

ORIGINAL ARTICLE

Maintenance Therapy with Certolizumab Pegol for Crohn's Disease

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ABSTRACT

BACKGROUND

Certolizumab pegol is a pegylated humanized Fab' fragment with a high binding affinity for tumor necrosis factor α that does not induce apoptosis of T cells or monocytes.

METHODS

In our randomized, double-blind, placebo-controlled trial, we evaluated the efficacy of certolizumab pegol maintenance therapy in adults with moderate-to-severe Crohn's disease. As induction therapy, 400 mg of certolizumab pegol was administered subcutaneously at weeks 0, 2, and 4. Patients with a clinical response (defined as reduction of at least 100 from the baseline score on the Crohn's Disease Activity Index [CDAI]) at week 6 were stratified according to their baseline C-reactive protein level and were randomly assigned to receive 400 mg of certolizumab pegol or placebo every 4 weeks through week 24, with follow-up through week 26.

RESULTS

Among patients with a response to induction therapy at week 6 (428 of 668 [64%]), the response was maintained through week 26 in 62% of patients with a baseline C-reactive protein level of at least 10 mg per liter (the primary end point) who were receiving certolizumab pegol (vs. 34% of those receiving placebo, $P < 0.001$) and in 63% of patients in the intention-to-treat population who were receiving certolizumab pegol (vs. 36% receiving placebo, $P < 0.001$). Among patients with a response to induction therapy at week 6, remission (defined by a CDAI score of ≤ 150) at week 26 was achieved in 48% of patients in the certolizumab group and 29% of those in the placebo group ($P < 0.001$). The efficacy of certolizumab pegol was also shown in patients taking and those not taking glucocorticoids or immunosuppressants and in patients who had and those who had not previously taken infliximab. Infectious serious adverse events (including one case of pulmonary tuberculosis) occurred in 3% of patients receiving certolizumab pegol and in less than 1% of patients receiving placebo. Antinuclear antibodies developed in 8% of the patients in the certolizumab group; antibodies against certolizumab pegol developed in 9% of all patients who entered the induction phase.

CONCLUSIONS

Patients with moderate-to-severe Crohn's disease who had a response to induction therapy with 400 mg of certolizumab pegol were more likely to have a maintained response and a remission at 26 weeks with continued certolizumab pegol treatment than with a switch to placebo. (ClinicalTrials.gov number, NCT00152425.)

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THE PROINFLAMMATORY CYTOKINE tumor necrosis factor α (TNF- α) is highly expressed in the blood, colonic tissue, and stool of patients with Crohn's disease.¹⁻⁴ Infliximab and adalimumab are engineered IgG1 monoclonal antibodies that bind to TNF- α (the first represents a chimeric molecule and the latter has been derived from human origin) and are effective in the induction and maintenance of response and remission in patients with Crohn's disease.⁵⁻⁷ The efficacy of infliximab in the treatment of Crohn's disease has been attributed to multiple mechanisms, including reverse signaling through membrane-bound TNF- α and the induction of apoptosis of T cells and monocytes.⁸⁻¹¹

Certolizumab pegol, a pegylated humanized Fab' fragment of an anti-TNF- α monoclonal antibody, has several characteristics that differentiate it from infliximab and adalimumab. In vitro, certolizumab pegol has a higher affinity for TNF- α , is devoid of the Fc portion of the antibody, and does not induce complement activation, antibody-dependent cellular cytotoxicity, or apoptosis.¹¹⁻¹³ One study by our group¹⁴ suggested that induction treatment with certolizumab pegol might be effective for the treatment of moderate-to-severe active Crohn's disease: a 400-mg dose of certolizumab pegol every 4 weeks was effective in patients with a serum C-reactive protein (CRP) level of at least 10 mg per liter; response rates at week 12 were significantly higher than those in the placebo group. In that study, however, we did not prospectively stratify patients according to CRP level; such stratification occurred later in the clinical trial program.

The Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy 1 (PRECISE 1) trial involved a placebo-controlled induction phase and a 26-week treatment phase in a population of patients with active Crohn's disease; it is reported on elsewhere in this issue of the *Journal*.¹⁵ PRECISE 2, which we present in this article, was a 26-week trial involving maintenance and withdrawal therapy with certolizumab pegol in patients with moderate-to-severe Crohn's disease who were selected for having a response to open-label induction therapy.

METHODS

A committee of academic investigators and UCB Pharma scientists (the Study Advisory Board) designed the study. Data were collected by a contract

research organization (ICON Clinical Research) and analyzed by the sponsor and external experts. The academic authors vouch for the veracity and completeness of the data and data analyses presented. Both the academic and industry authors wrote the first and subsequent drafts of the manuscript and hold the data, and the decision to publish was made by an academic author.

PATIENTS

Our multicenter, randomized, double-blind, placebo-controlled trial was conducted worldwide at 147 centers, from February 2004 until May 2005. The protocol was approved by the institutional review board or ethics committee at each center. All patients gave written informed consent.

Adults were eligible if they had a 3-month history of active Crohn's disease, defined as a Crohn's Disease Activity Index (CDAI) score of 220 to 450.¹⁶ The CDAI is a weighted, composite index of eight items (stool frequency, severity of abdominal pain, degree of general well-being, presence or absence of extraintestinal manifestations or fistula, use or nonuse of antidiarrheal agents, presence or absence of an abdominal mass, hematocrit, and body weight), with scores ranging from 0 to 600 and higher scores indicating more severe disease activity. Permitted concomitant therapies for Crohn's disease were stable doses of 5-aminosalicylates, 30 mg or less of prednisolone per day (or equivalent), azathioprine, 6-mercaptopurine, methotrexate, and antibiotics. Exclusion criteria were the presence of the short-bowel syndrome, ostomy, obstructive symptoms with strictures, abscess, history of tuberculosis, positive chest radiograph, positive tuberculin purified-protein-derivative (PPD) skin test, demyelinating disease, and cancer. (Exclusion criteria did not include a positive PPD skin test in combination with previous vaccination with bacille Calmette-Guérin and a negative chest radiograph.) Patients who had received any certolizumab pegol, who had received an anti-TNF agent or other biologic therapy within 3 months before enrollment, or who had a severe hypersensitivity reaction or no clinical response after initial dosing with an anti-TNF were also excluded. Reasons for discontinuation of any previous anti-TNF treatment were not reported.

