Table 2 continued

	Group 1 ($n = 84$)	Group 2 ($n = 175$)	Group 3 ($n = 349$)	Group 4 ($n = 369$)	Group 5 ($n = 124$)	p[a]
Other prior medication						
GCs > 5 mg/day	14 (16.7)	27 (15.4)	56 (16.0)	72 (19.5)	30 (24.2)	0.0854
GCs > 7.5 mg/day	10 (11.9)	11 (6.3)	21 (6.0)	31 (8.4)	11 (8.9)	0.0886
DMARDs (excluding MTX)	24 (28.6)	45 (25.7)	68 (19.5)	73 (19.8)	29 (23.4)	0.1987

Group 1, >0–<4 mg; group 2, ≥4–<6 mg; group 3, ≥6–<8 mg; group 4, ≥8–<10 mg; group 5, ≥10 mg. Values are means ± SD or n (%). [a]Chi-square test for categorical variables, Kruskal–Wallis test used for continuous variables. [b]Includes patients with a past or current history of pulmonary disease (e.g., pneumonia, asthma, and obstructive pulmonary disease) and those with abnormal chest radiographic findings. A weighted average dose was used to calculate mean MTX dose. *DAS28-ESR* disease activity score for 28 joints based on the erythrocyte sedimentation rate, *DMARDs* disease-modifying antirheumatic drugs, *GCs* glucocorticoids, *MTX* methotrexate, *RA* rheumatoid arthritis

DAS28-ESR scores at baseline did not differ by MTX dose in either patient population, and both populations had similar scores (Tables 1, 2).

LDA and remission rates at week 24 are summarized in Fig. 1. In the 1996 biologic-naïve patients, LDA rates were 39.2, 43.0, 49.7, 49.8, and 50.5% in groups 1 through 5, respectively (Fig. 1A, left), and remission rates were 19.6, 19.0, 28.4, 26.5, and 29.2%, respectively (Fig. 1B, left). There was a tendency toward a dose-dependent increase in both LDA and remission rates among groups 1, 2, and 3; however, the rates did not increase further in groups 4 and 5. A contrast test adjusted for differences in baseline patient characteristics revealed that the LDA and remission rates by MTX dose in biologic-naïve patients were in the order group 1 < group 2 < group 3 = group 4 = group 5 (LDA, $p = 0.0440$; remission, $p = 0.0422$). In the 1101 biologic-exposed patients, in contrast, LDA rates were 15.5, 20.0, 24.9, 24.4, and 39.5% in groups 1 through 5, respectively (Fig. 1A, right), and remission rates were 4.8, 9.1, 10.6, 12.5, and 13.7%, respectively (Fig. 1B, right). The contrast test also revealed that LDA and remission rates by MTX dose in biologic-exposed patients were in the order group 1 < group 2 < group 3 < group 4 < group 5 (LDA, $p = 0.0009$; remission, $p = 0.0143$).

With respect to safety evaluation of the 5494 patients receiving ADA and MTX, neither serious ADRs nor serious infections differed significantly across the five groups. The incidence of ADRs was significantly higher in group 1 than in the other groups. The incidence of infections was significantly higher in group 5 than in groups 2, 3, and 4 (Table 3).

DISCUSSION

The major finding from post hoc analysis of the MELODY study is that in biologic-naïve patients, MTX in combination with ADA increased LDA and remission rates at week 24 up to a MTX dose of 6–<8 mg/week and then plateaued at higher doses, whereas in biologic-treated patients there was a dose-dependent increase up to ≥10 mg/week of MTX. The dose–response profile in the biologic-naïve patients appears similar to that observed in the CONCERTO trial [11]. In that trial, biologic-naïve patients who received MTX

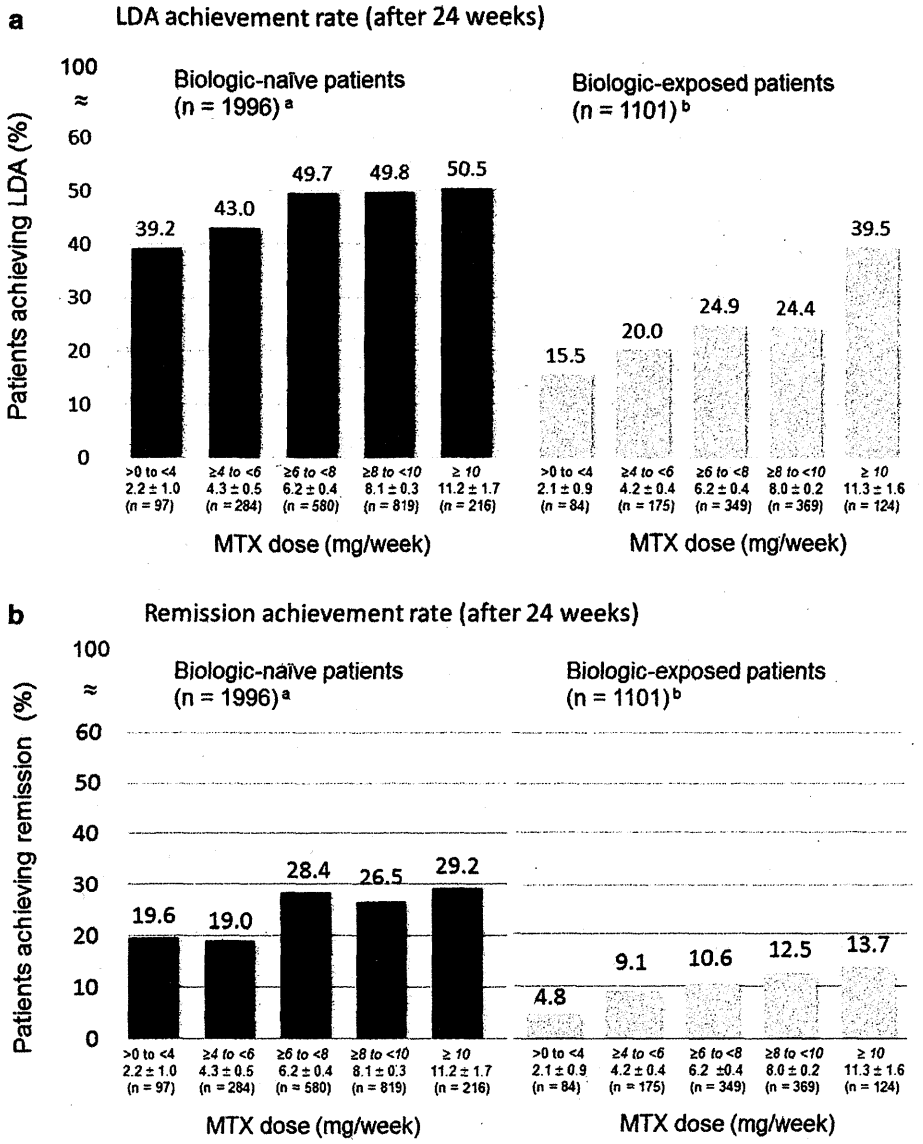

Fig. 1 Percentages of patients achieving LDA (**a**) and remission rate (**b**) after treatment with MTX and adalimumab for 24 weeks. Patients were stratified by weighted average dose of concomitant weekly MTX as follows: group 1, >0–<4 mg; group 2, 4–<6 mg; group 3, 6–<8 mg; group 4, 8–<10 mg; and group 5, ≥10 mg; one degree of freedom for each. [a]AIC, 2479.177. Contrast test results adjusted for baseline DAS28-ESR (continuous), age (1: <20 years, 2: 20–29 years, 3: 30–39 years, 4: 40–49 years, 5: 50–59 years, 6: 60–69 years, 7: 70–79 years, and 8: ≥80 years; continuous), class (I–II, III–IV), previous or coexisting diabetes mellitus (yes, no), and sex. Patients received any biologic treatment other than adalimumab before starting adalimumab treatment; [b]AIC, 1116.088. Contrast test results adjusted for baseline DAS28-ESR (continuous), class (I–II, III–IV), sex, and past biologic treatment (infliximab only, etanercept only, both infliximab and etanercept, and any others). *AIC*, Akaike's information criterion. *DAS28-ESR* disease activity score for 28 joint counts based on the erythrocyte sedimentation rate, *LDA* low disease activity, *MTX* methotrexate. Values are expressed as mean ± standard deviation

in combination with ADA were evaluated for the MTX dose–response of the therapeutic outcomes, including LDA, and there was a statistically significant trend toward better clinical outcomes at higher MTX doses, although no differences were observed in

Table 3 Adverse drug reactions in adalimumab-treated RA patients by weekly MTX dose ($n = 5494$)

	Group 1 ($n = 356$)	Group 2 ($n = 894$)	Group 3 ($n = 1651$)	Group 4 ($n = 2005$)	Group 5 ($n = 588$)
ADRs					
n, (%)	111 (31.2)	201 (22.5)	367 (22.2)	409 (20.4)	137 (23.3)
p value (vs. Group 1)[a]	NR	0.0022	0.0009	<0.0001	0.0148
p value (vs. Group 2)[a]		NR	0.9735	0.2816	0.6537
p value (vs. Group 3)[a]			NR	0.1822	0.6400
p value (vs. Group 4)[a]				NR	0.1482
Serious ADRs					
n, (%)	19 (5.3)	35 (3.9)	66 (4.0)	85 (4.2)	19 (3.2)
p value (vs. Group 1)[b]	NR	0.2509	0.4077	0.6596	0.2256
p value (vs. Group 2)[b]		NR	0.5949	0.2897	0.8135
p value (vs. Group 3)[b]			NR	0.3933	0.4669
p value (vs. Group 4)[b]				NR	0.2670
Infection					
n, (%)	34 (9.6)	57 (6.4)	97 (5.9)	140 (7.0)	61 (10.4)
p value (vs. Group 1)[c]	NR	0.0831	0.0310	0.2111	0.4343
p value (vs. Group 2)[c]		NR	0.7408	0.3874	0.0032
p value (vs. Group 3)[c]			NR	0.1480	0.0003
p value (vs. Group 4)[c]				NR	0.0080
Serious infection					
n, (%)	13 (3.7)	19 (2.1)	26 (1.6)	49 (2.4)	12 (2.0)
p value (vs. Group 1)[d]	NR	0.2106	0.1056	0.7095	0.5138
p value (vs. Group 2)[d]		NR	0.7647	0.2170	0.5903
p value (vs. Group 3)[d]			NR	0.0683	0.3950
p value (vs. Group 4)[d]				NR	0.2052

Group 1, >0–<4 mg; group 2, ≥4–<6 mg; group 3, ≥6–<8 mg; group 4, ≥8–<10 mg; group 5, ≥10 mg. [a]The analysis was conducted with a stepwise Cox regression analysis, including 5491 patients from the safety population ($n = 5494$). Group, Steinbrocker's stage (I and II vs. III and IV), past history of tuberculosis, respiratory comorbidity, cardiovascular comorbidity, and hematologic comorbidity were included in a stepwise Cox regression model. [b]The analysis was conducted with a stepwise Cox regression analysis, including 5493 patients from the safety population ($n = 5494$). Age (per 10 years), sex, comorbidity of respiratory and comorbidity of hematologic were included in a stepwise Cox regression model. [c]The analysis was conducted with a stepwise Cox regression analysis, including 5491 patients from the safety population ($n = 5494$). Group, Steinbrocker's stage (I and II vs. III and IV), past history of interstitial pneumonia, and cardiovascular comorbidity were included in a stepwise Cox regression model. [d]The analysis was conducted with a stepwise Cox regression analysis, including 5400 patients from the safety population ($n = 5494$). Age (per 10 years), Steinbrocker's stage (I and II vs. III and IV), past history of interstitial pneumonia, cardiovascular comorbidity, hematologic comorbidity, and prior medication with glucocorticoids (none, >0–≤5 mg/day, >5 mg/day) were included in a stepwise Cox regression model. A weighted average was used to calculate mean MTX dose. *ADRs* adverse drug reactions, *MTX* methotrexate, *NR* not reported, *RA* rheumatoid arthritis

clinical, radiographic, and functional responses between 10 and 20 mg/week of MTX. However, these results suggest that for patients with prior treatment with biologics, MTX dose increase in combination with biologics should be carefully considered.

