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Original article

Certolizumab inhibits radiographic progression in patients with early rheumatoid arthritis and high rheumatoid factor levels: A pooled, post-hoc analysis of the phase 3 C-EARLY and C-OPERA trials

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ABSTRACT

Objective: To assess radiographic progression in patients with early rheumatoid arthritis (RA) and poor prognostic factors treated with certolizumab pegol (CZP) + methotrexate (MTX) versus placebo (PBO) + MTX, stratified by rheumatoid factor (RF) level.

Methods: In a pooled, post-hoc analysis of phase 3 randomized trials (C-EARLY [NCT01519791] and C-OPERA [NCT01451203], patients were stratified by baseline RF level (low: < 200 IU/mL; high: ≥ 200 IU/mL). Change from baseline (Δ) in modified Total Sharp Score (mTSS) and components, predicted risk of RP, and disease activity are reported up to Week (Wk)52.

Results: Eight hundred and thirteen CZP + MTX-randomized (low RF: $n = 571$; high RF: $n = 242$) and 367 PBO + MTX-randomized (low RF: $n = 242$; high RF: $n = 125$) patients were included. Baseline characteristics were similar between treatments; however, patients with high RF had more severe disease. The proportion of patients with clinically meaningful radiographic worsening (ΔmTSS > 5) at Wk24 was more comparable between patients with high and low RF levels randomized to CZP + MTX (low RF: 1.0% vs high RF: 0.0%) and was numerically lower than with PBO + MTX (2.8% vs 6.5%) and this pattern was maintained through Wk52. Clinical outcomes were generally favorable with PBO + MTX, but better with CZP + MTX.

Conclusion: In MTX-naïve patients with early RA, radiographic progression was more similar between CZP + MTX-treated patients with high and low RF levels, and consistently numerically lower, than PBO + MTX-treated patients. Irrespective of RF level, CZP + MTX better attenuated than MTX alone and was associated with more favorable clinical outcomes. Our findings suggest that RF level does not adversely influence radiographic response to CZP + MTX.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune condition that leads to joint pain and damage and gradually reduces physical function [1]. Persistent high disease activity, presence of early erosions or structural damage, high swollen joint count (SJC) and positivity for autoantibodies are key prognostic factors in assessing severity and for treatment decision-making [2,3].

High rheumatoid factor (RF) level is a prognostic factor of clinical significance. RFs bind the crystallizable fragment (Fc) of immunoglobulin G (IgG), including therapeutic monoclonal antibodies such as most tumor necrosis factor inhibitors (TNFis). This results in large immune complexes that are internalized by macrophages through the Fc gamma receptor (FcγR) and undergo lysosomal degradation, thereby reducing plasma levels of TNFis [4–7]. Patients with RA and elevated RF levels typically have higher disease severity and decreased response to biologic disease-modifying antirheumatic drugs (bDMARDs) than those with lower RF levels [8–12]. Indeed, high RF levels are a key risk factor for patients developing difficult-to-treat RA, even with the use of two or more biologic or targeted synthetic DMARDs [13,14]. Elevated RA disease activity is also associated with progression of radiographic joint damage, particularly in RF-positive individuals [14].

Pertinently, radiographic progression drives irreversible changes in joints and is linked with functional disability, which negatively impacts patients' quality of life (QoL) and impairs work productivity [15,16]. Even upon treatment with bDMARDs, high RF level is predictive of radiographic progression in patients with RA [17]. Prevention of radiographic progression and irreversible functional impairment, as distinct from impairment caused by the active disease process [18,19], is therefore a key goal in treatment of RA and a robust marker for response [20,21].

CZP is a PEGylated TNFi without an Fc; RFs do not bind to CZP due to the absence of an Fc region, whereas RFs do bind to Fc-containing TNFis [6,22]. Therefore, CZP plasma levels are not reduced in patients with high RF levels [23]. In a retrospective analysis of patients with RA, serum concentrations of Fc-containing TNFis, such as infliximab and adalimumab, were significantly lower in patients with high baseline RF levels than in those with lower baseline RF levels, while serum CZP levels were similar irrespective of baseline RF level [24]. Other recent data suggest that patients with RA and higher RF levels may achieve and maintain greater clinical improvement with TNFis without an Fc region compared with TNFis with an Fc region [23]. Concordantly, a post-hoc analysis of four pooled trials of patients with RA showed consistent efficacy of CZP for improving disease activity and achieving clinical remission across baseline RF levels [25].

There are no specific recommendations regarding which biologics should be initiated or switched to in patients with high RF levels, and there is limited evidence regarding treatment effectiveness for the prevention of radiographic progression in these patients [2,26]. Available studies, however, have demonstrated that Fc-containing TNFis less effectively control radiographic progression in patients with high RF levels than low RF levels [9].

