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EXTENDED REPORT

Clinical benefit of 1-year certolizumab pegol (CZP) add-on therapy to methotrexate treatment in patients with early rheumatoid arthritis was observed following CZP discontinuation: 2-year results of the C-OPERA study, a phase III randomised trial

Tatsuya Atsumi,[1] Yoshiya Tanaka,[2] Kazuhiko Yamamoto,[3] Tsutomu Takeuchi,[4] Hisashi Yamanaka,[5] Naoki Ishiguro,[6] Katsumi Eguchi,[7] Akira Watanabe,[8] Hideki Origasa,[9] Shinsuke Yasuda,[1] Yuji Yamanishi,[10] Yasuhiko Kita,[11] Tsukasa Matsubara,[12] Masahiro Iwamoto,[13] Toshiharu Shoji,[14] Osamu Togo,[14] Toshiyuki Okada,[15] Désirée van der Heijde,[16] Nobuyuki Miyasaka,[17] Takao Koike[1,18]

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For numbered affiliations see end of article.

Correspondence to
Professor Tatsuya Atsumi, Division of Rheumatology, Endocrinology and Nephrology, Graduate School of Medicine, Hokkaido University, North 15, West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan; at3tat@med.hokudai.ac.jp

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ABSTRACT

Objectives To investigate the clinical impact of 1-year certolizumab pegol (CZP) therapy added to the first year of 2-year methotrexate (MTX) therapy, compared with 2-year therapy with MTX alone.

Methods MTX-naïve patients with early rheumatoid arthritis (RA) with poor prognostic factors were eligible to enter Certolizumab-Optimal Prevention of joint damage for Early RA (C-OPERA), a multicentre, randomised, controlled study, which consisted of a 52-week double-blind (DB) period and subsequent 52-week post treatment (PT) period. Patients were randomised to optimised MTX+CZP (n=159) or optimised MTX +placebo (PBO; n=157). Following the DB period, patients entered the PT period, receiving MTX alone (CZP+MTX→MTX; n=108, PBO+MTX→MTX; n=71). Patients who flared could receive rescue treatment with open-label CZP.

Results 34 CZP+MTX→MTX patients and 14 PBO +MTX→MTX patients discontinued during the PT period. From week 52 through week 104, significant inhibition of total modified total Sharp score progression was observed for CZP+MTX versus PBO +MTX (week 104: 84.2% vs 67.5% (p<0.001)). Remission rates decreased after CZP discontinuation; however, higher rates were maintained through week 104 in CZP+MTX→MTX versus PBO+MTX→MTX (41.5% vs 29.3% (p=0.026), 34.6% vs 24.2% (p=0.049) and 41.5% vs 33.1% (p=0.132) at week 104 in SDAI, Boolean and DAS28(erythrocyte sedimentation rate) remission. CZP retreated patients due to flare (n=28) showed rapid clinical improvement. The incidence of overall adverse events was similar between groups.

Conclusions In MTX-naïve patients with early RA with poor prognostic factors, an initial 1 year of add-on CZP to 2-year optimised MTX therapy brings radiographic and clinical benefit through 2 years, even after stopping CZP.

Trial registration number NCT01451203.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by progressive inflammatory synovitis. This results in the destruction of articular cartilage and marginal bone, which is generally thought to be irreversible.[1] Recent studies have demonstrated that the early treatment of patients with antirheumatic drugs is associated with a reduction in inflammation, greater inhibition of structural damage and better long-term outcomes.[2 3] Furthermore, early aggressive treatment with biological disease-modifying antirheumatic drugs (bDMARDs), such as antitumour necrosis factors (TNFs), was reported to be highly effective at reducing disease progression.[4] The effect of treatment discontinuation/tapering following successful inhibition of disease progression as a result of using bDMARDs early in the course of the disease has yet to be fully investigated; however, there is the possibility that the positive disease trajectory may be maintained following treatment cessation.

Certolizumab pegol (CZP) is a humanised anti-TNF antibody fragment conjugated to polyethylene glycol, approved for the treatment of inflammatory diseases, including RA. The efficacy and safety of CZP in combination with methotrexate (MTX) during the early stages of RA was assessed in the Certolizumab-Optimal Prevention of joint damage for Early RA (C-OPERA) study. This study consisted of two periods: a 52-week double-blind (DB) period during which patients received either CZP or placebo (PBO) together with MTX, and a subsequent 52-week post-PBO/CZP treatment (PT) period in which patients received MTX therapy without CZP or PBO. Results from the DB period, which showed significant inhibition of structural damage and a reduction in the severity of RA symptoms following treatment with CZP+MTX compared with PBO +MTX, have been reported.[4] Here, we report the

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2-year overall results including the PT period, which investigated whether the clinical benefits of initial 1-year CZP+MTX therapy were sustained through a subsequent 1-year period where patients received MTX alone.

