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

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See editorial on page 1114.

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.\textsuperscript{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.

\textbf{Materials and Methods}

\textbf{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)\textsuperscript{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 an immune response, or had showed a lack of clinical response that was suspected or confirmed to be associated 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.

\textbf{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.

\textbf{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.

\textbf{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), Italy (5), Russia (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 were then 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
assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ). Our own translations were used in Russian, Serbian, and Afrikaans.

Standard laboratory tests, including hematology, biochemistry, and urinalysis, together with measurement of serum C-reactive protein (CRP) levels, were performed at each visit up until week 20 or on withdrawal from the study. Investigators were blinded to the results of the CRP analyses. Certolizumab plasma concentrations were measured using an enzyme-linked immunosorbent assay with a lower limit of sensitivity of .41 μg/mL.

AEs were monitored throughout the study. The duration and intensity of each event were recorded by the investigator, together with its putative relationship to the study drug, and its outcome and seriousness. Any patient requiring a change in baseline therapy or hospitalization to manage an exacerbation of the disease was considered to be a treatment failure and was withdrawn from the study.

Written informed consent to participate in the trial was obtained from each patient and the independent ethics committee/institutional review board at each study center approved the protocol before commencement. The trial was performed in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, which have their origins in the Declaration of Helsinki.

**Outcomes and Primary Statistical Analysis**

A sample size of 260 patients was considered adequate for this study, with 65 patients being allocated to each treatment group. This would give approximately 83% power to detect a true difference of 23% between treatment groups for the primary end point (clinical response) based on a placebo response rate of 12%. The efficacy was analyzed for the intent-to-treat (ITT) population. This included all patients recruited who received at least 1 injection and had at least 1 efficacy measurement after the first injection. Patients who terminated the trial prematurely were advanced to the end-of-study visit.

A clinical response was defined as a decrease in CDAI score of 100 points or greater or remission (CDAI score, ≤150 points). The primary efficacy end point was the percentage of patients achieving a clinical response at week 12. The percentage of patients who showed a clinical response at weeks 2, 4, 6, 8, and 10 was a secondary efficacy variable, as was the percentage of patients in remission at weeks 2, 4, 6, 8, 10, and 12. Statistical analyses of these outcomes were performed using the χ² test to compare among the treatment groups and 95% confidence intervals (CI) were calculated.

Mean CDAI scores and mean IBDQ scores, summed over all categories, were summarized at weeks 0, 2, 4, 6, 8, 10, and 12. Serum CRP concentrations (geometric means) at all time points were analyzed using descriptive statistics. (The geometric mean is the nth root of the product of n values.)

All treatment comparisons for efficacy were made using a 2-sided significance level of .05. A closed testing procedure was used for the analysis of the primary end point. Results from patients receiving certolizumab 400 mg were compared with placebo. If the comparison was not significant at the 5% level, no further analysis was performed. If significance was apparent, comparisons of certolizumab 200 mg vs placebo and certolizumab 100 mg vs placebo were performed simultaneously. For the analysis of secondary end points, there was no adjustment for multiple efficacy end points. Additional subgroup analyses (including effect of stratum) were for exploratory purposes only and therefore no adjustments for multiplicity were made.

The safety analysis (safety population) included all patients who received at least 1 dose of study medication and subsequently had a postbaseline safety evaluation. Actual values and changes from baseline relating to vital signs and laboratory data were analyzed using descriptive statistics.

**Post Hoc Analyses**

In an exploratory analysis, changes from baseline IBDQ total score for each treatment group were compared with the placebo group by using a comparison of least-squares means. Least-squares means were adjusted for stratum, and pooled country and baseline IBDQ scores.

In addition, patients were stratified according to baseline CRP concentrations of less than 10 mg/L or 10 mg/L or greater in an exploratory analysis. The percentage of patients with a clinical response and the percentage of patients in remission in the certolizumab- and placebo-treated groups were analyzed according to baseline concentrations of CRP. A further series of analyses was also performed using breakpoint baseline CRP concentrations of 5, 6, 7, 8, and 9 mg/L. The χ² test was used to compare treatment groups.

