FRONTIERS IN MULTIPLE SCLEROSIS: CLINICAL RESEARCH AND THERAPY

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Copolymer 1 in relapsing–remitting multiple sclerosis: a multi-centre trial

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INTRODUCTION

Multiple sclerosis (MS) is a chronic neurological disease, affecting mainly young adults.[1] The disease is caused by inflammation and demyelination of various areas of the central nervous system (CNS) and has diverse clinical manifestations, such as impairment of motor, sensory, cerebellar, visual, cognitive, urogenital and mental functions,[2] in a relapsing–remitting (RR) or chronic–progressive (CP) course. The cause and pathogenesis of the disease are still not known although the leading hypothesis is of an autoimmune attack on CNS myelin.[3,4] Multiple therapeutic interventions have failed to reduce significantly the relapse rate or the progression of disability.[5] Recently, however, interferon beta-1b (IFNβ-1b), was shown to reduce the relapse rate in RR patients,[6,7] and IFNβ-1b has been approved in the U.S. for the treatment of ambulatory RR MS patients.

Copolymer 1 is the acetate salt of a controlled mixture of synthetic polypeptides with an average molecular weight of 4700 to 13 000 Daltons. It is composed of four L-amino acids: alanine, glutamic acid, lysine and tyrosine, and has been shown to cross-react with the myelin basic protein (MBP) on both the humoral and cellular levels.[8,9] Copolymer 1 was shown to prevent the induction and to reduce the clinical score of EAE as well as brain pathology induced by CNS material in a variety of rodents and to cure the disease in monkeys without any evidence of encephalitogenic activity.[10] The proposed mechanism of action for copolymer 1 involves binding to the class II major histocompatibility complex molecules on antigen-presenting cells,[11,12] followed by stimulation of antigen-specific suppressor T-cells[13,14] and/or inhibition of the activation of antigen-specific effector T-cells.[15–17]

Preliminary studies, including a previous phase II double-blind, placebo-controlled clinical trial, showed a marked beneficial effect of copolymer 1, given by daily s.c. injections of 20 mg, in reducing the relapse rate and slowing progression of disability in RR MS patients.[18–20] A second double-blind study revealed a potential, though not conclusive, effect in slowing progression of disease in chronic–progressive patients administered 30 mg (15 mg b.i.d.) of copolymer 1 daily.[21] In these studies copolymer 1 was found to be safe, with only minimal and well-tolerated adverse effects. These results were recently corroborated by a phase III double-blind, placebo-controlled, multi-centre study in RR MS.[22]

Here we report interim results of a long-term multi-centre, open-label, phase III clinical trial of copolymer 1 in RR and relapsing–progressive (RP) MS patients. The objectives of this trial were to evaluate the long-term safety of copolymer 1 and to monitor the course of the disease in the treated patients.

METHODS

Patients

Patients were enrolled in four medical centres in Israel. The study was approved by the respective institutional review boards and the Israeli health ministry, and all patients gave informed consent. All patients had clinically definite or laboratory-supported definite MS.[23] Subjects of both sexes had to be between 18 and 60 years of age, be ambulatory with an EDSS score not greater than 6, and should have had at least two documented exacerbations during the two years prior to study entry. Patients had to be clinically stable for at least one month before entry with no steroid treatment during this period. A washout period of six months from any previous immunosuppressive or immunomodulating treatment was required. Existence of any other chronic disease or pregnancy excluded patients from participating in the trial, as well as significant abnormalities in ECG, chest X-rays, blood VDRL, ANF, HIV, vitamin B_{12} and folic acid.

Preparation, characterization and administration of copolymer 1 for injection (Copaxone)

Copolymer 1, the active ingredient of Copaxone, was manufactured by Teva Pharmaceutical Industries Ltd in Israel, essentially as previously described,[24] by reacting the protected and activated derivatives of L-alanine, L-glutamic acid, L-lysine and L-tyrosine in the appropriate ratios. The molar fraction ranges for each amino acid residue in the final product are, L-ala: 0.392–0.462; L-glu; 0.129–0.153; L-lys: 0.30–0.374, and L-tyr; 0.086–0.10. The average molecular mass is 4700–13 000 Daltons. Each batch was rigorously controlled during its production and the final product was quality-controlled for its amino acid composition, molecular weight distribution and chromatographic profile, as well as by various other quality control tests. Some batches were also monitored for cross-reactivity with myelin basic protein using four different monoclonal antibodies and for their capacity to block EAE in mice. Copolymer 1 for injection was supplied as a sterile, lyophilized material, in single-dose vials containing 20 mg of the active drug and 40 mg of mannitol. The medication was reconstituted before administration with sterile water for injection supplied concomitantly. Patients or their companions were instructed how to prepare and administer the medication subcutaneously. The first three injections were administered at the medical centre under close observation for six hours. Thereafter, new supplies were provided at three-month intervals and patients continued to self-administer daily.