METHODS

for the DB period were previously
re provided in the online supplementary

1203) was a multicentre, DB,
ised, parallel-group study conducted in
ly described.[4] Full details of the study
e online supplementary materials.

e performed every 8 weeks during the
analysis of the PT period was change in
total Sharp score (mTSS) from baseline
pared the progression of joint damage
TX→MTX and PBO+MTX→MTX
t damage progression was assessed using
and 104; mTSS was evaluated by two
n accordance with previously reported
l analyses comparing clinical efficacy
included disease activity score (DAS)28
on rate (ESR)), simple disease activity
joint count (SJC), tender joint count
ment Questionnaire Disability Index

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(HAQ-DI), physician's and patient's global assessments of disease activity (PtGADA), patient's assessment of arthritis pain, ESR and C-reactive protein (CRP) levels. Clinical remission was defined as achieving SDAI ≤3.3, DAS28(ESR) <2.6 or ≤1 on all four of the following criteria (Boolean remission): the number of TJC (in 28 joints), number of SJC (in 28 joints), CRP (mg/dL) and PtGADA (100 mm visual analogue scale (VAS) data converted to cm).

Safety assessments

All safety events during the PT period were recorded as adverse events (AEs) or serious AEs (SAEs). Laboratory tests (haematological, blood chemistry, urinalysis), chest radiographs and ECG were also evaluated.

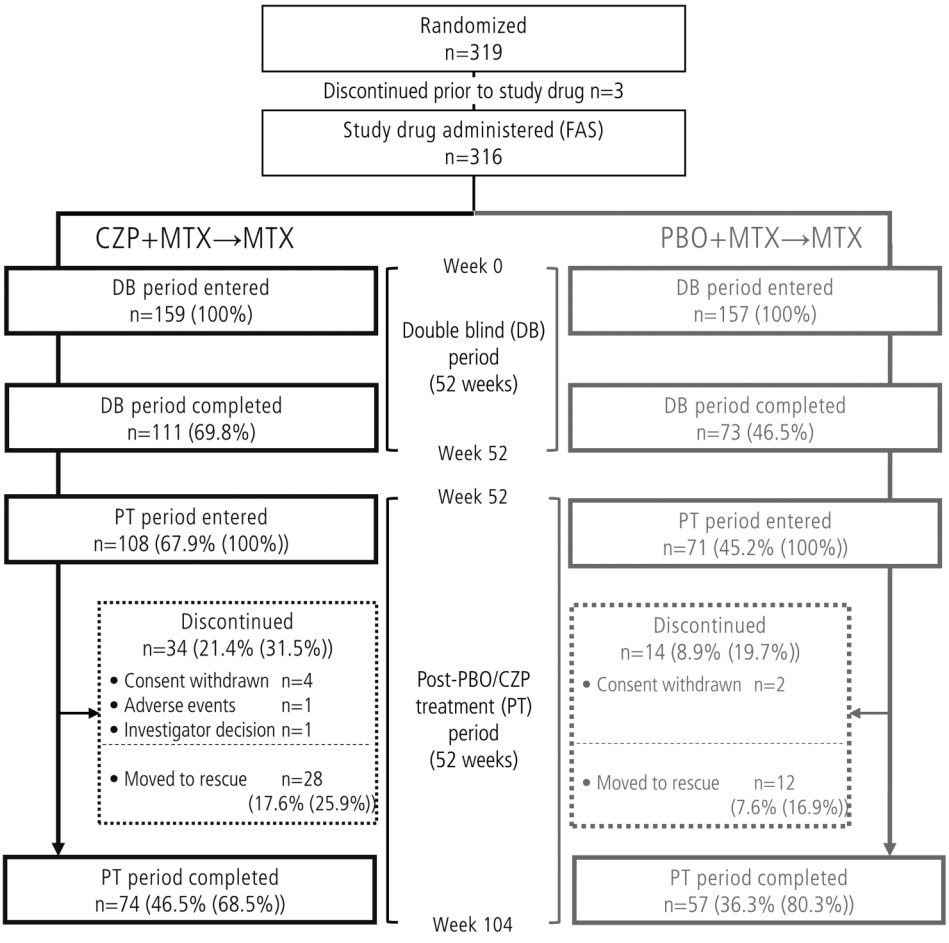
Statistical analyses

Full details of the statistical analyses can be found in the online supplementary materials. In brief, the full analysis set (FAS; defined as all patients who received ≥1 dose of study drug and provided any efficacy data thereafter) was used for all efficacy measurements. Missing data were imputed using linear extrapolation for mTSS and last observation carried forward (LOCF) for all other efficacy variables. Change from baseline in mTSS at weeks 52 and 104 was analysed using an analysis of covariance (ANCOVA) model. Fisher's exact test was used to compare rates of mTSS non-progression (mTSS change from baseline ≤0.5) and clinical remission at weeks 52 and 104, between the PBO and CZP groups.

