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Author(s)	Atsumi, Tatsuya; Tanaka, Yoshiya; Yamamoto, Kazuhiko et al.
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Clinical Benefit of 1-Year Certolizumab Pegol (CZP) Add-on Therapy to Methotrexate Treatment in Early Rheumatoid Arthritis Patients was Observed Following CZP Discontinuation: 2-Year Results of the C-OPERA Study, a Phase III Randomized Trial

T Atsumi, Y Tanaka, K Yamamoto, T Takeuchi, H Yamanaka, N Ishiguro, K Eguchi, A Watanabe, H Origasa, S Yasuda, Y Yamanishi, Y Kita, T Matsubara, M Iwamoto, T Shoji, O Togo, T Okada, D van der Heijde, N Miyasaka, T Koike

SUPPLEMENTARY MATERIAL

Supplementary Methods

Patients Eligible patients were MTX-naïve, ≤12 months from the onset of persistent RA symptoms with at least moderate disease activity (DAS28[ESR] ≥3.2), fulfilled the 2010 ACR/EULAR classification criteria, and had poor prognostic factors (high-positive for anti-cyclic citrullinated peptide [anti-CCP; >3xULN], and were rheumatoid factor [RF] positive and/or had bone erosions on radiographs of the hands or feet).

Study Design C-OPERA (NCT01451203) was a multicenter, DB, PBO-controlled, randomized, parallel-group study conducted in Japan. It was composed of two 52-week periods; the first 52-week DB period assessed the efficacy and safety of CZP plus MTX compared with PBO plus MTX, in MTX-naïve patients with early RA and poor prognostic factors. Patients who completed the 52-week DB period were eligible to enter the 52-week PT period where either CZP or PBO was discontinued, and patients received only optimized dose MTX.

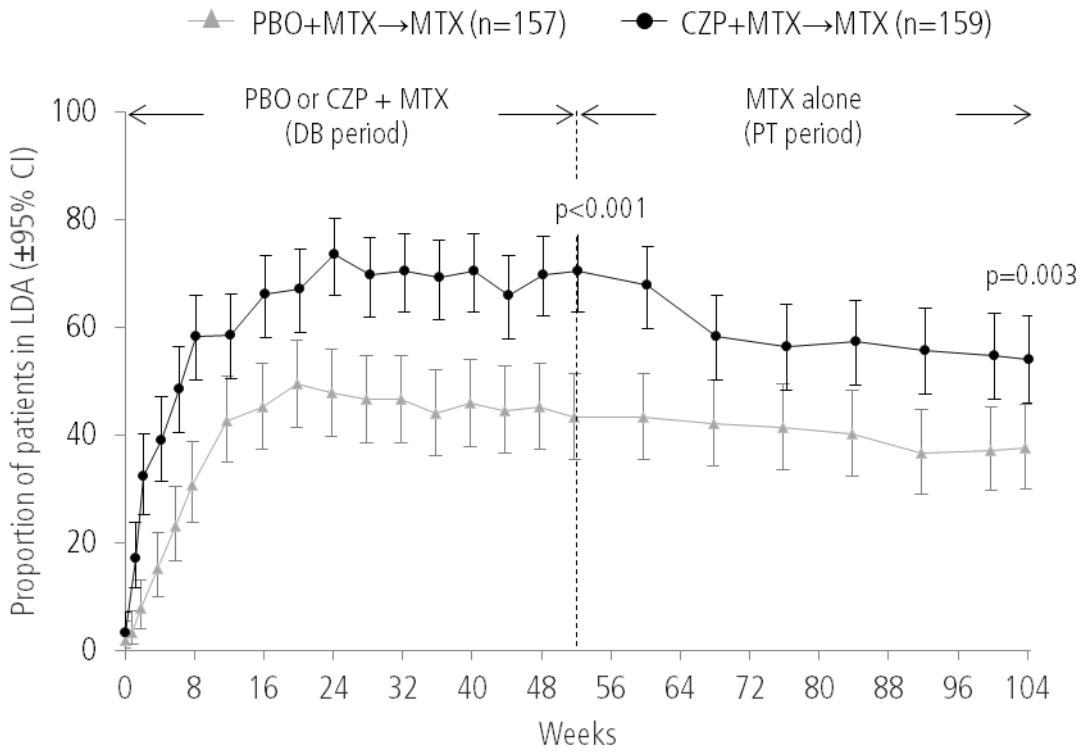
Optimized oral MTX was initiated at 8 mg/week and escalated to 16 mg by Week 8, if tolerated. The maximal tolerated dose of MTX was maintained during the DB period. If required, MTX dose change or temporal discontinuation was permitted.

Patients with moderate or high disease activity (DAS28[ESR] ≥3.2), persisting for ≥4 weeks at or after DB Week 24 through to the end of the PT period, were eligible to be withdrawn from the original study schedule and receive rescue treatment with open-label CZP.

