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Comparison of glatiramer acetate (Copaxone®) and interferon β-1b (Betaferon®) in multiple sclerosis patients: an open-label 2-year follow-up

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Abstract

Objective: To compare the clinical efficacy, as expressed by relapse rate and disability accumulation, and safety profile of glatiramer acetate (Copaxone®; COP-1) and Interferon β-1b (Betaferon®; IFNβ-1b) administered to multiple sclerosis patients during a 2-year follow-up on an open-label parallel design, as compared to their clinical condition in the 2-year period prior to treatment. *Background*: Copaxone and IFNβ-1b have been recently introduced for the treatment of relapsing forms of MS. Both medications have been proven to have a relatively safe profile and are used extensively world-wide. *Methods*: 58 consecutive patients with relapsing forms of MS were enrolled from the MS out-patient clinic, during three months. After being informed in detail of the two approved treatment options existing at the time in Israel, the patients chose by themselves to receive either: (a) Copaxone 20 mg subcutaneously (sc) daily (Copaxone dly, 20 patients), or (b) Copaxone 20 mg sc alternate-day (Copaxone alt, 18 patients) or (c) IFNβ-1b 8 MIU sc in alternate day (20 patients). Mean relapse rate/year and mean EDSS/year were calculated for each group of patients during the 2 years prior to the onset of treatment, and during the year prior to the onset of treatment. Statistical significance was observed in the relapse rate in the year prior to the onset of treatment between the IFNβ-1b group and the two Copaxone groups ($p = 0.05$). This statistical difference has no effect on the overall data of the 2 years prior to starting the treatment and on the results. No statistical significance was observed in the total number of relapses, and on the 2-year relapse rate, prior to the onset of treatment. Mean relapse rate/year and mean EDSS/year were calculated for each group during the first and second year of treatment. Wilcoxon anaylsis for clinical data and chi-square for adverse events were applied. *Results*: The three groups were statistically comparable concerning mean relapse/year in the 2 years before the trial started and no statistical significance was observed among the three groups. A statistically significant reduction in the mean relapse rate in the 2 years after onset of treatment was observed in the three group of patients: Copaxone daily (dly) 1.1 ± 0.6 ($p = 0.0001$); Copaxone alternate (alt) 0.9 ± 0.6 ($p = 0.0004$) and IFNβ-1b 1.2 ± 0.7 ($p = 0.0001$). Disability as expressed by EDSS score prior to the onset of treatment and after 2 years of treatment showed deterioration in the three groups although more significant in the Copaxone groups: Copaxone dly 3.3 ± 1.4 to 3.8 ± 1.6 ($p = 0.007$); Copaxone alt 2.4 ± 1.1 to 2.8 ± 1.3 ($p = 0.04$); IFNβ-1b 3.1 ± 1.3 to 3.3 ± 2.0 (N.S.). The most common adverse events reported were: (1) flu-like symptoms 7 pts (35%) in the IFNβ-1b group; 10 pts (26%) of the two Copaxone groups; (2) increased spasticity of lower limbs 3 pts (15%), only in the IFNβ-1b group; (3) site injection reaction (SIR): 16 SIR (80%) in the IFNβ-1b group; 12 SIR (67%) in the Copaxone alt group; 14 SIR (70%) in the Copaxone dly group; and (4) systemic reaction 3 pts (15%) in the IFNβ-1b group; 4 pts (22%) in the Copaxone alt group; 6 pts (30%) in the Copaxone dly group. Premature termination occurred in five patients treated with Copaxone (3 in the alternate group and 2 in the daily group). *Conclusion*: The present study, despite the limitations of an open-label study, shows that Copaxone dly, Copaxone alt and IFNβ-1b treatment seem to be equally effective for the control of exacerbations in MS. The adverse event profile, as reported by the patients, was also similar. However, the adverse events profile registered indicated that Copaxone is somewhat less detrimental, whereas disability as measured by EDSS accumulation showed that the interferon β-1b patients demonstrated a slower progression of the disability.