**Results**

**Patients**

The trial profile for the participating patients is shown in Figure 1. A total of 292 patients were enrolled in the study. A total of 291 patients were included in the ITT population and received either certolizumab 100 mg (n = 74), 200 mg (n = 72), or 400 mg (n = 72), or placebo (n = 73). One patient who received certolizumab 400 mg did not provide any postinjection efficacy measurements and therefore was excluded from the ITT population before breaking the blind. The safety population comprised all 292 enrolled patients. The demographic characteristics of the patients at screening are shown in Table 1. The majority of the patients (96.6%) were Caucasian. Patient characteristics were generally well balanced among treatment groups, although the mean age of patients receiving certolizumab 200 mg (40.1 y) was slightly higher than in the other groups, in which the mean ages of patients ranged from 33.5 to 35.9 years. The greatest difference among the groups was a small preponderance of women in the placebo group (67.1%) in comparison with both the certolizumab 100
mg (52.7%) and 400 mg (55.6%) groups. The concomitant medications with which the patients were being treated were broadly similar in both the placebo and the certolizumab treatment groups (Table 2). The most notable difference was observed for overall glucocorticoid use: 39.7% for the placebo group vs 30.6% for the certolizumab 400-mg group. In the ITT population, 15.5% of the patients had concomitant medication with both immunomodulators and steroids, and 21.6% of the patients had received prior anti-TNF therapy with a biologic agent.

Eighteen patients (24.7%) in the placebo group withdrew from the study by week 12. The corresponding numbers for the certolizumab 100-, 200-, and 400-mg treatment groups were 22 (29.7%), 15 (20.8%), and 20 (27.4%) patients, respectively. In all groups, the major-

### Table 1. Baseline Demographic Characteristics of Patients (ITT Population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 73)</th>
<th>Certolizumab 100 mg (n = 74)</th>
<th>Certolizumab 200 mg (n = 72)</th>
<th>Certolizumab 400 mg (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>35.8 (19–64)</td>
<td>33.5 (18–56)</td>
<td>40.1 (19–71)</td>
<td>35.9 (18–67)</td>
</tr>
<tr>
<td>Sex, n (% of patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (32.9)</td>
<td>35 (47.3)</td>
<td>22 (30.6)</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>Female</td>
<td>49 (67.1)</td>
<td>39 (52.7)</td>
<td>50 (69.4)</td>
<td>40 (55.6)</td>
</tr>
<tr>
<td>Mean body mass index, kg/m² (range)</td>
<td>23.03 (16.3–38.6)</td>
<td>23.06 (15.0–37.3)</td>
<td>24.14 (16.2–40.7)</td>
<td>22.73 (13.5–38.1)</td>
</tr>
<tr>
<td>Mean duration of disease, y (range)</td>
<td>7.95 (.1–27.6)</td>
<td>7.73 (0.0–31.8)</td>
<td>8.84 (0.0–30.7)</td>
<td>8.43 (.2–26.5)</td>
</tr>
<tr>
<td>Previous anti-TNF therapy, n (% of patients)</td>
<td>16 (21.9)</td>
<td>18 (24.3)</td>
<td>17 (23.6)</td>
<td>12 (16.7)</td>
</tr>
<tr>
<td>CRP concentrations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean, mg/L (range)</td>
<td>7.3 (.3–86.1)</td>
<td>6.2 (.2–141.0)</td>
<td>6.5 (.2–127.0)</td>
<td>7.7 (.4–128.2)</td>
</tr>
<tr>
<td>≥10 mg/L, n (% of patients)</td>
<td>28 (38.4)</td>
<td>31 (42.5)</td>
<td>28 (38.9)</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>Disease site, n (% of patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>1 (1.4)</td>
<td>5 (6.8)</td>
<td>2 (2.8)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Ileum</td>
<td>54 (74.0)</td>
<td>57 (77.0)</td>
<td>51 (70.8)</td>
<td>56 (77.8)</td>
</tr>
<tr>
<td>Cecum</td>
<td>37 (50.7)</td>
<td>45 (60.8)</td>
<td>32 (44.4)</td>
<td>41 (56.9)</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>31 (42.5)</td>
<td>35 (47.3)</td>
<td>35 (48.6)</td>
<td>36 (50.0)</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>33 (45.2)</td>
<td>32 (43.2)</td>
<td>33 (45.8)</td>
<td>37 (51.4)</td>
</tr>
<tr>
<td>Descending colon</td>
<td>42 (57.5)</td>
<td>39 (52.7)</td>
<td>40 (55.6)</td>
<td>47 (65.3)</td>
</tr>
<tr>
<td>Rectum</td>
<td>36 (49.3)</td>
<td>36 (48.6)</td>
<td>33 (45.8)</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>Perianal</td>
<td>23 (31.5)</td>
<td>20 (27.0)</td>
<td>23 (31.9)</td>
<td>21 (29.2)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6.8)</td>
<td>9 (12.2)</td>
<td>4 (5.6)</td>
<td>7 (9.7)</td>
</tr>
<tr>
<td>Resection performed, n (% of patients)</td>
<td>27 (37.0)</td>
<td>27 (36.5)</td>
<td>25 (34.7)</td>
<td>27 (37.5)</td>
</tr>
</tbody>
</table>

