

ORIGINAL ARTICLE

Certolizumab Pegol for the Treatment of Crohn's Disease

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ABSTRACT

BACKGROUND

Certolizumab pegol is a pegylated humanized Fab' fragment that binds tumor necrosis factor α .

METHODS

In a randomized, double-blind, placebo-controlled trial, we evaluated the efficacy of certolizumab pegol in 662 adults with moderate-to-severe Crohn's disease. Patients were stratified according to baseline levels of C-reactive protein (CRP) and were randomly assigned to receive either 400 mg of certolizumab pegol or placebo subcutaneously at weeks 0, 2, and 4 and then every 4 weeks. Primary end points were the induction of a response at week 6 and a response at both weeks 6 and 26.

RESULTS

Among patients with a baseline CRP level of at least 10 mg per liter, 37% of patients in the certolizumab group had a response at week 6, as compared with 26% in the placebo group ($P=0.04$). At both weeks 6 and 26, the corresponding values were 22% and 12%, respectively ($P=0.05$). In the overall population, response rates at week 6 were 35% in the certolizumab group and 27% in the placebo group ($P=0.02$); at both weeks 6 and 26, the response rates were 23% and 16%, respectively ($P=0.02$). At weeks 6 and 26, the rates of remission in the two groups did not differ significantly ($P=0.17$). Serious adverse events were reported in 10% of patients in the certolizumab group and 7% of those in the placebo group; serious infections were reported in 2% and less than 1%, respectively. In the certolizumab group, antibodies to the drug developed in 8% of patients, and antinuclear antibodies developed in 2%.

CONCLUSIONS

In patients with moderate-to-severe Crohn's disease, induction and maintenance therapy with certolizumab pegol was associated with a modest improvement in response rates, as compared with placebo, but with no significant improvement in remission rates. (ClinicalTrials.gov number, NCT00152490.)

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TUMOR NECROSIS FACTOR α (TNF- α) IS IMPORTANT in the pathogenesis of Crohn's disease.¹ Accordingly, infliximab and adalimumab, IgG1 monoclonal antibodies that bind TNF, are effective therapy for patients with active Crohn's disease who have not received anti-TNF- α therapy.^{2,3} Scheduled maintenance therapy is also effective for patients who have a response to induction therapy with these agents.^{4,5} However, the long-term efficacy of such drugs in patients who were not selected for their response to anti-TNF therapy is unknown. Specifically, no TNF antagonist has been evaluated in an induction trial extending beyond 12 weeks in patients with active Crohn's disease.

Certolizumab pegol is a pegylated humanized Fab' fragment of an anti-TNF monoclonal antibody with a high affinity for TNF- α . Certolizumab pegol, unlike other monoclonal antibodies such as infliximab and adalimumab, does not contain an Fc portion and therefore does not induce in vitro complement activation, antibody-dependent cellular cytotoxicity, or apoptosis.^{6,7} A previous study suggested that induction treatment with certolizumab pegol might be effective in patients with moderate-to-severe Crohn's disease.⁸ In patients with an elevated baseline level of C-reactive protein (CRP) of at least 10 mg per liter, a dose of 400 mg of certolizumab pegol every 4 weeks produced response rates that were significantly different from those of placebo from week 4 to 12. Consequently, we designed two additional clinical trials in patients with active Crohn's disease who were stratified according to their baseline CRP level.

Our study, called Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy 1 (PRECISE 1), was a 26-week placebo-controlled trial of induction and maintenance treatment with certolizumab pegol in patients with active Crohn's disease. Elsewhere in this issue of the *Journal*, in another 26-week study, called PRECISE 2, Schreiber et al.⁹ show that maintenance therapy with certolizumab pegol is effective in patients with moderate-to-severe Crohn's disease who had had a response to open-label induction.

METHODS

PATIENTS

This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 171 centers between December 2003 and May 2005. The protocol was approved by the institutional review board at each center. All patients gave written informed consent.

