Multiple Sclerosis: Trial of a Synthetic Polypeptide

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A synthetic polypeptide, copolymer I (COP I), composed of alanine, glutamic acid, lysine, and tyrosine, has been demonstrated to be nonencephalitogenic and nontoxic in laboratory animals, yet it is capable of suppressing experimental allergic encephalomyelitis. A preliminary open trial examined the ability of COP I to alter the course of disease in 12 patients with chronic progressive and 4 with exacerbating-remitting multiple sclerosis (MS). After therapy for as long as two years or more, no undesirable side reaction was noted in any patient. Three patients with chronic progressive MS and 2 with exacerbating-remitting disease are better. These results, which may represent simply a placebo effect or may be a significant response, are now being examined in randomized, placebo-controlled, double-blind pilot trials.

Bornstein MB, Miller AI, Teitelbaum D, Arnon R, Sela M: Multiple sclerosis: trial of a synthetic polypeptide. Ann Neurol 11:317–319, 1982

The purpose of this report is to present the results of a preliminary trial of a synthetic polypeptide, Copolymer I (COP I), on patients with multiple sclerosis (MS). According to the Ad Hoc Working Group on the Design of Clinical Studies to Assess Therapeutic Efficacy in Multiple Sclerosis [3], such a preliminary trial is "conducted for the purpose of establishing dosages, studying toxicity, and obtaining a lead as to the possible efficacy of a new treatment for MS. Such a study is the first organized application of a new treatment, which may be a new investigative drug . . . Different dosages with different schedules . . . are tried on a few patients, who are very closely monitored for toxic reactions. For the assessment of therapeutic dosages, the patient with MS will serve as his own control. Therefore, the physician-investigator should be well acquainted with the medical history and past clinical course of MS in each patient . . . In most instances, it will not be necessary to involve more than perhaps 10 patients in a given preliminary trial. If the preliminary trial brings forth evidence of therapeutic efficacy and little or no evidence of serious toxicity, it would be reasonable to move on to the next stage of investigation, the pilot trial."*

Materials and Methods

The synthetic polypeptide COP I, as developed by Dr Michael Sela of the Weizmann Institute, Rehovot, Israel, and supplied by the Institute, is composed of alanine, glutamic acid, lysine, and tyrosine in the molar ratios of 6.0, 1.9, 4.7, and 1.0, respectively, and has a molecular weight ranging from 22,000 to 24,000. It is nonencephalitogenic [2] and nontoxic (Meshorer A: personal communications), yet is capable of suppressing experimental allergic encephalomyelitis in rabbits, guinea pigs, mice, rats, monkeys, chimpanzees, and baboons [2, 4–9]. Abramsky et al [1] first examined COP I for its effect on human patients, 3 with acute disseminated encephalomyelitis and 4 with "terminal" MS. The 3 patients with encephalomyelitis recovered rapidly and completely; the MS patients may have demonstrated slight improvement. What is more important in these first clinical studies was the absence of any major or undesirable side reactions.

Before being shipped from the Weizmann Institute, each preparation of COP I is tested for its biological activity of suppressing experimental allergic encephalomyelitis in guinea pigs and for immunological cross reaction with the basic encephalitogenic protein. On receipt in our laboratory, the sterile, lyophilized COP I is stored frozen until use. At that time, bacteriostatic sodium chloride is injected into the vial to dissolve the polypeptide. The final concentration of COP I in saline has varied from 5 to its present concentration of 20 mg per milliliter. The solution is distributed into sterile empty Dosette vials (Product no. 250380, Elkins-Sinn Inc., Cherry Hill, NJ) and recapped with a sterile aluminum cap that is firmly crimped into place. The vials, containing a single daily dose, are frozen. A sterility check is made of the COP I solution in both tryptic soy broth and thioglycollate. More than 700 batches of COP I have been prepared. Only 1 was suspect on sterility check and was discarded. At the time of use, a single-dose vial is thawed. The solution is injected subcutaneously.

Sixteen MS patients participated in the preliminary trial. They represented a broad spectrum of neurological involvement, including 12 with chronic progressive disease, some of whom were confined to bed or to a wheelchair, and 4 with the exacerbating-remitting type, who were fully active and employed between attacks. All had been well known to the principal investigator (M. B. B.) for years prior to their entry into the study. Informed consent was obtained.

The preliminary trial was conducted as an open study; patients were given the COP I and all knew they were receiving it. The evaluating neurologist (A. I. M.) also was aware that all patients were being treated. The initial dos-

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Results of Preliminary Trial of Copolymer I Therapy in 16 Patients with Multiple Sclerosis

