Do High Rheumatoid Factor Levels Impact Response to Certolizumab Pegol in Patients with Inadequately Controlled Rheumatoid Arthritis? A Post Hoc Analysis of a Phase 3b Trial

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Objective

To assess the impact of rheumatoid factor (RF) levels and previous therapies on certolizumab pegol (CZP) efficacy in patients with rheumatoid arthritis (RA), in a post hoc analysis of the REALISTIC trial.

Background

- In patients with RA, high RF levels are associated with higher disease activity and decreased response to monoclonal antibodies targeting tumor necrosis factor (TNF).[1,2,3]
- Such patients may have better clinical responses to TNF inhibitors (TNFis) without a fragment crystallizable (Fc) portion, such as CZP, compared to TNFis with an Fc.[4,5,6]
- However, in patients with RA and high RF levels who have had previous inadequate responses or intolerance to TNFis (TNFi-IR), data on response to CZP are limited. These patients generally have poorer responses to subsequent biologic or targeted synthetic disease-modifying anti rheumatic drugs (DMARDs).[7]

Methods

- REALISTIC (NCT00717236) was double-blind and placebo-controlled to Week 12.[8] Patients with inadequately controlled RA were randomized 4:1 to receive either CZP (400 mg subcutaneous [SC] at Weeks 0, 2, and 4, followed by 200 mg SC every 2 weeks) or placebo (PBO) for a 12-week period, after which all patients received open-label CZP.
- We report the following outcomes to Week 36: Disease Activity Score 28 C-reactive protein (DAS28-CRP), DAS28-CRP <2.6, Clinical Disease Activity Index (CDAI), and CDAI remission (CDAI ≤2.8).
  - Results are stratified by baseline RF level (<4th quarter [≤Q3] vs 4th quarter [Q4]) and prior TNFi use; data are reported as observed case (OC).

Results

Patient Characteristics

- Overall, 751 CZP-randomized patients (RF ≤Q3 [<180 IU/mL]: n=560, RF Q4 [≥180 IU/mL]: n=191) and 179 PBO-randomized patients (RF ≤Q3: n=135; RF Q4: n=44) were included. Baseline demographics were generally similar between patients with RF ≤Q3 and Q4, including number of previous DMARDs (**Table 1**).

Clinical Outcomes

- At Week 12, TNFi-naïve patients treated with CZP had lower DAS28-CRP than PBO-randomized patients regardless of RF levels, indicating no effect of RF on response to CZP (**Figure 1**).
  - In TNFi-IR patients DAS28-CRP was similar in CZP-treated patients with RF ≤Q3 and RF Q4; in PBO-randomized patients the difference was larger. There was a greater difference in DAS28-CRP between CZP- and PBO-randomized patients in those with RF Q4 compared with RF ≤Q3.
  - Responses increased to Week 36 in all CZP-randomized groups.
- Similar results were observed for CDAI (**Figure 1**).
- At Week 36, the proportions of CZP-randomized patients who achieved DAS28-CRP <2.6 and CDAI ≤2.8 were similar across RF levels and prior TNFi use (**Figure 2**).

Conclusions

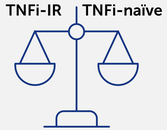
Patients with RA and high RF levels who were treated with certolizumab pegol had similar clinical responses to those with low RF levels regardless of previous TNFi treatment, indicating that RF level does not influence response to certolizumab pegol. These data support previous findings,[5] and expand them to a TNFi-IR population. Results may have treatment choice implications in patients with RA and high RF levels who have had inadequate responses to previous TNFi treatment.

Summary

The **impact of rheumatoid factor level and prior TNFi use** on efficacy outcomes over 36 weeks in patients with **rheumatoid arthritis** who received treatment with **certolizumab pegol** or placebo was assessed

Clinical response to CZP

CZP-treated patients with high RF levels experienced **similar clinical responses** to patients with lower RF levels



Clinical response to CZP

Similar clinical responses were observed with CZP treatment across RF level stratifications, **irrespective of previous TNFi use**

These findings indicate that **RF level does not influence response to CZP**, and thus support the use of CZP in patients with RA and high RF levels. Furthermore, these data **expand this notion to those with prior inadequate response to TNFis**