STUDY DESIGN

Eligible patients received induction therapy, consisting of subcutaneous injections of 400 mg of certolizumab pegol at weeks 0, 2, and 4. A clinical

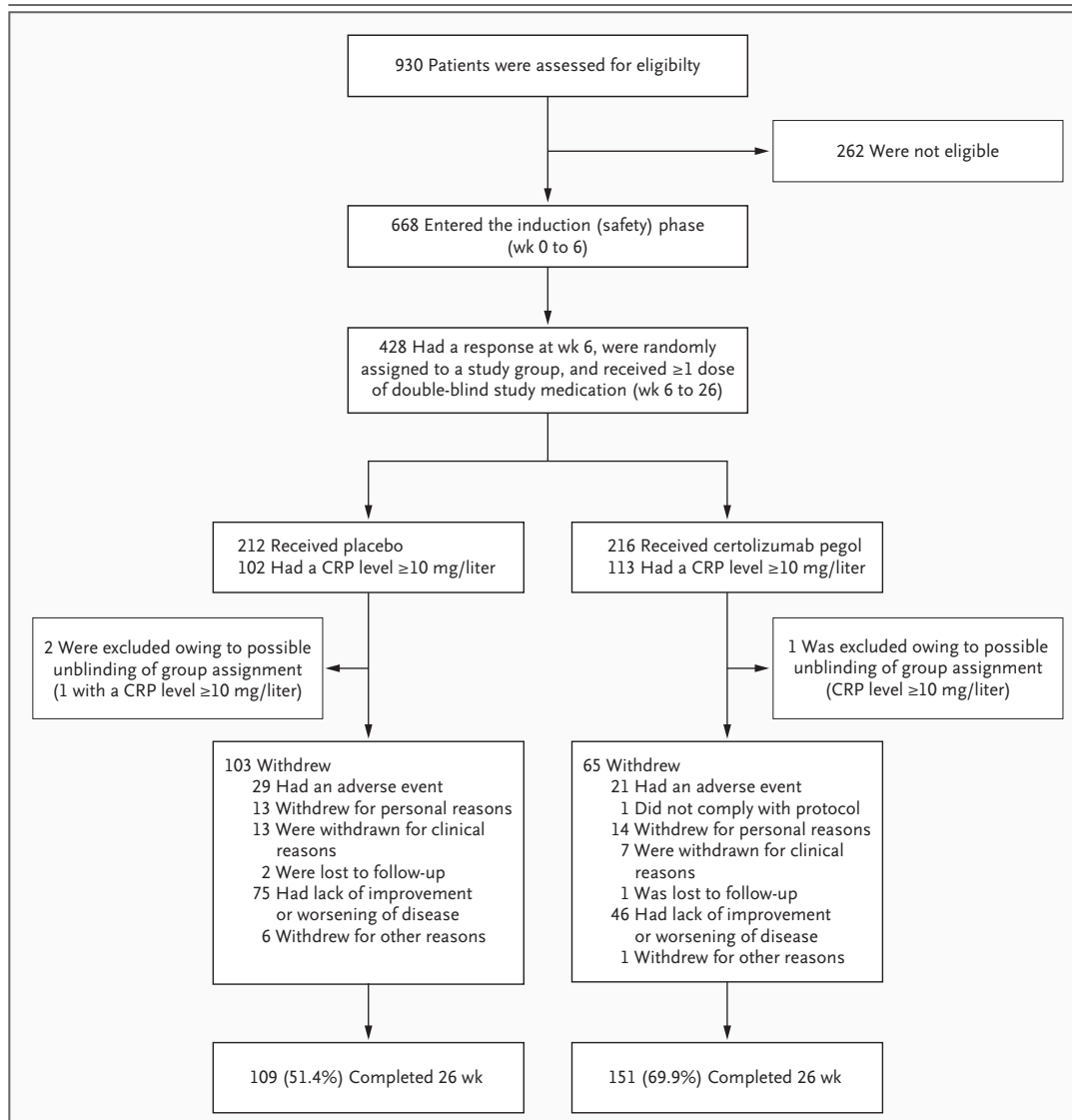


Figure 1. Enrollment, Group Assignments, and Follow-up.

The 668 patients with moderate-to-severe Crohn's disease received induction therapy with certolizumab pegol, 400 mg subcutaneously, at weeks 0, 2, and 4. Of these patients, 428 had a response to induction therapy at week 6 and were randomly assigned to receive maintenance therapy with either certolizumab pegol or placebo and were stratified according to whether their baseline CRP level was at least 10 mg per liter or less than 10 mg per liter. The intention-to-treat population consisted of 425 patients who had a response to the induction therapy with certolizumab pegol and who were not excluded owing to possible unblinding of group assignment, 210 of whom received maintenance placebo and 215 of whom received maintenance certolizumab pegol. Patients could have more than one reason for withdrawal after randomization.

response was defined as a reduction of at least 100 from the baseline score on the CDAI; remission was defined as a CDAI score of 150 points or less.¹⁶ Patients who had a response to induction therapy at week 6 were randomly assigned to receive 400 mg of certolizumab pegol (certolizumab group) or placebo (placebo group) at weeks 8, 12, 16, 20, and

24 and were followed through week 26. The study was centrally randomized, and group assignment was stratified according to serum CRP level (≥ 10 mg per liter or < 10 mg per liter), concurrent use of glucocorticoids (yes or no), and concurrent use of immunosuppressive agents (yes or no). The randomization code consisted of eight separate lists

(one for each stratum) and was generated by an independent contractor. Randomization was centralized by means of an interactive voice-recognition system. Patients and investigators were unaware of the group assignment.

Doses of concomitant medications were kept constant except for those of glucocorticoids, for which the dose could be reduced but no forced tapering was required. Any escalation of dose above baseline levels qualified as a failure of therapy.

