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Long-term follow up of glatiramer acetate compassionate use in Belgium

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Abstract

Between June 1995 and November 1998, 228 patients with relapsing-remitting Multiple Sclerosis started treatment with glatiramer acetate (Copaxone®) 20 mg once daily in the frame of a "compassionate use" protocol in 15 Belgian centers. Following an average treatment period of 5.8 years, treating neurologists were requested to fill in follow-up forms indicating neurological disability status and side effects during the previous 6 months. These data were available for 134 patients. In this group, the Expanded Disability Status Scale (EDSS) improved in 26.3% of patients. An additional 36.8% of patients remained neurologically stable. The Ambulation Index (AI) showed similar results : 12.5% of patients improved, 50% of patients remained stable, and 37.5% worsened. Only 10% of patients dropped out due to several reasons. The adverse events occurring in the period preceding the follow-up survey were non-serious and consistent with the current product information of glatiramer acetate.

Among the 94 patients no longer followed-up in the compassionate program, reasons for lost to follow-up were obtained for 63 ; most of them (41) had stopped GA treatment or switched to another disease-modifying treatment.

Overall these results are very similar to the ones reported in the extension study of the pivotal trial (Johnson et al., 2000), and indicate that patients treated with glatiramer acetate have a better outcome than expected on the basis of the natural course of the disease. Despite limitations of the study design, this report confirms the sustained efficacy of glatiramer acetate in reducing the disease progression in patients with relapsing-remitting multiple sclerosis treated in day-to-day clinical practice.

Key words : Multiple sclerosis ; disease-modifying drugs ; glatiramer acetate and long-term follow-up.

Introduction

Glatiramer acetate (GA ; Copaxone®) is a synthetic amino acid copolymer composed of the four amino acids L-alanine, L-glutamine, L-lysine and L-tyrosine. It was initially developed to mimic myelin basic protein (MBP), a major component of the myelin sheath, and to induce experimental autoimmune encephalomyelitis (EAE). Unexpectedly, the drug was shown to inhibit the disease in both rodents and monkeys (Teitelbaum *et al.*, 1974).

Further studies in humans suggest that the beneficial clinical effects of GA in relapsing-remitting Multiple Sclerosis (MS) patients may be attributed to the release of anti-inflammatory cytokines by GA specific T cells. GA is postulated to induce a shift in GA-specific T cell clones from a Th1 to a Th2/Th3 cytokine profile, leading to bystander suppression (Miller *et al.*, 1998 ; Neuhaus *et al.*, 2001).

Several clinical and MRI studies have demonstrated the efficacy, safety and tolerability of daily subcutaneous injections of 20 mg GA (Ziemssen *et al.*, 2001). The clinical efficacy of GA in terms of both reducing the relapse rate and slowing progression of neurological disability has been documented in the pivotal placebo-controlled study with a total duration of 35 months (Johnson *et al.*, 1995 and 1998) followed by an open-label extension study, which is still ongoing (Wolinsky *et al.*, 2001). The results of the cohort of patients, which were treated with GA for 6 years since randomization, were published in 2000 (Johnson *et al.*, 2000).

The positive effect of GA on gadolinium enhanced and T2 MRI lesions was reported in a separate placebo-controlled study of 9 months duration (Comi *et al.*, 2001) followed by a 9-month open-label extension (Wolinsky *et al.*, 2002).

In Canada, the United States and Israel, GA has been registered for treatment of relapsing-remitting MS since 1997. Europe followed in 2001 when central registration of the drug was obtained in 13 countries. At this moment GA is available and reimbursed in almost all European countries.

In 1995 GA was not yet commercially available to patients in the Benelux. As its efficacy and

tolerability had been demonstrated by the pivotal, double blind, placebo-controlled study of Johnson *et al.* (Johnson *et al.*, 1995 and 1998), it was decided to start a compassionate use program. The aim of this program was to provide GA to relapsing remitting MS patients who could not be adequately treated with other drugs available at that time. The patients were treated under strict supervision of their neurologist.

Here we present an overview of the disability status of relapsing remitting MS patients in Belgium that were treated with GA for 5-7 years. Additional long-term safety data were also collected.

