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Certolizumab Pegol Plus Methotrexate Is Significantly More Effective Than Placebo Plus Methotrexate in Active Rheumatoid Arthritis

Findings of a Fifty-Two–Week, Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

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Objective. **To evaluate the efficacy and safety of 2 dosage regimens of lyophilized certolizumab pegol (a novel PEGylated anti–tumor necrosis factor agent) as adjunctive therapy to methotrexate (MTX) in patients with active rheumatoid arthritis (RA) with an inadequate response to MTX therapy alone.**

Methods. **In this 52-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, 982 patients were randomized 2:2:1 to receive treatment with subcutaneous certolizumab pegol at an initial dosage of 400 mg given at weeks 0, 2, and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus MTX, or placebo plus MTX. Co-primary end points were the response rate at week 24 according to the American College of Rheumatology 20% criteria for improvement (ACR20) and the mean change from baseline in the modified total Sharp score at week 52.**

Results. **At week 24, ACR20 response rates using**

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nonresponder imputation for the certolizumab pegol 200-mg and 400-mg groups were 58.8% and 60.8%, respectively, as compared with 13.6% for the placebo group. Differences in ACR20 response rates versus placebo were significant at week 1 and were sustained to week 52 ($P < 0.001$). At week 52, mean radiographic progression from baseline was reduced in patients treated with certolizumab pegol 200 mg (0.4 Sharp units) or 400 mg (0.2 Sharp units) as compared with that in placebo-treated patients (2.8 Sharp units) ($P < 0.001$ by rank analysis). Improvements in all ACR core set of disease activity measures, including physical function, were observed by week 1 with both certolizumab pegol dosage regimens. Most adverse events were mild or moderate.

Conclusion. **Treatment with certolizumab pegol 200 or 400 mg plus MTX resulted in a rapid and sustained reduction in RA signs and symptoms, inhibited the progression of structural joint damage, and improved physical function as compared with placebo plus MTX treatment in RA patients with an incomplete response to MTX.**

The introduction of the tumor necrosis factor (TNF) inhibitors constituted a major advance in the treatment of rheumatoid arthritis (RA). Treatment with the 3 currently available TNF inhibitors in combination with methotrexate (MTX) can significantly improve the signs and symptoms of disease (1–3), decrease the progression of joint damage (3–5), and improve physical function and health-related quality of life (3,5). Although these agents have shown similar efficacy in clinical trials, they have different modes of action and exhibit individual pharmacokinetics, safety, and efficacy profiles (1–5), and patient responses to them in clinical practice may be variable (6). Some patients may respond to one anti-TNF but not to another, while others may discontinue therapy because of poor tolerability or loss of efficacy over time (6,7).

Certolizumab pegol is a novel TNF inhibitor, consisting of a humanized Fab′ fragment fused to a 40-kd polyethylene glycol (PEG) moiety. This unique structure may avoid potential Fc-mediated effects seen in vitro, such as complement-dependent or antibody-dependent cell-mediated cytotoxicity or apoptosis (8). PEGylation increases the half-life of certolizumab pegol to ~14 days and may contribute to its preferential distribution to inflamed tissues (as observed in animal models) (9). Intravenous monotherapy with certolizumab pegol was shown to effectively control the signs and symptoms of RA in a phase II trial (10). Phase III clinical trials were subsequently designed to evaluate the efficacy of subcutaneous certolizumab pegol monotherapy and to evaluate the efficacy of 2 different certolizumab pegol formulations (liquid and lyophilized) as add-on therapy to MTX.

We present here the results of the RA Prevention of Structural Damage 1 (RAPID 1) trial, which evaluated the efficacy and safety of 2 dosage regimens of subcutaneous lyophilized certolizumab pegol as add-on therapy to MTX in patients with active RA despite treatment with MTX alone.

PATIENTS AND METHODS

Patients. Eligible patients were ≥18 years of age and had a diagnosis of RA, as defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria (11) for ≥6 months prior to screening but for <15 years. Active disease was defined as ≥9 tender and 9 swollen joints at screening and at baseline, with either an erythrocyte sedimentation rate (ESR; Westergren) ≥30 mm/hour or a C-reactive protein (CRP) level >15 mg/liter. Patients were required to have received MTX for ≥6 months, with a stable dosage of ≥10 mg/week for ≥2 months prior to baseline.

Exclusion criteria consisted of diagnoses of any other inflammatory arthritis or a secondary noninflammatory arthritis that could have interfered with our evaluation of the effects of certolizumab pegol on RA. Patients with a history of tuberculosis or a chest radiograph showing active or latent tuberculosis were also excluded. Patients with positive findings on a purified protein derivative (PPD) skin test were excluded, unless the PPD positivity was associated with previous vaccination with BCG (PPD positive by local standard). If there was no clinical or radiographic suspicion of tuberculosis in these latter patients, they were enrolled at the discretion of the investigator. Patients who, in the investigator's opinion, were at a high risk of infection were excluded, as were patients who had a history of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease. Patients who had received any biologic therapy within 6 months (or had received etanercept and/or anakinra within 3 months) of baseline and/or any previous biologic therapy that resulted in a severe hypersensitivity or anaphylactic reaction were excluded, as were patients who had previously failed to respond to treatment with an anti-TNF agent.

Protocol. The RAPID 1 trial was a 52-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult patients with active RA despite treatment with MTX. The study was conducted at 147 centers worldwide between February 2005 and October 2006. The Institutional Review Board or Ethics Committee at each participating center approved the study protocol. All patients gave their written consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Eligible patients were randomized 2:2:1 to receive treatment with 1 of 2 regimens of lyophilized certolizumab

pegol (400 mg at weeks 0, 2, and 4, followed by 200 mg or 400 mg every 2 weeks thereafter, administered subcutaneously as a reconstituted, preservative-free injection) plus MTX or with a regimen of placebo (saline) plus MTX. All patients had to continue MTX at the same dosage they were taking at study entry.