*Data missing for 1 patient.
ity of withdrawals were a consequence of disease progression.

**Efficacy**

**Primary end point: clinical response and dose-ranging results.** The percentage of patients reaching the primary end point (a decrease in CDAI score of ≥100 points or remission at week 12) in the ITT population is shown in Figure 2. An onset of effect was evident at 2 weeks postinjection, when all doses of certolizumab produced a statistically significant benefit compared with placebo (week 2: placebo, 15.1% [95% CI, 6.2–24.0] vs certolizumab 100 mg, 29.7% [95% CI, 18.6–40.8; \( P = .033 \); 200 mg, 30.6% [95% CI, 19.2–41.9; \( P = .026 \]; 400 mg, 33.3% [95% CI, 21.8–44.9; \( P = .010 \]). Certolizumab also showed significantly higher efficacy compared with placebo at weeks 4 (400 and 200 mg), 8 (400 and 100 mg), and 10 (400 mg). Patients receiving certolizumab 400 mg showed the highest response rate at all time points, with the highest response observed at week 10 (52.8% [95% CI, 40.6–65.0] vs 30.1% [95% CI, 18.9–41.3] in the placebo group \( P = .006 \)). At all time points, the rate of response among patients receiving certolizumab was higher than in those receiving placebo. However, at week 12 (the primary end point) the difference between the certolizumab- and placebo-treated groups did not reach statistical significance (week 12 remission rates: certolizumab 400, 200, and 100 mg 26.4% [95% CI, 15.5–37.3], 19.4% [95% CI, 9.6–29.3], and 27.0% [95% CI, 16.2–37.8], respectively, vs placebo 23.3% [95% CI, 12.9–33.7]).

**Biologic response.** CRP concentrations (geometric means) in the 4 treatment groups are shown in Figure 4. At week 2, CRP concentrations were reduced in all active treatment groups. At this time point, the 95% CIs for the mean CRP concentrations in the placebo group did not overlap with those of the certolizumab 100-mg or 400-mg treatment groups, giving an indication of a significant difference between these groups and placebo. The data support the anti-inflammatory effect of certoli-
The lowest geometric mean concentration of CRP was measured at week 2 in patients being treated with certolizumab 400 mg (2.8 mg/L). The corresponding value for the placebo group at this time point was 7.1 mg/L. The results over the 12-week study period suggest that treatment with certolizumab 200 mg and 400 mg may be more effective at maintaining a biologic response than treatment with certolizumab 100 mg. A statistically significant relationship between the extent of reduction in CRP from weeks 0 to 2 and clinical outcome at week 12 in the ITT population was not detected.

