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ORIGINAL ARTICLE

Addition of another disease-modifying anti-rheumatic drug to methotrexate reduces the flare rate within 2 years after infliximab discontinuation in patients with rheumatoid arthritis: An open, randomized, controlled trial

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Abstract

Objectives. We examined whether the addition of another conventional disease-modifying anti-rheumatic drugs (DMARDs) to methotrexate (MTX) upon infliximab (IFX) discontinuation in well-controlled rheumatoid arthritis (RA) patients could suppress subsequent disease flare.

Methods. RA patients maintaining DAS28-CRP (Disease Activity Score of 28 joints with C-reactive protein) scores < 2.6 for ≥ 6 months with IFX were randomized either to receive addition of bucillamine (BUC) to MTX (BUC + MTX group; $n = 24$) or not (MTX group; $n = 31$) upon discontinuing IFX. The primary endpoint was the flare rate within 2 years of IFX discontinuation.

Results. Six patients discontinuing MTX during the study were excluded from analyses. Seventeen patients (63.0%) experienced flares in the MTX group, which was significantly reduced in the BUC + MTX group (31.8%; $p = 0.045$). Further, the flare rates differed significantly between remission and non-remission by a Boolean definition upon IFX discontinuation in the MTX group (40.0% vs. 91.7%, respectively; $p = 0.014$), but they were comparable in the BUC + MTX group. BUC treatment was interrupted in seven patients due to rash, proteinuria and incompliance.

Conclusions. DMARDs combination therapy may be a better treatment strategy than MTX monotherapy for maintaining RA control after successful discontinuation of biological agents.

Keywords

Biological agents, Bucillamine, DMARD combination, Flare, Remission

History

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Introduction

Rheumatoid arthritis (RA) is characterized by persistent polyarthritis and presence of autoantibodies to post-translationally modified self-antigens, such as citrullinated proteins [1]. Early and aggressive treatment strategies targeted at achieving clinical remission or at least low disease activity as well as the introduction of biological agents in RA therapy have successfully led to achievement of radiographic and functional remission in a significant portion of RA patients [2]. However, the staggering expense of biological agents often limits their use to severe and refractory patients [3].

From a socio-economical point of view, the limited utility of biological agents for a specific period of the clinical course gives legitimate reason to seek improved cost-effectiveness. Although anti-tumor necrosis factor (anti-TNF) biological agents such as infliximab (IFX) have been successfully withdrawn in early RA patients [4,5], rarely can they be discontinued without subsequent disease flare in RA patients who have shown an inadequate response to MTX [6,7]. One exception comes from the RRR (remission induction by Remicade in RA) study, which demonstrated the potential for maintenance of disease control after discontinuation of IFX therapy in RA patients who had a mean disease duration of 7.7 years [8]. However, even in that study, flare developed in 45% of RA patients within the relatively short follow-up period of 1 year after discontinuation of IFX.

We have therefore conceived a clinical trial to determine whether or not the addition of another non-biological disease-modifying anti-rheumatic drug (DMARD) is useful in the maintenance of RA remission or low disease activity and in the suppression of disease flare after discontinuation of IFX. Bucillamine (BUC) was chosen because previous studies have suggested its usefulness in combination with MTX [9,10]. BUC is a D-penicillamine derivative agent (2-mercapto-2-methylpropanoyl-L-cystein) which contains two thiol residues. The mode of action of BUC has been reported to regulate T-cell [11,12] and B-cell function [13], suppress interleukin (IL)-6, IL-8 and IL-1β formation [14,15], and suppress vascular endothelial growth factor formation [16].

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Here we report the first results from the BUC Study of Holding remission after IFX Dose-Off (BuSHIDO) trial, evaluating the treatment strategy of DMARD combination therapy after successfully achieving disease control using biological agents (ClinicalTrials.gov Identifier NCT00716248).

Patients and methods

Patients

RA patients (aged ≥ 20 years) in whom at least six doses of IFX had resulted in satisfactory control of disease activity were eligible to participate in this study. "Satisfactory control of disease activity" was defined as Disease Activity Scores of 28 joints using a C-reactive protein score (DAS28-CRP) < 2.6 or, when CRP values were not available, a DAS28-erythrocyte sedimentation rate (ESR) < 3.2, because of the reported correspondence of DAS28-CRP value of 2.7 to DAS28-ESR value of 3.2 [17]. Maintenance of these values on each infusion visit for ≥ 6 months was required for inclusion in the study. All patients satisfied the 1987 American College of Rheumatology (ACR) revised criteria for the classification of RA [18]. Exclusion criteria were contraindications to BUC, including hematological and renal disorders, and a history of adverse events with BUC.

Study design

This open, randomized, controlled, single center study was performed in compliance with the Helsinki Declaration, with the approval of the Ethics Committee of Saitama Medical Center, Saitama Medical University. Registration of patients in this study commenced in January 2007 and was completed on December 31, 2009. Patients who provided written informed consent for participation in the study were randomly allocated to the BUC + MTX group (addition of BUC upon IFX discontinuation) or MTX group (no BUC) (Figure 1). BUC was administered at 100 mg twice a day. The dosing method and dosage of other drugs including MTX were unchanged throughout the study period.

The following parameters were analyzed every 3 months: swollen joint count (SJC), tender joint count (TJC), patient global assessment of disease activity (PGA), physician global assessment of disease activity (PhGA), Health Assessment Questionnaire-disability index (HAQ-DI) score, and serum levels of CRP and matrix metalloproteinase-3 (MMP-3) as well as ESR. In addition, a modified total Sharp score (mTSS) was examined for baseline radiographic damage by two experienced evaluators [19], and the average of their ratings was taken.

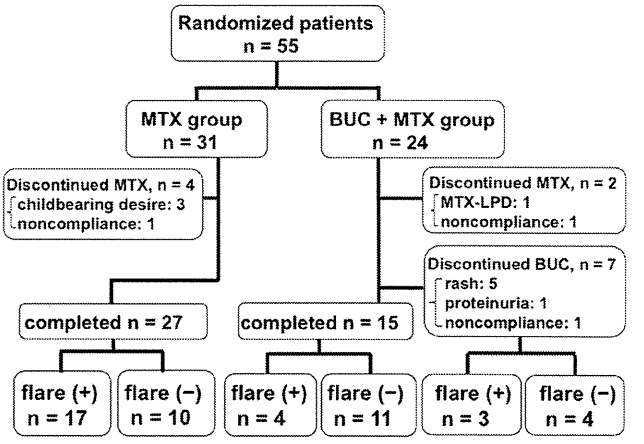

Figure 1. Disposition of randomized patients through the 2 years. Patients who discontinued MTX were excluded from further analyses.

Primary endpoint

The primary endpoint of the study was the disease flare rate within the 2-year follow-up period. Disease flare was defined by meeting both DAS28-CRP ≥ 2.6 and DAS28-ESR ≥ 3.2.

Statistical analyses

A sample size of 25 patients per treatment group was first calculated to provide 80% power ($\alpha = 0.05$, $\beta = 0.2$) with a 10% non-completion rate for the 2 years of IFX discontinuation. This calculation assumed that the flare rate would be 20% in the BUC + MTX group and 65% in the MTX group. The proportions of participants who met the given criteria were compared with Fisher's exact test or χ^2 test, while Wilcoxon's rank sum test was

Table 1. Baseline characteristics of randomized patients.

	MTX	BUC + MTX	*P* value
Total	31	24	
Gender (% female)	27 (87.1)	15 (62.5)	$p = 0.070^a$
Age, years; mean ± SD (range)	50.4 ± 13.7 (22–73)	53.8 ± 14.2 (23–71)	$p = 0.266^b$
Disease duration (years); mean ± SD (range)	7.1 ± 5.7 (1–19)	8.5 ± 7.3 (1–33)	$p = 0.322^b$
RF positive (%)	50.0	40.9	$p = 0.779^a$
DAS28-CRP			
At start of IFX; mean ± SD (range)	4.4 ± 1.5 (1.0–7.3)	4.7 ± 1.4 (2.3–7.3)	$p = 0.546^b$
0 months; mean ± SD (range)	1.6 ± 0.5 (1.0–2.9)	1.3 ± 0.3 (1.0–1.9)	$p = 0.011^b$
HAQ-DI			
At start of IFX; mean ± SD (range)	1.2 ± 0.7 (0.0–2.8)	0.9 ± 0.7 (0.0–2.1)	$p = 0.314^b$
0 months; mean ± SD (range)	0.3 ± 0.4 (0.0–1.6)	0.2 ± 0.4 (0.0–1.4)	$p = 0.565^b$
mTSS			
0 months; mean ± SD (range)	52.0 ± 76.9 (1.0–282.0)	34.8 ± 39.8 (0.0–139.5)	$p = 0.706^b$
MTX dose (mg/week); mean ± SD (range)	7.8 ± 1.4 (6–12.5)	8.3 ± 2.6 (2–15)	$P = 0.260^b$
Prednisolone			
User (%)	7 (22.6)	8 (33.3)	$P = 0.560^a$
Dose (mg/day); mean ± SD (range)	1.1 ± 2.1 (0–5)	0.9 ± 1.4 (0–4)	$p = 0.787^b$
IFX dose (mg/infusion); mean ± SD (range)	186.5 ± 19.9 (140–200)	193.1 ± 31.8 (138–300)	$p = 0.485^b$
Number of IFX infusion; mean ± SD (range)	14.9 ± 7.1 (6–36)	13.9 ± 7.2 (6–36)	$p = 0.580^b$

Data were at 0 months (upon IFX discontinuation) unless otherwise described.
SD, standard deviation; RF, Rheumatoid factor.
[a]χ^2 test.
[b]Wilcoxon's rank sum test.

used to compare continuous data. The Kaplan–Meier analysis and log-rank test were used for the comparison of survival curves between groups. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient disposition and overall safety

Of the 55 patients enrolled in the present study (MTX group, $n = 31$; BUC + MTX group, $n = 24$; Figure 1), six who discontinued MTX before the primary endpoint were excluded from the following analyses, comprising four and two patients in the MTX and BUC + MTX groups, respectively, due to the risk of teratogenicity in childbirth ($n = 3$), MTX-associated lymphoproliferative disease (MTX-LPD) at 12 months ($n = 1$) and noncompliance ($n = 2$). BUC was interrupted in another seven patients because of rash ($n = 5$), reversible proteinuria ($n = 1$) and noncompliance ($n = 1$). Those seven patients were followed-up for disease flare during the study period. No other clinically relevant adverse events were reported.

Baseline demographic and clinical features

Baseline (0 months at the time of IFX discontinuation unless otherwise stated) demographic and clinical features of the 55 patients were analyzed and compared between treatment groups (Table 1). All demographic and clinical features were similar between groups, including gender ratios, age, disease duration, serological state, disease activity, physical disability, joint damage, and the dose of concomitant MTX and prednisolone. The one exception was the baseline DAS28-CRP value, which was lower in the BUC + MTX group (1.3 ± 0.3) than in the MTX group (1.6 ± 0.5; $p = 0.011$), which had considerably improved from that at start of IFX in the both groups (Table 1).

Primary endpoint

The flare rate after IFX discontinuation for 2 years was compared between the two treatment groups for primary endpoint analysis. The flare rate was 63.0% in the MTX group, which was significantly greater than the rate of 31.8% in the BUC + MTX group ($p = 0.045$ by Fisher's exact test; Figure 2), indicating that the primary endpoint was met. In addition, the flare rate within 2 years was 26.7% in patients continuing BUC but 42.9% in those who had BUC treatment interrupted due to adverse events, suggesting the potential importance of BUC continuation in maintaining disease control.

