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Copolymer 1 (Glatiramer Acetate) in Relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration

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Summary: Daily 20-mg doses of Copolymer 1 have been shown to significantly decrease the relapse rate in patients with multiple sclerosis (MS). In the present open-label study, patients with relapsing MS were treated with the same dose of Copolymer 1 administered on alternate days. Sixty-eight patients were recruited: fifty-one and forty-one patients completed 1 and 2 years of treatment respectively. The relapse rate during the 2 years of treatment decreased by 80.8% compared with the 2 years before treatment (means, 0.56 ± 1.02 versus 2.91 ± 1.10, respectively; $p < 0.0001$). This lower rate is comparable with that obtained with daily open-label administration previously reported by the authors. The score on the Expanded Disability Status Scale did not differ from that at baseline after the first year of treatment, although it increased somewhat at the end of the second year (baseline = 2.72 ± 1.55, 1 year = 2.71 ± 1.59, 2 years = 2.97 ± 1.80; $p < 0.008$). The drug was very well tolerated. This preliminary open-label study suggests that alternate-day therapy has beneficial effects and is well tolerated, comparing favorably with the effects of daily injections of Copolymer 1 in patients with relapsing MS. These results should be confirmed by randomized double-blind examinations. **Key Words:** Multiple sclerosis—Copolymer-1—Alternate-day therapy—Glatiramer acetate—Treatment—Mechanisms

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Multiple sclerosis (MS) is a common chronic neurologic disease of unknown etiology. This inflammatory demyelinating disease may present with a relapsing-remitting (RR) or a chronic-progressive course. In the more common RR form, the relapses may leave patients with residual deficits, causing neurologic disability that accumulates over time. The aim of therapy in patients with RR MS is to prevent exacerbation and the accumulation of disability. Recently, in double-blind, placebo-controlled studies, interferon β-1a, interferon β-1b, and Copolymer 1 (glatiramer acetate) were shown to decrease the relapse rate (1–5) and possibly slow down the accumulation of disability in patients with MS (6–8). All three agents have been approved in several European countries and in the U.S. for the treatment of patients with RR MS. Copolymer 1 is a synthetic polypeptide with a molecular weight of 4.700–13.000 Dalton; it is composed of four amino acids: alanine, glutamic acid, lysine, and tyrosine. Copolymer 1 prevents the induction of experimental autoimmune encephalomyelitis and may reverse or ameliorate neurologic deficits in animal models (9,10). Clinical double-blind, placebo-controlled studies with Copolymer 1 showed beneficial effects of this drug when it was given by daily, subcutaneous (SC) injections of 20 mg. In these studies, Copolymer 1 reduced the relapse rate and slowed the accumulation of disability (2,11–13). The safety profile of Copolymer 1 compares favorably with the safety profile of interferons (14). However, the dose and frequency of administration of Copolymer 1 were rather arbitrarily selected. We report here the results of a long-term, multicenter, phase III, open-label study of RR MS. The objectives of this study were to evaluate the long-term neurologic course of the disease and the long-term safety of Copolymer 1 in patients in whom 20 mg was administered SC on an alternate-day basis. Using a protocol identical to that used by us in a previous open-label study of daily Copolymer 1 administration, analyses were performed on two efficacy pa-

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rameters: frequency of exacerbations and score on the Expanded Disability Status Scale (EDSS) (15).

MATERIALS AND METHODS

Patients

After obtaining the approval of the respective ethical committees and individual informed consents, sixty-eight patients were enrolled in dedicated MS clinics at four medical centers. The inclusion criteria were identical to those of our previous open-label study with daily Copolymer 1 injections (15). Patients had clinically definite or laboratory-supported definite MS. Fifty-eight were of the relapsing-remitting type and ten were of the relapsing-progressive type with at least two exacerbations during the 2 years before study entry. Patients had to be clinically stable for at least 1 month before entry. No steroids or other immuno-modulators could be used during 6 months before study entry. The EDSS score at baseline had to be less than 6.0. Men and women ages 18 and over were eligible, but existence of any other chronic disease or pregnancy excluded patients from the study. Evaluations included physical and neurologic examinations, laboratory data (hematology, blood chemistry, urinalysis), and vital signs.