Throughout the study, all investigators and healthcare professionals involved in safety or efficacy assessments were blind to the study medications administered during the DB treatment period. All patients were blind to the treatment received during the DB period (PBO or CZP) and through to the end of the PT period.

Statistical analyses The full analysis set (FAS), defined as patients who received ≥1 dose of study drug and provided any efficacy data thereafter, was used. Missing data were imputed using linear extrapolation for mTSS (unless otherwise indicated) and last observation carried forward (LOCF) for all other efficacy variables. Change from baseline in mTSS at Week 52 and 104 was analyzed using an analysis of covariance (ANCOVA) model in which actual scores were converted to rank scores, using the treatment group as a factor and baseline rank score as a covariate. For the rates of mTSS non-progression (mTSS change from baseline ≤0.5) and clinical remission at Week 52 and 104, the 95% confidence intervals (CIs) of the PBO and CZP groups were presented and a Fisher's exact test was used for comparison between groups. The effect of CZP re-treatment was assessed in patients from the time of CZP restart through to the end of the PT period in observed cases. Multiplicity of the statistical testing was not considered in this study.

Supplementary Figure S1 The proportion of patients achieving low disease activity during the C-OPERA study



FAS. LOCF. Low disease activity (LDA) defined as DAS28(ESR) ≤3.2.

Supplementary Tables

Supplementary Table S1 Extended baseline demographics and patient characteristics

	CZP+MTX to MTX			PBO+MTX to 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)
RA duration <3 months, n (%)*	60 (37.7)	38 (35.2)	-	57 (36.3)	26 (36.6)	-
RA duration 3–<6 months, n (%)*	60 (37.7)	36 (33.3)	-	56 (35.7)	22 (31.0)	-
RA duration 6–12 months, n (%)*	39 (24.5)	34 (31.5)	-	44 (28.0)	23 (32.4)	-
Anti-CCP antibody: ≥300 U/mL, n (%)	50 (31.4)	33 (30.6)	18 (16.7)	50 (31.8)	22 (31.0)	16 (22.5)
Anti-CCP antibody: Titer (U/mL)†	176.7 ±107.5	173.5 ±106.9	128.0 ±105.4	185.2 ±107.7	169.4 ±111.3	134.6 ±110.7
RF positive: ≥60 U/mL, n (%)	119 (74.8)	80 (74.1)	33 (30.6)	117 (74.5)	53 (74.6)	24 (33.8)
RF positive: Titer (U/mL)†	182.5 ±177.4	183.7 ±179.4	61.1 ±92.3	167.3 ±166.5	165.3 ±163.8	63.0 ±76.0
PtGADA (mm)	50.4 ±22.4	51.6 ±23.3	8.9 ±11.0	52.9 ±22.7	43.1 ±20.9	8.8 ±7.9
PhGADA (mm)	56.7 ±20.5	55.5 ±20.8	6.6 ±7.4	58.4 ±21.4	50.4 ±21.2	6.0 ±7.2
MMP-3 (ng/mL)	130.4 ±135.4	125.3 ±135.4	47.7 ±25.7	185.4 ±214.9	167.3 ±204.3	52.5 ±31.1
mTSS negative (≤0.5), n (%)	65 (40.9)	45 (41.7)	44 (40.7)	67 (42.7)	34 (47.9)	30 (42.3)
Erosion score negative (≤0.5), n (%)	92 (57.9)	62 (57.4)	62 (57.4)	85 (54.1)	43 (60.6)	39 (54.9)
Joint space narrowing score negative (≤0.5), n (%)	98 (61.6)	68 (63.0)	66 (61.1)	90 (57.3)	46 (64.8)	46 (64.8)

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. CCP, cyclic citrullinated peptide; CRP, C-reactive protein; CZP, certolizumab pegol; DB, double-blind; MMP-3, matrix metalloproteinase-3; mTSS, modified total sharp score; MTX, methotrexate; PBO, placebo; PhGADA, physician's global assessment of disease activity; PtGADA, patient's global assessment of disease activity; RA, rheumatoid arthritis; RF, rheumatoid factor; ULN, upper limit of normal.

