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A prospective open-label study of glatiramer acetate: over a decade of continuous use in multiple sclerosis patients

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A decade of continuous glatiramer acetate (GA) use by relapsing remitting multiple sclerosis (RRMS) patients was evaluated in this ongoing, prospective study, and the neurological status of 'Withdrawn' patients was assessed at a 10 year long term follow up (LTFU) visit. Modified intention to treat (mITT, $n=232$) patients received ≥ 1 GA dose since 1991; 'Ongoing' patients ($n=108$) continued in November 2003. Of 124 patients, 50 Withdrawn patients returned for LTFU. Patients were evaluated every six months (EDSS). Mean GA exposure was 6.99, 10.1 and 4.26 years for mITT, Ongoing, and Withdrawn/LTFU patients, respectively. While on GA, mITT relapse rates declined from 1.18/year prestudy to ~ 1 relapse/5 years; median time to ≥ 1 EDSS point increase was 8.8 years; mean EDSS change was 0.73 ± 1.66 points; 58% had stable/improved EDSS scores; and 24, 11 and 3% reached EDSS 4, 6 and 8, respectively. For Ongoing patients, EDSS increased 0.50 ± 1.65; 62% were stable/improved; and 24, 8 and 1% reached EDSS 4, 6 and 8, respectively. For Withdrawn patients at 10 year LTFU, EDSS increased 2.24 ± 1.86; 28% were stable/improved; and 68, 50 and 10% reached EDSS 4, 6 and 8, respectively. While on GA nearly all patients (mean disease duration 15 years) remained ambulatory. At LTFU, Withdrawn patients had greater disability than Ongoing patients. *Multiple Sclerosis* 2006; **12**: 309 320. www.multiplesclerosisjournal.com

Key words: disability; disease modifying therapy; EDSS; glatiramer acetate; immunomodulator; relapse; relapsing remitting multiple sclerosis

Introduction

Currently, the best therapeutic options for relapsing remitting multiple sclerosis (RRMS) patients are the disease-modifying therapies: glatiramer acetate (GA) and the beta-interferons, subcutaneous (SC) IFNβ-1b, SC IFNβ-1a, and intramuscular (IM) IFNβ-1a [1]. There is growing consensus that immunomodulatory therapy should begin shortly after RRMS diagnosis, and to prevent or delay progression of disability, continuous therapy may be recommended for many years [1–3]. However, evidence of long-term clinical efficacy, safety, and patient acceptance of immunomodulatory therapy is scarce. Indeed, the designation 'long-term' to describe clinical data for immunomodulators is arbitrary – three to five years [4–6], is a relatively short interval considering the predicted treatment duration and disease course noted in MS natural history studies [2].

The ongoing US Glatiramer Acetate Trial began in 1991 and is unique in that it is the only organized, ongoing, open-label study of more than 10 years duration to prospectively evaluate

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continuous immunomodulatory therapy in RRMS patients. Prospective clinical efficacy data were reported for continuous IFNβ-1b (Betaseron®) use at four to five years, continuous IFNβ-1a SC (Rebif®) at four years, and continuous IFNβ-1a IM (Avonex®) at approximately two years after initiation of their respective pivotal double-blind trials [4–6]. Further data have since been collected in non-continuous and/or retrospective, open-label extensions of these studies. In some cases, data were collected retrospectively after considerable intervals in which patients were not monitored and during which they may have discontinued, switched, or added other medications to the immunomodulatory therapy under study. Another MS treatment, natalizumab (Tysabri®) remains under investigation; reported efficacy data reflect only two years of clinical experience and the full serious side effect profile of this drug remains uncertain [7].

This GA study began with a double-blind, placebo-controlled phase in which 251 RRMS patients were randomized to receive GA (20 mg) or placebo by SC injection daily [8,9]. After double-blind treatment for a mean of 30 months, all patients were offered active treatment as part of an ongoing, prospective, open-label study. Reported clinical efficacy results six and eight years after randomization of GA therapy comparing differences in clinical outcomes between patients who received GA from study inception versus those in patients who began treatment approximately 2.5 years later (ie, patients originally randomized to placebo), demonstrate the benefits of early GA therapy compared with delayed therapy [10–12].

This paper describes long-term experience with GA in all patients who received it during the double-blind and/or open-label phases of the study. The primary aim was to determine the long-term effects of GA in carefully monitored patients who had received continuous GA for a mean of 10 years. A secondary goal was to gather information on patients who had withdrawn from the study – their disease course while in the study and why they discontinued. Those who agreed to return for the long-term follow-up (LTFU) visit were evaluated for their neurologic status approximately 10 years after they had initiated GA therapy.

