Effects of oral glatiramer acetate on clinical and MRI-monitored disease activity in patients with relapsing multiple sclerosis: a multicentre, double-blind, randomised, placebo-controlled study

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Summary

Background **Parenterally administered glatiramer acetate reduces the frequency of relapses and the formation of active brain lesions seen with MRI in multiple sclerosis. This study assessed whether two doses of glatiramer acetate given orally could improve clinical and MRI measures of inflammation and neurodegeneration in a large cohort of patients with relapsing-remitting multiple sclerosis.**

Methods **1912 patients with relapsing-remitting multiple sclerosis were screened and 1651 were randomised to receive 50 mg or 5 mg of glatiramer acetate or placebo by daily oral administration over 14 months. The intention-to-treat cohort consisted of 1644 patients who took at least one dose of study medication (50 mg glatiramer acetate [n=543], 5 mg glatiramer acetate [n=553], placebo [n=548]). After baseline investigation, clinical assessments were done every 2 months and MRI was obtained for all patients at baseline and at study exit. Additionally, MRI was undertaken every 2 months for a cohort of 486 patients. The primary outcome was the total number of confirmed relapses observed during the study period. Several prespecified clinical and MRI secondary and tertiary outcomes assessed treatment efficacy on inflammation and neurodegeneration due to multiple sclerosis.**

Findings **The cumulative number of confirmed relapses did not differ between the two active treatment groups and the placebo group. Relative to placebo, the rate ratio for the 50 mg glatiramer acetate treated group was 0·92 (95% CI 0·77–1·08, p=0·30) and for the 5 mg glatiramer acetate treated group was 0·98 (0·83–1·15, p=0·76). No drug effect was seen for any of the secondary and tertiary endpoints. The study drug was safe and well tolerated.**

Interpretation **5 mg and 50 mg glatiramer acetate administered orally on a daily basis do not affect relapse rate or other clinical and MRI parameters of disease activity and burden in patients with relapsing-remitting multiple sclerosis. Treatment with oral formulations of glatiramer acetate at the doses tested cannot be recommended.**

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Introduction

Glatiramer acetate is a specific multiple sclerosis immunomodulator, which when injected subcutaneously each day reduces the frequency of relapses and the formation of active brain lesions as seen with MRI.[1–7] Treatment can also slow the development of MRI-measured brain atrophy and the evolution of MRI active lesions into permanently damaged black holes.[5,7] Although the exact mechanism of action of glatiramer acetate in multiple sclerosis is not known, emerging data suggest that the drug mainly induces specific regulatory T cells of the T-helper 2 and T-helper 3 type, which are formed close to the site of injection.[8–10] These cells then circulate to the CNS where they are reactivated by myelin basic protein and other myelin antigens and secrete protective anti-inflammatory cytokines, such as interleukin 4, 5, and 6, transforming growth factor, and brain-derived growth factor, near the site of the multiple sclerosis lesions.[11] This bystander suppression is probably the basis of the effects of glatiramer acetate on clinical and MRI measures of inflammation and neurodegeneration.

All currently approved drugs for multiple sclerosis are administered parenterally. However, long-term treatment with injected drugs is not without problems. These include patient discomfort and the occurrence of adverse events associated with frequent injections, such as local injection site reactions. These issues, through reduction of patient compliance, probably negatively affect patients' use of all available drugs. Thus, there is a strong rationale for assessment of whether drugs that are known to be effective when given parenterally also exert positive effects on clinical and MRI measures of disease activity when given orally. With a double-blind, randomised, placebo-controlled trial we aimed to ascertain the effect of two doses of oral glatiramer acetate on clinical and MRI measures of inflammation and neurodegeneration in a large cohort of patients with relapsing-remitting multiple sclerosis.