Methods and materials

The compassionate use program

This open-label, fixed-dose, compassionate use (CU) program with GA involved multiple centers in Belgium, the Netherlands and Luxemburg.

Inclusion criteria required patients to be 18 years of age or older, with definite MS according to the Poser criteria defined in 1983, and Kurtzke Expanded Disability Status Scale (EDSS) below 6.0. All patients signed an informed consent form prior to the start of treatment. Twenty milligram GA was self-administered by daily subcutaneous injection. GA was supplied by TEVA Pharmaceutical Industries Ltd. ; Israel in single-dose vials containing 20 mg lyophilized GA, the active ingredient, and 40 mg lyophilized mannitol. The solvent (sterile water for injections), and injection attributes (syringes and needles) were provided by the company.

Initially the protocol was designed for one year but the program was extended to allow treatment of longer duration.

Participants

Between June 1995 and November 1998, 228 patients fulfilling the eligibility criteria for the program were recruited in 15 centers in Belgium.

Conduct of the study

In the first year of treatment patients were evaluated every 6 months. Evaluation included physical and neurological examinations, hematology and blood chemistry tests, urinalysis and vital signs. Details of adverse experiences and concomitant medications were also collected. All data were recorded in Case Record Forms that were monitored for correctness.

One amendment to the initial protocol was implemented in 1998. This amendment allowed for an extended duration of treatment, i.e. beyond one year. However, monitoring and data collection were discontinued. Only Serious Adverse Events were reported and actively followed.

In 2001 GA was registered in Belgium and a procedure to obtain reimbursement for the drug was started. The CU program was planned to stop once reimbursement was obtained. Because the large cohort of patients still participating in the CU program at the end of 2001 represented a valuable source of data on the long-term effects of GA, it was decided to perform a final survey.

Final survey

All investigators participating in the CU program were sent follow-up forms. On these forms, the follow-up was requested of the current Ambulation Index (AI) and the AI at entry, the current EDSS and the EDSS at entry, whether the patients were still on treatment with GA, whether other treatment had been used and whether the patient had experienced any adverse events in the past 6 months. Reasons for “lost to follow-up” within the CU program were also asked for.

The number of relapses was not recorded, because of practical problems. First, the variation in visit schedules between the different study centers and even between patients, would make it impossible to analyze the number of relapses at regular time intervals (e.g., 3 months). Second and most important, in daily clinical practice the definition of “confirmed relapse” as commonly used in clinical studies, is not used.

Statistics

The collected data were used to generate descriptive summary statistics (number, mean and standard deviation) for continuous parameters. For the Ambulation Index and the EDSS the values at entry were compared to those at the time of follow-up. “Worsened” was defined as an increase of at least one EDSS step, and “improved” as a decrease of at least one EDSS step. “Unchanged” was scored if the EDSS value remained the same or did not change more than 0.5 points. An exception was made only for those patients with a baseline EDSS of 5.5 ; these patients were scored as “worsened” when the EDSS had increased by at least 0.5 point.

Results

Baseline demographic and clinical data of the whole Benelux compassionate use (CU) study population is reported in table 1.

Clinical follow-up data were collected from 134, or 59%, out of the 228 patients initially included in the CU program in Belgium and fulfilling the inclusion criteria. The average treatment duration was 69 months (range 2-88 months) or 5.8 years. Before treatment was started, the patients had been

Table 1

Baseline demographic and clinical characteristics of the Copaxone CU patients in the Benelux

	N	Mean	SD	Min	Max
Age (years)	350	36.2	8.9	17	71
Disease Duration (months)	350	90.8	71.6	2	368
EDSS score	350	2.7	1.6	0	7.5
Prior 2-yr relapse rate	348	2.9	1.6	0	12
Sex	350	243 female (69%) and 107 male (31%)			

diagnosed with MS for an average of 5 years (year of diagnosis ranged from 1975 to 1998). EDSS data were available for all 134 patients and Ambulation Index data for 112 patients.

The average EDSS score at entry was 2.42 ± 1.28. At the end of the follow-up period, the EDSS score had increased slightly to 2.73 ± 1.96. The average AI score was 1.14 ± 0.96 at entry and 1.59 ± 1.53 at the end of follow-up.