The objective of this post-hoc analysis was to assess radiographic progression in patients with RA, stratified by baseline RF levels, in two phase 3, placebo (PBO)-controlled trials of CZP and methotrexate (MTX).

2. Methods

2.1. Study design

The study designs of the C-EARLY and C-OPERA studies included in this pooled, post-hoc analysis have been reported previously [27,28]. C-EARLY (NCT01519791) was a phase 3, randomized, placebo-controlled study in Europe, Australia, North America, and Latin America. C-EARLY assessed the efficacy and safety of CZP (400 mg at Weeks 0, 2 and 4 followed by 200 mg every 2 weeks) + dose-optimized MTX (10 mg weekly and increased to 25 mg after 6–8 weeks if well-tolerated, with at least 15 mg weekly) versus PBO + dose-optimized MTX in inducing and sustaining clinical remission in DMARD-naïve patients with moderate-to-severe, active, progressive RA, with poor baseline prognostic factors, over 52 weeks [27]. Radiographic progression in participants was assessed as change from baseline (represented as Δ), in van der Heijde modified total Sharp score (mTSS) [27]. The primary efficacy endpoint in C-EARLY was the proportion of patients with sustained Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28-ESR) < 2.6 at Weeks 40 and 52 [27].

C-OPERA (NCT01451203) was a phase 3, multicenter, randomized, PBO-controlled study in Japan that evaluated the efficacy and safety of combination therapy using CZP (400 mg at Week 0, 2 and 4, followed by 200 mg every two weeks) + MTX (8 mg per week, increased to 16 mg from Week 8 onwards) versus PBO + MTX as first-line treatment for MTX-naïve patients with early RA and poor baseline prognostic factors over a 52-week double-blind period [28]. The primary efficacy endpoint in C-OPERA was ΔmTSS at Week 52, evaluated by two independent readers [28].

In C-EARLY, patients who did not achieve DAS28-ESR ≤ 3.2 and/or ≥ 1.2-point improvement in DAS28-ESR from baseline at Weeks 20 and 24 were switched to a complementary medication [27]. In C-OPERA, patients with moderate or higher disease activity (DAS28-ESR ≥ 3.2) that persisted for ≥ 4 weeks at or after Week 24 were eligible to receive rescue treatment with open-label CZP [28]. Patients who stopped receiving PBO + MTX at Weeks 20 or 24 are referred to as 'PBO early escapers'. Patients who did not require escape therapy and continued to receive PBO + MTX are referred to as 'PBO continuers'.

C-EARLY and C-OPERA were conducted after approval by the Institutional Review Boards designated by each study site, in compliance with the ethical principles described in the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent to participate in the two studies. As this was a post hoc analysis of anonymized data, no ethics committee or institutional review board approvals were required. In C-EARLY, participant race and ethnicity were self-reported by patients through selection from a fixed set of categories; ethnicity data were not collected for C-OPERA.

2.2. Outcomes

A pooled post-hoc analysis of participants from both trials was performed (full analysis set [FAS], including all patients who received at least one administration of study drug and had valid post-baseline efficacy data). Patients were stratified by baseline RF level (low RF: < 200 IU/mL; high RF: ≥ 200 IU/mL), in line with published strata, with patients with RF levels ≥ 200 IU/mL being at high risk for radiographic progression [9,29].

Due to confounding by early escapers who received therapy other than PBO after Week 24, PBO data are predominantly reported to Week 24, during which patients only received PBO + MTX in both trials. Outcomes reported include Δ and minimal detectable difference (MDD) in mTSS, mTSS components (erosion and joint space narrowing [JSN]) scores and the proportion of patients with ΔmTSS > 3 SHS U/year, and > 5 SHS U/year (which are commonly used thresholds indicative of clinically meaningful radiographic progression) [9,17,30,31]. To provide further insight, Week 52 mTSS and mTSS component data for PBO data are also tabulated alongside the equivalent CZP data. Other outcomes also included the predicted risk of radiographic progression ≥ 3 SHS U/year and ≥ 5 SHS U/year.

Additionally, the following outcomes were examined, stratified by baseline RF level: DAS28-ESR and the proportion of patients achieving DAS28-ESR low disease activity (LDA; DAS28-ESR ≤ 3.2), DAS-28 components (SJC and Tender Joint Count [TJC]), Health Assessment Questionnaire-Disability Index (HAQ-DI), Simplified Disease Activity In-

dex (SDAI) LDA (SDAI ≤ 10) and Clinical Disease Activity Index (CDAI) LDA (CDAI ≤ 10) through Week 52. DASR28-CRP and CDAI PBO data are further stratified by PBO early escaper and continuer status (presented in the Supplementary Material).