Methods

Patients

1912 patients were screened, after giving written informed consent, at 158 participating clinical centres worldwide. Of these, a total of 1651 patients with clinically definite relapsing-remitting multiple sclerosis were randomly assigned enteric-coated tablets

containing 50 mg or 5 mg of glatiramer acetate (Teva Pharmaceuticals) or placebo by daily oral administration. One patient received a randomisation number through mistaken use of the interactive voice response system and six participants never received study medication. This left an intention-to-treat cohort of 1644 randomised participants who took at least one dose of study medication (50 mg glatiramer acetate [n=543], 5 mg glatiramer acetate [n=553], placebo [n=548]). The first patient was enrolled on March 13, 2000, and the last on Sept 3, 2000. The last date of follow-up was Nov 26, 2001.

Each participant was required to have clinically definite multiple sclerosis,[12] a disease duration from onset of at least 6 months, and a relapsing-remitting course, to be age 18–50 years, have an inclusive expanded disability status scale (EDSS) score [13] at baseline of 0·0–5·0, and have had at least one documented relapse in the year before study entry. All participants were relapse free and had not used steroids for at least 30 days before screening or before randomisation. Men and women were asked to use birth control when appropriate. Prior use of glatiramer acetate, oral myelin, cladribine, and total body irradiation or total lymphoid irradiation were not allowed. The use of immunosuppressive drugs in the 12 months before study entry, or the use of interferons, intravenous immunoglobulins, more than 30 consecutive days of chronic steroid treatment, or participation in clinical studies of experimental drugs in the 6 months before study entry were not allowed. Patients were excluded if they had life-threatening or unstable clinically significant disease, were pregnant or lactating, had major current gastrointestinal disorders, used medication that could cause major gastrointestinal disturbances, or had medical or psychiatric conditions that could affect their ability to give informed consent. Participants were also excluded for known sensitivity to gadolinium chelates or an inability to undergo MRI. The study was approved by local ethics committees.

Procedures

The study was a double-blind, placebo-controlled, randomised trial lasting 56 weeks. For trial purposes a month was defined as 4 weeks or 21–35 days. Eligible patients underwent physical and neurological examination including assessment with EDSS, ambulation index, timed 25 foot walk, electrocardiogram, chest radiography, and laboratory studies. The coordinating centre reviewed the results of the screening assessments and, if all inclusion and exclusion criteria were satisfied, gave approval for patient enrolment. Eligible patients returned within 28 days of screening, again gave written informed consent, had an interval history taken, underwent repeat neurological examination and laboratory testing, and had a brain MRI scan with administration of gadolinium chelates. They were then randomly assigned to a group and received their first dose of study medication under observation. Study drug was provided as 50 mg glatiramer acetate with matching 5 mg placebo, 5 mg glatiramer acetate with matching 50 mg placebo, or as 50 mg and 5 mg matching placebo tablets formulated for enteric release. The randomisation list, stratified by study centres, was computer generated by the Teva Pharmaceuticals Statistics and Data Management Department. Equal allocation of the three treatment groups was used. Eligible participants were assigned a study number by an automated interactive voice response system (ClinPhone, Princeton, NJ, USA).

At each study site a treating neurologist was responsible for the overall medical management of the patient, including safety monitoring. An examining neurologist was responsible for all scheduled neurological examinations and exacerbation follow-ups. All patients had neurological assessments every 2 months (56±7 days); additional assessments were undertaken for symptoms suggestive of a relapse. MRI was done for all patients at 56 weeks and for a cohort of 486 individuals seen at 41 of the sites every 2 months. Safety assessments that included vital signs, haematology, and biochemical tests were done at all regularly scheduled clinical visits. All personnel involved in the study were unaware of the treatment allocation. Both the treating neurologist and the patient were informed of the importance of not discussing safety issues with the examining neurologist.