FOLLOW-UP AND EFFICACY AND SAFETY EVALUATIONS

Patients were followed up at weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, and 26. At each visit, diary data were collected, clinical assessments of Crohn's disease were undertaken, adverse events and the use of concomitant medications were recorded, and laboratory samples were collected. Data for determining the CDAI score were collected for 7 days by means of a diary card completed daily by the patient. Safety evaluations included the checking of vital signs, physical examinations, hematologic analysis, serum biochemistry tests, and urinalysis. Antibodies against certolizumab pegol were assayed with the use of previously published methods, with a lower detection limit of 2.4 U per milliliter (an increase by a factor of 2 over the level in a reference population).¹⁷ CRP measurements were made at a central laboratory (MDS Pharma Services, Central Lab) (normal range, 0 to 4 mg per liter). The health-related quality of life was assessed at weeks 0, 6, 16, and 26 with the use of the Inflammatory Bowel Disease Questionnaire, scores for which range from 32 to 224, with higher scores indicating a better quality of life.¹⁸

STATISTICAL ANALYSIS

The primary end point was a clinical response at week 26 in patients with a baseline CRP level of at least 10 mg per liter. Secondary end points included response at week 26, remission at week 26 in the intention-to-treat population, and remission in the group with a baseline CRP level of at least 10 mg per liter. If patients received rescue therapy during the study, their treatment was considered to have failed, starting at the time of the administration of the first rescue therapy. The intention-to-treat population included all patients who were randomly assigned to a study group, who received

at least one injection of certolizumab pegol or placebo, and who had at least one efficacy evaluation after the first double-blind injection.

Percentages of patients having a response or remission were compared between the two study groups with the use of logistic regression (with adjustment for geographic region, use of glucocorticoids, use of immunosuppressive agents, and baseline CRP level in the intention-to-treat population only). A closed test procedure was used to control for multiple comparisons across secondary end points.¹⁹ A two-sided significance level of 0.05 was used in all comparisons. Hypothesis testing of major secondary variables was performed only if the primary end point was significant. Baseline characteristics were compared between the two study groups with the use of either the chi-square test or Fisher's exact test for categorical variables or analysis of variance for continuous variables. Safety variables were compared between the two groups with the use of Fisher's exact test. All efficacy analyses were performed according to the intention-to-treat principle. Post hoc analyses were performed to determine the CDAI scores with the last observation carried forward for each visit and to explore the effect of certolizumab pegol as compared with placebo in subpopulations receiving concomitant glucocorticoids, receiving concomitant immunosuppressants, or that previously received infliximab.

We anticipated that 55% of 712 patients receiving induction treatment with certolizumab pegol would have a response at week 6. We calculated that the random assignment of 392 patients who had a response (196 patients with a CRP level ≥ 10 mg per liter and 196 with a CRP level < 10 mg per liter) would result in a statistical power of 80% to detect a difference in the response rate during the maintenance phase, assuming a rate of 45% in the certolizumab group and 25% in the placebo group.

RESULTS

PATIENTS

Figure 1 shows the disposition of the study patients. Baseline demographic and disease characteristics were similar in the two study groups. Twenty-four percent (103 of 425) of patients in the intention-to-treat population had previously received infliximab (Table 1).

Table 1. Demographic and Disease Characteristics of Patients in the Intention-to-Treat Population, According to Type of Maintenance Therapy.*

Characteristic	Placebo Group (N=210) [†]	Certolizumab Group (N=215)	P Value
Age — yr			0.92
Mean ±SD	38±12	38±11	
Range	18–69	18–67	
Male sex — no. of patients (%)	109 (52)	92 (43)	0.06
Body-mass index [‡]	25±5	24±5	0.13
Duration of disease — yr			0.09
Mean	7	9	
Median	5	7	
Range	<1–43	<1–33	
Current smoker — no. of patients (%)	76 (36)	64 (30)	0.16
CDAI score [§]			0.45
Mean ±SD	301±62	306±61	
Range	183–583	179–504	
CRP — mg/liter [¶]			0.95
Geometric mean	10	10	
Range	2–244	2–183	
Disease site — no. of patients (%)			0.53
Terminal ileum	53 (25)	48 (22)	
Colon	61 (29)	57 (27)	
Ileocolon	96 (46)	110 (51)	
Previous infliximab therapy — no. of patients (%) ^{**}	51 (24)	52 (24)	0.98
No. of infusions			
Median	3	4	
Range	1–23	1–26	
Previous acute hypersensitivity reaction to infliximab — no. of patients (%)	5 (2)	9 (4)	
Previous bowel resection performed — no. of patients (%)	73 (35)	64 (30)	0.27
Concurrent treatment of Crohn's disease at study entry — no. of patients (%) ^{††}			0.79
Glucocorticoids only	44 (21)	47 (22)	
Immunosuppressive agents only	52 (25)	59 (27)	
Glucocorticoids plus immunosuppressive agents	34 (16)	28 (13)	
Neither glucocorticoids nor immunosuppressive agents	80 (38)	81 (38)	

* Plus-minus values are means ±SD.

[†] The placebo group received three doses of certolizumab pegol during the induction phase, followed by placebo during the maintenance phase.

[‡] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[§] CDAI scores were available for 209 patients in the placebo group.

[¶] Serum CRP levels were available for 208 patients in the placebo group and 213 patients in the certolizumab group.

^{||} Patients could have more than one disease site. If the upper gastrointestinal tract was the disease site, another site also had to be involved.

^{**} Primary infliximab failure was an exclusion criterion. Documentation of a previous loss of response to infliximab was not necessary for inclusion.

^{††} Immunosuppressive agents used were azathioprine, mercaptopurine, and methotrexate.

EFFICACY*Response to Induction at Week 6*

At week 6 (after three 400-mg doses of certolizumab pegol), 64% of patients (428 of 668) had a response and 43% (289 of 668) had a remission. The remaining 36% of patients who did not have a response (240 of 668) were not followed further for efficacy analyses.