Supplementary Table S2 Extended treatment-emergent adverse events

	CZP+MTX to MTX			PBO+MTX to MTX		
	Week 0–52 CZP+MTX (n=159)	Week 52–104 MTX (n=108)	Week 0–104 CZP+MTX to MTX (n=159)	Week 0–52 CZP+MTX (n=157)	Week 52–104 CZP+MTX (n=71)	Week 0–104 PBO+MTX to MTX (n=157)
Patient years	136.2	87.7	223.6	116.0	63.4	179.4
Serious Infection	5 (3.1)	0	5 (3.1)	7 (4.5)	1 (1.4)	8 (5.1)
Pneumocystis jiroveci pneumonia	3 (1.9)	0	3 (1.9)	2 (1.3)	0	2 (1.3)
Bronchitis	1 (0.6)	0	1 (0.6)	0	0	0
Meningitis fungal	1 (0.6)	0	1 (0.6)	0	0	0
Pneumonia bacterial	1 (0.6)	0	1 (0.6)	2 (1.3)	0	2 (1.3)
Pneumonia	0	0	0	1 (0.6)	0	1 (0.6)
Pneumonia chlamydial	0	0	0	0	1 (1.4)	1 (0.6)
Pneumonia mycoplasmal	0	0	0	1 (0.6)	0	1 (0.6)
Pyelonephritis acute	0	0	0	1 (0.6)	0	1 (0.6)
Hematopoietic cytopenias[§]	12 (7.5)	3 (2.8)	12 (7.5)	13 (8.3)	0	13 (8.3)
Nausea/Vomiting/Decreased appetite	39 (24.5)	6 (5.6)	43 (27.0)	32 (20.4)	7 (9.9)	38 (24.2)
Stomatitis	19 (11.9)	13 (12.0)	27 (17.0)	26 (16.6)	5 (7.0)	27 (17.2)
Injection site reaction	5 (3.1)	0	5 (3.1)	2 (1.3)	0	2 (1.3)

All data are n (%). PY=total summation of individual patient years. n=number of subjects reporting at least one TEAE; [§]Including following preferred terms: granulocytopenia, leukopenia, lymphopenia, lymphocyte count decreased, white blood cell count decreased; MedDRA v14.1.

Supplementary Table S3 Change from baseline in mTSS at Week 104 by baseline factors

Baseline factor		CZP+MTX to MTX mTSS CfB n	Mean	SD	PBO+MTX to MTX mTSS CfB n	Mean	SD
RA duration (months)*	<3	59	1.61	7.11	57	3.39	13.38
	≥3–<6	60	-0.23	3.76	56	3.27	7.58
	≥6	39	0.59	4.21	44	2.17	5.58
Baseline erosion	Yes	78	0.94	7.54	80	2.84	7.08
	No	78	0.35	1.39	75	3.15	11.97
DAS28	< 3.2	5	0	0	3	0	0
	≥ 3.2	153	0.68	5.47	154	3.07	9.75
mTSS	≤ 0.5	64	0.36	1.18	67	0.82	1.93
	> 0.5	94	0.86	6.92	90	4.63	12.44
HAQ-DI	< 0.5	43	0.44	3.43	43	1.24	5.48
	> 0.5–≤ 1.0	44	0.43	1.98	41	3.16	8.14
	> 1.0	71	0.93	7.44	73	3.96	12.05
RF (IU/mL)	< 20	6	-0.36	0.94	11	4.27	10.34
	≥ 20–< 60	33	-0.12	1.17	29	1.27	5.77
	≥ 60	119	0.92	6.15	117	3.32	10.36
CRP (mg/dL)	≤ 0.5	75	0.09	0.97	69	0.9	4.27
	> 0.5–≤ 1.0	22	0.24	1.61	27	3.22	6.41
	>1.0	61	1.51	8.51	61	5.3	13.92
MMP-3 (ng/mL)	< 50	36	0.08	0.76	33	0.11	0.75
	50–< 100	59	0.39	1.44	50	2.75	6.09
	≥ 100	63	1.23	8.39	74	4.47	12.98
TNF-alpha (pg/mL)	≤ 0.55	44	0.62	3.48	53	1.77	4.53
	> 0.55–≤ 1.79	80	0.52	6.83	73	2.54	6.71
	> 1.79	34	1.04	3.15	31	6.22	18.11
IL-6 (pg/mL)	≤ 0.30	0	0	0	1	0	-
	> 0.30–≤ 2.41	26	0.37	1.32	26	0.77	1.88
	> 2.41	132	0.71	5.86	130	3.48	10.53
Baseline steroids	Yes	25	0.33	2.4	31	6.15	17.5
	No	133	0.72	5.78	126	2.23	6.33
MTX Exposure (mg/week)	0–8	24	-0.03	1.28	22	1.31	4.63
	8 <–12	64	0.96	8.03	63	2.33	5.68
	12 <–16	70	0.62	2.49	72	4.12	12.97

*Time from onset of persistent arthritic symptoms. CRP, C-reactive protein; CZP, certolizumab pegol; DAS: Disease Activity Score; HAQ-DI: Health Assessment Questionnaire Disability Index; MMP-3, matrix metalloproteinase-3; mTSS, modified total sharp score; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; RF, rheumatoid factor; SD: standard deviation; TNF: tumor necrosis factor.