In the safety analysis, despite no differences in serious ADRs or serious infections, the incidence of ADRs and infections differed significantly between lower- and higher-dose MTX groups. The significantly higher incidence of infections in patients of group 5, who received the highest MTX dose in our study, was consistent with findings from the previous safety analysis of the all-case study [6]. That analysis revealed that the use of MTX at >8 mg/week represents a risk factor for infections, respiratory infections, severe respiratory infections, and pneumonia. In the present analysis, incidences of ADRs and infections were also significantly higher in patients of group 1 who received MTX at the lowest dose range. Patients of group 1 tended to be older, had longer disease duration, and more concomitant diseases, which are factors for higher risk of ADRs and infections.

As a post hoc analysis of an observational study, this study had several limitations. Of note, the Japan College of Rheumatology has published its guidelines for the use of MTX in the treatment of RA, including the supplementation with folic acid, and, in the present study, Japanese patients with RA were treated accordingly. First, the dose of MTX could be changed whenever necessary during combination treatment with ADA. Second, although we adjusted the contrast tests for differences in baseline data, baseline characteristics of patients were different among the groups. Third, as outcome measures available for analysis depend on the original all-case survey, no radiologic or functional data were analyzed in this study, and the efficacy of treatment was analyzed only with clinical measures. A direct comparison between our findings with and those in non-Japanese populations could not be made. To confirm these data in the Japanese population, a randomized clinical study is needed. To date, there is no scientifically sound explanation for the observation that biologic-exposed patients need higher doses of MTX than biologic-naïve patients to achieve LDA and remission. To address this question in a future study, we must measure disease activity more accurately and use a more clinically relevant endpoint.

CONCLUSION

In the treatment of RA, the effects of MTX in combination with ADA on LDA and remission rates showed a different dose–response profile between biologic-naïve and biologic-exposed patients. In biologic-naïve patients, the effects of MTX plateaued at a dose of 6–<8 mg/week, suggesting that 8 mg/week is sufficient for this patient population.

ACKNOWLEDGMENTS

Sponsorship and article processing charges for this study were funded by AbbVie GK, Tokyo, Japan (formerly Abbott Japan Co., Ltd., Japan) and Eisai Co., Ltd., Tokyo, Japan, who provided funds for data collection. AbbVie contributed to the design of the study, the data analysis and interpretation, and in the drafting, review, and approval of the manuscript.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

We express our sincere thanks to the participating investigators, fellows, nurses, and research coordinators at each medical institution. We also deeply thank the patients

who participated in this study for their contribution. We thank Jungo Sawa, Ph.D., a contracted biostatistician of AbbVie GK, for his dedicated support in the development of the statistics plan and interpretation of the results. We also thank Naoki Agata, Ph.D. and Sarina Kurimoto, M.D., Ph.D. for critical review of this work, and Rie Moriguchi, R&A Medical Translation Service, who provided medical writing support on behalf of AbbVie.

Part of the work was presented in an abstract form at the 59th Annual General Assembly and Scientific Meeting of the Japan College of Rheumatology (on April 24, 2015 in Nagoya, Japan).

Disclosures. Doctors T. Koike, M. Harigai, N. Ishiguro, S. Inokuma, S. Takei, T. Takeuchi, H. Yamanaka, and Y. Tanaka are members of the Postmarketing Surveillance (PMS) Committee of the Japan College of Rheumatology. It is the belief of the authors that this does not constitute a conflict of interest. The doctors participated in review and analysis of the PMS data in their capacity as committee members. The financial relationships of the authors with manufacturers of biological products used in the management of RA are as listed. T. Koike has received consultancies, speaking fees, and honoraria from Abbott Japan, AbbVie GK, Astellas Pharma Inc., Bristol-Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Santen Pharmaceutical, Takeda Pharmaceutical, Teijin Pharmaceutical, and Pfizer. M. Harigai has received research grants, speaking fees, or honoraria from Abbott Japan, AbbVie GK, Astellas Pharma Inc., Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai Pharmaceutical, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma Corporation, Santen Pharmaceutical, Takeda Pharmaceutical, UCB Japan, and Pfizer and has received consultant fees from Abbott Japan, Bristol-Myers Squibb, Chugai Pharmaceutical, and Janssen Pharmaceutical. N. Ishiguro has received research grants from AbbVie GK, Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Eisai Co., Ltd., Janssen Pharmaceuticals, Inc., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., and Takeda Pharmaceutical Company. S. Inokuma has nothing to disclose. S. Takei has received research grants, consulting fees, and/or speaking fees from Eisai, Chugai, Takeda, Bristol-Myers K.K., Teijin, Pfizer, Mylan, Mitsubishi Tanabe, Asahi Kasei, and Astellas. T. Takeuchi has received grants from AbbVie GK, Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Nippon Shinyaku Co., Ltd., Pfizer Japan Inc., Sanofi K.K., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company, and Teijin Pharma Limited, has received speaking fees from AbbVie GK, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., and Takeda Pharmaceutical Company, and has received consultant fees from AstraZeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Corporation, and Asahi Kasei Medical Co., Ltd. H. Yamanaka has received research grants from AbbVie GK, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical, Pfizer Japan Inc., Takeda Pharmaceutical Company, and UCB Japan Co., Ltd., and has received speaker honoraria/consulting fees from AbbVie GK,

Bristol-Myers Squibb, Chugai Pharmaceutical Co., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical, Pfizer Japan Inc., Takeda Pharmaceutical Company, and UCB Japan Co., Ltd. Y. Takasaki has received grants and research from Santen Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb, AstraZeneca plc, Astellas Pharma Inc., MSD K.K., Chugai Pharmaceutical Co., Ltd., Asahi Kasei Pharma Corporation, Eisai Co., Ltd., and Janssen Pharmaceutical K.K. T. Mimori has received grant and research support from Asahi Kasei Pharma Corporation, Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Merck & Co., Inc., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., Santen Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd., and is on the speakers' bureaus for Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., Santen Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd. Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from AbbVie GK, Chugai Pharmaceutical Co., Astellas Pharma, Takeda Pharmaceutical Company, Santen Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., Janssen Pharmaceutical K.K., Eisai Co., Ltd., Daiichi-Sankyo Co., Ltd., UCB Japan Co., Ltd, GlaxoSmithKline K.K., and Bristol-Myers Squibb, and has received research grants from Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., MSD K.K., Astellas Pharma, and Novartis Pharma K.K. K. Hiramatsu and S. Komatsu are full-time employees of AbbVie GK and may have AbbVie stock or stock options.

Compliance with ethics guidelines. This article does not contain any new studies with human subjects performed by any of the authors.

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OPEN ACCESS

EXTENDED REPORT

The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression

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Received 26 February 2015
Revised 3 June 2015
Accepted 6 June 2015
Published Online First 2 July 2015

To cite: Atsumi T, Yamamoto K, Takeuchi T, *et al. Ann Rheum Dis* 2016;**75**:75–83.

ABSTRACT

Objectives To evaluate efficacy and safety of combination therapy using certolizumab pegol (CZP) and methotrexate (MTX) as first-line treatment for MTX-naive, early rheumatoid arthritis (RA) with poor prognostic factors, compared with MTX alone.

Methods MTX-naive, early RA patients with ≤12 months persistent disease, high anti-cyclic citrullinated peptide, and either rheumatoid factor positive and/or presence of bone erosions were enrolled in this multicentre, double-blind, randomised placebo (PBO)-controlled study. Patients were randomised 1:1 to CZP+MTX or PBO+MTX for 52 weeks. Primary endpoint was inhibition of radiographic progression (change from baseline in modified Total Sharp Score (mTSS CFB)) at week 52. Secondary endpoints were mTSS CFB at week 24, and clinical remission rates at weeks 24 and 52.

Results 316 patients randomised to CZP+MTX (n=159) or PBO+MTX (n=157) had comparable baseline characteristics reflecting features of early RA (mean disease duration: 4.0 vs 4.3 months; Disease Activity Score 28-joint assessment (DAS28)) (erythrocyte sedimentation rate (ESR)): 5.4 vs 5.5; mTSS: 5.2 vs 6.0). CZP+MTX group showed significantly greater inhibition of radiographic progression relative to PBO+MTX at week 52 (mTSS CFB=0.36 vs 1.58; p<0.001) and week 24 (mTSS CFB=0.26 vs 0.86; p=0.003). Clinical remission rates (Simple Disease Activity Index, Boolean and DAS28 (ESR)) of the CZP+MTX group were significantly higher compared with those of the PBO +MTX group, at weeks 24 and 52. Safety results in both groups were similar, with no new safety signals observed with addition of CZP to MTX.

Conclusions In MTX-naive early RA patients with poor prognostic factors, CZP+MTX significantly inhibited structural damage and reduced RA signs and symptoms, demonstrating the efficacy of CZP in these patients.

Trial registration number (NCT01451203).

INTRODUCTION

The emergence of biological agents targeting inflammatory cytokines such as tumour necrosis factor (TNF), which play key roles in the pathogenesis of rheumatoid arthritis (RA), has been of great importance. The effectiveness of these agents at inhibiting joint damage progression, in addition to providing symptom relief, has brought a paradigm shift to RA treatment.[1] Since joint damage progression is rarely reversible,[2 3] earlier treatment with effective drugs would be relevant in clinical practice.

