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ORIGINAL RESEARCH

Do high rheumatoid factor levels impact response to certolizumab pegol in patients with inadequately controlled rheumatoid arthritis? A post hoc analysis of the phase IIIb REALISTIC trial

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ABSTRACT

Objectives To assess the impact of rheumatoid factor (RF) levels and previous inadequate responses/intolerance to tumour necrosis factor inhibitors (TNFi-IR) on the efficacy of certolizumab pegol (CZP) in patients with rheumatoid arthritis (RA) through a post hoc analysis of the RA Evaluation in Subjects Receiving TNF Inhibitor CZP (REALISTIC) trial.

Methods In the phase IIIb REALISTIC trial, patients with RA were randomised to CZP (400 mg at weeks 0, 2 and 4, then 200 mg every 2 weeks) or placebo (PBO) for 12 weeks, followed by open-label CZP (minimum 16 weeks). Outcomes reported to week 36 include Disease Activity Score 28 C-reactive protein (DAS28-CRP) and Clinical Disease Activity Index (CDAI) scores, rates of DAS28-CRP <2.6 and CDAI remission (CDAI ≤2.8) and components of each. Data were stratified by baseline RF level (≤3rd quarter (≤Q3; <180 kU/L) vs 4th quarter (Q4; 'high RF'; ≥180 kU/L)) and prior TNFi use (TNFinaïve vs TNFi-IR).

Results A total of 930 patients were included: 751 CZP-randomised and 179 PBO-randomised. At week 12, CZP-randomised patients experienced marked and similar improvements in disease activity, irrespective of RF level and prior TNFi use, while PBO-randomised patients did not. Responses generally improved through week 36 in CZP-treated patients (including PBO-randomised switchers), with similar efficacy across subgroups.

Conclusions Patients with high and low RF levels experienced similar clinical responses to CZP treatment, irrespective of previous inadequate responses or intolerance to TNFis. These findings expand previous observations, supporting CZP as an effective treatment for patients with RA who have high RF levels and prior inadequate responses to TNFis.

Trial registration number NCT00717236.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with rheumatoid arthritis (RA) and high rheumatoid factor (RF) levels have poorer prognosis compared with patients with lower RF levels.
⇒ Unlike most tumour necrosis factor inhibitors (TNFis) used for RA, certolizumab pegol (CZP) does not have a fragment crystallisable region that can be bound by RF.
⇒ Among patients with higher RF levels, CZP-treated patients demonstrate higher drug concentrations and greater efficacy compared with other TNFis.

WHAT THIS STUDY ADDS

⇒ We demonstrate that patients with high and low RF levels experienced similar clinical responses to CZP treatment, irrespective of previous inadequate responses or intolerance to TNFis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings support CZP as an effective treatment for patients with RA who have high RF levels and prior inadequate responses to TNFis.

INTRODUCTION

A common feature of rheumatoid arthritis (RA) is the presence of circulating autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), which are detectable in up to 80% of patients with established RA and provide important diagnostic and prognostic information.[1 2] RFs target the fragment crystallisable (Fc) portion of immunoglobulin G (IgG), leading to the formation of immune complexes that are crucial in the pathogenesis of RA.[3] Patients with RA and high levels of RF have poorer prognosis, more aggressive and destructive disease, higher cardiovascular risk and higher risk of radiographic progression,

as well as increased levels of tumour necrosis factor (TNF), compared with patients with lower RF levels or absence of RF.[4–11] These consequences are well known to be driven by high disease activity in patients with high RF levels.[5 8 10–12] Moreover, RF level has been more strongly associated with disease activity than ACPA level.[2 13]

Most TNF inhibitors (TNFis) used in the treatment of RA are monoclonal antibodies or receptor constructs with an Fc region (Fc-mAbs) that can be bound by RF.[14] Binding of IgM-RF to TNFis enables the formation of large protein complexes,[14] which can be subsequently internalised and undergo lysosomal degradation by macrophages.[15 16] Clearance of Fc-containing TNFis is therefore enhanced in patients with high RF levels, appearing to lead to the reduced efficacy observed in these patients.[11 14 17 18] These findings provide molecular insights into why patients with RA and high RF levels may have worse treatment outcomes with Fc-containing TNFis compared with those with lower RF levels.

Certolizumab pegol (CZP), a PEGylated TNFi without an Fc fragment, is effective for the treatment of RA and does not form complexes with IgM-RF.[14 19] Thus, patients with RA and high RF levels may benefit from treatment with Fc-free TNFis. Indeed, in post hoc analyses and retrospective studies, among patients with higher baseline RF levels, CZP-treated patients have consistently demonstrated drug concentrations comparable to patients with lower baseline RF levels, and these patients have experienced greater efficacy with CZP compared with other TNFi treatments.[15 17 20 21] Specifically, in a post hoc analysis of the phase IV EXXELERATE trial which included biological disease-modifying anti-rheumatic drug (bDMARD)-naïve patients with RA, CZP-treated patients with high RF levels (>204 IU/mL; the highest quartile in the study) exhibited similar CZP drug concentrations and clinical responses as patients with RA and lower RF levels.[22] On the other hand, patients with RA and high RF levels treated with the human TNFi adalimumab (ADA) had lower drug concentrations and poorer clinical outcomes than CZP-treated patients with low RF levels.[22]

While it has been observed that high levels of RF are associated with lower clinical effectiveness of treatment with Fc-mAbs, it remains unknown whether this only pertains to patients with insufficient prior response to csDMARDs such as methotrexate (MTX), or also to those with inadequate response or intolerance to prior TNFis (TNFi-IR).