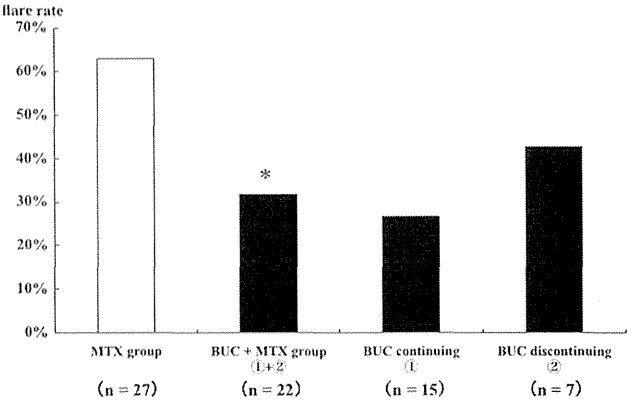

Figure 2. Effects of BUC on the flare rate after IFX discontinuation. *$P = 0.045$ versus MTX group by Fisher's exact test.

Cumulative disease flare and adverse events during the 2 years

Using Kaplan–Meier survival curve analyses, we investigated and compared the time points of disease flare and adverse events, both of which are used to evaluate usefulness of ongoing treatments. Continuation of allocated treatment was not significantly different between treatment regimens ($p = 0.427$ by Log-rank test; Figure 3A). However, comparisons of time-dependent disease flare between groups confirmed significantly less disease flare in the BUC + MTX group than in the MTX group ($p = 0.017$, Log-rank test; Figure 3B). Of note, all six instances of discontinuing BUC due to adverse events occurred within the first 6 months.

Factors associated with disease flare

In the analysis of differences in background variables with respect to the presence or absence of flare among the entire population for efficacy analysis ($n = 49$), TJC, SJC, PGA and DAS28-CRP upon IFX discontinuation differed significantly between the flare-positive

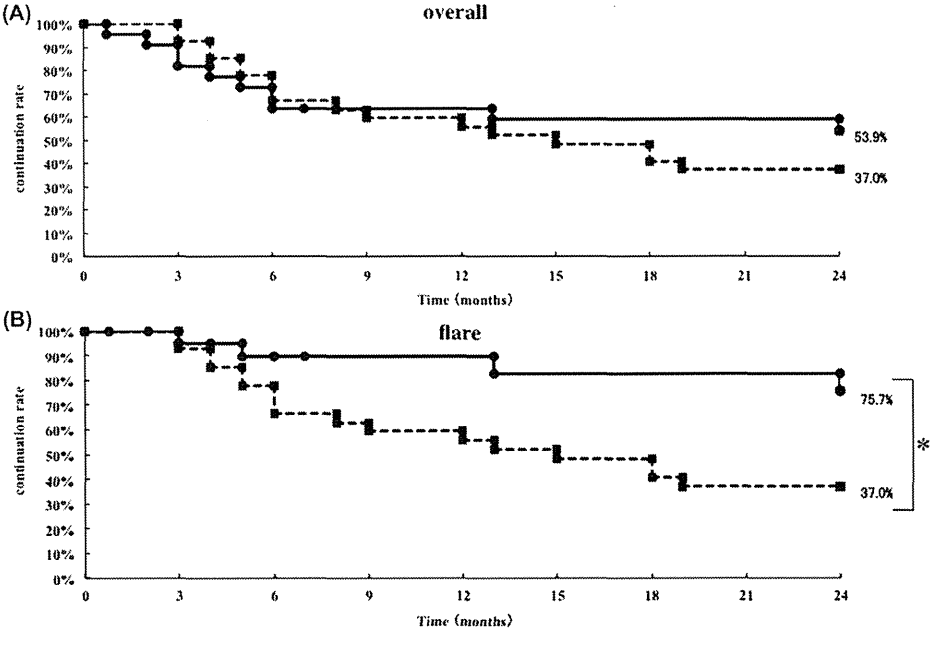

Figure 3. Comparison of treatment survival by Kaplan–Meier analysis. (A) Overall treatment survival was compared between BUC + MTX (circles connected by solid lines) and MTX groups (squares connected by dashed lines). $P = 0.427$ by Log-rank test. (B) Treatment survival focused on flare favored the BUC + MTX group (circles connected by solid lines) over the MTX group (squares connected by dashed lines). *$P = 0.017$ by Log-rank test.

Table 2. Comparisons between patients with and without flares.

	Total			MTX			BUC + MTX		
	Flare (−)	Flare (+)	*p* value	Flare (−)	Flare (+)	p value	Flare (−)	Flare (+)	p value
Total	25	24		10	17		15	7	
Gender (% female)	16 (64.0)	20 (83.3)	$p = 0.227^a$	8 (80.0)	15 (88.2)	$p = 0.983^a$	8 (53.3)	5 (71.4)	$p = 0.735^a$
Age (years); mean ± SD (range)	52.1 ± 14.0 (23–73)	55.0 ± 11.6 (32–73)	$p = 0.555^b$	50.6 ± 14.3 (27–73)	54.0 ± 12.1 (32–73)	$p = 0.481^b$	53.1 ± 14.3 (23–70)	57.4 ± 10.8 (38–71)	$p = 0.621^b$
Disease duration (years); mean ± SD (range)	8.2 ± 7.4 (1–33)	8.2 ± 5.8 (1–19)	$p = 0.748^b$	6.3 ± 4.1 (1–13)	8.5 ± 6.7 (1–19)	$p = 0.614^b$	9.5 ± 8.9 (1–33)	7.4 ± 2.9 (4–12)	$p = 0.697^b$
RF at start of IFX (U/ml); mean ± SD (range)	207.6 ± 599.3 (10–2980)	59.9 ± 53.9 (9–214)	$p = 0.495^b$	378.5 ± 921.2 (10–2980)	48.6 ± 41.6 (9–126)	$p = 0.406^b$	85.6 ± 96.9 (10–352)	92.0 ± 74.6 (10–214)	$p = 0.773^b$
TJC (28 joints)									
At start of IFX; mean ± SD (range)	6.7 ± 7.2 (0–28)	5.8 ± 5.0 (0–19)	$p = 0.992^b$	7.4 ± 7.6 (0–19)	5.1 ± 3.8 (0–14)	$p = 0.899^b$	6.3 ± 7.1 (0–28)	7.4 ± 7.2 (0–19)	$p = 0.859^b$
0 months; mean ± SD (range)	0.0 ± 0.0 (0–0)	0.3 ± 0.6 (0–2)	$p = 0.008^b$	0.0 ± 0.0 (0–0)	0.5 ± 0.7 (0–2)	$p = 0.038^b$	0.0 ± 0.0 (0–0)	0.0 ± 0.0 (0–0)	–
SJC (28 joints)									
At start of IFX; mean ± SD (range)	9.4 ± 6.9 (1–28)	9.0 ± 7.2 (0–28)	$p = 0.681^b$	11.2 ± 7.5 (1–24)	8.9 ± 6.6 (0–27)	$p = 0.392^b$	8.2 ± 6.4 (1–28)	9.0 ± 9.2 (2–28)	$p = 0.776^b$
0 months; mean ± SD (range)	0.2 ± 0.6 (0–3)	0.6 ± 1.0 (0–4)	$p = 0.033^b$	0.4 ± 1.0 (0–3)	0.8 ± 1.1 (0–4)	$p = 0.200^b$	0.0 ± 0.0 (0–0)	0.0 ± 0.0 (0–0)	–
PGA (mm VAS)									
At start of IFX; mean ± SD (range)	47.5 ± 25.5 (4–100)	52.5 ± 25.4 (2–100)	$p = 0.441^b$	45.7 ± 26.5 (4–100)	47.8 ± 27.0 (2–100)	$p = 0.763^b$	48.7 ± 25.6 (11–90)	63.7 ± 17.9 (43–84)	$p = 0.158^b$
0 months; mean ± SD (range)	4.4 ± 7.0 (0–33)	11.8 ± 14.6 (0–62)	$p = 0.038^b$	2.5 ± 3.6 (0–8)	12.3 ± 14.8 (0–62)	$p = 0.006^b$	5.7 ± 8.4 (0–33)	10.4 ± 15.0 (0–37)	$p = 0.803^b$
PhGA (mm VAS)									
At start of IFX; mean ± SD (range)	53.7 ± 20.3 (18–94)	50.9 ± 19.1 (7–92)	$p = 0.655^b$	52.6 ± 18.3 (32–86)	52.9 ± 21.0 (7–92)	$p = 0.910^b$	54.5 ± 22.4 (18–94)	45.3 ± 12.2 (33–64)	$p = 0.313^b$
0 months; mean ± SD (range)	1.6 ± 2.7 (0–10)	2.7 ± 2.8 (0–9)	$p = 0.053^b$	1.7 ± 3.1 (0–10)	3.4 ± 2.8 (0–9)	$p = 0.041^b$	1.5 ± 2.5 (0–8)	1.0 ± 1.9 (0–5)	$p = 0.653^b$
DAS28-CRP									
At start of IFX; mean ± SD (range)	4.7 ± 1.4 (2.6–7.3)	4.6 ± 1.4 (1.0–7.3)	$p = 0.812^b$	4.8 ± 1.5 (3.1–7.3)	4.4 ± 1.4 (1.0–6.7)	$p = 0.688^b$	4.5 ± 1.3 (2.6–7.1)	5.2 ± 1.3 (3.7–7.3)	$p = 0.392^b$
0 months; mean ± SD (range)	1.3 ± 0.3 (1.0–2.0)	1.7 ± 0.5 (1.0–2.9)	$p = 0.005^b$	1.4 ± 0.3 (1.0–2.0)	1.8 ± 0.6 (1.0–2.9)	$p = 0.048^b$	1.3 ± 0.3 (1.0–1.9)	1.4 ± 0.2 (1.2–1.7)	$p = 0.135^b$
HAQ− DI									
At start of IFX; mean ± SD (range)	0.9 ± 0.7 (0.0–2.1)	1.2 ± 0.7 (0.0–2.8)	$p = 0.151^b$	1.0 ± 0.5 (0.4–1.9)	1.3 ± 0.7 (0.0–2.8)	$p = 0.305^b$	0.9 ± 0.8 (0.0–2.1)	1.1 ± 0.7 (0.0–1.8)	$p = 0.692^b$
0 months; mean ± SD (range)	0.2 ± 0.3 (0.0–1.4)	0.3 ± 0.4 (0.0–1.6)	$p = 0.200^b$	0.2 ± 0.3 (0.0–0.8)	0.4 ± 0.5 (0.0–1.6)	$p = 0.330^b$	0.2 ± 0.4 (0.0–1.4)	0.1 ± 0.2 (0.0–0.5)	$p = 0.569^b$
mTSS									
0 months; mean ± SD (range)	41.4 ± 58.7 (0.0–262.0)	54.6 ± 73.8 (1.0–282.0)	$p = 0.804^b$	54.9 ± 79.9 (1.5–262.0)	61.0 ± 83.7 (1.0–282.0)	$p = 0.937^b$	32.4 ± 39.8 (0.0–139.5)	39.8 ± 45.7 (1.0–120.5)	$p = 0.944^b$
MTX dose (mg/week); mean ± SD (range)	8.2 ± 2.2 (4–15)	7.3 ± 1.5 (2–10)	$p = 0.156^b$	7.6 ± 1.3 (6–10)	7.5 ± 1.1 (6–10)	$p = 0.906^b$	8.7 ± 2.6 (4–15)	6.9 ± 2.3 (2–8)	$p = 0.130^b$
Prednisolone									
User (%)	7 (28.0)	6 (25.0)	$p = 1.000^a$	2 (20.0)	4 (23.5)	$p = 1.000^a$	5 (33.3)	2 (28.6)	$p = 1.000^a$
Dose (mg/day); mean ± SD (range)	1.0 ± 1.7 (0–5)	1.0 ± 1.9 (0–5)	$p = 0.938^b$	1.0 ± 2.1 (0–5)	1.2 ± 2.2 (0–5)	$p = 0.834^b$	0.9 ± 1.4 (0–4)	0.6 ± 1.1 (0–3)	$p = 0.701^b$
IFX dose (mg/infusion); mean ± SD (range)	191.9 ± 31.4 (138–300)	190.1 ± 18.4 (140–200)	$p = 0.939^b$	192.4 ± 16.1 (159–200)	188.5 ± 20.1 (140–200)	$p = 0.602^b$	191.6 ± 39.0 (138–300)	194.7 ± 13.1 (168–200)	$p = 0.546^b$
Number of IFX infusion; mean ± SD (range)	14.1 ± 5.8 (6–28)	14.3 ± 7.5 (6–36)	$p = 0.779^b$	16.7 ± 7.3 (9–28)	13.9 ± 7.6 (6–36)	$p = 0.279^b$	12.3 ± 3.8 (6–19)	15.3 ± 7.8 (7–26)	$p = 0.479^b$

Data were at 0 months (upon IFX discontinuation) unless otherwise described.
VAS, visual analog scale.
[a]χ^2 test.
[b]Wilcoxon's rank sum test.

and flare-free groups (Table 2). Regarding the MTX group, TJC, PGA, PhGA and DAS28-CRP at IFX discontinuation were significantly greater in the flare-positive group than in the flare-free group. In contrast, no significant differences in background variables were demonstrated between flare-positive and flare-negative patients in the BUC + MTX group.