Methods

Patients in this study were originally enrolled in the US Glatiramer Acetate Pivotal Trial, a double-blind, randomized, placebo-controlled study that began in October 1991. RRMS patients who had experienced two or more medically documented relapses in the previous two years and had EDSS scores between 0 and 5 at entry, were randomized to receive SC GA (20 mg) or placebo daily, administered by self-injection. After double-blind treatment, all patients who had entered the study were given the option to continue in an open-label extension phase. Those patients originally randomized to GA continued to take the drug and those randomized to placebo switched to GA. Details of the double-blind and open-label phases of the study are described elsewhere [8–12]. The modified intention-to-treat (mITT) population in the study reported here differs from the original ITT cohort in the pivotal trial [8], in that this analysis includes only patients who have received at least one dose of GA (19 patients initially randomized to placebo in the pivotal study declined entry into the open-label extension and are excluded from this mITT cohort).

Data cut-off for this analysis occurred in November 2003, a mean of 10.1 years from the beginning of GA therapy for the 108 patients continuing in the ongoing study. Because 10 years was the *mean* treatment duration, patients who had received GA from randomization had been treated for up to 12 years and patients originally randomized to placebo had been actively treated for approximately eight to nine years.

This organized, prospective study is ongoing. The 11 original US academic centers continue to participate, and the Institutional Review Boards at all centers continue to approve the study.

Study design

Ongoing study procedure

Briefly, in the open-label study, neurological status is evaluated in the clinic every six months using the Kurtzke Expanded Disability Status Scale (EDSS) [13]. Patients are examined, usually within seven days, if they experience symptoms suggestive of a relapse (appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours, preceded by a stable or improving neurological state of at least 30 days duration [8–12]). Incidence, severity, and potential cause of adverse events are recorded; serious adverse events are reported to the sponsor and to the FDA as required by protocol. The safety of GA therapy in these patients at 2 [8], 3 [9], 6 [10], and 8 [12], years has been reported previously. During the open-label phase, laboratory assessments (chemistry panel) and vital signs are documented at six-month study visits. In most cases, the same neurologists and study co-ordinators continue to assess patients at each visit.

Any patient who discontinued daily GA, for whatever reason, and/or took another immunomodulator was withdrawn. Therefore, those who remain in the study represent a group of RRMS patients receiving only continuous GA monotherapy for disease modification.

Upon withdrawal, patients were classified by study personnel as: (1) withdrawal due to adverse event; (2) lost-to-follow-up, which included withdrawal from the study without attending a final visit or providing a reason for withdrawal; (3) withdrawal due to 'patient decision'; or (4) withdrawal for other reason(s). Because of overlap in reasons for leaving, the 'patient decision' and 'other' categories were combined. The 'patient decision/other' category was divided into subcategories based on comments patients provided at termination. Subcategories included (but were not limited to) pregnancy, inability to adhere to study protocol (eg, lack of transportation or moving away), a desire to switch or combine therapies, and perceptions of disease worsening. Patients were assigned to a subcategory based on the consensus judgment of three study personnel who independently reviewed patient comments provided at the final visit.

Long-term follow-up visit procedure

Personnel at each center made repeated attempts to contact all study patients who had received GA and withdrawn, to invite them to return for a single LTFU visit at approximately 10 years after GA start. LTFU visits were conducted between July and December 2003. At the LTFU visit, patients underwent neurological evaluation by EDSS, medical history during the time between study discontinuation and LTFU was recorded, and patients were asked what MS medications they had taken during the period between withdrawal and the LTFU visit.

Patient cohorts

The mITT cohort ($n = 232$) included all patients who had received at least one GA dose since study inception. Data reported for the mITT cohort reflect outcomes measured while patients were receiving GA. The mITT cohort was subdivided into the following cohorts: Ongoing, which comprised patients continuing in the study (and, by definition, continuing on GA) at the time of data cut-off, November 2003; Withdrawn Total, which comprised all patients who withdrew from the study before November 2003; Withdrawn with LTFU cohort, which included patients who withdrew from the study and returned for a single LTFU visit 10 years after GA start; and Withdrawn without LTFU cohort, which included patients who withdrew from the study and could not be reached or declined LTFU.

Statistical methods

Baseline demographic and disease characteristics were analysed using descriptive statistics and statistical inference tests (SAS® software, SAS Institute, Cary, NC, USA); comparisons among cohorts were performed using χ^2 for categorical variables and the Wilcoxon non-parametric test for continuous variables. Time to study withdrawal was estimated using Kaplan–Meier survival analysis.

Outcome measures

The yearly relapse rate was calculated by dividing the total number of relapses by the total number of patients in the mITT cohort entering a given treatment year. Accumulated disability was measured by mean EDSS and mean change in EDSS from GA start to the last observation while on GA in all study cohorts, and at LTFU in the Withdrawn with LTFU cohort. Confirmed progression of disability was defined as an increase of ≥ 1.0 EDSS point sustained for at least two clinical assessments, six months apart. Categorical analyses of patients' neurological status were performed; patients were classified as 'stable/improved' if EDSS scores increased by ≤ 0.5 EDSS points, did not change, or decreased from onset of treatment. Categorical analyses were repeated with patients stratified by entry EDSS score (0–2 or ≥ 2.5).

The number of patients who reached confirmed scores of EDSS 4, 6 or 8 while on GA were obtained for the mITT, Ongoing, and Withdrawn Total cohorts (only patients who began GA therapy with EDSS scores lower than the endpoint were included in these analyses). Additionally, Kaplan–Meier survival analysis was used to estimate the time to EDSS 4, 6 and 8 while on GA.

