Clinical Trials of Copolymer I in Multiple Sclerosis

M. B. BORNSTEIN,[a] A. I. MILLER,[a] S. SLAGLE,[a]
R. ARNON,[b] M. SELA,[b] AND D. TEITELBAUM[b]

[a]*The Albert Einstein College of Medicine*
Bronx, New York 10461

[b]*The Weizmann Institute*
Rehovot, Israel

INTRODUCTION

The understanding of the pathogenetic mechanisms involved in multiple sclerosis (MS) and the search for an effective treatment have been intimately associated with the laboratory model, experimental allergic encephalomyelitis (EAE). The validity of EAE as such a model system has been clearly and convincingly presented by Paterson in a series of scholarly publications.[1-4] Our own work in tissue culture[5] also served to relate MS, as a naturally occurring disorder, to its laboratory counterpart, EAE. Organotypic cultures of mammalian CNS tissue respond with identical patterns of demyelination,[6] swollen myelin sheaths,[7] and eventual "sclerosis"[8] when exposed to serum from EAE (whole white matter)-affected animals and MS patients. The demyelinating effect is not produced by these EAE sera on cultured peripheral nerve which, nevertheless, are responsive to serum from animals with experimental allergic neuritis.[9,10] The cultures also demonstrated the capacity of mammalian CNS to remyelinate after being demyelinated by antisera.[5,8] These laboratory demonstrations provided further support for the extension to MS patients of therapeutic possibilities arising from animal studies.

The synthetic polypeptide, copolymer I (COP I), was prepared from alanine, glutamic acid, lysine, and tyrosine (TABLE 1) as one of a series of compounds which, alone or in combination with various lipids, might simulate the ability of myelin basic protein (MBP) to induce EAE (Sela, personal communication). None of the preparations proved to be encephalitogenic, *i.e.*, capable of inducing EAE, but some, particularly COP I, did suppress EAE in animals challenged with either whole white matter or MBP in complete Freund's adjuvant. The numerous laboratory investigations of the effectiveness of COP I in EAE, involving mice, rats, guinea pigs, rabbits, monkeys, chimpanzees and baboons are of particular interest to the clinical trials and have recently been reviewed by Arnon and Teitelbaum.[11] In addition, extensive laboratory studies failed to demonstrate any toxicological or other undesirable side reactions in experimental animals exposed to COP I under a variety of testing situations (A. Meshorer, personal communication). Finally, Abramsky *et al.*[12] first examined COP I for its effect on three patients with acute disseminated encephalomyelitis (ADE) and four with terminal MS. The three ADE patients recovered rapidly and completely. The MS patients may have demonstrated slight improvements. What is more important in these first clinical studies was the absence of any significant undesirable side reactions.

This report presents the data derived from a preliminary trial of the effectiveness of copolymer I in patients with the exacerbating-remitting (ER) and chronic progressive

(CP) types of MS. It will also describe the extensions of that study to pilot trials in each group of patients, their organizational aspects and present position.

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 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 onto the next stage of investigation, the pilot trial.[13]

CONDUCT OF THE PRELIMINARY TRIAL

Sixteen MS patients participated in the preliminary trial. They represented a broad spectrum of neurological involvement ranging from those of the chronic

TABLE 1. Composition of Copolymer I[a]

Amino Acid	*N*-Carboxyanhydride Used for Reaction	Amount Used in the Reaction (mM)		Molar Ratio of Amino Acid in Copolymer
alanine	alanine	8.6	75	6.0
glutamic acid	benzyl glutamate	6.0	23	1.9
lysine	*N*-trifluoroacetyl-lysine	14.0	52	4.7
tyrosine	tyrosine	3.0	14	1.0

[a]Molecular weight: 23,000.

progressive type, some of whom were essentially bed or wheelchair bound, to those of the exacerbating-remitting type who were fully active and employed between attacks. There were four of the ER type and twelve of the CP type. All patients had been well known to the principal investigator (MBB) for years prior to their entry into the study. Some had participated as volunteers in earlier clinical and laboratory studies whereas others had been unsuccessfully tried on immunosuppressant therapy.

The preliminary trial was conducted as an open study.[14] All patients were given the COP I and all knew they were receiving it. The evaluating neurologist (AM) was also aware that this was an open study and that all patients were being treated. The initial dosage schedule was suggested by the group at the Weizmann Institute on the basis of their previous studies with laboratory animals,[11] such as nonhuman primates, as well as the brief trial that was performed by Dr. Oded Abramsky.[12] Thus, it was planned to prepare the COP I at a concentration of 5 mg per ml 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.

