Optimization of immunomodulating therapy with glatiramer acetate daily 20 mg sc in combination with a patient self-monitoring program in The Netherlands (OPTIVIT): baseline results.

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Abstract:

Background: Benefit of immunomodulating therapy in relapsing-remitting multiple sclerosis (RRMS) depends on the individual clinical effect as well as on patient compliance to therapy. In clinical studies, the effect of glatiramer acetate on relapse rate and other clinical parameters has been confirmed. A marked reduction in relapse rate has also been observed in patients with insufficient response to prior beta-interferon therapy. However, patient compliance to glatiramer acetate seems lower in patients that used prior immunomodulating therapies than in those that did not. As it is known that perception of self-control and self-efficacy are important factors determining adherence to therapy, it was decided to set up a web-based self-monitoring programme for patients starting on glatiramer acetate in The Netherlands.

Objectives: To evaluate the relapse rate (RR) reduction in patients starting on Copaxone, supported by the online self-monitoring application, and to evaluate possible differences between patients previously treated with IFN beta (group A) and patients naïve to immunomodulating therapy (group B).

Methods: This ongoing study is designed to include a total of 200 patients in 40 participating centres in The Netherlands. Patients are invited to participate by the attending neurologist. Evaluation of RR, disability score (EDSS), and adverse events (AEs) is done at inclusion and at regular visits thereafter (usually at 6, 12, and 24 months). Patients join an online self-monitoring and support programme. At monthly intervals, patients submit a questionnaire evaluating fatigue (MFIS score), Quality of Life (Leeds scale), satisfaction with therapy (VAS scale) and compliance (number of missed injections). The questions are easy to answer online or by using a data-entry helpdesk. Patients also receive at pre-determined intervals newsletters on disease- and treatment-related topics, designed to increase compliance. From 7 months onwards, both patient and neurologist receive online feedback on the patient's individual scores. This feedback is designed to visualize the patient's individual response to therapy.

Results: From October 2004 - May 2006, a total of 102 patients has been enrolled, of which 96 patients (94%) joined the online self-monitoring programme and submitted at least the first questionnaire. 17 Patients have completed one year of follow-up. In 9 of these patients, the neurologist recorded no relapses (53%), in 4 cases 1 relapse, and 2 resp. 5 relapses in the remaining cases (for 2 cases no entry is available). No difference in number of relapses was noted between group A and group B patients. 6 Patients (5 in group A and 1 in group B) have discontinued Copaxone therapy, but opted to continue the online support programme.

Conclusion: These preliminary data indicate that a combined approach of online simple questionnaires, targeted information on disease and therapy, and visualization of the patient's individual progression may improve adherence to Copaxone therapy, especially in patients pre-treated with other immunomodulating drugs. Additional one-year data will be presented.

Introduction and Purpose:

Benefit of immunomodulating therapy in relapsing-remitting multiple sclerosis depends on individual clinical effect as well as patient compliance. Compliance to Copaxone® (glatiramer acetate; GA) is lower in patients who previously used one or more other immunomodulating therapy (IMT) than in those who did not (ref Fraser). It is known that perception of self-control and self-efficacy are important factors determining adherence to chronic treatment, therefore an online self-monitoring programme for patients starting GA therapy was set up in The Netherlands. In order to evaluate this self-monitoring tool, it was incorporated into a post-marketing surveillance study named "Optivit". The primary efficacy parameter of the Optivit study is to evaluate the relapse rate (RR) reduction in patients using GA, supported by the online self-monitoring application, after 1 year of treatment. Secundary parameters are the percentage of patients adhering to GA therapy after 1 and 2 years of treatment, EDSS score and safety. Presumed differences between patients previously treated with other IMT including interferon-ß (IFN-B) and patients completely naïve to immunomodulating therapy are assessed as well.