Categorical analysis of the changes in EDSS score show that 25.4% (34/134) of the patients improved, 37.3% (50/134) remained unchanged and 37.3% (50/134) worsened after long-term treatment with GA (Fig. 1).

With regard to the Ambulation Index 12,5% (14/112) of the patients improved, 50% (56/112) remained unchanged and 37,5% (42/112) worsened (Fig. 2).

The follow up data further show that only 10% (13/134) of the patients had discontinued their treatment with GA. One patient stopped because of pregnancy, 3 patients stopped due to adverse events, 4 patients stopped because of disease progression, 1 patient stopped after a relapse, and 4 patients discontinued their treatment for unknown reasons. Reviewing the current EDSS score of these dropouts, 3 patients improved (23.1%), 3 remained stable (23.1%) and 7 worsened (53.8%) compared to their initial disability status.

The majority of the patients (110 or 83%) did not experience any adverse events during the six months preceding the follow-up survey. The adverse events that were reported for the remaining 17% of patients are detailed in table 2. These adverse events are consistent with the current product information of GA.

In addition, all investigators were asked to provide a reason for the "lost to follow-up" status of those patients for whom no follow-up form had been completed (Table 3). This reason was provided for 63 patients out of a total of 94 patients. As was to be expected, the main reason for lost to follow-up (n = 41 or 63%) was that the patient had (temporarily) stopped or switched immunomodulatory therapy and was no longer followed-up within the Copaxone CU program.

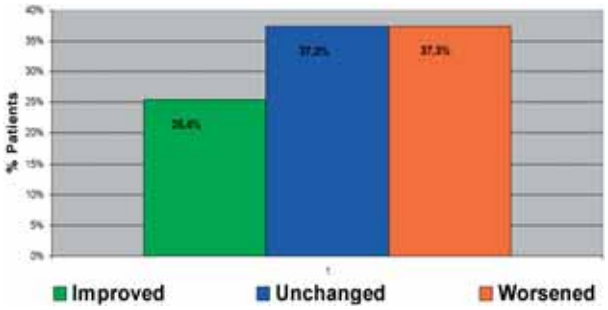

FIG. 1. — Change in EDSS (= OR > 1 EDSS step) of 134 patients after an average of 69 months treatment with Glatiramer Acetate.

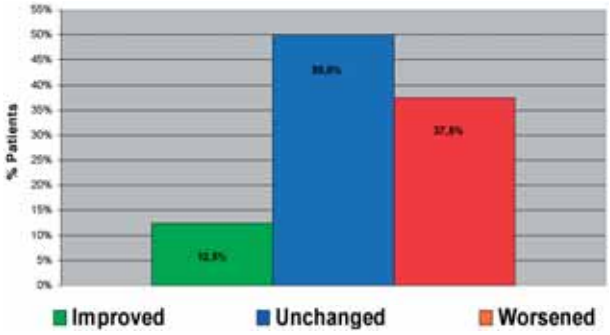

FIG. 2. — Change in AI of 112 patients after an average of 69 months treatment with Glatiramer Acetate.

Table 2

Adverse events during follow-up

Description of event	Nr of patients
MS(-relapse) related symptoms	7
Unspecified adverse event	5
Flushing and/or dyspnoea following injection	4
Infection	3
Injection site reactions	1
Depression	2
Muscle spasm following injection	2
Asthma	1
Cyst	1
Worsening of headache	1
Sweating	1

The table specifies the number of patients experiencing an adverse event during the 6 months preceding the date of follow-up examination. The total number of patients reporting one or more adverse events was 24.

Discussion

For a chronic, disabling disease such as MS it is important to study the long-term efficacy of the available disease modifying therapies such as glatiramer acetate (GA). Furthermore, safety and tolerability of the therapy are equally important to achieve continued patient compliance. Once registered and marketed, it is often assumed that the clinical effectiveness and safety of an immunomodulatory drug will follow the same course as predicted in the clinical registration studies.