Flare rate stratified by remission status

Because some patients had minimal disease activity, namely not in remission, upon IFX discontinuation and the baseline DAS28-CRP value was slightly higher in the MTX group compared with the BUC + MTX group (Table 1), we compared flare rates stratified by remission status according to ACR/EULAR (European League Against Rheumatism) Boolean criteria for RA remission, which are regarded as stringent remission criteria [20]. The frequency of remission at IFX discontinuation was not significantly different between treatment groups. Interestingly, 11 of 12 (91.7%) patients developed disease flare in the MTX group when remission had not been achieved upon IFX discontinuation, while only two of five (40.0%) patients did in the BUC + MTX group despite non-remission status upon IFX discontinuation ($p = 0.053$). Further, the state of remission significantly influenced the disease flare rate in the MTX group (91.7% and 40.0% in non-remission and remission patients, respectively; $p = 0.014$), although values were comparable between non-remission and remission patients in the BUC + MTX group (40.0% and 29.4%, respectively; $p = 1.00$), suggesting the effect of BUC on maintaining minimal disease activity.

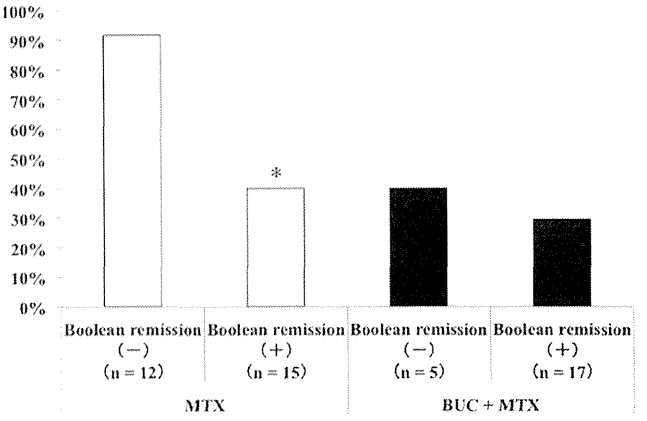

Figure 4. Comparison of flare rates stratified by treatment groups and the achievement of remission by ACR/EULAR Boolean definition upon IFX discontinuation. $^*P = 0.014$ versus Boolean remission (−) in the MTX group by Fisher's exact test.

Discussion

To our knowledge, this is the first clinical trial to examine the usefulness of non-biological DMARD combination therapy after disease control with biological agents. Approximately 50% reduction in incidence of disease flare after discontinuation of IFX was demonstrated by adding another DMARD, namely BUC, to MTX therapy, suggesting that DMARD combination therapy should be considered not only for remission induction before application of biological agents, but also for the maintenance of disease control after withdrawal of biological agents.

In a real-world clinical setting, remission due to treatment discontinuation of anti-TNF biological agents is generally only 2–6% [21], although a recent observational cohort showed that IFX could be discontinued in 16% and down-titrated in 45% of RA patients [22]. In this context, the RRR study was designed to evaluate the possibility of maintaining remission, or at least low disease activity, of RA in 114 patients with various disease durations (range: 0.1–38.0 years, mean: 5.9 years) [8]. The flare rate at 1 year after discontinuation of IFX was 45% ($n = 46$) in patients for whom a DAS28-ESR < 3.2 was maintained for 24 weeks with IFX therapy. This flare rate was reproducible in the MTX group in the BuSHIDO trial, as 44.4% and 63.0% of patients at 1 and 2 years after discontinuation, respectively, showed disease flare.

In addition, the RRR study revealed that significantly more patients with DAS28 < 2.225 at study entry (IFX discontinuation) maintained DAS28 < 3.2 after 1 year than did those with DAS28 ≥ 2.225 at entry (71.4% versus 32.6%). Similarly, in the BuSHIDO trial, the DAS28-CRP value at IFX discontinuation was significantly greater in flare-positive patients than in flare-free ones for all patients as well as in the MTX group, but not in the BUC + MTX group. The addition of BUC at IFX discontinuation appeared to increase the critical threshold of disease activity status for clinical flare in conjunction with the results shown in Figure 4.

Further, duration of combination treatment may influence disease suppression, as we noted a decreasing trend in instances of disease flare in BUC-continuing vs. BUC-discontinuing or MTX-alone patients. Previous BUC users without adverse events were 7 of 22 (31.8%) patients in the BUC + MTX group and 17 of 27 (63.0%) patients in the MTX group. The flare rate was comparable between previous BUC users and non-users in the BUC + MTX group (37.5% vs. 28.6%). After the disease flare, IFX was re-introduced for 10 and 3 patients, respectively, in the MTX group and the BUC + MTX group, which was successful in all the patients. MTX dose was increased in three patients and one patient, respectively, and BUC was added to MTX in one patient in the MTX group.

We have previously shown that BUC is similarly effective whether it is used before or after MTX [9]. Further, therapeutic effects of the combination of MTX and BUC have been compared with each monotherapy in early RA patients [10]. At 96 weeks, the ACR20 response rate was 79.2% in the BUC + MTX group, which was significantly higher than the rates of 45.8% for the BUC group and 43.5% for the MTX group. Given that BUC is a strongly recommended DMARD (grade A) according to the guideline for RA management from a national study group in Japan, this compound has been widely used as monotherapy or in combination with MTX or salazosulfapyridine [23].

As for its safety profile, all adverse events observed in this study were non-serious and subsided upon BUC discontinuation. As previously reported [9], rash was the most frequent adverse event within 3 months, while proteinuria developed around 6 months after BUC commencement. Yellowed fingernails and taste disturbance are other well-known adverse events [24], although they were not reported in the present study.

Several limitations to the present study warrant mention, namely its small patient number, low dose of weekly MTX (8.3 ± 2.6 mg and 7.8 ± 1.4 mg in the BUC + MTX and MTX groups, respectively), and the current availability of BUC being limited mostly to Japan and South Korea, meaning it is a drug unfamiliar to people in other countries. Therefore, the future studies including other DMARDs than BUC, such as salazosulfapyridine, hydroxychloroquine and tacrolimus, will be warranted. While the officially approved maximum dose of MTX in Japan was raised from 8 to 16 mg/week starting in February 2011, that was more than 1 year after the completion of the patient enrollment in this study.

In conclusion, The BuSHIDO trial demonstrated that the addition of BUC to MTX reduced the flare rate for 2 years after IFX discontinuation due to remission or reduced disease activity sustained for > 6 months. These present findings suggest that DMARD combination therapy may be a preferable choice upon achieving good disease control by biological agents with respect

to minimizing the risk of disease flare that occurs after the discontinuation of such agents. Further clinical trials using different DMARD combinations and biological agents should be considered to build upon these findings.

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Conflict of interest

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M Kishimoto is a full-time employee of Santen Pharmaceutical Co. Ltd.

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ORIGINAL ARTICLE

Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial

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Abstract

Objectives. This 24-week, multicenter, double-blind, randomized, placebo-controlled study (NCT00791999) compared efficacy and safety of certolizumab pegol (CZP) in combination with methotrexate (MTX) vs placebo plus MTX in Japanese rheumatoid arthritis (RA) patients with inadequate response to MTX.

Methods. In total, 316 patients were randomized 1:1:1:1 to subcutaneous CZP 100, 200, or 400 mg (induction dose: 200 mg or 400 mg CZP at Weeks 0, 2, and 4) plus MTX or placebo plus MTX every 2 weeks. Primary endpoint was ACR20 response at Week 12.

Results. ACR20 response rates were 62.5%, 76.8%, 77.6%, and 28.6% at Week 12, and 61.1%, 73.2%, 71.8%, and 24.7% at Week 24 for CZP 100, 200, and 400 mg, and placebo groups, respectively, with statistical significance between each CZP group and placebo. Change in Total Sharp Score over 24 weeks was significantly smaller in CZP 200 and 400 mg groups vs placebo. Improvements in health-related quality of life (HRQoL) were observed in all three CZP groups vs placebo. Incidence of adverse events was similar between CZP groups.

Conclusions. CZP plus MTX resulted in rapid, sustained reductions in RA signs and symptoms in Japanese patients with inadequate response to MTX, with significant inhibition of radiographic progression and improved HRQoL.

Keywords

Certolizumab pegol, Methotrexate, Randomized controlled trial, Rheumatoid arthritis, Tumor necrosis factor-alpha inhibitor

History

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Introduction

Tumor necrosis factor alpha (TNF-α) inhibitors have significant beneficial effects on the signs and symptoms of rheumatoid arthritis (RA), the progression of joint damage, and on physical functioning and health-related quality of life (HRQoL), as shown in randomized controlled clinical trials [1–8]. As biologic agents, TNF inhibitors are recommended either as monotherapy or in combination with non-biologic agents for RA patients responding inadequately to synthetic disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX) [9,10].

Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF-α agent. The RA Prevention of Structural Damage (RAPID) 1 and RAPID 2 international studies demonstrated that CZP plus MTX significantly improved the signs and symptoms of RA in patients with active disease despite MTX treatment [5,8]. The objective of the Japan RAPID (J-RAPID) study presented here was to investigate the efficacy and safety of CZP with concomitant MTX therapy in Japanese patients with active RA who have failed to respond adequately to MTX.

Materials and methods

Study overview

J-RAPID was a 24-week, phase 2/3 multicenter, double-blind, randomized placebo-controlled study (NCT00791999), conducted between 19 November 2008 and 18 August 2010 in 67 centers across Japan, in which patients with active RA and

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an inadequate response to MTX received CZP or placebo while continuing to take their previous dosage of MTX. The MTX regimen could not be changed after initiation of the study treatment.

Patients were randomized 1:1:1:1 to subcutaneous CZP 100, 200, or 400 mg plus MTX, or saline placebo plus MTX, every 2 weeks (Q2W). Block randomization was used to allocate patients to treatment arms. The random allocation sequence was generated using uniform random numbers from SAS® RANUNI function. The study drug allocation center was responsible for preparation and storage of the randomization table, study drug allocation, and confirmation of indistinguishability of study drugs, while the registration center was responsible for assignment of study drug numbers to patients. Patients randomized to CZP plus MTX received induction doses of 200 mg (100 mg group) or 400 mg (200 and 400 mg groups) at Weeks 0, 2 and 4. Patients randomized to placebo received an equivalent injection regimen of saline solution to maintain blinding. Study drug administration was performed by non-blinded personnel who were not allowed to engage in any other study activities. The MTX regimen could not be changed after initiation of the study treatment. The dose of MTX was set to 6–8 mg/week in accordance with the approved dose in Japan at the time of the clinical trial.

Patients who did not achieve an ACR20 response (i.e., $\geq$ 20% improvement according to the criteria of the American College of Rheumatology [ACR] [11]) at Weeks 12 and 14 (ACR20 non-responders) were withdrawn from the study at Week 16 and were eligible to enter an open-label extension study thereafter.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the Pharmaceutical Affairs Law Standards for the Conduct of Clinical Trials on Drugs (Ministry of Health, Labour and Welfare Ordinance no. 28, 27 March 1997) and related notifications. Institutional review board approval was obtained at all centers and written informed consent was provided by all patients.