Here, we present the results of a post hoc analysis of RA Evaluation in Subjects Receiving TNF Inhibitor CZP (REALISTIC), a phase IIIb, randomised trial which assessed the efficacy of CZP versus placebo (PBO) in a large cohort of patients with RA. In REALISTIC, almost 40% of the RA patients had experienced a TNFi previously and CZP was associated with rapid and consistent clinical responses and improved physical function, irrespective of the type of previous therapy.[23] Here, we report the clinical efficacy of CZP in patients with RA, further stratified by baseline RF level as well as previous TNFi use, to assess the potential impact of these differential characteristics on the efficacy of CZP treatment across different RA populations. Building on previous observations, our hypothesis was that patients with RA would experience consistent clinical responses to CZP, irrespective of high RF levels and inadequate response or intolerance to previous TNFis.

METHODS

Study design

The phase IIIb REALISTIC (NCT00717236) trial was a multicentre study conducted in 230 centres in the USA, Canada and Europe to evaluate the safety and efficacy of CZP administered to patients with moderate to severe RA.[24] The trial comprised a 12-week, double-blind, PBO-controlled, randomised phase, followed by an open-label extension in which all patients received CZP. The full study design has been reported previously.[23]

At baseline, patients were stratified by MTX use (yes vs no), previous TNFi use (yes vs no) and disease duration (<2 vs ≥2 years) and were randomised 4:1 to receive either CZP (400 mg subcutaneous (SC) at weeks 0, 2 and 4, followed by 200 mg SC every 2 weeks (Q2W)) or PBO injection (0.9% sodium chloride) for a 12-week period. CZP or PBO was administered in addition to current RA treatment (if any), which could include any combination of the following: DMARDs (MTX, leflunomide, sulfasalazine, chloroquine or hydroxychloroquine, azathioprine and/or gold), tetracyclines, glucocorticoids (prednisone equivalent ≤10 mg/day) and non-steroidal anti-inflammatory drugs (cyclo-oxygenase-2 inhibitors), or none of these. Following this, patients who completed 12 weeks of treatment with either CZP or PBO were eligible to either continue, or start receiving, open-label 200 mg CZP Q2W for a minimum of 16 weeks and up to 28 weeks or until CZP commercial availability in the relevant region, whichever was latest.

Patients

Included patients were ≥18 years old, with a diagnosis of adult-onset RA of at least 3 months, as defined by the 1987 American College of Rheumatology (ACR) classification criteria,[25] and with active RA disease as defined by: ≥5 tender joints, ≥4 swollen joints (out of 28 joints), a C-reactive protein (CRP) concentration ≥10 mg/L and/or an erythrocyte sedimentation rate ≥28 mm/hour at screening. Patients must have also had an unsatisfactory response or intolerance to at least one csDMARD.

Reasons for patients being excluded included: having received experimental biological or non-biological treatment for RA in the last 3 months or within five half-lives prior to the baseline visit or having received treatment with more than two TNFis prior to enrolment. Full exclusion criteria have been reported previously.[23]

Outcomes

Effectiveness outcomes were stratified by baseline RF level quarter (≤3rd quarter (≤Q3; 'low RF'; <180 kU/L) vs 4th quarter (Q4; 'high RF'; ≥180 kU/L)) and any prior TNFi use (TNFi-IR (previous inadequate response or intolerance) vs TNFi-naïve). Data are reported to week 12 for PBO-randomised patients and week 36 for all CZP-treated patients, including those who switched from PBO to open-label CZP at week 12.

Response to treatment was assessed using the 28-joint Disease Activity Score (DAS28) with CRP and Clinical Disease Activity Index (CDAI). Mean DAS28-CRP and CDAI scores, and rates of DAS28-CRP <2.6 and ACR-European Alliance of Associations for Rheumatology (ACR-EULAR) index-based remission[26] (CDAI remission; CDAI ≤2.8) are reported to week 12 for both treatment groups, and to week 36 for patients who continued to receive CZP, or switched to open-label CZP, after week 12. As a sensitivity analysis, mean DAS28-CRP and CDAI are additionally reported stratified by lowest baseline RF level quarter (1st quarter (Q1; 'very low RF'; ≤13 kU/L) vs Q4).

Additionally, mean scores for each of the following individual components of DAS28-CRP and CDAI are reported to week 36: swollen joint count (SJC), tender joint count (TJC), patient global assessment (PtGA) and physician global assessment (PhGA) of disease activity, as well as mean CRP level.

