or between-group difference	
Responders†	15/39 (38.5%)	29/42 (69.0%)	Odds ratio 3.51 (1.39, 8.88)	0.0078
	NNT = 2.6	NNT = 1.5		
Responders‡	5/37 (13.5%)	13/40 (32.5%)	Odds ratio 3.12 (1.00, 11.13)	0.0049
	NNT = 7.4	NNT = 3.1		

* 39 of 44 subjects on 20 mg and 42 of 46 subjects on 40 mg had at least one MRI scan at month 7, 8, or 9.
† Relapse free with no gadolinium-enhancing (GdE) lesions at months 7, 8, and 9 or a reduction in the mean number reduced by at least 50% vs baseline.
‡ Relapse free, no Expanded Disability Status Scale (EDSS) progression, no GdE lesions at months 7, 8, and 9; and no new T2-hyperintense lesions at the last assessment vs baseline.

GA = glatiramer acetate; LOV = last observed value; MSFC = multiple sclerosis functional composite; NNT = number needed to treat.

group and 75% in the GA 40 mg group ($p < 0.0001$ for both; figure 2). The advantage of 40 mg over 20 mg was apparent as early as month 3 (figure 2). Trends favoring 40 mg were seen in change from baseline to last observed value of GdE lesion volume, total number of new GdE lesions at months 8 and 9, and new T2-hyperintense lesions at months 8 and 9. There were no differences in change from baseline to last observation in total T2-hyperintense or T1-hypointense lesion volumes.

Clinical outcomes. On-study relapse rate decreased in both groups compared with the previous year. Mean on-study relapse rate showed a trend favoring GA 40 mg, with a greater proportion of relapse-free subjects and delay in the time to first confirmed relapse. EDSS and T25FW did not change in either treatment group, and there were no between-group differences at any time point. In a post hoc analysis, two definitions of treatment responders were used, both showing benefit favoring GA 40 mg.

Safety and tolerability. Safety profiles of the two GA doses were similar. There were no deaths or significant effects on vital signs. There were two serious adverse events. A subject treated with GA 40 mg was hospitalized after an IPIR and subsequently discontinued from the study. A subject treated with GA 20 mg was involved in a motor vehicle accident, classified as unrelated to study drug.

Injection site reactions were the most frequent adverse event for both doses, occurring in 38 (86.4%) subjects in

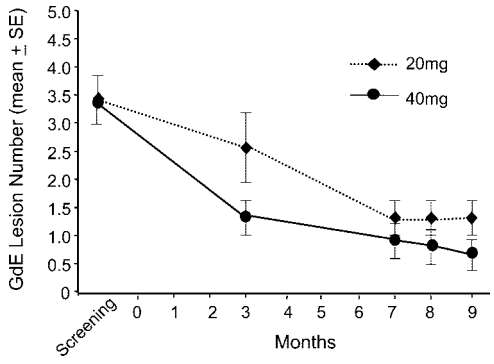

Figure 2. Gadolinium-enhancing (GdE) lesion number at each visit.

the 20-mg group and 39 (84.8%) in the 40-mg group. Injection site manifestations reported with at least 5% higher incidence for GA 40 mg included burning, mass, pain, and urticaria (table 3). Skin necrosis and lipoatrophy were not observed. Thirty-nine IPIRs occurred in 10 (22.7%) subjects on GA 20 mg vs 52 IPIRs in 15 (32.6%) subjects on GA 40 mg. The incidence in the 20-mg group was consistent with previous large studies of GA.[1,3] IPIRs were categorized most often as moderate severity in the 40-mg group and mild in the 20-mg group. All IPIRs resolved without sequelae, although one in the 40-mg group led to hospitalization and subsequent discontinuation from the study. The greatest difference among IPIR component symptoms (flushing, palpitations, tachycardia, dyspnea, and chest pain) was in palpitations. Affect lability was reported by 6 subjects (13%) treated with GA 40 mg and by none in the GA 20 mg group. All cases were assessed as not related to study drug by the investigator, and in no case was study drug discontinued.

Postbaseline shifts to abnormal laboratory values were seen for white blood cell count, platelets, eosinophils, glucose, cholesterol, and liver enzymes. In general, these abnormalities were transient, mild, and uncommon and occurred with equal incidence in the two groups. Most of the potentially clinically significant laboratory abnormalities seemed to be related to concomitant medical conditions. An unexpected finding of isolated occurrences of hypocalcemia in approximately 18% of subjects in both groups was without clear-cut explanation. No EKG abnormality was attributed to GA.