Patients

Since the international RAPID 2 study was used as a bridging model, J-RAPID adopted the same inclusion criteria, including disease duration, with some exceptions.

Eligible patients were aged from 20–74 years and had a diagnosis of RA defined by ACR (1987) criteria [12] for 0.5–15 years. Disease duration was set in accordance with the criteria in the RAPID 2 study, whereas the lower age limit differed among the two studies, 18 years in the RAPID 2 study and 20 years in the present study, set in order to avoid including minors in the study. In addition, from a safety perspective, an upper limit of up to age 75 was set. Patients must have had active RA as defined by at least nine tender and nine swollen joints (among 68 and 66 joints of ACR definition, respectively) at screening and baseline, and have satisfied at least one of the following criteria at screening: erythrocyte sedimentation rate (ESR) of $\geq$ 30 mm/hour or C-reactive protein (CRP) of $\geq$ 1.5 mg/dL.

Patients must have received treatment with MTX (with or without folic acid) for 6 or more months before study drug administration, with the MTX dose fixed for 2 or more months beforehand and within the range of 6–8 mg/week.

Patients were excluded if they had received any biologic therapy for RA within the 6 months preceding the study (3 months for etanercept) or had received any investigational drug in the preceding 3 months. Patients who had received previous treatment with $\geq$ 2 TNF inhibitors or who had not initially responded to previous TNF inhibitor therapy were also excluded, as were those who had previously shown severe hypersensitivity or had an anaphylactic reaction. Oral corticosteroids (up to 10 mg/day prednisone equivalent), nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors were permitted as long as doses had been stable for $\geq$ 28 and $\geq$ 14 days, respectively, preceding study entry. Use of parenteral corticosteroids, intra-articular hyaluronic acid, azathioprine, cyclosporine, or DMARDs (with the exception of MTX) was not permitted within the 28 days before study Day 1. Patients were also excluded if they had history of demyelinating or convulsive disease of the central nervous system (e.g., multiple sclerosis and epilepsy), New York Heart Association Class III or IV congestive heart failure, infectious disease, hepatitis B or hepatitis C, malignant tumor or lymphoproliferative disorder, including lymphoma or signs and symptoms suggestive of lymphoproliferative disease. Patients with any indication of current or past tuberculosis as shown by clinical history, chest X-ray and/or positive tuberculin reaction test were also excluded unless preventive therapy by isoniazid was first taken.

Study assessments

After a screening period of 1–4 weeks prior to randomization, efficacy assessments were carried out over the 24-week treatment period as follows: at baseline, Weeks 1, 2, 4, 6, 8, 12, 14, 16, 20 and 24 or time of discontinuation. Safety was assessed at every visit. The primary efficacy endpoint was ACR20 response rate at Week 12. The key secondary endpoint was ACR20 response rate at Week 24.

Additional endpoints were: ACR20 response at other time points, and ACR50 and ACR70 response rates; individual ACR core component scores: number of tender joints, number of swollen joints, assessment of physical function using Health Assessment Questionnaire Disability Index (HAQ-DI), patient assessment of arthritis pain using Visual Analog Scale (VAS), patient global assessment of disease activity using VAS, physician global assessment of disease activity using VAS, CRP, and ESR; prevention of progression of joint destruction (change in van der Heijde modified Total Sharp Score [mTSS]) at Week 24; duration of morning stiffness; Disease Activity Score 28-joint assessment with ESR (DAS28[ESR]) remission rates and European League Against Rheumatism (EULAR) response [13].

Radiographic assessments were performed at baseline and at Week 24 or at discontinuation using the mTSS [14,15]. The degree of joint erosion was assessed in 44 joints and joint space narrowing (JSN) in 42 joints. Radiographs were independently evaluated by two experienced assessors who were blinded to the treatment regimen and timing of radiography. Mean scores across two radiographic readers were used for analysis. Erosions and JSN were summed to obtain the mTSS. mTSS non-progression was defined as change from baseline in mTSS $\leq$ 0.5 units at Week 24.

HRQoL was assessed at baseline, Week 12, and Week 24 using the Short Form-36 Health Survey (SF-36), including the eight domains of Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health, scored from 0 to 100 [16].

Plasma samples were analyzed for determination of concentrations of CZP and anti-CZP antibody at every visit to Week 8, then at Weeks 12 and 24 or the time of discontinuation. Safety was assessed at all visits and at 12-week follow-up, and included adverse events (AEs), laboratory findings, body weight and vital signs, 12-lead ECGs and radiography of the chest. Serious AEs (SAEs) were those that resulted in death, were life-threatening, required or prolonged hospitalization, or resulted in significant disability or incapacity or were congenital anomalies/birth defects.

Statistical analysis

The sample size was based on an expected ACR20 response rate of 22% in the placebo group and ≥ 50% in the 200 mg and 400 mg groups, as per previous clinical experience with CZP. Verification of superiority of the 200 mg and 400 mg doses over placebo for the primary endpoint would then have 90% power at a two-sided significance level of 2.5% in order to preserve the overall Type I error rate at $\alpha = 0.05$, with 71 patients per group (300 overall, pre-randomization).

The primary population for analysis of the primary endpoint was the full analysis set (FAS) of patients who received ≥ 1 dose of study drug and provided ≥ 1 efficacy data thereafter. The safety population contained all patients who received ≥ 1 dose of study drug.

ACR responses were determined using non-responder imputation. Patients who violated study protocol, received rescue medication, or withdrew for any reason were considered non-responders from that time point onward.

Logistic regression was used for ACR response comparisons. Changes in ACR core parameters and changes in total tender and swollen joint scores between baseline and Week 24 were examined using analysis of covariance (ANCOVA) with the baseline value as the covariate, and using last observation carried forward (LOCF) imputation for missing data. Changes from baseline to the assessment time point for DAS28(ESR), SF-36 and duration of morning stiffness, were also analyzed using ANCOVA (LOCF) with treatment group as a factor and the baseline value as a covariate. For EULAR response (good, moderate or no response), intergroup comparisons using logistic regression at each time point were carried out using LOCF imputation.

Radiographic outcomes were summarized for those patients with complete radiographic data available for two assessment points (at baseline and post-drug administration). mTSS values at Week 24 were estimated employing linear extrapolation in patients in whom administration was discontinued before Week 24 using values obtained at the discontinuation visit. mTSS values at Week 24 for early withdrawals were estimated by linear extrapolation of the last available value to Week 24, assuming disease progression occurred at the same rate between baseline and withdrawal, as commonly used for missing mTSS data [5,17,18]. In order to examine the change in rank from baseline, ANCOVA on the ranks was performed with treatment as factors and rank baseline mTSS as covariate.

Treatment-emergent AEs (TEAEs) included all events from after the administration of the study drug until the last evaluation visit (not including the safety follow-up visit). TEAEs were coded by system organ class and preferred term using MedDRA terminology (v11.1).

Results

Patient characteristics and disposition

A total of 316 patients (FAS) were randomized (Figure 1) to CZP 100 mg ($n = 72$), CZP 200 mg ($n = 82$), CZP 400 mg ($n = 85$) or placebo ($n = 77$). In the CZP 100, 200 and 400 mg groups, 51, 66 and 65 patients completed 24 weeks of double-blind treatment, respectively, compared with 25 patients in the placebo group. There were no marked differences in the patient background characteristics or severity of the disease at baseline among the four groups (Table 1).

More placebo plus MTX-treated patients withdrew at Week 16 due to a lack of ACR20 response at Weeks 12 and 14 relative to the CZP 100 mg, 200 mg and 400 mg plus MTX groups; fewer patients randomized to placebo plus MTX completed 24 weeks' treatment than in the CZP 100 mg 200 mg, and 400 mg plus MTX groups (Figure 1).

Clinical efficacy

All active treatment groups showed higher ACR responses at Weeks 12 and 24 compared to placebo plus MTX (Figure 2a and b). The superiority of all CZP plus MTX groups compared to placebo plus MTX in ACR20 response was statistically significant at Weeks 12 and 24 ($p < 0.0001$) (Figure 2a and b).

ACR50 responses were statistically significantly higher with all doses of CZP at Weeks 12 and 24 compared to those of placebo, and ACR70 responses were significantly higher at Week 24 (Figure 2a and b). Statistical analysis could not be performed for ACR70 at Week 12 because of the 0% response in the placebo group. ACR responses in the 100 mg CZP group were less pronounced compared to those of the higher dose groups. The onset of response with CZP plus MTX was rapid across groups, with a significantly improved ACR20 response compared to placebo reported from Week 1 ($p < 0.001$). For all doses, the ACR20 response

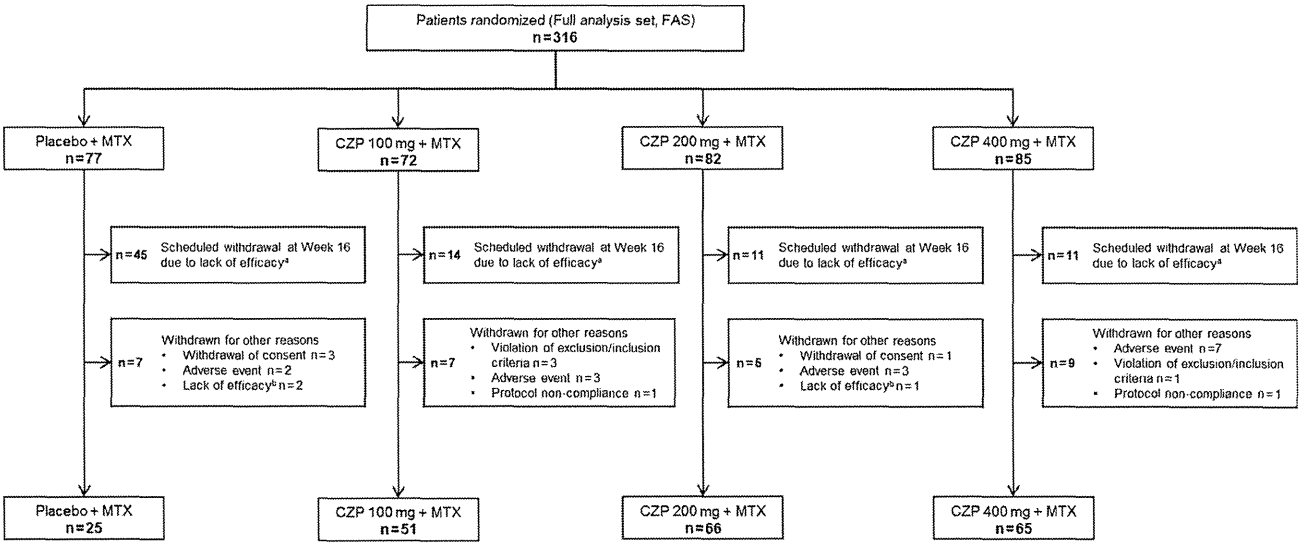

Figure 1. Patient disposition. [a]ACR20 response was not achieved at Weeks 12 and 14; [b]Efficacy of study drug was insufficient at times other than at Weeks 12 and 14. Patients not showing an ACR20 response at Weeks 12 and 14 were withdrawn from the study at Week 16 and were eligible to enter an open-label extension, as were patients completing the study.

Table 1. Patient demographics and disease status at baseline (FAS population).

