Long-term, single-arm, open-label, multicenter phase 2/4 study of glatiramer acetate by subcutaneous injection in Japanese patients with relapsing–remitting multiple sclerosis

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Abstract
Objective Glatiramer acetate (GA) has been shown to be a well-tolerated and effective treatment for patients with multiple sclerosis (MS) with relapse. The present open-label study aimed to evaluate the efficacy and safety of long-term treatment with GA.

Methods Japanese patients with relapsing–remitting MS received up to 52-weeks’ treatment with GA 20 mg/mL once daily in the phase 2 study. In phase 4, patients continued to receive treatment after marketing approval in Japan until commercial availability. Key end-points were safety and tolerability of GA. Other analyses included numbers and volumes of gadolinium-enhancing and T2-weighted (T2) lesions.

Results Of 17 patients initially treated, 13 completed 52 weeks’ therapy and 10 completed the phase 4 extension (efficacy assessment: 104 weeks; maximum treatment period/long-term safety assessment: up to 5 years). No new safety signals were observed; most adverse events were mild or moderate, with injection site reactions being the most common. The number of T1 gadolinium-enhancing lesions declined from 2.9 (baseline) to 1.3 (week 104), and the number of T2 lesions increased from 1.7 to 6.7. T1 and T2 lesion volume changes were not clinically meaningful (changes of ~0.090 and 0.088 mL, respectively, by week 104). The mean annualized relapse rate was 2.01 (baseline) and 1.78 (week 104); the mean Expanded Disability Status Scale scores indicated reduced levels of disability.

Conclusions These findings suggest the favorable tolerability and safety profile of GA in Japanese patients, and provide supportive evidence for the efficacy of GA in reducing MS recurrence and improving disability in Japanese MS patients.

Introduction

Multiple sclerosis (MS) is an incurable inflammatory disease with a relapsing, progressive course that is defined by the autoimmune destruction of myelin in the brain tissue and spinal cord.1,2 In Japan, the estimated prevalence of MS is 14 per 100,000; while low compared with Western countries, studies indicate that this figure is increasing.3 There is no curative treatment for MS; however, in recent years, a number of disease-modifying treatments have emerged that not only limit the probability of relapse, but also prevent new disease activity.4 Nevertheless, disease progression cannot be prevented completely, and axonal injury eventually leads to brain atrophy and disability.5 Furthermore, MS presents with a number of
health-related quality of life issues ranging from psychosocial factors, including depression and lack of self-efficacy, to neuropsychiatric complications, such as cognitive dysfunction, fatigue and physical impairment. MS is considered the leading cause of non-traumatic disability in young- and middle-aged adults in developed countries. Glatiramer acetate (GA; Copaxone, Teva Pharmaceutical Industries, Petach Tikva, Israel and Takeda Pharmaceutical Company, Tokyo, Japan) is a synthetic amino acid polymer analog of myelin basic protein, considered to exert clinical activity in MS by immunomodulatory and neuroprotective mechanisms. In use for >20 years in multiple countries, a wealth of evidence shows that GA is an effective agent in reducing the incidence of relapse of relapsing-remitting MS (RRMS), and consequently in preventing disease progression. GA is also well tolerated.

Recently, we reported the results of a phase 2 study of GA 20 mg/mL QD in 17 Japanese patients with RRMS. In that study, GA was shown to significantly reduce the total number of T1 gadolinium-enhancing (GdE) lesions from an adjusted mean of 5.66 lesions pre-treatment to an adjusted mean of 1.94 during 36 weeks of treatment, a 65.66% reduction. In addition, the point estimate of the total number of new T2 lesions decreased from an adjusted pre-treatment mean of 3.28 to 1.49 post-treatment. GA also showed an acceptable safety profile, with adverse events (AE) that were exclusively mild-to-moderate in severity in this patient population. The most common drug-related AE were local injection site reactions, including erythema, pain and induration; three patients reported serious AE and no patients died on-study.

Here, we present the results of the extension part of this phase 2 study evaluating the long-term efficacy and safety outcomes associated with the long-term use of GA 20 mg/mL QD in Japanese patients with RRMS.

Methods

Study design

The present long-term, single-arm, open-label, multicenter study was carried out in patients with RRMS who were enrolled in a phase 2 study at eight sites in Japan. Details of the phase 2 study design and methods have previously been reported, and are briefly summarized here, along with additional methods relevant to the extension section of the study.

Initially, eligible patients underwent an 8-week pre-treatment screening phase, followed by 52 weeks of treatment with subcutaneous GA administered at 20 mg/mL QD by self-injection. For the extension section, consenting patients continued to receive GA until the drug became commercially available, with key efficacy end-points being assessed up to 104 weeks, and long-term safety being assessed up to 5 years after the commencement of the phase 2 study. Patients were followed up for 30 weeks after treatment was discontinued.