Treatment guidelines and recommendations published by the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR) and the Japan College of Rheumatology recommend that all patients with RA should be treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) from the point of diagnosis.[4–6] Methotrexate (MTX), either as monotherapy or in combination with other csDMARDs, should be given first-line unless contraindicated. For patients at risk of rapid disease progression, addition of a biologic can be considered if treatment targets are not achieved using csDMARDs alone. Earlier recognition of RA has become possible for many patients by application of the 2010 ACR/EULAR classification criteria.[7 8] Ultimately, early diagnosis and intervention with effective therapeutics maximises the chance of preventing joint damage progression in order to maintain quality of life.[9]

Certolizumab pegol (CZP) is a humanised anti-TNF antibody fragment conjugated to polyethylene glycol, approved for treatment of inflammatory diseases, including RA. Efficacy and safety of CZP in established RA has been demonstrated in several studies[10–13] but is previously unreported in MTX-naive early RA.

Herein, we conducted the Certolizumab–Optimal Prevention of joint damage for Early RA (C-OPERA) study, designed to include MTX-naive, early RA patients with poor prognostic factors. The study was double-blind (DB) for 1 year, with either CZP or placebo (PBO) administered concomitantly with MTX. Following this, the trial was open label

for another year, whereby completers of the DB period were maintained on MTX monotherapy after discontinuing CZP. This report comprises results from the 1-year DB period.

METHODS

Patients

Eligible patients were 20–64 years old with RA fulfilling the 2010 ACR/EULAR classification criteria. Patients had ≤12 months of persistent arthritic symptoms, at least moderate disease activity (Disease Activity Score 28-joint assessment (DAS28) with erythrocyte sedimentation rate (ESR) ≥3.2) and were MTX-naive. In addition, patients had poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody (≥3× upper limit of normal (ULN)) and either positive rheumatoid factor (RF) and/or presence of bone erosions (based on radiographs of hands/feet, assessed by the investigator at each study site). Patients with high risk of infection (current use of antibiotics, history of serious/chronic infection treated by antibiotics within 6 months) or history of/active tuberculosis or malignancy, and patients previously exposed to MTX, leflunomide or biological DMARDs were excluded.

Study design

C-OPERA, a phase III multicentre study (NCT01451203), was DB and PBO-controlled to week 52, with a subsequent 52-week follow-up period when patients received MTX monotherapy. Patients were randomised 1:1 to either CZP+MTX or PBO +MTX (MTX monotherapy) via an interactive web-response system. Drug administration was performed by dedicated non-blinded persons due to distinguishability of CZP from PBO; however, these personnel were not permitted to engage in other study activities to maintain blinding. All investigators and healthcare professionals involved in safety/efficacy assessments were blind to study medications. Study drugs were subcutaneously administered as a loading dose of CZP 400 mg or PBO at weeks 0, 2 and 4, followed by CZP 200 mg or PBO every two weeks from week 6 to week 50. Oral MTX (8 mg/week) was initiated simultaneously. MTX dose was increased to 12 mg/week at week 4, 16 mg/week at week 8 and maintained at 16 mg/week thereafter. As per protocol, dose escalation of MTX could be postponed only for safety concerns or due to adverse events (AEs), in which case the dose was maintained at the highest tolerable dose. Patients who did not achieve an improvement of symptoms at or after week 24, that is, if moderate or higher disease activity (DAS28 (ESR) ≥3.2) persisted ≥4 weeks, in either treatment arm, were eligible to receive rescue treatment with open-label CZP after discontinuing DB period. Co-administration of any DMARD except MTX was prohibited during the study.

The study was conducted from October 2011 to August 2013 at 73 sites in Japan after approval by the Institutional Review Board designated by each site, in compliance with ethical principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

Efficacy assessments

The primary efficacy endpoint was inhibition of joint damage progression, assessed as change from baseline (CFB) in van der

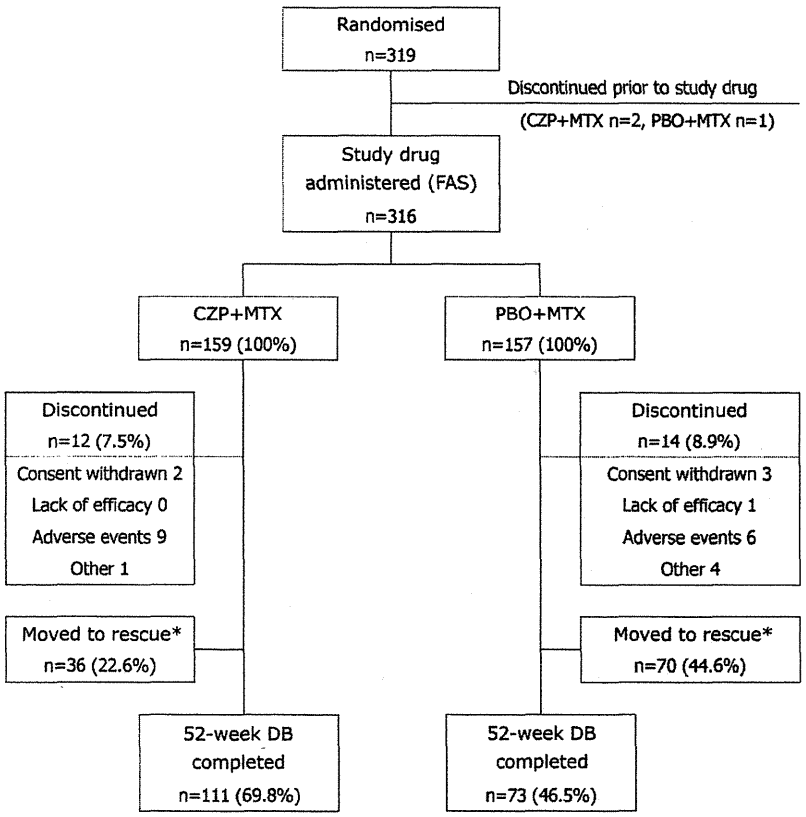

Figure 1 Patient disposition. *Patients who did not achieve an improvement of RA symptoms (defined as the persistence of DAS28[ESR] ≥3.2 for 4 weeks or longer) after Week 24 were eligible to withdraw from DB and move to rescue treatment with open label CZP. CZP, certolizumab pegol; DAS28, Disease Activity Score 28-joint assessment; DB, double blind; ESR, erythrocyte sedimentation rate; FAS, full analysis set; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis.

Heijde modified Total Sharp Score (mTSS) at week 52. The same measure at week 24 was a secondary efficacy endpoint. mTSS was evaluated by two independent readers in accordance with previously reported methods.[14 15] In addition to mTSS CFB, non-progression (defined: mTSS CFB ≤0.5) and the rapid radiographic progression rate (RRP; defined: yearly progression (YP) >5)[16 17] were analysed. Other secondary efficacy endpoints included clinical remission rates, assessed by ACR/EULAR criteria (Simple Disease Activity Index (SDAI)-based and Boolean-based) and DAS28 (ESR) at weeks 24 and 52.

Signs and symptoms were assessed by clinical remission rates (SDAI, Boolean and DAS28 (ESR)), functional remission rates (Health Assessment Questionnaire Disability Index (HAQ-DI)) and ACR20/50/70 responses, evaluated at each time point.

Safety assessments

All undesirable events during the DB period were recorded as AEs or serious AEs. Safety was evaluated by laboratory tests (haematological, blood chemistry, urinalysis), chest radiographs and ECGs.

Statistical analyses

Sample size was based on expected difference in mTSS CFB at week 52 between CZP and PBO groups of 2.57±6.75. Verification of superiority of CZP+MTX over MTX monotherapy for primary endpoint would then have 90% power at a two-sided significance level of 5% with 146 patients per group (thus the planned number was 150 patients).

Primary analyses used the full analysis set, defined as patients who received ≥1 dose of study drug and provided any efficacy data thereafter. For the imputation of missing data, linear extrapolation was used for mTSS and last observation carried forward used for other efficacy variables. Non-responder imputation was added as a sensitivity analysis for clinical remission analyses. For the primary endpoint, an analysis of covariance (ANCOVA) model was used for mTSS CFB by converting measured values to rank scores and using treatment group as a factor and baseline rank score as a covariate. Fisher's exact test was used for analyses of non-progression, RRP in mTSS, clinical remission and ACR20/50/70 response.

RESULTS

Patient baseline demographics/characteristics

Of 319 patients randomised, 316 (159, CZP+MTX; 157, PBO +MTX) received study drug. Of these, 111 patients (69.8%) in the CZP+MTX group and 73 patients (46.5%) in the PBO +MTX group completed the 52-week DB period (figure 1). Fewer PBO+MTX patients completed DB period than CZP +MTX patients, mainly due to the increased number of discontinuations (figure 1).

Treatment groups were generally balanced with respect to demographic and baseline characteristics (table 1). Overall, patients' mean age was 49 years (range 21–64 years). Mean RA duration (time from onset of persistent arthritic symptoms) was approximately 4 months in both groups. All patients had high titre (≥3 times ULN) anti-CCP antibody; approximately 95% were RF positive. Bone erosion was confirmed in 50% of patients. Mean±SD DAS28 (ESR) was 5.4±1.1 for CZP+MTX and 5.5±1.2 for PBO+MTX. Mean (median) mTSS in CZP +MTX and PBO+MTX groups was 5.2 (1.5) and 6.0 (1.5), and no radiographic damage (mTSS ≤0.5) was observed in 35.2% and 35.7% of patients, respectively. There was no difference between groups in mean baseline body weight (57.4±11.3 in CZP+MTX, 57.4±10.6 in PBO+MTX; kg, mean±SD) or average weekly MTX dose throughout the study period (11.6 ±3.0 in CZP+MTX, 11.6±2.7 in PBO+MTX; mg/week).

Inhibition of joint damage progression

For the primary endpoint, mTSS CFB (mean±SD) at week 52 was 0.36±2.70 with CZP+MTX and 1.58±4.86 with PBO +MTX, statistically significant by ANCOVA on the ranks ($p<0.001$). At week 24, smaller mTSS CFB was observed with CZP+MTX compared with PBO+MTX (0.26±1.55 vs 0.86 ±2.37; $p=0.003$) (figure 2A).

The percentage of patients with non-progression (mTSS CFB ≤0.5) at week 52 was higher with CZP+MTX than with PBO +MTX (82.9% vs 70.7%; $p=0.011$ by Fisher's exact test).