In consideration of the disease severity in these study patients, those who failed to achieve a response according to the ACR criteria for 20% improvement (ACR20) (12) at weeks 12 and 14 were designated treatment failures and were withdrawn from the study at week 16. Patients who withdrew at week 16 or who successfully completed the trial were offered enrollment in an open-label extension study of certolizumab pegol 400 mg every 2 weeks. Patients who withdrew early for reasons other than withdrawal of consent underwent mandatory radiographic assessment at the time of withdrawal and at week 52.

Concomitant treatment with oral corticosteroids ($\leq$10 mg/day of prednisone or equivalent, with a stable dosage for 4 weeks prior to baseline and continuing throughout the study), nonsteroidal antiinflammatory drugs/cyclooxygenase 2 inhibitors, and analgesics were allowed. Parenteral corticosteroids were not permitted. Disease-modifying antirheumatic drugs (DMARDs; exclusive of MTX) had to be discontinued 28 days prior to baseline, except for leflunomide, which had to be discontinued 6 months prior to baseline unless a cholestyramine washout was performed.

Efficacy and safety evaluations. Efficacy and safety assessments were performed at weeks 1 and 2, then every 2 weeks until week 16, and then every 4 weeks thereafter until week 52 or at the time of withdrawal. Radiographs of the hands (anteroposterior) and feet (posteroanterior) were obtained at baseline, week 24 or early withdrawal, and week 52. Radiographs were read at a central location by 3 independent readers, such that radiographs from every patient were scored by 2 readers; each reader reviewed two-thirds of the radiographs, and radiographs were read in equal pairs between the readers. Readers were blinded as to the patient's identity, clinical data, treatment, and time point (sequence) at which the radiograph was taken. The modified total Sharp score (13), erosion score, and joint space narrowing score of the 2 radiograph readings per patient were used. Interobserver and intraobserver reliability were assessed before and during the treatment phase of the study.

Co-primary end points were the ACR20 response rate at week 24 and the mean change from baseline in the modified total Sharp score at week 52. Major secondary end points included the change from baseline in modified total Sharp score at week 24, the change from baseline in the disability Index (DI) of the Health Assessment Questionnaire (HAQ) (14) at weeks 24 and 52, the ACR20 responder rate at week 52, and the ACR50 and ACR70 responder rates at weeks 24 and 52.

Additional secondary end points included mean changes from baseline in the following features: erosion and joint space narrowing scores, swollen (n = 66 joints) and tender (n = 68 joints) joint counts, physician's and patient's global assessments of disease activity, patient's assessment of arthritis pain, physical function (according to the HAQ DI), the Disease Activity Score 28-joint assessment (DAS28) (15), the ESR, and the CRP level. The proportion of patients achieving clinically meaningful improvements in physical function was indicated by the minimum clinically important difference (MCID), which was defined as a decrease in the HAQ DI of $\geq$0.22 points from baseline (16).

Safety assessments included measurement of vital signs, physical examination, hematologic analysis, serum biochemical analysis, and urinalysis. Systolic and diastolic blood pressure was measured at each visit, before and after injection of the study drug. Adverse events were monitored at every visit. Treatment-emergent adverse events were defined as adverse events occurring after the first administration of study drug and up to 12 weeks after the last dose was administered. These were classified according to the Medical Dictionary for Regulatory Activities (version 9.0), by primary system organ class and preferred term. Concomitant medications were monitored at each visit according to protocol requirements. Plasma concentrations of anti–certolizumab pegol antibodies were measured by an enzyme-linked immunosorbent assay; levels $>$2.4 units/ml were considered positive.

Statistical analysis. Sample size was determined on the basis of anticipated differences between the certolizumab pegol groups and placebo for both of the primary efficacy end points. For the ACR20 response, a sample size of 590 patients was required in order to have 90% power to detect a statistical difference of $\geq$20% between the certolizumab pegol groups and placebo with a 2-sided significance level of 2.5%. For the modified total Sharp score, a sample size of 950 patients was determined to be sufficient to detect differences of $\geq$2.2 Sharp units between an active drug group and a control group with $\geq$90% power (assuming an SD of 7 Sharp units). The sample size was based on the larger estimate to control for Type II error.

Efficacy analyses were conducted on an intent-to-treat (ITT) population, which consisted of all patients who were randomized into the study. Primary analyses were performed using nonresponder imputation. Patients who received rescue medication or who withdrew for any reason, including safety, were considered nonresponders from that time point onward. Hypothesis testing for the co-primary end points was performed in a hierarchical manner. First, comparisons of the ACR20 responses at week 24 between the placebo group and each of the 2 certolizumab pegol dosage groups were performed using logistic regression, with treatment and geographic region as factors. The treatment effect was estimated using odds ratios and corresponding 97.5% confidence intervals obtained by fitting this model. Rejection of the null hypothesis for the ACR20 response enabled comparison of each active treatment with placebo in terms of the change from baseline in the modified total Sharp score at week 52. This latter analysis was performed using analysis of covariance (ANCOVA) on the ranks, with treatment and geographic region as factors and with the ranked baseline modified total Sharp score as the covariate.

