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ARTICLE

Exposure–Response Relationship of Certolizumab Pegol and Achievement of Low Disease Activity and Remission in Patients With Rheumatoid Arthritis

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Anti-tumor necrosis factor (anti-TNF) drugs are often prescribed for the treatment of rheumatoid arthritis (RA) and other immune-mediated inflammatory diseases. Although this treatment has been shown to be effective in many patients, up to 40% of patients do not achieve disease control. Drug concentration in plasma may be a factor affecting the observed variability in therapeutic response. In this study, we aimed to identify the plasma concentrations of the anti-TNF certolizumab pegol (CZP), associated with improvement in disease activity in patients with RA. Data were pooled from three randomized, controlled clinical trials with a combined total of 1,935 patients analyzed. Clinical outcomes of low disease activity (LDA) and remission were defined as Disease Activity Score in 28 joints with C-reactive protein (DAS28(CRP)) ≤ 2.7 and < 2.3, respectively. Quartile analysis results indicated that there may be an exposure–response relationship between CZP concentration and LDA/remission outcomes at weeks 12 and 24; the association was strongest for LDA ($P < 0.05$). Receiver operating characteristic (ROC) analysis showed that CZP concentrations ≥ 28.0 μg/ml at week 12, and ≥ 17.6 μg/ml at week 24, were associated with a greater likelihood of achieving LDA/remission outcomes. Although confirmatory studies are warranted to define the optimal CZP therapeutic range at weeks 12 and 24, these data indicate that CZP concentrations may be associated with improvement of disease activity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Anti-tumor necrosis factor (anti-TNF) drugs are often prescribed for the treatment of immune-mediated inflammatory diseases such as rheumatoid arthritis (RA). However, although many patients achieve disease control with anti-TNFs, over one third of patients initiating these agents do not respond adequately. Part of the explanation for this may relate to drug concentrations.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study aimed to identify minimum plasma concentrations of the anti-TNF certolizumab pegol (CZP) associated with improvement of disease activity in patients with RA during treatment with approved doses of CZP.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ An association between CZP plasma concentration and clinical outcomes of low disease activity (LDA) and remission was observed. CZP concentration cutoffs of 28.0 μg/ml at week 12 and 17.6 μg/ml at week 24 were associated with a greater likelihood of achieving LDA and remission.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The results of this study suggest possible minimum CZP concentration thresholds associated with important improvements in RA disease activity. An optimal therapeutic range will depend on patients' disease characteristics and clinical goals.

Anti-tumor necrosis factor (anti-TNF) drugs have been used in clinical practice for over a decade as an effective treatment option for immune-mediated inflammatory diseases such as rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), psoriasis, and Crohn's disease (CD), using different dosing regimens and administration modes (subcutaneous and intravenous). However, the exposure–response relationship of anti-TNFs is still poorly understood. Although many patients respond well to anti-TNF therapy and are able to achieve major

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disease control and remission, up to 40% of patients either do not respond adequately or lose response by 1 year of treatment.[1–6] One factor that may explain part of the variation in response to anti-TNF treatment may be drug concentration. Several studies have shown that good responders tend to have higher blood drug concentrations than nonresponders.[1,3,7–15]

Poor compliance to therapy (particularly for subcutaneously administered anti-TNFs, which can be self-injected by patients) and the development of antidrug antibodies (ADAb) are possible explanations for subtherapeutic plasma or serum drug concentrations.[16] Neutralizing ADAb may reduce the efficacy of anti-TNFs by blocking the cytokine-binding site,[17,18] preventing drug absorption from the injection site,[19] and/or by accelerating drug clearance.[15,20–22] Varying rates of immunogenicity have been reported for anti-TNFs, depending on the drug and assay used.[16,23–26] In addition to immunogenicity, factors such as body mass index (BMI), serum albumin concentration, gender, disease activity, and concomitant methotrexate (MTX) use impact the pharmacokinetics of anti-TNFs, explaining some of the clinically relevant variability in drug concentration between individuals.[27–33]

Therapeutic drug monitoring (TDM) may be helpful for the purpose of optimizing treatment for individual patients,[6,30,34–36] and is currently recommended in CD treatment guidelines in both Europe and the US.[37,38] By contrast, in rheumatology, the utility and thus relevance of TDM in routine clinical practice remains unclear. Key obstacles to the adoption of TDM in rheumatology compared with gastroenterology include the availability of a wider range of biopharmaceuticals with different modes of action, the lack of robust evidence supporting the clinical benefits of TDM, lack of guidance with regard to the appropriate target drug concentrations, and the best timepoints for the monitoring of drug concentration, the time-consuming nature of most methods currently used to measure drug concentration, and the availability of such tests in the clinical setting.[30,39,40]