RESULTS

Patient characteristics and disposition

Of the 316 patients who were randomised and received at least one dose of study drug (FAS population), 179 patients entered



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the PT period and 131 patients completed the study (figure 1). The proportion of patients completing the PT period (from the patients who entered the PT period) was 68.5% and 80.3% in the CZP+MTX→MTX group and the PBO+MTX→MTX group, respectively (figure 1).

Patient baseline demographics and disease characteristics at period entry (week 52) are shown in plementary table S1. At DB baseline, nd disease characteristics were similar both groups, disease activity at baseline s slightly lower than in the total popula- m baseline through week 52 following P+MTX or PBO+MTX.

ge progression in the total

at week 52 the change from baseline in e CZP+MTX→MTX group compared MTX group (0.36±2.70 vs 1.58±4.86,), and the rate of radiographic non- in the CZP+MTX→MTX group com- TX→MTX group (82.9% vs 70.7%; exact test).[4] During the PT period, changes from baseline (mean±SD) for 8 vs 3.01±9.66 (p=0.001)), erosion .43±4.40 (p=0.003)) and joint space narrowing score (0.36±4.27 vs 1.58±7.17 (p=0.002)) were lower for the CZP+MTX→MTX group compared with the PBO+MTX→MTX group using linear extrapolation for missing data imputation (figure 2A). A sensitivity analysis using an LOCF imputation method (figure 2A) confirmed the results of the primary analysis (linear extrapolation). At week 104, the proportion of patients with radiographic non-progression (ie, mTSS change from baseline ≤0.5) was higher for the CZP +MTX→MTX group compared with the PBO+MTX→MTX group (84.2% vs 67.5%, p<0.001). Furthermore, the proportion of patients with rapid radiographic progression (RRP: mTSS yearly change from baseline ≥5) at week 104 was lower for CZP+MTX→MTX group compared with the PBO +MTX→MTX group (3.2% vs 9.6%, p=0.022). Subgroup analyses revealed that high baseline mTSS, CRP or TNF was associated with poor week 104 radiographic outcomes in the PBO +MTX→MTX group. The CZP+MTX→MTX group also showed higher inhibition of radiographic progression in these populations (see online supplementary table S3). Consistent with radiographic findings, the proportion of patients with HAQ remission (HAQ ≤0.5) at week 104 was numerically higher in the CZP+MTX→MTX group than the PBO +MTX→MTX group (73.0% vs 63.7%, p=0.09). In addition, the proportion of the patients who achieved HAQ remission at week 104 was higher in patients who showed non-radiographic progression at week 104 than those who did not (76.7% vs

raphics and patient characteristics

	CZP+MTX→MTX			PBO+MTX→MTX		
	Total patients n=159	Patients entering PT period n=108		Total patients n=157	Patients entering PT period n=71	
	DB baseline (Week 0)	DB baseline (Week 0)	PT baseline (Week 52)	DB baseline (Week 0)	DB baseline (Week 0)	PT baseline (Week 52)
	49.4±10.6	48.8±11.2	–	49.0±10.3	48.6±10.8	–
	129 (81.1)	85 (78.7)	–	127 (80.9)	58 (81.7)	–
	57.4±11.3	57.0±11.5	–	57.4±10.6	57.4±10.3	–
	22.4±3.9	22.2±3.7	–	22.5±3.7	22.4±3.7	–
	4.0±2.9	4.4±3.1	–	4.3±2.8	4.4±3.1	–
)	159 (100.0)	71 (100.0)	–	157 (100.0)	108 (100.0)	–
	153 (96.2)	104 (96.3)	–	146 (93.0)	68 (95.8)	–
ian), n (%)	79 (49.7)	41 (47.2)	–	80 (51.0)	34 (47.9)	–
	8.4±6.1	7.5±5.8	0.5±1.1	8.9±6.5	7.3±6.1	0.6±1.6
	8.3±5.3	7.6±4.6	0.3±0.7	8.4±5.3	7.0±4.2	0.4±1.4
	38.4±25.3	36.3±23.7	12.8±9.9	43.7±28.2	36.5±22.2	15.5±14.3
	1.29±1.82	1.12±1.51	0.06±0.13	1.52±1.91	1.03±1.39	0.17±0.37
	130.4±135.4	125.3±135.4	47.7±25.7	185.4±214.9	167.3±204.3	52.5±31.1
	5.4±1.1	5.2±1.1	1.9±0.8	5.5±1.2	5.1±1.0	2.2±0.7
	28.7±12.5	27.0±11.2	2.4±2.6	30.0±13.6	24.6±11.3	2.7±3.1
	1.01±0.64	1.04±0.63	0.14±0.26	1.05±0.69	0.79±0.57	0.07±0.14
	4.1±7.4	3.8±7.4	3.7±7.4	5.5±15.0	3.2±6.2	3.4±6.3
	1.9±4.0	1.6±3.9	1.6±3.7	2.5±7.8	1.6±3.3	1.8±3.2
	2.1±4.6	2.2±4.8	2.2±4.8	2.9±8.3	1.5±4.0	1.6±4.1
week)†	11.4±3.1	11.3±3.2	10.9±4.1	11.5±2.8	11.5±3.1	11.1±3.7