Statistical analysis

The analyses included patients from the full analysis set comprising all randomised patients who had an RF assessment at baseline. Data are reported as observed case (OC). Non-responder imputation (NRI) data are also presented for DAS28-CRP <2.6 and CDAI remission rates in the online supplemental material. As a post hoc analysis, only descriptive statistics are presented for all outcomes. In the absence of formal hypothesis testing, results should be considered exploratory rather than confirmatory.

RESULTS

Patient disposition and baseline characteristics

A total of 930 patients were included in this study: 751 patients were randomised to CZP and 179 to PBO. Baseline characteristics are presented in table 1. Most patients were women (722/930; 77.6%) and the mean (SD) age was 55.0 (12.7) years. The majority of patients had a disease duration of ≥2 years (695/930; 74.7%) and over two-thirds of patients were on concomitant treatment with MTX (642/930; 69.0%). More than one-third of patients had prior TNFi use (352/930; 37.8%); of patients with TNFi-IR, approximately half had stopped their prior TNFi due to efficacy reasons. The TNFi-IR population had longer mean disease duration at baseline than the TNFi-naïve population; this pattern was consistent across treatment groups and RF subgroups. Baseline demographics, including number of previous DMARDs, were similar between patients with low RF (≤Q3) and high RF (Q4) levels, and between those randomised to each treatment arm.

DAS28-CRP and CDAI

In the TNFi-IR population, mean DAS28-CRP and CDAI were similar at week 12 in CZP-randomised patients irrespective of RF levels, and were consistently lower than in PBO-randomised patients, with a numerically larger difference between CZP-treated and PBO-treated patients seen in those with high RF levels (DAS28-CRP: 4.2 (CZP) and 5.7 (PBO); CDAI: 20.4 (CZP) and 35.4 (PBO)) compared with those with low RF levels (DAS28-CRP: 4.2 (CZP) and 4.7 (PBO); CDAI: 21.6 (CZP) and 26.0 (PBO); figure 1a). Responses were generally similar at week 36 in all CZP-treated groups.

TNFi-naïve patients treated with CZP had numerically lower mean DAS28-CRP and CDAI scores at week 12 than PBO-randomised patients, regardless of RF level (figure 1b). The differences between PBO-treated TNFi-naïve patients with high and low RF levels at week 12 were numerically smaller than in TNFi-IR patients, while CZP-randomised patients demonstrated similar efficacy across TNFi subgroups irrespective of RF level. Similar consistent efficacy was seen at week 36 across TNFi and RF subgroups of CZP-treated patients (comprising both CZP-randomised patients and PBO-randomised patients who received CZP from week 12). In patients who switched from PBO to CZP at week 12, broadly similar patterns in DAS28-CRP and CDAI were observed through week 36 as those seen in CZP-randomised patients between baseline and week 12 (data not shown). Similar outcomes were observed in the overall population (figure 1c).

Sensitivity analyses comparing DAS28-CRP and CDAI in patients with baseline RF level in the lowest quarter (Q1) with those in Q4 demonstrated a broadly similar pattern (online supplemental figure S2).

Rates of DAS28-CRP <2.6 and CDAI remission (≤2.8)

In TNFi-IR patients, no PBO-randomised patients with high RF levels achieved DAS28-CRP <2.6 or CDAI remission (≤2.8) at week 12, while these were achieved by 8.0% and 6.0% of patients with low RF levels, respectively. The proportions of TNFi-IR CZP-treated patients who achieved these thresholds were similar across RF levels (DAS28-CRP: 14.9% (high RF) and 10.5% (low RF); CDAI remission: 8.1% (high RF) and 5.8% (low RF); figure 2a). Similarly, among TNFi-naïve patients, the proportions of patients achieving DAS28-CRP <2.6 and CDAI remission (≤2.8) were consistently higher in CZP-randomised patients compared with PBO-randomised patients at week 12, including in patients with high RF levels (figure 2b). At week 36, the proportion of TNFi-naïve CZP-treated patients who achieved DAS28-CRP <2.6 and CDAI remission (≤2.8) was similar across RF levels. Generally, similar patterns were observed using NRI (online supplemental figure S1). In patients who