Keywords: Multiple sclerosis; Glatiramer acetate; Interferon β-1b; Follow-up

1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating immune mediated disease which may present in relapsing or progressive form. The prime task of therapy in the relapsing

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forms of MS is to prevent the relapses and to slow down the neurological deterioration.

Recently, Interferon β-1b (Betaferon®), Interferon β-1a (Rebif®, Avonex®) and Copolymer-1 (COP-1, Glatiramer Acetate, Copaxone®) were shown to decrease the relapse rate [1–7] and to slow down the accumulation of the neurological disability [as measured by the expanded disability status scale (EDSS)] [8–12]. All three products have been approved for the treatment of relapsing MS. Since the decision of injecting Copaxone 20 mg sc on a daily basis was an arbitrary one based on pre-clinical studies [13,14], we have decided to compare the effect of alternate-day injection vs. daily injection. Moreover, we assume that the effect of Copaxone is not dose related, but is related to the exposure of the immune system to its presence.

We report the results of a 2-year open-label prospective follow-up with Copaxone and IFNβ-1b in relapsing forms of MS. The study was performed in an open-label design aimed at evaluating the clinical course of the disease, as expressed by re lapse rate and disability accumulation and to evaluate the long-term safety, in a population of 58 relapsing MS patients divided into three groups, 2 years prior to starting the treatment and within 2 years of treatment; two groups of patients receiving 20 mg of Copaxone sc on a daily or alternate-day basis, and a third group of patients, each patient received 8 MIU of IFNβ-1b sc on an alternate-day basis.

2. Patients and methods

Fifty-eight consecutive MS patients with clinically definite MS [15], who were followed in our MS clinic for more that 2 years before enrolling to the study, were enrolled on a randomly basis in a 3-month period. In order to be eligible for entry into the study, the patients had to meet the following inclusion criteria: patients were of both genders; 18 years and older, no significant neurological, psychiatric, hematologic, renal, hepatic, endocrinological, cardiovascular, cerebro-vascular, active malignancy and auto-immune diseases had to be present. Women of child-bearing potential had to practice a clinically accepted method of contraception. No immune-modulating drug should be used in the three months prior to entering the study. The drugs available at that time in Israel, namely: Copaxone and Betaferon, were presented by the treating neurologist in detail to each patient, explaining very carefully the diversity between the two drugs. In addition, patients were given the opportunity to choose between Copaxone on daily injection or on every other day. After considering the possible benefits and adverse events of each drug, the patient alone decided on which of the options to take and a written consent for the treatment was obtained. Once each arm was filled, by the patients free election, it was closed. The enrolment period lasted 3 months. A pre-condition to inclusion in the study was at least two exacerbations documented by a neurologist, and by reviewing the medical charts, during the 2 years prior to starting the treatment. The EDSS in every patient had to be stable for at least six months before starting the treatment. Patients' evaluation was performed on scheduled visit every 3 months by a qualified neurologist on the MS out-patient clinic, and included physical neurological and laboratory examinations (haematologic, urinalysis, blood chemistry). During each visit, adverse events were recorded. In the case of the appearance of an acute relapse (which was defined as the appearance of a new neurological symptom, or severe deterioration in a pre-existing symptom that lasted for at least 24 h causing the deterioration in the EDSS with 1 point), the patient was examined on an unscheduled visit within 1 to 3 days after the onset of symptoms and was treated with corticosteroids according to the severity of the presenting symptom (1 g of prednisolone intravenous for five consecutive days). Symptomatic therapy was permitted if required. Assessment of the course of the disease was done by monitoring the annual relapse rate and the change of the EDSS score. Once an acute relapse occurred, the EDSS registered on the unscheduled visit was not taken into account on the statistical evaluation. Compliance of the treatment was assessed by specialised nurses who were involved with each patient from the beginning of the treatment. The data obtained during the 2-year follow-up period were compared with the data of the same patients registered in our files during the 2 years of follow-up in the MS clinic, prior to starting the treatment.

The medication was supplied to each patient by the respective medical insurance company.