Primary End Point

In total, 213 patients (32% of the 668 patients who entered the induction phase and 50% of the 428 who had a response to induction therapy) had a baseline serum CRP level of at least 10 mg per liter. During the maintenance phase, of these 213 patients, 62% in the certolizumab group (69 of 112) had a response at week 26, as compared with 34% in the placebo group (34 of 101) ($P<0.001$) (Fig. 2A).

Secondary End Points

Of the 428 patients in the intention-to-treat population who had a response to induction therapy at week 6, 63% in the certolizumab group (135 of 215) also had a response at week 26, as compared with 36% (76 of 210) in the placebo group ($P<0.001$) (Fig. 2B). The difference in response between treatment with certolizumab pegol and treatment with placebo was sustained throughout the maintenance phase, and the magnitude of the difference was similar in the intention-to-treat population and in patients with a baseline CRP serum level of at least 10 mg per liter (Fig. 2C). The response rate during the maintenance phase of 63% of patients in the intention-to-treat population who had a response to induction therapy at week 6 is equivalent to a combined response rate during the induction and maintenance phases of 40% (with a combined remission rate of 31%) in the 668 patients who entered the induction phase.

Among all patients in the intention-to-treat population who had a response at week 6, remission rates at week 26 were 48% (103 of 215) in the certolizumab group and 29% (60 of 210) in the placebo group ($P<0.001$) (Fig. 2D). In the subgroup with baseline CRP serum levels of at least 10 mg per liter, remission rates at week 26 were 42% (47 of 112) in the certolizumab group and 26% (26 of 101) in the placebo group ($P=0.01$) (Fig. 2D). Figure 2E depicts the results of an exploratory analysis, showing a reduction of the median CDAI scores in the intention-to-treat population after

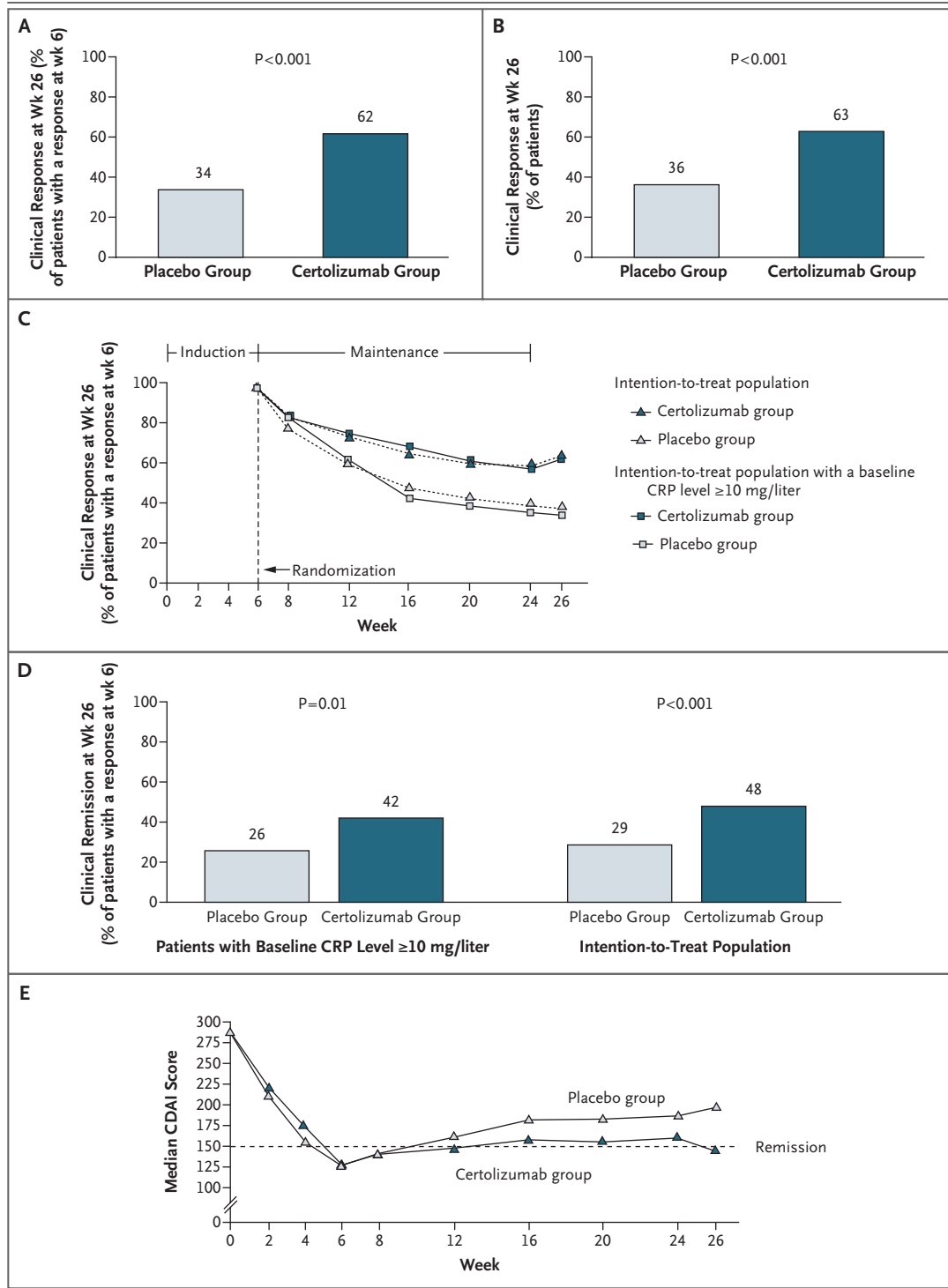
Figure 2 (facing page). Efficacy of Maintenance Therapy with Certolizumab Pegol in Patients with a Response to Induction Therapy at Week 6.