Characteristic	Placebo + MTX ($n = 77$)	CZP 100 mg Q2W + MTX ($n = 72$)	CZP 200 mg Q2W + MTX ($n = 82$)	CZP 400 mg Q2W + MTX ($n = 85$)
Patient demographics and characteristics				
Mean age (SD), years	51.9 (11.1)	54.3 (10.6)	50.6 (11.4)	55.4 (10.3)
Female, n (%)	66 (85.7)	58 (80.6)	69 (84.1)	69 (81.2)
Mean body weight (SD), kg	56.2 (12.0)	52.9 (8.3)	56.3 (11.3)	56.4 (10.6)
Mean disease duration (SD), years	5.8 (4.1)	6.0 (4.1)	5.6 (4.2)	6.0 (3.9)
Mean no. of prior DMARDs (SD), including MTX	1.8 (0.9)	1.8 (0.8)	1.7 (0.8)	1.8 (0.9)
Mean MTX dose (SD), mg/week	7.4 (0.9)	7.4 (0.9)	7.6 (0.8)	7.5 (0.8)
Baseline corticosteroid use, n (%)	46 (59.7)	47 (65.3)	56 (68.3)	59 (69.4)
Prior anti-TNF use, n (%)	15 (19.5)	7 (9.7)	11 (13.4)	10 (11.8)
RF-positive (≥ 14 IU/mL), n (%)	66 (85.7)	65 (90.3)	71 (86.6)	76 (89.4)
Median, Mean RF level at baseline (SD), IU/mL	73.0, 189.0 (305.5)	83.5, 158.9 (220.3)	69.5, 154.9 (197.7)	93.0, 176.2 (217.9)
Disease activity status				
Mean DAS28(ESR) (SD)	6.5 (0.9)	6.3 (0.9)	6.2 (0.8)	6.3 (0.8)
Mean (SD) no. of tender joints (0–68)	19.6 (10.4)	21.2 (13.3)	19.0 (9.0)	20.5 (10.2)
Mean (SD) no. of swollen joints (0–66)	17.4 (10.0)	18.4 (10.7)	16.6 (8.4)	16.6 (7.4)
Patient's assessment of pain (100 mm VAS), mean (SD)	60.9 (22.6)	57.3 (20.8)	55.6 (20.6)	57.4 (21.9)
Patient's assessment of global disease activity (100 mm VAS), mean (SD)	57.8 (21.8)	55.8 (21.7)	53.0 (19.6)	56.0 (21.1)
Physician's assessment of global disease activity (100 mm VAS), mean (SD)	65.5 (15.5)	61.6 (19.2)	61.2 (16.2)	61.8 (16.2)
CRP (mg/dL), geometric mean (CV)	1.6 (165.2)	1.3 (144.9)	1.4 (123.0)	1.6 (146.8)
ESR (mm/h), geometric mean (CV)	47.6 (58.9)	44.5 (47.9)	46.3 (60.9)	49.0 (46.8)
Mean HAQ-DI (SD)	1.2 (0.7)	1.2 (0.7)	1.1 (0.7)	1.1 (0.6)
Mean duration of morning stiffness (SD), h	4.9 (8.3)	4.2 (7.0)	4.7 (7.5)	4.9 (7.7)
SF-36 component score				
Mean SF-36 PCS (SD)	26.4 (11.6)	27.1 (10.5)	26.0 (10.3)	27.6 (11.1)
Mean SF-26 MCS (SD)	45.7 (12.8)	46.7 (10.5)	46.9 (12.6)	47.2 (11.0)
Indicators of radiographic progression				
Total mTSS:				
Median (Q1, Q3)	37.5 (10.5, 75.5)	27.5 (8.5, 84.5)	31.3 (9.5, 86.0)	40.0 (7.5, 77.3)
Mean (SD)	52.7 (57.3)	54.8 (62.5)	50.4 (53.4)	49.9 (47.2)
mTSS erosion score:				
Median (Q1, Q3)	15.0 (5.0, 40.0)	14.8 (5.5, 43.0)	13.5 (4.0, 39.5)	18.5 (4.3, 42.3)
Mean (SD)	28.2 (33.3)	29.4 (35.9)	25.6 (30.0)	26.0 (25.9)
mTSS joint space narrowing score:				
Median (Q1, Q3)	16.0 (5.0, 37.0)	15.0 (2.5, 39.5)	18.0 (5.0, 42.0)	22.3 (1.3, 38.8)
Mean (SD)	24.5 (25.6)	25.4 (28.1)	24.7 (24.5)	24.0 (22.9)

CRP, C-reactive protein; CZP, certolizumab pegol; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire – Disability Index; MCS, mental component score; mTSS, modified Total Sharp Score; MTX, methotrexate; PCS, physical component score RF, rheumatoid factor; SD, standard deviation; VAS, visual analog scale.

had peaked by Week 8 and was sustained to Week 24 (Figure 2c). ACR50 responses were also rapid, with statistical significance reported from Week 2 with 100 mg and 200 mg doses, and all doses were significantly better than placebo at Week 4 (data not shown).

CZP plus MTX treatment was also associated with statistically significant improvements in all ACR core components at Weeks 12 and 24 (Table 2). This was statistically significant from Week 1 for all CZP doses compared to placebo for all ACR components ($p < 0.001$). A marked improvement in DAS28(ESR) was observed with all doses of CZP plus MTX from Week 1 ($p < 0.0001$) and sustained throughout the trial (Figure 2d). DAS28(ESR) remission rates (DAS28(ESR) < 2.6) were also markedly higher with CZP than with placebo plus MTX at Week 12 (8.3%, 16.0% and 11.8% for CZP 100 mg, 200 mg and 400 mg plus MTX, respectively, vs 0% for placebo plus MTX) and at Week 24 (20.8%, 17.1% and 25.9%, vs 0% placebo plus MTX).

Moderate or good EULAR responses were reported in 76.4%, 86.4% and 90.6% of patients receiving CZP 100 mg, 200 mg and 400 mg plus MTX, respectively, compared with 36.4% of patients on placebo plus MTX at Week 12 and 77.8%, 85.4% and 89.4% vs 29.9% at Week 24.

Physical function and HRQoL

HAQ-DI was significantly improved with all doses of CZP plus MTX at Week 12 and Week 24 ($p < 0.0001$, except for CZP 100 mg at Week 12 $p < 0.001$ and Week 24 $p < 0.005$) (Table 2). These improvements were significant from Week 1 and sustained at each visit throughout the trial (Figure 2e).

Least squares mean changes in SF-36 scores showed the beneficial effects of CZP plus MTX on HRQoL. Changes in physical component summary scores from baseline were significant for all CZP groups compared to placebo at Week 12 and sustained at Week 24 (Table 2). Similarly, changes in mental component summary scores were significant at Week 12 for the 200 and 400 mg CZP groups compared to those of placebo and maintained at Week 24 (Table 2).

Inhibition of progression of structural damage

Radiographic data were available at both baseline and after drug administration for 76 of 77 placebo patients and 70 of 72, 81 of 82, and 84 of 85 patients in the CZP 100, 200, and 400 mg groups, respectively. CZP plus MTX inhibited the progression of structural damage compared to placebo at Week 24 (Figure 3a and b). Mean changes from baseline to Week 24 in total mTSS were significantly lower in the CZP 200 mg ($p < 0.001$) and CZP 400 mg ($p < 0.01$) plus MTX groups compared to placebo. The progression in joint erosion was also significantly lower in all CZP groups compared to placebo. The mean change in JSN was significantly lower for the CZP 200 mg dose compared to placebo. Numerically, across all three radiographic measures

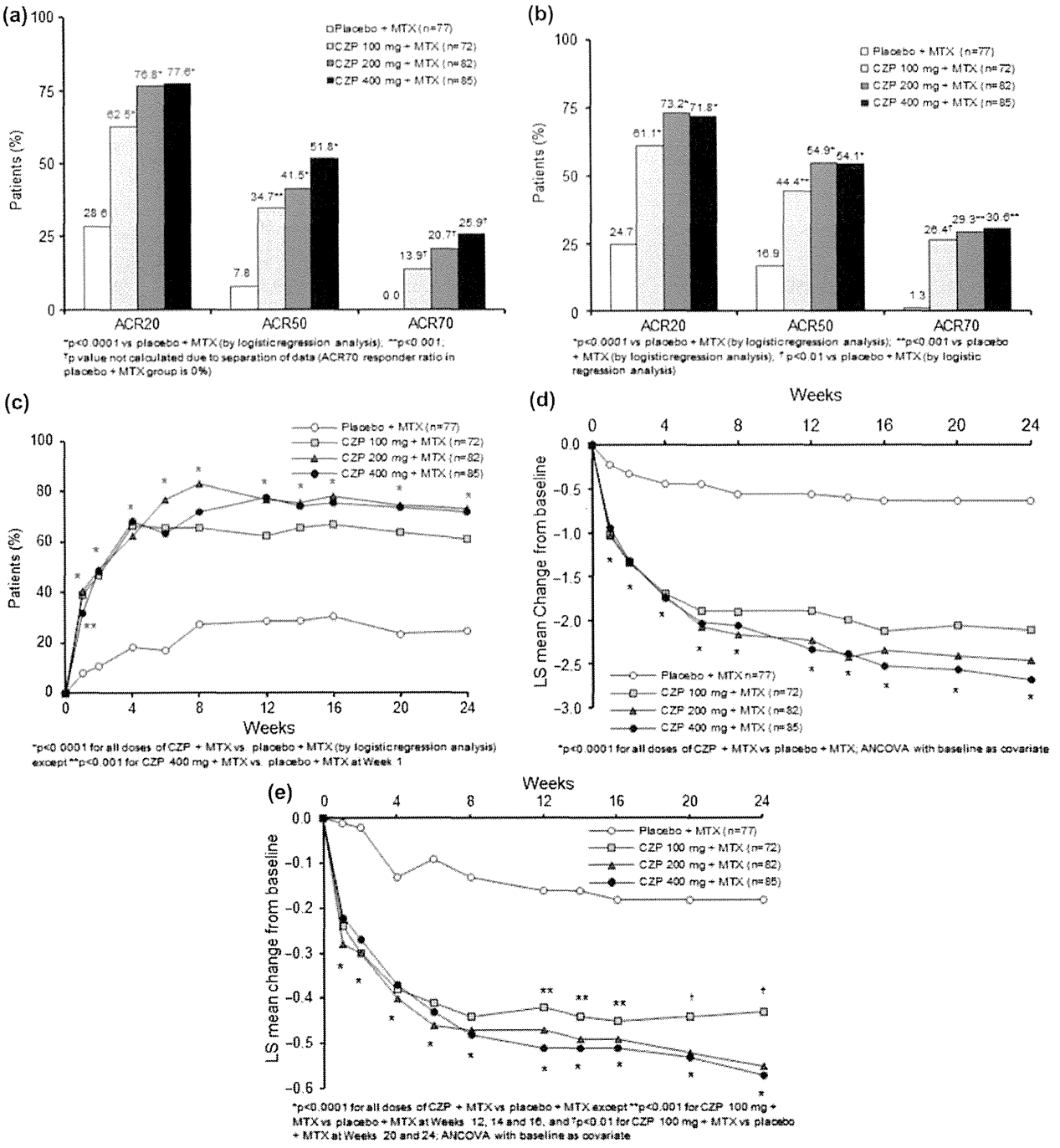

Figure 2. ACR response rates and improvements in DAS28(ESR) and HAQ-DI scores up to Week 24: (a) ACR20, ACR50, and ACR70 response rates at Week 12, (b) ACR20, ACR50, and ACR70 response rates at Week 24, (c) ACR20 response over time (FAS population; NRI: patients who received rescue medication, or who withdrew for any reason, were considered non-responders from that time point forward), (d) Improvements in DAS28(ESR) over time (FAS population; LOCF), (e) Improvements in HAQ-DI over time (FAS population; LOCF).

the greatest inhibition in the progression of joint damage was seen with CZP 200 mg plus MTX (Figure 3a). A higher percentage of patients who received CZP 200 mg or 400 mg plus MTX achieved mTSS non-progression at Week 24 than with placebo plus MTX (47.4% of patients on placebo plus MTX compared with 74.1% ($p < 0.001$) and 70.2% ($p < 0.01$) of patients receiving CZP 200 mg and 400 mg plus MTX, respectively). Linear extrapolation was used to impute missing radiographic data in 51/76 placebo patients (including those who withdrew at Week 16) and 21/70, 15/81 and 20/84 CZP 100, 200 and 400 mg patients, respectively.

