expedited publication

Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis:

Results of a phase III multicenter, double-blind, placebo-controlled trial

K.P. Johnson, MD; B.R. Brooks, MD; J.A. Cohen, MD; C.C. Ford, MD; J. Goldstein, MD; R.P. Lisak, MD; L.W. Myers, MD; H.S. Panitch, MD; J.W. Rose, MD; R.B. Schiffer, MD; T. Vollmer, MD; L.P. Weiner, MD; J.S. Wolinsky, MD; and the Copolymer 1 Multiple Sclerosis Study Group*

Article abstract—We studied copolymer 1 (Copaxone) in a multicenter (11-university) phase III trial of patients with relapsing-remitting multiple sclerosis (MS). Two hundred fifty-one patients were randomized to receive copolymer 1 (n = 125) or placebo (n = 126) at a dosage of 20 mg by daily subcutaneous injection for 2 years. The primary end point was a difference in the MS relapse rate. The final 2-year relapse rate was 1.19 ± 0.13 for patients receiving copolymer 1 and 1.68 ± 0.13 for those receiving placebo, a 29% reduction in favor of copolymer 1 ($p = 0.007$) (annualized rates = 0.59 for copolymer 1 and 0.84 for placebo). Trends in the proportion of relapse-free patients and median time to first relapse favored copolymer 1. Disability was measured by the Expanded Disability Status Scale (EDSS), using a two-neurologist (examining and treating) protocol. When the proportion of patients who improved, were unchanged, or worsened by ≥1 EDSS step from baseline to conclusion (2 years) was evaluated, significantly more patients receiving copolymer 1 were found to have improved and more receiving placebo worsened ($p = 0.037$). Patient withdrawals were 19 (15.2%) from the copolymer 1 group and 17 (13.5%) from the placebo group at approximately the same intervals. The treatment was well tolerated. The most common adverse experience was an injection-site reaction. Rarely, a transient self-limited systemic reaction followed the injection in 15.2% of those receiving copolymer 1 and 3.2% of those receiving placebo. This reaction was characterized by flushing or chest tightness with palpitations, anxiety, or dyspnea and commonly lasted for 30 seconds to 30 minutes. This rigorous study confirmed the findings of a previous pilot trial and demonstrated that copolymer 1 treatment can significantly and beneficially alter the course of relapsing-remitting MS in a well-tolerated fashion.

NEUROLOGY 1995;45:1268-1276

Progress in identifying effective therapies for multiple sclerosis (MS) has accelerated during this decade as pathogenic factors active in the disease have been identified. We now report that treatment with copolymer 1 (Copaxone), given subcutaneously (s.c.) at a dosage of 20 mg per day in a rigorously controlled 2-year trial, significantly reduced the relapse rate in patients with relapsing-remitting MS. Neuro-

See also page 1245

*See pages 1275 and 1276 for the Copolymer 1 Multiple Sclerosis Study Group participants.

From the Department of Neurology (Drs. Johnson and Panitch), University of Maryland, Baltimore, MD; the Department of Neurology (Dr. Brooks), University of Wisconsin, Madison, WI; the Department of Neurology (Dr. Cohen), University of Pennsylvania, Philadelphia, PA; the Department of Neurology (Dr. Ford), University of New Mexico, Albuquerque, NM; the Department of Neurology (Drs. Goldstein and Vollmer), Yale University, New Haven, CT; the Department of Neurology (Dr. Lisak), Wayne State University, Detroit, MI; the Department of Neurology (Dr. Myers), University of California, Los Angeles, CA; the Department of Neurology (Dr. Rose), University of Utah and the Veterans Administration Medical Center, Salt Lake City, UT; the Department of Neurology (Dr. Schiffer), University of Rochester, Rochester, NY; the Department of Neurology (Dr. Weiner), University of Southern California, Los Angeles, CA; and the Department of Neurology (Dr. Wolinsky), University of Texas, Houston, TX.