Table 1 Patient demographics and baseline disease characteristics

	RF≤Q3 (<180 KU/L) (n=695)				RF Q4 (≥180 KU/L) (n=235)			
	TNFi-IR (n=259)		TNFi-naïve (n=436)		TNFi-IR (n=93)		TNFi-naïve (n=142)	
Baseline population characteristic	**PBO (n=52)**	**CZP (n=207)**	**PBO (n=83)**	**CZP (n=353)**	**PBO (n=16)**	**CZP (n=77)**	**PBO (n=28)**	**CZP (n=114)**
Mean age, years (SD)	50.3 (13.6)	54.2 (12.3)	54.7 (13.1)	55.3 (13.4)	57.3 (6.6)	54.9 (11.5)	53.6 (12.7)	57.6 (11.4)
Female, n (%)	45 (86.5)	168 (81.2)	65 (78.3)	282 (79.9)	10 (62.5)	53 (68.8)	21 (75.0)	78 (68.4)
Mean disease duration, years (SD)	9.7 (9.3)	11.8 (9.8)	8.4 (9.8)	6.3 (7.7)	11.8 (7.6)	11.1 (9.0)	5.9 (6.2)	7.0 (7.1)
Disease duration <2 years, n (%)	7 (13.5)	17 (8.2)	29 (34.9)	133 (37.7)	0 (0)	5 (6.5)	9 (32.1)	35 (30.7)
Positive RF (≥14 IU/mL) at baseline, n (%)	43 (82.7)	141 (68.1)	50 (60.2)	223 (63.2)	16 (100)	77 (100)	28 (100)	114 (100)
RF level, IU/mL, mean (SD)	58.4 (49.5)	47.3 (46.0)	47.8 (46.9)	45.6 (46.3)	714.4 (1265.3)	602.3 (558.7)	519.9 (399.1)	544.4 (435.8)
Prior TNFi reason for discontinuation, n (%)*								
Efficacy	23 (44.2)	92 (44.4)	–	–	11 (68.6)	29 (37.7)	–	–
Non-efficacy	29 (55.8)	111 (53.6)	–	–	4 (25.0)	47 (61.0)	–	–
Concomitant DMARD use, n (%)	37 (71.2)	163 (78.7)	69 (83.1)	307 (87.0)	11 (68.8)	54 (70.1)	24 (85.7)	94 (82.5)
Concomitant bDMARD use, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Concomitant csDMARD use, n (%)	37 (71.2)	163 (78.7)	69 (83.1)	307 (87.0)	11 (68.8)	54 (70.1)	24 (85.7)	94 (82.5)
Number of previous csDMARDs, n (%)								
0	13 (25.0)	59 (28.5)	32 (38.6)	134 (38.0)	7 (43.8)	19 (24.7)	15 (53.6)	39 (34.2)
1	25 (48.1)	81 (39.1)	32 (38.6)	130 (36.8)	4 (25.0)	37 (48.1)	9 (32.1)	40 (35.1)
2	8 (15.4)	26 (12.6)	10 (12.0)	59 (16.7)	2 (12.5)	10 (13.0)	4 (14.3)	22 (19.3)
≥3	6 (11.5)	41 (19.8)	9 (10.8)	30 (8.5)	3 (18.8)	11 (14.3)	0 (0)	13 (11.4)
Concomitant methotrexate use, n (%)	35 (67.3)	142 (68.6)	55 (66.3)	255 (72.2)	9 (56.3)	46 (59.7)	23 (82.1)	77 (67.5)
DAS28-CRP Score, mean (SD)	5.7 (0.9)	5.7 (0.8)	5.6 (0.8)	5.6 (0.8)	6.3 (1.0)	6.0 (1.1)	5.7 (0.8)	5.9 (1.0)
CDAI Score, mean (SD)	38.2 (12.5)	38.5 (11.6)	37.2 (11.1)	37.2 (12.2)	44.5 (14.0)	42.4 (14.7)	37.7 (10.2)	39.4 (13.0)
ACPA, kIU/L, mean (SD)	139.0 (194.0)	111.5 (188.4)	99.5 (171.8)	115.2 (194.6)	260.8 (309.4)	302.7 (285.0)	340.3 (322.7)	268.5 (256.7)

Only those patients with a non-missing RF assessment at baseline are included.
*If a patient had lack of response from either a primary or secondary TNFi, they were categorised under 'efficacy reasons'.
ACPA, anti-citrullinated protein antibodies; bDMARD, biological DMARD; CDAI, clinical disease activity index; CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; CZP, certolizumab pegol; DAS28-CRP, 28-joint Disease Activity Score C reactive protein; DMARD, disease-modifying anti-rheumatic drugs; PBO, placebo; Q3, third quarter; Q4, fourth quarter; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor; TNFi-IR, inadequate response or intolerance to TNFi.