Panel A shows the percentage of patients with a baseline CRP serum level of at least 10 mg per liter whose response (defined as a reduction of ≥ 100 from the baseline score on the CDAI) at week 6 was maintained at week 26. Panel B shows the percentage of all patients in the intention-to-treat population who had a response to induction therapy at week 6 who had a response at week 26. Panel C shows the response over time in patients in the intention-to-treat population who had a response to induction therapy at week 6, as well as the response in the subgroup of patients with a CRP level of at least 10 mg per liter. The percentage of patients who had a response at week 26 was greater in the certolizumab group than in the placebo group in both populations ($P<0.001$). The 95% confidence intervals for the certolizumab group and for the placebo group did not overlap at any time point in the intention-to-treat population and did not overlap at weeks 16 through 26 in the high-CRP subgroup. Panel D shows the percentage of patients with clinical remission (defined as a CDAI score ≤ 150) at week 26 in the intention-to-treat population and in the subgroup of those with baseline CRP serum levels of at least 10 mg per liter. Panel E shows the median CDAI scores (as calculated with the use of the last-observation-carried-forward method) over time in the intention-to-treat population. The median score was significantly lower in the certolizumab group than in the placebo group at week 16 ($P=0.03$), week 20 ($P=0.02$), week 24 ($P=0.008$), and week 26 ($P<0.001$).

induction therapy with certolizumab pegol and the gradual rise in disease activity during the maintenance phase in the placebo group, as compared with the certolizumab group.

Fourteen percent of patients in the intention-to-treat population who had a response to induction therapy with certolizumab pegol (58 of 425) had draining fistulas at baseline (28 patients in the certolizumab group and 30 patients in the placebo group). During the study, of the 58 patients, 54% (15 of 28 patients) in the certolizumab group had fistula closure (defined as the absence of drainage on gentle compression at any two consecutive post-baseline visits at least 3 weeks apart), as compared with 43% (13 of 30) in the placebo group.

Among patients who had a response to induction therapy, a significantly greater percentage of patients in the certolizumab group (60% [129 of 214 patients]) also had a response as measured with the use of the Inflammatory Bowel Disease Questionnaire (an increase in the total score of at least 16 points) at week 26, as compared with



those in the placebo group (43% [90 of 210 patients]) ($P < 0.001$). Mean scores on the questionnaire were 123 at week 0 and 175 at week 6 among patients in the intention-to-treat population; during the maintenance phase, at week 16

mean scores were 169 in the certolizumab group and 158 in the placebo group and at week 26 they were 176 and 168, respectively. Adjusted mean scores were 170 in the certolizumab group and 162 in the placebo group ($P = 0.008$) at week 16

and 171 and 163 ($P=0.007$), respectively, at week 26.

Exploratory Analyses

In the intention-to-treat population, response rates at week 26 were significantly greater among patients receiving maintenance therapy with certolizumab pegol than among those receiving placebo, both for patients receiving concomitant immunosuppressive agents (61% [53 of 87] vs. 33% [28 of 86], $P<0.001$) and those not receiving concomitant immunosuppressive agents (64% [82 of 128] vs. 39% [48 of 124], $P<0.001$). A significant difference in the response rates at week 26 between the certolizumab group and the placebo group was found for patients who had previously received infliximab (44% [23 of 52] vs. 25% [13 of 51], $P=0.02$) and those who had not previously received infliximab (69% [112 of 163] vs. 40% [63 of 159], $P<0.001$). Neither the response rate nor the remission rate differed significantly between the two groups for patients who were and those who were not receiving concomitant glucocorticoids, immunosuppressive agents, or both.

For rates of response and remission, there were no significant interactions between group assignment and smoking status or body-mass index. A response was maintained at 26 weeks in 56% of current smokers (36 of 64 patients) in the certolizumab group and 34% in the placebo group (26 of 76 patients).

Among patients with a baseline CRP serum level of less than 10 mg per liter, response rates at week 26 were significantly greater in the certolizumab group (64% [66 of 103]) than in the placebo group (39% [42 of 109], $P<0.001$). Remission rates were 54% (56 of 103 patients) in the certolizumab group, as compared with 31% (34 of 109 patients) in the placebo group ($P<0.001$).

SAFETY

Serious adverse events occurred in 6% (12 of 216) of patients in the certolizumab group and 7% (14 of 212) of those in the placebo group (Table 2). Serious infection occurred in 3% (6 of 216) of patients in the certolizumab group and in less than 1% (2 of 212) of patients in the placebo group. The most frequently reported adverse events were similar in the two groups. One patient died of an accidental fentanyl overdose during the open-label phase of this trial. No deaths, solid-organ or hematologic cancers, demyelinating diseases, or lupus occurred during the maintenance phase. De-

spite the absence of a reaction to the PPD skin test at screening, one patient treated with five doses of certolizumab pegol and concomitant azathioprine had pulmonary tuberculosis, which responded to standard combination therapy with antibiotics. One or more local reactions to injection occurred in 3% (6 of 216) of patients in the certolizumab group and 15% (31 of 212) of patients in the placebo group (Table 2).

Autoimmune Antibodies

Among patients for whom values were available at both the baseline visit and the final visit, new antinuclear antibodies developed in 8% (16 of 192) of patients receiving certolizumab pegol and in 1% (2 of 178) of patients receiving placebo. New antibodies against double-stranded DNA developed in 1% (2 of 192) of patients in the certolizumab group and in 1% (1 of 178) of patients in the placebo group.

Antibodies against Certolizumab Pegol

Of the 668 patients who entered the induction phase, 58 (9%) had detectable antibodies against certolizumab pegol at some point during the study (Table 3). Three of the four patients in whom antibodies developed during the induction phase were randomly assigned to receive maintenance therapy, one with certolizumab pegol and two with placebo. In the remaining 54 patients, antibodies developed during the maintenance phase. Eighty percent of the antibodies were neutralizing antibodies. Rates of antibody formation were low in patients who received concomitant immunosuppressive agents and in those who received continuous therapy with certolizumab pegol (during the induction and maintenance phases) (Table 3).

