17. Schade DS, Eaton RP. The regulation of plasma ketone body concentration by counterregulatory hormones in man. I. Effects of norepinephrine in diabetic man. Diabetes 1977; 26:989-96.
18. McDonald-Gibson RG, Young M. The use of an automatic solids injection system quantitative determination of plasma long chain non-esterified fatty acids by gas–liquid chromatography. Clin Chim Acta 1974; 53:117-26.
19. Wolfe RR. Tracers in metabolic research: radioisotope and stable isotope mass spectrometry methods. New York: Alan R. Liss, 1984:261-3.
20. Faloona GR, Unger RH, Jaffe BM. Glucagon. In: Jaffe BM, Behrman HR, eds. Methods of hormone radioimmunoassay. New York: Academic Press, 1974:317-38.
21. Hussain MN, Benedict CR. Radioenzymatic microassay for simultaneous estimations of dopamine, norepinephrine, and epinephrine in plasma, urine, and tissues. Clin Chem 1985; 31:1861-4.
22. Hagenfeldt L, Wahren J, Pernow B, Räf L. Uptake of individual free fatty acids by skeletal muscle and liver in man. J Clin Invest 1972; 51: 2324-30.
23. Spitzer JJ, Gold M. Studies on the metabolism of free fatty acids in diabetic and fasting dogs. Ann NY Acad Sci 1965; 131:235-49.
24. Wolfe RR, Peters EJ, Klein S, Holland OB, Rosenblatt JI, Gary H Jr. Effect of short-term fasting on lipolytic responsiveness in normal and obese human subjects. Am J Physiol 1987; 252:E189-E196.
25. Dixon M, Webb EC. Enzymes. 3rd ed. New York: Academic Press, 1979:842-3.
26. Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington, D.C.: Carnegie Institution of Washington, 1919:40-4.
27. Vaugh M. The production and release of glycerol by adipose tissue incubated in vitro. J Biochem 1962; 237:3354-8.
28. Wilmore DW, Aulick LH. Metabolic changes in burned patients. Surg Clin North Am 1978; 58:1173-87.
29. Kien CL, Young VR, Rohrbaugh DK, Burke JF. Increased rates of whole body protein synthesis and breakdown in children recovering from burns. Ann Surg 1978; 187:383-91.
30. Jahoor F, Desai M, Herndon DN, Wolfe RR. Dynamics of the protein metabolic response to burn injury. Fed Proc 1987; 46:879. abstract.
31. Jahoor F, Herndon DN, Wolfe RR. The role of insulin and glucagon in the response of glucose and alanine kinetics in burn-injured patients. J Clin Invest 1986; 78:807-14.
32. Vaughan GM, Becker RA, Unger RH, et al. Nonthyroidal control of metabolism after burn injury: possible role of glucagon. Metabolism 1985; 34:637-41.
33. Chenoweth M, Dunn A. Fructose-6-phosphate substrate cycling and hormonal regulation of gluconeogenesis in vivo. Am J Physiol 1978; 235: E295-E303.

A PILOT TRIAL OF COP 1 IN EXACERBATING–REMITTING MULTIPLE SCLEROSIS

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Abstract Cop 1 is a random polymer (molecular weight, 14,000 to 23,000) simulating myelin basic protein. It is synthesized by polymerizing L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. It suppresses but does not induce experimental allergic encephalomyelitis, an animal model of multiple sclerosis. It is not toxic in animals.

In a double-blind, randomized, placebo-controlled pilot trial, we studied 50 patients with the exacerbating–remitting form of multiple sclerosis, who self-injected either 20 mg of Cop 1 dissolved in 1 ml of saline or saline alone daily for two years.