rwise indicated. Data in DB baseline columns represent average during weeks 0–104, whereas data in PT baseline columns represent average during

rthritic symptoms.
g/week and escalated to the maximum tolerated dose (up to 16 mg/week) by week 8.
ic citrullinated peptide; CRP, C reactive protein; CZP, certolizumab pegol; DB, double blind; ESR, erythrocyte sedimentation rate; HAQ-DI, Health ility Index; MMP-3, matrix metalloproteinase-3; mTSS, modified total Sharp score; MTX, methotrexate; PBO, placebo; PT, post treatment; RA, rheumatoid JC, swollen joint count; TJC, tender joint count.

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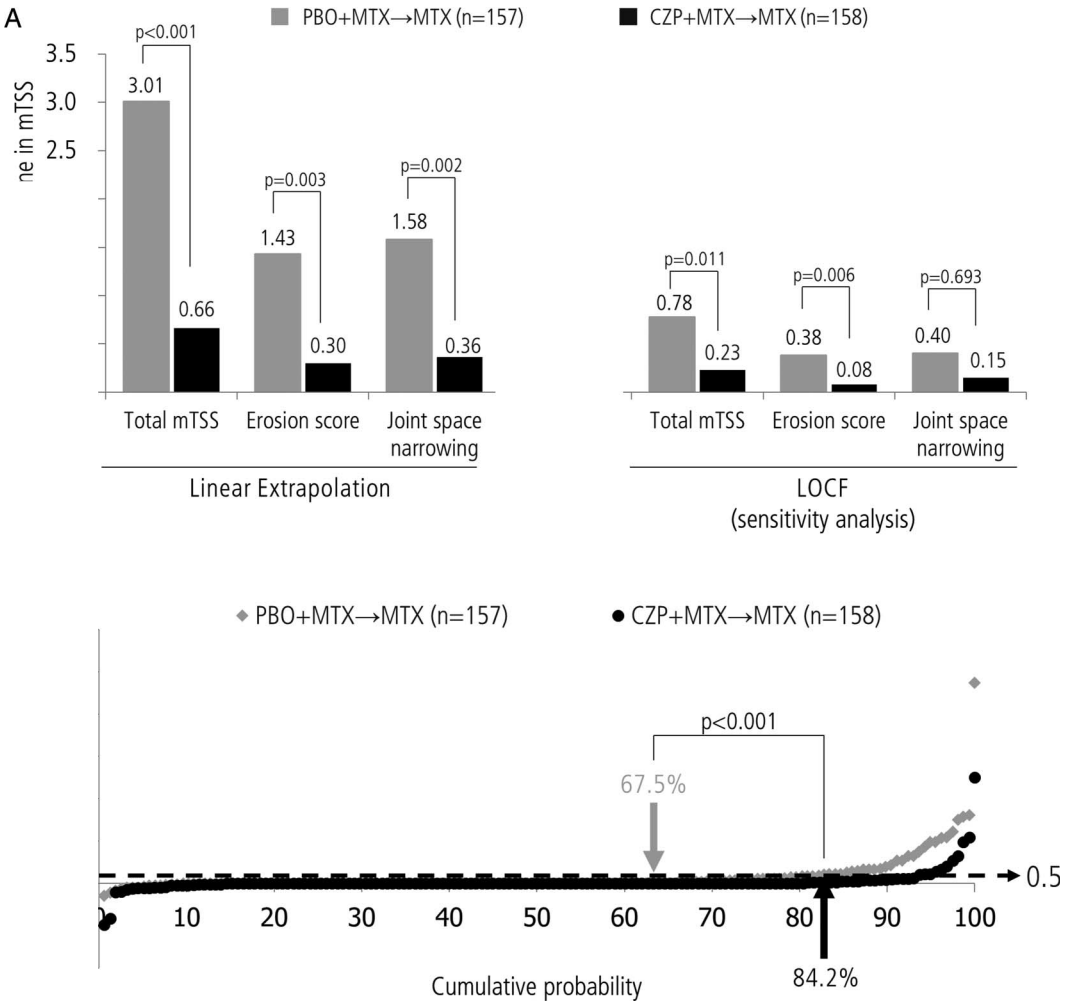

baseline in modified total Sharp score (mTSS) at week 104. (B) Cumulative probability plot of mTSS change from oth PBO+MTX→MTX and CZP+MTX→MTX groups. Change from baseline in mTSS was analysed using an analysis of actual scores were converted to rank scores, using the treatment group as a factor and baseline rank score as a n-progression (mTSS change from baseline ≤0.5) was compared using Fisher's exact test. CZP, certolizumab pegol; LOCF, ward; MTX, methotrexate; PBO, placebo.