The protocol for this research project was approved by the institutional review board of each study site, and conforms to the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written, informed consent.

Patients

Key inclusion and exclusion criteria for the present study have previously been described. In brief, eligible patients were Japanese and had confirmed RRMS as per the Revised McDonald Criteria (2005); at least one MS recurrence in the previous year, but no relapse in the 30 days before screening; 1–15 GdE lesions on any three screening magnetic resonance imaging (MRI) scans; and Expanded Disability Status Scale (EDSS) of 0–5.0. Key exclusion criteria included the use of specified treatments within certain time periods before the study (e.g. corticosteroids or adrenocorticotropic hormones within 30 days, immunosuppressive treatments [except azathioprine] within 6 months and any prior cladribine, natalizumab, total body or lymphoid irradiation or stem cell treatment); a diagnosis of opticospinal MS; and/or prior GA use.

End-points and assessments

Key end-points investigated during the extension section of the study included the number of GdE lesions at each time-point; the number of T2-weighted (T2) lesions; the change in the volumes of GdE and T2 lesions (measured as change from baseline to specified time-points); annualized relapse rate (ARR); change in EDSS, functional systems and Ambulation Index scores; neurological symptoms; safety and tolerability. GdE and T2 lesions were evaluated using MRI scans, which were sent electronically to an MRI reading center for blinded, unbiased interpretation of the results. All assessments were carried out during screening to obtain baseline values, then at
regular intervals up to week 52. During the extension section after week 52, MRI assessments were undertaken at week 104, whereas EDSS scores were evaluated at week 78 and week 104, then every 26 weeks until study completion or study drug discontinuation. Disease relapse was evaluated at weeks 65, 78, 91 and 104, then every 13 weeks, and an ARR was calculated.

Safety was assessed every 26 weeks for up to 5 years by AE, laboratory tests, vital signs, physical examination and electrocardiogram. AE were coded using MedDRA/J version 17 (MedDRA MSSO, McLean, VA, USA).

Serum samples were analyzed for the presence of anti-GA antibodies (an immunological end-point).

Statistical analysis

Two analysis datasets were defined. The full analysis set was used for efficacy analysis, and included all patients who received at least one dose of study drug and had one or more MRI scan result at 28, 32 or 36 weeks during phase 2. The safety analysis set included all patients who received at least one dose of study drug. Efficacy and safety outcomes were reported using descriptive statistics.

Results

Study population

From an initial 40 eligible patients, 17 were treated, with 13 completing 52 weeks of treatment. All 13 patients continued into the extension section of the study, which continued until GA was commercially available; three patients discontinued and 10 patients completed the extension study (Fig. 1). The median duration of treatment for the entire study for all 17 patients was 1577.0 days (range 28–1875); median rate of treatment adherence during the extension section was 99.6% (range 86.0–100.0%).

Of the 17 treated patients, 16 were female and the mean age was 38.8 years (standard deviation [SD 7.5 years]). Patients had a disease duration of 84.8 months (SD 83.7 months), with an average of 2.0 (SD 2.2) relapses in the previous year. The mean EDSS was 2.5 (SD 1.2).

Number and volume of T1 GdE lesions

Table 1 shows that after an initial decline in T1 GdE lesion number in the phase 2 portion of the study (from 2.9 at baseline to 0.4 at week 36), the mean number of GdE lesions increased slightly by week 52 (1.2), then leveled out at week 104 (1.3), equating to an overall decline in number versus baseline. The mean change from baseline in the volume of GdE lesions was −0.122 mL at week 36, −0.056 mL at week 52 and −0.090 mL at week 104 (Table 1).

Number and volume of new T2 lesions

After an initial fall in the number of new T2 lesions during the phase 2 part of the study (from 1.7 at baseline to 0.6 at 36 weeks), the mean number of new T2 lesions rose in the phase 4 period of the study from 3.5 at 52 weeks, to 6.7 at 104 weeks (Table 2). T2 lesion volume fell initially during the phase 2 portion of the study, but then rose at
104 weeks, giving a mean change from baseline (week 0) of 0.088 mL (Table 2).

Annualized relapse rate

The ARR was calculated for all 17 phase 2 patients up to 104 weeks, regardless of whether patients were still receiving treatment. The ARR dropped from a mean of 2.01 (SD 2.27) at baseline to 1.88 (SD 3.28) at 36 weeks, 1.91 (SD 3.21) at 52 weeks and 1.78 (SD 3.18) at 104 weeks.

EDSS, functional systems and Ambulation Index scores

Mean EDSS scores were slightly lower than baseline (week 0) at all post-administration assessments during the extension period (Table 3), indicating less disability. The change in mean EDSS score from baseline to 52 weeks was minimal (−0.03); however, the change from baseline improved during follow-up, from −0.29 at 104 weeks to a maximum of −0.64 at 182 weeks. No changes from baseline were seen in functional systems or Ambulation Index score during the phase 4 portion of the study (data not shown).