Methods:

This ongoing observational study is designed to include a total of 200 patients in 40 participating centres in The Netherlands. All patients starting on GA are eligible. Evaluation of prior 2-year relapse rate, disability score (EDSS), and adverse events (AEs) is done at inclusion and at regular intervals during a two year follow-up period. A minimum of 3 study visits is required at approximately 6 months, 1 year and 2 years of therapy. All study procedures can be performed within the normal neurological practice. At study start patients are invited to join an online self-monitoring programme. A questionnaire including the 5-item Modified Fatigue Impact Scale (MFIS), Leeds' Quality of Life scale, satisfaction with therapy by VAS scale and compliance is completed by patients at monthly intervals. The questions are easy to answer online or through regular mail. Patients also receive at specific points in time newsletters on treatment-related topics, designed to increase compliance. From 7 months onwards, both patient and treating neurologist receive online feedback designed to visualize the patient's personal response to therapy.

Results:

The study is currently ongoing and recruiting until end of 2006. From October 2004 until May 2006, a total of 103 patients have been enrolled (46% naïve, 54% pre-treated) in 36 active centres. Almost all of these patients (94%) joined the online self-monitoring programme and submitted at least a first questionnaire. In table I the baseline characteristics of the participating patients are presented. The cohort has been divided into patients that received other IMT before the study and those that were treatment-naïve. With regard to age and sex the groups are comparable ($p > 0.05$). Number of years since diagnosis was significantly greater in the IMT pre-treated group ($p = 0.0003$) which is not surprising. Also the number of relapses in the 2 years prior to start of Copaxone ($p = 0.014$), and EDSS score at baseline ($p = 0.03$) appeared significantly greater in the IMT pre-treated group. Quality of Life (QoL) score and MFIS-score were not significantly different between groups ($p > 0.05$, Student's t-test). However, satisfaction with therapy was significantly worse in the IMT pre-treated group ($p = 0.03$). In table II, the baseline characteristics of the treatment-naïve patients are compared with the GA group in the pivotal GA registration study by Johnson et al[2] and with the treatment-naïve group of the prospective open-label study by Zwibel HL et al[1]. This 3.5 year open-label study evaluated the efficacy of GA in treatment-naïve patients and in patients who had previously received IFN-B-1b. Finally, the baseline characteristics of the prior IFN-B-treated patient group are compared with the same group of the open-label study by Zwibel HL et al[1] in table III.

Table I: Baseline characteristics of the OPTIVIT study cohort

	Total group	IMT pre-treated group	Naïve group
N	103	55	48
Age, Mean ± SD Range, (median)	40.0 ± 8.6 22-60 (40)	41.0 ± 8.3 22-60 (41)	39.4 ± 8.9 23-58 (39)
Gender	Male: 26 (25%) Female: 72 (70%) NR: 5 (5%)	Male: 17 (30%) Female: 37 (66%) NR: 2 (4%)	Male: 10 (20%) Female: 35 (73%) NR: 3 (7%)
Years from diagnosis to study entry Mean ± SD Range, (median)	5.0 ± 4.9 0-22 (4)	6.7 ± 4.6 0-18 (6)	2.9 ± 4.5[#] 0-22 (1)
Relapses in the 2 years before study entry, Mean ± SD Range (median)	2.2 ± 1.7 0-12 (2)	2.6 ± 2.1 0-12 (2)	1.9 ± 0.8 0-5 (2)
Baseline EDSS, Mean ± SD Range (median)	3.2 ± 2.2 0-8 (3)	3.7 ± 2.1 0-7 (4)	2.45 ± 2.16[#] 0-8 (1.5)
Leeds QoL score* Mean ± SD Range (median)	19.4 ± 4.4 11-29 (20)	19.2 ± 4.3 11-28 (20)	19.7 ± 4.6 11-29 (20)
MFIS-5 score** Mean ± SD Range (median)	11.9 ± 4.5 0-20 (14)	12.4 ± 4.1 0-18 (13)	11.1 ± 4.8 0-20 (14)
Baseline satisfaction with therapy (VAS) *** Mean ± SD Rang,e (median)	6.4 ± 2.7 0.1-10 (7)	5.7 ± 3.0 0.1-10 (6.2)	7.0 ± 2.2[#] 1.0-10 (7.5)