P+MTX→MTX, and 70.8% vs 49.0% X→MTX).

total population

s achieving SDAI, Boolean and DAS28 alculated throughout both the DB and t the end of the DB period (week 52), were significantly higher in the CZP ompared with the PBO+MTX→MTX

al remission observed for the CZP ecreased during the first 16 weeks of the rate stabilised from week 68 (week 16 h week 104. The remission rates of the up during the PT period were similar to change in clinical remission observed om the end of DB to the PT period. n of the PT period, the rates of clinical her in the CZP+MTX→MTX group +MTX→MTX group (41.5% vs 29.3% 4.2% (p=0.049) and 41.5% vs 33.1% (p=0.132) at week 104 in SDAI, Boolean and DAS28(ESR), respectively). The proportion of patients with low disease activity (DAS28(ESR) ≤3.2) was also higher in the CZP +MTX→MTX group compared with the PBO+MTX→MTX group throughout the PT period (see online supplementary figure S1).

Impact of CZP discontinuation in the CZP+MTX→MTX group

The impact of CZP discontinuation was assessed on patients who entered the PT period (PT population) from the CZP +MTX group (n=108). Of these, 74 patients (68.5%) completed the 1-year PT period with MTX therapy (figure 4A). Rates of radiographic non-progression during the PT period (94.4% (102/108); figure 4B) were similar to the rates observed during the DB period (91.7% (99/108)), as were mean changes in mTSS (±SD) during the first and second 52-week periods (DB period (weeks 0–52): −0.03 (±0.80); PT period (weeks 52 −104): 0.06 (±0.76)). Conversely, clinical remission rates in the PT population of the CZP+MTX→MTX group showed decreases in SDAI, Boolean and DAS28(ESR) definitions of

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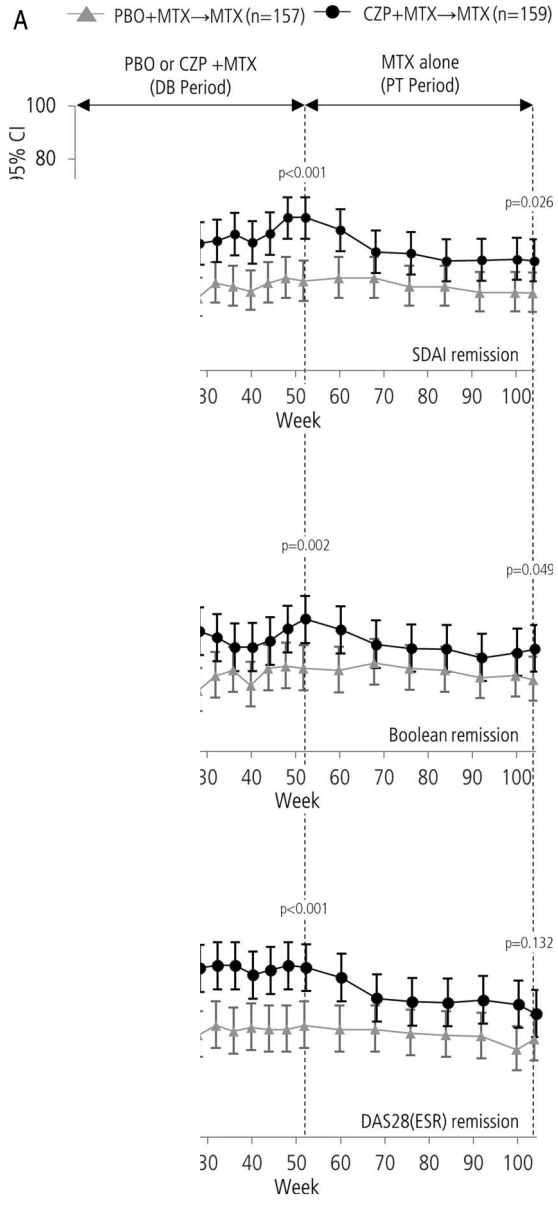

of patients achieving (A) SDAI remission, C) DAS28(ESR) remission during the ntion of joint damage for Early rheumatoid BO+MTX→MTX and CZP+MTX→MTX weeks 52 and 104 were compared using tolizumab pegol; DB, double blind; tion rate; MTX, methotrexate; tment.

to 104 (from 79.6% to 55.6%, 61.1% 6%, respectively; figure 4C).

r symptom flare in CZP+MTX→MTX

o withdrew during the PT period, 28 e treatment, restarting CZP therapy as a m flares (figure 1). Improvements were of patients (figure 4D); mean disease DAS28(ESR) 4.40 at CZP restart 2 weeks (n=25; observed case). Of the cue treatment, 26 continued retreatment dy. The majority of patients receiving CZP retreatment for ≥12 weeks (n=25) responded positively; using DAS28(ESR) criteria, 24/25 achieved low disease activity and 21/25 achieved remission on at least one study visit.