Table 1 Demographics and baseline characteristics (FAS population)

Parameter	CZP+MTX n=159	PBO+MTX n=157
Age (years)	49.4±10.6	49.0±10.3
Female, n (%)	129 (81.1)	127 (80.9)
Weight (kg)	57.4±11.3	57.4±10.6
BMI (kg/m^2)	22.4±3.9	22.5±3.7
RA duration (months)*	4.0±2.9	4.3±2.8
<3 months, n (%)	60 (37.7)	57 (36.3)
3–<6 months, n (%)	60 (37.7)	56 (35.7)
6–12 months, n (%)	39 (24.5)	44 (28.0)
Previous DMARDs use, n (%)	31 (19.5)	29 (18.5)
Steroid use at baseline, n (%)	26 (16.4)	31 (19.7)
Anti-CCP antibody positive, n (%)	159 (100.0)	157 (100.0)
High titre (≥3 times of ULN), n (%)	159 (100.0)	157 (100.0)
Titre (U/mL)†	176.7±107.5	185.2±107.7
RF positive, n (%)	153 (96.2)	146 (93.0)
High titre (≥3 times of ULN), n (%)	119 (74.8)	117 (74.5)
Titre (U/mL)†	182.5±177.4	167.3±166.5
Bone erosion (judged by physician), n (%)	79 (49.7)	80 (51.0)
TJC (/28 joints)	8.4±6.1	8.9±6.5
SJC (/28 joints)	8.3±5.3	8.4±5.3
PtGADA (mm)	50.4±22.4	52.9±22.7
PhGADA (mm)	56.7±20.5	58.4±21.4
ESR (mm/h)	38.4±25.3	43.7±28.2
CRP (mg/dL)	1.3±1.8	1.5±1.9
MMP-3 (ng/mL)‡	130.4±135.4	185.4±214.9
DAS28 (ESR)	5.4±1.1	5.5±1.2
SDAI	28.7±12.5	30.0±13.6
HAQ-DI score	1.0±0.6	1.1±0.7
mTSS	5.2±8.8	6.0±15.3
Negative (≤0.5), n (%)	56 (35.2)	56 (35.7)
Erosion score	2.2±4.4	2.8±7.9
Negative (≤0.5), n (%)	82 (51.6)	80 (51.0)
Joint space narrowing score	2.9±5.8	3.2±8.6
Negative (≤0.5), n (%)	87 (54.7)	82 (52.2)
Average weekly MTX dose (mg/week)	11.6 (3.0)	11.6 (2.7)

Values are mean±SD unless otherwise indicated.
*Time from onset of persistent arthritic symptoms.
†Data exceeding measurement upper limit (≥300 U/mL) are regarded as 300 U/mL.
‡Normal range: 36.9–121 (male), 17.3–59.7 (female) ng/mL.
BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C reactive protein; CZP, certolizumab pegol; DAS28 (ESR), Disease Activity Score 28-joint assessment; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; MMP-3, matrix metalloproteinase-3; mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; PhGADA, physician global assessment of disease activity; PtGADA, patient's global assessment of disease activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simple Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; ULN, upper limit of normal.

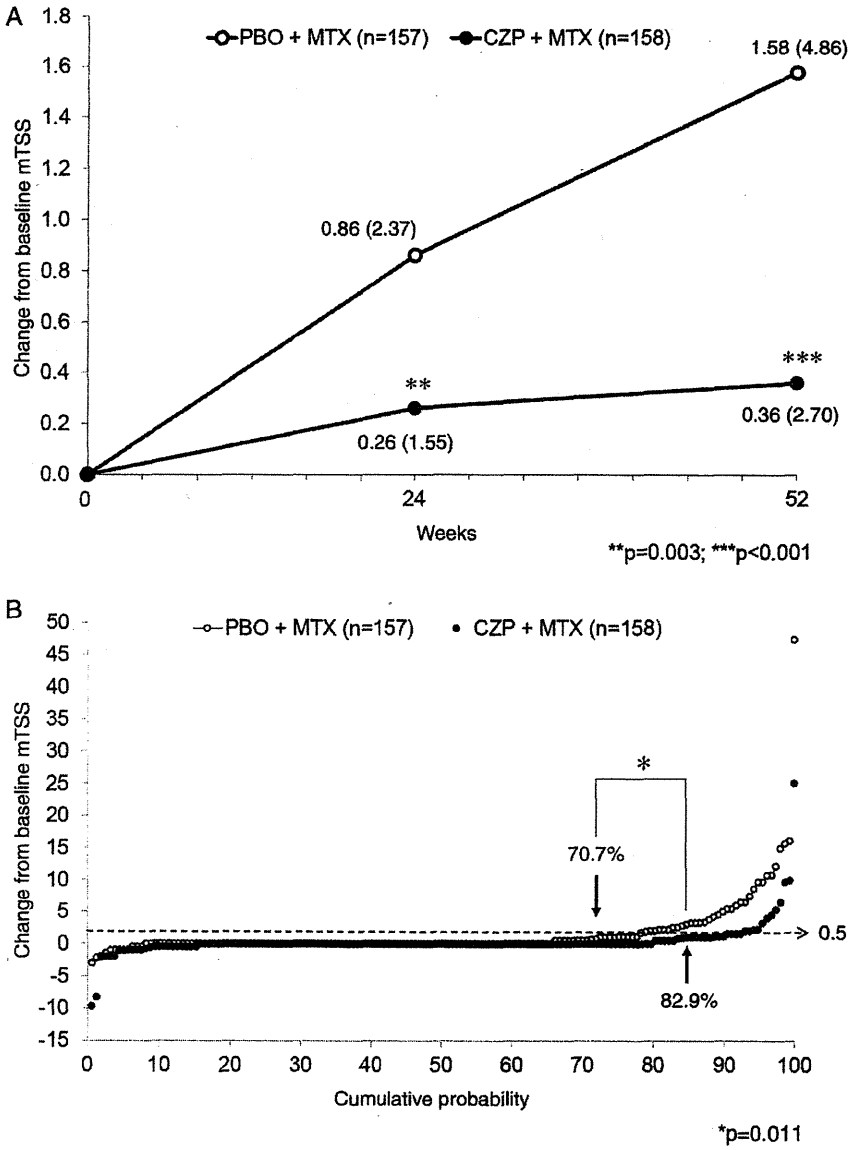

Figure 2 (A) Change from baseline in modified Total Sharp Score (mTSS CFB) at weeks 24 and 52. For calculation of p values, an ANCOVA model was used for mTSS CFB by converting measured values to rank scores and using treatment group as a factor and baseline rank score as a covariate. Values in the figure indicate mean (SD) at each time point and treatment group. (B) Cumulative probability plot of mTSS CFB at week 52. Percentages in the figure indicate non-progression (mTSS CFB ≤0.5) rates of each treatment group. P value is calculated by Fisher's exact test. The mTSS data used in (A) and (B) are all imputed using linear extrapolation (LINEAR) for FAS. The number of patients in the CZP+MTX group is 158 despite the FAS reported as 159 because one patient in the group had no mTSS data after treatment. CZP, certolizumab pegol; MTX, methotrexate; mTSS, modified total Sharp score; PBO, placebo.

Individual patient data are presented in the cumulative probability plot of mTSS CFB at week 52 (figure 2B). In addition, 3.2% of patients with CZP+MTX exhibited RRP (defined as YP >5), compared with 10.8% with PBO+MTX (p=0.008).

Clinical responses

Higher ACR/EULAR remission rates were observed with CZP +MTX compared with PBO+MTX (SDAI remission at week 24: 48.4% vs 29.3%, p<0.001; at week 52: 57.9% vs 33.8%, p<0.001, respectively, and Boolean remission at week 24: 36.5% vs 22.3%, p=0.007; at week 52: 45.3% vs 28.0%, p=0.002, respectively). Similarly, DAS28 (ESR) remission rates at week 24 were approximately 20% higher with CZP+MTX than PBO +MTX (52.8% vs 30.6%; p<0.001); this difference was maintained until week 52 (57.2% vs 36.9%; p<0.001) (figure 3A).

ACR responses were higher at all time points with CZP +MTX compared with PBO+MTX, and a significant difference between the two arms was observed from week 1 in ACR20 and ACR50, and week 2 in ACR70 (figure 3B–D). ACR responses at week 52 in CZP+MTX vs PBO+MTX groups were 78.6% vs 68.8% (p=0.055 by Fisher's exact test) in ACR20, 73.0% vs 51.6% (p<0.001) in ACR50 and 57.2% vs 34.4% (p<0.001) in ACR70, respectively. A similar time course for HAQ-DI remission rates is shown in figure 3E.

Subgroup analyses for joint damage

Subgroup analyses of mTSS CFB at week 52, stratified by baseline parameters including anti-CCP antibody, RF, C-reactive protein (CRP), matrix metalloproteinase (MMP)-3, HAQ-DI, DAS28 (ESR), mTSS and average concomitant MTX dose are