Safety

TEAEs were similar between treatment groups, as reported in Table 3. The majority of events were of mild to moderate severity. SAEs were infrequent, occurring in 13 patients: 3 (4.2%), 4 (4.9%), 5 (5.9%) and 1 (1.3%) for CZP 100 mg, 200 mg and 400 mg plus

Table 2. Least squares (LS) mean change from baseline or ratio of geometric mean to BL at Weeks 12 and 24 in ACR core components and other endpoints (FAS population with LOCF).

	Week 12				Week 24			
Characteristics	Placebo + MTX ($n = 77$)	CZP 100 mg Q2W + MTX ($n = 72$)	CZP 200 mg Q2W + MTX ($n = 82$)	CZP 400 mg Q2W + MTX ($n = 85$)	Placebo + MTX ($n = 77$)	CZP 100 mg Q2W + MTX ($n = 72$)	CZP 200 mg Q2W + MTX ($n = 82$)	CZP 400 mg Q2W + MTX ($n = 85$)
LS mean change from baseline (SE)								
Tender joint count*	–3.44 (0.96)	–10.79 (0.99)	–13.46 (0.93)	–12.46 (0.91)	–2.75 (1.02)	–11.79 (1.05)	–14.41 (0.99)	–13.44 (0.97)
Swollen joint count*	–2.70 (0.74)	–8.28 (0.76)	–11.36 (0.71)	–10.89 (0.70)	–2.39 (0.81)	–9.55 (0.84)	–11.71 (0.79)	–11.74 (0.77)
Patient's assessment of pain, 100 mm VAS*	–8.9 (2.4)	–23.8 (2.5)	–25.6 (2.3)	–28.7 (2.3)	–10.6 (2.6)	– 26.9 (2.6)	–27.9 (2.5)	–31.9 (2.4)
Patient's assessment of global disease activity, 100 mm VAS*	–5.7 (2.4)	–22.1 (2.5)	–24.2 (2.4)	–27.5 (2.3)	–7.3 (2.6)	–25.2 (2.7)	–27.2 (2.5)	–31.3 (2.5)
Physician's assessment of global disease activity, 100 mm VAS*	–11.7 (2.4)	–32.5 (2.4)	–34.5 (2.3)	–37.0 (2.2)	–11.6 (2.5)	–34.5 (2.5)	–36.0 (2.4)	–38.4 (2.3)
HAQ-DI**	–0.16 (0.05)	–0.42 (0.05)	–0.47 (0.05)	–0.51 (0.05)	–0.18 (0.06)	–0.43 (0.06)	–0.55 (0.05)	–0.57 (0.05)
DAS28(ESR)*	–0.56 (0.13)	–1.89 (0.14)	–2.23 (0.13)	–2.33 (0.13)	–0.63 (0.15)	–2.11 (0.16)	–2.46 (0.15)	–2.69 (0.14)
Duration of morning stiffness, h†	–0.97 (0.54)	–2.22 (0.56)	–2.23 (0.52)	–2.79 (0.52)	–1.07 (0.54)	–2.08 (0.56)	–2.44 (0.52)	–3.09 (0.51)
SF-36 component score								
SF-36 PCS‡	2.5 (1.1)	8.2 (1.1)	9.0 (1.0)	9.8 (1.0)	4.3 (1.1)	8.9 (1.2)	10.2 (1.1)	11.4 (1.1)
SF-36 MCS§	1.2 (1.1)	3.7 (1.1)	4.8 (1.0)	5.9 (1.0)	1.2 (1.1)	3.2 (1.1)	5.6 (1.0)	5.8 (1.0)
Mean, ratio to baseline[b]								
CRP	0.84	0.26	0.25	0.21	0.76	0.30	0.28	0.20
ESR	0.9	0.5	0.5	0.4	0.8	0.5	0.4	0.4

ACR, American College of Rheumatology; CRP, C-reactive protein; CZP, certolizumab pegol; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire – Disability Index; LS, least squares; LOCF, last observation carried forward; MCS, mental component score; MTX, methotrexate; PCS, physical component score; SE, standard error; VAS, visual analog scale.

*$p < 0.0001$ for all comparisons of active treatment vs placebo.

**$p < 0.0001$ for CZP 200 mg and 400 mg vs placebo, $p < 0.001$ at Week 12 and $p < 0.005$ at Week 24 for CZP 100 mg vs placebo.

†$p < 0.05$ at Week 12 and $p < 0.01$ at Week 24 for CZP 400 mg vs placebo.

‡$p < 0.001$, except for $p < 0.005$ at Week 24 for CZP 100 mg vs placebo.

§$p < 0.005$ at Week 12 for CZP 400 mg vs placebo and Week 24 for CZP 200 mg and CZP 400 mg vs placebo and $p < 0.05$ at Week 12 for CZP 200 mg vs placebo, CZP 100 mg vs placebo was not significant at Weeks 12 and 24.

[a]Errors for LS mean values were estimated using standard error (SE).

[b]Geometric mean.

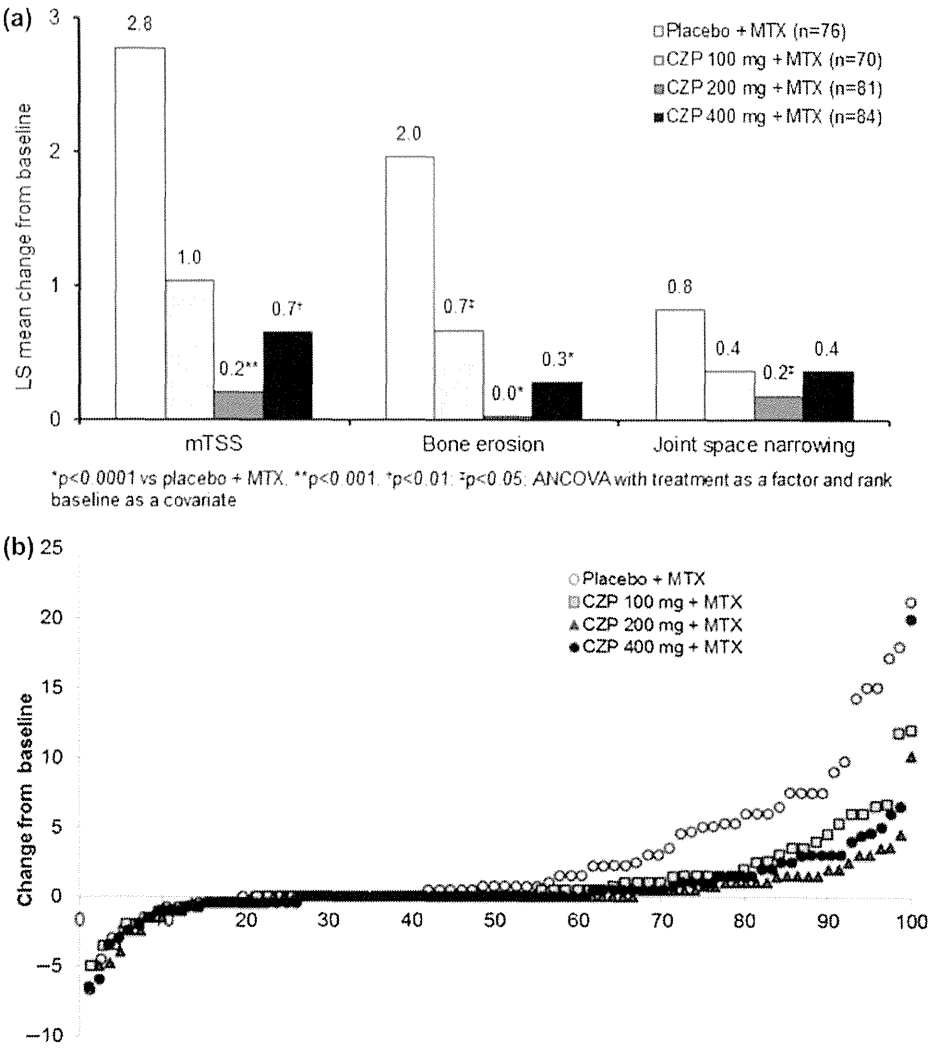

Figure 3. Inhibition of progression of structural damage: (a) Change from baseline in total mTSS, bone erosion and joint space narrowing at Week 24 (FAS population, linear extrapolation). *$p < 0.0001$ vs placebo + MTX; **$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$; ANCOVA with treatment as a factor and rank baseline as a covariate, (b) Cumulative probability plot of change from baseline in mTSS at Week 24 (FAS population, linear extrapolation).

MTX and placebo plus MTX, respectively (Table 3). There were no cases of tuberculosis or malignant disease and no deaths during these 24 weeks of the study.

The most frequent AE by system organ class was infections and infestations, occurring in 84 patients (35.1%) in the CZP-treated groups and 19 patients (24.7%) in the placebo group. Administration site reaction (2.5% and 0.0%), injection site erythema (0.8% and 0.0%), injection site hematoma (0.4% and 0.0%), injection site hemorrhage (0.0% and 1.3%), injection site mass (0.4% and 0.0%) and injection site reaction (0.4% and 1.3%) were reported in CZP-treated groups and placebo group, respectively, and the majority of reactions were mild. In the CZP groups, the proportions of patients who showed high aspartate aminotransferase and alanine aminotransferase levels after administration despite normal values at baseline were slightly higher than in the placebo group.

Anti-CZP antibodies were noted in 11 patients; 9 (12.5%) were in the 100 mg group and 1 each (1.2%) in the 200 and 400 mg groups, which may have partially contributed to the lower efficacy in the 100 mg group compared with the higher doses (Week 24 ACR20 response rate: CZP 100 mg, 61.1%; CZP 200 mg, 73.2%; and CZP 400 mg, 71.8%). There were no differences in the safety profile between patients with and without anti-CZP antibodies.

Discussion

In this study, treatment with CZP plus MTX was associated with a rapid and significant reduction in the signs and symptoms of RA, inhibition of the progression of joint damage, and improved physical function and HRQoL in Japanese patients with active RA and an inadequate response to MTX.

The primary efficacy endpoint, ACR20 response at Week 12, was met by significantly more patients in the CZP 100, 200 and 400 mg groups compared to those in the placebo group. Higher responses vs placebo plus MTX were obtained with CZP plus MTX within the first week of treatment, and were sustained to Week 24. These differences were statistically significant. Rapid and sustained effects of active treatment were evident for all ACR core components, indicated by the effects on tender and swollen joint counts, on physical functioning (HAQ-DI) and on the patient's perception of pain, similar to other clinical trials [5,7,8,19]. Overall HRQoL significantly improved with all doses of CZP plus MTX; improvement in a greater number of individual subscales was seen with the two higher doses.

Both CZP 200 mg and CZP 400 mg plus MTX groups demonstrated statistically significant inhibition of joint damage vs placebo. Furthermore, CZP 200 mg plus MTX showed numerically better efficacy and greater inhibition of joint damage than CZP 100 mg plus MTX, and no additional benefit of the higher CZP 400 mg plus MTX dose over the 200 mg plus MTX dose was observed. These findings support the results of the previous Phase III studies, and confirm 200 mg Q2W as the optimum dose of CZP [5,8].

The CZP 100 mg Q2W group was included in the study on the assumption that the average body weight of the Japanese patients may be lower than that in the patients enrolled in the international

Table 3. Treatment-emergent adverse events (safety population).