For patients who withdrew early (before week 52) and who had radiographs taken at their withdrawal visit, the modified total Sharp score at week 52 was estimated by linear extrapolation of the scores on the radiographs taken at the early withdrawal visit or, if this was not performed, at week 24. Multiple sensitivity analyses were performed on the radiographic data under various assumptions on the imputation of missing values, including an analysis of the per-protocol pop-

Table 1. Baseline characteristics of the intent-to-treat population of 982 patients with active rheumatoid arthritis despite treatment with MTX*

	Placebo plus MTX (n = 199)	CZP 200 mg plus MTX (n = 393)	CZP 400 mg plus MTX (n = 390)
Patient demographics and characteristics			
Age, mean ± SD years	52.2 ± 11.2	51.4 ± 11.6	52.4 ± 11.7
Sex, % female	83.9	82.4	83.6
Duration of disease, mean ± SD years	6.2 ± 4.4	6.1 ± 4.2	6.2 ± 4.4
No. of previous DMARDs (except MTX), mean ± SD	1.4 ± 1.4	1.3 ± 1.3	1.3 ± 1.3
MTX dosage, mean ± SD mg/week	13.4 ± 4.2	13.6 ± 4.3	13.6 ± 4.0
% RF positive (≥14 IU/ml)	82.8	79.6	83.6
Disease activity status			
No. of tender/painful joints, mean ± SD	29.8 ± 13.0	30.8 ± 12.4	31.1 ± 13.3
No. of swollen joints, mean ± SD	21.2 ± 9.7	21.7 ± 9.9	21.5 ± 9.8
HAQ DI, mean ± SD	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6
DAS28 using the ESR, median (minimum, maximum)	7.0 (4.9, 8.7)	6.9 (4.3, 8.9)	6.9 (4.8, 9.1)
CRP, median (minimum, maximum) mg/liter	16.0 (2.0, 162)	16.0 (1.0, 234)	14.0 (2.0, 273)
ESR, median (minimum, maximum) mm/hour	45.0 (14.0, 138)	43.5 (5.0, 138)	42.5 (3.0, 141)

* MTX = methotrexate; CZP = certolizumab pegol; DMARDs = disease-modifying antirheumatic drugs; RF = rheumatoid factor; HAQ = Health Assessment Questionnaire; DI = disability index; DAS28 = Disease Activity Score 28-joint assessment; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein (normal 0–6 mg/liter).

ulation, which consisted of a subset of the ITT population, excluding patients who had at least 1 major protocol deviation, as confirmed during a preanalysis review prior to unblinding of the data. Sensitivity analyses were also performed using the last observation carried forward (LOCF) method for imputation of missing scores.

Comparison of active treatment versus placebo for the major secondary end points was tested at the 5% level of significance. Analysis of the ACR20, ACR50, and ACR70 responder rates was performed using logistic regression, with treatment and geographic region as factors. Analysis of secondary continuous efficacy end points was performed using ANCOVA, with geographic region and treatment as factors and baseline values as the covariate. Analysis of the responders according to the MCID for the HAQ DI values was post hoc and was analyzed using a repeated-measures logistic regression.

Safety analyses were conducted on the safety population, which consisted of all patients who received at least 1 dose of medication. Adverse events are presented as either the number of events or the incidence rate per 100 patient-years to adjust for differences between certolizumab pegol and placebo exposure.

RESULTS

Patient characteristics. Overall, 982 patients were randomized into the study. A total of 255 of the 393 patients (64.9%) randomized to receive 200 mg of certolizumab pegol plus MTX and 274 of the 390 patients (70.3%) randomized to receive 400 mg of certolizumab pegol plus MTX completed 52 weeks of treatment, as compared with 43 of the 199 patients (21.6%) randomized to receive placebo plus MTX. At week 16 of the study, 62.8% of the placebo-treated patients withdrew because of lack of efficacy, as compared with 21.1% and 17.4% of patients in the groups receiving certolizumab pegol 200 mg and 400 mg, respectively. One patient in each group was lost to followup. The baseline demographic features and disease activity status of the study patients were similar among the 3 treatment groups (Table 1).

Treatment efficacy. Treatment with certolizumab pegol plus MTX significantly reduced the signs and symptoms of RA as compared with placebo plus MTX. At week 24, ACR20 response rates for the groups taking 200 mg and 400 mg of certolizumab pegol plus MTX were 58.8% and 60.8%, respectively, compared with 13.6% for the placebo plus MTX group (Figure 1A). These differences in ACR20 responses were statistically significant ($P < 0.001$ for each comparison) and remained significant through week 52 ($P < 0.001$ for each comparison) (Figure 1B). The proportions of patients taking the 2 certolizumab pegol dosages who achieved an ACR20 response were not significantly different at any time point examined. ACR50 and ACR70 responses with certolizumab pegol plus MTX treatment were also superior to placebo plus MTX ($P < 0.001$).

The onset of action of certolizumab pegol was rapid and was evident after the first injection. At week 1, significantly more patients in the certolizumab pegol 200-mg and 400-mg groups achieved an ACR20 response than did those in the placebo group ($P < 0.001$); responder rates were 22.9% and 22.3% versus 5.6%, respectively. The ACR20 response rate peaked at week 12 and was sustained to week 52 (Figure 1B). By week 2,