Safety

Study drug exposure during both the total study period and the PT period was higher for the CZP+MTX→MTX group (total: 223.6 patient-years (PY), PT: 87.7 PY) compared with the PBO +MTX→MTX group (total: 179.4 PY, PT: 63.4 PY; table 2). This difference could be attributed to the higher withdrawal rate in the PBO+MTX→MTX group. Overall, no clinically relevant difference was observed in the total incidence of AEs between the CZP+MTX→MTX group and the PBO +MTX→MTX group through week 104 (154 patients (96.9%) vs 150 patients (95.5%)), or SAEs (17 patients (10.7%) vs 18 patients (11.5%)). Incidence rates of some types of AEs including infections and infestations, pneumonia and hepatic disorders were higher during the DB period (weeks 0–52) compared with the PT period (weeks 52–104); however, this increase was observed for both the CZP+MTX→MTX and the PBO +MTX→MTX group (table 2 and see online supplementary table S2).

DISCUSSION

Biological DMARDs are considered second-line therapies for patients who cannot achieve treatment targets using conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in the management of RA.[7] However, it has been reported that the inhibitory effect of bDMARDs on joint damage is superior to that of csDMARDs, including MTX.[4 8] Although there is some evidence of bone erosion repair following treatment with bDMARDs,[9] joint destruction in patients with RA is generally considered to be irreversible.[10] Consequently, prevention of significant joint damage is crucial to avoid permanent functional disability,[11] supporting early treatment with bDMARDs.

Concerns have been raised that initiating aggressive treatment with a bDMARD may be excessive for some patients and so identifying patients who would particularly benefit from initial aggressive treatment is critical when considering it. The feasibility of bDMARD withdrawal after achieving a therapeutic target is also of importance from both safety and economical points of view. If these issues are overcome, there is the possibility of a clinical approach where RA therapy is initiated with a bDMARD in the early stage of disease, leading to improved outcomes that can be maintained even after withdrawal of the initial aggressive treatment.[12]

C-OPERA was designed to assess the clinical benefit of CZP treatment concomitant with MTX as first-line therapy for early RA, particularly for patients who were considered to require aggressive treatment. Patients who had poor prognostic factors, including a high titre of anticyclic citrullinated peptide antibody in addition to either rheumatoid factor positivity or bone erosions, were eligible to enter the study. C-OPERA was a study composed of two periods. The results from the first year of the study demonstrated the clinical benefit of adding CZP to MTX therapy (DAS28(ESR) remission and radiographic non-progression was achieved in more than 50% and 80% of patients, respectively), suggesting that the introduction of CZP at a very early stage led to substantial therapeutic effects, despite poor prognosis.[4] In this report, we assessed whether the clinical benefit of initial 1-year CZP+MTX treatment was observed after stopping CZP and continuing with MTX therapy for 1 year.