**Antibodies.** In this patient population with various concomitant medications (only 37.5% of the patients from the certolizumab 400-mg group were on concomitant immunomodulators at baseline), we found that 12.3% (n/H110059 of 73) of the patients receiving certolizumab 400 mg had at least 1 positive result for anticertolizumab antibodies (period, 0–12 weeks). The plasma concentrations of certolizumab appeared to be lower in the antibody-positive patients (data not shown), however, no decrease in efficacy was seen—the proportion of responder patients at week 12 was similar in antibody-positive and antibody-negative patients, with 44% of patients responding in both subgroups.

**IBDQ.** Baseline IBDQ total scores (mean ± SD) were 122.9 ± 26.60, 132.2 ± 30.60, 122.9 ± 27.07, and 126.5 ± 25.20 for the placebo and the 100-, 200-, and 400-mg certolizumab groups, respectively. For all treatment groups, there was an increase in IBDQ total scores within 2 weeks of treatment that paralleled the changes in CDAI scores. The largest change from baseline at week 2 (22.8 points) was observed in the certolizumab 400-mg group, compared with 10.6 points for patients receiving placebo (P = .002). From weeks 2 to 12, patients receiving 400 mg certolizumab had greater changes from baseline at any time point than patients receiving placebo (P < .05). In addition, patients receiving 200 mg certolizumab had significantly greater changes from baseline at weeks 2 and 4 than those receiving placebo (P < .05). At week 12, IBDQ total scores (mean ± SD) were 156.4 ± 37.36 in the certolizumab 400-mg group compared with 140.5 ± 35.88 in the placebo group.

**Post hoc analyses according to baseline CRP concentration.** Baseline CRP measurements were obtained from 290 of the 291 patients in the ITT population. Of these patients, 119 (41.0%) had a baseline serum CRP concentration of 10 mg/L or greater and 171 (59.0%) had serum levels less than 10 mg/L.

**Efficacy of certolizumab according to a CRP breakpoint of 10 mg/L.** In the initial post hoc analysis, in patients with baseline CRP levels of 10 mg/L or greater, treatment with certolizumab 400 mg resulted in a statistically significant benefit at all time points throughout the 12-week study in terms of both rates of clinical response (a decrease in CDAI score of ≥100 points or remission [CDAI score, ≤150 points]) (Figure 5A) and remission (CDAI score, ≤150 points) (Figure 5B). There was clearer separation between the certolizumab treatment groups and the placebo group in this subanalysis than in the overall ITT population.

In patients with baseline CRP levels less than 10 mg/L, none of the active treatments achieved a statistical difference from placebo for the primary end point of clinical response at week 12. A high placebo response was observed in these patients. At week 12, 46.7% of the patients who had received placebo showed a clinical response, compared with 38.1%, 38.6%, and 37.5% for the certolizumab 100-, 200-, and 400-mg groups, respectively. The percentages of certolizumab-treated patients achieving remission were not significantly different from placebo and, as with the primary variable, relatively high rates of placebo response (up to 31.1% at week 12) were evident.
Efficacy of certolizumab in patients with baseline CRP breakpoint concentrations between ≥5 and ≥10 mg/L. Further post hoc analyses, showing the primary end point of clinical response at week 12 for patients with baseline CRP breakpoint concentrations between ≥5 and ≥10 mg/L, are shown in Figure 6. For each of the CRP breakpoints analyzed, clinical response rates for patients in the certolizumab 400-mg treatment group were higher than those in the other treatment groups at this time point (50.0%, 50.0%, 51.4%, 51.4%, 51.5%, and 53.1% for certolizumab 400-mg treatment at baseline CRP concentrations of ≥5 mg/L, ≥6 mg/L, ≥7 mg/L, ≥8 mg/L, ≥9 mg/L, and ≥10 mg/L, respectively). In patients with baseline CRP levels of ≥7–10 mg/L who received certolizumab 400 mg, the primary clinical response rates at week 12 showed statistically significant differences from placebo. Placebo response rates decreased with increasing baseline CRP concentration (34.9%, 31.6%, 28.6%, 25.0%, 20.0%, and 17.9% for baseline CRP concentrations of ≥5 mg/L, ≥6 mg/L, ≥7 mg/L, ≥8 mg/L, ≥9 mg/L, and ≥10 mg/L, respectively).