In this study we aimed to identify plasma concentrations of the anti-TNF certolizumab pegol (CZP) associated with improvement of disease activity in patients with moderate to severe RA, to help clinicians optimise CZP treatment in patients. The study used data from patients treated with approved doses of CZP in the Rheumatoid Arthritis PreventIon of structural Damage (RAPID)1 and RAPID2 randomized, controlled trials (RCTs), their respective open-label extensions (OLEs), and the EXXELERATE trial.[41–45]

MATERIALS AND METHODS

Patients

In this *post hoc* analysis, data were pooled across the RAPID1 and RAPID2 RCTs (NCT00152386/NCT00160602), their respective OLEs (NCT00175877/NCT00160641) and the EXXELERATE trial (NCT01500278).[41–45] RAPID1 and RAPID2 were the phase III pivotal studies used to evaluate the efficacy and safety of CZP in patients with RA. EXXELERATE was a head-to-head phase IV study that compared the efficacy and safety of CZP with adalimumab in patients with RA; only patients randomized to CZP who did not switch to adalimumab treatment were included in this analysis.

Patients who had received any biologic therapy within 6 months of baseline, or who had previously failed to respond to treatment with other anti-TNFs, were excluded from this analysis. As per the CZP label, all patients received a loading dose of CZP 400 mg at weeks 0, 2, and 4; this was followed by a maintenance dosing regimen of CZP 200 mg every 2 weeks (Q2W), or 400 mg Q2W (RAPID1 and RAPID2 only),[16,46] both in combination with MTX (stable doses of ≥10 mg/week equivalent; **Figure S2**). The loading dose is administered to reduce the time needed to achieve steady-state plasma concentrations of CZP and increase the likelihood of response to treatment, as shown in various clinical studies.[16,46] All study protocols and consent forms were approved by institutional review boards or ethics committees at the study sites, and studies were conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients provided written informed consent before study participation.

Measurement of plasma CZP concentration

Plasma samples were collected at baseline and immediately before each CZP administration (C_{trough}) at multiple patient visits as defined by the study protocols; all samples were frozen for storage and subsequently thawed for measurement of CZP concentration.[41–44]

In the RAPID1 and RAPID2 studies, plasma CZP concentrations were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) developed by UCB Pharma and validated according to the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) regulatory requirements for use in clinical trials.[47] All samples were measured according to the same method in the same laboratory (Covance, Chantilly, VA). In brief, microtiter plates precoated with recombinant human TNF-α were used to capture the CZP present in the plasma samples. Bound CZP was revealed with a polyclonal goat anti-human kappa light-chain antibody, labeled with horseradish peroxidase.[22] The lower limit of quantification (LLOQ) of the assay was 0.4 μg/ml; dilution linearity ensured a measurable range of 0.4–1,332.0 μg/ml.

In EXXELERATE, CZP plasma concentrations were measured using the commercially available LISA-TRACKER CZP assay according to the manufacturer's instructions (Theradiag, Marne-la-Vallée, France; available in the US as an OptimAbs assay, operated by HalioDx, Richmond, VA). The assay uses an anti-polyethylene glycol (PEG) antibody to detect CZP with an LLOQ of 3 μg/ml and has a calibration range of 3–84 μg/ml.

Disease activity outcomes

Disease activity was assessed at weeks 12 and 24 of CZP treatment using Disease Activity Score in 28 joints with C-reactive protein (DAS28(CRP)). Low disease activity (LDA) and remission were defined as DAS28(CRP) ≤ 2.7 and < 2.3, respectively.[48]

CZP exposure–response curve and quartile analysis

Exposure–response curve analyses were performed to examine the relationship between CZP concentration and improvement in disease activity. Patients were grouped according to measured plasma CZP concentration in increments of 5 μg/ml. Patients' plasma CZP concentration at week

12 was correlated with change from baseline at week 12 in DAS28(CRP); a similar analysis was performed at week 24. To evaluate the trend between CZP concentration and achievement of DAS28(CRP) LDA and remission outcomes, patients' CZP concentrations at weeks 12 and 24 were grouped into quartiles and the corresponding proportions of patients achieving the outcome in each quartile were calculated.