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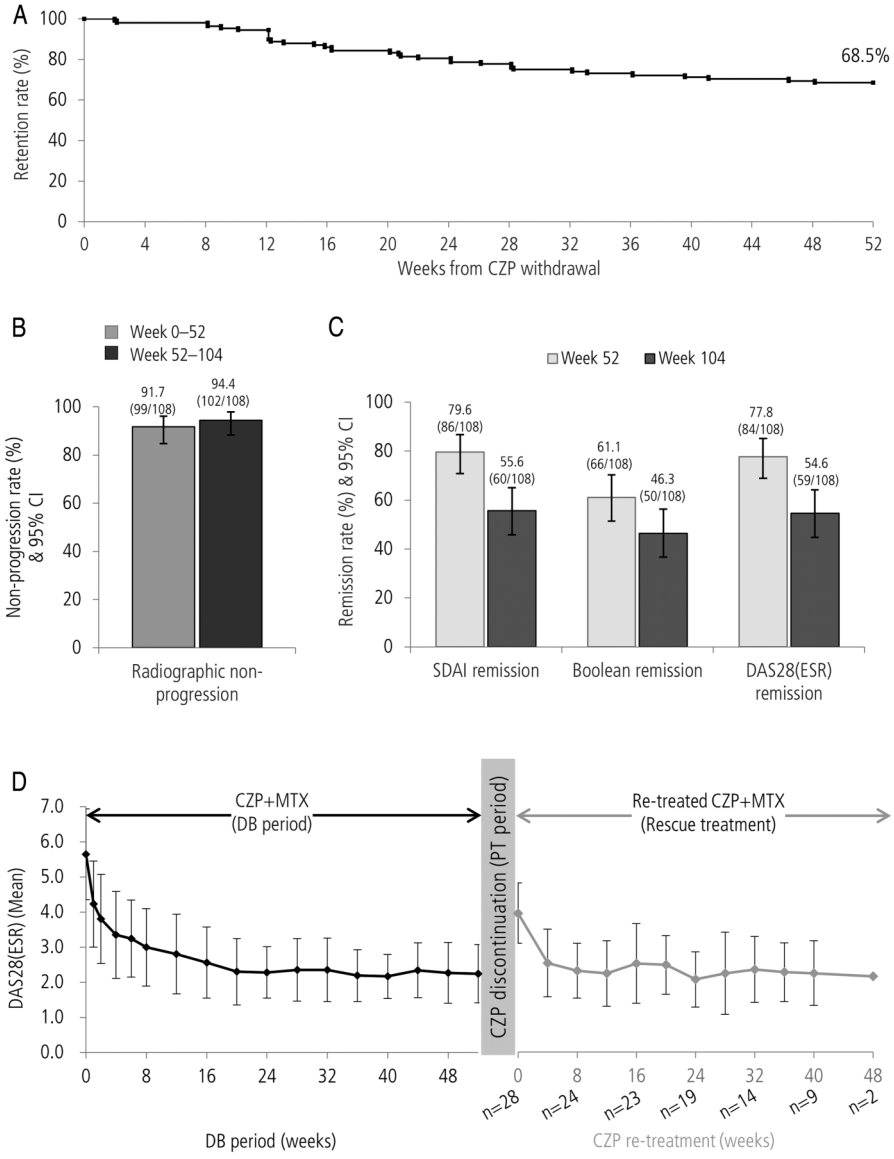

Figure 4 (A) Retention rate after discontinuation of CZP (Kaplan-Meier plot), (B) modified total Sharp score non-progression rate during and after 52-week CZP therapy for patients who entered the PT period from the CZP mission at DAS28 period and who were CZP, uble blind; tion rate; t treatment.

e PT period reported here, was that the ter an initial 1 year of treatment with discontinuing CZP therapy when the optimised. Radiographic progression, trapolation, remained lower in the CZP ompared with the PBO+MTX→MTX ar extrapolation, patient withdrawal can on of mTSS change from baseline. To were repeated using LOCF imputation, of CZP co-administration. The rate of gression observed in the CZP population during the PT period was during the DB period in the same popu- at joint destruction may be prevented on of CZP in patients who responded atment with CZP+MTX. These data, lower rate of RRP in the CZP ompared with the PBO+MTX→MTX, ses (see online supplementary table S3) eatment with CZP+MTX benefits those ographic progression. The rate of HAQ in patients with radiographic non-progression compared with those with radiographic progression, suggesting that radiographic progression associates with functional disability even during the 2 years of the study. These results suggest that early treatment with CZP during the initial stages of the disease, when rapid joint damage may take place,[13] could prevent long-term progression of joint damage and functional disability as previously suggested in the 'window of opportunity' concept.[8 14–16]

In addition to joint damage prevention, the rates of clinical remission throughout the PT period remained higher in the CZP +MTX→MTX group compared with the PBO+MTX→MTX group. After CZP discontinuation, approximately 25% of the patients flared; however, they showed rapid response to CZP retreatment, with recovery to preflare disease activity levels. Although joint destruction was consistently prevented in the PT population following CZP withdrawal, clinical remission was sometimes lost. Discrepancies in clinical and radiographic efficacy have been reported for adalimumab (ADA);[17] similar differences in the clinical and radiographic efficacies of CZP that continue following treatment discontinuation could be responsible for the results observed here. A decrease in remission rate was mainly observed during the first 16 weeks after CZP

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Table 2 Summary of treatment-emergent adverse events (TEAE)

CZP+MTX→MTX			PBO+MTX→MTX		
Week 0–52 CZP+MTX n=159	Week 52–104 MTX n=108	Week 0–104 CZP+MTX→MTX n=159	Week 0–52 PBO+MTX n=157	Week 52–104 MTX n=71	Week 0–104 PBO+MTX→MTX n=157
136.2	87.7	223.6	116.0	63.4	179.4
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
153 (96.2)	85 (78.7)	154 (96.9)	148 (94.3)	57 (80.3)	150 (95.5)
542.0	286.1	442.4	548.2	250.7	444.3
13 (8.2)	4 (3.7)	17 (10.7)	14 (8.9)	4 (5.6)	18 (11.5)
11.0	6.8	9.4	12.9	6.3	10.6
0	0	0	0	0	0
n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
97 (61.0)	45 (41.7)	114 (71.7)	87 (55.4)	30 (42.3)	93 (59.2)
5 (3.1)	0	5 (3.1)	7 (4.5)	1 (1.4)	8 (5.1)
7 (4.4)	1 (0.9)	8 (5.0)	8 (5.1)	2 (2.8)	10 (6.4)
0	0	0	0	0	0
5 (3.1)	2 (1.9)	7 (4.4)	1 (0.6)	0	1 (0.6)
1 (0.6)‡	1 (0.9)‡	2 (1.3)‡	0	0	0
68 (42.8)	12 (11.1)	73 (45.9)	69 (43.9)	9 (12.7)	73 (46.5)

ent-years.
at least one TEAE within System Organ Class/Preferred Term.