According to the methods described, 58 consecutive patients, comprising 43 females (74%) and 15 males (26%), were assigned into three groups. Group 1 comprised 20 patients, 15 females (75%) and 5 males (25%), who received IFNβ-1b 8 MIU sc by alternate-day injection; group 2 comprised 18 patients, 15 females (83%) and 3 males (17%), who received Copaxone 20 mg sc by alternate-day injection and group 3 comprised 20 patients, 13 females (65%) and 7 males (35%), who received 20 mg sc Copaxone by daily injection.

2.1. Statistics

Statistical analysis using the Wilcoxon and chi-square analysis was carried out to evaluate changes in the parameters during the course of the treatment. Changes in the annual relapse rate and in the EDSS score were compared, to evaluate whether the results differed significantly among groups.

3. Results

All three groups were comparable considering gender, mean age, mean disease duration prior to the onset of treatment, mean total number of relapses 2 years prior to the onset of treatment and mean EDSS score prior to the inclusion in this study.

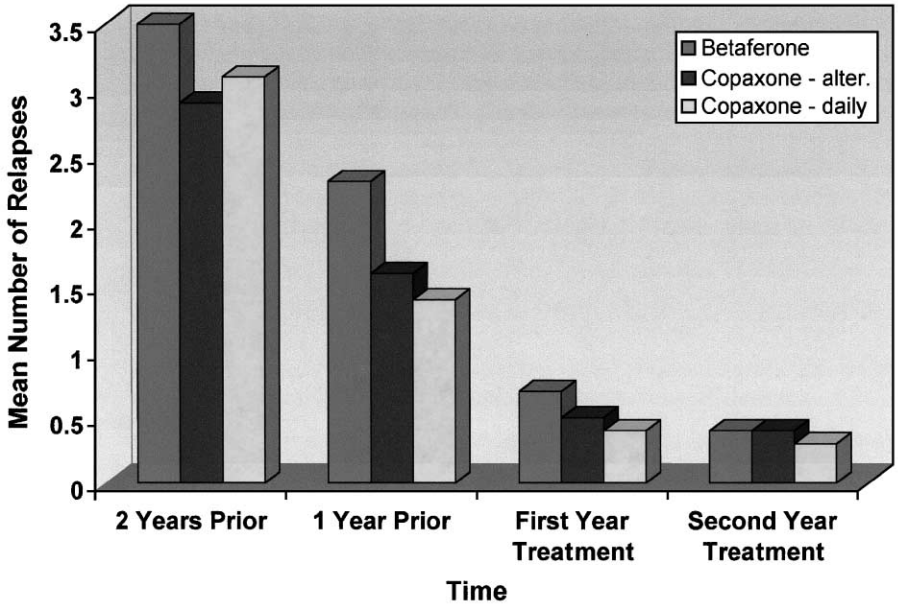

Fig. 1. Difference in relapse rate 2 years and 1 year prior to the onset of treatment and 1 year and 2 years after the onset of treatment.

3.1. Exacerbations during the treatment

Fig. 1 demonstrates the differences in number of relapses, as well as the differences in relapse rate, prior to and after the onset of the treatment. The difference between the total number of relapses in the year prior to the onset of treatment and the number of relapses during the first year of treatment was statistically significant for all groups (INFβ-1b mean 1.6 ± 1.3 $p = 0.0001$; Copaxone alternate day mean 1.1 ± 0.7 $p = 0.0005$; Copaxone daily mean 1.0 ± 0.9 $p = 0.0007$). The mean difference between relapse rate in the 2 years prior to the onset of treatment and the 2 years after starting the treatment was significant for all groups (IFNβ-1b mean 1.2 ± 0.7 $p = 0.0001$; Copaxone daily mean 1.1 ± 0.6 $p = 0.0001$, Copaxone alternate day mean 0.9 ± 0.6 $p = 0.0004$). Fifty relapses were registered during the 2 years of follow-up; 22 on the Betaferon group, 16 on the Copaxone alternate-day group, and 12 on the Copaxone daily group. Twenty-six relapses were considered of clinical significance (10 in the Betaferon group, 9 in the Copaxone alternate group and 7 in the Copaxone daily group) and required hospitalisation and treatment with a course of prednisolone according to the protocol mentioned above.