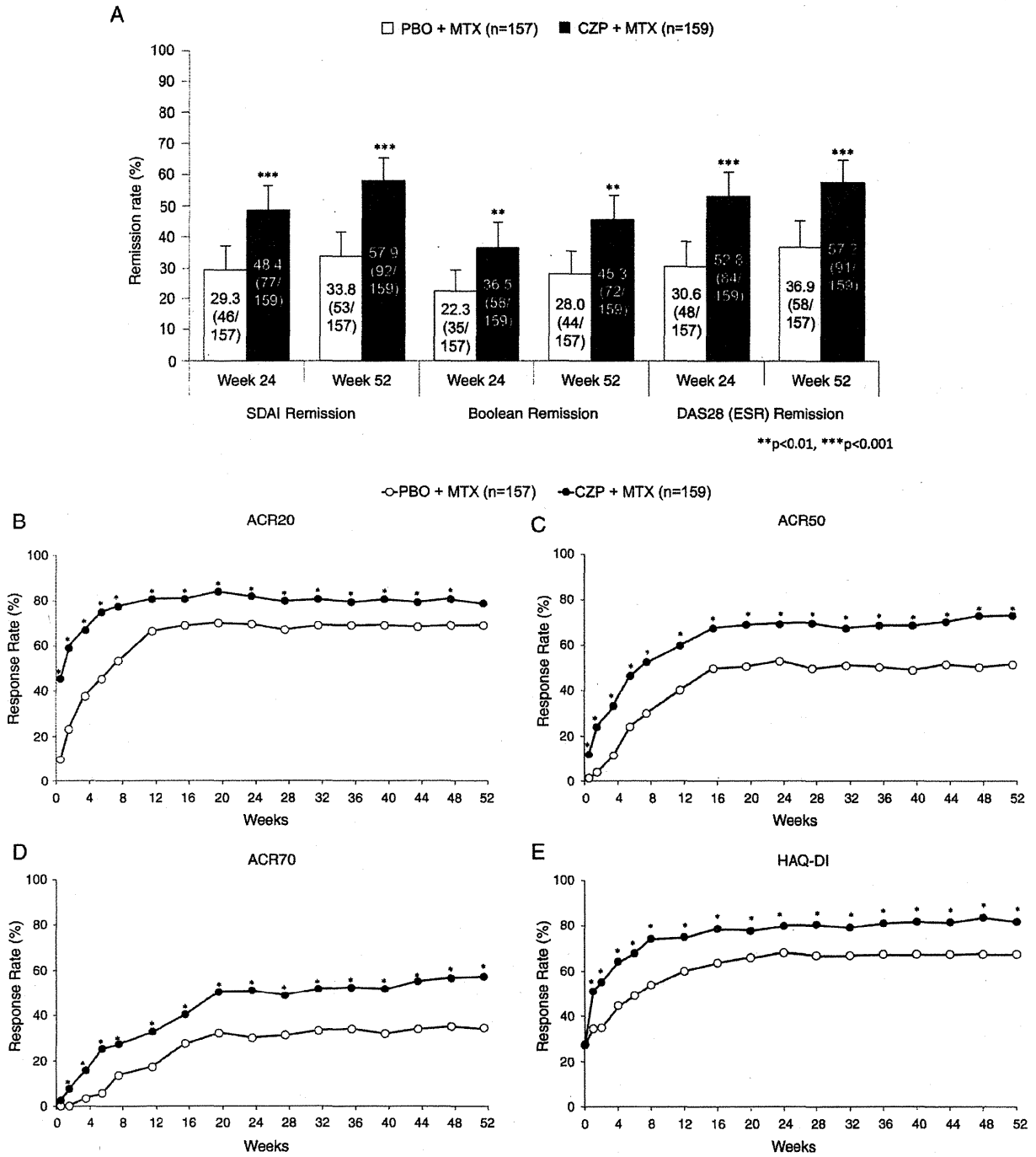

Figure 3 (A) Clinical remission rates at weeks 24 and 52 by Simple Disease Activity Index (SDAI), Boolean and Disease Activity Score 28-joint assessment (DAS28) (erythrocyte sedimentation rate (ESR)) criteria analysed using full analysis set (FAS), last observation carried forward (LOCF) data set. Error bars indicate 95% confidence interval of each remission rate. P values are calculated by Fisher's exact test. (B-E) Time course of American College of Rheumatology (ACR) response rates of (B) ACR20, (C) ACR50, (D) ACR70 and (E) Health Assessment Questionnaire Disability Index (HAQ-DI) remission rates. *p<0.05 between the groups at each particular time point, calculated by Fisher's exact test. CZP, certolizumab pegol; MTX, methotrexate; PBO, placebo.

shown in table 2. A comparison of mTSS CFB between treatment groups consistently showed less progression with CZP +MTX compared with PBO+MTX in all categories of these parameters, except for patients with baseline DAS28 (ESR) <3.2 (a small number of patients, n=8). Meanwhile, intra-parameter comparison of mTSS CFB revealed a trend of greater mTSS CFB with higher titres of anti-CCP and RF, higher serum CRP and MMP-3, and higher HAQ-DI, DAS28 (ESR) and mTSS at baseline, which was greater in the PBO+MTX group relative to CZP+MTX. In contrast, with regard to concomitant MTX dose, the expected dose-dependent inhibitory effect was not found in either group.

Table 2 Subgroup analysis of mTSS CFB at week 52 by baseline parameters and concomitant MTX dose (FAS, LINEAR)

		CZP+MTX		PBO+MTX	
Parameter at baseline	Subgroup	n	mTSS CFB mean±SD	n	mTSS CFB mean±SD
Anti-CCP antibody (U/mL)	<100	51	−0.03±0.69	51	1.34±3.11
	100–<300	57	0.11±1.99	56	1.52±3.79
	≥300	50	1.05±4.21	50	1.91±7.01
RF (IU/mL)	<20	6	−0.26±0.45	11	2.20±5.14
	20–<60	33	0.06±1.09	29	0.82±3.07
	≥60	119	0.48±3.06	117	1.72±5.20
CRP (mg/dL)	≤0.5	75	0.13±0.74	69	0.39±2.12
	>0.5–≤1.0	22	0.00±0.52	27	1.85±3.23
	>1.0	61	0.78±4.25	61	2.82±6.97
MMP-3 (ng/mL)	<50	36	0.09±0.50	33	0.01±0.42
	50–<100	59	0.31±0.97	50	1.44±3.17
	≥100	63	0.57±4.17	74	2.38±6.47
HAQ-DI	≤0.5	43	0.27±1.61	43	0.52±2.71
	>0.5–≤1.0	44	0.10±0.98	41	1.60±4.09
	>1.0	71	0.58±3.76	73	2.21±6.04
DAS28 (ESR)	<3.2	5	0.10±0.22	3	0.00±0.00
	3.2–5.1	60	0.20±0.83	54	0.71±3.14
	>5.1	93	0.49±3.46	100	2.10±5.59
mTSS	≤0.5	55	0.20±0.64	56	0.42±0.99
	>0.5	103	0.45±3.32	101	2.23±5.93
Concomitant MTX—average dose (mg/week)	0–8	18	0.07±0.88	21	0.61±2.37
	8–≤12	64	0.38±4.01	59	1.40±2.98
	>12–16	76	0.42±1.27	77	1.99±6.31

CCP, cyclic citrullinated peptide; CFB, change from baseline; CRP, C reactive protein; CZP, certolizumab pegol; DAS28, Disease Activity Score 28-joint assessment; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LINEAR, linear extrapolation; MMP-3, matrix metalloproteinase-3; mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; RF, rheumatoid factor.

Table 3 Summary of treatment-emergent adverse events

Parameter	CZP+MTX n=159 PY=136.2 n (%)	PBO+MTX n=157 PY=116.0 n (%)
AE summary		
Any AEs	153 (96.2) 542.0*	148 (94.3) 548.2*
Serious AEs	13 (8.2) 11.0*	14 (8.9) 12.9*
Deaths	0	0
AEs of interest		
Infections and infestations	97 (61.0)	87 (55.4)
Serious infection	5 (3.1)	7 (4.5)
Pneumocystis jiroveci pneumonia	3 (1.9)	2 (1.3)
Bronchitis	1 (0.6)	0
Meningitis fungal	1 (0.6)	0
Pneumonia bacterial	1 (0.6)	2 (1.3)
Pneumonia	0	1 (0.6)
Pneumonia mycoplasmal	0	1 (0.6)
Pyelonephritis acute	0	1 (0.6)
Pneumonia	7 (4.4)	8 (5.1)
Pneumonia bacterial	4 (2.5)	2 (1.3)
Pneumocystis jiroveci pneumonia	3 (1.9)	3 (1.9)
Bronchopneumonia	1 (0.6)	0
Pneumonia	0	2 (1.3)
Pneumonia mycoplasmal	0	1 (0.6)
Tuberculosis	0	0
Interstitial lung disease	5 (3.1)	1 (0.6)
Malignancies†	1 (0.6)	0
Hepatic disorders‡	68 (42.8)	70 (44.6)
Hematopoietic cytopenias§	12 (7.5)	13 (8.3)
Nausea/vomiting/decreased appetite	39 (24.5)	32 (20.4)
Stomatitis	19 (11.9)	26 (16.6)
Injection site reaction	5 (3.1)	2 (1.3)

*Event rate: per 100 patients-years.
†Cervix carcinoma.
‡Including following preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic function abnormal, hepatic enzyme increased, hepatic steatosis, hyperbilirubinaemia, liver disorder, liver function test abnormal.
§Including following preferred terms: granulocytopenia, leucopenia, lymphopenia, lymphocyte count decreased, white blood cell count decreased.
AE, adverse event; CZP, certolizumab pegol; MTX, methotrexate; PBO, placebo; PY, total summation of individual patient-years.

Safety

Study drug exposure during treatment period was greater in the CZP+MTX group (136.2 patient-years) compared with the PBO+MTX group (116.0 patient-years), as more PBO+MTX -treated patients withdrew (mainly due to lack of efficacy). Overall, 153 patients (96.2%) in the CZP+MTX group and 148 patients (94.3%) in the PBO+MTX group reported any AEs. Serious AEs were reported by 13 patients (8.2%) in the CZP+MTX group and 14 patients (8.9%) in the PBO+MTX group. No clinically relevant difference between groups was observed in overall incidence of AEs and serious AEs (table 3).

Overall incidence of infections and infestations was higher with CZP+MTX (61.0%) compared with PBO+MTX (55.4%), with no difference in the rate of serious infections (3.1% in CZP+MTX vs 4.5% in PBO+MTX). Similar incidences were observed for pneumonia (10 events reported in seven patients [4.4%] for CZP+MTX vs 10 events in eight patients [5.1%] for PBO+MTX), including three cases of *Pneumocystis jiroveci* pneumonia in each group.

There was no difference in the severity pattern of pneumonia events between CZP+MTX (four serious events) and PBO +MTX (six serious events). There was an apparent correlation between MTX dose and the occurrence of pneumonia since only one patient in each group experienced an event of bacterial pneumonia while receiving low MTX dose (0–8 mg/week) versus five and four patients in the CZP+MTX and PBO +MTX groups, respectively, who experienced ≥1 pneumonia event with high MTX dose (>12–16 mg/week).

The incidence of hepatic events was high (mostly abnormal hepatic function) although it was similar between groups (hepatic disorders: 42.8% with CZP+MTX, 44.6% with PBO +MTX; 'investigations' system organ class in hepatic disorders: 6.9% with CZP+MTX; 8.9% with PBO+MTX), indicating that there was no increased risk with the addition of CZP. No patients were withdrawn from the study due to hepatic events, and almost all events were resolved by temporarily discontinuing or reducing MTX dose. No cases of tuberculosis, demyelinating disorders, lupus-like syndrome, serious allergic reactions or serious haematological disorders were reported.

DISCUSSION

Compared with similar studies of anti-TNF agents in MTX-naive early RA patients, C-OPERA is characterised by two unique features. First, as far as we know, this is the first randomised controlled trial (RCT) to employ the 2010 ACR/EULAR classification criteria as the main inclusion criteria. Thus, patients enrolled in C-OPERA had very early stages of disease, strictly defined as the time from initiation of persistent arthritic

symptoms identified by medical interview (RA duration ≤12 months). Approximately 35% of patients had no joint damage (mTSS ≤0.5) in baseline radiographs, and mean baseline mTSS of 5.6 units (5.2–6.0) was the lowest among similar RCTs of biologics (approximately 10–20 units).[18–22] Second, we intentionally enrolled only patients with high anti-CCP antibody titres, which is highly specific for RA,[23 24] compensating for a relatively low specificity of classification criteria. Since positive anti-CCP antibody predicts poor prognosis and rapid progression,[25–29] these patients are more likely to require and benefit from aggressive treatment during early disease.

Regarding radiographic joint damage, a statistically significant inhibitory effect was consistently confirmed in patients receiving CZP by analyses of mTSS CFB, non-progression rate, YP and RRP rate. In addition, an absolutely small mean YP (0.37) and high non-progression rate (82.9%) at week 52 in patients with CZP indicate that concomitant use of CZP with MTX brings proven benefits for inhibition of joint damage progression.

