A Randomized, Placebo-Controlled Trial of Certolizumab Pegol (CDP870) for Treatment of Crohn's Disease

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Background & Aims: **To investigate the efficacy and safety of certolizumab pegol (a polyethylene-glycolated Fab′ fragment of anti–tumor necrosis factor, CDP870) in Crohn's disease.** ***Methods:*** **In a placebo-controlled, phase II study, 292 patients with moderate to severe Crohn's disease received subcutaneous certolizumab 100, 200, or 400 mg or placebo at weeks 0, 4, and 8. The primary end point was the percentage of patients with a clinical response at week 12 (a Crohn's Disease Activity Index decrease of ≥ 100 points or remission [Crohn's Disease Activity Index ≤ 150 points]) in the intent-to-treat population.** ***Results:*** **All certolizumab doses produced significant clinical benefit over placebo at week 2 (placebo, 15.1%; certolizumab 100 mg, 29.7% [*P* = .033]; 200 mg, 30.6% [*P* = .026]; 400 mg, 33.3% [*P* = .010]). At all time points, the clinical response rates were highest for certolizumab 400 mg, greatest at week 10 (certolizumab 400 mg, 52.8%; placebo, 30.1%; *P* = .006) but not significant at week 12 (certolizumab 400 mg, 44.4%; placebo, 35.6%; *P* = .278). Patients with baseline C-reactive protein levels of 10 mg/L or greater (n = 119) showed clearer separation between active treatment and placebo (week 12 clinical response: certolizumab 400 mg, 53.1%; placebo, 17.9%; *P* = .005; post hoc analysis) owing to a lower placebo response rate than patients with C-reactive protein levels of less than 10 mg/L. Adverse events were similar among groups.** ***Conclusions:*** **Certolizumab 400 mg may be effective and is well tolerated in patients with active Crohn's disease. High placebo response rates in the large patient subgroup with low C-reactive protein levels may have obscured statistical separation between certolizumab and placebo. Ongoing phase III trials are necessary to establish the clinical efficacy of certolizumab.**

The proinflammatory cytokine tumor necrosis factor (TNF) is a key mediator of the inflammation associated with Crohn's disease.[1–6] It can be detected at high concentrations in diseased areas of the bowel wall,[2,4,6] and in the blood and feces of patients with the disease.[1,3]

Several biologic products targeted toward the neutralization of TNF have shown clinical efficacy in patients with Crohn's disease.[7–12] Infliximab is the only anti-TNF agent currently approved for use in the management of the disease.[13,14] Infliximab is administered by intravenous infusion and has proven efficacy in the treatment of both refractory luminal and fistulizing Crohn's disease.[8,12,15,16] The use of infliximab has been associated with a number of potentially serious adverse events (AEs), in addition to the development of human antichimeric antibodies, which can lead to infusion reactions and may reduce the duration of response.[17–20]

Certolizumab pegol (CDP870) hereafter referred to as certolizumab is a polyethylene glycolated Fab′ fragment of a humanized anti–TNF-α monoclonal antibody intended for subcutaneous administration. Subcutaneous delivery of the drug has cost and convenience advantages compared with intravenous dosing. Certolizumab has been constructed by grafting the short hypervariable complementarity-determining regions derived from the murine monoclonal antibody HTNF40 onto an other-

Abbreviations used in this paper: AE, adverse event; CI, confidence interval; CRP, C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent to treat; TNF, tumor necrosis factor.

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wise virtually human Ig Fab′ fragment (IgG γ1κ). The engineered Fab′ fragment retains the biologic potency of the original antibody. The Fab′ fragment is linked via a maleimide to 2 cross-linked chains of polyethylene glycol that each have a molecular weight of 20 kilodaltons. This site-specific polyethylene glycolation increases the half-life of the antibody fragment to approximately 2 weeks in plasma, thereby reducing the frequency of required dosing. In phase II studies in patients with rheumatoid arthritis, certolizumab has been shown to be clinically effective and well tolerated.[21,22] We have assessed the efficacy and safety of subcutaneous administration of certolizumab in a phase II, randomized, double-blind, placebo-controlled, dose-response study in patients with moderate to severe Crohn's disease.