Six of 23 patients in the placebo group (26 percent) and 14 of 25 patients in the Cop 1 group (56 percent) had no exacerbations (P = 0.045). There were 62 exacerbations in the placebo group and 16 in the Cop 1 group, yielding two-year averages of 2.7 and 0.6 per patient, respectively. Among patients who were less disabled on entry (Kurtzke disability score, 0 to 2), there were 2.7 exacerbations in the placebo group and 0.3 in the Cop 1 group over two years. Among patients who were more affected (Kurtzke disability score, 3 to 6), there was an average of 2.7 exacerbations in the placebo group and 1.0 in the Cop 1 group. Over two years, less disabled patients taking Cop 1 improved an average of 0.5 Kurtzke units; those taking placebo worsened an average of 1.2 Kurtzke units. More disabled patients worsened by 0.3 (Cop 1 group) and 0.4 (placebo group) unit. Irritation at injection sites and rare, transient vasomotor responses were observed as side effects.

These results suggest that Cop 1 may be beneficial in patients with the exacerbating–remitting form of multiple sclerosis, but we emphasize that the study is a preliminary one and our data require confirmation by a more extensive clinical trial. (N Engl J Med 1987; 317:408-14.)

COP 1 is synthesized by the random polymerization of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in the ratio of 6.0:1.9:4.7:1.0 (molecular weight, 14,000 to 23,000). It was one of a series of polypeptides prepared to simulate myelin basic protein, a natural component of the myelin sheath.[1-3] Myelin basic protein in Freund's complete adjuvant induces experimental allergic encephalomyelitis, an animal model of multiple sclerosis. In saline, it suppresses the response in challenged animals.[4,5] Some of the polypeptides simulating myelin basic protein, particularly Cop 1, proved incapable of inducing experimental allergic encephalomyelitis, yet suppressed the disease in rabbits, guinea pigs, mice, and nonhuman primates.[1,6-9] Studies in mice suggest that it acts through the production of antigen-specific suppressor T cells.[10,11] Cop 1 is also nontoxic during short-term and longer-term (three to six months) administration in mice, rabbits, and dogs (Meshorer A: personal communication).

In view of these characteristics and the reported

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first on 4 severely affected patients with multiple sclerosis[16] and later on 12 patients with the chronic, progressive form of the disease and 4 patients with the exacerbating–remitting form.[17] Those studies led to this double-blind, randomized, matched-pair, placebo-controlled pilot trial of Cop 1 in patients with the exacerbating–remitting form of the disease.

Methods

The trial was approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine and by the Food and Drug Administration (Cop 1 was assigned the investigational-new-drug number 14,115).

Preparation and Characterization of Cop 1

Cop 1 was first prepared at the Weizmann Institute of Science, Rehovot, Israel,[1] and later by the Bio-Yeda Company in Rehovot. All batches were analyzed for their amino acid composition, molecular weight, cross-reactivity with myelin basic protein, and suppression of experimental allergic encephalomyelitis in guinea pigs. Suppression was expressed as the difference in the percentage of diseased animals between the group treated with Cop 1 and the controls. The 12 batches from the Weizmann Institute had a suppression rate ranging from 10 to 80 percent (average, 33.5 percent); the rate for 14 batches produced by Bio-Yeda ranged from 10 to 75 percent (average, 40.6 percent). In an attempt to reduce inflammatory reactions at injection sites, we used an in vitro method to evaluate cell damage (basophil degranulation) by serotonin release.[18] All the batches in this study produced releases of less than 30 percent.

Cop 1 was dissolved in bacteriostatic saline at a concentration of 20 mg per milliliter. Sterile single-dose vials containing 1 ml of bacteriostatic saline alone or the Cop 1 solution were stored at −20°C until they were used. Each patient received a monthly supply of 32 vials of the appropriate solution. The preparation and distribution of vials and patient compliance were monitored by a clinical assistant under the direction of the statistician responsible for the randomization of patients (see Study Design below).