The presence of certolizumab pegol in vivo may have interfered with the antibody assay because it can form complexes with drug antibodies. Therefore, in analyses of data for the certolizumab group during the maintenance phase, we also used a reduced-trough plasma certolizumab pegol level as an indirect measure of the presence of antibodies. The number of patients who were positive for antibodies against certolizumab pegol increased from the 17 detected with the use of the assay to 21. As a result, the number of patients who may have had false negative results on the antibody assay, owing to interference by circulating levels of certolizumab pegol forming complexes with drug antibodies, was low. Of the 17 patients with positive tests for antibodies against certolizumab peg-

Table 2. Summary of Adverse Events in the Safety Population.*

Adverse Event	Induction Phase with Certolizumab Pegol (Wk 0–6) (N=668)	Maintenance Phase (Wk 6–26)	
		Placebo Group (N=212)† no. of patients (%)	Certolizumab Group (N=216)
Any	392 (59)	143 (67)	140 (65)
Occurring in ≥5% of any group‡			
Headache	84 (13)	14 (7)	15 (7)
Nasopharyngitis	25 (4)	8 (4)	12 (6)
Cough	5 (<1)	2 (<1)	12 (6)
Crohn's disease (exacerbation)	36 (5)	25 (12)	9 (4)
Pain at injection site	8 (1)	11 (5)	1 (<1)
Related to study drug (as determined by investigator)	161 (24)	58 (27)	49 (23)
Any local reaction to injection§	13 (2)	31 (15)	6 (3)
Serious adverse events¶	47 (7)	14 (7)	12 (6)
Important serious adverse events			
Infection or infestation	12 (2)	2 (<1)	6 (3)
Abdominal abscess	4 (<1)	1 (<1)	0
Perianal abscess	4 (<1)	0	1 (<1)
Perineal abscess	0	0	2 (<1)
Bacteremia	0	1 (<1)	0
Otitis media	0	1 (<1)	0
Pneumonia	0	0	1 (<1)
Pyelonephritis	0	0	1 (<1)
Tuberculosis	0	0	1 (<1)
Viral gastroenteritis	1 (<1)	0	0
Infection	1 (<1)	0	0
Lobar pneumonia	1 (<1)	0	0
Pelvic inflammatory disease	1 (<1)	0	0
Any gastrointestinal disorder**	29 (4)	9 (4)	4 (2)
Obstructive events	7 (1)	1 (<1)	0
Abdominal pain	1 (<1)	1 (<1)	2 (<1)
Exacerbation of Crohn's disease	19 (3)	5 (2)††	1 (<1)
Diarrhea	1 (<1)	0	1 (<1)
Other	1 (<1)	2 (2)	0
Blood and lymphatic-system disorder	1 (<1)	0	1 (<1)
Iron-deficiency anemia	0	0	1 (<1)
Anemia	1 (<1)	0	0
Immune-system disorders	1 (<1)	1 (<1)	0
Benign, malignant, or unspecified neoplasm (including cysts and polyps)	1 (<1)	0	0
Leading to withdrawal‡‡	51 (8)	28 (13)	18 (8)
Leading to death§§	1 (<1)	0	0

* The number of patients was the same as the number of adverse events, unless otherwise noted. One case of Bowen's disease was reported on day 1 and was not considered to be related to the study medication.

† The placebo group received three doses of certolizumab pegol during the induction phase, followed by placebo during the maintenance phase.

‡ P values for the comparison between the numbers of patients in the placebo group and in the certolizumab group during the maintenance phase were 0.01 for patients with cough, 0.004 for those with Crohn's disease, and 0.003 for those with pain at the injection site.

§ Local reactions to injection included all events that occurred at the injection site and were temporally related to the injection of the study medication.

¶ During the induction phase, the group had 56 events; during the maintenance phase, each group had 19 events.

|| Important serious adverse events were those that are attributable to the drug class that contains certolizumab pegol.

** The total number of adverse events involving gastrointestinal disorders was 31 during the induction phase, and 10 in the placebo group and 5 in the certolizumab group during the maintenance phase.

†† These five patients had six episodes of exacerbation of their Crohn's disease.

‡‡ Four patients had adverse events during the induction phase that led to withdrawal during the maintenance phase (one patient in the placebo group and three in the certolizumab group).

§§ One patient died from an overdose of fentanyl (used in a patch as analgesia) after the first dose of certolizumab pegol.

Table 3. Summary of Data on Antibodies against Certolizumab Pegol, According to Use of Immunosuppressive Agents.

Group	Induction Phase with Certolizumab Pegol (Wk 0–6)	Maintenance Phase (Wk 6–26)*	
		Placebo Group no./total no. (%)	Certolizumab Group
Patients positive for antibodies against certolizumab pegol	4/668 (<1)†	37/209 (18)	17/213 (8)
Patients receiving certolizumab pegol monotherapy	4/407 (1)	30/123 (24)	15/126 (12)
Patients receiving certolizumab pegol and immunosuppressive agents	0/261	7/86 (8)	2/87 (2)

* The antibody assay was not performed in all patients during the maintenance phase.

† One of the four patients did not have a response to induction therapy. Of the three patients who had a response, two were randomly assigned to receive placebo, and one was randomly assigned to receive certolizumab pegol, as maintenance therapy.

ol, 12 (71%) had a response through week 26, as compared with 121 of 196 patients (62%) with negative tests for the antibodies.

DISCUSSION

The results of our trial show that continued administration of certolizumab pegol subcutaneously every 4 weeks is superior to administration of placebo in the 64% of our patients with moderate-to-severe active Crohn's disease (despite the use of conventional treatments) who had a response to 6 weeks of induction therapy with 400 mg of certolizumab pegol (given at weeks 0, 2, and 4). The combined response rate during the induction and maintenance phases was 40%. However, the open-label study design results in an overestimation of the rate of induction of a response, and response rates to placebo are substantial among patients with Crohn's disease. Contrary to a finding in a previous phase 2 study,¹⁴ continued treatment with certolizumab pegol was equally effective in patients with high baseline CRP serum levels and those with low levels, and the response rate at week 26 did not depend on the baseline CRP level. Long-term improvement in the health-related quality of life was greater in the certolizumab group than in the placebo group. Antinuclear antibodies developed in 8% of patients treated with certolizumab pegol, an incidence that does not exceed that in healthy persons.²⁰ Antibodies to certolizumab pegol developed in 9% of patients.