Eligible patients were adults who had had active Crohn's disease for at least 3 months with a Crohn's Disease Activity Index (CDAI) score of 220 to 450.¹⁰ 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 approximately 0 to 600, with a higher score indicating more severe disease activity. Patients could receive concomitant therapy with stable doses of 5-aminosalicylates, prednisolone or its equivalent (at a dose of 30 mg per day or less), azathioprine, 6-mercaptopurine, methotrexate, or antibiotics. Patients with the short-bowel syndrome, an ostomy, obstructive symptoms with strictures, an abscess, a history of tuberculosis, positive results on chest radiography or the purified-protein-derivative tuberculin skin test, demyelinating disease, or cancer were not eligible. Patients who had received any anti-TNF agent within the previous 3 months or who had had a severe hypersensitivity reaction or a lack of response to the first dose of another TNF antagonist were also ineligible.

STUDY DESIGN

Patients were randomly assigned to receive subcutaneous injections of certolizumab pegol at a dose of 400 mg (certolizumab group) or placebo at weeks 0, 2, and 4 and then every 4 weeks. They were followed through week 26. Randomization was performed centrally and was stratified according to the serum level of CRP (≥ 10 or < 10 mg per liter), the use of concurrent glucocorticoids, and the use of concurrent immunosuppressive drugs. Decreas-

es of at least 100 points and 70 points in the CDAI score were calculated, and remission was defined as an absolute CDAI score of 150 or less.^{10,11} Patients provided responses to the Inflammatory Bowel Disease Questionnaire (IBDQ), with scores ranging from 32 to 224, with higher scores indicating a better quality of life. A response was defined as an increase of at least 16 points in the total score, as compared with the score recorded during the first week of the study.¹² Patients with fistulas were evaluated for closure with the use of pre-defined criteria.^{13,14}

Doses of concomitant medications remained constant, except that the dose of glucocorticoids could be reduced at the discretion of the investigator. Treatment was considered to have failed in any patient in whom the glucocorticoid dose was increased above the baseline dose.

A committee of academic investigators and UCB Pharma scientists designed the study. Data were collected and analyzed by ICON Clinical Research. The academic authors vouch for the veracity and completeness of the data and data analyses. Both the academic and industry authors wrote the first and subsequent drafts of the manuscript.

EFFICACY AND SAFETY

At weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, and 26, patients were evaluated in the clinic. Data were collected from diaries kept by patients, adverse events and concomitant medications were recorded, and laboratory tests were performed. Antibodies to certolizumab pegol were assessed with the use of an enzyme-linked immunosorbent assay. An antibody level of more than 2.4 U per milliliter (an increase by a factor of 2 over the value in a reference population)¹⁵ was defined as the lower limit of detection. The health-related quality of life was measured at weeks 0, 6, 16, and 26 with the use of the IBDQ.¹²

STATISTICAL ANALYSIS

Primary end points were a decrease of at least 100 points in the CDAI score at week 6 and at both weeks 6 and 26 in patients with a baseline serum CRP level of at least 10 mg per liter. Secondary end points included remission at week 6 and at both weeks 6 and 26 in patients with a baseline serum CRP level of at least 10 mg per liter and a decrease of at least 100 points in the CDAI score and remission at week 6 and at both weeks 6 and 26 among all patients, regardless of the CRP concentration.

Patients who discontinued either certolizumab pegol or placebo were considered either not to have a response or not to be in remission from the time of discontinuation. 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 had received at least one injection of study drug and had had at least one efficacy evaluation after the first injection.

Baseline characteristics were compared with the use of the chi-square test for categorical variables and analysis of variance for continuous variables. The proportions of patients who had a decrease of at least 100 points in the CDAI score, remission, or IBDQ response in each study group were compared with the use of logistic regression with adjustment for geographic region, use of glucocorticoids, use of immunosuppressive drugs, and the baseline CRP level (overall population only). A closed testing procedure was used to control for multiple comparisons across secondary end points.¹⁶ All comparisons were made with the use of a two-sided significance level of 0.05. Testing of hypotheses was performed for the secondary outcomes only if the primary end point was significant. Safety measures were compared with the use of the chi-square test. All efficacy analyses were performed according to the intention-to-treat principle.