Patient, Age (yr), and Sex	MS Type	Date of Entry	Date of Termination	Result
I. Y. 46, F	C-P	4/25/78	5/27/81	No effect
R. H. 25, M	C-P	5/15/78	5/29/79	No effect
G. T. 35, F	C-P	5/30/78	9/20/79	No effect
P. P. 30, F	E-R	5/30/78	. . .	No effect
A. T. 23, M	C-P	6/27/78	2/8/79	No effect
P. McL. 39, F	C-P	7/18/78	. . .	Arrested; marked improvement
J. P. 39, F	E-R	7/18/78	10/27/78	Withdrew at time of exacerbation
J. W. 32, M	C-P	6/27/78	6/5/79	No effect
K. J. 33, F	C-P	7/31/78	12/30/80	No effect
C. N. 32, M	E-R	8/7/78	. . .	Cessation of characteristic attacks
W. R. 49, M	C-P	10/3/78	. . .	Arrested; slight improvement
S. McC. 42, F	C-P	10/16/78	. . .	No effect
H. W. 36, M	C-P	10/24/78	11/13/78	No effect
S. R. 38, F	C-P	10/24/78	. . .	No effect
F. H. 27, F	E-R	11/7/78	. . .	Cessation of characteristic attacks
J. M. 34, F	C-P	11/20/78	. . .	Arrest and improvement

C-P = chronic-progressive disease; E-R = exacerbating-remitting disease.

age schedule was based on studies with nonhuman primates [5, 7] and a brief clinical trial [1]. The COP I first was prepared at a concentration of 5 mg per milliliter of sterile saline solution. This was to be given to each patient intramuscularly five times a week for the first three weeks, three times a week for the next three weeks, twice a week for the next three weeks, and, finally, once a week for the balance of a six-month period, at which time we originally planned to terminate the trial.

Results

During institution of the COP I treatment, many patients reported, and in fact demonstrated, early improvements in various neurological functions. As time went on and as the dosage was reduced, these early improvements disappeared. Most patients returned to their previous neurological status and continued their chronic-progressive course. During the ensuing months the dosage was gradually increased. By the end of the first eighteen-month period, those patients who were still on the COP I regimen were receiving 20 mg per day in 1 ml of saline. Eight patients have been taking COP I for more than two years.

As for side reactions, rarely patients reported transient slight pain, discomfort, or itching at the injection site. No local reactions of swelling or redness were noted. No systemic or general undesirable reactions of any kind were noted or reported. Examinations of urine were unremarkable. Occasionally, studies of peripheral blood cellular elements revealed a transient eosinophilia, reaching 16% in one instance. No significant change in blood chemistry determinations appeared. Examinations of blood obtained before and at various times after the institution of COP I have revealed no change in lymphocyte transformation in response to COP I, myelin basic protein, or phytohemagglutinin. The ability of cells and serum alone and together, with and without complement, to affect central nervous system myelin culture was not altered.

The observed results are listed in the Table. One of the patients with exacerbating-remitting disease withdrew from the study at the onset of an attack. A second has had a single, moderately severe exacerbation. F. H., who previously had experienced a severe exacerbation during the late summer to early fall every year for eleven years, has had no such attack in over two years. C. N., who was affected by moderately severe attacks four to six times a year during the three years prior to admission to the trial, has been free of such episodes. Their mild to moderate re-

sidual symptoms have also decreased. Of the 12 patients with chronic progressive MS, 3 are arrested and have improved. The other 9 have continued their previous downhill courses.

Discussion

In more than two years of the preliminary trial, no undesirable side reaction to COP I has occurred at doses ranging up to 20 mg daily. Two of 4 patients with exacerbating-remitting MS and 3 of 12 with chronic progressive disease are better. The question now is whether this change is due to the COP I or simply represents a placebo effect. To answer that question, a pilot study of patients with exacerbating-remitting MS was started about a year ago. It is planned to involve from 50 to 60 randomly distributed patients in a placebo-controlled, double-blind examination of the ability of COP I at 20 mg daily to affect the frequency of attacks, their severity and duration, and the degree of disability demonstrated during a two-year period. The pilot study will soon be extended to a group of patients with chronic progressive disease.

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Valproate-Induced Hyperammonemia

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A patient with carbamyl phosphate synthetase deficiency had four episodes of hyperammonemia, up to 226 μM, associated with valproate (VPA) treatment. These were accompanied by vomiting, lethargy, and coma. A group of epileptic patients receiving VPA remained asymptomatic but had significantly higher mean plasma ammonium levels when compared to epileptic patients receiving other anticonvulsants: 33.6 ± 1.9 (SEM) versus 23.6 ± 1.5 μM. Thus, VPA caused symptomatic hyperammonemia in a patient with an impairment in urea synthesis and resulted in mildly elevated ammonium levels in epileptic patients. These data suggest that ammonium levels should be monitored in patients receiving VPA who exhibit signs of vomiting or lethargy.

Batshaw ML, Brusilow SW: Valproate-induced hyperammonemia. Ann Neurol 11:319–321, 1982

As the use of sodium valproate (VPA) has increased, so have the reports of hyperammonemia, usually but not always associated with hepatic failure [5, 6, 8a, 10, 13]. We report VPA-induced hyperammonemia unassociated with hepatocellular damage in a patient with carbamyl phosphate synthetase (CPS) deficiency and in a group of epileptic patients.

Subjects and Methods

The patient with partial CPS deficiency had had symptomatic hyperammonemia manifested by intermittent vomiting and lethargy from 13 months to 12 years of age [1]. From the ages of 13 to 17 years she was treated with a combination of essential amino acids and keto acids [2]. Mean plasma ammonium level obtained monthly between 16 and 17 years of age was 33 ± 5 μM; the normal range is 15 to 30 μM [1].

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