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Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled trial

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Summary

Background Glatiramer acetate, approved for the treatment of relapsing-remitting multiple sclerosis, reduces relapses and disease activity and burden monitored by MRI. We assessed the efficacy of early treatment with glatiramer acetate in delaying onset of clinically definite multiple sclerosis.

Methods In this randomised, double-blind trial, undertaken in 80 sites in 16 countries, 481 patients presenting with a clinically isolated syndrome with unifocal manifestation, and two or more T2-weighted brain lesions measuring 6 mm or more, were randomly assigned to receive either subcutaneous glatiramer acetate 20 mg per day (n=243) or placebo (n=238) for up to 36 months, unless they converted to clinically definite multiple sclerosis. The randomisation scheme used SAS-based blocks stratified by centre, and patients and all personnel were masked to treatment assignment. The primary endpoint was time to clinically definite multiple sclerosis, based on a second clinical attack. Analysis was by intention to treat. A preplanned interim analysis was done for data accumulated from 81% of the 3-year study exposure. This study was registered with ClinicalTrials.gov, number NCT00666224.

Findings All randomly assigned participants were analysed for the primary outcome. Glatiramer acetate reduced the risk of developing clinically definite multiple sclerosis by 45% compared with placebo (hazard ratio 0·55, 95% CI 0·40–0·77; p=0·0005). The time for 25% of patients to convert to clinically definite disease was prolonged by 115%, from 336 days for placebo to 722 days for glatiramer acetate. The most common adverse events in the glatiramer acetate group were injection-site reactions (135 [56%] glatiramer acetate *vs* 56 [24%] placebo) and immediate post-injection reactions (47 [19%] *vs* 12 [5%]).

Interpretation Early treatment with glatiramer acetate is efficacious in delaying conversion to clinically definite multiple sclerosis in patients presenting with clinically isolated syndrome and brain lesions detected by MRI.

Funding Teva Pharmaceutical Industries, Israel.

Introduction

Multiple sclerosis is an inflammatory demyelinating disease of the CNS with axonal injury and loss, which are closely associated with the acute inflammatory phase of lesion development. The extent of axonal injury correlates with the degree of inflammation, which depends on disease duration and clinical categorisation.[1] Clinically isolated syndrome is the term commonly used for a neurological attack, lasting at least 24 h, which is presumably caused by inflammatory demyelination in one or more sites of the CNS. Patients who present with clinically isolated syndrome do not have evidence of the dissemination in time or space that is required for diagnosis of multiple sclerosis,[2] but have a variable risk to develop this disease.[1,3,4]

Pathological and MRI studies, especially those using new techniques exploring structural nervous damage, have shown that irreversible axonal damage is already detectable at the first attack of multiple sclerosis, probably because of the inflammation-induced axonal transection produced in the acute lesions.[5–8] Moreover, the amount of inflammatory activity at clinical presentation of the disease has some predictive value for long-term disability.[9] Thus, some investigators have suggested early treatment with disease-modifying drugs to prevent or delay the initiation or progression of irreversible neuronal damage.[1,10,11] Six disease-modifying drugs are approved for use in relapsing forms of this disease.[12] Of these drugs, intramuscular interferon beta-1a[13] and subcutaneous interferon beta-1b[14] have been approved for reducing risk and delaying time to a second demyelinating event in patients with clinically isolated syndrome.

Glatiramer acetate (Copaxone) is approved for reduction in the frequency of relapses in patients with relapsing-remitting multiple sclerosis. Daily subcutaneous injection of glatiramer acetate reduces relapse rate, MRI activity, and disease burden.[15–17] On the basis of glatiramer acetate's mechanism of action, its proven efficacy, and favourable safety profile, this drug was regarded as a promising candidate for the treatment of patients with

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clinically isolated syndrome. The PreCISe (early glatiramer acetate treatment in delaying conversion to clinically definite multiple sclerosis in subjects Presenting with a Clinically Isolated Syndrome) study was therefore designed to assess the effect of glatiramer acetate compared with placebo on the time to clinically definite multiple sclerosis.

Methods

Study design and patients

The PreCISe trial was a randomised, double-blind, placebo-controlled, parallel group phase 3 study. It was undertaken in 16 countries worldwide, in 80 sites from the USA, Europe, Argentina, Australia, and New Zealand.