Since only 14% of patients had draining fistulas and inclusion in the study was based primar-

ily on the overall disease activity, our trial was not powered to examine the efficacy of certolizumab pegol for fistula closure. Additional studies will be required to address this issue.

Our results also show that certolizumab pegol was effective in patients who had previously taken infliximab. The efficacy of maintenance treatment with certolizumab pegol was also seen in patients with and those without concomitant therapy with immunosuppressants. The development of antibodies against certolizumab pegol during the maintenance phase differed modestly between patients receiving and those not receiving concomitant immunosuppressive agents (2% vs. 12% in the certolizumab group and 8% vs. 24% in the placebo group).

Maintenance therapy with certolizumab pegol was associated with a safety profile that was consistent with profiles in previous studies.^{14,17,21,22} Two patients in the placebo group and six in the certolizumab group had serious adverse events consisting of infection, including one case of pulmonary tuberculosis. No solid-organ or hematologic cancers, demyelinating disease, or lupus were reported during the maintenance phase. With regard to the patient who died of a fentanyl overdose, to our knowledge there is no specific interaction between fentanyl and certolizumab pegol. Ongoing follow-up of patients in open-label treatment programs has not resulted in any new safety signals to date. Longer-term exposure of large cohorts of patients will be required to better characterize the adverse events associated with certolizumab pegol.

In conclusion, patients with moderate-to-severe active Crohn's disease who had a response to induction therapy with certolizumab pegol and continued to receive certolizumab pegol as maintenance therapy were more likely to have a maintained response and remission at 26 weeks than were those who switched to placebo.

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APPENDIX

The following investigators participated in the PRECISE 2 trial: **Australia:** Flinders Medical Centre, Bedford Park — P. Bampton; Alfred Hospital, Melbourne — F. Dudley; Royal Adelaide Hospital, Adelaide — D. Hetzel; Fremantle Hospital, Fremantle — I.C. Lawrance; Canberra Hospital, Garran — P. Pavli; Royal Prince Alfred Hospital Medical Centre, Newtown — W. Selby; **Canada:** Liver and Intestinal Research Centre, Vancouver, BC — F. Anderson; Health Sciences Centre, Winnipeg, MB — C. Bernstein; Sir Mortimer B. Davis-Jewish General Hospital, Montreal — A. Cohen; St. Paul's Hospital, Vancouver, BC — R. Enns; Mount Sinai Hospital, Toronto — G. Greenberg; Dalhousie University, Halifax, NS — M. Khaliq-Kareemi; Centre Hospitalier Regionale de Lanaudiere, Quebec, QC — P. Laflamme; **Denmark:** Glostrup Hospital, Glostrup — P. Bytzer; Aarhus Hospital, Aarhus C — J.F. Dahlerup; Vejle Hospital, Vejle — E. Ejlersen; Aalborg Hospital, Aalborg — J. Fallingborg; Gentofte Hospital, Hellerup — E. Langholz; Odense University Hospital, Odense — K. Lauritsen; Hvidovre Hospital, Hvidovre — A. Mertz-Nielsen; Bispebjerg Hospital, Copenhagen — E. Philipsen; Rigshospitalet, Copenhagen — M. Staun; Herlev Hospital, University of Copenhagen, Herlev — O.O. Thomsen; **Germany:** Charité-Campus Virchow Klinikum, Berlin — A. Dignass; University Rostock, Rostock — J. Emrich; Reinhard-Nieter-Krankenhaus, Wilhelmshaven — P. Herzog; Rothenbaumchaussee 26, Hamburg — S. Howaldt; Universität Freiburg, Freiburg — W. Kreisel; Heekweg 15, Münster — T. Krummenerl; Universitätsklinikum Göttingen, Göttingen — G. Ramadori; Hospital of the University of Leipzig, Leipzig — I. Schiefke; Hospital for General Internal Medicine, Christian Albrechts University, Kiel — S. Schreiber; Hospital Essen-Nord, Essen — A. Stallmach; University of Ulm, Ulm — C. von Tirpitz; **Hungary:** Peterfy Teaching Hospital, Peterfy, Budapest — L. Bene; Pándy Kálmán Hospital, Gyula — Z. Gurzó; Veszprém County Csolnoky Ferenc Hospital, Veszprém — L. Lakatos; Petz Aladar County Teaching Hospital, Győr — I. Rácz; St. Janos Hospital, Budapest — G. Székely; Szent Pantaleon Hospital, Dunaújváros — L. Varga Szabó; Semmelweis University, Budapest — T. Zádóni; **Ireland:** St James' University Hospital, Dublin — D. Kelleher; Beaumont Hospital, Dublin — F. Murray; St. Vincent's Hospital, Dublin — D. O'Donoghue; **Israel:** Tel Aviv Sourasky Medical Center, Tel Aviv — I. Dotan; Rambam Medical Center, Haifa — R. Elyakim; the Soroka University Medical Center, Beer Sheva — A. Fich; Rabin Medical Center, Petah Tikva — G.M. Fraser; Hadassah Medical Organization, Jerusalem — E. Goldin; Bnai-Zion Medical Center, Haifa — A. Lavy; Assaf Harofeh Medical Center, Beer Yaakov — E. Scapa; **Lithuania:** Kaunas Medical University Hospital, Kaunas — L. Kupcinskas; Public Institution Vilnius University Hospital, Vilnius — J. Valentinas; **New Zealand:** Christchurch Hospital, Christchurch — M. Barclay; Auckland Hospital, Auckland — M. Lane; Tauranga Hospital, Tauranga — D. Shaw; Shakespeare Specialist Group, Auckland — I. Wallace; Waikato Hospital, Hamilton — F. Weiler; Wellington Hospital, Wellington — J. Wyeth; **Norway:** Haugesund Hospital, Bedriftssjukkontoret Haugesund — K. Bakkevold; University Hospital of Tromsø, Tromsø — J.R. Florholmen; Aker University Hospital, Oslo — J. Jahnsen; Ullevål University Hospital, Oslo — I. Lygren; Diakonhjemmet Hospital, Oslo — N. Stray; Sentralsjukehuset I Hedmark, Hamar — R. Torp; Regionsykehuset I Trondheim, Trondheim — Waldum HL; **Poland:** Centrum Leczenia Chorob, Warsaw — A. Bochenek; Nzoz Polimedica, Lodz — E. Czajkowska-Kaczmarek; Centrum Medyczne SOPMED Sopot, Sopot — M. Horynski; EuroMediCare Instytut Medyczny Wrocław, Wrocław — J. Leszczyszyn; Niepubliczny Zakład Opieki Zdrowotnej VIVAMED, Warsaw — R. Petryka; 10 Szpital Wojskowy w Bydgoszcz, Warszawa 5, Bydgoszcz — J. Rudzinski; Wojewódzki Szpital Zespolony im. J. Śniadeckiego, Białystok — J. Sasiewicz; **Serbia:** Klinički Bolnički Centar Zvezdara, Belgrade — N. Jojic; Klinički Bolnički Centar Srbije, Belgrade — M. Krstic; Klinički Bolnički Centar Bežanijska Kosa, Belgrade — N. Milinic; Klinički Bolnički Centar Nis, Nis — A. Nagorni; Military Medical Academy, Belgrade — D. Tarabar; **Singapore:** National University Hospital — K.Y. Ho; Singapore General Hospital — C.J. Ooi; **South Africa:** Greenacres Hospital, Port Elizabeth — E. Fredericks;