2.3. Statistical analysis

Data for ΔmTSS are reported as observed case (OC). The Δ and MDD in mTSS, mTSS erosion score and JSN score, proportion of patients with ΔmTSS > 3 SHS U/year, and > 5 SHS U/year, predicted risk of radiographic progression, DAS28-ESR and DAS28-ESR LDA, SJC, TJC, HAQ-DI, SDAI LDA and CDAI LDA are reported as OC. The predicted risk of radiographic progression ≥ 3 SHS U/year and ≥ 5 SHS U/year was calculated as a function of baseline RF level. As these are post-hoc analyses, only descriptive statistics are presented for all outcomes.

3. Results

3.1. Patient disposition and baseline characteristics

A total of 813 CZP-randomized (CZP + MTX; low RF: *n* = 571; high RF: *n* = 242) and 367 PBO-randomized (PBO + MTX; low RF: *n* = 242; high RF: *n* = 125) patients with baseline RF measurements, pooled from both trials, were included in the FAS. 56 PBO + MTX-randomized patients were early escapers at Week 24 and switched to CZP for the remaining 28 weeks.

Baseline characteristics were similar between CZP + MTX and PBO + MTX-treated patients within both RF strata (Table 1). Patients with high RF had more severe disease at baseline, with numerically higher mean C-reactive protein (CRP), anti-citrullinated protein antibodies, mTSS, and erosion scores than those with low RF (Table 1). Mean (standard deviation [SD]) MTX dose at baseline was similar in patients with high and low RF levels across treatment arms (Table 1). Patients from C-OPERA had lower mean MTX dose at baseline overall (All patients, *n* = 316: 7.5 [1.9] mg), compared with patients in C-EARLY (All patients, *n* = 868: 10.4 [1.50] mg), consistent with the lower dose recommended in Japanese guidelines [32,33]; moreover, these doses have been shown to be sufficiently high when combined with TNFis [34,35].

Baseline characteristic data for PBO early escapers and continuers are provided in Supplementary Table S1.

3.2. Change from baseline in mTSS over time

At baseline, mean (SD) mTSS was 6.24 (12.11) and 8.18 (14.83) in CZP + MTX-randomized patients with low (*n* = 567) and high (*n* = 242) RF levels, respectively, while mean (SD) mTSS was 6.38 (14.56) and 9.56 (20.10) in the overall group of PBO + MTX-randomized patients with low (*n* = 242) and high (*n* = 124) RF levels.

In CZP + MTX-randomized patients with both low RF and high RF levels, mean (SD) ΔmTSS was low at both Week 24 (low RF: 0.09 [1.50]; high RF: 0.14 [1.24]) and Week 52 (low RF: 0.14 [3.11]; high RF: 0.28 [2.63]; Fig. 1). In the overall PBO-MTX group, ΔmTSS was numerically higher in those with high RF compared with low RF at Week 24 (low RF: 0.70 [1.65]; high RF: 1.15 [2.93]) and was numerically higher overall than in CZP + MTX-randomized patients.

The MDD of mTSS at Week 24 was 0.193 and 0.242 for CZP + MTX patients with low RF and high RF levels, respectively; at Week 52 the MDD was 0.40 and 0.51, respectively. The MDD of mTSS at Week 24 was numerically greater in PBO + MTX patients, being 0.32 and 0.80 for patients with low RF and high RF levels, respectively.

Data for PBO + MTX patients, stratified by early escaper and continuer status are presented in Supplementary Table S2.

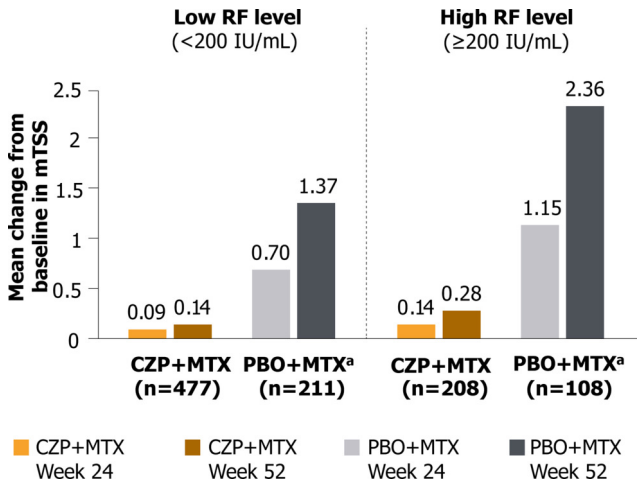

Fig. 1. Change from baseline in mTSS, stratified by baseline RF (low [< 200 IU/mL] vs high [≥ 200 IU/mL]) over time (OC)[a]. Full analysis set. [a]PBO group included Week 24 continuers and early escapers; data presented are observed case, except for PBO early escapers, where linear extrapolation is employed. CZP: certolizumab pegol; mTSS: modified total sharp score; MTX: methotrexate; OC: observed case; PBO: placebo; RF: rheumatoid factor.