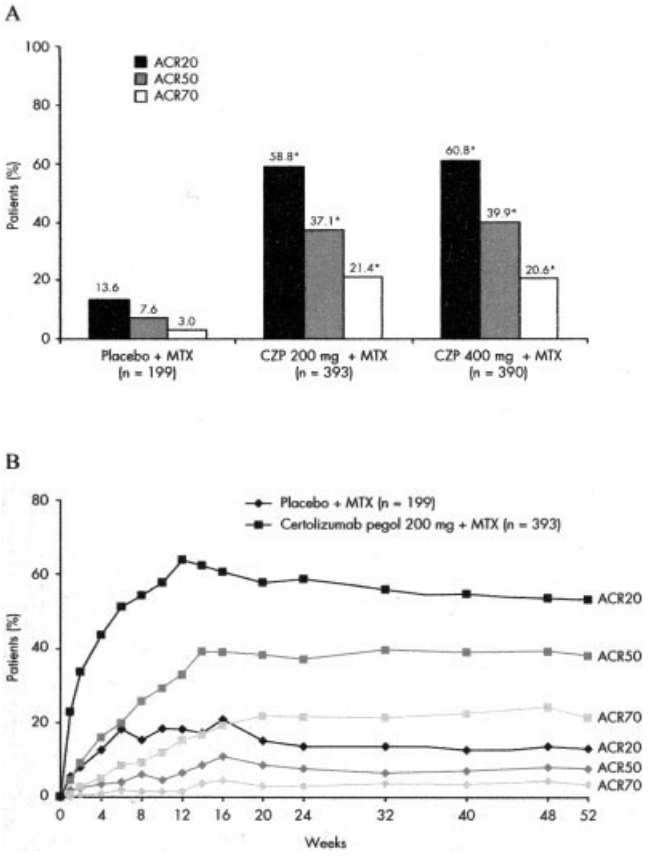

Figure 1. Efficacy of certolizumab pegol (CZP) 200 mg or 400 mg plus methotrexate (MTX) versus placebo plus MTX in the treatment of patients with active rheumatoid arthritis (RA) despite MTX therapy, as determined by the American College of Rheumatology criteria for 20% improvement (ACR20), in the intent-to-treat population of 982 patients. **A,** Percentages of patients who achieved a response according to the ACR20 criteria, as well as the ACR criteria for 50% improvement (ACR50) and the ACR criteria for 70% improvement (ACR70) at week 24. Values at the top of the bars are the actual percentages represented by the bars. $* = P < 0.001$ versus placebo. **B,** Percentages of patients treated with certolizumab pegol 200 mg plus MTX versus placebo plus MTX who achieved an ACR20, ACR50, or ACR70 response over time. Responses to this dosage of certolizumab pegol were statistically significant compared with placebo (for the ACR20 response, $P < 0.001$ at weeks 1–52; for the ACR50 response, $P < 0.01$ at week 2 and $P < 0.001$ at weeks 4–52; and for the ACR70 response, $P \leq 0.05$ at week 4, $P \leq 0.01$ at weeks 6 and 8, and $P < 0.001$ at weeks 10–52).

the ACR50 responses in the certolizumab pegol groups (200 and 400 mg) were significantly higher than that in the placebo group ($P \leq 0.01$ for each comparison). ACR70 responses were significantly higher by week 4 in the certolizumab pegol 200-mg group ($P \leq 0.05$ versus placebo) and by week 6 in the certolizumab pegol 400-mg group ($P \leq 0.05$ versus placebo). Maximum ACR50 and ACR70 response rates in the group taking 200 mg of certolizumab pegol were achieved by weeks 14–20 of treatment (Figure 1B).

Significant improvement in each component of the ACR core set of disease activity measures was evident at week 1 with certolizumab pegol therapy. These improvements continued rapidly over the first 4–12 weeks of treatment (Table 2) and remained significant relative to placebo at weeks 24 and 52 (data not shown). Treatment with certolizumab pegol plus MTX was also associated with greater improvement in the DAS28-ESR at week 52, with a mean ± SD change from baseline of -3.3 ± 1.3 in the 200-mg group and -3.4 ± 1.4 in the 400-mg group, as compared with -2.4 ± 1.3 in the placebo group. The improvement with certolizumab pegol compared with placebo was statistically significant at all time points examined ($P < 0.001$).

Findings of radiographic evaluations. Certolizumab pegol plus MTX therapy inhibited the progression of structural damage to a significantly greater extent than did placebo plus MTX therapy. At week 52, the mean change from baseline in the modified total Sharp score was smaller in patients treated with certolizumab pegol 200 mg (0.4 Sharp units) or 400 mg (0.2 Sharp units) than in placebo-treated patients (2.8 Sharp units) ($P < 0.001$ by rank analysis) (Figure 2A). Significant differences between the certolizumab pegol and placebo groups were also observed at 24 weeks ($P < 0.001$) (Figure 2A). Results from the primary analysis were confirmed by multiple sensitivity analyses. Using linear extrapolation in the per-protocol population, changes from baseline in the modified total Sharp score were 0.4 and 0.3 Sharp units, respectively, in the groups taking 200 mg and 400 mg of certolizumab pegol and 2.7 Sharp units in the group taking placebo ($P < 0.001$ by rank analysis). Results from the LOCF analysis in the ITT population, which reflect data from 60% of the placebo-treated patients at week 16 as compared with 60–70% of the certolizumab pegol–treated patients at week 52, also showed a significant improvement ($P < 0.001$) (Figure 2D). Similar improvements in the modified total Sharp score scores were observed with analyses of the observed data and the log-transformed data (data not shown). In addition, for patients who withdrew at week 16, there was significantly less radiographic progression in those treated with either of the certolizumab pegol dosages (combined data) at week 16 as compared with those treated with placebo (Figure 2D). In a post hoc analysis, linear extrapolation of these data suggested that a significant treatment difference would also have been observed at week 52.