Linksfield Park Clinic, Johannesburg — L. Jackson; Johannesburg General Hospital, Johannesburg — K. Karlsson; Pretoria Academic Hospital, Pretoria — O. Mwantembe; Parklands Hospital, Durban — K.E. Pettengell; Medpark Building, Cape Town — S.J. Schmidt; Kloof Hospital, Pretoria — P.R. Spiess, C.C.M. Ziady; Rosebank Clinic, Johannesburg — M. Strimling; New Groote Schuur Hospital, Cape Town — G.A.A. Watermeyer; **Spain:** Hospital Clinic de Barcelona, Barcelona — J. Panés Díaz; **Ukraine:** City Hospital No. 7, Dnepropetrovsk — N. Chukhriyenko; Lviv City Clinic No. 5, Konovaltsa Str 22 — R. Dutka; Crimean Medical University, Autonomous Republic of Crimea — I. Klyaritskaya; Odessa Central Regional Hospital, Odessa — E. Levchenko; City Clinical Hospital No. 6, Dnepropetrovsk — T. Pertseva; Hospital of the Security Service of Ukraine, Kiev — M.P. Zakharash; **United States:** Medical Associates Research Group, San Diego, CA — M. Bennett; Center for Medicine Research, Manchester, CT — J. Breiter; Rochester Institute for Digestive Diseases, Rochester, NY — W. Chey; Mountain West Gastroenterology, Salt Lake City — S. Desautels; Houston — A. Ertan; Wasatch Clinical Research, Salt Lake City — E.J. Eyring; Wisconsin Center for Advanced Research, Milwaukee — D.J. Geenen; Clinical Research Associates, Huntsville, AL — C.A. Goetsch; Harmony Clinical Research, Oro Valley, AZ — C.G. Gross; Comprehensive Clinical Research, Berlin, NJ — D.R. Hassman; the Vancouver Clinic, Vancouver, WA — V. Hee; Lynn Health Science Institute, Oklahoma City — J. Hogin; Piedmont Medical Research Associates, Winston-Salem, NC — R. Holmes; Gastroenterology United of Tulsa, Tulsa, OK — D. James; Medical Center for Clinical Research, San Diego, CA — W.D. Koltun; University of Washington Medical Center, Seattle — S.D. Lee; Advanced Research Institute, South Ogden, UT — J.E. Lowe; Targeted Research, Dayton, OH — D. Lutter; Gastroenterology and Hepatology Associates, Alexandria, VA — S. Malhotra; Carolina Research Center, Greenville, NC — S.P. Marcuard; Midwest Clinical Research Associates, Moline, IL — R. Movva; Charlottesville Medical Research, Charlottesville, VA — D.J. Pambianco; Bethany Medical Center, High Point, NC — L. Peters; Southeastern Indiana Gastroenterology, Columbus, IN — S.D. Pletcher; Tacoma Digestive Research Center, Tacoma, WA — W.M. Priebe; Torrance Clinical Research, Torrance, CA — M. Raikhel; New River Valley Research Institute, Christiansburg, VA — M. Ringold; Atlanta Gastroenterology Associates, Atlanta — B.A. Salzberg; Southern Clinical Research Consultants, Hollywood, FL — W. Schonfeld; Vanderbilt University Medical Center, Nashville — D. Schwartz; Lynn Institute of the Rockies, Colorado Springs, CO — A. Shafiq; Penn State Milton S. Hershey Medical Center, Hershey, PA — J.P. Smith; Community Clinical Trials, Orange, CA — D. Stanton; Washington University School of Medicine, St. Louis — C. Stone; Jefferson City Medical Group, Jefferson City, MO — J. Wang; Clinical Research of West Florida, Clearwater, FL — L.M. Weiss.

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CORRECTION

Maintenance Therapy with Certolizumab Pegol for Crohn's Disease

Maintenance Therapy with Certolizumab Pegol for Crohn's Disease . The second sentence of the first paragraph (page 240) should have read "Infliximab and adalimumab are engineered IgG1 monoclonal antibodies that bind to TNF- α (the first represents a chimeric molecule and the latter has been derived from human origin) and are effective in the induction and maintenance of response and remission in patients with Crohn's disease," rather than "Infliximab and adalimumab are IgG1 chimeric monoclonal antibodies that bind to TNF- α and are effective in the induction and maintenance of response and remission in patients with Crohn's disease." Also, the last sentence in the legend for Figure 2 (page 244) should have read "The median score was significantly lower in the certolizumab group than in the placebo group at week 16 (P=0.03), week 20 (P=0.02), week 24 (P=0.008), and week 26 (P<0.001)" rather than "The median score was significantly higher." The text has been corrected on the *Journal's* Web site at www.nejm.org. We regret the errors.