Patient Recruitment and Enrollment

To be eligible for the study, patients had to fulfill all the diagnostic criteria for definite multiple sclerosis,[19] be 20 to 35 years of age, have an above-average exacerbation rate, consisting of at least two well-demarcated and well-documented episodes of exacerbation in the two years before admission, have a score no higher than 6 (ambulatory with assistance) on the Kurtzke Disability Status Scale, and be emotionally stable as determined by psychosocial evaluation. The Kurtzke Disability Status Scale[20] represents degrees of neurologic dysfunction in units from 0 (no disability) to 10 (death from multiple sclerosis); a related scale measures functioning in eight areas: pyramidal, cerebellar, brain-stem, sensory, bowel and bladder, visual, mental, and other.

Questionnaires completed by 932 volunteers were reviewed; 140 of these candidates were evaluated in neurologic and psychosocial examinations. Ninety of the 140 were excluded — 23 because of age; 21, low frequency of exacerbations; 19, lack of documentation; 15, psychosocial inadequacy; 8, transition to a chronic, progressive course; 3, distance from the clinic; and 1, pregnancy. Fifty patients were accepted into the trial.

Study Design and Data Collection

Study patients were matched according to sex, number of exacerbations per year within ±1 exacerbation, and degree of disability as measured by the Kurtzke Scale in three strata: 0 to 2, 3 to 4, and 5 to 6. The random assignment of the first patient of a pair determined the assignment of both. Treatment assignments were made known to the clinical assistant responsible for the production, labeling, and ly enrolled in the study after another explanation of the trial, instruction in the method of self-injection, and signing of a consent form.

Eight patients who had an exacerbation between screening and acceptance into the study were enrolled after their conditions had become stable. One patient was enrolled after being weaned from corticosteroids over a period of a month.

Data from a personal and disease history and a neurologic examination and status evaluation using Kurtzke's Disability Status Scale and Eight Functional Groups were recorded at the time of screening and on the patient's entry into the study. Patients visited the clinic one month later and every three months thereafter for two years. At each visit, a neurologist unaware of the patient's treatment group completed a neurologic examination and status evaluation. The patient's self-evaluation of local or generalized side effects and changes in neurologic status were reported to the clinical assistant, who was not blinded to treatment.

Patients were also seen at the times of suspected exacerbations — i.e., when reporting the rapid onset of new symptoms or a worsening of preexisting symptoms that persisted for 48 hours or more. The neurologist verified exacerbations on the basis of study criteria. An event was counted as an exacerbation only when the patient's symptoms were accompanied by observed objective changes on the neurologic examination involving an increase of at least one grade in the score for one of the eight functional groups or the Kurtzke Scale. Sensory symptoms unaccompanied by objective findings or transient neurologic worsening were not considered to represent an exacerbation. Patients experiencing an acute exacerbation were evaluated at frequent intervals — usually every two weeks — until a new, stable neurologic base line had been established. Seventy-four percent of 62 exacerbations in the placebo group and 75 percent of 16 exacerbations in the Cop 1 group were treated with steroids. Symptomatic medications, such as cholinergic and spasmolytic drugs, were permitted.

Laboratory Tests

Blood and urine samples were obtained from each patient upon entry into the trial and at each three-month visit. Routine urinalyses, blood chemistry (SMA 20) determinations, and complete blood counts were performed. Aliquots of serum and cells were stored in a deep freezer or in liquid nitrogen (at −90° or −180°C, respectively) for future studies.

HLA typing of HLA-A, B, C, and DR was performed by the tissue-typing laboratory of the Department of Surgery, Montefiore Medical Center, Bronx, New York.

Statistical Methods

The base-line characteristics of the study population in the two treatment arms were compared with use of two-tailed t-tests for continuous variables and chi-square tests with Yates' correction for discrete variables. Differences in side effects according to treatment arm were evaluated with a chi-square test.

The principal end point was the proportion of exacerbation-free patients. The other end points were frequency of exacerbations, change in Kurtzke score from that at base line, and length of time before progression, as defined below.