Drug Supply

Copolymer 1 was manufactured and supplied by Teva Pharmaceuticals (Petah Tikva, Israel). It was supplied as a sterile lyophilized material in single-dose vials containing 22 mg of the active drug and 40 mg of mannitol. Patients or family members were instructed how to prepare and administer the drug. New supplies of Copolymer 1 were provided at 3-month intervals during scheduled visits. On each scheduled and unscheduled visit, adverse events were recorded. The annual relapse rate and the change of the EDSS score were monitored to assess the neurologic course of the disease.

Premature Discontinuation

Treatment was discontinued in any of the following circumstances: serious or intolerable adverse events, patient's decision to discontinue treatment for any reason, investigator's judgment that continuation of treatment was not in the best interest of the patient, poor compliance (fewer than 75% of scheduled injections), disease progression (EDSS progression over 6.0), and loss to follow-up.

TABLE 1. *Demographic and clinical characteristics of patients treated with Copolymer 1*

Gender: Male/Female	17/51
Age (years)	
Mean ± SD	35.4 ± 9.8
Range	19–61
Age when first symptom appeared (years)	
Mean ± SD	28.5 ± 8.9
Range	14–52
Total number of relapses reported before trial entry	
Mean ± SD	5.8 ± 3.8
Range	2–20
Number of relapses reported 2 years before trial entry	
Mean ± SD	2.9 ± 1.5
Range	1–12
EDSS score before onset of treatment	
Mean ± SD	2.7 ± 1.5
Range	1–8

EDSS, Expanded Disability Status Scale.

Statistics

The aim of the statistical analysis was to assess changes in efficacy parameters during the course of the treatment. Comparison of changes in EDSS scores and in annual relapse rates was performed. Paired *t*-tests were conducted to examine whether the results differed significantly from zero. In addition, we compared the results of this study to those of the previous open-label study in which daily injections were performed in the same centers by the same investigators (15). For these comparisons we used an unpaired *t*-test or χ^2 test, as appropriate.

RESULTS

Table 1 shows demographic and clinical characteristics of the sixty-eight patients who were enrolled (consisting of fifty-one females [75%] and seventeen males [25%]). Mean age was 35.4 years (± SD 9.8) and ranged from 19 to 61 years. The mean age when MS

TABLE 2. *Distribution of exacerbations*

	Number of patients	Total number of exacerbations	Mean ± SD	Range Min–Max
Two years before trial entry	68	195	2.9 ± 1.1* (41/68)	1–12
Two–year completers	41	23	0.56 ± 1.02 (41/41)	0–4

* $p = 0.0001$, comparing baseline relapse frequency in 41 patients who completed 2 years of treatment with that during the study.

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TABLE 3. *EDSS scores and difference in EDSS scores at yearly intervals*

	N	Mean	SD	Min	Max	Mean difference	SD	*P*-value
Screening (first day of study)	68	2.72	1.55	1	8			
After first year of treatment (last visit of first year-12 months of study)	53	2.71	1.59	1	7.5			
After second year of treatment (last visit of second year-24 months of study)	41	2.79	1.80	0	6.5			
Screening vs. first year of treatment	53					0.132	0.54	0.084
Screening vs. second year of treatment	41					0.426	0.99	0.008
First year of treatment vs. second year of treatment	41					0.29	0.78	0.021

EDSS, Expanded Disability Status Scale.

symptoms first appeared was 28.5 years (± SD 8.9) and ranged from 14 to 52 years. The total number of self-reported exacerbations before trial entry ranged from 2–20 (mean 5.8 ± SD 3.8). The mean number of exacerbations reported during the 2 years before trial entry was 2.9 (± SD 1.5) and ranged from 1 to 12. The mean baseline EDSS score was 2.7 (± SD 1.5) and ranged from 1 to 8. (One patient with an EDSS score of 8 was included in the study by mistake, as well as one patient with only a single relapse in the 2-year period before entry. Inclusion of these cases did not change the results or their significance).