Enrolment started in January, 2004, and was completed in January, 2006. Patients aged between 18 and 45 years inclusive, with one unifocal neurological event, and positive brain MRI at screening scan were included. Brain MRI was positive if there were at least two cerebral lesions on the T2-weighted images at least 6 mm in diameter. Lesion size was assessed visually on hard copies, and only lesions that were present on two consecutive slices—each of which was 3 mm thick—were considered to meet this inclusion criterion. Patients had to be enrolled within 90 days after onset of their first clinical attack. Patients with multifocal clinical presentation, diseases other than multiple sclerosis responsible for the clinical or MRI presentation, use of experimental or investigational drugs, any use of beta interferon or chronic corticosteroids treatment within 6 months of screening, a relapse between screening and baseline visits, pregnancy or breastfeeding, and a known sensitivity to mannitol or gadolinium were excluded. The protocol and consent documents were approved by the institutional review boards and ethics committees of the participating centres. Patients provided written informed consent before undergoing any study-related procedures.

An Eligibility Evaluation Committee (EEC) supervised the enrolment process. The committee consisted of two expert neurologists (VM, MRo, or LM) who reviewed all the documentation received from the sites for every patient who was screened. The decision regarding the eligibility of patients and their classification to unifocal and multifocal presentations had to be unanimous. Unifocal presentation was defined by signs and symptoms that could only be attributed to a single lesion in the cerebrum, above foramen magnum (excluding the optic nerve), both infratentorial and supratentorial or spinal cord or optic nerve; multifocal presentation was defined by signs and symptoms that could be explained by the presence of multiple lesions. In case of disagreement between the two members, the final decision was made by the chairman (GC) of the EEC.

Randomisation and masking

Patients were treated with a daily subcutaneous injection of either a single-use prefilled syringe containing 1 mL solution consisting of glatiramer acetate (Teva Pharmaceutical industries, Kfar Saba, Israel) 20 mg, 40 mg mannitol, and water; or matching placebo. During the screening period, patients were assigned a screening number. After meeting the inclusion or exclusion criteria, assignment of patients to a treatment group was done according to the randomisation scheme produced by the sponsor of the study (Teva Pharmaceuticals), with a 1:1 assignment ratio. The randomisation scheme used SAS-based blocks with block size of 4, stratified by centre.

Scheduled site visits occurred during the placebo-controlled phase at screening, baseline, month 1, and every 3 months thereafter. A planned interim analysis was done for possible early termination of the study when 81% of the 3-year placebo-controlled study exposure, pertaining to the primary endpoint, was accumulated.

Study drugs were packaged and labelled in a way that maintained the masked nature of the study; the appearance, shape, colour, and smell were identical. Patients and all personnel were masked to the treatment assignment. Patient and investigator masking was not formally assessed. The unmasked statistician presented unmasked results to the Data Monitoring Committee (DMC), as per their request. For the interim analysis, all necessary procedures for using the codes and maintaining the masking were done in accordance with the sponsor's standard operating procedures. Treating and examining neurologists at the sites were masked to MRI results during the study.

Procedures

Onset of clinically definite multiple sclerosis was defined by a second relapse—ie, the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities lasting at least 48 h and preceded by a fairly stable or improving neurological state for at least 30 days. The second relapse had to occur in the absence of fever or known infections. This criterion differed from the clinical definition of exacerbation of at least 24 h duration of symptoms and from Poser criteria.[18] An event was counted as a relapse only when the patient's symptoms were accompanied by observed objective neurological changes, consistent with an increase of at least 0·5 points on the expanded disability status scale (EDSS) or one grade in the score of two or more of the seven functional systems (FS); or two grades in the score of one of the FS compared with the previous assessment. Patients were instructed to telephone their local centre immediately if any symptoms suggestive of a relapse occurred. The treating neurologist assessed patients within 7 days of the patient notification to the site. The examining neurologist undertook a complete neurological assessment including Kurtzke EDSS, FS assessment, and ambulation index.

Treatment for relapses was determined by the examining neurologist and consisted of a fixed dose of