Table 2. Percentage change from baseline or ratio to baseline values for each component of the ACR core set of disease activity measures assessed at weeks 1, 4, and 12 in the intent-to-treat population of 982 patients with active rheumatoid arthritis despite treatment with MTX*

	Week 1			Week 4			Week 12		
	Placebo (n = 199)	CZP 200 mg (n = 393)†	CZP 400 mg (n = 390)†	Placebo (n = 199)	CZP 200 mg (n = 393)†	CZP 400 mg (n = 390)†	Placebo (n = 199)	CZP 200 mg (n = 393)†	CZP 400 mg (n = 390)†
% change from baseline, mean									
Swollen joint count	−4.5	−18.2	−18.8	−10.3	−37.3	−40.4	−10.7	−56.7	−61.5
Tender joint count	−6.7	−18.9	−19.1	−11.4	−36.2	−37.0	−10.8	−52.6	−56.8
Physician's global assessment	−3.3	−19.0	−18.8	−9.4	−35.2	−33.6	−11.8	−49.7	−47.9
Patient's global assessment	−2.9	−12.9	−16.1	−6.5	−10.4	−27.9	−4.9	−38.3	−39.2
Patient's assessment of arthritis pain	−1.0	−20.6	−19.0	−5.0	−26.6	−28.8	−4.8	−38.2	−39.6
HAQ DI	−2.4	−13.5	−10.9	−5.4	−21.5	−21.9	−8.2	−30.4	−27.6
Ratio to baseline values of acute-phase reactants, geometric mean (CV)									
ESR	0.96	0.73	0.70	0.90	0.59	0.54	0.84	0.53	0.52
CRP	1.01	0.35	0.34	0.97	0.44	0.41	0.87	0.45	0.43

* Analyses were performed using the last observation carried forward method for imputation of missing scores. The percentage change from baseline was calculated as follows: % change from baseline = (initial visit − baseline visit)/baseline visit × 10. ACR = American College of Rheumatology; MTX = methotrexate; CZP = certolizumab pegol; HAQ = Health Assessment Questionnaire; DI = disability index; CV = coefficient of variation. † $P < 0.001$ for change from baseline versus placebo, as determined by analysis of covariance (ANCOVA), with geographic region and treatment as factors and with baseline values as the covariate, except for the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level, which were determined by ANCOVA using log-transformed data, with geographic region and treatment as factors and log-transformed baseline values as the covariate.

Rank analysis also demonstrated significantly greater inhibition of the progression of erosions ($P < 0.001$) and joint space narrowing ($P \leq 0.01$) in patients treated with certolizumab pegol plus MTX as compared with placebo plus MTX at weeks 24 and 52 (Figures 2B and C). No difference between the groups receiving 200 mg and 400 mg of certolizumab pegol was observed with regard to inhibition of the progression of erosions and joint space narrowing. Post hoc analysis revealed that 69.0% and 71.6% of patients taking 200 mg and 400 mg of certolizumab pegol, respectively, exhibited no radiographic progression (defined as ≤0-unit increase in the modified total Sharp score) as compared with 51.9% of patients taking placebo ($P \leq 0.05$).

Changes in physical function. Patients in both of the certolizumab pegol dosage groups experienced significant improvement in physical function as compared with patients in the placebo group ($P < 0.001$) (Figure 3). These improvements were evident at week 1 and were sustained to week 52. Significantly more certolizumab pegol–treated patients also experienced clinically meaningful improvements in physical function as compared with placebo-treated patients, as indicated by the MCID in the HAQ DI values from week 1 through study end ($P < 0.001$) (data not shown).

Treatment safety. Since the mean exposure to study treatment was markedly longer in the 2 certolizumab pegol groups than in the placebo group, adverse events were analyzed as the number of patients experiencing the event per 100 patient-years or as the incidence rate per 100 patient-years (Table 3). The overall rates of treatment-emergent adverse events were 125.9 per 100 patient-years in the placebo group and 96.6 per 100 patient-years and 94.6 per 100 patient-years in the certolizumab pegol 200-mg and 400-mg dosage groups, respectively. Most adverse events were mild or moderate in intensity. An analysis of adverse events leading to withdrawal versus time revealed a similar pattern of withdrawals for the placebo and active treatment arms. More withdrawals happened in the first quartile as compared with later quartiles; however, it should be noted that at each quartile, the number of patients in the study had decreased. The rates of adverse events that led to withdrawal were 3.3, 5.6, and 7.0 per 100 patient-years in patients treated with placebo, certolizumab pegol 200 mg, and certolizumab pegol 400 mg, respectively.

Infections led to discontinuation of the study drug in 6 patients in each certolizumab pegol dosage group and in 0 patients in the placebo group. Other reasons for early withdrawal were protocol noncompliance (7 patients overall) and the patient's decision (10–15 patients in each group).

All adverse events leading to death (8 overall) were considered unlikely to be related, or were unre-