Adverse events	Number of patients (%)			
	Placebo + MTX[a] ($n = 77$)	CZP 100 mg Q2W + MTX[b] ($n = 72$)	CZP 200 mg Q2W + MTX[c] ($n = 82$)	CZP 400 mg Q2W + MTX[d] ($n = 85$)
Any adverse event	51 (66.2)	54 (75.0)	63 (76.8)	64 (75.3)
Intensity				
Mild	28 (36.4)	30 (41.7)	41 (50.0)	36 (42.4)
Moderate	22 (28.6)	24 (33.3)	20 (24.4)	24 (28.2)
Severe[e]	1 (1.3)	0	2 (2.4)	4 (4.7)
Treatment-related[f]	21 (27.3)	29 (40.3)	31 (37.8)	35 (41.2)
Serious adverse events (total)	1 (1.3)	3 (4.2)[g]	4 (4.9)[h]	5 (5.9)[i]
Malignancy	0	0	0	0
Deaths	0	0	0	0
Most common adverse event[j] *(≥ 5% in any group)*				
Nasopharyngitis	9 (11.7)	8 (11.1)	11 (13.4)	13 (15.3)
Abnormal hepatic function	4 (5.2)	8 (11.1)	3 (3.7)	5 (5.9)
Eczema	2 (2.6)	4 (5.6)	3 (3.7)	4 (4.7)
Rheumatoid arthritis exacerbation	9 (11.7)	3 (4.2)	4 (4.9)	3 (3.5)
Upper respiratory tract infection	3 (3.9)	5 (6.9)	2 (2.4)	3 (3.5)
Pharyngitis	3 (3.9)	5 (6.9)	5 (6.1)	2 (2.4)
Allergic conjunctivitis	1 (1.3)	4 (5.6)	2 (2.4)	1 (1.2)
Serious adverse events				
Interstitial lung disease n, (%)				2 (2.4)
Acute myocardial infarction n, (%)				1 (1.2)
Rheumatoid arthritis n, (%)			1 (1.2)	1 (1.2)
Meningitis noninfective n, (%)				1 (1.2)
Corneal perforation n, (%)				2 (1.2)
Bronchitis n, (%)			1 (1.2)	
Pyelonephritis n, (%)			1 (1.2)	
Purulent myositis n, (%)			1 (1.2)	
Subcutaneous tissue abscess n, (%)			1 (1.2)	
Urosepsis n, (%)			1 (1.2)	
Viral enterocolitis n, (%)		1 (1.4)		
Spinal compression fracture n, (%)		1 (1.4)		
Organized pneumonia n, (%)		1 (1.4)		
Bone marrow failure n, (%)		1 (1.4)		
Anal fistula n, (%)	1 (1.3)			

[a]Total exposure: 25.16 patient-years.
[b]Total exposure: 30.50 patient-years.
[c]Total exposure: 36.80 patient-years.
[d]Total exposure: 36.78 patient-years.
[e]Severe adverse event defined as an event that prevents work or daily activities.
[f]Treatment-emergent adverse events for which the relationship to the study drug cannot be ruled out.
[g]4 events in 3 patients.
[h]6 events in 4 patients.
[i]7 events in 5 patients.
[j]Preferred terms according to MedDRA terminology.

studies. Consequently, the efficacy of the lower dose (CZP 100 mg) was compared to the standard CZP 200 mg Q2W dose, and was found to give lower ACR20, ACR50 and ACR70 response rates at both Weeks 12 and 24 (Figure 2), as well as less inhibition of joint damage at Week 24 (Figure 3). In addition, subgroup analysis revealed that the efficacy of CZP was not associated with the patients' body weight (data not shown).

There were slight differences in the baseline history of TNF inhibitor usage between the placebo and CZP 100 mg groups (7/77 patients in the CZP 100 mg group vs 15/72 patients in the placebo group). In subgroup analyses, ACR20 response rates were higher in the CZP groups than in the placebo group, regardless of prior TNF inhibitor exposure (data not shown), therefore it is presumed that the effect of previous TNF inhibitor usage on ACR20 response rate was limited.

The difference in the efficacy between dosing regimen of CZP 400 mg at Weeks 0, 2, and 4 (Figure 2c: CZP 200 mg group and 400 mg group) and CZP 200 mg at Weeks 0, 2, and 4 (Figure 2c: CZP 100 mg group) was not very clear. In order to investigate the additive effect of induction doses on ACR20 response rate in Japanese RA patients, simulation of two dosing regimens was performed, (1) with induction dose (CZP 400 mg at Weeks 0, 2 and 4, followed by 200 mg Q2W) and (2) without induction dose (CZP 200 mg Q2W from Week 0), using a pharmacokinetic (PK) model and a PK/pharmacodynamic (PD) model. The results predicted that use of the induction doses improves the efficacy of CZP during the initial stage of treatment, which peaks at Weeks 7 and 8. The median ACR20 response rates at the peak time points were around 68% and 69% with the induction doses vs around 56% and 57% without the induction doses, suggesting approximately 10% increase in ACR20 is predicted by administering the induction dose. The PK/PD model predicts that the beneficial effect of the induction dose will remain apparent at Week 12.

CZP plus MTX was well-tolerated at all three doses assessed, with low rates of discontinuation due to AEs, with the CZP 100 mg and 200 mg groups showing similar rates to the placebo group. Most events were of mild to moderate severity and SAEs were infrequent, occurring in 4.2–5.9% of CZP patients. Overall, there were no differences in the safety profile among the doses in the CZP-treated groups. Although the rates of AEs were higher compared to RAPID 1 [8] and RAPID 2 [5], this was true for both the placebo and the CZP-treated patients. The safety profile of CZP was similar to the results of previous clinical studies, as expected for anti-TNF agents. There was no new event in terms of safety in these Japanese patients in comparison with the international data.

A relatively high incidence of tuberculosis in Japan (24.8 cases per 100,000 per year, five times the US incidence [20]) has given rise to concerns over the possibility of increased rates of this infection with TNF inhibitor therapy [21]. However, in the present study there were no reports of tuberculosis. Although confirmation needs to be obtained through postmarketing surveillance studies, the findings herein are concordant with such data for infliximab [20] and etanercept [22], where early fears over increased risk of serious respiratory infection in Japanese patients specifically were shown to be unfounded.

Limitations of this study exist due to the specific design herein; patients with history of use of ≥ 2 TNF inhibitors and those who had not previously responded to TNF inhibitor therapy were excluded. Consequently, the results of this study may not accurately reflect treatment of CZP with MTX in patients with these profiles. Likewise, as the study was only 24 weeks in length, the safety and efficacy of CZP will need further assessment during the long-term open-label extension of this study.

Adoption of a tight control approach to treatment, through regular patient follow-up with appropriate adaptation of therapy, to reach a state of low disease activity within 3–6 months of treatment is among the key recommendations of an international task force examining the treat-to-target approach in RA [9]. A treatment regimen with a rapid response may facilitate early decision making and enable the treatment of non-responding patients to be optimized quickly in line with these recommendations [23]. A post-hoc analysis of the international RAPID 1 study demonstrated that the majority of DAS28 response with CZP (DAS28 improvement of ≥ 1.2) was reported within 12 weeks of initiating treatment, and that early DAS28 non-response is a predictor of poorer long-term outcomes [24]. In this study with Japanese patients, reduction in the signs and symptoms of RA by treatment with CZP plus MTX was similarly rapid, and significant improvement was achieved at Week 12, suggesting the possibility of early prediction of response at Week 12. This will be further examined using long-term data from the open-label extension of this trial.

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Conflicts of interest

The competing interests of all authors are provided below.

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- TT has served as a consultant for AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe and Asahi Kasei, and has received research support from Abott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has served on speaker bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.
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- YT has received research funding from BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbott, Eisai and Janssen, and has served on speaker bureaus for UCB Pharma, Mitsubishi-Tanabe, Abbott, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, Quintiles Transnational and Ono.
- KE has served as a consultant for UCB Pharma.
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- HO has served as a consultant for UCB Pharma and Astellas.

- TS is an employee of Otsuka.
- YS is an employee of UCB Pharma.
- DvH has served as a consultant for, and received research support from, AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Daiichi, Eli Lilly, GSK, Janssen, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma and Vertex. DvH is also director of Imaging Rheumatology bv.
- NM has received research support from Pfizer, Takeda, Mitsubishi-Tanabe, Chugai, Abbott, Eisai and Astellas.
- TK has served on speaker bureaus for UCB Pharma, Pfizer, Chugai, Abbott, Mitsubishi-Tanabe, Takeda, Eisai, Santen, Astellas, Taisho-Toyama, BMS, Teijin and Daiichi-Sankyo.

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ORIGINAL ARTICLE

Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: The HIKARI randomized, placebo-controlled trial

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Abstract

Objective. This 24-week, placebo-controlled, double-blind, randomized study (NCT00791921) investigated efficacy and safety of certolizumab pegol (CZP) in Japanese rheumatoid arthritis (RA) patients in whom methotrexate (MTX) cannot be administered.

Methods. A total of 230 patients were randomized to subcutaneous CZP 200 mg (induction dosing: 400 mg at Weeks 0, 2 and 4) or placebo every 2 weeks.

Results. ACR20 responses with CZP were rapid and significant versus placebo at Week 1, sustained to Week 12 (67.2% vs. 14.9%) and Week 24 (63.8% vs. 11.4%). Week 24-modified Total Sharp Score (mTSS) change from baseline (CFB) was 0.48 (CZP) versus 2.45 (placebo). CZP treatment was associated with higher Week 12 ACR20 responses versus placebo (with non-MTX disease modifying antirheumatic drugs [DMARDs], 74.2% vs. 20.0%; without [monotherapy], 59.3% vs. 8.2%) and inhibition of radiographic progression at Week 24 (mTSS CFB; with non-MTX DMARDs, 0.24 vs. 1.61; monotherapy, 0.68 vs. 3.65). Incidences of serious adverse events were 11.2% (CZP) and 2.6% (placebo); one CZP patient died of dissecting aortic aneurysm.

Conclusion. CZP treatment with and without non-MTX DMARDs in Japanese patients in whom MTX cannot be administered resulted in rapid, sustained reductions in RA signs and symptoms. Notably, CZP monotherapy showed significant inhibition of radiographic progression.

Keywords

Certolizumab pegol, Monotherapy, Randomized controlled trial, Rheumatoid arthritis, Tumor necrosis factor-alpha inhibitor

History

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Introduction

The efficacy of inhibiting tumor necrosis factor alpha (TNF-α) in the management of rheumatoid arthritis (RA) has been demonstrated in both Japanese and non-Japanese patients [1–8].

Certolizumab pegol (CZP) is a PEGylated Fc-free anti-TNF-α agent. The efficacy of CZP plus methotrexate (MTX) has previously been demonstrated in patients with active RA who did not respond adequately to disease-modifying antirheumatic drugs (DMARDs) including MTX in the RAPID 1 and RAPID 2 studies [5,6]. Treatment with CZP plus MTX has also shown a rapid reduction of RA signs and symptoms and inhibition of structural joint damage in Japanese patients with active RA who had an inadequate response to MTX [Yamamoto et al. 2013].

However, MTX cannot be administered in all patients due to lack of efficacy, tolerability concerns or contraindications related to its antimetabolite action [9]. The efficacy of CZP treatment without concomitant DMARDs (i.e. monotherapy) for non-Japanese patients with active RA who had failed to respond to DMARDs has been demonstrated in the FAST4WARD trial [10].

The objective of the HIKARI study was to investigate the efficacy and safety of CZP 200 mg every 2 weeks (Q2W) in Japanese patients with active RA in whom MTX cannot be administered.

Materials and methods

Study overview

HIKARI was a 24-week, phase 3, multicenter, double-blind, randomized placebo-controlled study (NCT00791921) conducted

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between 19 November 2008 and 16 September 2010 in 66 centers across Japan in patients with active RA who could not receive MTX due to insufficient efficacy, safety concerns or previous discontinuation for safety reasons.

Patients were randomized 1:1 to subcutaneous CZP 200 mg or saline placebo Q2W after a 1–4 week screening period. Block randomization was used to allocate participants to treatment arms. The random allocation sequence was generated using uniform random numbers from SAS® RANUNI function. The study drug allocation center was responsible for preparation and storage of the randomization table, study drug allocation and confirmation of indistinguishability of study drugs, while the registration center was responsible for assignment of study drug numbers to patients. Patients randomized to CZP received 400 mg induction doses at Weeks 0, 2 and 4. Patients randomized to placebo received an equivalent injection regimen. Study drug administration was performed by non-blinded personnel who were not allowed to engage in other study activities.