Overall, clinical remission rates were relatively high in patients receiving MTX monotherapy (SDAI: 33.8%; Boolean: 28.0%; DAS28 (ESR): 36.9% at week 52; figure 3A) compared with similar RCTs of biologics,[18–22] but were higher in the group receiving CZP (SDAI: 57.9%; Boolean: 45.3%; DAS28 (ESR): 57.2%). Moreover, patients receiving CZP had better ACR responses and HAQ-DI remission rates as early as week 1.

By protocol, MTX dose was increased to 16 mg/week at week 8, unless there were safety concerns. Consequently, average MTX dose throughout the 52 weeks was approximately 12 mg/week, relatively low compared with reports from similar early RA studies, mainly conducted in the USA or the EU (15–17 mg/week).[18–22] However, considering the difference in average patient body weight between C-OPERA (57 kg) and the above studies (74–79 kg), actual MTX dose per body weight was similar. Moreover, it has been reported that concentrations of MTX polyglutamates, a potential marker for MTX use, in red blood cells are relatively higher in the Japanese study compared with the US study, suggesting a lower dose of MTX may be sufficient in Japanese patients.[30] This is the first Japanese study to mandate use of maximum MTX dose (16 mg/week) by protocol, which may explain better MTX monotherapy results relative to those in previous Japanese studies.

Results of subgroup analyses stratified by MTX dose for mTSS CFB at week 52 (table 2) failed to prove the dose-dependent effect of MTX on joint damage inhibition, regardless of concomitant CZP. This was despite higher DAS28 (ESR) remission rates at week 52 with high-dose MTX (>12–16 mg/week) (42.9%) compared with lower doses (8–≤12 mg/week) (30.5%) in patients on MTX monotherapy. Alternatively, the DAS28 (ESR) remission rates in patients with concomitant CZP were not different between high-dose and low-dose MTX groups (59.2% and 56.9%, respectively). It should be noted that MTX dose was not randomly selected, but only adjusted if there were issues of tolerability. There were some variations in baseline characteristics among the subgroups that could have affected the outcomes.

The Combination Therapy with Adalimumab in Subjects with Early Rheumatoid Arthritis (CONCERTO) study[31] of adalimumab in early RA demonstrated a statistically significant trend of improved efficacy with increasing concomitant MTX dose, from 2.5 to 20 mg/week. However, clinical, functional and radiographic assessments at week 26 were similar between groups receiving 10 and 20 mg/week of concomitant MTX. This is consistent with our current findings from C-OPERA in terms of the lack of clear association between MTX dose and efficacy on joint damage inhibition, suggesting that higher doses of MTX may not always be necessary when administered with concomitant anti-TNF agents. However, this is far from conclusive, requires further investigation and may be limited to effects on joint damage progression.

The number of AEs per 100 patient-years was approximately 1.3–1.5 times higher in C-OPERA than the Japan RA Prevention of Structural Damage (J-RAPID) study.[12] J-RAPID was similar to C-OPERA; it was conducted in Japanese patients with RA (although these patients had established RA and previous inadequate response to MTX), but average weekly MTX dose was lower (J-RAPID: 6–8 mg/week; C-OPERA: 12 mg/week). In the system, organ classes 'infections and infestations', 'gastrointestinal disorders' and 'hepatobiliary disorders' AEs were more frequently observed in C-OPERA than J-RAPID; these AEs were increased in both PBO and CZP arms, and there was no meaningful difference between the groups. This suggests that the increased frequency of these AEs in C-OPERA may have been associated with the higher MTX dose. Moreover, as all patients were MTX-naive at study entry, their tolerance to MTX treatment could not be anticipated. Of note, hepatic events, including abnormal investigations, were resolved by temporarily discontinuing or reducing MTX dose and no additional safety risk was identified with CZP, based on the lack of a clinically significant difference between the two treatment groups in terms of the incidence or pattern of AEs.

Study limitations included not assessing the effect of CZP monotherapy, which is of interest in early RA treatment. As the current RA treatment recommendations suggest that MTX and/or conventional synthetic DMARDs should be used for initial treatment,[5 32] a CZP monotherapy arm was not included in this study.

These efficacy and safety findings from C-OPERA in MTX-naive early RA suggest that CZP could be used as possible first-line treatment concomitantly with MTX in patients with poor prognostic factors, as typified by high-titre anti-CCP antibody. Patients with higher disease activity, functional disability or bone erosion in the early stages of RA will have a higher chance of preventing joint damage and disease progression.

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Correction notice This article has been corrected since it was published Online First. Figure 3E has been corrected.

Acknowledgements The authors would like to acknowledge all the patients, investigators and support staff who participated in the study. The authors also acknowledge Costello Medical Consulting, Cambridge, UK, for writing assistance, which was funded by UCB Pharma, and 'Matladi N. Ndlovu, PhD, UCB Pharma, Brussels, Belgium and Tomoko Suzuki, UCB Pharma, Tokyo, Japan, for publication coordination.

Contributors All the authors made substantial contributions to evaluation of the study results and to develop and review the manuscript.

Funding This study was sponsored by Otsuka Pharmaceutical Co. (Tokyo, Japan), Astellas Pharma (Tokyo, Japan) and UCB Pharma (Tokyo, Japan). UCB Pharma sponsored the study and the development of the manuscript. In addition to content approval by the authors, UCB signed off on the manuscript following a full review to ensure that the publication did not contain any information that has the potential to damage the intellectual property of UCB.

Competing interests TA has taken part in speakers' bureaus for Astellas, Bristol-Myers, Chugai and Mitsubishi-Tanabe; KY has received consultancy fees from Abbott, BMS, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, Roche and UCB Pharma, and has received research grants from Abbott, Eisai, Mitsubishi-Tanabe, Pfizer, Santen and UCB Pharma; TT has received consultancy fees from AstraZeneca, Asahi Kasei, Eli Lilly, Mitsubishi-Tanabe and Novartis, research grants from Abbott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has taken part in speakers' bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda and UCB Pharma; HY has received consultancy fees from Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda and UCB Pharma, and has received research grants from Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda and UCB Pharma; NI has received research grants from Abbott, Astellas, BMS, Takeda, Chugai, Eisai, Janssen, Kaken Mitsubishi-Tanabe and Pfizer, and has taken part in speakers' bureaus for Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Kaken, Mitsubishi-Tanabe, Otsuka, Pfizer, Taisho-Toyama and Takeda; YT has received research grants from Astellas, AbbVie, BMS, Chugai, Daiichi-Sankyo, Mitsubishi-Tanabe, MSD, has received consultancy fees from Abbott, AbbVie, Asahi Kasei, Astellas, AstraZeneca, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen, Mitsubishi-Tanabe, MSD, Pfizer, Quintiles, Takeda and UCB Pharma, and has taken part in speakers' bureaus for Abbott, AbbVie, Asahi Kasei, Astellas, AstraZeneca, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen, Mitsubishi-Tanabe, MSD, Pfizer, Quintiles, Takeda and UCB Pharma; KE has received consultancy fees from UCB Pharma; AW has received research grants from Daiichi-Sankyo, Dainippon-Sumitomo, Kyorin, Meiji Seika; Shionogi, Taiho, Taisho and Toyama Chemical, and has taken part in speakers' bureaus for Daiichi-Sankyo, Dainippon-Sumitomo, GSK, Mitsubishi-Tanabe, MSD, Pfizer, Shionogi and Taisho-Toyama; HO has received consultancy fees from Astellas and UCB Pharma; SY has received research grant from BMS and taken part in speakers' bureaus for AbbVie, Astellas, Chugai, Eizai, Pfizer, Mitsubishi-Tanabe and Takeda; YY has no competing interests to disclose; YK has received speakers' bureau from Astellas, Chugai, and Ono; TM has received speaker honoraria from Pfizer Japan, Janssen Pharmaceutical Co. and Astellas Pharma; and research grants form Quintiles Transnational Japan K.K, Janssen Pharmaceutical Co., Takeda Chemical Industries, Daiichi Sankyo Co., Astellas Pharma, Eli Lilly Japan K.K., MSD Co., Nippon Kayaku Co., Parexel International Corp., Pfizer Japan and Bristol-Myers Squibb; MI has received payment for lectures from Astellas, Chugai, Ono and Tanabe-Mitsubishi, has received research grants from Pfizer and a royalty fee from Chugai; TS is an employee of UCB Pharma; TO is an employee of Astellas; DvdH has received consultancy fees from AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma and Vertex; and is the Director of Imaging Rheumatology bv; NM has received research grants from Abbott, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer and Takeda; TK has received consultancy fees from AbbVie, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Taisho-Toyama, Takeda, Teijin and UCB Pharma, and has taken part in speakers' bureaus for Abbott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Taisho-Toyama, Takeda, Teijin and UCB Pharma.

Patient consent Obtained.

Ethics approval This study was conducted after approval by the Institutional Review Board designated by each study site, in compliance with the ethical principles described in the Declaration of Helsinki and Good Clinical Practice.

Provenance and peer review Not commissioned; externally peer reviewed.

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Japan College of Rheumatology
MODERN RHEUMATOLOGY

http://informahealthcare.com/mor
ISSN 1439-7595 (print), 1439-7609 (online)

Mod Rheumatol, 2015; Early Online: 1–7

DOI: 10.3109/14397595.2015.1012786

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ORIGINAL ARTICLE

Long-term safety and efficacy of treatment with subcutaneous abatacept in Japanese patients with rheumatoid arthritis who are methotrexate inadequate responders

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Abstract

Objective. To assess the long-term safety, immunogenicity, and efficacy of subcutaneous (SC) abatacept in combination with methotrexate (MTX) in Japanese patients with rheumatoid arthritis who were MTX inadequate responders, in a long-term extension (LTE) to a double-dummy, double-blind study (NCT01001832).

Methods. Patients, who had previously received SC or intravenous (IV) abatacept with MTX (6–8 mg/week) for 24 weeks, received SC abatacept (125 mg/week) with MTX for an additional 52 weeks. Safety, immunogenicity, and efficacy were assessed.

Results. The LTE included 112 patients. SC abatacept was generally well tolerated in the LTE, with no new safety signals. American College of Rheumatology 20, 50, and 70 response rates, disease activity score 28 (C-reactive protein) remission rates (<2.6), and Health Assessment Questionnaire-Disability Index response rates (≥ 0.3 improvement from baseline) achieved at the end of the double-blind period were maintained over the LTE and were comparable in patients who received SC or IV abatacept in the double-blind period. Seropositivity for immunogenicity occurred in 4 (3.6%) patients. Self-injection of SC abatacept was well controlled and not associated with additional safety events.

Conclusions. SC abatacept had acceptable safety and was well tolerated and effective over the LTE (76 weeks in total), with low rates of immunogenicity in Japanese patients.