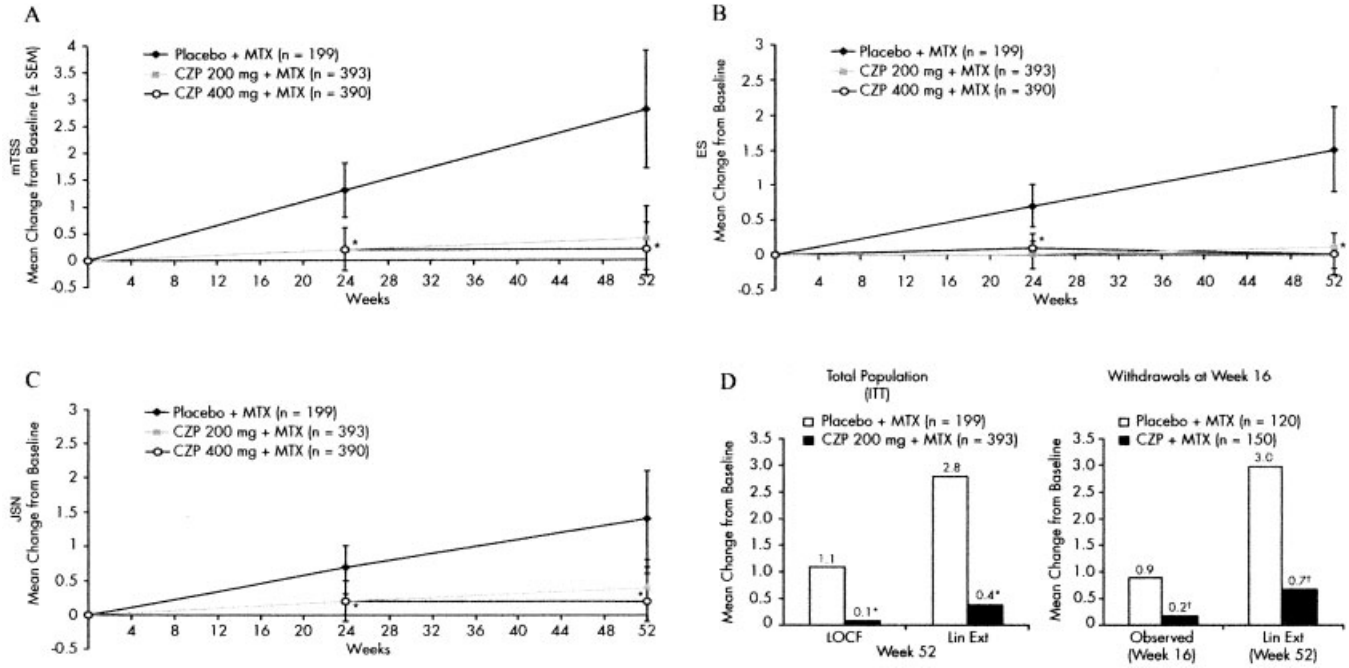

Figure 2. Efficacy of certolizumab pegol (CZP) 200 mg or 400 mg plus methotrexate (MTX) versus placebo plus MTX in the treatment of patients with active rheumatoid arthritis (RA) despite MTX therapy, as determined by radiographic evidence of response, in the intent-to-treat (ITT) population of 982 patients. **A,** Change from baseline in the modified total Sharp score (mTSS) at weeks 24 and 52. $* = P < 0.001$ for both dosages of active drug versus placebo. **B,** Change from baseline in erosion scores (ES) at weeks 24 and 52. $* = P < 0.001$ for both dosages of active drug versus placebo. **C,** Change from baseline in joint space narrowing (JSN) scores at weeks 24 and 52. $* = P \leq 0.05$ for both dosages of active drug versus placebo. Values in **A–C** are the mean ± 95% confidence interval. **D,** Change from baseline in the modified total Sharp score in the total ITT population of patients taking 200 mg of certolizumab pegol and placebo at week 52 (left) and in the population of patients taking active drug (both dosages) and placebo who withdrew at week 16 (right). Analyses were performed using the last observation carried forward (LOCF) method for imputation of missing scores in the total ITT population and the actual scores (observed) in those who withdrew at week 16. In addition, post hoc analyses using linear extrapolation (Lin Ext) of these data to week 52 were performed. Values at the top of the bars are the actual percentages represented by the bars. $* = P < 0.001$; $\dagger = P < 0.05$ for both dosages of active drug versus placebo.

lated, to administration of the study drug. Seven patients died during treatment. One patient taking placebo plus MTX died of a myocardial infarction (after 7 injections of study drug). Two deaths occurred in the group taking 200 mg of certolizumab pegol plus MTX: one patient died of a hepatic neoplasm (after 2 injections of study drug), and the other patient died of cardiac arrest (after 9 injections). One other patient in this dosage group died of peritonitis, cirrhosis, and general deterioration of physical health during the posttreatment period (>84 days after the last injection). Four deaths occurred in the group taking 400 mg of certolizumab pegol plus MTX: 1 patient each died of cerebral stroke (after 2 injections of study drug), myocardial necrosis (after 8 injections), cardiac arrest (after 2 injections), and atrial fibrillation and fatigue (after 19 injections).

The most frequent noninfectious adverse events were headache, hypertension, and back pain. Of these, headache occurred more frequently in patients treated

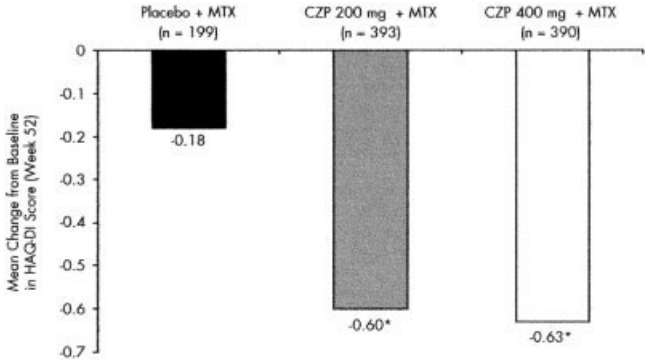

Figure 3. Efficacy of certolizumab pegol (CZP) 200 mg or 400 mg plus methotrexate (MTX) versus placebo plus MTX in the treatment of patients with active rheumatoid arthritis (RA) despite MTX therapy, as determined by the Health Assessment Questionnaire (HAQ) disability index (DI), in the intent-to-treat population of 982 patients. The mean change from baseline in the HAQ DI score at week 52 is shown for each treatment group. Values at the bottom of the bars are the actual values represented by the bars. $* = P < 0.001$ for both dosages of active drug versus placebo.