For the primary end point of a decrease of at least 100 points in the CDAI score at both weeks 6 and 26, we estimated that 302 patients were needed to provide a power of 85% to detect a difference of 15% between study groups in response rates in patients with a baseline CRP level of at least 10 mg per liter, assuming a rate of response of 30% in the certolizumab group and 15% in the placebo group. We planned to recruit an equal number of patients with a baseline CRP level of less than 10 mg per liter into a separate stratum, yielding a total sample size of 604 patients.

RESULTS

PATIENTS

Figure 1 shows the assignments of patients to study groups. The baseline characteristics were similar in the two groups. Of patients in the overall population, 185 of 659 (28%) had previously received and discontinued infliximab (Table 1).

EFFICACY*Primary End Points*

Among patients with a baseline CRP level of at least 10 mg per liter, 54 of 145 in the certolizumab group (37%) had a decrease of at least 100 points in the CDAI score at week 6, as compared with 40 of 154 in the placebo group (26%, $P=0.04$). At both weeks 6 and 26, the corresponding values were 31 of 144 (22%) and 19 of 154 (12%), respectively ($P=0.05$).

Secondary End Points and Exploratory Analyses

In the overall population, 115 of 327 patients in the certolizumab group (35%) had a decrease of at least 100 points in the CDAI score at week 6, as compared with 87 of 325 in the placebo group (27%, $P=0.02$). At both weeks 6 and 26, 75 of 325 patients in the certolizumab group (23%) had a response, as compared with 52 of 325 in the placebo group (16%, $P=0.02$). Use of immunosuppressive agents, concomitant glucocorticoid therapy, previous treatment with infliximab, and smoking status were not associated with the magnitude of response either at week 6 or at both weeks 6 and 26 (Table 2). Differences between the certolizumab group and the placebo group were significant by week 2 and remained so at week 26 (Fig. 2A and 2B).

Rates of remission at week 6 and at both weeks 6 and 26 among patients with a baseline CRP level of at least 10 mg per liter and in the overall population did not differ significantly in the two study groups (Table 2). The rate of remission was compared at nine time points, and the difference was significant at weeks 4 and 26 (Fig. 2C).

The median CDAI scores and the mean CRP levels over time are shown in Figures 2D and 2E. Through week 26, 14 of 46 patients in the certolizumab group (30%) had fistula closure, as compared with 19 of 61 patients in the placebo group (31%).

Among all patients, 140 of 331 in the certolizumab group (42%) had an IBDQ response at week 26, as compared with 108 of 328 in the placebo group (33%, $P=0.01$). The mean (\pm SD) increase in IBDQ total scores for all patients from baseline to week 26 was 26.4 ± 35.1 points in the certolizumab group and 20.5 ± 33.1 points in the placebo group ($P=0.03$, by analysis of covariance with the last observation carried forward).

ADVERSE EVENTS

The incidence of adverse events was generally similar in the two study groups (Table 3). Nasopharyn-