Safety

The incidence and pattern of AEs were similar in the active treatment and placebo groups (Table 3). The majority of AEs were of mild or moderate intensity. The most frequently reported events among patients treated with certolizumab during the double-blind treatment period were headache not otherwise specified (13.2% vs 16.4% for placebo), aggravation of Crohn’s disease (11.9% vs 13.7% for placebo), nausea (11.4% vs 5.5% for placebo), nasopharyngitis (9.1% vs 4.1% for placebo), dizziness (excluding vertigo) (6.4% vs 4.1% for placebo), arthralgia (5.9% vs 2.7% for placebo), abdominal pain not otherwise specified (5.9% vs 5.5% for placebo), pharyngolaryngeal pain (5.0% vs 5.5% for placebo), and pyrexia (5.0% vs 4.1% for placebo). None of these AEs occurred with an incidence of 5% or more in certolizumab-treated patients during the safety follow-up period. The most common serious AE during both the double-blind and safety follow-up periods was aggravated Crohn’s disease (23 reports). This was considered possibly related to the study drug in 4 instances. There were no deaths during the study; no cases of lymphoma, lupus, tuberculosis, or increases in opportunistic infections were recorded. During the double-blind period, 17 patients in the placebo group (23.3%) and 58 certolizumab-treated patients (26.5%) experienced AEs of infections. Over the safety follow-up period, 10 patients in the placebo group (13.7%) and 31 patients in the certolizumab group (14.2%) experienced AEs of infection. Details of AEs representing infectious complications are shown in Table 4.

The following serious adverse events were reported during the double-blind period: 4 placebo patients experienced aggravated Crohn’s disease, and genital warts and arthralgia were experienced by 1 patient each. Two patients in the certolizumab 100-mg group experienced...
aggravated Crohn’s disease; another patient had nonspecific abdominal pain and aggravated Crohn’s disease. Rectal hemorrhage, abdominal mass, and reduced visual acuity were experienced by 1 patient each in the certolizumab 100-mg group and 1 patient had abdominal pain, pyrexia, vomiting, and paralytic ileus. Five patients in the certolizumab 200-mg group experienced aggravated Crohn’s disease, 1 patient had aggravated Crohn’s disease and pyrexia, 2 patients had blurred vision, 1 patient had breast hyperplasia, and 1 patient had ankle ulcer, aphthous stomatitis, and thrombocytopenia. Two patients in the certolizumab 400-mg group experienced aggravated Crohn’s disease and 1 patient had abdominal pain and aggravated Crohn’s disease; 1 patient had abdominal pain, diarrhea, and pyrexia; pyrexia and perianal abscess were experienced by 1 patient each.

The number (%) of patients who experienced injection-site AEs was 2 (2.7%), 5 (6.8%), 4 (5.6%), and 2 (2.7%) in the placebo, 100-mg, 200-mg, and 400-mg certolizumab treatment groups, respectively. All of the injection-site reactions were classified as mild or moderate in intensity, and none resulted in withdrawal from the trial. The most common of the injection-site AEs occurring within 30 minutes of administration of the study medication was injection-site burning—occurring on 3 occasions in the same patient in the placebo group and twice each in patients who received certolizumab 100 and 200 mg. There were 2 reports of injection-site erythema (in 1 certolizumab-treated patient); 1 each of injection-site inflammation, pain, and rash; and 1 other injection-site reaction was not otherwise specified. There were no incidences of anaphylaxis. Subcutaneous administration of certolizumab and placebo was generally well tolerated, with the majority of patients (78.1%) receiving all 3 injections of study medication.