3.2. Disability

Analysis conducted on the differences between EDSS scores are presented in Fig. 2. EDSS registered during unscheduled visit because of an acute relapse was not included in the statistical evaluation. EDSS scores 2 years after onset of treatment were significantly higher than EDSS scores prior to the onset of treatment for the Copaxone daily group

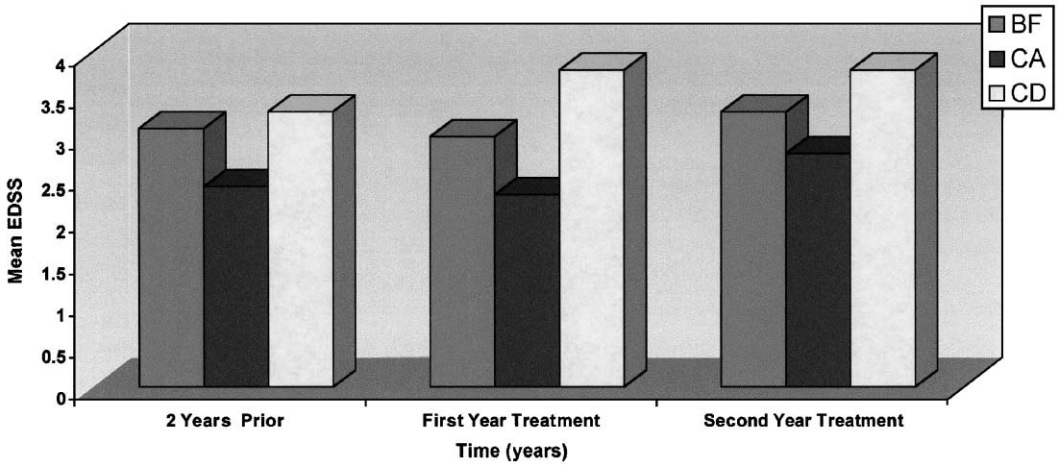

Fig. 2. Difference in EDSS score prior to and after 1 year and 2 years of treatment.

($p = 0.007$), and Copaxone alternate-day group ($p = 0.04$). No significant difference was observed in the EDSS score in the IFNβ-1b ($p = 0.3$). The results demonstrated have to be considered carefully, since the groups were composed of a small number of patients and the duration of the follow-up was 2 years.

3.3. Adverse events

A chi-square analysis was applied for analysis of the major adverse events occurring at least once per patient and at least in 5% of patients in each group. The results were summarised in Table 1. No statistically significant differences were found among the three groups. Flu-like symptoms were observed in 7 (35%) in the IFNβ-1b group; increased spasticity of lower limbs occurred in 3 (15%) in the IFNβ-1b group. Local injections site reactions were reported as 16 (80%) in the IFNβ-1b group, 12 (67%) in the Copaxone alternate-day group, and 14 (70%) in the Copaxone daily group. Depression was observed in 11 patients, 4 (20%) in the IFNβ-1b group, and 7 (18%) in the Copaxone groups. A systematic adverse reaction, manifested by chest pain, palpitations and tachypnea was reported by 3 patients (15%) in the IFNβ-1b group, 4 (22%) in the Copaxone alternate-day group, and 6 (30%), in the Copaxone daily group. These reactions occurred immediately following drug administration, and resolved without any treatment. Some other systematic reactions such as lymphadenopathy were observed in 2 patients (10%) in the Copaxone daily group. Lypodystrophy was observed in 3 patients (15%) in the Copaxone daily group. Adverse reactions were reported especially during the first six months of treatment. The majority of them resolved in a short time. Routine laboratory examinations showed no clinically significant changes.

3.4. Premature termination

Table 1 summarises the reasons for termination in all three groups of patients. Of the 58 patients who started the treatment, 5 patients dropped out during the first 2 years of treatment. Three patients from the Copaxone alternate-day treated group, and two patients from the Copaxone daily treated group. No drop-outs were observed in the IFNβ-1b group. The five patients who dropped-out were assigned for interferon treatment, but were not included in the final analysis.