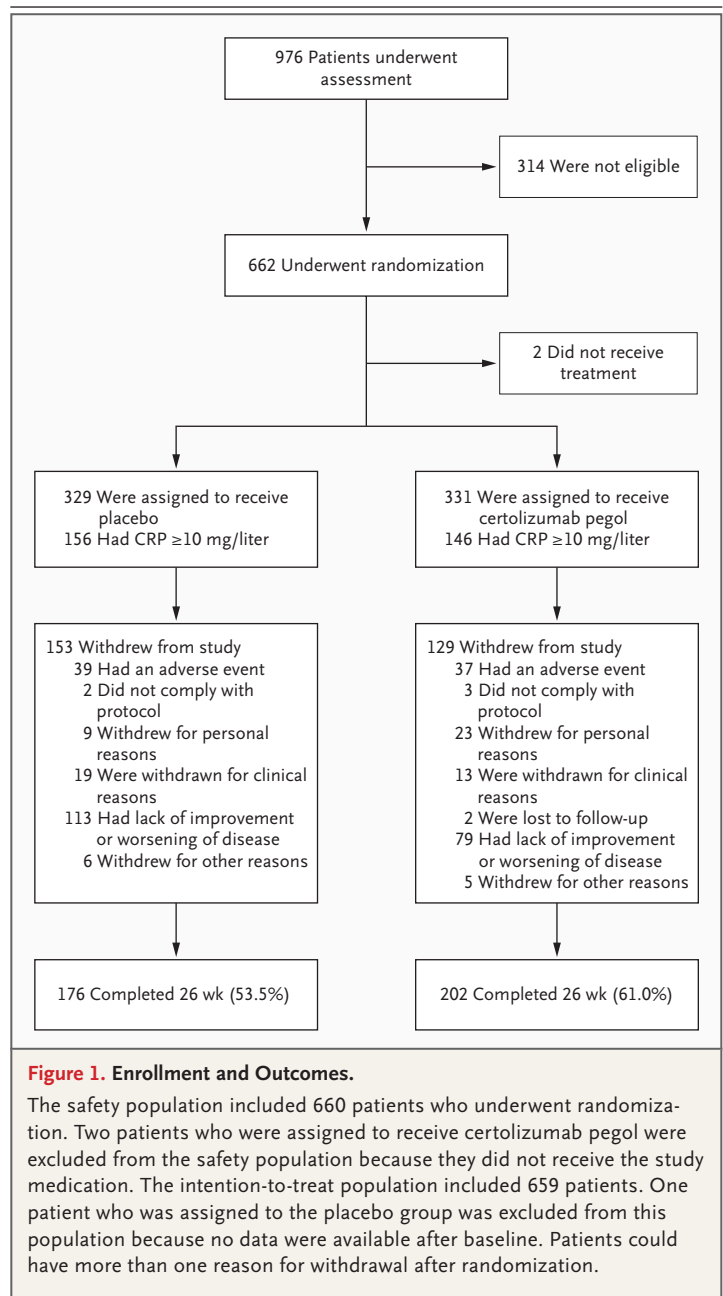


Figure 1. Enrollment and Outcomes.

The safety population included 660 patients who underwent randomization. Two patients who were assigned to receive certolizumab pegol were excluded from the safety population because they did not receive the study medication. The intention-to-treat population included 659 patients. One patient who was assigned to the placebo group was excluded from this population because no data were available after baseline. Patients could have more than one reason for withdrawal after randomization.

gitis occurred in 13% of patients in the certolizumab group and 8% in the placebo group ($P=0.03$). One 22-year-old male patient in the certolizumab group died from an acute myocardial infarction, hypertensive heart disease, and metastatic lung cancer. He had received three doses of certolizumab pegol during a 41-day period and then had discontinued therapy 10 months before his death. He had received 19 infusions of infliximab previously, and at the time of his death he was receiving

Table 1. Characteristics of the Patients in the Intention-to-Treat Population.*

Variable	Placebo Group (N=328)†	Certolizumab Group (N=331)	P Value
Mean age — yr (range)	38±12 (18–77)	37±12 (18–73)	0.26
Male sex — no. (%)	131 (40)	157 (47)	0.52
Mean body-mass index‡	24±5	24±5	0.94
Duration of disease — yr§			0.48
Mean	8	7	
Median	5	5	
Range	<1–40	<1–44	
Current smoker — no. (%)	107 (33)	104 (31)	0.74
CDAI score			
Mean	297±62	300±64	0.59
Range	161–513	149–491	
Geometric mean of CRP — mg/liter (range)	9 (2–244)	8 (2–205)	0.64
Disease site — no. (%)¶			
Terminal ileum	87 (27)	95 (29)	0.53
Colon	74 (23)	87 (26)	0.27
Ileocolon	167 (51)	149 (45)	0.13
Previous infliximab therapy			
Any therapy — no. (%)	85 (26)	100 (30)	0.22
Median infusions — no. (range)	5 (1–22)	4 (1–29)	
Previous hypersensitivity reaction — no. (%)	17 (5)	17 (5)	
Resection performed — no. (%)	113 (34)	118 (36)	0.75
Concurrent treatment at study entry — no. (%)**			
Glucocorticoids only	75 (23)	72 (22)	0.73
Immunosuppressive agents only	66 (20)	69 (21)	0.82
Glucocorticoids combined with immunosuppressive agents	55 (17)	57 (17)	0.88
Neither glucocorticoids nor immunosuppressive agents	132 (40)	133 (40)	0.99