Table 3 *Number and percentage of subjects experiencing adverse events with frequency differing by 5% or greater in the 40-mg group compared with the 20-mg group*

Adverse event	GA 20 mg (n = 44)	GA 40 mg (n = 46)
Injection site burning	6 (13.6%)	13 (28.3%)
Injection site mass	9 (20.5%)	16 (34.8%)
Injection site pain	9 (20.5%)	14 (30.4%)
Urticaria	1 (2.3%)	5 (10.9%)
Any symptom of IPIR	10 (22.7%)	15 (32.6%)
Palpitations	1 (2.3%)	5 (10.9%)
Flushing	6 (13.6%)	9 (19.6%)
Affect lability	0	6 (13%)
Muscle cramp	0	3 (6.5%)
Pharyngitis	0	3 (6.5%)
Headache	4 (9.1%)	7 (15.2%)
Hypoesthesia	4 (9.1%)	7 (15.2%)
Paresthesia	6 (13.6%)	1 (2.2%)

GA = glatiramer acetate; IPIR = immediate postinjection reaction.

Discussion. The safety and efficacy of GA at the currently approved 20-mg daily dose are supported by three pivotal trials,[1-4] a meta-analysis of those studies,[5] a long-term follow-up study,[6] and postmarketing experience. This 9-month multicenter, randomized, double-blind, parallel-group trial represents the first dose-comparison study of GA. There was a trend favoring the 40-mg dose on the primary endpoint, total number of GdE lesions at months 7, 8, and 9, which was supported by significant results or trends favoring 40 mg on other secondary and exploratory MRI endpoints, relapse-related endpoints, and responder analyses.

There have been three previous trials of the MRI effects of GA. In a small, single-arm crossover study,[15] Mancardi et al. demonstrated a 57% reduction in the frequency of new GdE lesions during 20 mg GA treatment compared with the pretreatment baseline period. In an ancillary study of 27 subjects enrolled at one site in the US pivotal trial in RRMS,[16] GA treatment produced significant reductions in GdE lesions and brain volume loss. The most definitive study was the European/Canadian MRI trial,[4] which demonstrated significant reduction in cumulative GdE lesions on monthly MRI scans over 9 months favoring GA 20 mg over placebo. Consistent differences favoring active treatment were seen on other GdE-related endpoints, new T2-hyperintense lesions, and relapse rate (33% reduction). Treatment with GA also reduced the proportion of new lesions that evolved into chronic T1-hypointense lesions ("black holes"),[17] which are thought to indicate more severe tissue damage.[18,19]

The design of the current trial was modeled after the European/Canadian MRI trial. In general, subjects treated with GA 20 mg in the current study fared somewhat better than the GA 20 mg group in the European/Canadian MRI trial. For example, the mean number of GdE lesions at termination was reduced by approximately 65% compared with 48% in the previous study. This variability probably is due to differences in study populations. Subjects enrolled in the European/Canadian MRI trial had more active disease as indicated by a mean of 4.2 GdE lesions on the baseline MRI vs 3.4. Other factors also may have played a role, including different "regression to the mean" or unknown confounders.

In the European/Canadian MRI trial, the mean and median cumulative numbers of GdE lesions in the two treatment groups seemed to diverge between months 3 and 6.[4] This result has been interpreted as

suggesting a 3- to 6-month lag in the onset of action of GA 20 mg on MRI-detected disease activity. In the present study, an advantage of the 40-mg dose on suppressing GdE lesions was already evident at month 3 and, in fact, was more prominent compared with months 7, 8, and 9. Similarly, results based on the first relapse, e.g., time to first relapse and proportion of relapse-free subjects, were more robust than measures based on the 9-month study period, e.g., relapse rate. These results suggest that the onset of action of the 40-mg dose is more rapid compared with 20 mg. A larger, longer study will be necessary to confirm the sustainability of the efficacy advantage of the higher dose.

GA at the currently approved 20-mg dose has been safe and well tolerated in previous trials and postmarketing experience. The overall safety and side effect profile of the 40-mg dose in this trial was similar, although it was associated with a greater incidence of certain adverse effects. For example, although the overall incidence of injection site reactions was similar, some aspects were more common with the higher dose, and the injections seemed to be somewhat more painful. IPIRs also were somewhat more common and severe. Qualitatively, both side effects were similar to what has been seen previously.

The other adverse event of note was affect lability reported in 13% of subjects treated with 40 mg but none on 20 mg. Mood disorders are common in MS, and a relationship between mood disorders and GA 20 mg has not been seen in previous trials or postmarketing surveillance. In the US pivotal trial in RRMS, affect lability occurred with a higher incidence in the placebo group. All of the cases in the current study were assessed as unrelated to study drug by the site investigator. In no case was study drug discontinued because of this adverse effect. Thus, a causal relationship to the 40-mg dose is unlikely. Nevertheless, this issue needs to be assessed further in other studies of the higher dose.

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