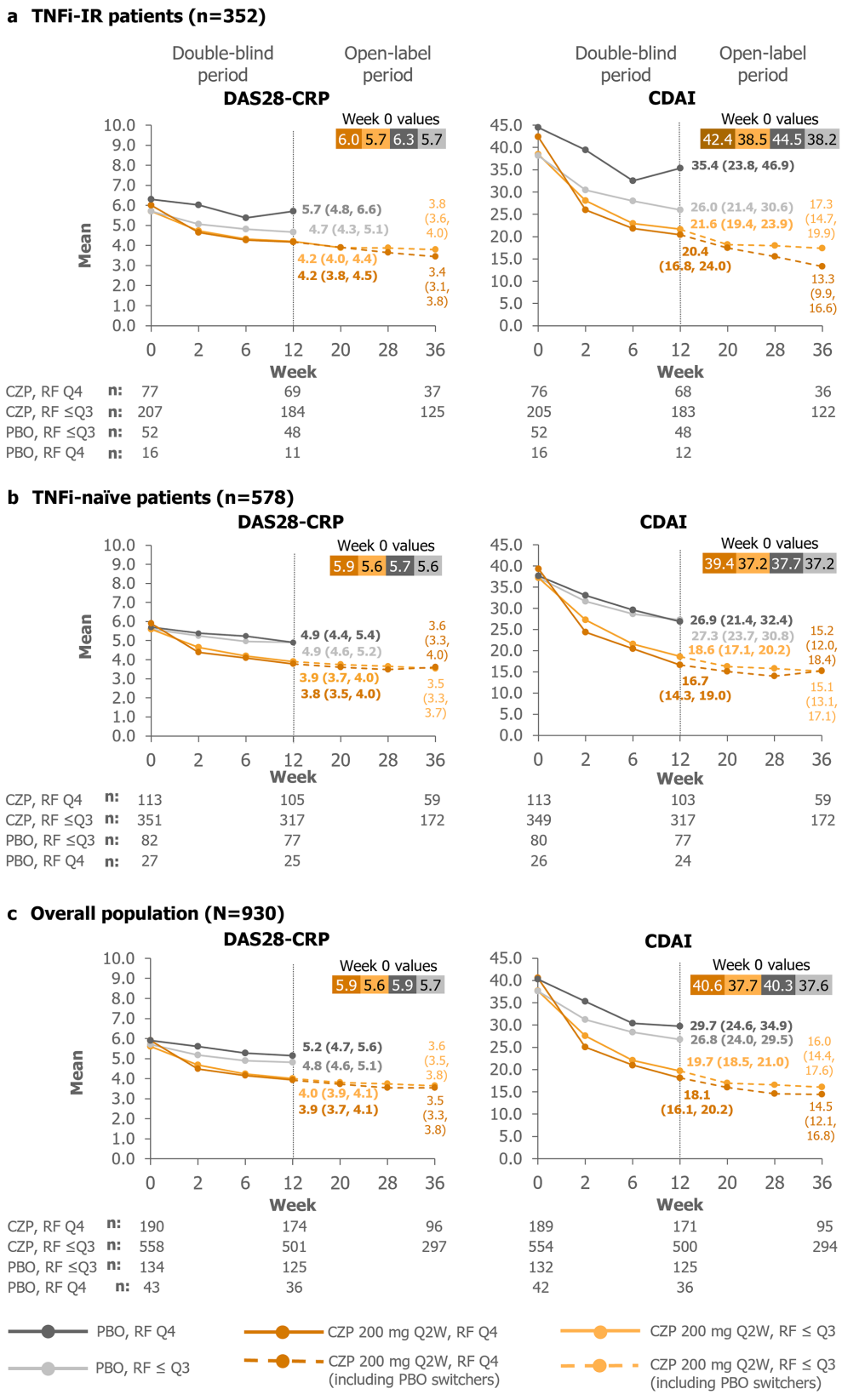

Figure 1 28-joint Disease Activity Score C reactive protein (DAS28-CRP) and Clinical Disease Activity Index (CDAI) in (a) inadequate response or intolerance to tumour necrosis factor inhibitors (TNFi-IR) patients, (b) TNFi-naïve patients and (c) overall population, stratified by rheumatoid factor (RF) level (<180 kU/L (≤Q3) vs ≥180 kU/L (Q4)) (observed case). Data are reported (as mean [95% confidence interval]) to Week 12 for PBO-randomised patients and Week 36 for CZP-treated patients, including those who switched from PBO to open-label CZP from Week 12. CZP, certolizumab pegol; PBO, placebo; Q2W, every 2 weeks; Q3, third quarter; Q4, fourth quarter.