Follow-up visits schedule

Adverse experiences were recorded every three months. In addition the patients were evaluated every six months. Each visit included general and neurological examinations, establishment of the functional system (FS) and EDSS scores,[25] routine blood and urine tests, recording of adverse events and patients' self-evaluations.

Monitoring of safety and of the neurological course of disease

The safety of copolymer 1 was evaluated by monitoring the occurrence and severity of adverse events (AEs) as reported by the patients or observed by the treating physician during each visit. Haematological analysis, levels of serum electrolytes, liver and kidney functions, as well as other serum chemistries and urine analysis, were performed to monitor metabolic changes and disturbances in organ function throughout the trial.

The neurological course of the disease was assessed by monitoring the annual relapse rate, the proportion of relapse-free patients and the time to first relapse as well as the change in EDSS score from baseline, with a significant change defined as a change of 1.0 unit or more in any direction relative to the baseline value. In addition, progression of disease was defined as a sustained ($\geq$90 days) increase of at least 1.0 unit in the EDSS score relative to baseline.

Premature discontinuation

Treatment was discontinued in any of the following circumstances: intolerable AEs; patient's decision to discontinue treatment for any reason; investigator's judgment that continuation of treatment is not in the best interest of the patient; poor compliance, i.e. failure to administer the drug for more than 25 per cent of the time (compliance less than 75 per cent), pregnancy, with patient planning to carry it to term, and loss to follow-up.

Exacerbations

An exacerbation was defined as the appearance of a new symptom or a marked worsening of an old symptom attributable to MS, accompanied by new neurological signs. A minimal duration of 24 hours for these symptoms was required, and they had to be preceded by a minimum of 30 days of stabilization or improvement to be considered a new relapse. The patients were instructed to report immediately any symptom suggesting a relapse and were evaluated within 4–7 days. Patients were subsequently examined every 2–4 weeks until they returned to baseline or stabilized. A short course (up to 28 days) of steroids was allowed during exacerbations.

Statistical methods

Analysis included all patients enrolled (n=271), with subgroup analysis of those who were treated for at least 12, 24 or 36 months. Improvement or worsening in the EDSS score was defined as a change of at least 1 unit in either direction relative to the baseline value.

Comparison of changes in EDSS score and in the annual relapse rate were performed using the Wilcoxon test. The life-table estimates of survival curves (Kaplan–Meier analysis) were used to determine time to disease progression and time to first relapse. The Wilcoxon test for homogeneity was applied to test differences in survival curves between patients who continued treatment and those who withdrew prematurely. Analyses were performed using the V6.09 SAS statistical software with an Ultrix Dec Station. All p-values denoted are two-tailed.

RESULTS

Demographic and baseline disease characteristics

Two hundred and seventy one patients were enrolled in four centres (Table 25.1), 155 (57.2 per cent) females and 116 (42.8 per cent) males. The patients' age range was 18–59 years, with a mean of 36.7 (±9.9) years. Mean disease duration was 8.3 (±6.4) years. The mean baseline EDSS score was 3.3 (±1.8), and the annual relapse rate in the two years prior to study entry, calculated from historical data, was 1.4 (±0.7). To date, 188, 107 and 45 patients have completed one, two and three years of treatment, respectively.

Premature terminations

Table 25.2 summarizes the distribution of patients with regard to their reason for withdrawal. Due to the open-label design of the trial, which enabled normal conclusion after one, two or three years, a relatively high proportion of patients are categorized as 'normal conclusion' (11.8 per cent of the total). Only 24 patients (8.8 per cent) were reported to have AEs at the time of premature termination, after a mean duration of treatment of 6.9 (±6.5) months. The AEs associated with treatment discontinuation were usually those observed at the highest incidence (see next section). In addition, three patients withdrew due to symptoms that could be associated with an allergic reaction (rash, urticaria).

Adverse events and laboratory studies

The administration of copolymer 1 was associated with relatively minor AEs. More than 30 per cent of all patients participating in the trial (102/271) did not report any AE during the

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