A relapse was defined as the appearance of one or more new neurological symptoms or the reappearance of one or more previously experienced neurological symptoms.[4,14] Patients were instructed to telephone their local centre immediately if they perceived that they might be experiencing a relapse. A visit was arranged within 7 days of notification. Neurological deterioration had to last at least 48 h and be preceded by a relatively stable or improving neurological state in the prior 30 days. An event was counted as a relapse only when the patient's symptoms were accompanied by objective changes in the neurological examination corresponding to an increase of at least 0·5 points on the EDSS, or one grade in the score of two or more functional systems or two grades in one functional system. Deterioration associated with fever or infections that can cause transient, secondary impairment of neurological function in patients with multiple sclerosis was not regarded as a relapse. Change in bowel, bladder, or cognitive function alone was not accepted as a relapse. The trial principal investigator (GC) reviewed all exacerbation reports to check their consistency with this relapse definition. Relapses could be treated with a standard dose of 1·0 g intravenous methylprednisolone for 3 consecutive days.

The primary outcome was the total number of relapses observed for the intention-to-treat population during the 56 weeks of study treatment. Secondary outcome measures consisted of the number of relapses treated with corticosteroids, the area under the curve for the

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change in EDSS from baseline, the number and volume of enhancing lesions, the number of new lesions on T2-weighted images, and the number of new enhancing lesions in a subcohort of participants undergoing more frequent MRI monitoring. Tertiary outcomes included the change in EDSS from entry to 56 weeks, the timed 25 foot walk, ambulation index, proportion of patients who were relapse free, time to first relapse, proportion of patients who were relapse free by trimester on study, time to the second relapse, number of relapses requiring hospitalisation, brain atrophy, and the number and volume of hypointense lesions on T1-weighted enhanced scans.

Before any clinical site could enrol study participants they were required to image a volunteer patient with clinically definite multiple sclerosis twice with repositioning according to a strict study imaging protocol using imagers with minimum field strength of 1·0 Tesla. These test images were sent to the neuroimaging research unit in Milan as film and electronic data for review to ensure that the site could perform high-quality imaging; 158 MRI sites were approved. Conventional or fast spin echo sequences (TR 2200–2800, TE 15–50/80–120, 3 mm slice thickness and 44 contiguous axial slices) were used to obtain proton density and T2-weighted images. T1-weighted images (TR 600–650, TE 10–20, 3 mm slice thickness and 44 axial slices) were obtained 5 min after the injection of 0·1 mmol/kg of gadolinium chelates. A series of axial, coronal, and sagittal images was obtained to create an axial reference scan for the subsequent careful repositioning of each patient at the follow-up session. Image quality was reviewed centrally according to predetermined criteria. Identification of enhancing lesions, high-signal intensity lesions on T2-weighted images, and hypointense lesions on T1-weighted enhanced images was done by consensus of two experienced observers. Trained technicians then outlined the lesions using a semi-automated segmentation technique based on local thresholding, with reference to the marked hardcopies.[15] Brain atrophy was measured as previously described.[16]

Statistical analysis

The power of the trial was calculated on the basis of a simulation study by use of an SAS random number generator with assumptions that a patient on placebo would have a relapse rate of ┐ and be randomly selected from an exponential distribution with Θ=└┐/n representing the use of the negative binomial distribution with *r*=1. The expected annual placebo relapse rate (Θ) for the study was 0·90. The simulation study was adjusted for two interim analyses according to Lan and DeMet's correction for type I error, leaving final analysis at an alpha level of 0·0428 for the power estimation. Adjustment for two contrasts (5 mg glatiramer acetate *vs* placebo and 50 mg glatiramer acetate *vs* placebo), testing according to Hochberg's modification to Bonferroni's method, based on two-tailed tests, was also taken into account. Power assessment suggested that for a projected treatment effect of 30% or more for the 50 mg glatiramer acetate cohort and of 10% or more for the 5 mg glatiramer acetate group, a 56 week study enrolling 1275 patients would provide 91% power.

The main statistical analysis was based on the outcome of two contrasts (5 mg glatiramer acetate *vs* placebo and 50 mg *vs* placebo) derived from the baseline-adjusted, exposure-weighted, quasi-likelihood (over-dispersed) poisson regression (SAS Proc GENMOD version 9.1.3). This model was predefined for the analysis of the primary endpoint, reflecting our previous experience with relapse count data with a variance larger than the mean rate.[4] Baseline EDSS score, number of relapses in the previous year, age, and sex were predefined in the statistical analysis plan as covariates and thus were included in the analysis model. Study centres were pooled into countries that were also included in the model as prespecified in the statistical analysis plan. The country-by-treatment interaction term was tested, at alpha level of 0·10, with the –2 log likelihood ratio test. Since the interaction term was not statistically significant (p┘ 0·10), it was not included in the model.