rms: alanine aminotransferase increased, aspartate aminotransferase increased, γ-glutamyltransferase increased, hepatic function abnormal, hepatic sis, hyperbilirubinaemia, liver disorder, liver function test abnormal; MedDRA V.14.1.
umab pegol; MTX, methotrexate; PBO, placebo.

culate that patients who still produce e flared as the concentration of CZP

uggest that initial aggressive treatment be a potential treatment option at the specially for patients who have a poor nts achieve their treatment targets, ould be withdrawn. This treatment ial to prevent irreversible joint damage, Es and be a more cost-effective way to g term. This approach is supported by e Optimal Protocol for Methotrexate ination Therapy in Early Rheumatoid y demonstrated minimal loss of clinical ant radiographic progression after ADA ith early RA who initiated combination hile, The High Induction Therapy with HIT HARD) study showed better radio- significant difference in disease activity n the ADA+MTX→MTX group com- .[18] Differences in the results of these C-OPERA suggest that the condition of ance' regimen[12] may be important. w needed to identify the appropriate required to achieve continued disease P withdrawal, and to identify patient d particularly benefit from first-line oreover, additional analyses are also ether this approach has significant clin- s failing to respond to MTX therapy s the approach currently recommended es.[19]

similar rates of SAEs for both the CZP +MTX→MTX groups over the 2 years of the C-OPERA study, indicating that there are no major safety concerns when adding CZP to optimised MTX therapy. Incidences of AEs and SAEs during the PT period were lower compared with the initial DB period in both groups. One reason for this may be 'survival bias', where patients discontinued the study because of an intolerance to the study drugs (CZP and/or MTX) in the first period, resulting in a lower AE rate in the second.[20]

This study has several limitations. In clinical practice, only patients failing to respond to MTX would receive CZP therapy, and so it is not known how this approach compares with initial CZP therapy. No patients received CZP for a full 2 years or were treated with a reduced dose of CZP, so it was not possible to compare these treatment regimens with CZP discontinuation. CZP withdrawal had not been optimised; therefore, there is the potential for further investigation regarding the appropriate treatment targets and the timing of CZP withdrawal in different patient populations. There were differences between the study design of C-OPERA and current RA treatment recommendations. For example, in clinical practice, treatment recommendations for patients with poor prognostic factors include using additional DMARDs in addition to MTX,[7 21] which was prohibited in C-OPERA. C-OPERA was not designed as an intercontinental global study; thus, it is not known whether these results are generalisable to ethnicities other than Japanese. In particular, the MTX dose of 16 mg is low compared with similar RA studies from the European Union and USA (15–17 mg/week).[22–26] However, when considering differences in patient body weight and MTX metabolism,[27] a lower dose of MTX in this study may correspond to the doses used in those previous studies. Finally, as non-responding patients were eligible to receive rescue treatment from 24 weeks onwards, we cannot exclude the possibility that a proportion of the 70 PBO+MTX patients switching to rescue therapy in the first year may have achieved clinical response if treated for a longer period of time.[4]

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Overall, these results suggest that patients with early RA would benefit from the addition of CZP to MTX therapy during the early stages of disease, particularly with respect to the prevention of joint destruction. Although this aggressive therapeutic strategy would not be recommended for all patients, it may be a potential option for those patients with a high risk int destruction. How to identify these requires further investigation.

chool of Medicine, Sapporo, Japan
l Medicine, University of Occupational and
u, Fukuoka, Japan
umatology, Graduate School of Medicine,
apan
artment of Internal Medicine, Keio University School

sity, Tokyo, Japan
ool and Faculty of Medicine, Nagoya, Japan
e Center, Sasebo Chuo Hospital, Sasebo, Nagasaki,

n
ical Epidemiology, The University of Toyama
yama, Japan
c, Hiroshima, Japan
ohama, Japan
, Kato, Japan
Clinical Immunology, Jichi Medical University,

pan
Leiden University Medical Centre, Leiden, The

Tokyo Medical and Dental University, Tokyo, Japan
C, Sapporo, Hokkaido, Japan

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Ethics approval This study was conducted after review and approval by the institutional review board designated by each study site after consideration of the ethical, scientific and medical justification for the conduct of the study.

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