Supported by the Federal Food and Drug Administration Orphan Drug Program no. FD-R000559-01, the National Multiple Sclerosis Society no. RG 2202-A-6, and Teva Pharmaceutical Industries, Ltd., Petah Tiqva, Israel.

Presented at the annual meeting of the American Neurological Association, San Francisco, October 1994.

Received April 27, 1995. Accepted in final form May 1, 1995.

Address correspondence and reprint requests to Dr. Kenneth P. Johnson, Department of Neurology, N4W46, University of Maryland Hospital, 22 South Greene Street, Baltimore, MD 21201.

logic impairment, as measured by the Expanded Disability Status Scale (EDSS),[1] was also favorably affected, and patients tolerated treatment well, with a low frequency of side effects. Thus, copolymer 1 joins interferon beta-1b (IFNB-1b) (licensed in 1993) as a treatment shown to positively alter the natural course of relapsing-remitting MS.[2]

Copolymer 1 is the acetate salt of a mixture of synthetic polypeptides composed of four amino acids, L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, in a molar ratio of 4.2, 1.4, 3.4, and 1.0, respectively, and with an average molecular weight of 4,700 to 13,000 daltons. First synthesized in 1967 by M. Sela, R. Arnon, D. Teitelbaum, and their colleagues at the Weizmann Institute of Science in Israel, copolymer 1 suppresses or modifies experimental allergic encephalomyelitis (EAE)[3] in several species of mammals including nonhuman primates.[4] Other studies[5] suggest that copolymer 1 acts through cross-reactivity with myelin basic protein (MBP) and inhibition of the cell-mediated immune response to this antigen.

Extensive preclinical findings encouraged Abramsky et al[6] to treat a small number of patients who had advanced MS or acute disseminated encephalomyelitis with copolymer 1. They used a low dose and observed no toxicity. Bornstein et al[7] then treated four MS patients in the relapsing-remitting and 12 in the chronic-progressive stages of disease with copolymer 1 and noted fewer relapses or neurologic improvement in five. They used various doses and routes of administration for up to 6 months. This open trial was later extended and the dose increased from 5 mg i.m. to 20 mg s.c. daily for up to 3 years without significant side effects or laboratory abnormalities.

These early human studies indicated that copolymer 1 could be given safely and prompted a 2-year, placebo-controlled, double-blind pilot trial to evaluate its effects on the MS relapse rate, disability, and patient tolerance.[8] Forty-eight patients with relapsing-remitting MS, a high mean annual relapse rate of 1.9, and a mean disability status scale (EDSS) score of 3.0 were entered. Twenty-five received 20 mg of copolymer 1 s.c. daily and 23 received s.c. placebo. During 2 years, there were 62 relapses in the placebo group but only 16 in the copolymer 1 group, a highly significant difference. Fifty-six percent of the copolymer 1 group and 26% of those receiving placebo remained relapse-free. The effect was most pronounced in patients with the lowest EDSS ratings at entry, and there was a trend toward benefit of copolymer 1 over placebo in terms of progression of disability, especially in the patients with the lower EDSS scores at entry. Patient tolerance was very good, and there were no laboratory abnormalities.[8]

Copolymer 1 was then studied in patients with chronic-progressive MS at two centers, the Albert Einstein College of Medicine, Bronx, NY, and the Baylor College of Medicine, Houston, TX.[9] Patients with EDSS ratings from 2.0 to 6.5, inclusive, were observed for at least 12 months before randomization to document progression of their disease. One hundred six patients (mean age 42 years, mean EDSS score 5.6) were treated in a double-blind trial. They received either placebo or 15 mg of copolymer 1 twice daily by s.c. self-injection, and tolerated the therapy well. The combined results showed a trend toward benefit with copolymer 1 treatment, which was, however, not statistically significant.[9]

Table 1. Participating universities and the number of patients randomized to each treatment group

Center	Copolymer 1	Placebo
University of California, Los Angeles	16	14
University of Maryland*	14	14
University of New Mexico	13	14
University of Pennsylvania	14	13
University of Rochester	15	13
University of Southern California	6	8
University of Texas, Houston	9	11
University of Utah	12	12
Wayne State University	12	12
University of Wisconsin	6	7
Yale University	8	8

* National coordinating center.