Premature Discontinuation

According to the open-label design of the study, discontinuation was allowed after 1 or 2 years. Of the sixty-eight patients enrolled, fifty-three (77.9%) completed the first year and forty-one (60.3%) completed the second year of treatment. Twenty-seven patients (39.7%) dropped out during this period: eight (11.8%) as a result of adverse experience, six (8.8%) withdrew voluntarily, seven (10.3%) as a result of investigator's judgment, five (7.3%) were lost to follow-up, and one (1.5%) as a result of poor compliance and disease progression.

Relapses During the Study

Table 2 displays mean values and ranges of the number of exacerbations per patient before the study and during the first 2 years of the study. At the end of the first year, 65% of the patients who were still being treated remained relapse-free (33/51), corresponding to 49% of the total cohort. At the end of the second year (Fig. 1), 71% of the patients who continued the treatment throughout the second year (29/41) remained relapse-free. The annual relapse rate during succeeding years decreased. The mean relapse rate for these patients who completed 2 years of treatment (n = 41) decreased from 2.9 (± 1.1) in the 2 years before study entry to 0.56 (± 1.02) at the end of the second year. This represents an 80.8% reduction in relapse rate and is highly statistically significant ($p = 0.0001$).

Disability Accumulation

Evaluation of EDSS scores during the study revealed that the condition of most of the forty-one patients who completed 2 years of treatment remained stable, and that of only a few deteriorated. Table 3 displays EDSS scores at screening and after each year of treatment and mean differences between EDSS scores at screening and after 1 and 2 years of treatment. Differences were computed by subtracting the value at an earlier interval from the value obtained at the later interval. The results obtained show that EDSS scores remained stable during the first year of treatment ($p = 0.084$) and subsequently mildly deteriorated (Fig. 2).

Adverse Experiences

Table 4 displays all adverse experiences recorded, coded according to the COSTAR system. More than 17% of all patients participating in the trial (12/68) did not report any adverse events during the study. The most frequent adverse event, injection-site reaction,

TABLE 4. *Incidence and frequency of adverse experiences*

	Number of reports	% of reports	Number of patients	% of patients
Total	332	100	56	82.4
Injection site reaction*	120	36.1	34	60.7
Idiosyncratic systemic adverse reaction	38	11.4	16	28.6
Rash	6	1.8	4	7.1
Lymphadenopathy	6	1.8	1	1.8

* Including local sensitivity (10.5%), pain (7.8%), edema (6.0%), mass (4.8%), atrophy (3.6%), inflammation (0.6%), hemorrhage (0.6%), cyst (0.3%), and other local site reactions (1.8%).

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TABLE 5. *Disease characteristics and results of alternate and daily-treated patients with MS*

	Alternate-day treatment	Daily treatment*
Number of patients	68	271
Mean disease duration in years (± SD)	6.9 (± 0.9)	8.3 (± 6.4)
Mean annual relapse rate before 2 years (± SD)	1.4 (± 0.6)	1.4 (± 0.7)
Mean EDSS score before onset of treatment (± SD)	2.7 (± 1.6)	3.3 (± 1.8)
Mean relapse rate in the first 2 years of treatment (± SD)	0.56 (± 1.02)	0.3 (± 0.5)
Mean EDSS score at the end of the second year of treatment (± SD)	2.97 (± 1.80)	Not available
Number of patients who completed two years of treatment (%)	41/68 (60.3%)	107/271 (39.5%)
Number of patients relapse-free at the end of second year of treatment (%)	29/41 (70.7%)	58/107 (54.2%)
Premature terminations (total)	27/68 (39.7%)	99/271 (36.5%)
Due to voluntary withdrawal	6/27 (22.2%)	29/99 (29.3%)
Due to adverse events	8/27 (29.6%)	24/99 (34.2%)
Loss to follow up	5/27 (18.5%)	26/99 (26.3%)
Others	8/27 (29.6%)	20/99 (20.2%)

MS, multiple sclerosis; EDSS, Expanded Disability Scale.
* Data from Meiner et al. (1997).

was reported in 36% of the total number of reports. A self-limited idiosyncratic systemic adverse reaction manifested through transient chest pain, palpitations, and tachypnea was reported as 16.6% of the total number of adverse events reported. These sporadic, brief (2–20 minutes) reactions occurred immediately after drug administration and resolved without any treatment. No clinically significant changes were observed in any of the routine laboratory examinations.