4. Discussion

Both IFNβ-1b and Copaxone in well-designed studies (double blind placebo control) were found to be effective in the treatment of multiple sclerosis reducing the number of exacerbations, and modulating the course of the disease as shown by EDSS accumulation [3,4,7,10].

In the present study, we report a 2-year follow-up of an open-label parallel design follow-up, comparing Copaxone (daily and alternate-day administration) and IFNβ-1b. Our follow-up shows that there was a significant benefit in decreasing the relapse rate in MS in all three groups, without any difference among them. These data, despite the relatively small number of patients in each group and the open-label design, show similar results with those published in the previous studies of IFNβ-1b and the Copaxone [9,17].

The data presented here showing that Copaxone on alternate-day injection is equally effective to Copaxone daily injection have to be evaluated very carefully since the study performed was an open-label uncontrolled one, and further studies should be considered to confirm results.

The safety profile observed during our follow-up was similar to that registered in previous studies [4,10,16]. Adverse experiences were reported by 16 (80%) patients of the Copaxone daily injected group, 14 (78%) patients of the Copaxone alternate-day injected group and 17 (85%) patients of the IFNβ-1b group. The most frequent being the local injection site reaction observed in all three groups, followed by flu-like symptoms reported by the IFNβ-1b injected group, transient self-limited systematic reactions (i.e. flushing, tachycardia, tachypnea, dyspnea, chest pain) which resolved spontaneously within a short time. Three patients (16.6%) of the Copaxone alternate-day injection group withdrew from the treatment because of increasing

Table 1
Major adverse events and* premature termination, occurring at least one per patient and at least in 5% of patients in each group

Adverse events		Group			
		Betaferon	Copaxone alternate day	Copaxone daily	*P* value
Flu-like symptoms	No. (%)	7 (35.5)	1 (5.5)	2 (10.0)	N.S
Increased spasticity of the lower limbs	No. (%)	3 (15.0)	–	–	
Site of injection reaction	No. (%)	16 (80.0)	12 (67.0)	14 (70.0)	N.S
Systemic reaction	No. (%)	3 (15.0)	4 (22.2)	6 (30.0)	N.S
Lymphadenopathy	No. (%)	–	–	2 (10.0)	
Lypodystrophy	No. (%)	–	–	3 (15.0)	
Severe clinical deterioration *	No. (%)		1 (5.5)		
Patient's decision *	No. (%)		1 (5.5)		
Adverse events *	No. (%)			1 (5.0)	
Acute relapse+* severe deterioration	No. (%)			1 (5.0)	
Low compliance *			1 (5.5)		

disability and poor compliance. Two patients (10%) of the Copaxone daily injection group stopped the treatment because of adverse events and acute relapse. No withdrawal was observed in the IFNβ-1b group. The frequency of the adverse events decreased after a few months of treatment in all three groups.

Although our follow-up label prospective uncontrolled study and its results should be considered carefully, it still demonstrates that Copaxone on alternate-day injection has the same beneficial effect as daily injection on the relapse rate, and is equally effective as IFNβ-1b considering this parameter, as it was shown in previous studies [3,4,7,10]. On the other hand, assessment of disability accumulation as demonstrated by the EDSS score shows that in the Copaxone groups disability accumulation was higher than Betaferon-treated patients. This change may not necessarily reflect disease progression (since there are many reasons for EDSS to fluctuate in a small sample, particularly in the 2.5–4.0 range); that observation, too, has to be considered carefully since the follow-up is an open one. Adverse events were manageable in most of the patients on both medications.

In summary, although our study is an open-label one, it shows that IFNβ-1b injected subcutaneously on alternate day, and Copaxone injected subcutaneously either daily or on alternate day, may modulate disease activity in a similar way and to a similar extent.

The choice of the appropriate medication for each patient still remains an individual decision since the effects of IFNβ-1b and Copaxone seem to be similar [17,18]. The fact that Copaxone injected on alternate day seems to be equally effective as the Copaxone injected daily is important to patients with injection-related adverse events and, from an economic point of view, as a cost-effective measure. Moreover, considering that there is no available data supporting daily vs. alternate-day Copaxone injection, in our view a well-designed post-marketing study is required, in order to confirm or refute the results obtained in our study.

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