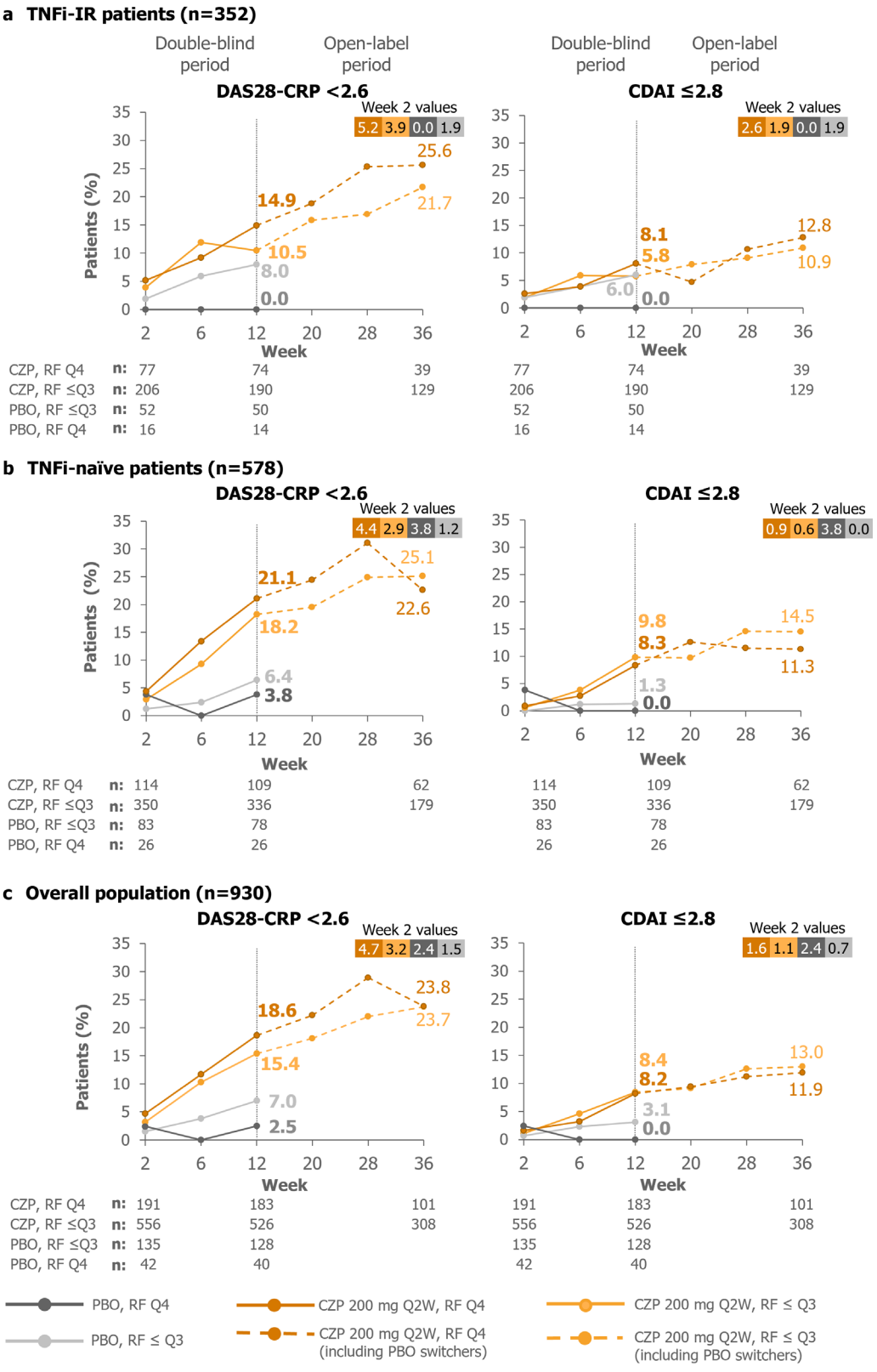

Figure 2 Rates of 28-joint Disease Activity Score C reactive protein (DAS28-CRP) <2.6 and Clinical Disease Activity Index (CDAI) remission (CDAI ≤2.8) in (a) inadequate response or intolerance to tumour necrosis factor inhibitors (TNFi-IR) patients, (b) TNFi-naïve patients and (c) overall population, stratified by rheumatoid factor (RF) level (<180 kU/L (≤Q3) vs ≥180 kU/L (Q4)) (observed case). Data are reported to Week 12 for PBO-randomised patients and Week 36 for CZP-treated patients, including those who switched from PBO to open-label CZP from Week 12. CDAI remission defined as CDAI ≤2.8. CDAI: Clinical Disease Activity Index; CZP, certolizumab pegol; PBO, placebo; Q2W, every 2 weeks; Q3, third quarter; Q4, fourth quarter.

Table 2 Individual DAS28-CRP and CDAI components in the overall population, TNFi-IR patients and TNFi-naïve patients, stratified by RF level (RF (<180 kU/L (≤Q3) vs ≥180 kU/L (Q4)) (OC)