Table 3

Reasons for lost to follow-up status of 63 patients for whom no CU follow-up form was completed (out 94)

Patient no longer examined by the same investigator	14
Patient died	2*
Patient failed to return (no data available)	6
Patient no longer followed-up within CU cohort because of stop or switch of DMT	41

The table specifies the number of patients for whom the above reason was deemed most appropriate to explain the lost to follow-up status. In total 7 patients were still treated with Copaxone. (DMT : disease-modifying treatment).

* One patient died of suicide due to severe depression already present before start of Copaxone treatment, one patient died by accidental drowning. Both deaths were judged by the investigators as unrelated to the study drug.

However, the normal daily practice of a neurologist may well differ from the controlled environment of a registration trial for a clinical drug. Therefore it was of interest to study the disability status of a group of patients who had received GA for a long period of time as part of a CU program with only a very limited number of study procedures.

In the CU program disease progression was defined as an increase in the EDSS score by at least one step from entry into the program until its completion in 2002. This definition is the same as in the pivotal studies with GA (Johnson *et al.*, 2000 ; Comi *et al.*, 2001). Given this definition, the results of the CU program show that after an average treatment period of 69 months (5.8 years) a minority of the 134 followed-up patients (37.3%) experiences progression of disease while for the remaining 62.7% the EDSS remained stable or has improved.

The present cohort represents 59% of the total number of participating patients. In the extension phase of the USA study with GA (Johnson *et al.*, 2000) 60% of the originally randomized patients completed the extension. The median treatment duration was 5.83 years. At the end of this study, 69.3% of the patients were neurologically unchanged or had improved by at least one step on the EDSS. Despite the obvious limitations of the simplified design of the present open-label follow-up study, the close similarity of our data with the ones of Johnson et al (2000) suggests that the adoption of the pivotal study results in daily clinical practice can be advocated.

In order to put the data into perspective, it is instructive to compare the results of the present study with natural history data. Johnson *et al.* (2000) used the natural history study by Weinshenker *et al.* (1991) to calculate the predicted progression for a similar cohort of patients after 6 years. Based on this calculation, the EDSS score of 77% of patients will have increased by one point or more within 6 years, while 23% of the patients are expected to remain stable. Thus, it can be concluded that the described GA treated cohort showed less progression than would have been expected without therapy.

Although the majority of patients were followed up for more than 5 years on average, the current disease status of the remainder of patients is unknown. This could hamper the interpretation of the reported treatment efficacy and side effects, as we do not know if these patients are now faring worse or better. Indeed, a potential bias in the results could occur if the patients that were lost to follow-up (n = 94, or 41%) fared worse than the patients that were still regularly examined by their original neurologist (n = 134, or 59%). For this reason, an additional analysis was done on the original EDSS data obtained at randomization from all 228 patients. Only a slight difference in mean EDSS score at randomization into the CU program between the group of patients that were lost to follow-up (mean EDSS 2.69 ± 1.42) and the group of patients that were followed-up (mean EDSS 2.44 ± 1.29) was found. This difference was not significant (Wilcoxon's signed rank test for non-normally distributed variables ; p = 0.178), indicating that both groups were comparable with regard to initial disability.

However, to account fully for the missing follow-up data, a worst-case scenario should be applied. In such a scenario it is assumed that all patients who discontinued or were lost to follow-up deteriorated. This would mean that 63% ((50 + 94) / 228) have worsened and 37% would have improved or remained stable.

A more likely scenario is that the cohort of 94 patients, who were lost to follow-up, had the same outcome as the 13 patients that discontinued GA treatment but were still followed-up in the CU program. Following this scenario, 44% of patients ({(94 x 53.8%) + 50} / 228) have worsened and 56% have remained stable or improved with regard to disability status. Thus, although not tested for statistical significance, when correcting for potential bias, the percentage of patients in the study that deteriorated remains lower compared to that expected from natural history studies.

Finally, it should be noted that the adverse events reported during the present study are non-serious and do not differ from those reported during the pivotal GA study.

In conclusion, the results of this open-label trial are similar to the ones reported in the extension phase of the pivotal GA study (Johnson *et al.*, 2000) and show that in a less controlled environment, similar to the day-to-day practice with

patients treated outside the strict regimen of a clinical study, the efficacy of GA (Copaxone®) is not compromised.

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