* Plus-minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters.

† Data were not available after baseline for one patient.

‡ Data are for 329 patients in the certolizumab group.

§ Data are for 327 patients in the placebo group.

¶ For patients with disease in the upper gastrointestinal tract, another section also had to be involved. Patients could have more than one disease site.

|| Documentation of a previous loss of response to infliximab was not required for study inclusion.

** Immunosuppressive agents included azathioprine, mercaptopurine, and methotrexate.

methotrexate, azathioprine, and prednisone. No other study patients died.

Cancer developed in four patients: two in the certolizumab group (the above-mentioned 22-year-old man with metastatic lung cancer and a 44-year-old man with adenocarcinoma of the rectum, who received two doses of certolizumab pegol for 20 days in combination with prednisone) and two in the placebo group (a 21-year-old woman with carcinoma in situ of the cervix, who received placebo for 161 days in combination with prednisone,

and a 33-year-old woman with Hodgkin's lymphoma, who received placebo for 117 days in combination with 6-mercaptopurine).

Serious infections occurred in 7 of 331 patients in the certolizumab group (2%) and 3 of 329 in the placebo group (<1%) (Table 3). One or more injection-site reactions occurred in 9 of 331 patients in the certolizumab group (3%) and 47 of 329 patients in the placebo group (14%) (Table 3). No clinically significant changes in laboratory values occurred in either study group. For patients for

Table 2. Summary of Primary and Secondary End Points and Exploratory Analyses in the Intention-to-Treat Population.*

Variable	Placebo Group <i>no./total no. (%)</i>	Certolizumab Group <i>no./total no. (%)</i>	P Value
A decrease of ≥ 100 points in the CDAI score			
With baseline CRP level of ≥ 10 mg/liter			
At week 6	40/154 (26)	54/145 (37)	0.04
At weeks 6 and 26	19/154 (12)	31/144 (22)	0.05
All patients			
At week 6	87/325 (27)	115/327 (35)	0.02
At weeks 6 and 26	52/325 (16)	75/325 (23)	0.02
No immunosuppressive agents at baseline			
At week 6	57/204 (28)	70/202 (35)	0.14
At weeks 6 and 26	33/204 (16)	47/201 (23)	0.08
Immunosuppressive agents at baseline			
At week 6	30/121 (25)	45/125 (36)	0.06
At weeks 6 and 26	19/121 (16)	28/124 (23)	0.20
No glucocorticoids at baseline			
At week 6	49/195 (25)	72/200 (36)	0.02
At weeks 6 and 26	33/195 (17)	46/199 (23)	0.13
Glucocorticoids at baseline			
At week 6	38/130 (29)	43/127 (34)	0.37
At weeks 6 and 26	19/130 (15)	29/126 (23)	0.08
No previous treatment with infliximab			
At week 6	70/240 (29)	91/229 (40)	0.01
At weeks 6 and 26	43/240 (18)	60/228 (26)	0.03
Previous treatment with infliximab			
At week 6	17/85 (20)	24/98 (24)	0.47
At weeks 6 and 26	9/85 (11)	15/97 (15)	0.41
Patients with remission			
With baseline CRP level of ≥ 10 mg/liter			
At week 6	26/154 (17)	32/146 (22)	0.29
At weeks 6 and 26	13/154 (8)	19/145 (13)	0.24
All patients			
At week 6	57/326 (17)	71/329 (22)	0.17
At weeks 6 and 26	32/326 (10)	47/327 (14)	0.07