At the time of introduction into the study, the first five patients were hospitalized at the General Clinical Research Center of the Albert Einstein College of Medicine.

They were examined and evaluated by Dr. Miller, samples of peripheral blood and cerebrospinal fluid were taken, and the copolymer injections were started. In the beginning, the patients were hospitalized during the first three weeks of treatment, because we had no knowledge as to whether or not there would be any significant local or systemic effects in patients who had multiple sclerosis. We did not, however, note any undesirable side reactions of any significance and soon found it unnecessary to keep the participants in the hospital for any period longer than was prudent following the lumbar puncture, usually 24 to 48 hours. The patients were seen, however, on an outpatient basis at the Clinical Research Center and their neurological status reevaluated at various times during the course of the following months.

The specific aims of the preliminary trial were to determine the following: (1) Did COP I produce any apparent significant or undesirable side reactions? (2) Did COP I produce any apparent desirable effects? (3) Could a dosage schedule be established for further (pilot) trials should they appear to be warranted?

RESULTS OF THE PRELIMINARY TRIAL

During the institution of the copolymer treatment, many patients reported and, in fact, demonstrated early improvements in various neurological functions. As time went on, however, and the dosage of COP I was reduced as originally planned, these early improvements disappeared and most patients returned to their previous neurological status and continued their chronic progressive course. Over the period of the next months, the dosage was gradually increased in an effort to determine whether or not the previously observed effect was dose related. By the end of the first eighteen-month period, those patients who were still on the copolymer were receiving 20 mg a day in 1 ml of saline, 7 days a week. Three patients are still on this schedule, some 3–4 years later. This is the dosage currently being used in the pilot study.

As for undesirable side reactions, patients occasionally reported transient slight pain, discomfort, itching, swelling or redness at the injection site. No systemic or general reactions of any kind were noted or reported during the preliminary trial. Examinations of urine were unremarkable. Of the sixteen patients, two of the ER type withdrew from the study at the time of an acute attack. One later returned. Of the balance, all remained in the study for at least six months as originally planned. Finally, three patients have been maintained to this date on 20 mg daily. In general, 11 of the 16 patients demonstrated no apparent favorable effects in that they either had an exacerbation during the course of the study or continued their chronic progressive course. On the other hand, 5 of the 16 patients have demonstrated a definite change for the better. (See TABLE 2.)

Nine patients received COP I for over two years, a few for over four years. No patient in this group has had any significant or undesirable local or systemic side reaction.

LABORATORY DATA

Laboratory examinations have included CBC, routine urinalysis and culture and blood chemistry analyses (SMA 6 and 12) VDRL, CSF protein and glucose and cells. Except for an occasional and transient eosinophilia (reaching 16% in one instance) no significant changes have been noted in any of these clinical tests. There has been no evidence of albuminuria or other evidence of altered kidney function. No pertinent

alteration of the patient's serum demyelinating potency on CNS cultured tissues has been observed. Several sera have been examined for antibody titers against COP 1. In general, they have not been elevated. Lymphoblast transformation in response to phytohemagglutinin, MBP and COP I has not occurred.

EXTENSION TO PILOT TRIALS

The question now is whether or not the demonstrated improvements were, in fact, due to the polypeptide. As stated by Brown *et al.*,[13] the aim of a pilot trial is "to

TABLE 2. Results of Preliminary Trial of Copolymer I Therapy in 16 Patients with Multiple Sclerosis

Patient	Type	Age	Sex	Date of Entry	Date of Termination	Results
IY	CP[a]	46	F	4/25/78	5/27/81	no effect
RH	CP	25	M	5/15/78	5/29/79	no effect
GT	CP	35	F	5/30/78	9/20/79	no effect
PP	ER[b]	30	F	5/30/78	2/5/79 (6/83)	no effect
AT	CP	23	M	6/27/78	2/8/79	no effect
PM	CP	39	F	7/18/78	—	arrested (not terminated) marked improvement
JP	ER	39	F	7/18/78	10/27/78	withdrew at time of exacerbation
JW	CP	32	M	6/27/78	6/5/78	no effect
KJ	CP	33	F	7/31/78	12/30/80	no effect
CN	ER	32	M	8/7/78	5/1/82	cessation of characteristic attacks
WR	CP	49	M	10/3/78	5/16/82	arrest (slight improvement)
SM	CP	42	F	10/16/78	9/20/82	no effect
HW	CP	36	M	10/24/78	11/13/78	no effect
SR	CP	38	F	10/24/78	1/28/80	no effect
FH	ER	27	F	11/7/78	—	cessation of characteristic attacks (not terminated)
JM	CP	34	F	11/20/78	—	arrest and improvement (not terminated)