In the design of the study, patients were supposed to have an EDSS score of 6 or lower; one patient with an EDSS of 8, however, was erroneously included. The same holds true for another patient who had only a single relapse in the 2-year period preceding randomization. We decided to include these patients in the final analysis and presentation. However, their exclusion did not change the results of the study.

Comparison of Daily with Alternate-Day Treatment

The results of the present alternate-day treatment were slightly better than those of the previous study with daily treatment; results were not significantly different, except for a lower dropout rate in the present study (Table 5).

DISCUSSION

Copolymer 1 was introduced for the management of MS based on a specific scientific assumption and proved useful in animal models of the disease (9,10). Its introduction into therapeutic studies, however, has bypassed the usual dose-finding phase, and the dose and frequency of administration have been slightly arbitrarily determined. Double-blind, placebo-controlled studies of Copolymer 1 demonstrated efficacy and safety (2,13), and the results of parallel, large-scale, open-label studies conducted in Israel support the long-term safety of the drug (15). Clinical data that were meticulously collected in these open-label studies showed an impressive reduction in exacerbation rate when compared with that in a 2-year period before entry into

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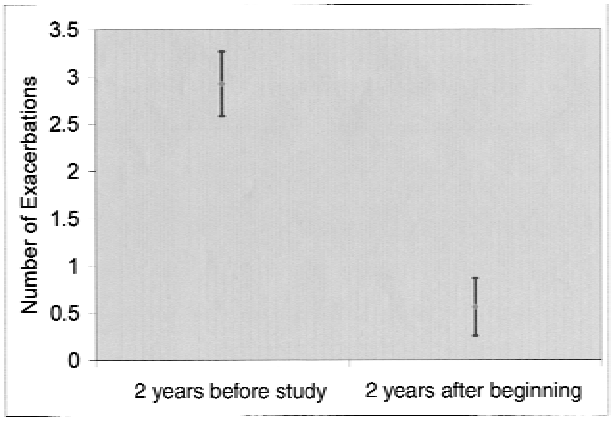

FIG. 1. Mean number of exacerbations for the 2 years before and the 2 years during treatment.

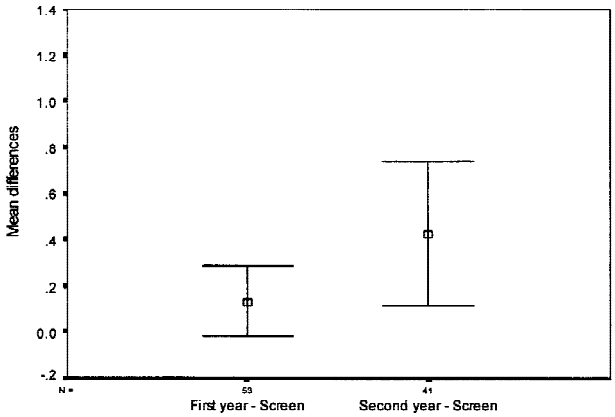

FIG. 2. Mean differences in Expanded Disability Status Scale (EDSS) scores relative to screening score. Ninety-five percent confidence intervals are given.

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the study (15). These open-label studies are important because they are more similar than Phase IV studies to the clinical situation that will occur when the drug reaches the open market.

The study reported here was uncontrolled; therefore, all conclusions cannot be used to prove efficacy. Nevertheless, it should be emphasized that the design of the present study was methodologically identical to that of the previous open-label study performed by us (15), except that injections were administered on alternate days rather than daily. The results of the two studies were surprisingly similar in terms of efficacy and tolerability as is demonstrated in Table 5; in particular, although the populations of both studies were roughly similar, the disease severity was reduced by the same degree (Table 5). It should be stressed that the dropout rate was lower in the alternate-day group than in the daily-injection regime (39.7% versus 60.3%, $p < 0.01$). The high rate of premature termination was not necessarily caused by inefficacy or an adverse event. During the same period, an aggressive campaign for the introduction of ß-interferons had a significant effect as well. If these results are confirmed, treatment with Copolymer 1 will become even more desirable than interferon therapy, as the side-effect profile is more benign than that of IFN-β. Our results may indicate that the dose of 20 mg of Copolymer 1 on alternate days already has a maximal effect, and daily injections are unnecessary. It is possible that the biologic effect of Copolymer 1 is not dose-related but is related to the exposure of the immune system to its presence by the continuity of administering the drug with rechallenging the immune system, thus making daily injections unnecessary.