Table 3. Treatment-emergent adverse events in the safety population*

	Placebo plus MTX (n = 199)	CZP 200 mg plus MTX (n = 392)	CZP 400 mg plus MTX (n = 389)
Exposure, no. of patient-years	91.4	303.3	315.2
Treatment-emergent adverse events			
Any treatment-emergent adverse event	125.9	96.6	94.5
Intensity			
Mild	98.5	80.4	80.6
Moderate	72.2	57.4	56.2
Severe	14.2	10.5	12.1
Related to study drug	54.7	55.1	52.7
Serious adverse events	12.0 (11)	14.8 (45)	15.2 (48)
Adverse events leading to death	1.1 (1)	0.7 (2)	1.3 (3)
Adverse events leading to withdrawal	3.3 (3)	5.6 (17)	7.0 (22)
Most frequent noninfectious adverse events			
Headache	12.0	7.3	5.7
Hypertension	2.2	8.2	10.2
Back pain	2.2	5.6	6.4
Malignancy	1.1	2.3	1.3
Most frequent infectious adverse events			
Infections and infestations	56.9	56.4	58.4
Urinary tract infection	14.2	7.6	10.5
Nasopharyngitis	3.3	6.9	9.5
Upper respiratory tract infection	5.5	7.9	6.7
Most frequent serious infectious adverse events			
Serious infections and infestations	2.2	5.3	7.3
Lower respiratory tract/lung infection	0	1.0	1.3
Gastroenteritis	1.1	0	0
Urinary tract infection	0	0.7	1.0
Tuberculosis infection	0	0.7	1.0
Upper respiratory tract infection	0	0.3	0.6
Herpes viral infection	0	0.3	0.3
Bacterial peritonitis	0	0.3	0
Opportunistic infection	0	0	0

* Treatment-emergent adverse events, defined as adverse events occurring after the first administration of study drug and up to 12 weeks after administration of the last dose, were classified according to the Medical Dictionary for Regulatory Activities (version 9.0), by system organ class and preferred term. Values are the incidence rate per 100 patient-years; numbers in parentheses are the number of cases. MTX = methotrexate; CZP = certolizumab pegol.

with placebo plus MTX, whereas hypertension was more common in patients receiving certolizumab pegol plus MTX (Table 3). The reporting of hypertension was at the discretion of the investigator, and no preset guidelines for changes in the systolic or diastolic blood pressure were defined. Hypertensive events were not related to previous hypertensive status, were transitory, and were not related to the study injection. Mean changes in the systolic and diastolic blood pressure, respectively, at the last visit or at the time of withdrawal as compared with baseline were as follows: –2.1 mm Hg and –0.7 mm Hg in the group taking 200 mg of certolizumab pegol, –1.3 mm Hg and –0.6 mm Hg in the group taking 400 mg of certolizumab pegol, and –0.7 mm Hg and –0.4 mm Hg in the group taking placebo. The incidence of hematologic abnormalities was low: 1 case each of decreased hemoglobin was reported in the groups taking placebo and 400 mg of certolizumab pegol, and 2 cases were reported in the group taking 200 mg of certolizumab pegol. One case of increased platelet count was reported in the group taking placebo, with 0 and 2 cases reported in the groups taking 200 mg and 400 mg of certolizumab pegol, respectively. There was a low incidence of injection site pain and injection site reaction in those taking 200 mg (2% and 2.3%, respectively) or 400 mg (1.3% and 0.8%, respectively) of certolizumab pegol. There were no reports of injection site pain or reaction in the placebo group.

The frequency of infectious adverse events was comparable between groups (56–58 per 100 patient-years). Urinary tract infections, nasopharyngitis, and upper respiratory tract infections were the most frequently reported infectious adverse events. Serious infections were observed more frequently with certoli-

zumab pegol treatment than with placebo (5.3 per 100 patient-years and 7.3 per 100 patient-years in the 200-mg and 400-mg certolizumab pegol groups, respectively, versus 2.2 per 100 patient-years in the placebo group). Among the most frequent serious infectious adverse events were lower respiratory tract infections, gastroenteritis, urinary tract infections, and tuberculosis infections. A total of 5 patients (1 each from Estonia, Bulgaria, and Ukraine, and 2 from Russia) developed tuberculosis after 1.5–9 months of treatment. Three of these 5 patients were PPD positive at baseline (≥5-mm reaction; allowed to enroll according to protocol because of a history of BCG vaccination with negative findings on chest radiography), and 1 patient (PPD negative) was a worker in a tuberculosis clinic. Overall, in the ITT population, 172 patients (17.5%) with a PPD test result of ≥5 mm at baseline were enrolled according to protocol at the physician's discretion. No cases of tuberculosis with certolizumab pegol treatment were reported in patients living in North America.

Malignant neoplasms were observed in 12 patients: 1 receiving placebo (1.1 per 100 patient-years; thyroid neoplasm), 7 receiving 200 mg of certolizumab pegol (2.3 per 100 patient-years; 3 basal cell carcinomas [1 with metastasis to the central nervous system], 1 adrenal adenoma, 1 hepatic neoplasm, 1 esophageal carcinoma, and 1 uterine cancer), and 4 receiving 400 mg of certolizumab pegol (1.3 per 100 patient-years; 2 tongue neoplasms, 1 extranodal marginal-zone B cell lymphoma, and 1 papilloma). Anti–certolizumab pegol antibodies were detected at week 52 in 6.4% of patients receiving certolizumab pegol.