The study design included planned subgroup analyses according to the disability status of the patients when they were randomized (Kurtzke units 0 to 2, 3 to 4, and 5 to 6). However, only one patient entered with a score of 4, and three with a score of 5. Therefore, we combined two of the three strata (3 to 4 and 5 to 6), creating two strata (0 to 2 and 3 to 6) with approximately equal numbers of patients for subgroup analyses.

For the matched-pair analysis, the difference between treatment arms was tested with use of a McNemar's statistic for the 22 matched pairs. A two-tailed Fisher's exact test was used for other two-by-two contingency tables. The chi-square test was used to test two-by-three contingency tables for frequency of exacerbations.

Survival curves were calculated with life-table methods[21] for the

Table 1. Base-Line Characteristics of the Study Population.

Characteristic	Treatment Group		
	Placebo		Cop 1
	randomized	*included in analysis*	
No. entered	25	23	25
Average age (yr)	31.0	31.1	30.0
Average duration of disease (yr)	6.1	6.4	4.9
Sex			
Male	10	10	11
Female	15	13	14
Race/ethnic group			
White	25	23	23
Black/Hispanic	0	0	2
Disability score (Kurtzke Scale)			
0–2	11	10	13
3–4	7	7	5
5–6	7	6	7
Average disability score	3.2	3.1	2.9
Prior exacerbation rate (over 2-yr period)	3.9	3.9	3.8

noted at the time of the visit during which it was observed; however, it had to be maintained for at least three months to be counted. Data on patients lost to follow-up were censored at the time of withdrawal. The log-rank statistic was used to test for comparability of the survival curves for each treatment arm. The curves were also tested for a difference at the discrete point of 24 months.[21]

Multiple logistic-regression analyses were undertaken to test the effect of treatment on the outcome, with adjustment for other variables, including sex, the duration of disease, the previous exacerbation rate, disability at the time of entry into the study, and various interactions of these variables. Odds ratios were calculated from the regression coefficients.[22]

Study Population

Fifty patients were enrolled: 48 in 24 matched pairs, and 2 unmatched patients, 1 randomly assigned to each study group. Table 1 shows the base-line characteristics of the total study population and of the 48 patients included in the analyses. The distributions of these characteristics were similar in the two treatment arms.

In order to guard against any possible bias that might be introduced by subjects dropping out of the study, we tried to include all the randomized patients in the analyses. There were seven patients who did not complete the two years of the trial. Of these, two patients in the placebo group were excluded from all the analyses because of unusable data. Both had been dropped from the trial for psychological reasons. The partial data obtained from the other five patients were included in the analyses. One patient taking Cop 1 dropped out during a period of exacerbation after two months of treatment. This patient had a second exacerbation shortly after stopping medication. Both were counted as study exacerbations in the data analyses.

Results

The design of the study specified the recruitment of patients in matched pairs, one patient randomly assigned to each treatment arm, with the proportion of exacerbation-free patients as the principal end point.* The matched analysis of the principal end point included 22 pairs, or 44 patients. An unmatched analysis permitted the inclusion of an additional four patients — two who were unmatched and two who had been matched to two patients who were subsequently excluded (Fig. 1). Analyses of exacerbation data are reported both as matched and unmatched. Subsequent analyses were performed on an unmatched basis.

*See NAPS document no. 04520 for supplementary material on the subjects. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only)

Exacerbations during the Two-Year Study Period

In the 22 matched pairs, there were 12 discordant pairs: 2 patients in the placebo group had no exacerbations, whereas their matches in the Cop 1 group did; 10 patients in the Cop 1 group had no exacerbations, whereas their matches in the placebo group did. The remaining 10 pairs had concordant results. The difference in discordant pairs between treatment groups was significant ($P = 0.039$). An unmatched analysis of the presence or absence of exacerbations was also significant ($P = 0.045$).