For comparison at 10 years between Ongoing and Withdrawn with LTFU patients, numbers of patients who reached predefined EDSS thresholds by the last observation for Ongoing patients and at the single LTFU visit for Withdrawn with LTFU patients were assessed. Efficacy comparisons at 10 years were made using analysis of covariance (ANCOVA) for change from GA start in EDSS, in which EDSS at GA start was a covariate in the model; χ^2; and when appropriate, Fisher's Exact

Test for categorical change in EDSS and for attainment of predefined EDSS thresholds.

Results

Patient characteristics

A total of 232 patients from 11 US study sites who had received at least one dose of GA since study inception comprised the mITT cohort (Figure 1). One patient discontinued after receiving GA but before undergoing neurological evaluation; therefore, the efficacy evaluable mITT cohort included 231 patients. As of November 2003, 108/232 patients (47%) remained in the study and comprised the Ongoing cohort. Of 124 (53%) patients in the Withdrawn Total cohort, 50 returned for the LTFU visit (Withdrawn with LTFU cohort). In the Withdrawn without LTFU cohort ($n=74$), 27 patients declined the LTFU visit and 47 could not be reached, including five patients known to have died. Deaths occurred one to six years after study withdrawal; three deaths were at least partly attributed to MS complications, there was no information about one death, and one death was listed as sudden and unexplained.

There were no differences among study cohorts in age, gender, disease duration, or annualized relapse rate in the two years before beginning GA (Table 1). Mean MS disease duration at GA start was 8.3 years in the mITT cohort.

Patient withdrawal

The Kaplan–Meier estimate of the median time from GA start to withdrawal in the mITT cohort was 9.2 years. Patients who withdrew had slightly higher EDSS scores at GA start than those who remained in the study (3.00 ± 1.59 [SD] versus 2.56 ± 1.35, respectively; $P=0.03$). Mean duration of GA treatment was 4.26 ± 3.13 [SD] years (range: 0.2–11.5 years) in the Withdrawn Total cohort (Table 2). When separated into subcohorts, GA exposure was 4.47 ± 2.95 years (range: 0.2–10.4) in the Withdrawn with LTFU cohort, and 4.13 ± 3.26 years (range: 0.2–11.5) in the Withdrawn without LTFU cohort. There were no statistical differences in demographic or disease characteristics at GA start between Withdrawn patients who returned for LTFU and Withdrawn patients who did not return (Table 1).

Reasons for patient withdrawal are listed in Table 3. The most common ($\geq1\%$) adverse events leading to discontinuation were local injection-site reactions (eg, erythema, pain), vasodilation, dyspnea, and urticaria. Patients who left due to the perception that their disease was worsening were not evaluated by objective neurological testing at the time of withdrawal; therefore, whether individual patients had worsened by objective criteria is unknown. The mean change in EDSS score from GA start to the last observed on-treatment EDSS value for all patients in the patient decision/other category ($n=87$) was 1.16 ± 1.65 [SD] and mean EDSS changes in the Withdrawn Total and

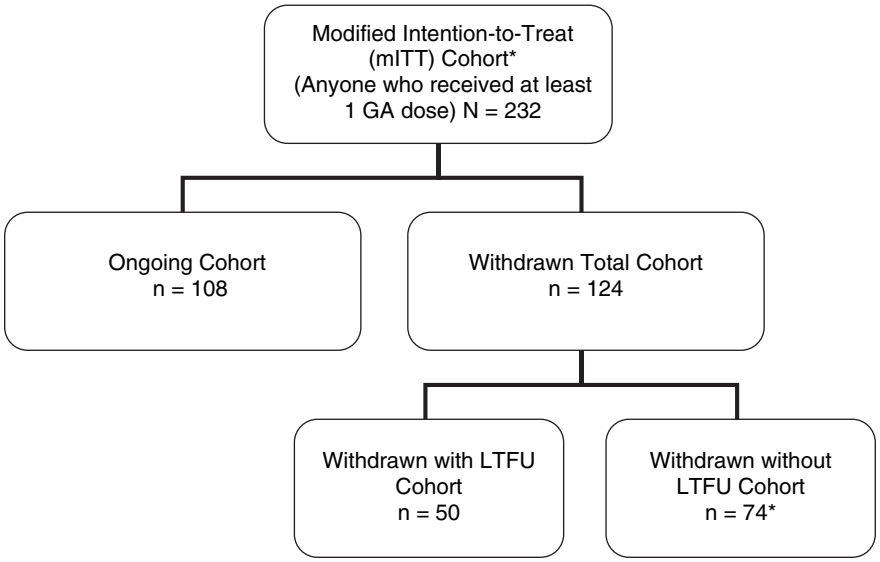

Figure 1 Study cohorts. One patient (in the Withdrawn without LTFU cohort) withdrew after a single GA dose and before an on treatment neurological evaluation; therefore, 231 patients comprised the efficacy evaluable mITT cohort.

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