Cerolizumab treatment did not result in any clinically relevant effects on oral temperature, blood pressure, pulse rate, respiration rate, or electrocardiogram recordings. Serial hematologic and biochemical measurements, together with urinalysis, did not show the treatment to have any untoward effects.

Additional analyses of AEs, stratifying these according to a CRP breakpoint of 10 mg/L, did not show any differences among the groups (data not shown).

**Discussion**

The results of this phase II study suggest that the polyethylene glycolated Fab’ fragment of a humanized anti-TNF monoclonal antibody, cerolizumab, administered subcutaneously at 4-week intervals is clinically effective and well tolerated in the treatment of moderate to severe Crohn’s disease. The onset of treatment effect was rapid, being evident 2 weeks after administration (when all doses produced significant benefit compared with placebo). In this dose-ranging study, cerolizumab 400-mg treatment had the greatest efficacy, with patients in this treatment group showing the highest rates of clinical response at all time points. Statistical separation was evident at weeks 2, 4, 8, and 10, indicating the clinical effect of the study drug. Because the differences between the cerolizumab 400-mg treatment group and
placebo did not reach statistical significance at week 12 (the primary end point), phase III studies will be necessary to confirm the efficacy of certolizumab and to assess the extent of the difference compared with the placebo population. The clinical effect of certolizumab was corroborated by a secondary analysis of remission rates, together with improvements in patients’ quality of life (as measured by the IBDQ) and a reduction in serum concentrations of CRP in the certolizumab groups.

Serum concentrations of CRP, an acute-phase protein, provide an objective criterion of inflammatory activity. Serum concentrations of CRP, an acute-phase protein, provide an objective criterion of inflammatory activity. Patients with stable quiescent IBD are characterized by geometric mean CRP concentrations of approximately 1.5 mg/L. CRP is induced by interleukin-6, TNF-α, and other proinflammatory cytokines that are produced within the intestinal lamina propria. Increased serum concentrations of CRP have been reported as a regular feature of patients with active Crohn’s disease in both clinical cohorts and on a population level (M. Vatn, personal communication, May 17, 2005). In asymptomatic patients, increased levels of this protein may indicate subsequent clinical relapse, and acute-phase proteins have been included in clinical indices formulated to predict relapse.

The clinical trial described here included a surprisingly high percentage of patients (59%) with low baseline concentrations of CRP. In post hoc analyses of the certolizumab data, there was a clearer separation between active treatment and placebo among patients with increased baseline concentrations of CRP (41% of patients) than in the overall ITT population, in terms of both rates of clinical response and rates of remission. Dose separation was also clearly apparent. In the patients with baseline CRP levels of 10 mg/L or greater, subcutaneous dosing with certolizumab 400 mg every 4 weeks resulted in statistically significant rates of clinical response and remission at all time points up to week 12. Statistically significant primary clinical responses were associated with certolizumab 400-mg treatment at week 12 in patients with baseline CRP concentrations of 7 mg/L or greater, 8 mg/L or greater, and 10 mg/L or greater. In contrast to the certolizumab 400-mg group, clinical response and remission rates for patients receiving certolizumab 200 mg were not generally significantly different from rates in patients receiving placebo, irrespective of baseline CRP levels. Certolizumab 400 mg therefore is the dose that should be evaluated in phase III studies.

The use of patients’ baseline CRP measurements to show clear separation between active treatment and placebo has been reported in recent trials of a number of biologic agents for Crohn’s disease. For example, in phase