3.3. Proportion of patients with clinically meaningful worsening of radiographic progression

A numerically higher proportion of PBO + MTX-randomized patients with high RF experienced ≥ 5 SHS U/year worsening of radiographic progression than those with low RF at Week 24 (2.8% [low RF] vs 6.5% [high RF]) (Table 2). A numerically smaller proportion of CZP + MTX patients experienced worsening ≥ 5 SHS U/year than PBO + MTX patients, and this was more similar between patients with low and high RF (Week 24: 1.0% [low RF] vs 0.0% [high RF], respectively). A similar pattern was seen when applying a threshold of ≥ 3 SHS U/year (Table 2).

3.4. mTSS components (erosion and joint space narrowing) over time

At baseline, mean (SD) mTSS erosion score was 3.54 (6.67) and 4.81 (8.94) in CZP + MTX-randomized patients with low (*n* = 567) and high (*n* = 242) RF levels, respectively. Mean (SD) mTSS erosion score was 3.15 (6.68) and 5.41 (10.52) in the overall group of PBO + MTX-randomized patients with low (*n* = 242) and high (*n* = 124) RF levels. Mean (SD) baseline JSN score was 2.70 (6.42) and 3.36 (6.94) in CZP + MTX-randomized patients with low (*n* = 567) and high (*n* = 242) RF levels, respectively, and was 3.24 (8.86) and 4.15 (11.11) in of PBO + MTX-randomized patients with low (*n* = 242) and high (*n* = 124) RF levels (Table 1).

In CZP + MTX-randomized patients with both low RF and high RF levels, mean (SD) ΔmTSS erosion score was low at both Week 24 (low RF: 0.13 [0.65]; high RF: 0.12 [0.96]) and Week 52 (low RF: –0.10 [1.73]; high RF: 0.06 [1.32]) (Table 2). In PBO + MTX-randomized patients, ΔmTSS erosion score was numerically higher in those with high RF compared with low RF at Week 24 (low RF: 0.36 [1.11]; high RF: 0.72 [1.25]) and was numerically higher than in CZP + MTX-randomized patients.

ΔmTSS JSN score was low in CZP + MTX-randomized patients, regardless of RF level, at both Week 24 (low RF: 0.24 [1.47]; high RF: 0.02 [0.58]) and Week 52 (low RF: 0.09 [1.18]; high RF: 0.21 [0.93]) (Table 2). ΔmTSS JSN score was also numerically higher for PBO + MTX-randomized patients with high RF compared with low RF at Week 24 (low RF: 0.25 [0.81]; high RF: 0.76 [2.81]) and was numerically higher than in CZP + MTX-randomized patients.

Table 1
Baseline demographics and disease characteristics stratified by baseline RF level.

Baseline characteristic, mean (SD) unless stated otherwise	Low RF level (< 200 IU/mL)		High RF level (≥ 200 IU/mL)	
	CZP + MTX (n = 571)	PBO + MTX (n = 242)	CZP + MTX (n = 242)	PBO + MTX (n = 125)
Age, years	49.8 (13.3)	50.3 (11.7)	51.4 (12.4)	50.4 (12.5)
Female, n (%)	451 (79.0)	195 (80.6%)	175 (72.3%)	100 (80.0%)
BMI, kg/m^2	26.5 (5.9)	25.8 (6.1)	27.7 (6.4)	26.8 (6.4)
Disease duration, years	3.2 (4.9)	3.5 (2.9)	2.8 (2.7)	3.4 (3.0)
Rheumatoid factor, IU/mL	71.22 (50.96)	71.96 (45.64)	518.72 (486.17)	472.98 (355.38)
CRP, mg/dL	15.16 (23.20)	10.13 (17.10)	23.18 (34.06)	18.48 (31.76)
DAS28-ESR score	6.38 (1.05)	6.14 (1.20)	6.55 (1.15)	6.50 (1.18)
ACPA, IU/mL	381.25 (693.93)	419.29 (854.94)	605.58 (972.45)	648.68 (1531.15)
mTSS				
Mean	6.24 (12.11)	6.38 (14.56)	8.18 (14.83)	9.56 (20.10)
Median (IQR)	2.00 (0.50, 7.00)	2.00 (0.50, 6.00)	3.00 (0.50, 9.00)	2.75 (0.50, 6.50)
Erosion score	3.54 (6.67)	3.15 (6.68)	4.81 (8.94)	5.41 (10.52)
JSN score	2.70 (6.42)	3.24 (8.86)	3.36 (6.94)	4.15 (11.11)
HAQ-DI score	1.46 (0.65)	1.38 (0.75)	1.56 (0.67)	1.48 (0.72)
SJC	11.30 (5.59)	10.60 (5.94)	12.17 (5.77)	11.99 (5.95)
TJC	14.05 (7.01)	12.65 (7.42)	14.51 (7.01)	14.11 (7.44)
PhGA	64.3 (17.5)	63.0 (20.1)	67.5 (17.8)	66.8 (18.6)
PtGA	61.9 (22.6)	60.0 (23.6)	63.5 (23.2)	59.6 (23.0)
MTX dose, mg[a]	9.9 (1.8)	9.0 (2.6)	9.8 (1.8)	9.4 (2.4)