To further evaluate copolymer 1 treatment of patients with relapsing-remitting MS, we conducted a large, placebo-controlled, multicenter trial and have observed patients in a blinded fashion for 2 years.

Methods. The objectives of the current study were to compare the patient tolerance and therapeutic impact of daily s.c. injections of 20 mg of copolymer 1 or placebo over 24 months, using the number of MS relapses as the primary variable. The study was designed and the patients recruited to confirm the conclusions of the previously published pilot trial.[8]

Participants. Eleven universities with active MS centers and experience in conducting clinical neurologic research participated in the trial (table 1). The University of Maryland served as the administrative and clinical coordinating center. After an intensive training session for neurologists and study coordinators, the trial began in October 1991.

Study design. The primary end point, determined prospectively in this phase III study, was a comparison of the mean number of relapses experienced by copolymer 1- or placebo-treated relapsing-remitting MS patients during 2 years of treatment. A relapse was defined as the appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours and immediately preceded by a relatively stable or improving neurologic state of at least 30 days. A relapse was confirmed only when the patient's symptoms were accompanied by objective changes on the neurologic examination consistent with an increase of at least a half a step on the EDSS, two points on one of the seven functional systems,[1] or one point on two or more of the functional

systems. Events associated with fever were excluded. A change in bowel/bladder or cognitive function could not be solely responsible for the changes in either the EDSS or the functional system scores. Several secondary end points were also predetermined: proportion of relapse-free patients, time to first relapse after initiation of therapy, proportion of patients with sustained disease progression (defined as an increase of at least one full step on the EDSS that persisted for at least 3 months), and mean change in EDSS and ambulation index between the copolymer 1 and placebo groups from baseline to conclusion. All patients had periodic, standardized neuropsychological tests, and a subset of patients underwent serial gadolinium-enhanced MRIs; results will be reported in separate publications.

Conduct of the study. Patients were screened to determine eligibility and then randomized within 21 days. A centralized randomization scheme was used. All patients met the criteria of clinically definite MS or laboratory-supported definite MS.[10] Male and female patients between the ages of 18 and 45 years were eligible. They were all ambulatory with an EDSS score of 0 through 5.0, a history of at least two clearly identified and documented relapses in the 2 years prior to entry, onset of the first relapse at least 1 year before randomization, and a period of neurologic stability and freedom from corticosteroid therapy of at least 30 days prior to entry. Patients were excluded if they had ever received copolymer 1 or previous immunosuppressive therapy with cytotoxic chemotherapy (azathioprine, cyclophosphamide, or cyclosporine) or lymphoid irradiation. Other exclusion criteria included pregnancy or lactation, insulin-dependent diabetes mellitus, positive HIV or HTLV-I serology, evidence of Lyme disease, or required use of aspirin or chronic nonsteroidal anti-inflammatory drugs during the course of the trial. All women were required to use an adequate method of contraception.

The study medication was supplied by Teva Pharmaceutical Industries, Ltd, Petah Tiqva, Israel, under a manufacturing protocol approved by the US Food and Drug Administration. It was distributed to each of the 11 cooperating university centers by an independent data management and coordination center, National Medical Research Corporation, Hartford, CT. Study medication was supplied in single-dose vials of lyophilized material along with ampules of sterile water diluent. Patients were given a 1-month supply each month and were instructed in reconstitution and s.c. self-administration of the study medication. At each monthly visit, patients received medication and reported adverse events and use of concomitant medications. Every 3 months, the patients underwent a complete evaluation that employed a two-neurologist protocol. Each patient was assigned a single examining neurologist who evaluated only the objective neurologic condition without discussing symptoms or side effects. A second treating neurologist evaluated symptoms and adverse events and was responsible for determining the need for steroid therapy at the time of a confirmed relapse. A nurse coordinator at each center distributed medication, noted concomitant treatments, and obtained blood and urine specimens for laboratory analysis. The nurse coordinator and both neurologists were blinded to study medication assignment throughout the trial. Patients were allowed to use the conventional medications they were receiving at the time of randomization for spasticity, bladder control, fatigue, and other MS symptoms. An approved protocol for steroid therapy was employed by the treating neurologist at the time of confirmed relapse. Use of immunosuppressive, cytotoxic, or experimental drugs or aspirin and chronic nonsteroidal anti-inflammatory drugs were proscribed.