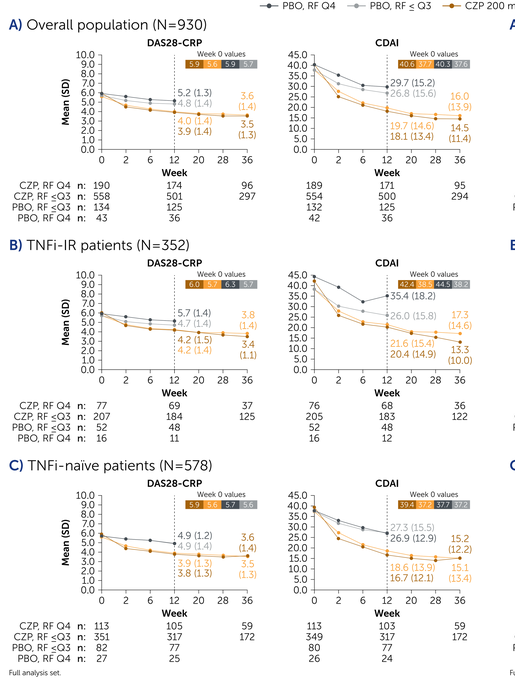
Table 1 Baseline demographics and disease characteristics, stratified by RF level and prior TNFi use

Baseline population characteristic	RF ≤Q3 (<180 IU/mL) (N=695)				RF Q4 (≥180 IU/mL) (N=235)			
	TNFi-IR (N=259)		TNFi-naïve (N=436)		TNFi-IR (N=93)		TNFi-naïve (N=142)	
	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)
Mean RF, IU/mL (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)
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)
Number of previous DMARDs, 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)
Mean DAS28-CRP (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)
Mean CDAI (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)
Mean anti-CCP (ACPA), IU/mL (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)

Full analysis set.

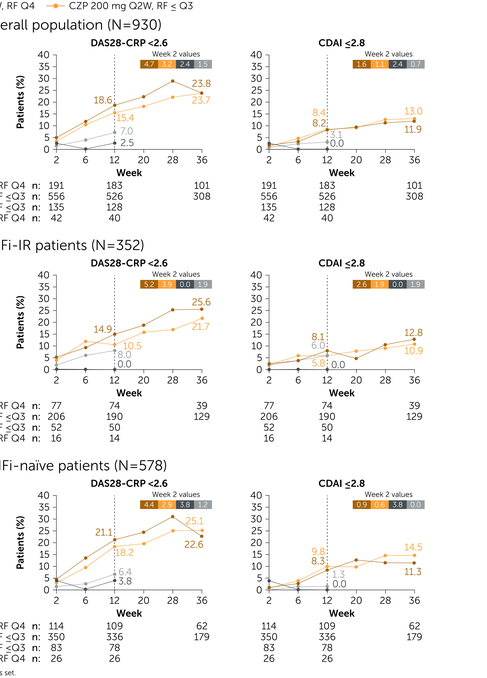
ACPA: anti-citrullinated protein antibody; **anti-CCP:** anti-cyclic citrullinated peptide; **CDAI:** clinical disease activity index; **CZP:** certolizumab pegol; **DAS28-CRP:** Disease Activity Score 28 - C-reactive protein; **DMARD:** disease-modifying antirheumatic drug; **Fc:** fragment crystallizable; **IU/mL:** international units per milliliter; **PBO:** placebo; **OC:** observed case; **≤Q3:** <4th quarter; **Q4:** 4th quarter; **RA:** rheumatoid arthritis; **RF:** rheumatoid factor; **SC:** subcutaneous; **SD:** standard deviation; **TNF:** tumor necrosis factor; **TNFi:** tumor necrosis factor inhibitor; **TNFi-IR:** prior inadequate response or intolerance to tumor necrosis factor inhibitors.

Figure 1 Mean DAS28-CRP and CDAI over time in a) overall population, b) TNFi-IR patients, and c) TNFi-naïve patients, stratified by RF level (RF ≤Q3 [<180 IU/mL] or Q4 [≥180 IU/mL]) (OC)



Full analysis set.

Figure 2 Proportions of patients achieving DAS28-CRP <2.6 and CDAI ≤2.8 in a) overall population, b) TNFi-IR patients, and c) TNFi-naïve patients, stratified by RF level (RF ≤Q3 [<180 IU/mL] or Q4 [≥180 IU/mL]) (OC)



Full analysis set.

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