Full analysis set.
[a] Pooled randomized set. Data for PBO early escapers and continuers are provided in Supplementary Table S1. ACPA: anti-citrullinated protein antibodies; BMI: body mass index; CRP: C-reactive protein; CZP: certolizumab pegol; DAS28-ESR: Disease Activity Score-28 joint count-erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; IU/mL: international units per milliliter; JSN: joint space narrowing; mg/dL: milligrams per deciliter; mTSS: modified total sharp score; MTX: methotrexate; PBO: placebo; PhGA: Physician Global Assessment of disease activity; PtGA: Patient Global Assessment of disease activity; RF: rheumatoid factor; SD: standard deviation; SJC: swollen joint count; TJC: tender joint count.

Table 2
mTSS over time, stratified by baseline RF (low [< 200 IU/mL] vs high [≥ 200 IU/mL]) (OC)[a].

	Low RF level (< 200 IU/mL)		High RF level (≥ 200 IU/mL)	
	CZP + MTX (n = 571)	PBO + MTX (n = 242)	CZP + MTX (n = 242)	PBO + MTX (n = 125)
Proportion of patients with ΔmTSS > 5, (%)				
Week 24	1.0	2.8	0.0	6.5
Week 52	3.1	10.4	5.3	17.6
Proportion of patients with ΔmTSS > 3, (%)				
Week 24	2.1	9.0	0.0	11.1
Week 52	5.0	17.1	11.1	24.1
mTSS erosion score, mean (SD)				
Week 24	1.78 (3.04)	2.08 (3.61)	3.38 (6.36)	5.34 (13.14)
Week 52	2.87 (4.61)	3.14 (4.94)	3.47 (5.72)	3.90 (5.49)
ΔmTSS erosion score, mean (SD)				
Week 24	0.13 (0.65)	0.36 (1.11)	0.12 (0.96)	0.72 (1.25)
Week 52	–0.10 (1.73)	0.47 (1.24)	0.06 (1.32)	0.38 (1.60)
mTSS JSN score, mean (SD)				
Week 24	3.01 (5.83)	2.40 (5.56)	3.29 (6.37)	5.96 (13.57)
Week 52	2.43 (4.45)	2.75 (5.98)	2.83 (5.53)	2.98 (7.36)
ΔmTSS JSN score, mean (SD)				
Week 24	0.24 (1.47)	0.25 (0.81)	0.02 (0.58)	0.76 (2.81)
Week 52	0.09 (1.18)	0.19 (1.85)	0.21 (0.93)	0.26 (0.84)

Full analysis set. Data for PBO early escapers and continuers are provided in Supplementary Table S2. CZP: certolizumab pegol; JSN: joint space narrowing; mTSS: modified total sharp score; OC: observed case; PBO: placebo; RF: rheumatoid factor; SD: standard deviation.
[a] Not all participants with baseline mTSS data had Week 24 and Week 52 change from baseline data available.

Data for PBO + MTX patients, stratified by early escaper and continuer status are presented in Supplementary Table S2.

3.5. Predicted risk of radiographic progression

The predicted risk of radiographic progression ≥ 3 SHS U/year and ≥ 5 SHS U/year at Weeks 24 and 52 are presented in Fig. 2. The risk of radiographic progression was consistently greater in PBO-randomized patients compared with CZP-randomized patients, with greater separation seen at higher thresholds.