Materials and Methods

Patient Selection

Eligible patients were at least 18 years old with a clinical diagnosis of Crohn's disease as confirmed by radiologic, endoscopic, or histologic evidence following established diagnostic criteria. Patients had moderate to severe disease, defined by a score of 220–450 points on the Crohn's Disease Activity Index (CDAI)[23] over a 7-day screening period before the first study dose was administered.

Patients were excluded from the study if they had a suspected or diagnosed abscess at screening, a bowel perforation or evidence of noninflammatory obstruction during the 6 months before screening, extensive bowel resection, a functional colostomy or ileostomy, a positive stool culture for enteric pathogens, or a known history of tuberculosis. Other exclusion criteria included treatment for Crohn's disease with sodium cromoglycate, mycophenolate, or cyclosporin within 4 weeks of study entry, or receipt of other anti-TNF therapy with a biologic agent within 12 weeks of screening. Patients were also excluded from the study if they had been treated previously with any anti-TNF agent and either had experienced an infusion reaction that was suspected or confirmed to be associated with an immune response, or had showed a lack of clinical response to the first dose. Any patients who had participated in another clinical trial with certolizumab were ineligible to take part in the study, as were those who had been involved in any other clinical drug trial within the 4 weeks before screening.

All patients had an anteroposterior chest radiograph for tuberculosis at screening (or within the 12 weeks before screening) and at the final study visit.

Concomitant Medication

Concomitant medication was permitted if the patient was on a stable dose that could be continued throughout the 12-week duration of the double-blind phase of the study. The minimum stable treatment periods required before screening were as follows: 2 weeks for steroids (≤9 mg/day budesonide, ≤24 mg/day methylprednisolone, or ≤30 mg/day prednisone or prednisolone) and any topical anorectal treatment; 4 weeks for long-term anti-infectives and mesalamine or mesalamine analogs (eg, sulfasalazine, olsalazine, or balsalazide); and 8 weeks for the immunosuppressants azathioprine, 6-mercaptopurine, and methotrexate.

Study Medication

Because certolizumab and placebo did not have the same color or viscosity, full blinding was not possible. Consequently, patients received their treatment from a nurse or physician who was not involved in the study. All other staff involved in the study remained blind to treatment. Certolizumab 100 mg, 200 mg, 400 mg, or placebo was administered subcutaneously. Certolizumab was supplied as a clear, colorless to pale yellow solution at a nominal concentration of 200 mg/mL in 50 mmol/L sodium acetate buffer and 125 mmol/L sodium chloride solution. Saline was used for dilution and for placebo injections. Each patient received 2 subcutaneous injections (1 mL each) at separate injection sites in the lateral abdominal wall or the outer upper thigh. Patients remained at the study site for 30 minutes after drug administration and any AEs were reported. Patients received the first dose at week 0 and further doses of the same medication at weeks 4 and 8.

Study Design

This was a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response study, recruiting patients from tertiary referral centers. The study was designed to assess the efficacy and safety of subcutaneous administration of certolizumab. It was conducted between February 15, 2001, and March 12, 2002, at 58 centers in a total of 10 countries (the number of centers in each country is shown in parentheses): Belgium (4), Canada (16), Denmark (6), Germany (8), Ireland (5), Russia (5), Serbia (5), South Africa (2), Sweden (4), and the United Kingdom (3). The 3 active treatment groups (certolizumab 100, 200, or 400 mg) were compared with placebo.

At screening, patients were stratified into 1 of 2 groups according to whether or not they were receiving concomitant steroids, immunosuppressants, or long-term anti-infectives. They then were randomized to 1 of the 4 treatment groups (1:1:1:1 certolizumab 100 mg:certolizumab 200 mg:certolizumab 400 mg:placebo). The randomization code was prepared by an independent statistician and patients were assigned to treatment by the use of a randomization allocation schedule managed via an interactive voice response system. Efficacy assessments were performed every 2 weeks up until week 12, with a further 8-week follow-up evaluation for safety.

Before dosing, demographic data were recorded for each patient, together with any significant past medical history and all concomitant diseases. Disease activity (by using the CDAI) was assessed prospectively in the week before screening, after 0, 2, 4, 6, 8, 10, and 12 weeks of treatment, and on withdrawal from the study (if appropriate). Patients kept a daily diary of their symptoms throughout the study. At weeks 0, 2, 4, 6, 8, 10, 12, and study end point, the patients' quality of life was