Role of the funding source

The study was fully sponsored by Teva Pharmaceutical Industries. Study design, conduct, and analysis were run

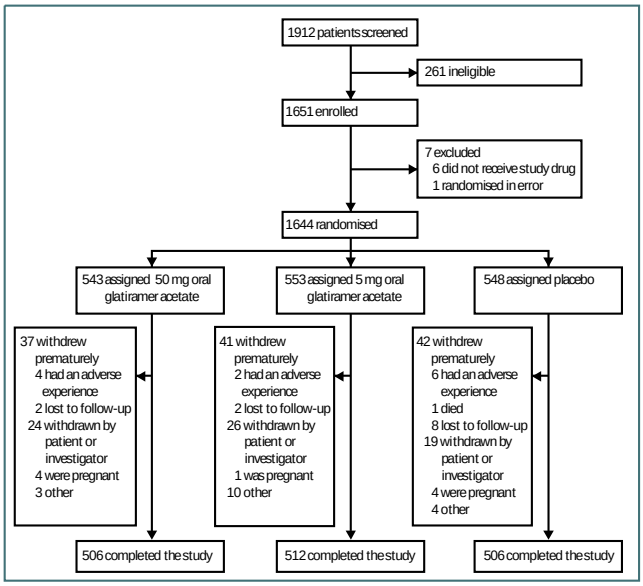

Figure 1: **Trial profile**

	50 mg glatiramer acetate	5 mg glatiramer acetate	Placebo
Age, years	36·8	(7·3)36·1	[illegible]
Women	406	(75%)412	[illegible]
Disease duration, years	7·9		
Prior 2-year relapse rate			
Prior 1-year relapse rate			1·5
EDSS	2·3	(1·1)2·2	[illegible]
Ambulation index	0·8	(0·8)0·8	
Past steroid use	328		(60%)330
Past interferon-beta use	49		
Patients with enhancement			258
Number of enhancing lesions at			
Enhancing lesion volume, mm³	285	(1073)329	[illegible]
T2 lesion volume, mL	13·5 (13·0)	15·1 (15·5)	14·6 (14·4)
T1 hypointense lesion volume, mL			
Central brain volume, mL			306

Data are mean (SD) or number (%).

Table 1: **Baseline characteristics of the intention-to-treat cohort**

under the supervision of an ad-hoc steering committee, made up of independent clinicians and scientists. An independent data safety monitoring committee was responsible for monitoring safety, the two interim analyses, and overseeing the overall progress and integrity of the study. The present manuscript was drafted and finalised independently of the sponsor. The funding source had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 1644 patients were included in the intention-to-treat cohort (figure 1). The study was planned to enrol 1275 patients—ie, much fewer than those who were actually enrolled. The increase in the number of patients enrolled was not driven by any statistical consideration, but reflected the fast recruitment rate (all patients were enrolled in 6 months) and the enthusiasm of the site investigators for an oral treatment for multiple sclerosis. 15 of the study sites enrolled 18 or more patients. The baseline demographics of the intention-to-treat cohort are provided in table 1. 120 patients withdrew from the study prematurely (69 based on the patient's or investigator's decision, 12 related to adverse events, 12 lost to follow-up, nine because of pregnancy, one death from pneumococcal meningitis, and 17 for other reasons). Median exposure to the study drug and time in the study were closely similar for all three treatment groups (data not shown).