3.6. DAS28-ESR and DAS28-ESR LDA achievement over time

At baseline, mean (SD) DAS28-ESR was 6.38 (1.05) and 6.55 (1.15) in CZP + MTX patients with low and high RF levels, and 6.14 (1.20) and 6.50 (1.18) in PBO + MTX-randomized patients with low and high

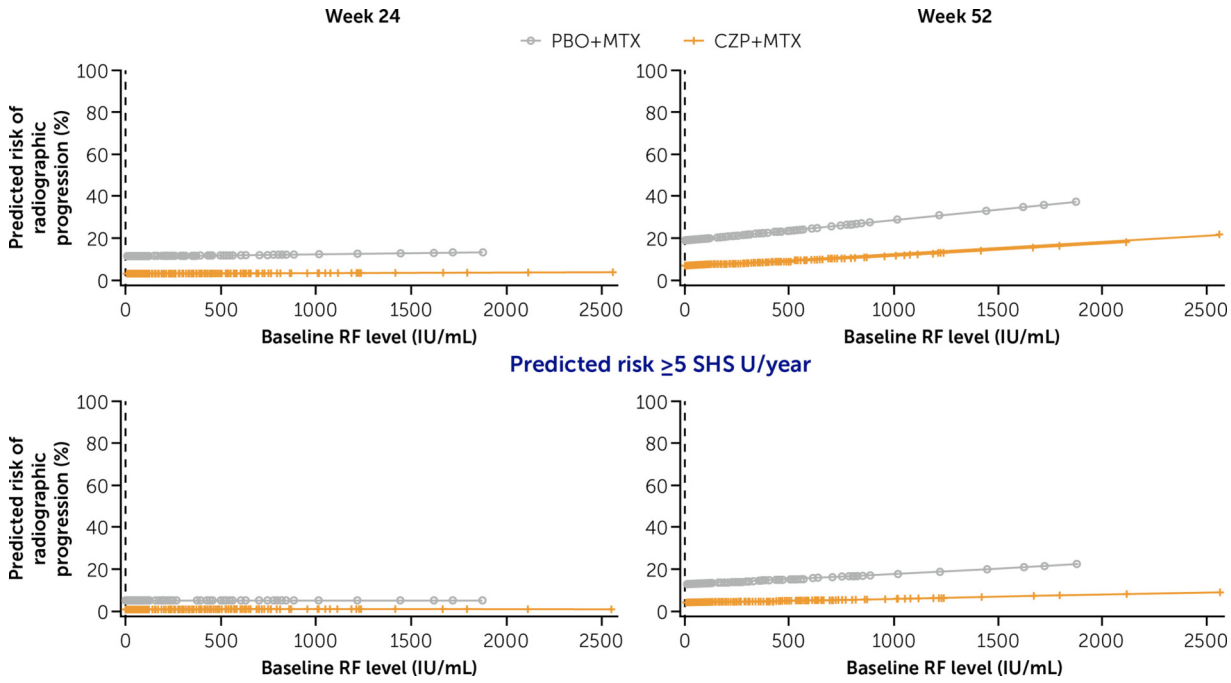

Fig. 2. The predicted risk of radiographic progression at Week 24 and Week 52. CZP: certolizumab pegol; MTX: methotrexate; PBO: placebo; RF: rheumatoid factor.

RF levels, respectively (Table 1). In both CZP + MTX and PBO + MTX-randomized patients, the high RF level groups had modestly numerically higher DAS28-ESR scores than the low RF level groups and the difference between the two RF strata was similar between treatment groups (Supplementary Fig. S1). However, mean (SD) DAS28-ESR was numerically higher in patients randomized to PBO + MTX versus CZP + MTX, irrespective of RF level.

At Week 24, a similar proportion of CZP + MTX patients with low and high RF levels achieved DAS28-ESR LDA (45.2% vs. 47.5%, respectively). Whereas, among those treated with PBO + MTX, there was less similarity between RF strata, with a smaller proportion of patients with high RF levels achieving LDA than those with low RF levels (PBO + MTX: 32.8% vs 40.5%). At Week 52, a similar proportion of CZP + MTX patients with low and high RF achieved DAS28-ESR LDA (56.0% vs. 57.4%, respectively; Supplementary Fig. S1).

3.7. Individual core set components (SJC and TJC) over time

At baseline, mean (SD) SJC score was 11.30 (5.59) and 12.17 (5.77) in CZP + MTX-randomized patients with low (n = 571) and high (n = 242) RF levels, respectively. In PBO + MTX-randomized patients with low (n = 242) and high (n = 124) RF levels, mean (SD) SJC score was 10.60 (5.94) and 11.99 (5.95), respectively. Mean (SD) TJC score was 14.05 (7.01) and 14.51 (7.02) at baseline for CZP + MTX-randomized patients with low (n = 571) and high (n = 242) RF levels, respectively and 12.65 (7.42) and 14.11 (7.44) for PBO + MTX-randomized patients with low (n = 242) and high (n = 124) RF levels, respectively.