Patients who did not achieve an ACR20 response (i.e. ≥ 20% improvement according to American College of Rheumatology [ACR] criteria [11]) at Weeks 12 and 14 (ACR20 non-responders) were withdrawn at Week 16 and were eligible to enter an open-label extension (OLE) study thereafter.

The study was carried out in accordance with the Declaration of Helsinki and Pharmaceutical Affairs Law Standards for the Conduct of Clinical Trials on Drugs (Ministry of Health, Labour and Welfare Ordinance No. 28, 27 March 1997) and related notifications. Institutional review board approval was obtained at all centers and written informed consent provided by all patients.

Patients

Eligible patients were aged 20–74 years and had a diagnosis of adult-onset RA as defined by ACR criteria of 0.5–15 years' disease duration [12]. Patients unable to receive MTX therapy due to prior insufficient efficacy or safety concerns were eligible to enter this study; MTX treatment must have been terminated ≥ 28 days prior to study entry. Patients must have failed treatment with, or been resistant to, ≥ 1 prior DMARDs (including MTX). Active disease was defined as ≥ 6 tender joints (68 joints evaluated) and ≥ 6 swollen joints (66 joints evaluated) at screening and baseline, and at least one of either erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or C-reactive protein (CRP) ≥ 2.0 mg/dL.

Non-MTX DMARDs were permitted provided that doses were fixed from ≥ 28 days before study drug administration to the end of the trial. Other permitted drugs were: non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors at doses that were stable for ≥ 14 days before study entry; sedatives; influenza and pneumococcus vaccines (all other live or attenuated vaccines were prohibited); one dose of intramuscular or intra-articular corticosteroid up to 8 weeks after study commencement; and oral corticosteroids (up to 10 mg/day prednisone equivalent).

Patients with inflammatory arthritis other than RA were excluded. Other exclusion criteria included previous treatment with biologic DMARDs in the 6 months preceding the study (3 months for etanercept); any investigational drug in the preceding 3 months; ≥ 2 TNF inhibitors; and failure to respond to previous TNF inhibitor therapy in the initial phase. Those patients who had displayed severe hypersensitivity or anaphylactic reaction to previous biologic DMARDs were excluded. Azathioprine and cyclosporine were not permitted in the 28 days prior to the start of trial drug administration and they, along with intravenous corticosteroids and intra-articular hyaluronic acid, were prohibited throughout the study.

Patients with any indication of current or past tuberculosis (by clinical history, chest X-ray and/or positive tuberculin reaction test) were excluded unless preventive therapy by isoniazid was taken.

Study assessments

Efficacy assessments were carried out over the 24-week treatment period as follows: at baseline, Weeks 1, 2, 4, 6, 8, 12, 14, 16, 20 and 24 or time of discontinuation. Safety was assessed at every visit and at 12-week follow-up. Patients not proceeding to the OLE underwent a further follow-up examination 12 weeks after final dose.

The primary efficacy endpoint was ACR20 response rate at Week 12. The secondary efficacy endpoint was ACR20 response rate at Week 24.

Additional endpoints included: ACR20 response at other time points; ACR50 and ACR70 response rates; ACR core component scores: number of tender and swollen joints, assessment of physical function by the Health Assessment Questionnaire Disability Index (HAQ-DI), patient's and physician's global assessment of disease activity (100 mm visual analog scale [VAS]), patient assessment of arthritic pain (VAS), CRP and ESR; prevention of progression of joint destruction (change in modifiied Total Sharp Score [mTSS]) at Week 24; duration of morning stiffness; Disease Activity Score 28-joint assessment with ESR (DAS28[ESR]) and European League Against Rheumatism (EULAR) response [13].

The structural integrity of the joints was assessed using the van der mTSS [14,15]. Radiographs of hands and feet at baseline and Week 24 or discontinuation were independently and blindly assessed by two experienced readers. Joint erosion was assessed in 44 joints and joint space narrowing (JSN) in 42 joints, and mean scores across readers were used for analysis. Erosions and JSN were summed to obtain mTSS, and mTSS non-progression was defined as change from baseline (CFB) in mTSS ≤ 0.5 units.

Health-related quality-of-life (HRQoL) was assessed at baseline, Weeks 12 and 24 using the Short Form-36 Health Survey (SF-36) [16].

Post-hoc analyses on patients receiving either CZP monotherapy or CZP with concomitant non-MTX DMARDs were performed to examine the effect on ACR20 response rates at Week 12 and on radiographic progression at Week 24.

Plasma samples were analyzed for determination of CZP concentration, and anti-CZP antibodies were also measured at every visit to Week 8, then at Weeks 12 and 24 or at the time of discontinuation. Safety assessments included adverse events (AEs), laboratory findings, body weight and vital signs. Serious AEs (SAEs) were those that resulted in death, were life-threatening, required or prolonged hospitalization, or resulted in significant disability, incapacity or congenital anomalies/birth defects.

Statistical analysis

Sample size was based on previous clinical experience in monotherapy trials with an expected 20% ACR20 response in the placebo group and ≥ 42% in the CZP group. A projected 91 patients were needed in each group to detect superiority of CZP 200 mg over placebo with 90% power at a two-sided significance level of 0.05. The target number of patients was 200 (full analysis set [FAS]), 100 patients per group, to allow for dropouts.

The primary population for efficacy analysis was the FAS of patients who received ≥ 1 study drug dose and provided ≥ 1 efficacy data thereafter. The safety population contained all patients who received ≥ 1 study drug dose.

ACR responses were determined using non-responder imputation (NRI). Patients who violated study protocol, received rescue medication or withdrew for any reason were considered non-responders from that time point.

ACR intergroup comparisons between CZP and placebo groups were carried out using logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Changes in ACR core components and in total tender and swollen joint counts between baseline and Week 24 were examined using analysis of covariance (ANCOVA) with baseline value as covariate and last observation carried forward (LOCF) imputation for missing data. Changes from baseline to the assessment time point for DAS28(ESR), SF-36 and duration of morning stiffness were analyzed using ANCOVA (LOCF) with treatment group as a factor and baseline value as covariate. For EULAR response (good, moderate or no response), intergroup comparisons using logistic regression at each time point were conducted using LOCF imputation.

For radiographic outcomes, in patients in whom administration was discontinued before Week 24, Week 24 values were estimated employing linear extrapolation using values obtained at the discontinuation visit. To examine change in rank from baseline, ANCOVA was performed using rank of baseline mTSS as covariate and treatment as a factor.

Treatment-emergent AEs (TEAEs) included all events from after administration of study drug until the last evaluation visit (not including the safety follow-up visit). TEAEs were coded by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) terminology (v11.1).

Results

Patient characteristics and disposition

A total of 230 patients (FAS) with active RA, 63.5% of which experienced safety problems or had safety concerns with MTX use, entered this study and were randomized to CZP 200 mg ($n = 116$) or placebo ($n = 114$). Fewer patients treated with CZP ($n = 24$) than placebo ($n = 88$) withdrew because of insufficient efficacy at Week 16, with 82 (70.7%) and 18 (15.8%) patients, respectively, completing 24 weeks of the double-blind study (Figure 1). The remaining 10 patients in the CZP group withdrew due to withdrawal of consent ($n = 1$), AEs ($n = 8$) and failed drug administration more than twice ($n = 1$) (Figure 1). In the placebo group, eight patients withdrew due to withdrawal of consent ($n = 2$), AEs ($n = 2$), lack of efficacy at times other than Week 12 or Week 14 ($n = 2$), protocol non-compliance ($n = 1$) or failed drug administration more than twice ($n = 1$) (Figure 1). Demographics and baseline characteristics were similar between CZP and placebo groups with mean DAS28(ESR) > 6 at baseline (Table 1).

Just over half of all patients were receiving non-MTX DMARDs at baseline; in the active group, 53.4% of patients were treated with CZP plus concomitant DMARDs compared with 46.6% treated with CZP monotherapy (i.e. no additional DMARDs).

Clinical efficacy

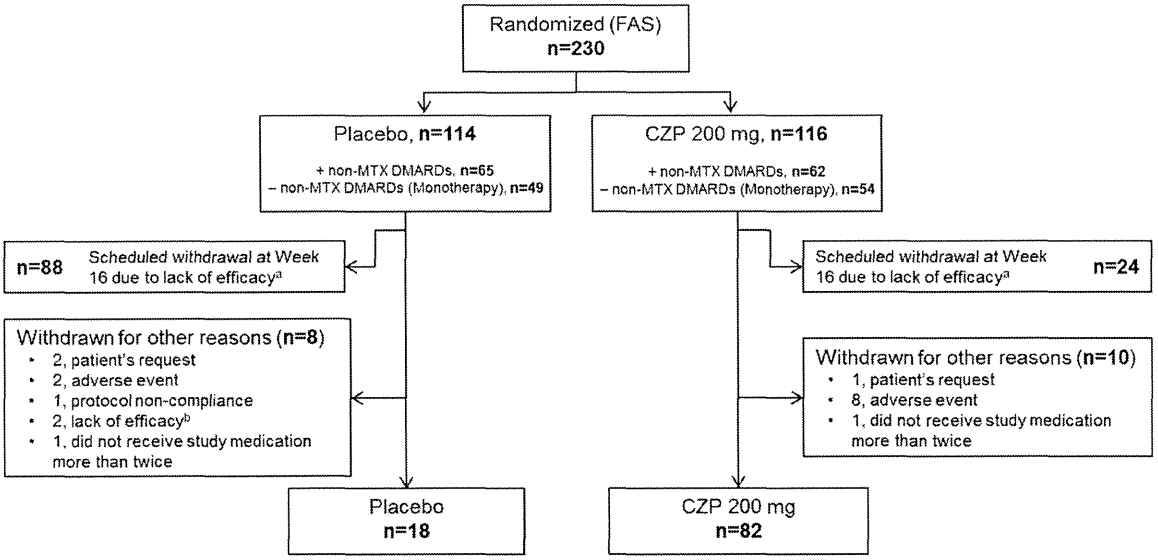
ACR20 responses were statistically significantly higher in the CZP group ($n = 116$) than in the placebo group ($n = 114$), at Weeks 12 and 24 (Figure 2a). Statistical significance was also reported for ACR50 responses at Weeks 12 and 24 and for ACR70 responses at Week 24. For ACR70 at Week 12, statistical analysis could not be performed due to zero response rate in the placebo group (Figure 2a).

The onset of response with CZP was rapid, with significantly greater ACR20 rates compared to placebo reported from Week 1 (32.8% vs. 5.3%; $p < 0.0001$). The ACR20 response peaked at Week 4 and was sustained to Week 24 (Figure 2b). ACR50 response was also rapid, with significant improvements compared to placebo reported from Week 1 ($p < 0.05$) (data not shown). CZP treatment was associated with significant improvement in all ACR core components (Table 2).

Mean DAS28(ESR) scores were significantly improved with CZP from Week 1 (Figure 2c). Significantly higher remission rates (DAS28[ESR] < 2.6) at Week 24 were achieved with CZP (16.4%) than with placebo (0.9%; $p < 0.005$). Moderate or good EULAR responses were more frequent among patients receiving CZP at Weeks 12 and 24 (82.8 and 77.6%, respectively) than placebo (28.1% and 21.9%, respectively; statistical analysis not undertaken).

HRQoL

Improvements in HAQ-DI with CZP over placebo were significant at Week 1 (CZP: −0.30, placebo: −0.01; $p < 0.0001$) and



[a]ACR20 response was not achieved at Week 12 and Week 14. [b]Efficacy of study drug was insufficient at times other than at Week 12 and Week 14. Patients not showing an ACR20 response at Week 12 and Week 14 were withdrawn from the study at Week 16 and were eligible to enter an open-label extension, as were patients completing the study.

Figure 1. Patient disposition.