The total number of confirmed relapses did not differ between the two active treatment groups and the placebo-treated patients (figure 2). The mean numbers of relapses were 0·54, 0·60, and 0·61 for the 50 mg glatiramer acetate, 5 mg glatiramer acetate, and placebo groups, respectively. The median values were 0 for all study groups. The rate ratio for the groups treated with 50 mg glatiramer acetate, relative to placebo, was 0·92 (95% CI 0·77–1·08, p=0·30) and for the 5 mg glatiramer acetate group, relative to placebo, was 0·98 (0·83–1·15, p=0·76). Post-study power reassessment accounting for the number of patients entered and the observed relapse rate remained at 91% for a 30% treatment effect and was 43% for a 15% treatment effect. The number and proportions of patients who were relapse free, as well as the entire relapse distributions did not differ between treatment groups (figure 3). There was no difference in the time to first confirmed relapse (data not shown). The number of unconfirmed relapses was similar between the three cohorts (0·74, 0·75, and 0·78 for 50 mg glatiramer acetate, 5 mg glatiramer acetate, and placebo groups, respectively). The mean change in EDSS from baseline to termination visit was similar between the treatment groups (–0·03, 0·00, and 0·04, respectively). Ambulation index changed little over the course of the trial for the treatment groups (0·07, 0·04, 0·08). There were no differences for any other secondary or tertiary clinical outcome (data not shown).

Baseline MRI data were available and adequate for analysis of 1590 patients; 1429 patients had adequate termination imaging. Paired imaging data were available for analysis for 1397 patients, or 85% of the intention-to-treat cohort. The mean number of distinct enhancements identified on MRI at study exit did not differ between the treatment groups (table 2). The rate ratio indicated no benefit for 50 mg glatiramer acetate treatment over that of placebo for both the intention-to-treat analysis and for the cohort of patients with active scans at baseline (rate ratio=1·1, 95% CI 0·9–1·35 and 1·03, 0·81–1·32, respectively). No significant differences emerged for any of the other MRI disease measures for the entire cohort with both baseline and

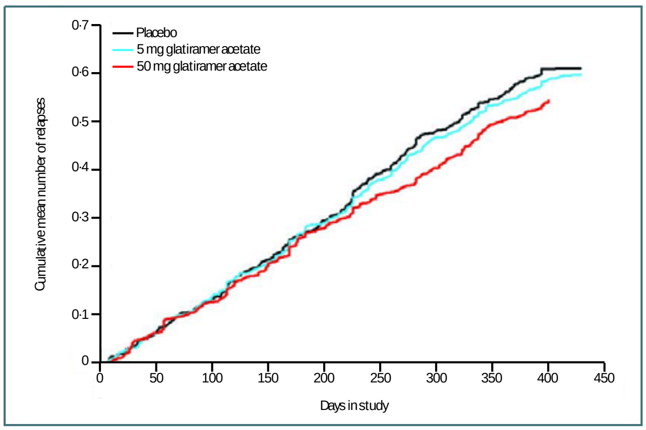

Figure 2: **Mean cumulative number of confirmed relapses during the 56-week trial duration, displayed as a function of the number of days the patients in each group were in the study**

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termination imaging (table 2), or for the subcohort of subjects who underwent bimonthly imaging (data not shown).

Most study patients reported one or more adverse events over the course of the study (table 3). The proportion of patients in any category of recorded events did not differ between the three study groups. The most commonly reported events (experienced at least once by at least 5% of any treatment cohort) in decreasing order of occurrence were infection of any type, headache, asthenia, pain, depression, accidental injury, paraesthesia, nausea, pharyngitis, sleep disorder, abdominal pain, arthralgia, back pain, urinary tract infection, diarrhoea, sinusitis, influenza syndrome, constipation, anxiety, and dyspepsia. Abnormal vital signs were infrequently encountered and were equally distributed among the study groups. No changes in laboratory values were reported in the group data.