* Leeds QoL score consists of 8 questions. Possible score range from 4-24. A higher score indicates a greater loss of QoL.
** MFIS score consists of 5 questions. Possible score ranges from 0-20. A higher score indicates a greater impact of fatigue on a patient's activities.
*** VAS scale is a continuous scale ranging from 0-10 with higher scores indicating greater satisfaction.
# Statistical significant difference ($p < 0.05$) between naive patient group and IMT-pre-treated patient group

Table II: Comparison of baseline characteristics of treatment-naïve patients (Optivit, Johnson, Zwibel)

	Optivit	Johnson	Zwibel
N	48	125	558
Age Mean ± SD Range, (median)	39.4 ± 8.9 23-58, (39)	34.6 ± 6.0	39.9 ± 9.2
Gender	Male: 10 (209%) Female: 35 (73%) NR: 3 (7%)	Male: 37 (30%) Female: 88 (70%)	Male: 134 (24%) Female: 424 (76%)
Years from diagnosis to study entry, Mean ± SD Range, (median)	2.9 ± 4.5 0-22 (1)	7.3 ± 4.9	6.7 ± 7.2
Relapses in the 2 years before study entry Mean ± SD Range, (median)	1.8 ± 0.8 0-5 (2)	2.9 ± 1.3	2.8 ± 2.0
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Table III: Comparison of baseline characteristics of prior IMT treated patients (Optivit, Zwibel)

	Optivit	Zwibel (IFN-B-1b only)
N	55 (50 prior IFN-B)	247
Age Mean ± SD	41.0 ± 8.3	42.3 ± 8.9
Sex	Male: 17 (30%) Female: 37 (66%) NR: 2 94%)	Male: 60 (24.3%) Female: 187 (75.7%)
Years from diagnosis to study entry, mean ± SD Range, (median)	6.7 ± 4.6 0-18 (6)	8.5 ± 7.2 0-37
Relapses in the 2 years before study entry Mean ± SD Range, (median)	2.6 ± 2.1 0-12, (2)	3.1 ± 2.2 0-15
Baseline EDSS score Mean ± SD Range, (median)	3.7 ± 2.1 0-7, (4)	3.8 ± 1.6 0-8
Months of prior IFN-B treatment Mean ± SD Range	32.0 ± 30.8 2-130	9.6 ± 8.6 8-63
Months between IFN-B stop and GA start Mean ± SD Range	18.0 ± 22.8 0-84	6.9 ± 7.0 5-33

Conclusion:

In the OPTIVIT study normal neurological practice is followed. Both naïve and IMT-pre-treated patients are started on GA therapy and followed for up to 2 years. The two patient groups are comparable in terms of demographics, relapse rate, QoL score and fatigue score at baseline. As can be expected, number of years from diagnosis and EDSS at baseline are significantly higher in the IMT pre-treated group. VAS score is significantly lower in this group, which might suggest that the IMT pre-treated patients started on GA therapy with a different set of expectations. Thus, although there are differences, the two patient groups seem sufficiently comparable at baseline. Therefore it is expected that the OPTIVIT study will provide valid data to conclude whether a combined approach of targeted information on disease and therapy and visualization of the patient's individual progression will improve adherence to GA therapy.
Furthermore it is interesting to observe the apparent early start of therapy in the Optivit study compared with the GA pivotal registration study[3] and the open-label study by Zwibel et al[1]. This is also reflected in the lower mean number of relapses and EDSS score in the Optivit study compared with both other studies. Besides the fact that the latter studies were performed when GA was not yet commercially available, this may also be explained by the growing awareness of the benefits of an early start of therapy and/or optimization of therapy by switching to GA.

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