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Copolymer-1

Agent for Multiple Sclerosis

Copaxone®
COP-1

Poly[L-Glu$^{13-15}$,L-Ala$^{39-46}$,L-Tyr$^{8.6-10}$,L-Lys$^{30-37}$].nCH_3COOH
n= 15-24

Mol wt: 4700-13,000

CAS: 147245-92-9
CAS: 028704-27-0 (as free base)

EN: 199999

Introduction

This article is an update of the monograph on copolymer-1, published in Drugs of the Future a year ago (1). It includes additional information based on unpublished data that were not available to the publishers at that time and on recent publications of scientific and clinical data.

This update summarizes the mechanism of action of copolymer-1, the toxicology and safety studies and the results of the pivotal phase III clinical trial recently completed.

Pharmacological Actions and Proposed Mechanism

The effect of copolymer-1 on the prevention, suppression and blocking of acute and chronic-relapsing experimental allergic encephalomyelitis (EAE) was studied in several animal species. EAE is the most extensively studied experimental autoimmune disease which serves as the primary animal model for multiple sclerosis (MS) (2-6). Copolymer-1 had a marked suppressive and preventive effect on EAE in the various species studied, including primates (7). Recently, it was demonstrated that copolymer-1 can also suppress chronic-relapsing (C-R) EAE, induced by either proteolipid protein (PLP) or myelin oligodendrocyte glycoprotein (MOG) (8, 9). Thus, it was shown that copolymer-1 does not manifest species specificity, either for the source of the encephalitogen or for the test animal (10, 11).

The mechanism of action of copolymer-1 has not been fully elucidated, but laboratory experiments indicate that the effect of copolymer-1 may be disease-specific. Copolymer-1 was originally synthesized to mimic suppressive determinants in the MBP molecule (12) and cross-reactivity with epitopes of MBP has been demonstrated both at the B-cell level with monoclonal antibodies (13) and at the T-cell level with cell-mediated responses (14).

A study of MBP-specific clones showed that copolymer-1 antigen-specific but not MHC-restricted fashion (15). It was demonstrated that copolymer-1 binds directly and avidly to class II MHC on living human antigen presenting cells of various HLA haplotypes (16, 17), inhibits the binding of MBP, PLP and MOG peptides to MHC class II on antigen presenting cells (18), and even displaces them from the MHC II groove (19). Processing of copolymer-1 is not required prior to its binding to the MHC (20). Interestingly, binding to MHC II, although required for copolymer-1 activity, is not sufficient. D-copolymer-1, a copolymer of identical amino acid composition as that of copolymer-1, but composed of D-amino-acids, while binding to the MHC II, fails to suppress EAE.

Suppression of MBP-specific T-cell activation by copolymer-1 was observed both in murine (15) and human cells (21). In the latter, it was demonstrated that while the suppression of proliferation, interleukin-2 and interferon-γ secretion by copolymer-1 was restricted to MBP-specific T-cell lines and clones, interferon-β exhibited a non-specific immunosuppressive activity (22). Interestingly, copolymer-1 plus interferon-β had additive and sometimes synergistic suppressive effects (22).

Studies of murine EAE have shown that copolymer-1 can induce MBP specific suppressor cells which mediate protection from EAE (23-25). T-cell hybridomas and T-cell lines induced with copolymer-1 were found to have suppressive properties and could inhibit the responses of MBP-specific T-cell lines *in vitro*, as well as prevent active induction of EAE (26).

These findings support the hypothesis that binding of copolymer-1 to the MHC II groove may lead to two effects that ameliorate the pathogenesis of EAE and multiple sclerosis: 1) copolymer-1 induces specific suppressor T-cells and 2) copolymer-1 inhibits specific effector T-cells. Based on the available data, it was concluded that copolymer-1 works through a unique mechanism and is MS-specific.

Pharmacokinetics

Radioiodinated copolymer-1 has been extensively used to decipher the fate of the administered drug in mice, rats and monkeys (27). After subcutaneous administration,

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copolymer-1 was readily absorbed and only a small fraction was retained at the injection site. The amount absorbed was proportional to the administered dose and maximal plasma concentrations were reached within 2-4 hours in monkeys and 1-2 hours in rats. Chronic exposure to daily drug injections for periods up to 178 days did not alter the basic pharmacokinetic parameters of a single radioactive dose.

Following subcutaneous injection, radiolabelled copolymer-1 is rapidly degraded into smaller molecular weight fragments. In skin and muscle homogenates a rapid proteolytic degradation of copolymper-1 to small oligopeptides and free amino acids was observed *in vitro*.

Based on animal studies, serum concentrations of copolymer-1 are presumed to be low or not detectable following subcutaneous administration of 20 mg once daily to man. Consequently, pharmacokinetic information in patients receiving the recommended dose is not available. However, several effects of copolymer-1 in man provide indirect evidence that subcutaneous copolymer-1 is bioavailable and biologically active. This evidence includes its efficacy in patients as demonstrated by the results of the clinical trials (29, 31) and the formation of systemic antibodies to copolymer-1 (28).