Keywords

Abatacept, Japan, Long-term, Rheumatoid arthritis, Subcutaneous injections

History

Received 24 July 2014
Accepted 22 January 2015
Published online 11 March 2015

Introduction

Abatacept is a fully human, soluble fusion protein that selectively modulates the CD80/CD86:CD28 co-stimulatory signal required for full T-cell activation [1]. Activated T-cells are implicated in the pathogenesis of rheumatoid arthritis (RA) [2]. By competing with CD28 for CD80/CD86 binding, abatacept modulates serum levels of inflammatory cytokines and autoantibodies [3].

Abatacept is available in intravenous (IV) and subcutaneous (SC) formulations. The efficacy and safety of SC abatacept in the treatment of RA, and its non-inferiority to IV abatacept, have been reported [4–8]. Both IV and SC abatacept are approved in the USA, Europe, and Japan for the treatment of RA. In Japan, IV abatacept was approved for the treatment of RA in 2010 and SC abatacept was approved for the treatment of RA in 2013. The long-term safety profile of IV abatacept in Japanese patients with RA has been described previously [9–12], but there is a lack of long-term safety and efficacy data for SC abatacept in this population.

The Abatacept Comparison of subQ versus intravenoUs in Inadequate Responders to mEthotrexate (ACQUIRE) study directly compared the efficacy and safety of IV and SC abatacept, with background methotrexate (MTX) [4]. SC abatacept had comparable efficacy and safety to IV abatacept in patients with an inadequate response to MTX, as well as low immunogenicity, low rates of injection-site reactions, and a high 6-month retention rate. ACQUIRE did not include Japanese patients, and so a double-dummy, double-blind, Phase II/III bridging study with Japanese patients was conducted [13]. Here we report the findings from a

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1-year (52 weeks), open-label, long-term extension (LTE) of the Japanese bridging study with the aim of assessing the long-term safety, immunogenicity, and efficacy of SC abatacept plus MTX after 52 additional weeks of treatment.

Methods

Patient population

All patients who completed the 6-month, double-dummy, double-blind, Phase II/III bridging study were eligible to enter the open-label LTE period. The patient population comprised Japanese adults (age ≥ 20 years) with a diagnosis of active RA who had an inadequate response to MTX. Inclusion and exclusion criteria for the short-term bridging study were reported previously [13]. All patients provided signed, written informed consent.

Study design

This study comprised a 6-month (24 weeks), multicenter, double-dummy, double-blind period followed by a 1-year (52 weeks) open-label LTE period, with an additional 6 months of follow-up (NCT01001832). The double-blind period was conducted across 34 sites in Japan between December 2009 and February 2011. During the double-blind period, patients were randomized (1:1) to SC abatacept (125 mg/week, IV loading of ~10 mg/kg on Day 1) or IV abatacept (~10 mg/kg, every 4 weeks), both with MTX (6–8 mg/week). In the LTE period, patients received SC abatacept (125 mg/week) with MTX for 52 weeks (Days 169–533); biweekly administration of SC abatacept was permitted only in patients with low body weight (≤ 50 kg). The MTX dose could be altered according to investigator discretion. Dose changes owing to adverse events (AEs) were prohibited, and non-biologic disease-modifying antirheumatic drugs were permitted. During the LTE period, SC abatacept was administered by self-injection (or by a caregiver), except where the investigator judged that injection at the study center was appropriate. Institutional Review Board/Independent Ethics Committee approval was received for the protocol and patient consent form, and the study was conducted in accordance with the Declaration of Helsinki [14] and the International Conference on Harmonization Guideline for Good Clinical Practice [15].

Assessments

Safety, immunogenicity, and efficacy were assessed in the intent-to-treat population during the LTE period. Safety assessments used data up to 8 weeks (56 days) post-treatment and included AE monitoring, physical examination, chest radiograph, electrocardiogram, physical measurements, breast cancer screening, vital signs, tuberculosis screening, and laboratory assessments. Blood samples were collected at Weeks 0, 12, 24, 36, 48, and 52 of the LTE period. Trough level serum abatacept concentration (C_{min}), C-reactive protein (CRP), and immunogenicity were assessed at Weeks 12, 24, 36, 48, and 52 of the LTE period; and rheumatoid factor (RF) was assessed at Week 52. In patients who discontinued, immunogenicity sampling was performed at 7, 28, 84, and 168 days after the last dose of SC abatacept. Anti-abatacept immunogenicity testing was performed using a sensitive, validated electrochemiluminescence immunoassay method (Meso-Scale Discovery, Rockville, Maryland, USA). The electrochemiluminescence assay differentiated between two antibody specificities: immunoglobulin (Ig)G and/or junction region, and cytotoxic T-lymphocyte antigen-4 (CTLA-4) and possibly Ig. Neutralizing antibodies were assessed as described previously [13]. Efficacy assessments included American College of Rheumatology (ACR) 20, 50, and 70 response rates over 533 days (the first administration of study drug in the double-blind period was Day 1); change in Disease Activity Score (DAS)28 (CRP) from baseline and the proportion of patients who achieved low disease activity (DAS28 < 3.2) and remission (DAS28 < 2.6) at Days 169 and 533; and change in Health Assessment Questionnaire-Disability Index (HAQ-DI) from baseline at Days 169 and 533 and the proportion of patients who achieved HAQ-DI response (reduction in HAQ-DI ≥ 0.3 units from baseline) over 533 days.

Sample size

Sample size calculations were based on Japanese guidelines for the assessment of RA drugs in clinical studies [16] and were reported previously [13].

Statistical analysis

No formal statistical tests were performed. Safety analyses included all treated patients in the LTE period, grouped according to the abatacept formulation received in the double-blind period. The evaluation of drug safety was based on AEs, vital signs, and laboratory abnormalities during the LTE period. Pharmacokinetic analyses included summarizing C_{min} at Weeks 12, 24, 36, 48, and 52 using geometric means and coefficients of variation. RF and CRP were summarized by treatment received in the double-blind period. Immunogenicity was assessed by testing serum samples for the development of antibodies against abatacept. The incidence of positive response was summarized by treatment received in the double-blind period. Efficacy analyses included all patients who started the LTE period and received at least one dose of SC abatacept during the LTE period. ACR 20, 50, and 70 response rates; DAS28 (CRP) remission rates; and HAQ-DI response rates with exact 95% confidence intervals (CIs) were summarized at each time point by treatment received in the double-blind period. Missing values were not imputed.

Results

Patients

In the 6-month, double-blind period, 118 patients were randomized and treated with abatacept plus MTX. A total of 112 patients entered the LTE (during which all patients received 125 mg/week SC abatacept plus MTX): 56 who previously received SC abatacept (SC group) and 56 who previously received IV abatacept (IV group). The LTE period was completed by 52 (92.9%) patients in the SC group and 51 (91.1%) patients in the IV group (Figure 1).

In the LTE period, the mean (standard deviation [SD]) duration of exposure to abatacept was 13.5 (0.9) months in the SC group and 13.3 (1.8) months in the IV group (median [range]: 13.8 [8–14] and 13.8 [4–14] months, respectively). With regard to adherence, 41 (73.2%) patients in the SC group and 47 (83.9%) patients in the IV group received all the planned doses of SC abatacept; 7 (12.5%) and 3 (5.4%) patients missed one dose, 7 (12.5%) and 3 (5.4%) patients missed two doses, and 1 (1.8%) and 3 (5.4%) patients missed three or more doses, respectively. SC abatacept was administered by self-injection at least once in the LTE period by 105 (93.8%) patients. Baseline characteristics of patients were comparable with those for the 6-month, double-blind period [13]. Characteristics were generally balanced in the SC and IV groups (Table 1); however, the SC group contained fewer women than the IV group (37 [66.1] vs. 46 [82.1%]), and patients in the SC group had longer mean (SD) disease duration (7.4 [8.8] vs. 5.3 [7.3] years) and lower mean (SD) CRP levels (1.90 [1.63] vs. 2.93 [2.79] mg/dL) than patients in the IV group. The mean (SD) weekly total MTX dose (expressed as mg/week) in the SC and IV groups, respectively, was 7.3 (1.0, $n = 56$) and 7.3 (0.9, $n = 56$) at baseline, 7.0 (1.7, $n = 56$) and 7.2 (1.2, $n = 56$) in the week includ-

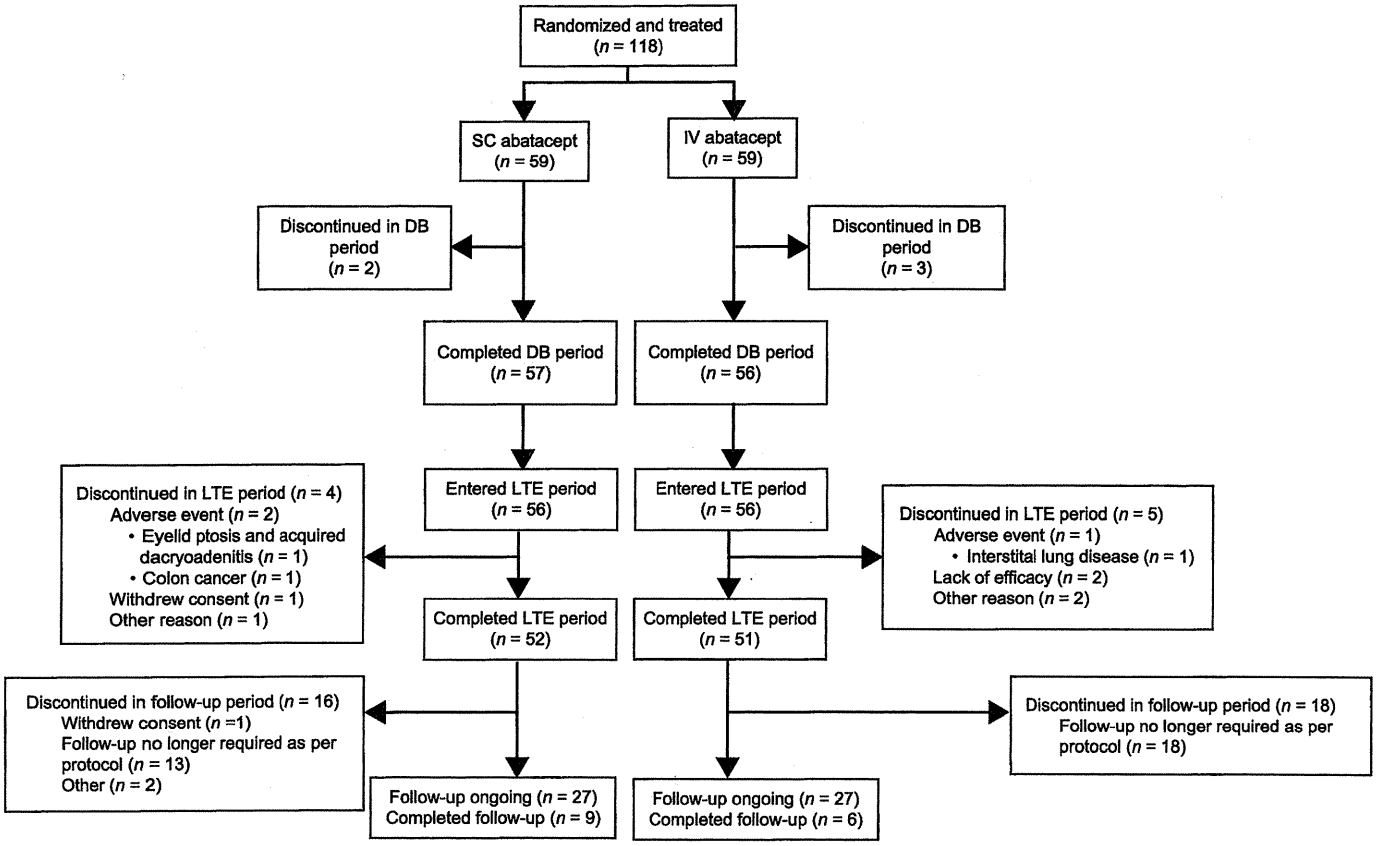

Figure 1. Patient flow. *DB* double-blind, *IV* intravenous, *LTE* long-term extension, *SC* subcutaneous.

ing Day 169, and 7.7 (2.5, $n = 52$) and 7.4 (2.1, $n = 51$) in the week including Day 533.