	Overall (N=930)				TNFi-IR (n=352)				TNFi-naïve (n=578)			
	PBO Baseline n=179		CZP Baseline n=751		PBO Baseline n=68		CZP Baseline n=284		PBO Baseline n=111		CZP Baseline n=467	
	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4
Swollen joint count, mean												
Week 0	10.9 n=135	12.3 n=44	11.4 n=559	12.7 n=191	11.0 n=52	13.5 n=16	11.4 n=207	13.3 n=77	10.8 n=83	11.6 n=28	11.4 n=352	12.4 n=114
Week 12	7.4 n=126	9.1 n=37	5.3 n=511	5.5 n=175	7.5 n=48	10.4 n=12	6.1 n=185	6.6 n=69	7.3 n=78	8.6 n=25	4.8 n=326	4.8 n=106
Week 36	–	–	4.2 n=299	4.5 n=99	–	–	4.5 n=125	4.4 n=38	–	–	4.0 n=174	4.7 n=61
Tender joint count, mean												
Week 0	14.5 n=135	15.4 n=44	14.4 n=559	15.3 n=191	14.6 n=52	16.8 n=16	14.8 n=207	16.1 n=77	14.5 n=83	14.7 n=28	14.1 n=352	14.8 n=114
Week 12	10.2 n=126	10.8 n=37	7.6 n=511	6.4 n=175	9.5 n=48	13.0 n=12	8.1 n=185	6.9 n=69	10.6 n=78	9.8 n=25	7.4 n=326	6.1 n=106
Week 36	–	–	6.1 n=299	4.9 n=99	–	–	6.6 n=125	3.7 n=38	–	–	5.7 n=174	5.7 n=61
CRP level (mg/L), mean												
Week 0	16.0 n=135	22.3 n=44	15.4 n=560	23.7 n=191	15.6 n=52	27.0 n=16	16.7 n=207	26.4 n=77	16.3 n=83	19.6 n=28	14.7 n=353	21.8 n=114
Week 12	17.9 n=125	21.5 n=36	9.1 n=507	12.5 n=176	14.8 n=48	31.7 n=11	11.1 n=185	16.1 n=70	19.9 n=77	17.0 n=25	8.0 n=322	10.1 n=106
Week 36	–	–	7.3 n=300	12.3 n=99	–	–	8.1 n=126	11.1 n=39	–	–	6.8 n=174	13.1 n=60
Patient's Global Assessment of Disease Activity												
Week 0	60.8 n=133	61.9 n=43	61.0 n=555	63.3 n=190	61.6 n=52	67.9 n=16	62.1 n=205	67.6 n=76	60.3 n=81	58.3 n=27	60.3 n=350	60.4 n=114
Week 12	41.2 n=125	45.8 n=36	30.4 n=504	27.1 m=174	40.9 n=48	60.8 n=12	32.3 n=183	29.9 n=69	41.4 n=77	38.3 n=24	29.4 n=321	25.3 n=105
Week 36	–	–	23.8 n=296	21.4 n=98	–	–	25.8 n=122	21.0 n=38	–	–	22.4 n=174	21.7 n=60
Physicians' Global Assessment of Disease Activity												
Week 0	60.9 n=134	61.8 n=43	57.9 n=559	62.6 n=190	64.6 n=52	74.6 n=16	60.9 n=207	63.0 n=77	58.6 n=82	54.2 n=27	56.1 n=352	62.3 n=113

Continued

Table 2 Continued

	Overall (N=930)				TNFi-IR (n=352)				TNFi-naïve (n=578)			
	PBO Baseline n=179		CZP Baseline n=751		PBO Baseline n=68		CZP Baseline n=284		PBO Baseline n=111		CZP Baseline n=467	
	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4	RF ≤Q3	RF Q4
Week 12	49.4 n=126	49.1 n=37	38.0 n=510	34.3 n=176	49.4 n=48	59.8 n=12	41.3 n=186	39.7 n=70	49.4 n=78	44.0 n=25	36.1 n=324	30.8 n=106
Week 36	–	–	34.2 n=298	29.5 n=97	–	–	38.5 n=125	27.1 n=37	–	–	31.1 n=173	30.9 n=60

Data are reported to week 12 for PBO-randomised patients and week 36 for CZP-treated patients, including those who switched from PBO to open-label CZP from week 12.
CDAI, clinical disease activity index; CRP, C reactive protein; CZP, certolizumab pegol; DAS28-CRP, 28-joint Disease Activity Score C reactive protein; OC, observed case; PBO, placebo; Q3, third quarter; Q4, fourth quarter; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor; TNFi-IR, inadequate response or intolerance to TNFi.

switched from PBO to CZP at week 12, similar patterns were observed through week 36 as those seen in CZP-randomised patients between baseline and week 12 (data not shown).

Similar outcomes were observed in the overall population (figure 2c).

DAS28-CRP and CDAI individual components

At week 12, mean SJC, TJC, CRP, PtGA and PhGA were numerically lower in CZP-randomised patients compared with PBO-randomised patients irrespective of RF levels and prior TNFi treatment (table 2; OC). At week 36, CZP-treated patients exhibited generally similar outcomes across all components, regardless of RF level and prior TNFi treatment.

DISCUSSION

The data reported in this post hoc analysis of the phase IIIb REALISTIC trial build on previous findings that patients with RA and high RF levels may achieve and maintain clinical improvement when treated with TNFis without an Fc region, such as CZP.[16 19 21] Here, the efficacy of CZP was not only confirmed across RF levels in bDMARD-naïve patients with RA, but extended to a large population of patients who had experienced prior TNFi use.[18 21 22]

Recent in vitro studies have provided molecular insight into the clinical outcomes of RA patients with high RF levels.[14 15] Increased clearance of TNFis with an Fc, such as ADA, has been observed in patients with RA and high RF.[27] Additionally, it has been reported that patients tend to maintain higher drug concentrations and achieve better clinical outcomes when treated with CZP compared with Fc-containing TNFis.[14 15 22] Pentameric IgM RF in particular has been shown to bind and enhance the clearance of Fc-containing bDMARDs. Therefore, the prominence of IgM RF may have particularly important clinical implications,[28] since these autoantibodies have been shown to bind Fc-containing bDMARDs, enhancing their clearance.[15]