| Table 4. AEs of Infection Occurring in ≥2 Patients (Safety Population) |
|--------------------------|--------------------------|--------------------------|--------------------------|
|                          | Placebo (n = 73)          | 100 mg (n = 74)           | 200 mg (n = 72)           | 400 mg (n = 73)           |
|                          | Weeks 0–12                |                           |                           |                           |
| Nasopharyngitis          | 3 (3, 4.1)                | 12 (9, 12.2)              | 7 (7, 9.7)                | 5 (4, 5.5)                |
| Influenza                | 3 (3, 4.1)                | 4 (4, 5.4)                | 3 (3, 4.2)                | 1 (1, 1.4)                |
| Fungal infection NOS     | 0                        | 2 (2, 2.7)                | 1 (1, 1.4)                | 2 (2, 2.7)                |
| Sinusitis NOS/acute      | 3 (3, 4.1)                | 2 (2, 2.7)                | 3 (2, 2.8)                | 0                        |
| Gastroenteritis NOS/E coli/Campylobacter | 0 | 1 (1, 1.4) | 1 (1, 1.4) | 1 (1, 1.4) |
| Bronchitis NOS/acute NOS | 2 (2, 2.7)                | 2 (2, 2.7)                | 1 (1, 1.4)                | 0                        |
| UTI NOS                  | 5 (5, 6.8)                | 1 (1, 1.4)                | 2 (1, 1.4)                | 0                        |
| Pharyngitis NOS          | 0                        | 0                        | 0                        | 2 (2, 2.7)                |
| Herpes zoster            | 1 (1, 1.4)                | 1 (1, 1.4)                | 0                        | 1 (1, 1.4)                |
| Herpes simplex           | 1 (1, 1.4)                | 1 (1, 1.4)                | 0                        | 1 (1, 1.4)                |
| Vaginosis NOS            | 2 (1, 1.4)                | 0                        | 2 (2, 2.8)                | 0                        |
| Oral candidiasis         | 1 (1, 1.4)                | 0                        | 1 (1, 1.4)                | 0                        |
| Abscess NOS              | 0                        | 2 (2, 2.7)                | 0                        | 0                        |
| Tooth abscess/infec tion | 1 (1, 1.4)                | 2 (2, 2.7)                | 0                        | 0                        |
| Weeks 13–20              |                           |                           |                           |                           |
| Nasopharyngitis          | 5 (4, 5.5)                | 4 (4, 5.4)                | 3 (3, 4.2)                | 3 (3, 4.1)                |
| Sinusitis NOS            | 0                        | 1 (1, 1.4)                | 2 (2, 2.8)                | 0                        |
| Bronchitis NOS           | 0                        | 1 (1, 1.4)                | 1 (1, 1.4)                | 0                        |
| Gastrointestinal infection NOS | 1 (1, 1.4) | 0 | 0 | 1 (1, 1.4) |
| Influenza                | 2 (2, 2.7)                | 0                        | 1 (1, 1.4)                | 0                        |
| Gastroenteritis NOS      | 2 (2, 2.7)                | 0                        | 0                        | 0                        |

NOTE. AEs are shown as number of events (number of patients, % of patients). NOS, not otherwise specified; URTI, upper respiratory tract infection; UTI, urinary tract infection.
III evaluation of the humanized monoclonal antibody to α4-integrin, natalizumab, a large placebo effect was apparent in the ITT population and the primary end point of clinical response (a >70-point reduction in CDAI score) at week 10 was not achieved. However, in a subanalysis of patients with increased baseline CRP levels, the placebo response was managed such that natalizumab treatment showed statistically significant greater rates of clinical response than placebo at week 10 and other time points.31

The therapeutic efficacy of infliximab was established in a population of Crohn’s disease patients with high mean baseline CRP concentrations—up to 23.2 mg/L in one of the treatment groups.8 In the certolizumab clinical trial reported here, although all patients had symptoms indicating moderate to severe Crohn’s disease activity (with CDAI scores of ≥220 points), only 119 of 290 (41.0%) patients had baseline serum CRP concentrations of 10 mg/L or greater. It is possible that the relatively low proportion of patients with biologic signs of disease activity may be a reflection of the consequent long-term use of immunosuppressive therapeutic agents (including infliximab) at tertiary referral centers, from where patients were recruited for this study. Alternatively, the patient selection may be a reflection of the availability of other therapies outside of this study. Both scenarios would influence a priori the availability and therefore the selection of clinically active patients for therapeutic study protocols.