At Week 24, mean ΔSJC score was similar for CZP + MTX-randomized patients with low and high RF levels (low RF: –9.17 [5.51]; high RF: –10.28 [5.61]). In PBO + MTX-randomized patients, ΔSJC score at Week 24 was–7.33 (5.17) and–8.32 (6.05) for patients with low and high RF, respectively. In CZP + MTX-randomized patients, the limited impact of RF level on SJC was observed through Week 52, whereby mean ΔSJC was comparable between RF strata (low RF: –10.26 [5.32]; high RF: –10.95 [5.51]).

Similar trends were observed for mean ΔTJC score, which was –10.62 (7.06) and –11.28 (7.33) at Week 24 for CZP-randomized patients with low and high RF levels, respectively. Mean ΔTJC score for PBO-randomized patients at Week 24 was –8.48 (7.15) and –9.95 (7.03) for low and high RF levels, respectively. Mean ΔTJC score was similar for CZP + MTX-randomized patients with low and high RF levels through Week 52 ΔTJC: low RF: –12.03 [6.89]; high RF: –12.62 [7.24]).

3.8. CDAI LDA achievement over time

At Week 24, the proportion of patients achieving CDAI LDA was similar across RF strata, (low RF: CZP + MTX: 59.0%; PBO + MTX: 50.8%; high RF levels: CZP + MTX: 59.1%; PBO + MTX: 49.6) (Supplementary Fig. S2). By Week 52, the proportion of patients achieving CDAI LDA was sustained in the CZP + MTX treatment group, regardless of RF strata (low RF: 62.0%; high RF: 64.0%).

3.9. Change from baseline in HAQ-DI over time

At baseline, mean (SD) HAQ-DI score was 0.96 (0.63) and 1.10 (0.67) for CZP + MTX-randomized patients with low (n = 103) and high (n = 56) RF levels, respectively. For PBO + MTX-randomized patients, baseline HAQ-DI score was 0.98 (0.69) and 1.18 (0.70) for patients with low (n = 107) and high (n = 50) RF levels, respectively.

At Week 24 in PBO + MTX-randomized patients, mean ΔHAQ-DI was similar regardless of RF level (low RF: –0.75 [0.62]; high RF: –0.76 [0.67]). At Week 24 in CZP + MTX randomized patients, ΔHAQ-DI (SD) was –0.86 (0.64) and –1.01 (0.66) for patients with low and high RF levels, respectively, and at Week 52, was –1.02 (0.68) and –1.14 (0.70), respectively.

4. Discussion

In this analysis of over 800 MTX-naïve patients with early RA, those with high baseline RF levels had more severe RA and early radiographic progression than those with low RF. Irrespective of baseline RF level, however, CZP + MTX was effective for minimizing radiographic progression from as early as 24 weeks of treatment. Evidence of radiographic progression was more similar between patients with high and low RF levels with CZP + MTX than with PBO + MTX, where deleterious effects of high RF level on radiographic progression were more pronounced.

mTSS component scores were consistently numerically more favorable with CZP + MTX than PBO + MTX, irrespective of baseline RF level. JSN and bone erosion (as measured by mTSS) are driven by different mechanisms; JSN primarily results from enzymatic digestion of cartilage by matrix metalloproteinases produced by synovial membranes, whereas bone erosion occurs through osteoclastic activity mediated by the RANKL-RANK pathway stimulated by TNF and interleukin (IL)-6 [36]. These data indicate that CZP + MTX positively affects both of these pathways, even in the presence of high levels of RF.

Although patients who received PBO + MTX generally experienced favorable clinical outcomes, reflecting the co-administration of MTX in an early-RA, MTX-naïve population, these patients still experienced relevant structural damage and exhibited worse radiographic progression compared to those receiving CZP + MTX. The difference in clinical outcomes between the two RF strata among PBO + MTX-treated patients was less pronounced than the pattern seen in the radiographic progression data. Thus, we show that clinically relevant structural damage occurred in these PBO + MTX-treated patients, despite favorable clinical outcomes. CZP + MTX-randomized patients also experienced consistently more favorable clinical outcomes through Week 52 than their PBO + MTX-continuing counterparts. Hence, in patients with high RF levels, CZP + MTX appears to attenuate the risk of radiographic progression more effectively than PBO + MTX.