DISCUSSION

Treatment with certolizumab pegol plus MTX met both primary study end points, significantly reducing the signs and symptoms of RA and inhibiting the progression of structural damage in patients with active RA who had had an inadequate response to MTX alone. The unique design of this study required withdrawal at week 16 for patients who failed to achieve an ACR20 response by weeks 12 and 14. This design facilitated the identification of differences between active treatment and placebo early during the course of treatment and allowed patients who failed to respond within a reasonable clinical time frame to receive active treatment for their disease. No statistically significant or clinically meaningful differences were observed between the 200-mg and 400-mg doses of certolizumab pegol for any of the reported outcomes, and the ACR response rates observed with certolizumab pegol treatment were comparable with those observed with other anti-TNF agents in combination with MTX (5,17,18). Although the mean weekly dosage of MTX in this trial was low by US standards, a post hoc analysis showed that the clinical response to certolizumab pegol is not affected by the baseline dosage of MTX (data not shown).

The onset of benefit with certolizumab pegol therapy was rapid, with a significant proportion of patients achieving an ACR20 response after the first week of treatment and with maximum ACR50 and ACR70 responses achieved by weeks 14–20. Furthermore, all of the individual components of the ACR20 improvement criteria showed significant improvement by week 1, the earliest time point evaluated. One published study of adalimumab plus MTX therapy reported a statistically significant improvement in the ACR20 response rate by week 2 (5). In addition, the effects of certolizumab pegol on the signs and symptoms of RA were sustained, with significant ACR20, ACR50, and ACR70 response rates persisting to week 52.

At weeks 24 and 52, patients treated with certolizumab pegol plus MTX exhibited significantly less radiographic progression than did those treated with placebo plus MTX. Inhibition of radiographic progression was demonstrable as early as 24 weeks despite the fact that >60% of the patients in the placebo arm withdrew at week 16 and entered open-label treatment with certolizumab pegol. No differences were observed between the 2 certolizumab pegol dosage regimens in terms of inhibition of radiographic progression. Multiple sensitivity analyses also demonstrated that certolizumab pegol was effective in inhibiting radiographic evidence of disease progression. An additional analysis of the radiographs from the patients who withdrew early per-protocol for failing to achieve an ACR20 response found that the progression of joint damage was inhibited by certolizumab pegol even though they had not achieved a clinical response, thereby confirming that radiographic response is not always associated with clinical response criteria. Taken together, these data suggest that certolizumab pegol, administered as add-on therapy with MTX, rapidly inhibits structural joint damage in the early stages of treatment and provides potential long-term benefits to the patient in terms of slowing radiographic evidence of disease progression.

The inhibition of structural joint damage and the reduction in signs and symptoms of active disease with certolizumab pegol therapy were accompanied by significant, clinically meaningful improvements in physical function. These benefits were rapid (occurring as early

as week 1), were sustained for up to 1 year, and were evident regardless of the dosage of certolizumab pegol.

Both doses of certolizumab pegol were associated with a low incidence of treatment discontinuation because of adverse events. The incidence of serious infectious adverse events observed in this study (5.3 and 7.3 per 100 patient-years for the 200-mg and 400-mg dosage groups, respectively) was also comparable with the findings of other certolizumab pegol studies (UCB: unpublished observations). The cases of tuberculosis reported during this trial all occurred in patients living in Eastern Europe, where the prevalence of latent tuberculosis is particularly high (19), mainly in PPD-positive individuals. No other differences in safety were observed across geographic regions or over time, and no regional differences were observed within any of the efficacy analyses. The incidence of injection site pain or injection site reaction observed with the combination of certolizumab pegol and MTX in this study was low, occurring at a rate of <3 per 100 patient-years.

The results of this trial demonstrate that the Fc region of an antibody, which is present in the currently available anti-TNF monoclonal antibody preparations, but is absent from certolizumab pegol, is not required for therapeutic efficacy in RA. The PEGylation of certolizumab pegol may minimize adverse events, such as injection site pain/reaction, may aid in maintaining effective plasma concentrations, and may promote its preferential distribution into inflamed tissues, as was observed in an animal model (9). Increased exposure to the drug at sites of inflammation may be particularly relevant for the effective treatment of inflammatory disorders such as RA and may account for the rapid onset of action and peak response seen with certolizumab pegol therapy.

Taken together, these results demonstrate that the combination of certolizumab pegol plus MTX has an acceptable safety profile and is effective in causing a rapid and sustained reduction in the signs and symptoms of RA and in inhibiting disease progression in patients with active RA who had an inadequate response to MTX therapy. Combination therapy with certolizumab pegol plus MTX in these patients can thus be considered an effective treatment option.

AUTHOR CONTRIBUTIONS

Dr. Keystone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Mason, Emery, Strand.

Acquisition of data. Van der Heijde, Emery, Strand, Pavelka, personnel at Quintiles, a contract research organization (Research Triangle Park, NC; nonauthors), Kristel Luijtens (UCB, Braine l'Alleud, Belgium; nonauthor).

Analysis and interpretation of data. Keystone, van der Heijde, Landewé, van Vollenhoven, Strand.

Manuscript preparation. Keystone, van der Heijde, Landewé, van Vollenhoven, Combe, Emery, Strand, Mease, Pavelka.

Statistical analysis. Strand, Desai.

Advice on selection of contract research organization and statistical analysis plan; analysis and interpretation of data for regulatory authorities. Strand.

ROLE OF THE STUDY SPONSOR

A committee of academic investigators and UCB scientists designed the study. The trial was registered with clinicaltrials.gov (trial identifier: NCT00152386). Data were collected by Quintiles (Research Triangle Park, NC) and were analyzed by UCB (performed by Kristel Luijtens, PhD, Senior Biostatistician, UCB, Braine l'Alleud, Belgium). The academic authors vouch for the veracity and completeness of the data and data analyses.

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