Safety and tolerability

Safety was assessed during the entire study, which was up to 5 years from the start of the phase 2 study, with the longest duration of safety assessment conducted after 247 weeks. All 17 patients (safety analysis set) from the entire study experienced ≥1 treatment-emergent AE (TEAE). Most TEAE were judged as mild or moderate; one patient experienced two severe TEAE (mental impairment and restlessness). Most common TEAE (≥3 cases) per preferred term included injection site reactions, (e.g. erythema, induration, pain; n = 16 [94.1%]), nasopharyngitis (n = 11 [64.7%]) and pyrexia (n = 5 [29.4%]). Rates across the entire study (up to 247 weeks) were not notably different from those for phase 2 only (52 weeks; Table 4).14 Almost all single occurrences of these AE were considered as drug-related. Six patients reported a total of seven serious AE (SAE), including two events of MS and one of MS relapse that were considered drug-related, and four events (one each of MS, sinus bradycardia, restlessness and psychotic disorder) that were considered unrelated to the study drug. Of these, three patients reported an SAE during the main administration period and three during the extended
administration period. No deaths occurred during the study.

Abnormal changes in laboratory values were generally transient, with none reported as SAE or leading to discontinuation. In urinalysis, one AE (proteinuria) was reported, which resolved in 36 days. There were no clinically significant changes in vital signs (body temperature, blood pressure, pulse) or electrocardiogram results. The most common findings on physical examination were skin-related and were mainly related to injection site reactions.

Immunological evaluation

At the last patient visit during the extension section of the study, which occurred after the 52-week phase 2 study, one or more serum samples were available from 12 patients for evaluation of anti-GA antibodies. After administration of GA between week 52 and the end of the study, three of 13 analyzed samples were anti-GA antibody-positive. Results of the anti-GA antibody evaluation during the phase 2 part of the study were previously reported.14

Discussion

The objective of the present extension study was to evaluate the longer-term efficacy and tolerability of GA when administered subcutaneously at 20 mg/mL QD to Japanese patients with RRMS. Our results suggest that, although MRI-assessed MS disease activity decreased during the initial 52 weeks, the number and volume of T1 GdE lesions did not continue to drop, but leveled out at values that were, nevertheless, below those observed during the screening period. The number of new T2 lesions, however, increased during the extension phase to levels that were well above those measured during the screening period (1.7 at baseline vs 6.7 at week 104).

EDSS scores improved throughout administration, and these improvements were sustained for as long as 234 weeks. However, the mean change was not quite of the magnitude (1 unit) that is considered to be clinically meaningful in patients with baseline EDSS scores of ≤5.16 Despite somewhat disappointing findings in terms of improvement in MRI-assessed disease activity and disability ratings, relapse rates continued to decline over time; from a mean of 2.01 at baseline to 1.78 at 104 weeks. Evidence suggests that with ongoing GA treatment, ARR would continue to decrease.17

Although this study does not show large improvements in MRI-assessed disease activity after long-term use of GA, other much larger studies have shown sustained reductions in the number and volume of T1 GdE and T2 lesions, with both short- and long-term GA treatment,10,18 along with efficacy in terms of reducing relapse and slowing progression of disability.8–12,19 In the open-label phase of a trial involving 224 mainly Caucasian patients with RRMS treated with GA, substantial, sustained reductions in GdE lesions (54% when switching from placebo;
additional 24.6% in patients remaining on GA) after 9 months of treatment were shown. Further analysis of that phase 3 study, after a mean 5.8 years of follow up, showed that, despite unchanged MRI parameters, disability status was improved. Similar results were observed in a Spanish population; although these patients did not achieve improved EDSS scores with GA, significant improvements were observed regarding time to EDSS progression and health-related quality of life for GA-treated patients when compared with non-GA-treated patients.

Perhaps most importantly, the present study confirms the safety and tolerability of subcutaneous GA at 20 mg/mL when given QD for at least 104 weeks in Japanese patients. The TEAE reported in the present study were consistent with the known side-effects of GA administration in predominantly Caucasian patients, including local injection site reactions (erythema, pain and edema) and symptoms associated with an immediate post-injection reaction, which can include vasodilation, chest pain, palpitation, tachycardia or dyspnea. Another long-term study has similarly reported sustained tolerability, with no evidence of cumulative toxicity. In comparison with other available treatments for RRMS, there is little evidence for the infusion-related reactions or the development of neutralizing antibodies that have been linked with interferon therapy. Similarly, there have been no reports to date of GA being associated with progressive multifocal leukoencephalopathy – an AE that has been observed during treatment with other disease-modifying agents, such as natalizumab, and to a lesser degree with fingolimod and dimethyl fumarate. We acknowledge, however, that patients might find the route of administration for GA in the form of daily injections to be a disadvantage compared with orally-available treatment options.