Around 40% of patients with RA are thought to have inadequate response or intolerance to TNFis.[29 30] Given this large proportion, it is important to optimise the treatment of this patient population in clinical practice. In this study, the notion that the efficacy of CZP is sustained irrespective of baseline RF levels is expanded to patients with previous inadequate response or intolerance to TNFis, with each reason (efficacy and non-efficacy) comprising approximately half of the included patient population. Following inadequate response to TNFis, clinicians may suggest a treatment switch to an alternative biologic, per current guidance from the ACR and the EULAR.[31 32] However, no specific recommendations are made with regard to which bDMARDs patients should switch to following inadequate response to a first-line TNFi, suggesting that the treating physician should take the patients' characteristics and history into account.[33]

Determining the patient's RF level may provide insight into whether an Fc-free TNFi may be more beneficial than an Fc-containing TNFi.

Here, CZP-treated patients with high RF levels exhibited similar clinical outcomes to those with low RF levels at week 12 and through week 36. These findings were further supported by a sensitivity analysis that stratified patients by Q1 versus Q4, which demonstrated a similar pattern of response as the ≤Q3 versus Q4 comparison. Furthermore, mean values of individual DAS28-CRP and CDAI components, including SJC, TJC, CRP, PtGA and PhGA were numerically lower in CZP-randomised patients compared with PBO-randomised patients at week 12, irrespective of RF levels, and a similar pattern was observed at week 36 in the overall CZP-treated patient group (including those who switched from PBO to open-label CZP from week 12). These results support previous findings that clinical outcomes are consistent in CZP-treated patients, irrespective of baseline RF level.[18 20 22]

In TNFi-IR patients at week 12, the difference in treatment responses achieved by patients who received CZP versus PBO was numerically greater in patients with high RF levels than in patients with low RF levels. The rates of DAS28-CRP <2.6 and ACR-EULAR index-based remission,[26] that is, CDAI remission, achieved at week 36 in CZP-treated patients were similar across patients with low and high baseline RF levels, and between TNFi-IR and TNFi-naïve patients. Together, this suggests that the benefit of CZP treatment is maintained in patients with high RF levels and also in those with prior inadequate response to a different TNFi.

While the present study provides an analysis demonstrating the consistent efficacy of CZP in patients with RA irrespective of RF level and TNFi-IR status, the REALISTIC trial was not designed to study TNFi-IR patients specifically. Nevertheless, at baseline, patients had been prospectively stratified according to prior TNFi use. Moreover, the results of this post hoc analysis are supported by previous studies which have reported the pattern of sustained CZP efficacy in patients with high RF levels.[15 18 21 22] Further, it should be noted that the TNFi-IR group included patients with prior TNFi discontinuation due to both efficacy and non-efficacy reasons (with each reason comprising approximately half of the included patient population). Thus, results described are a composite of patients with inadequate response as well as those with intolerance to previous TNFi treatment, for which different response mechanisms may be involved.[34] Future investigation into these two subgroups is warranted.

While studies have previously demonstrated numerically greater efficacy of CZP against comparator treatments in patients with high RF levels,[15 20 22] the current study did not include an active comparator arm. Therefore, it is not possible to directly contextualise the efficacy of CZP in TNFi-IR patients in the present study against other available treatments. Nevertheless, in this study, CZP efficacy was maintained both in patients with high RF levels and those with TNFi-IR. Furthermore, in the REALISTIC trial, patients treated with more than two TNFis, or rituximab and/or abatacept were excluded. Therefore, the findings of this post hoc analysis may not necessarily be applicable to these specific patient groups.[24]

Since the data presented in this manuscript are derived from a post hoc analysis of the REALISTIC trial, no formal statistical analyses were conducted. Thus, results must be considered as exploratory rather than confirmatory. However, by visual inspection, broad similarities between the CZP-treated patients in the high and low RF groups are evident, such as very similar changes in DAS28-CRP and CDAI over time. This is in line with previous findings using CZP[20–22] and is hereby expanded to a TNFi-IR population.

Finally, in the REALISTIC trial, owing to patients having active RA, a 4:1 CZP:PBO randomisation ratio was chosen, such that 20% of patients were exposed to PBO. The maximum duration that patients were exposed to PBO was 12 weeks, after which patients received CZP in the open-label period. This randomisation ratio and shorter-than-usual double-blind period was utilised in order to balance the need for scientific rigour and the ethical protection of patients.

These data collectively demonstrate that the effectiveness of CZP is maintained in patients with high RF levels and previous inadequate response or intolerance to TNFis, thus expanding earlier findings to the TNFi-IR patient subgroup. This is an important observation for this subset of patients, who constitute a substantial proportion of the overall RA patient population. This study further highlights the importance of personalising treatment choices based on patients' characteristics in the context of managing RA. Specifically, determining the patient's RF level may be beneficial to inform subsequent treatment decisions, including patients who have had inadequate response to other TNFis.

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