[a]Chronic progressive.
[b]Exacerbating-remitting.

determine whether a treatment that 'looked good' in a preliminary trial still 'looks good' when tested under more rigorously controlled conditions." For this purpose a double-blind, placebo-controlled, randomized pilot trial was started about three years ago. Since another purpose of a pilot trial is to determine whether or not a full clinical trial is justified and, in addition, how it may be structured, the following brief description presents the current organization of the pilot trial.

The clearly defined objectives of the pilot trial of the ER patient are (1) whether or not the frequency of attacks is different between the COP I and the saline-injected groups, and (2) whether there is a difference in the degree of disability developed after two years of participation in the trial.

The patient population of 50 ER MS patients was selected from 935 volunteers to have at least one and preferably two attacks a year in each of the two years prior to

entry into the trial, to be between the ages of 20 and 35, to be ambulatory, to be emotionally stable, and to have had no prior treatment with immunosuppressive drugs. The selected patients were matched for age, sex, frequency of attacks and degree of disability and randomly distributed by the statistician (SS) into the placebo or COP I groups. All information collected is sent to the Coordinating Center where it is edited, coded and stored in a data base specifically designed and constructed for this study.

The organizational structure for the pilot study includes an External Advisory Board, Steering Committee, Coordinating Center and Clinical Center. The External Advisory Board, an outside independent group which serves the trial in an advisory and consultative capacity, includes Dr. John Kurtzke, Professor of Neurology and Community Medicine, Georgetown University School of Medicine and chief of Neurology Service, Veterans Administration Medical Center; Dr. William Weiss, chief of Biometry and Field Studies at the National Institute of Neurological and Communicative Disorders and Stroke, NIH; and Dr. I. Herbert Scheinberg, chairman of the Clinical Investigation Committee at Albert Einstein College of Medicine. This group receives periodic reports from the Coordinating Center that describe the results of the trial to date and keep the members informed as to the conduct of the trial.

The Steering Committee is composed of Murray Bornstein, M.D., principal investigator (who is blinded); Dr. Sylvia Wassertheil-Smoller, Ph.D., head of the Division of Epidemiology and Biostatistics; and Ms. Susan Slagle, M.P.H., biostatistion. It is their function to monitor the progress of the trial on an ongoing basis as well as to make decisions as to the design and conduct of the trial. At the Clinical Center, patients are examined routinely every three months and more frequently at the time of exacerbations. The investigating neurologists and the principal investigator, as well as the patients themselves, are unaware of the treatment assignments to placebo or COP I. This blinding of patients and examiners is maintained through the use of a Coordinating Center, which is a separate unit responsible for matching, randomization, procedures, assignment to treatment and data management.

The pilot trial of the ER patients will end in December 1984. The code will be broken, the data analyzed and the results published.

A report summarizing the status of the ER trial as of 1 January 1983 was submitted to the External Advisory Committee. An excerpt from this report that shows current enrollment status of the pilot trial is presented in TABLE 3. Based on the recommendations from the External Advisory Committee after reviewing the report of January 1 and the fact that there have been few significant undesirable side effects or reactions observed or reported to date, the ER pilot trial is now being extended to chronic progressive (CP) patients. For this purpose, 80 participants will be entered into the trial, varying from 25 to 55 years of age. The conduct of the multicenter CP pilot trial differs in some respects from the ER pilot trial.

During a pretrial observation period, each CP patient must demonstrate a predetermined and sustained degree of worsening, specifically, at least two units in any one of Kurtzke's eight functional groups or one unit in any two unrelated functional groups. Once this is demonstrated and maintained, the patient becomes eligible to enter the trial and will then be randomly distributed into placebo or COP I groups. The dosage of COP I will be 15 mg in 0.75 of bacteriostatic saline subcutaneously, twice a day. The placebo consists of 0.75 ml of bacteriostatic saline. Patients will be evaluated at 1, 4, 8, 12, 16, 20 and 24 months after admission to the trial. The evaluation will be the same as those listed for the current ER pilot trial. The trial will of course be conducted in a double-blind manner.

The central statistic for the CP patients will be arrest of progression, which currently is defined as a change of not more than one unit in the eight functional groups

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.