Figure 1 shows the occurrence and time of exacerbations in each patient during the two years of the trial. There were 62 exacerbations among 23 patients in the placebo group (average, 2.7) and 16 among the 25 patients in the Cop 1 group (average, 0.6). The effect of treatment was also examined according to the base-line Kurtzke score. In the 0 to 2 stratum, there were 27 exacerbations in two years among 10 placebo-treated patients (average, 2.7) and 4 exacerbations among 13 Cop 1–treated patients (average, 0.3). In the 3 to 6 stratum, there were 35 exacerbations in the two years among 13 placebo-treated patients (average, 2.7) and 12 exacerbations among 12 Cop 1–treated patients (average, 1.0).

The distributions of exacerbations among the 48 patients are shown in Table 2. Fourteen of the 25 patients in the Cop 1 group (56 percent) were free of exacerbations, as compared with 6 of the 23 patients in the placebo group (26 percent). By contrast, 12 patients in the placebo group (52 percent) had three or more exacerbations, as compared with 1 in the Cop 1 group (4 percent). Patients were grouped according to whether they had no exacerbations, one to two, or three or more. The comparison between groups was significant at $P<0.001$.

Multiple logistic-regression analyses were carried out to evaluate the effect of a number of covariates. These included treatment, sex, duration of disease, prior exacerbation rate, Kurtzke score at base line, and various interactions of these variables. Only the treatment group and Kurtzke score at base line had a significant effect. The multiple logistic-regression analyses showed that treatment with Cop 1 independently increased the likelihood that a patient would be free of exacerbations ($P = 0.036$), as did a lower disability score at base line ($P = 0.003$). An estimate of relative risk with adjustment for sex, disability score at base line, and previous exacerbation rate

greater for a patient taking placebo than for a patient taking Cop 1.

There was a decrease in the number of exacerbations among the patients in the placebo group, from 41 in the first year to 21 in the second. The ratio of the number of exacerbations in the placebo group to that in the Cop 1 group was 4.9 for year 1 and 3.3 for year 2.

Fifteen patients were treated throughout the trial with Cop 1 supplied by the Weizmann Institute, and 10 with Cop 1 supplied by Bio-Yeda. Ten of the patients receiving the Weizmann product (67 percent) were free of exacerbations; there were seven exacerbations among the remaining 5 patients. Of the 10 patients receiving the Bio-Yeda product, 4 (40 percent) were exacerbation-free; the remaining 6 patients had nine exacerbations. This difference was not statistically significant.

Change in Disability Status

Table 3 shows the distribution of the two-year changes in Kurtzke score according to treatment group for the entire study population. A negative score indicates improvement, a positive score worsening, and zero no change. Eleven patients in the placebo group (48 percent) and 5 in the Cop 1 group (20 percent) had disease progression over the two-year period. The difference between treatment groups in the proportion of patients whose disability status worsened as compared with the proportion who remained stable or improved was of borderline significance ($P = 0.064$).

The change in disability status in the patients treated with the Weizmann product was similar to that in the patients treated with the Bio-Yeda product.

Table 3 also shows the distribution of the changes in Kurtzke score according to treatment group for each Kurtzke-score stratum. In the 0 to 2 stratum, Cop 1 had a significantly beneficial effect on disability status: 84.6 percent of the patients in the Cop 1 group were stable or improved, as compared with 30 percent of those in the placebo group ($P = 0.012$). The average change in Kurtzke score favored Cop 1 by 1.7 units (there was a worsening of 1.2 with placebo and an improvement of 0.5 with Cop 1). In the 3 to 6 stratum, the proportions of patients whose conditions were stable, improved, and worse were comparable in both treatment groups, as were the average changes in Kurtzke score (there was a worsening of 0.4 with placebo and of 0.3 with Cop 1).