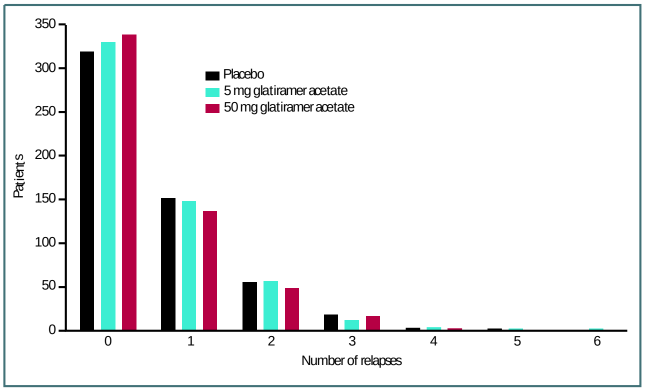

***Figure 3*: Total number relapses during the trial, by treatment group**

Discussion

Previous studies have shown that parenterally administered glatiramer acetate reduces clinical (relapse rate)[1–4,6] and MRI (formation of active lesions) [4] markers of inflammation in patients with relapsing-remitting multiple sclerosis. Data from the MRI-monitored trial, [4] prolonged observation of patients enrolled in the US trial,[3] and meta-analysis of all existing trials [6] have also identified a significant, albeit modest, effect of injected glatiramer acetate on MRI (formation of black holes and development of brain atrophy) [5,7] markers of irreversible tissue loss. On the basis of these findings and on the drug's safety profile, [1–4] glatiramer acetate has become one of several approved treatments for relapsing-remitting multiple sclerosis; the other being three interferon-beta preparations, natalizumab (use suspended) and mitoxantrone, which are all given parenterally. At present, more than 90 000 patients worldwide have been treated with injected glatiramer acetate. Because the drug must be subcutaneously administered on a daily basis and in view of the fact that multiple sclerosis is a lifelong chronic disorder, the availability of effective formulations of glatiramer acetate for oral administration would represent an important advance in the treatment of multiple sclerosis. Orally active treatment would decrease patient discomfort and avoid any local and systemic injection site reactions common to all available treatments. This advance should result in increased patient acceptance and compliance with treatment and, possibly, increased treatment efficacy. Admittedly, this study was undertaken without previous phase II trials on oral glatiramer acetate. Nevertheless, because such trials already existed for the injectable preparation and because these trials are mainly done to gain information about drug safety, it was felt that such trials would have delayed the availability of an oral preparation for the treatment of multiple sclerosis.

Disappointingly, the present double-blind, placebo-controlled, randomised, phase III trial of two doses of glatiramer acetate formulated as enteric-coated tablets yielded overall negative results for both clinical and MRI measures of multiple-sclerosis-related disease activity and irreversible tissue damage. Taking into account the sensitivity of the outcome measures used and the number of patients treated in the present trial, the lack of an effect seems to be a credible result. There are several possible explanations for such a result. First, trial primary outcome measure power calculations were based on an expected frequency of relapse that was

	50 mg glatiramer acetate	5 mg glatiramer acetate	Placebo
Enhancing lesion number	1·78	(4·06)1·82	
Patients with enhancement	206	(44%)200	
Change in enhancing lesion volume, mm³	–12·6	(1175·2)–97·9	(759·3)–89·4
New T2 lesions	6·5	(10·6)7·9	
Change in T2 lesion volume, mm³	792·4	(3205·2)772·7	(3639·8)882·22 (4320·7)
New T1 hypointense lesions	1·6		
Change in brain volume, mL	–7·5		

Data are mean (SD) or number (%).

***Table 2:* MRI findings at termination or change from baseline in the intention-to-treat cohort**

	50 mg glatiramer acetate	5 mg glatiramer acetate	Placebo
Any adverse event	456	(84%)462	
Cardiovascular system	61	(11%)53	(10%)63
Gastrointestinal system	182	(34%)175	(32%)173
Endocrine system	5	(1%)3	(1%5)
Haematic and lymphatic system	15		
Metabolic and nutritional disorders	40		
Musculoskeletal system	94	(17%)97	(18%)97
Nervous system	198	(37%)211	(38%)203
Respiratory system	136	(25%)128	(23%)126
Skin	81	(15%)88	(16%)91
Special senses	75	(14%)69	(13%)70
Urogenital system	123	(23%)127	(23%)119

***Table 3:* Number of adverse events, by body systems and treatment groups**

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