The results presented in this analysis are limited in power due to the small sample size, which might be due, in part, to the low prevalence of MS in Japan compared with other countries. Patients with suboptimal safety and efficacy would have been more likely to withdraw than those with better outcomes, who might have continued until the end of the study. As the trial was uncontrolled, this might have biased the safety as well as the efficacy evaluations. Furthermore, efficacy and safety outcomes in the current study were subject to only descriptive statistical analysis, meaning that the statistical relevance of the results is uncertain. Additionally, the gender imbalance present in our study might limit the applicability of the findings to Japanese men with RRMS; however, the evidence to date does not suggest that response to GA is influenced by gender.

Exactly why MRI-assessed disease activity and disability, as measured by EDSS, plateaued during the extension phase of the present study is unclear. Recent findings suggest that genetic factors might underlie the response of individual patients to GA, with a four-SNP genetic signature significantly associated with response in a mainly Caucasian population. Given that genetic differences have been observed between Caucasian and Japanese patients with MS, it seems possible that genetic variability at an individual level, and between Japanese and Caucasian individuals, might at least partly explain the differences in response seen in the extension phase of the present study compared with the more impressive responses reported after extended treatment in other, mostly Caucasian, populations.

We detected anti-GA antibodies in just three of 13 patient samples taken during the phase 4 portion of the study; in contrast, all patients were positive on at least one time-point during phase 2. The finding that the anti-GA antibody levels, which do not interfere with the efficacy or functioning of GA in vitro, are lower after extended time periods is in keeping with prior observations.

To conclude, in this extension section of the original 52-week, open-label, single-arm phase 2 study, although ARR continued to fall for up to 104 weeks after treatment commenced, the improvements in MRI-assessed disease activity plateaued after the first 52 weeks of treatment. The phase 4 portion of this study confirms the longer-term safety of GA in Japanese patients, with no new safety signals identified relative to Caucasian populations. Overall, these findings confirm the efficacy and safety of GA in reducing MS relapse and improving disability, and support its continuing use in Japanese RRMS patients.

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Disclosure of ethical statements

The participating study sites in Japan were: Sapporo Neurology Clinic, Sapporo; Obihiro Kosei General Hospital, Hokkaido; Yamaguchi University Graduate School of Medicine, Yamaguchi; Tokyo Women’s Medical University Yachiyo Medical Center, Chiba; National Hospital Organization Iou Hospital, Ishikawa; Juntendo University Hospital, Tokyo; Utano Hospital, Kyoto; and National Institute of Neuroscience and Multiple Sclerosis Center, National Center of Neurology and Psychiatry, Tokyo. The protocol for this research project was approved by suitably constituted ethics committees of each study site, and it conforms to the provisions of the Declaration of Helsinki. Written informed consent was obtained from all patients before participating in the study.

Conflict of interest

Author T.Y. has served on scientific advisory boards for Biogen Idec and Takeda Pharmaceutical; has received travel funding and/or speaker honoraria from Biogen Idec, Dainippon Sumitomo Pharma, Bayer Holding, Chugai Pharmaceutical, Takeda Pharmaceutical, Ono Pharmaceutical and Mitsubishi Tanabe Pharma; has received research support from Chugai Pharmaceutical, Teva Pharmaceutical, Takeda Pharmaceutical, Novartis Pharma, Nihon Pharmaceutical, Biogen Idec and Asahi Kasei Kuraray Medical. Author T.F. serves has served on scientific advisory boards for Bayer Pharma, Biogen Idec, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical and Novartis Pharma; has received funding for travel and speaker honoraria from Bayer Pharma, Biogen Idec, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical and Novartis Pharma. Author M.T. has received speaker honoraria from Biogen Idec Japan, Bayer Schering Pharma, Asahi Kasei Medical, Novartis Pharma, Takeda Pharmaceutical and Mitsubishi Tanabe Pharma. Author T.O. has served on the scientific advisory board for Biogen Idec, and has received speaker honoraria from Biogen Idec and Takeda Pharmaceutical. Author S.T. is an employee of Takeda Pharmaceutical. Author M.Y. was previously an employee of Takeda Pharmaceutical, and has received stock dividends from Takeda Pharmaceutical. Author H.H. serves on scientific advisory boards for Biogen Idec and Mitsubishi Tanabe Pharma, and has received speaker honoraria from Takeda Pharmaceutical. The research sites of Drs Yamamura, Fukazawa, Houzen and Tanaka received research support from Takeda Pharmaceutical for this phase 4 extension study.

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