The effect of the previously identified covariates on the comparison of worsening with the absence of change or improvement was evaluated with use of multiple logistic-regression analyses. These analyses demonstrated a beneficial effect of Cop 1 on disability status ($P = 0.033$). A patient taking placebo was four times more likely to have progression of disease than a patient taking Cop 1, after adjustment for sex, Kurtzke score at base line, and previous exacer-

For the end point length of time before progression, the survival curve for each treatment group is shown in Figure 2. Progression was defined as an increase of at least 1 unit in the Kurtzke score that was maintained for at least three months. Over the two-year period, the curves were significantly different ($P = 0.05$), with the placebo group having progression sooner than the Cop 1 group. Fifty percent of the

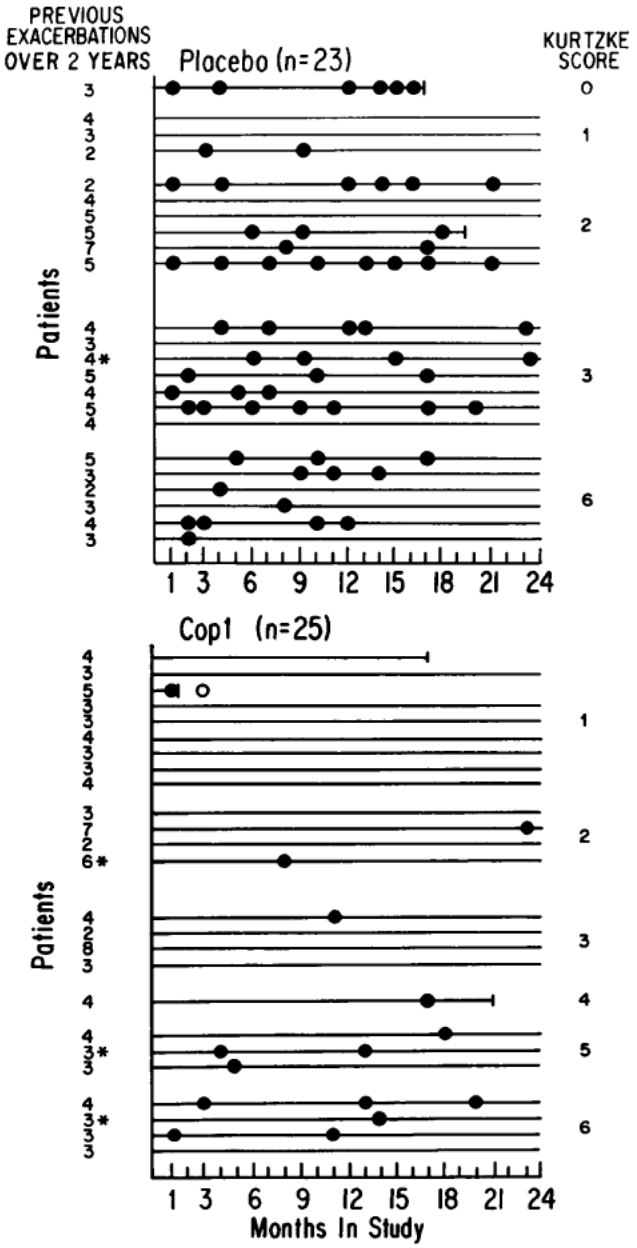

Figure 1. Exacerbations Occurring during the Two Years of the Trial.

Each line represents a patient, and each circle an exacerbation. Patients are grouped according to their Kurtzke score on entry. The number of pretrial exacerbations are indicated to the left. Discontinued lines represent patients who withdrew before completion. The open circle indicates an exacerbation occurring after withdrawal that was included as a study event. Patients who

Table 2. Exacerbations According to Treatment Group.

No. of Exacerbations per Patient	Treatment Group			
	Placebo		Cop 1	
	no.	%	*no.*	%
0	6	26.1	14	56.0
1	3	13.1	7	28.0
2	2	8.7	3	12.0
3	5	21.8	1	4.0
4	2	8.7	0	0.0
5	1	4.3	0	0.0
6	2	8.7	0	0.0
7	1	4.3	0	0.0
8	1	4.3	0	0.0
Totals	*23*	*100.0*	*25*	*100.0*

patients in the placebo group had progression by the end of 18 months, whereas only 20 percent of those in the Cop 1 group had progression by the end of 24 months. At 24 months, there was a significant difference ($P<0.005$) favoring the group treated with Cop 1.