At the time of suspected relapse, patients were instructed to call their center immediately to discuss symptoms with the nurse coordinator or treating neurologist and to arrange for an examination at the center within 7 days. In rare instances, weather conditions and other emergencies prohibited evaluation at the site within that time. Patients were followed as often as medically indicated after each confirmed relapse.

All patients had a chest x-ray and ECG at the screening visit and another ECG at the conclusion of the study. Urinalysis, hematologic studies, a serum chemistry panel, and anti-copolymer 1 antibodies were evaluated at 3-month intervals; all blood testing was done at a centralized laboratory and reported to the treating neurologist and to the data management and coordination center. An independent safety monitoring committee, composed of two clinical neurologists, a clinical pharmacologist, a statistician, and a representative of the National Multiple Sclerosis Society, met quarterly either in person or by conference call to review all safety information. At no time were representatives of the sponsor or the 11 study centers present when safety data or issues were discussed. The safety committee remained blinded throughout the course of the trial.

The protocol was approved by the institutional review boards of the participating clinical centers, and all patients gave written informed consent.

Statistical analysis. The final data set was evaluated using several cohort definitions. The intention-to-treat analysis of all randomized patients was considered primary. Other evaluated cohorts excluded patients who did not complete 6 months of treatment, patients who failed to complete 2 years (730 days) of treatment, and patients who missed over 5% of consecutive study medication doses or 10% of total doses during the study. There was strong internal consistency of statistically significant findings and trends among the various evaluated cohorts. Therefore, only the results of the most rigorous intention-to-treat analysis are presented here.

The proportions of withdrawals were compared using the Cochran-Mantel-Haenszel test. Time to withdrawal was analyzed using the log rank test. For demographic and medical history characteristics, two-sample t tests were used for continuous variables and exact probability tests for discrete variables.

Mean relapse rate was analyzed using ANCOVA, with tests for study-drug-by-center interaction and including a priori-defined covariates: sex, duration of disease (years), prior 2-year relapse rate, and baseline Kurtzke EDSS. Proportions of relapse-free patients were tested using logistic regression incorporating the same covariate effects. Time to first relapse was evaluated using Weibull regression. The proportion of progression-free patients was analyzed using logistic regression.

Changes from baseline for the Kurtzke EDSS and the ambulation index were assessed using repeated-measures ANCOVA. Analyses of the change from baseline to 24 months were also conducted. Categorical repeated-measures and 24-month end-point analyses were performed on Kurtzke EDSS score changes from baseline, classified as "improved" (reduction of at least one step) "worsened," (increase of at least one step), or "no change."

Results. *Baseline characteristics of subjects.* Between October 1991 and May 1992, 284 patients were screened and 251 randomized to the two treatment groups. The demographics of the randomized cohort are shown in table 2. The two groups were well matched for age, sex, race, duration of disease, mean relapse rate in the prior 2 years, EDSS, and ambulation index. As expected, the majority of randomized patients were women (73%) and white (94%). Among the patients randomized to receive copolymer 1, 51 were in the 0 to 2, 57 in the 2 to 4, and 17 in the >4 EDSS range. Of those randomized to receive placebo, 68 were in the 0 to 2, 46 in the 2 to 4, and 12 in the >4 EDSS range.

