Certolizumab Pegol for Active Crohn's Disease: A Placebo-Controlled, Randomized Trial

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BACKGROUND & AIMS: Certolizumab pegol (CZP) is a pegylated-conjugated Fab′ against tumor necrosis factor (TNF). Additional data are needed regarding the efficacy of induction therapy with CZP in active Crohn's disease (CD). **METHODS:** A placebo-controlled trial evaluated the efficacy of CZP therapy in 439 adults with moderate to severe CD naive to anti-TNF therapy. Patients were randomized to receive CZP (400 mg subcutaneously) or placebo at weeks 0, 2, and 4. The primary end point was clinical remission at week 6. **RESULTS:** Clinical remission rates at week 6 in the CZP and placebo groups were 32% and 25% ($P = .174$), respectively. Remission rates at weeks 2 and 4 in the CZP and placebo groups were 23% and 16% ($P = .033$) and 27% and 19% ($P = .063$), respectively. Clinical response rates at weeks 2, 4, and 6 in the CZP and placebo groups were 33% and 20% ($P = .001$), 35% and 26% ($P = .024$), and 41% and 34% ($P = .179$), respectively. There were significantly greater rates of clinical remission at week 6 for CZP in patients with increased concentrations of C-reactive protein (≥5 mg/L) at entry. Serious adverse events developed in 5% and 4% of patients in the CZP and placebo groups, respectively. **CONCLUSIONS: The primary end point did not reach statistical significance. Significant differences between CZP and placebo were observed in patients who had increased concentrations of C-reactive protein when the study began. Future clinical trials should emphasize the treatment of patients who have objective evidence of inflammation in addition to symptoms of active disease.**

Keywords: Biologic; Inflammatory Bowel Disease; Inflammatory Burden.

Crohn's disease is a chronic inflammatory disease of the small and large intestine that follows a relapsing and remitting disease course.[1–3] Patients with moderate to severe Crohn's disease unresponsive to conventional therapy are often treated with anti–tumor necrosis factor (TNF) antibodies, which include infliximab, adalimumab, and certolizumab pegol.[4,5] These anti-TNF antibodies are used to induce response and remission[6–10] and to maintain response and remission in patients who respond to induction therapy.[11–13]

Certolizumab pegol is a pegylated anti-TNF antibody Fab′ to TNF and is effective for the treatment of Crohn's disease and rheumatoid arthritis.[9,10,13–16] Two previous trials of certolizumab pegol in patients with active Crohn's disease were affected by higher than expected placebo response and remission rates.[9,10] Thus, additional data were needed regarding the efficacy of induction therapy with certolizumab pegol in patients with active Crohn's disease.

The present study was a 6-week placebo-controlled, randomized trial comparing certolizumab pegol with placebo for the treatment goals of clinical remission and response in patients with active Crohn's disease who were naive to anti-TNF therapy.

Materials and Methods

Patients

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 120 centers in 20 countries (Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Republic of Estonia, Finland, Germany, Hungary, Israel, Italy, Latvia, New Zealand, Poland, Romania, Russia, Ukraine, and the United States) between March 2008 and June 2009 (Appendix 1). The protocol was approved by the Institutional Review Board or Ethics Committee at each center. All patients gave written informed consent. The clinical study was conducted according to good clinical practices (GCP).

Eligible patients were male or female, aged 18–75 years, with active Crohn's disease (Crohn's Disease Activity Index [CDAI], 220–450).[17] The following concomitant medications were permitted at stable doses: oral corticosteroids, immunosuppressants, antibiotics, 5-aminosalicylic acid analogues, topical anorectal treatments, antidiarrheals, analgesics, and probiotics. Patients who had received prior treatment with any anti-TNF agent or other biological agent and those receiving intravenous corticosteroids were excluded. Patients were excluded from study participation if they had short bowel syndrome, symptomatic obstructive strictures, or bowel perforation in the last 6 months, abscess or suspected abscess, an ostomy or ileoanal pouch, actively draining perianal or enterocutaneous fistulae, other nonenterocutaneous fistulae, undergone bowel resection

Abbreviations used in this paper: **CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; GCP, good clinical practices; HBI, Harvey–Bradshaw Index; HRQoL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; ITT, intent-to-treat; TNF, tumor necrosis factor.**

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within the past 6 months or had 2 or more resections in total, a current diagnosis of ulcerative colitis, current infection with enteric pathogens, a serious infection, been hospitalized or treated with intravenous antibiotics for an infection within 3 months before screening, known or suspected latent or active tuberculosis, lymphoproliferative disease, demyelinating disease, malignancy, or previously been treated in a certolizumab pegol study.

Study Design

All eligible patients were randomized in a 1:1 ratio to receive injections of certolizumab pegol (CIMZIA; UCB Pharma, Brussels, Belgium) 400 mg or placebo (0.9% sodium chloride) administered subcutaneously at weeks 0, 2, and 4. They were followed through week 6. Randomization was performed centrally according to a computer-generated scheme and was stratified by country, C-reactive protein (CRP) concentration at entry ($<$10 mg/L, $\geq$10 mg/L), use of corticosteroids at entry, and use of immunosuppressants at entry. Patients had the opportunity to participate in an open-label extension study if they satisfied the relevant criteria.