Safety

SC abatacept was generally well tolerated during the LTE period and the safety profile was consistent with that in the double-blind period (Table 2). During the LTE period, the long-term safety remained comparable between patients who had received SC and IV abatacept in the double-blind period. Serious adverse events (SAEs) were reported in 10 patients (Table 2); treatment-related SAEs were reported in 7 patients: dacryocystitis, bacterial pneumonia, interstitial lung disease, breast cancer, lower abdominal pain and pyrexia, colonic polyp and colon cancer, and dermal cyst. Three patients discontinued SC abatacept owing to AEs (includes discontinuations owing to SAEs): colon cancer (SAE), acquired dacryoadenitis and eyelid ptosis, and interstitial lung disease.

Infections and infestations were reported in 58 (51.8%) patients; nasopharyngitis was the most frequently reported infection (28.6%). There were two serious infections: dacryocystitis and bacterial pneumonia. No opportunistic infections or autoimmune disorders were reported. Malignant neoplasms were reported in 2 patients during the LTE: colon cancer and breast cancer. Prespecified local injection-site reactions occurred in 2 patients; both cases were of mild severity and did not lead to discontinuation. Prespecified systemic injection reactions occurred in 5 patients; all cases were of mild or moderate severity and did not lead to discontinuation. There were no abnormalities in laboratory test values and vital signs. One patient died from B-cell lymphoma considered by the investigator to be related to the study drug. B-cell lymphoma occurred on Day 568, after the

Table 1. Patient and clinical disease characteristics at baseline.[a]

Characteristic	Subcutaneous abatacept ($n = 56$)	Intravenous abatacept ($n = 56$)	Total ($N = 112$)
Age, years	55.4 (12.2)	55.0 (13.7)	55.2 (12.9)
Women, *n* (%)	37 (66.1)	46 (82.1)	83 (74.1)
Weight, kg	56.3 (10.6)	53.3 (9.6)	54.8 (10.2)
Disease duration, years	7.4 (8.8)	5.3 (7.3)	6.3 (8.1)
DAS28 (CRP)	5.65 (0.85)	5.89 (0.89)	5.77 (0.88)
Tender joint count	21.3 (9.5)	22.2 (10.0)	21.7 (9.7)
Swollen joint count	16.5 (7.2)	17.5 (7.4)	17.0 (7.3)
Subject global assessment, VAS 100 mm	56.6 (23.2)	60.3 (21.3)	58.4 (22.3)
HAQ-DI	1.30 (0.67)	1.32 (0.66)	1.31 (0.66)
CRP, mg/dL	1.90 (1.63)	2.93 (2.79)	2.41 (2.33)
RF positive, *n* (%)	49 (87.5)	48 (85.7)	97 (86.6)
MTX dose, mg/week	7.3 (1.0)	7.3 (0.9)	7.3 (0.9)

CRP C-reactive protein, *DAS28* Disease Activity Score 28, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *VAS* visual analog scale

[a]All data are mean (standard deviation) unless stated otherwise.

Table 2. Safety profile of abatacept in the double-blind period and in the open-label LTE period [13].

Event, *n* (%)	Double-blind period[a]		Open-label extension[b]		
	Subcutaneous abatacept ($n = 59$)	Intravenous abatacept ($n = 59$)	Subcutaneous group ($n = 56$)	Intravenous group ($n = 56$)	Total ($N = 112$)
Deaths	0	0	1 (1.8)	0	1 (0.9)
SAEs	4 (6.8)	3 (5.1)	5 (8.9)	5 (8.9)	10 (8.9)
Related SAEs	3 (5.1)	2 (3.4)	4 (7.1)	3 (5.4)	7 (6.3)
Discontinued owing to SAEs	3 (5.1)	1 (1.7)	1 (1.8)	0	1 (0.9)
AEs	45 (76.3)	49 (83.1)	49 (87.5)	48 (85.7)	97 (86.6)
Related AEs	31 (52.5)	35 (59.3)	31 (55.4)	32 (57.1)	63 (56.3)
Discontinued owing to AEs[c]	3 (5.1)	3 (5.1)	2 (3.6)	1 (1.8)	3 (2.7)
AEs of special interest					
Infections and infestations	20 (33.9)	29 (49.2)	29 (51.8)	29 (51.8)	58 (51.8)
Serious infections and infestations	1 (1.7)	1 (1.7)	2 (3.6)	0	2 (1.8)
Malignancies	1 (1.7)	1 (1.7)	1 (1.8)	1 (1.8)	2 (1.8)
Local injection-site reactions	0	0	2 (3.6)	0	2 (1.8)

AE adverse event, *SAE* serious adverse event, *LTE* long-term extension
[a]Includes data up to 56 days post the last dose of the double-blind period or start of the first dose in the open-label LTE period, whichever occurred first.
[b]Includes data up to 56 days post the last dose of the open-label LTE period.
[c]Includes discontinuations owing to SAEs.

patient received his/her last dose of abatacept, and the patient died on Day 595. Overall, the long-term safety was similar in patients who received SC and IV abatacept in the double-blind period.

Immunogenicity

In the LTE period, seropositivity for anti-abatacept antibodies was detected in 2 (3.6%) patients from the SC group and in 2 (3.6%) patients from the IV group. Three patients demonstrated reactivity specific to the Ig and/or junction region, and 1 patient demonstrated reactivity specific to the CTLA-4 and possibly the Ig-specific region. Seropositivity for anti-abatacept antibodies did not appear to affect the efficacy or safety of abatacept. Rates of post-treatment immunogenicity were consistent with previous observation after a prolonged period of drug withdrawal [17].

Following the LTE, there was a 6-month follow-up period during which patients continued to be monitored for immunogenicity. In the follow-up period, seropositivity for anti-abatacept antibodies was detected in 9 (20.0%) patients in the SC group (7 were newly detected in the follow-up period, and 2 were initially detected in the LTE period and continuously in the follow-up period), and in 4 (10.3%) patients in the IV group. Among the 13 patients who tested positive for anti-abatacept antibodies, 7 patients from the SC group and 3 patients from the IV group underwent a neutralizing antibody assay. Neutralizing antibodies were found in 1 patient in the IV group with reactivity specific to the CTLA-4 and possibly the Ig-specific region. The development of anti-abatacept antibodies was not associated with autoimmune disease or hypersensitivity, and the efficacy and pharmacokinetic profile of SC abatacept was unchanged in patients who were seropositive, relative to those who were seronegative.

Pharmacokinetics

During the LTE, the abatacept geometric mean C_{min} was observed without stratification by the IV and SC groups, and remained consistent from Day 253 to Day 533, ranging from 33.34 to 39.09 μg/mL following SC administration. In patients who received weekly abatacept, the geometric mean C_{min} was 36.33 μg/mL in patients with a body weight of < 60 kg ($n = 58$) compared with 27.52 μg/mL in patients with a body weight of ≥ 60 kg ($n = 26$). Abatacept C_{min} decreased following a positive immunogenic response to abatacept in 1 patient from the IV group.

Efficacy

ACR 20, 50, and 70, DAS28 (CRP), and HAQ-DI response rates observed at the end of the double-blind period (Day 169) were at least maintained during the LTE, and showed a trend toward continued increases up to Day 533 in both the SC and the IV

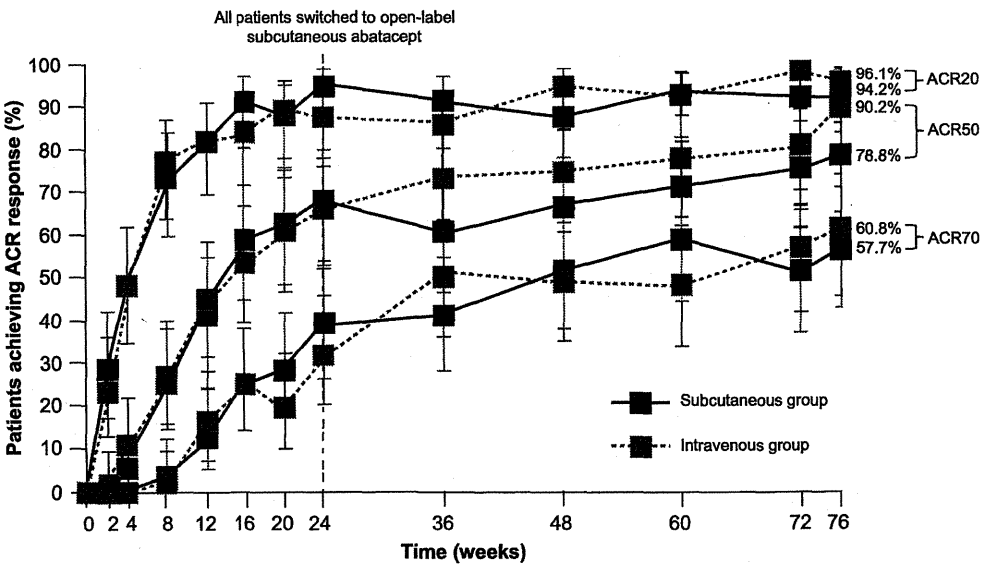

Figure 2. ACR 20, 50, and 70 response rates during the double-blind period (Weeks 0–24) and the open-label LTE period (Weeks 24–76)[a]. Error bars represent 95% CIs. [a]As-observed analysis. *ACR* American College of Rheumatology.