* Primary end points were a reduction of at least 100 points in the CDAI score at week 6 and at both weeks 6 and 26 in patients with a baseline serum CRP level of at least 10 mg per liter. Secondary end points included remission at week 6 and at both weeks 6 and 26 in patients with a baseline serum CRP level of at least 10 mg per liter and a decrease of at least 100 points in the CDAI score and remission at week 6 and at both weeks 6 and 26 among all patients, regardless of the CRP level. Post hoc exploratory analyses were conducted on the use of immunosuppressive agents, concomitant glucocorticoid therapy, and previous treatment with infliximab.

whom data were available at both the baseline and the final visits, new antinuclear antibodies developed in 5 of 279 patients in the certolizumab group (2%) and in 3 of 277 patients in the placebo group (1%).

ANTIBODIES TO CERTOLIZUMAB PEGOL

Detectable anti-certolizumab antibodies developed in 26 of 331 patients in the certolizumab group (8%). Antibodies developed in 5 of 126 patients who received concomitant immunosuppressive

Figure 2. Efficacy of Certolizumab Pegol, as Compared with Placebo.

As evaluated on the CDAI, percentages of patients with a reduction of at least 70 points (Panel A) or at least 100 points (Panel B) are shown. Also shown are rates of remission over time (Panel C), median CDAI scores (Panel D), and mean levels of CRP (Panel E). The asterisks indicate that values for the certolizumab group and the placebo group have nonoverlapping 95% confidence intervals.

agents (4%) and in 21 of 205 who did not receive such therapy (10%).

DISCUSSION

Treatment with certolizumab pegol was associated with a modest benefit in the rates of response at week 6 and at both weeks 6 and 26, as compared with placebo, but not with a significant improvement in remission. Significant differences in response were observed as early as week 2 after administration of certolizumab pegol, suggesting a rapid onset of action. Subgroup analyses showed a consistent effect in the certolizumab group regardless of the baseline CRP level, use of concomitant immunosuppressive therapy, use of glucocorticoids, or previous treatment with infliximab.

Patients with moderate-to-severe Crohn's disease were recruited for the PRECISE 1 and 2 trials at different sites during the same period with the use of identical inclusion and exclusion criteria. In the PRECISE 1 trial, patients were randomly assigned to receive blinded therapy with subcutaneous injections of either 400 mg of certolizumab pegol or placebo at 0, 2, and 4 weeks and then every 4 weeks. In the PRECISE 2 trial, patients received open-label therapy with 400 mg of certolizumab pegol at weeks 0, 2, and 4, and then patients who had a decrease of at least 100 points in the CDAI score at week 6 were randomly assigned to receive blinded treatment with 400 mg of certolizumab pegol or placebo every 4 weeks.⁹

In the PRECISE 1 trial, the rates of a decrease of at least 100 points in the CDAI score and remission in the certolizumab group at week 6 among all patients were 35% and 22%, respectively; in the PRECISE 2 trial, the values were 64% and 43%, respectively. The reasons for these differences are unclear. A meta-analysis of response rates among patients with Crohn's disease who received placebo showed wide variation among studies.¹⁷ Presum-