Efficacy and Safety Assessments

Patients were evaluated at weeks 0 (baseline), 2, 4, and 6 or at the withdrawal visit. At each visit, diary card data were collected, a clinical assessment of Crohn's disease and a physical examination were carried out, Crohn's disease activity was measured by using the CDAI and the Harvey–Bradshaw Index (HBI),[17,18] health-related quality of life (HRQoL) was measured by using the Inflammatory Bowel Disease Questionnaire (IBDQ),[19] adverse events and concomitant medications were reported, and samples were taken for laboratory analysis. A positive anti–certolizumab pegol antibody level was defined as $>$2.4 U/mL on at least 1 visit. A negative anti–certolizumab pegol antibody level was defined as $\leq$2.4 U/mL at all visits.

Efficacy Evaluations and Statistical Analysis

The primary efficacy outcome was clinical remission, defined as a CDAI score $\leq$150 points, at week 6. Secondary efficacy outcomes were as follows: the proportions of patients in clinical remission at weeks 2 and 4; the proportions of patients in clinical response ($\geq$100 point decrease from the week 0 CDAI score) at weeks 2, 4, and 6; the proportion in overall response (patients in clinical response or remission [$\geq$100 point decrease from the week 0 CDAI or CDAI score $\leq$150, respectively]); the total CDAI score and the change from week 0 in the total CDAI score by visit. Other secondary outcomes were the CRP concentration and change from week 0 in CRP concentration by visit, the certolizumab pegol concentration by visit, the proportions of patients with anti–certolizumab pegol antibodies by visit and cumulative through week 6, the proportions of patients in IBDQ remission (total IBDQ score $\geq$170 points) at weeks 2, 4, and 6, and the change from week 0 in the HBI score at week 6.

Repeated-measures analyses were performed to assess treatment effect on clinical remission, clinical response, overall response, and IBDQ remission. For each outcome, a generalized estimating equations model with an unstructured correlation structure was used. The predictors in each generalized estimating equations model included treatment, geographic region, CRP concentration at entry, use of corticosteroids at entry, use of immunosuppressants at entry, time, and time by treatment interaction.

Demographic and baseline characteristics, total CDAI scores and change from week 0 in CDAI scores, CRP concentrations and change from week 0 in CRP concentrations, certolizumab pegol concentrations, and the proportions of patients with anti–certolizumab pegol antibodies were summarized by descriptive statistics only. A 2-sided Cochran–Mantel–Haenszel χ^2 test stratified by geographic region, CRP concentration at entry, use of corticosteroids at entry, and use of immunosuppressants at entry was used to compare clinical remission, clinical response, overall response, and IBDQ remission. Patients were randomized by country, but the analysis was done by geographic region because of the large number of countries involved in the study. The consistency of treatment effect in 22 prespecified subgroups was analyzed by using logistic modeling, allowing for randomization strata and subgroup. A post hoc subgroup analysis of clinical remission stratified by both baseline CRP concentration and location of disease and certolizumab pegol concentration by visit, stratified by baseline CRP concentration, was also performed. In an exploratory analysis, patients were stratified according to the certolizumab pegol concentration and baseline CRP concentrations of $<$5 mg/L, $\geq$5 mg/L, and $\geq$10 mg/L. The percentages of remitters, nonremitters, responders, and nonresponders were analyzed according to CRP and certolizumab pegol concentrations.

The intent-to-treat (ITT) population was the primary population of interest for the analyses of efficacy. The ITT population was defined as all randomized patients who received at least 1 study treatment and had at least 1 efficacy measurement after the first treatment. However, the ITT population did not include patients from one site that entered patients in the Ukraine because of noncompliance with applicable US Food and Drug Administration regulations, GCP, and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. Patients who withdrew before completion of the study were classified as nonresponders/nonremitters from and including the time of withdrawal. Patients who did not have all the required data to derive a response status were classified as nonresponders/nonremitters at that particular time point. Patients who received rescue therapy or discontinued study treatment were classified as nonresponders/nonremitters from and including the time of the event, regardless of their score (CDAI, IBDQ, and HBI). Rescue therapy was defined as treatment for an exacerbation of their Crohn's disease with one or more of the following: anti-TNF therapy (other than certolizumab pegol), corticosteroids, immunosuppressants, surgery, and inpatient hospitalization. For patients already receiving corticosteroids and/or immunosuppressants at week 0, any increase in dose for exacerbation of their Crohn's disease was regarded as rescue therapy. For any other efficacy variables, no data were used from and including the time of the event (treatment with rescue therapy) in the summaries and analyses where relevant. The safety population included all patients enrolled (including all sites in the Ukraine) who received at least 1 injection of certolizumab pegol or placebo.

For the primary end point of clinical remission at week 6, it was estimated that 414 patients were needed to allow 85% power to detect a difference in remission rates of 12.5 percentage points between the certolizumab pegol and placebo groups,