The findings of this pooled analysis add to those of recent registry studies that reported better treatment response in patients with high RF levels treated with CZP compared to those treated with TNFis containing Fc regions [6,37]. Similarly, a post-hoc analysis of the EXXELERATE trial reported maintenance of CZP drug concentration and clinical efficacy across both low and high RF levels (defined in that study as ≤ 204 and > 204 IU/mL, respectively) in patients with RA, while adalimumab concentration and efficacy were lower in patients with high RF than low RF [23].

Recent *in vitro* studies have reported that RF binds Fc-containing bDMARDs, but not Fc-free CZP, providing insight into why patients with RA and high RF levels maintain higher drug concentrations and have better clinical outcomes with CZP compared with Fc-containing TNFis [11,29,38]. Increased clearance of Fc-containing TNFis, such as adalimumab, by macrophages have been predicted in patients with RA and high RF, leading to lower plasma concentrations in these patients, while CZP concentrations have been shown to remain consistent across RF levels [22]. These differences in the effects of RF levels on plasma concentrations of TNFis with versus without an Fc region likely explain the consistency of outcomes in patients across RF levels with CZP treatment, while Fc-containing TNFis are less effective in patients with high RF levels [9].

Current RA treatment guidelines recommend early escalation for individuals with poor baseline prognostic factors, including the presence of autoantibodies such as RF [2]. The findings of this pooled analysis demonstrate the value of CZP as a treatment option for such patients, as neither its clinical efficacy, nor its attenuation of radiographic progression, is impaired by the presence of high RF levels.

This post-hoc study was not without limitations. Stratification by RF level was not part of the original C-EARLY and C-OPERA study designs, resulting in an imbalance in the number of patients in the high and low RF groups. Due to issues regarding the power of inferential analyses and considerations of multiplicity, statistical hypothesis testing of differences in outcomes between the treatment groups and RF strata could not be regarded as conclusive, and therefore was not undertaken [39]. Furthermore, the C-EARLY and C-OPERA trials did not include an Fc-containing TNFi comparator. While the current analysis showed that CZP efficacy was preserved across RF strata, it cannot be concluded that high levels of RF differentially affect the radiographic progression-minimizing efficacy of Fc-containing TNFis vs CZP.

Mean, rather than median, was used to summarize average mTSS changes, since it was expected that in a cohort of patients with early RA, many would not exhibit radiographic progression and thus the median could lack sensitivity to change [40–43]. It should be acknowledged, however, that non-progressors and extreme progressors skew the mean results, limiting interpretation.

As C-EARLY and C-OPERA excluded patients with long-term active disease, these findings may not be generalizable for those with advanced RA [44]. Indeed, a systematic review by Hazlewood 2016 reported that, among MTX-naïve patients (early RA), MTX plus DMARD therapy (including CZP) was superior to oral MTX alone, supporting early DMARD use, while no statistically significant differences were found between combination therapy and MTX alone in MTX-nonresponders (advanced RA) [45]. Together, in line with guidelines, these findings emphasize the efficacy of early CZP use in patients with poor baseline prognostic factors, such as high RF level [2].

Finally, as this analysis pooled data from two trials (one in Japan and the other across Europe, Australia, North America, and Latin America), baseline MTX dosing differed, reflecting regional treatment practices. Potential heterogeneity between the two trials arises from the lower dosage utilized in Japan compared with other countries [33,46]. Extrapolation of these results is therefore limited to the studied populations.

In conclusion, patients with high baseline RF levels had more severe RA and early radiographic progression than those with low RF. Radiographic progression was more similar between patients with high and low RF levels treated with CZP + MTX and was lower than with PBO + MTX. While PBO + MTX treatment resulted in generally favorable clinical outcomes by Week 24 (and through Week 52 in PBO continuers), though less so than with CZP + MTX, these patients still experienced clinically relevant structural damage, which was most notable in the high RF group. Thus, irrespective of RF level, CZP + MTX better attenuated radiographic progression than MTX alone and was associated with more favorable clinical outcomes. Our findings suggest that RF level does not adversely influence radiographic response to CZP + MTX. These data further support CZP as an important treatment option for patients with RA and high RF levels.

Data sharing statement

Underlying data from this manuscript may be requested by qualified researchers six months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient-level data and redacted trial documents which may include: analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at http://www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password protected portal.

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Authors' contributions

Substantial contributions to study conception and design: JSS, PCT, GB, YT, TT, JRC, CLM, WHR, TH, PM, BL, BU, TRM; substantial contributions to analysis and interpretation of the data: JSS, PCT, GB, YT, TT, JRC, CLM, WHR, TH, PM, BL, BU, TRM; drafting the article or revising it critically for important intellectual content JSS, PCT, GB, YT, TT, JRC, CLM, WHR, TH, PM, BL, BU, TRM; final approval of the version of the

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Disclosure of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2026.106087.

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