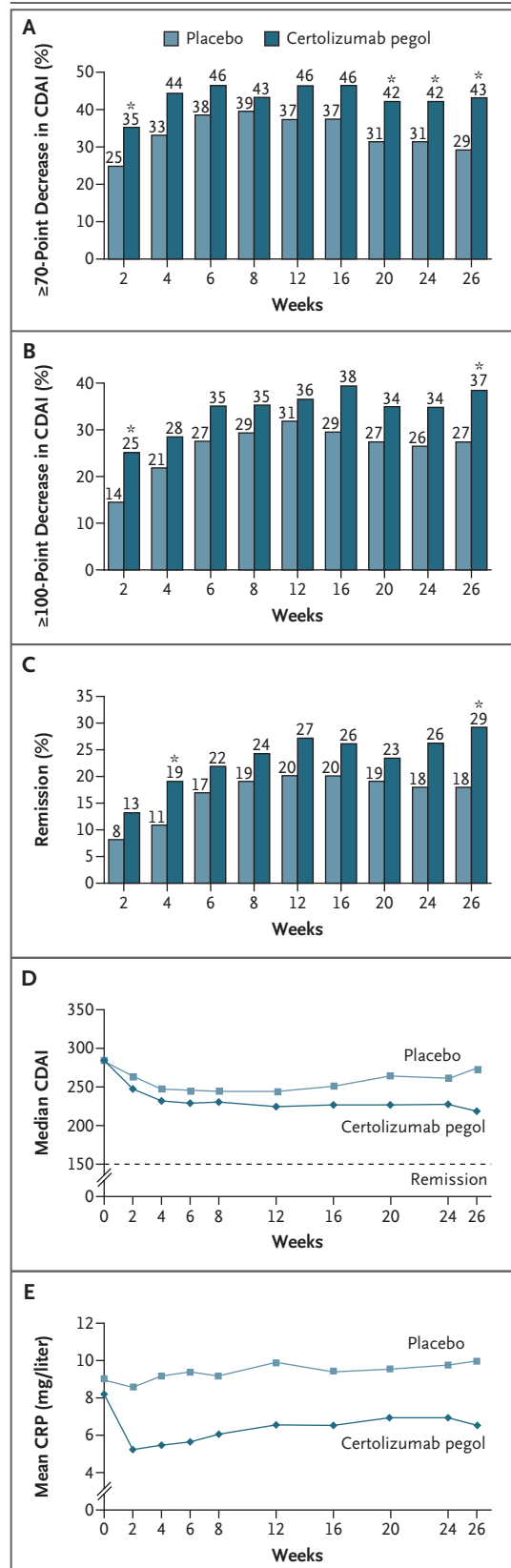


Table 3. Adverse Events in the Safety Population.

Event	Placebo Group (N = 329) <i>no. of patients (%)</i>	Certolizumab Group (N = 331) <i>no. of patients (%)</i>	P Value
Adverse events			
Any event	260 (79)	269 (81)	0.47
Event in ≥5% of group			
Headache	54 (16)	60 (18)	0.56
Nasopharyngitis	27 (8)	44 (13)	0.04
Abdominal pain	37 (11)	37 (11)	0.98
Exacerbation of Crohn's disease	37 (11)	33 (10)	0.59
Nausea	27 (8)	26 (8)	0.87
Urinary tract infection	17 (5)	25 (8)	0.21
Arthralgia	16 (5)	22 (7)	0.32
Pyrexia	22 (7)	21 (6)	0.86
Vomiting	11 (3)	18 (5)	0.19
Back pain	17 (5)	9 (3)	0.11
Injection-site pain	23 (7)	4 (1)	<0.001
Event related to study drug	120 (36)	108 (33)	0.30
Any injection-site reaction*	47 (14)	9 (3)	<0.001
Serious adverse events†	23 (7)‡	34 (10)§	0.13
Infection or infestation	3 (<1)	7 (2)¶	
Abscess			
Perianal	2 (<1)	4 (1)	
Muscle	0	1 (<1)‖	
Limb	0	1 (<1)	
Any	1 (<1)	0	
Gastroenteritis	0	1 (<1)	
Urinary tract infection	0	1 (<1)	
Neoplasm (benign, malignant, or unspecified, including cysts and polyps)	2 (<1)	2 (<1)	
Metastatic lung cancer	0	1 (<1)	
Rectal cancer	0	1 (<1)	
Cervical carcinoma, stage 0	1 (<1)	0	
Hodgkin's disease	1 (<1)	0	
Adverse events leading to withdrawal from study	39 (12)	36 (11)	0.79
Adverse events leading to death	0	1 (<1)**	

* Injection-site reactions included all events that occurred at the injection site and were temporally related to the injection of a study drug.