Recent Crohn’s disease clinical trials have often shown relatively high placebo response rates. In a systematic review of 21 randomized trials in Crohn’s disease, the pooled estimate of the placebo response rate was 19%, with substantial heterogeneity among different trials.32 Further investigation of placebo response rates in clinical trials in Crohn’s disease and, in particular, its relationship with CRP levels is warranted.

In this study of certolizumab, an overall placebo response rate of 35.6% was observed at week 12 in the ITT population. Patients with CRP concentrations less than 10 mg/L showed a particularly high placebo response rate (46.7% for the clinical response at week 12). The placebo response decreased with increasing baseline CRP concentrations. At week 12, the placebo response rate was 34.9% in patients with baseline CRP levels of 5 mg/L or greater and 17.9% for those with CRP levels of 10 mg/L or greater. A relationship between low CRP concentrations and high placebo response rates has also been found in a joint analysis of the primary data from 733 Crohn’s disease patients collated from a total of 13 randomized controlled trials.33 The lack of efficacy of anti-inflammatory drugs in populations of patients with low CRP levels could be explained either by therapeutic effects being obscured by the placebo response, or by the fact that patients with low CRP levels may have problems that are not necessarily amenable to anti-inflammatory treatment. For example, in our study the week 12 response rates in the high-dose group were greater than 50% in those with CRP levels of 10 mg/L or greater at baseline and only 37.5% in those with CRP levels of less than 10 mg/L at baseline.

In patients with low CRP levels, placebo effects may drive responses in both the active-treatment and control arms of clinical trials. Consequently, the use of baseline CRP measurements may be a useful addition to the CDAI (which contains subjective components and may be susceptible to placebo influence) in the assessment of Crohn’s disease patients entering clinical trials. Phase III clinical trials of certolizumab have been designed to address issues relating to high placebo response rates. In clinical practice, CRP levels might provide an objective indication of active inflammation and measurement of CRP levels may help to identify patients for whom anti-inflammatory therapy could be appropriate.

As previously shown in the treatment of patients with rheumatoid arthritis,21 subcutaneous administration of certolizumab was well tolerated in this study, with patients experiencing relatively few side effects. There were no deaths during the study, and no cases of malignancy, lupus, tuberculosis, lymphoma, or increases in opportunistic infections were recorded. Interestingly, the rate of AEs of infection was similar in the placebo- and certolizumab-treated patient populations (23.3% and 26.5% during the double-blind period, respectively). Although this finding has to be confirmed in the large phase III studies currently underway, it is possible that the subcutaneous route of drug administration could contribute to the good tolerability because peak serum concentrations are lower than would be achieved after intravenous delivery. Although complement-dependent cytotoxicity-effector mechanisms could potentially affect therapeutic safety, certolizumab is a Fab’ fragment and has been designed specifically not to fix complement; this may contribute to its favorable safety profile.

As previously reported with the recombinant proteins infliximab20 and adalimumab,54 an immune response directed against certolizumab was observed in this phase II study. However, the number of antibody-positive patients in the certolizumab 400-mg group was low (n = 9 of 73), even in the presence of immunosuppressants in only one third of the population, and larger phase III studies will allow further exploration of this observation.

In conclusion, this phase II study is the first evidence suggesting that certolizumab, administered subcutane-
ously at a dose of 400 mg 4 times weekly, is effective in patients with moderate to severe Crohn's disease and is well tolerated. The study was powered under the assumption of a placebo response rate of 12%; the placebo response rate actually observed was far greater (15.1%–35.6% over the study period). This may have contributed to a lack of statistical difference in clinical response at the week 12 end point. Therefore, these findings need to be confirmed in a phase III study. It may prove beneficial to consider the use of CRP measurements in the future clinical development of certolizumab and other anti-TNF agents: compared with the overall ITT population, patients with increased baseline CRP levels showed the greatest difference between certolizumab treatment and placebo in terms of both rates of clinical response and remission.

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