Patient exposure and withdrawals. The total patient exposure and duration of treatment is shown in table 3. The total patient exposure to copolymer 1 was 227 years and to placebo 232 years. Nineteen patients (15%) withdrew from the copolymer 1-treated group and 17 (13.5%) from the placebo group. The proportion of patients who withdrew and the time to withdrawal as shown in table 3 were statistically similar over the duration of the study. Three patients in the copolymer 1 group withdrew when they became pregnant, and one stopped medication because of disease progression. Two patients in the placebo group failed to comply with the protocol. Two copolymer 1 patients withdrew for serious adverse events: one, after 50 days on treatment, developed immediate flushing, chest tightness, dyspnea, nausea, and vomiting (see below), which lasted for more than 90 minutes after the injection, and one, after 131 days on treatment, developed generalized lymph node enlargement. Lymph node biopsy from that patient revealed only chronic inflammatory change. Three other patients receiving copolymer 1 and one patient receiving placebo withdrew because of transient self-limited systemic reactions that were brief and not considered serious.

MS relapse rates. During the 2-year trial, the copolymer 1-treated patients had 161 confirmed relapses and the placebo group had 210 confirmed relapses (table 4). The mean relapse rate (2 years) was 1.19 in the copolymer 1 group and 1.68 in the placebo group, a 29% reduction, which was statistically significant at the $p = 0.007$ level. Annualized relapse rates were 0.59 for the copolymer 1 group and 0.84 for those receiving placebo. The median time to first relapse from baseline for the copolymer 1 group was 287 days and for the placebo group it was 198 days, a difference that approached statistical significance ($p = 0.097$). Forty-two patients receiving copolymer 1 (33.6%) and 34 placebo patients (27.0%) were relapse-free throughout the trial ($p = 0.098$). This result also approached statistical significance. When the relapse data were summarized in relation to baseline EDSS scores, it was found that patients with greater disability at entry had more relapses during the trial (figure 1). However, the therapeutic effect appeared to be most pronounced in patients with the lowest EDSS scores at entry (0 to 2), in

Table 2. Demographics and MS characteristics at baseline (number screened = 284)

	Copolymer 1 (n = 125)	Placebo (n = 126)
Age (yr; mean ± SD)	34.6 ± 6.0	34.3 ± 6.5
Sex		
Women	88 (70.4%)	96 (76.2%)
Men	37 (29.6%)	30 (23.8%)
Race		
White	118 (94.4%)	118 (93.6%)
Other	7 (5.6%)	8 (6.3%)
Prior 2-year relapse rate (mean ± SD)	2.9 ± 1.3	2.9 ± 1.1
EDSS (mean ± SD)	2.8 ± 1.2	2.4 ± 1.3
Ambulation index (mean ± SD)	1.2 ± 1.0	1.1 ± 0.9
Duration of MS (yr; mean ± SD)	7.3 ± 4.9	6.6 ± 5.1

EDSS Expanded Disability Status Scale.

Table 3. Patient exposure and duration of treatment

Duration of treatment (mo)	Copolymer 1 (n = 125)			Placebo (n = 126)		
	n	%	Total patient months	n	%	Total patient months
≤3	3	2.4	5.6	4	3.2	3.8
>3-6	3	2.4	13.6	3	2.4	13.6
>6-9	2	1.6	13.9	0	0.0	0
>9-12	5	4	49.4	3	2.4	31.6
>12-15	2	1.6	27.0	3	2.4	41.2
>15-18	2	1.6	33.1	2	1.6	31.4
>18-21	1	0.8	18.9	1	0.8	20.5
>21-24	1	0.8	21.3	1	0.8	23.5
≥24	106	84.8	2,376.0	109	86.5	2,615.9
Total	125	100	2,725.3	126	100	2,781.5