† Patients could have more than one serious adverse event.

‡ Patients had 30 events.

§ Patients had 49 events.

¶ Patients had 9 events.

‖ Patient had 2 events.

** One death was reported more than 10 months after the patient (a 22-year-old man) had withdrawn from the study. Acute myocardial infarction, hypertensive heart disease, and metastatic lung cancer were recorded on the death certificate. In the opinion of the investigator, none of the conditions were considered to be related to certolizumab pegol.

ably, the fact that patients in the PRECISE 1 trial knew that they would receive 26 weeks of blinded therapy influenced their assessment of some of the more subjective measures of the CDAI score, such as abdominal pain and overall well-being.¹⁰ As reported in the meta-analysis, we observed a gradual rise in the rates of a decrease of at least 100 points in the CDAI score and remission in the placebo group until week 10. One possible explanation for this phenomenon is the effect of the concomitant baseline medications.

In a previous phase 2 study of induction therapy with certolizumab pegol in patients with active Crohn's disease, post hoc analyses showed a greater difference in rates of response and remission between the certolizumab group and the placebo group in patients with a baseline CRP level of at least 10 mg per liter.⁸ In contrast, in the PRECISE 1 and 2 trials, in which patients were prospectively stratified on the basis of whether they had a baseline CRP level of at least 10 mg per liter, there were no apparent significant differences in rates of a decrease of at least 100 points in the CDAI score and remission between patients with an elevated CRP baseline level and the overall population. Thus, our data, taken together with the data from the PRECISE 2 trial, do not indicate that the baseline CRP level is predictive of rates of either a decrease of at least 100 points in the CDAI score or remission or the treatment effect.

The absolute response rates after treatment with certolizumab pegol or placebo in the subgroup of patients who had previously been treated with infliximab were lower than the absolute rates in patients who had never received anti-TNF therapy. Subgroup analyses in other trials of anti-TNF agents and other biologic agents in patients with moderate-to-severe Crohn's disease have shown similar results.^{5,9,18,19}

The results of placebo-controlled induction therapy for 26 weeks with certolizumab pegol cannot be compared with results obtained with other TNF antagonists — infliximab and adalimumab — in induction trials with a duration of 4 weeks.^{2,3,19} Three TNF antagonists — infliximab, adalimumab, and certolizumab pegol — have been shown to be effective maintenance therapies in patients who have previously responded to open-label induction therapy with a TNF antagonist.^{4,5,9} In the PRECISE 1 trial, the remission rate at week 26 was 29% without preselection for a response to open-label induction, as seen in several maintenance trials, including A Crohn's Disease Clinical Trial

Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT),⁴ Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM),⁵ and the PRECISE 2 trial.⁹ A direct comparison of the results of these similarly designed trials is not appropriate. Randomized, double-blind, controlled trials comparing certolizumab pegol with other TNF antagonists are required to determine the efficacy of certolizumab pegol, as compared with other agents.

The rate of serious adverse events was 10% in patients treated with certolizumab pegol and 7% in patients treated with placebo. The development of serious fungal, bacterial, or viral infections is an important problem common to all TNF antagonists. Serious infection occurred in 2% of patients who received certolizumab pegol. Cancer developed in two patients in each study group. The rate of injection-site reaction with certolizumab pegol was low.

Anti-certolizumab pegol antibodies developed in 8% of the patients who received certolizumab pegol. These results are similar to those reported previously for patients with Crohn's disease.^{8,9} Although we observed a lower incidence of antibody formation in patients who received concomitant treatment with immunosuppressive agents, the relative therapeutic index of combination therapy in comparison to that of certolizumab pegol monotherapy is unknown.

In conclusion, certolizumab pegol was associated with a modest improvement in response but no improvement in remission rate, as compared with placebo, in patients with moderate-to-severe Crohn's disease.

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APPENDIX

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