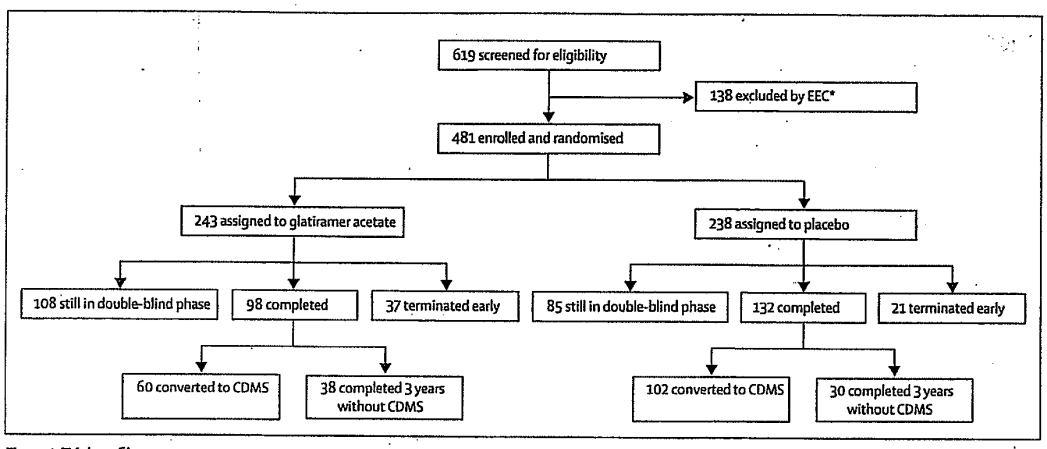

Figure 1: **Trial profile**
EEC=Eligibility Evaluation Committee. CDMS=clinically definite multiple sclerosis. *50 patients did not meet MRI criteria, 16 had multifocal presentation, 14 had diseases other than multiple sclerosis responsible for the clinical or MRI presentation, 14 relapsed between screening and randomisation, ten were outside timeframe for inclusion, and 34 withdrew consent or were lost to follow-up before the baseline visit.

1 g per day of intravenous methylprednisolone for a maximum of 3 consecutive days. The type of steroid treatment at the presenting event before randomisation was not regulated and uniformed. Once a patient converted to clinically defined multiple sclerosis, the patient was transferred to the active open-label phase of the study.

The Neuroimaging Research Unit in Milan, Italy, served as the MRI analysis centre. Before any site could enrol study participants they were required to image a volunteer patient with definite multiple sclerosis twice, with repositioning according to a strict study imaging protocol with use of imagers with minimum field strength of 1·0 T. Imaging assessments were done at screening for eligibility, at baseline, month 3, and every 3 months thereafter until conversion to clinically defined multiple sclerosis or the end of the placebo-controlled study. After conversion or after the end of the placebo-controlled phase and enrolment into the open-label study, MRI assessments were done every 6 months.

We used conventional or fast spin echo sequences (repetition time 2200–2800 ms, echo time 15–50/80–120 ms, echo train length 4–6, 3 mm slice thickness, and 44 contiguous axial slices) to obtain proton-density and T2-weighted images. Conventional spin echo T1-weighted images (repetition time 600 ms, echo time 10–20 ms) with the same scan geometry were obtained 5 min after injection of 0·1 mmol/kg of gadolinium. We obtained a series of axial, coronal, and sagittal images to create an axial reference scan for subsequent careful repositioning of every patient at the follow-up session.[19] Axial slices were positioned to run parallel to a line joining the most inferioanterior and inferioposterior parts of the corpus callosum.

Image quality was reviewed at the MRI analysis centre with predetermined criteria. Unsatisfactory images were rejected and repeated. The identification of Gd-enhancing T1-weighted (GdE), T2-hyperintense, and postcontrast T1-hypointense lesions was done by consensus of two experienced observers, as previously described.[20,21] At baseline, we counted the number of total GdE lesions and T2-hyperintense lesions. On follow-up scans, we counted the number of total and new GdE lesions, new T2-hyperintense lesions, and postcontrast new T1-hypointense lesions (on 6-monthly scans). Trained technicians then outlined the lesions with a semiautomated segmentation technique based on local thresholding with reference to the marked hardcopies. New T2-hyperintense lesions were defined as those appearing in an area of previously normal white matter and clearly separated by a rim of isointense signal from other possible hyperintense areas. We counted only new T2-hyperintense lesions. We decided a priori not to count enlarging lesions because there is no cut-off available and accepted to define lesion enlargement, and because such a counting method is poorly reproducible and does not add to the count of new T2-hyperintense lesions.

	Glatiramer acetate (n=243)	Placebo (n=238)
Adverse event	14 (5·8%)	4 (1·7%)
Failed to return	1 (0·4%)	2 (0·8%)
Patient's decision	15 (6·2%)	12 (5·0%)
Request of primary care physician or investigator	0	2 (0·8%)
Sponsor's decision	1 (0·4%)	0
Pregnancy	3 (1·2%)	2 (0·8%)
Non-compliance	1 (0·4%)	0
Death	1 (0·4%)	0
Other	3 (1·2%)	1 (0·4%)

Table 1: **Reasons for early termination of treatment**

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