Laboratory Studies and Side Effects

The HLA characteristics of the 48 patients were unrelated to the effects of treatment. Patient reactions were monitored during each routine clinic visit by means of urinalysis, blood examination, and the patient's evaluation of symptoms. Urinalyses and blood examinations revealed no apparent changes in the functions of the liver, spleen, kidney, bone marrow, gastrointestinal tract, heart, or lungs.

Table 4 shows the percentage of patients in each group who reported reactions at the injection sites and other reactions.

More patients taking Cop 1 reported reactions at the injection site involving soreness ($P<0.001$), swelling ($P<0.001$), and itching ($P<0.01$). In addition, soreness was reported during at least half the visits in 32 percent of the Cop 1 group as compared with 9 percent of the placebo group; itching was reported in 40 percent as compared with 4 percent; swelling, in 56 percent as compared with none; and redness, in 40 percent as compared with 9 percent.

Other reactions were reported with comparable frequencies in each group (Table 4). No symptom was a persistent problem in more than 12 percent of either group. Dizziness, constipation, and joint pain were the most common symptoms in the Cop 1 group, whereas headache, dizziness, constipation, and joint pain were the most common in the placebo group.

Two patients had a patterned, transient reaction to Cop 1. It began during or immediately after an injection and consisted of a flush, sweating, palpitations, a feeling of tightness around the chest, difficulty breathing, and associated anxiety. It lasted from 5 to 15 minutes and passed with no residual difficulties. In one patient, the reaction occurred three times in 21 months, and in the other, twice in 17 months. Medication was discontinued in these two patients, who remained under observation for the balance of the trial. The remaining patients were alerted to the possibility of such reactions, informed of precautionary measures, and given a kit containing epinephrine and antihistamine tablets.

After the trial was completed, one of the two patients who had had a reaction volunteered to take Cop 1 in an unblinded manner. This patient reported a hypersensitivity reaction that included urticaria, itching, and marked discomfort and that was controlled with epinephrine and steroids.

Blinding

Considerable efforts were made to maintain the blinding of this trial. The examining neurologist and the patients avoided discussing side effects. Patients reported such effects to the unblinded clinical coordinator.

After the trial, the effectiveness of the blinding was evaluated. The patients and the examining neurolo-

Table 3. Changes in Disability Status over Two Years According to Base-Line Kurtzke-Score Strata.

Change in Kurtzke Score	All Cases				Base-Line Kurtzke Stratum 0–2				3–6			
	Placebo		Cop 1		Placebo		Cop 1		Placebo		Cop 1	
	no.	%	*no.*	%	*no.*	%	*no.*	%	*no.*	%	*no.*	%
Worse												
4	1	4.4	0		1	10.0						
3	3	13.0	1	4.0	1	10.0			2	15.4	1	8.3
2	2	8.7	1	4.0	1	10.0			1	7.7	1	8.3
1	5	21.7	3	12.0	4	40.0	2	15.4	1	7.7	1	8.3
Subtotal	*11*	*47.8*	*5*	*20.0*	*7*	*70.0*	*2*	*15.4*	*4*	*30.8*	*3*	*24.9*
Stable (0)	9	39.1	12	48.0	2	20.0	5	38.4	7	53.8	7	58.4
Improved												
−1	2	8.7	5	20.0	1	10.0	4	30.8	1	7.7	1	8.3
−2	0		3	12.0			2	15.4			1	8.3
−3	1	4.4	0						1	7.7		
Subtotal	*12*	*52.2*	*20*	*80.0*	*3*	*30.0*	*11*	*84.6*	*9*	*69.2*	*9*	*75.0*

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