Table 4. Relapse experience of copolymer 1 and placebo groups

	Copolymer 1 (n = 125)	Placebo (n = 126)	Reduction vs placebo	*p* Value
Primary end points				
Relapse rate over 24 mo (covariate adjusted mean)	1.19	1.68	–29%	0.007
Annualized relapse rate	0.59	0.84		
Observed relapses over 24 mo	161	210		
Secondary end points				
Proportion of relapse-free patients	33.6%	27.0%		0.098
Median time to first relapse (days)	287	198		0.097
Number of relapses per patient				
0	42	34		
1-2	60	55		0.023
≥3	23	37		

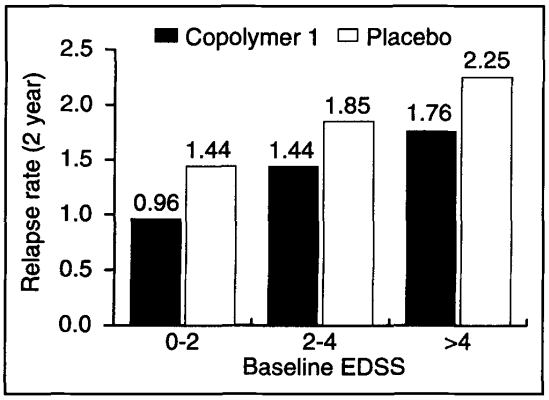

Figure 1. Changes in relapse rate observed over 2 years, by baseline EDSS score. The numbers above each bar represent the mean 2-year relapse rate for each group.

Table 5. Disability experience measured by EDSS and ambulation index of copolymer 1 and placebo groups

	Copolymer 1	Placebo	*p* Value
Proportion of patients with a change in disability between baseline and conclusion			
Improved (EDSS decrease ≥1)	24.8%	15.2%	
No change	54.4%	56.0%	0.037*
Worse (EDSS increase ≥1)	20.8%	28.8%	
EDSS change from baseline (mean ± SD)	–0.05 ± 1.13	0.21 ± 0.99	0.023†
Proportion of progression-free patients	78.4%	75.4%	NS
Ambulation index (mean ± SD)	0.27 ± 0.94	0.28 ± 0.93	NS

EDSS Expanded Disability Status Scale.
NS Not significantly different.
* Categorical repeated measures.
† Repeated-measures analysis of covariance.

whom there was a 33% difference in the relapse rate in favor of copolymer 1.

Neurologic disability. The effect of copolymer 1 therapy on neurologic disability was evaluated in a series of secondary end points (table 5) based on the EDSS and ambulation index, and determined every 3 months by the examining neurologist. Figure 2 shows that more patients receiving copolymer 1 were improved whereas more patients on placebo were worse by one or more EDSS steps when compared between baseline and 24 months. This finding was statistically significant in favor of copolymer 1 for both the categorical repeated-measures analysis ($p = 0.037$) and the analysis from baseline to 24 months ($p = 0.024$). The repeated-measures analysis of mean change in EDSS also significantly favored copolymer 1 ($p = 0.023$). When progression to sustained disability was defined as an increase of one or more EDSS steps maintained for more than 90 days—that is, for two consecutive scheduled visits—little difference was noted between groups. Of those patients treated with copolymer 1, 78.4% were free of progression, while of those receiving placebo, 75.4% showed no progression (NS). The mean ambulation index scores were also similar between groups, 0.27 for copolymer 1-treated patients and 0.28 for those on placebo (NS).

Adverse events. No clinically significant differences in vital signs were noted during the trial. The most commonly recognized adverse event was a localized injection-site reaction consisting of mild erythema and induration, which sometimes persisted for several days (table 6). It was observed at least once during 730 days of treatment in 90% of the copolymer 1-treated patients and in 59% of the patients receiving placebo. The other adverse event clearly related to therapy was a transient self-limited systemic reaction (table 7), which also was recognized in earlier copolymer 1 studies.[8,9] This reaction was sporadic and unpredictable, occurred within minutes of an injection, and was characterized by a variable combina-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.