The results of this study support previous reports concerning the safety of Copolymer 1 (2,12–15). The majority of adverse events reported were mild and transient, most frequently consisting of local injection-site reactions, which were reported by thirty-four patients (50%). Sixteen patients (23.5%) reported 38 episodes of one or more symptoms of the transient self-limited reactions (i.e., palpitations, flushing, dyspnea, or chest pain), which resolved spontaneously within a short time. These events, which were previously reported in placebo-controlled Copolymer 1 studies (2,14), did not follow any recognizable pattern of appearance, recurrence, and disappearance. Eight patients (11.8%) withdrew from the study because of adverse experiences; seven of these experiences are believed to be possibly or probably related to treatment with Copolymer 1. There were no deaths during the study. The frequency of adverse experiences reported decreased after the first 6 months of therapy.

We recorded very few relapses in patients who stayed in the trial. These results are similar to those of the previously reported phase II double-blind study (13), those of our own open-label study (15), and those of the multicenter phase III double-blind study conducted in the U.S. (2).

CONCLUSION

The results of this trial suggest that alternate-day treatment with Copolymer 1 is safe, well tolerated, and probably as effective as daily Copolymer 1 in reducing relapse rate and slowing neurologic deterioration. However, these preliminary observations will have to be examined in larger studies, preferably comparing daily with alternate-day administration of Copolymer 1 in a blinded manner.

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REFERENCES

1. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNβ-1b Multiple Sclerosis Study Group. *Neurology* 1993;43:655–61.
2. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces the relapse rate and improves disability in relapsing-remitting multiple sclerosis. Results of a phase III multicenter, double-blind, placebo-controlled trial. *Neurology* 1995;45:1268–76.
3. Jacobs LD, Cookfair DL, Rudick RA. Intramuscular interferon: ß-1a for disease progression in relapsing-remitting multiple sclerosis. *Ann Neurol* 1996;l39:285–94.
4. Ebers GC, Oger J, Paty DW, et al. The prisms study group prevention relapses and disability by Interferon: ß-1a subcutaneously in multiple sclerosis. *Ann Neurol* 1997;42:986.
5. Rudik RA, Cohen JA, Weinstock-Guttman B, et al. Management of multiple sclerosis. *New Engl J Med* 1997;337:1604–11.
6. Clark W. Therapeutic advances: ß-Interferon for multiple sclerosis. *J Clin Pharm Therap* 1996;21:195–9.
7. Lublin FD, Whitaker JN, Eideman BH, et al. Management of patients receiving interferon: ß-1b for multiple sclerosis: report of a consensus conference. *Neurology* 1996;46:12–8.
8. Goodkin DE, Rudick RA. *Multiple sclerosis: advances in clinical trial design, treatment and future prespectives.* Berlin, Germany: Springer-Verlarg, 1996:153–172.
9. Arnon R, Teitelbaum D, Sela M. Suppression of experimental allergic encephalomyelitis by Cop 1: relevance to multiple sclerosis. *Isr J Med Sci* 1989;25:686–9.
10. Teitelbaum D, Arnon R, Sela M. Copolymer 1: from basic research to clinical application. *Cell Mol Life Sci* 1997;53:24–8.
11. Borenstein MB, Miller A, Teitelbaum D, et al. Multiple sclerosis: trial of a synthetic polypeptide. *Ann Neurol* 1982;11:317–9.
12. Borenstein MB, Miller A, Slagle S, et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. *New Engl J Med* 1987; 317:408–14.
13. Borenstein MB, Miller A, Slagle S, et al. A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis. *Neurology* 1991;41:533–9.
14. Korczyn AD and Nisipeanu P. Safety profile of Copolymer 1: Analysis of cumulative experience in the United States and Israel. *J Neurol* 1996;243:23–6.
15. Meiner Z, Kott E, Schechter D, et al. Copolymer 1 in relapsing-remitting multiple sclerosis: a multicenter trial. In: Abramsky O and Ovadia H, ed. *Frontiers in Multiple Sclerosis* London: Martin Dunitz, 1997:213–21.

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