Toxicology and Safety Studies

Acute and chronic toxicity studies (27) have been completed in mice, rats, dogs and monkeys and several routes of administration have been used (s.c., i.p., i.m., i.v.). A chronic toxicity study in cynomolgus monkeys that lasted 52 weeks demonstrated that copolymer-1, injected s.c. daily, was well tolerated at doses up to 100 times the human therapeutic dose, except for some inflammatory reactions at the injection site.

Other studies showed no evidence of adverse effects of copolymer-1 on reproductive function. The drug was devoid of any mutagenic potential and was not genotoxic.

Immunogenicity and immunotoxicity studies were also performed. Following daily subcutaneous injections to rats and monkeys, copolymer-1-reactive antibodies were formed. The titers of copolymer-1 reactive antibodies peaked at 3 months and declined at 6 months. Selected additional parameters were chosen for immunotoxicity studies. No treatment-related changes were observed in the levels of B-lymphocytes, T-lymphocytes, $CD4^+$ T-lymphocytes, $CD8^+$ T-lymphocyte and $CD4^+/CD8^+$ ratio. No changes were observed also in natural killer cells and in the level of antinuclear antibodies or IgG and IgM. No treatment-related changes were observed in microscopic examination of lymphoid organs.

Serial antibody studies were performed (28) in the context of the recently completed U.S. phase III study with copolymer-1, in relapsing-remitting multiple sclerosis patients (29). No correlation was found between the level or time-dependent profile of antibodies and the occurrence of relapses or systemic adverse reactions. Furthermore, the clinical efficacy of copolymer-1 in reducing the MS relapse rate and slowing progression of disability was maintained throughout more than two years of treatment, regardless of the antibody profile. In addition, the [illegible] antibodies did not neutralize its biological activity, either *in vitro* or *in vivo*.

Clinical Studies

The results of a phase III multicenter, double-blind, placebo-controlled trial, demonstrating efficacy and safety of Copaxone® have been published (29). This was a 2-year study, involving 251 patients who daily self-injected subcutaneously either Copaxone® 20 mg (n = 125) or placebo (n = 126). The primary end point was the number of relapses reported during the treatment period. 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 ($p = 0.007$).

Trends in the proportion of relapse-free patients and median time to first relapse also favored copolymer-1.

Disability was measured by the Expanded Disability Status Scale (EDSS) (30), 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 (24.8% *vs.* 15.2%) receiving copolymer-1 were found to have improved and more patients receiving placebo (28.8% *vs.* 20.8%) worsened ($p = 0.037$). Repeated measures analysis also demonstrated a significant effect in favor of Copaxone® for mean change in EDSS score ($p = 0.023$). 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 experiences were injection-site reactions. 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 is characterized by vasodilatation or tightness of the chest with palpitations, anxiety and/or dyspnea. These symptoms generally resolve without sequelae. Studies of blood and urine for common metabolic changes or hematologic abnormalities showed no differences between groups and ECGs were unchanged. This rigorous study confirmed the findings of a previous pilot trial (31) and demonstrated that copolymer-1 treatment can significantly and beneficially alter the course of relapsing-remitting MS in a well-tolerated fashion.

The above double-blind trial was extended beyond the planned 24 months for an additional average of 5.2 months for copolymer-1 patients and 5.9 months for placebo patients (32). The final relapse rates over the entire course of the double-blind study were 1.34 ± 0.15 for patients receiving copolymer-1 and 1.98 ± 0.14 for those on placebo ($p = 0.002$), which represents a reduction of 32% in favor of copolymer-1. Annualized relapse rates, proportion of relapse-free patients, median time to first relapse and the proportion of patients who were improved, unchanged or worsened by ≥ 1 EDSS score between baseline and conclusion all favored copolymer-1 treatment, in a statistically

*When relating to the total number of injections to patients receiving Copaxone® and those receiving placebo, the number of systemic reaction episodes is very low, 0.037% and 0.0035%,

significant manner. A group of 27 patients in one center was also followed by serial quantitative MRI throughout treatment (32). A preliminary study, measuring Gd^{2+} enhanced-T1 lesions, showed a trend towards a beneficial effect of copolymer-1 treatment on both the number of enhancing lesions and the proportion of enhancement-free patients (33).

Summary

Copolymer-1 is effective in relapsing-remitting multiple sclerosis in reducing the frequency of relapses and slowing progression of disability. This clinical efficacy is maintained and even enhanced upon prolonged treatment. Its benign safety profile and good level of tolerance were repeatedly reported. It acts in MS via a unique and disease-specific mechanism.

Manufacturer

Teva Pharmaceutical Industries Ltd. (IL).

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