Statistical analysis

To evaluate DAS28(CRP) outcome trends across CZP concentration quartiles, the one-sided Cochran–Armitage trend test was employed. ROC analyses were used to identify the CZP concentration cutoffs associated with the likelihood of achieving DAS28(CRP) LDA and remission. Cutoff CZP concentration values were determined using the highest Youden index value (Youden index = sensitivity + specificity – 1) associated with ≥ 80% sensitivity. The area under the ROC curve (AUROC) was calculated with 95% confidence intervals (CI). ROC analyses were performed only on EXXELERATE data. As CZP concentrations in the EXXELERATE trial were measured using the LISA-TRACKER CZP assay, which is commercially available to healthcare professionals, these CZP concentrations cutoffs were considered more relevant to clinical practice than data obtained with the sponsor assay. All reported *P* values and CIs are nominal and can only be interpreted in an exploratory manner.

RESULTS

Patients

A total of 1,479 patients with moderate to severe, active RA were pooled across the RAPID1 and RAPID2 RCTs and OLEs. In EXXELERATE, 456 patients with RA and prognostic factors for severe disease progression randomized to CZP were included in this analysis.[45] Baseline patient characteristics are summarized in **Table 1**; all patients had moderate to high disease activity (mean (SD) DAS28(CRP): 6.1 (1.0) in RAPID1/RAPID2; 5.6 (0.9) in EXXELERATE) and received CZP in combination with MTX (≥10 mg/week equivalent).

Table 1 Baseline patient characteristics

	CZP-treated patients	
	RAPID1 and RAPID2[a] (*n* = 1,479)	**EXXELERATE[b] (*n* = 456)**
Patients randomized at start of RCTs, n (%)		
CZP 200 mg Q2W	606 (41.0%)	456 (100%)
CZP 400 mg Q2W	610 (41.2%)	NA
Placebo[c]	263 (17.8%)	NA
Female, *n* (%)	1,216 (82.2%)	359 (78.7%)
Age (years)	51.8 (11.6)	53.5 (12.3)
Disease duration (years)	6.1 (4.2)	6.0 (6.9)
Weight (kg)	73.3 (15.9)	77.9 (19.3)
BMI (kg/m^2), median (IQR)	26.2 (23.2–29.9)	28.5 (6.3)
BMI category (kg/m^2), n (%)		
<25	598 (40.4%)	160 (35.1%)
25–<30	510 (34.5%)	134 (29.4%)
≥30	366 (24.7%)	160 (35.1%)
DAS28(CRP)	6.1 (1.0)	5.6 (0.9)
HAQ-DI	1.6 (0.6)	1.5 (0.6)

Data expressed as mean (SD), unless noted otherwise, and shown for patients with available CZP concentration measurements.
ACR20, American College of Rheumatology 20% Improvement Criteria; BMI, body mass index; CZP, certolizumab pegol; DAS28(CRP), Disease Activity Score 28-joint assessment with C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; IQR, interquartile range; NA, not applicable; OLE, open-label extension; Q2W, once every 2 weeks; RCT, randomized, controlled trial; SD, standard deviation.
[a]Patients were pooled from the RAPID1 and RAPID2 randomized, controlled trials (NCT00152386, NCT00160602) and their OLE (NCT00175877, NCT00160641). [b]Patients randomized to CZP in the EXXELERATE study (NCT01500278). [c]At week 16, placebo patients with no ACR20 response at weeks 12 and 14 were withdrawn from the RAPID1/RAPID2 RCTs; some reconsented to enter the OLE and receive CZP treatment. Some placebo completers also reconsented to enter the OLE and receive CZP.

Measured exposure–response curves

Figure 1 shows the relationship between CZP plasma concentration and change in DAS28(CRP) from baseline in patients with RA from RAPID1/RAPID2 (**Figure 1a**) and EXXELERATE (**Figure 1b**). In RAPID1/RAPID2 (representing > 2,500 analyzable samples measured with the sponsor's ELISA), the median (interquartile range (IQR)) CZP concentration for the pooled population was 28.8 (20.3–48.6) μg/ml at week 12 and 28.5 (19.4–45.7) μg/ml at week 24 (**Table 2**). For the EXXELERATE population (using the commercial LISA-TRACKER CZP assay), median (IQR) CZP concentration was 42.4 (31.2–56.8) μg/ml at week 12 and 38.4 (28.0–50.4) μg/ml at week 24 (**Table 2**). For both data sets, the CZP exposure–response relationship varied among patients. Plasma CZP concentrations < 10 μg/mL were generally associated with smaller improvements from baseline in DAS28(CRP) compared with patients with higher CZP concentrations. A plateau effect in DAS28(CRP) response was apparent at higher CZP concentrations (**Figure 1**), but a maximum level was not defined in this analysis. The approximate ranges of CZP concentrations including the highest number of patients were 20–35 μg/ml in RAPID1/RAPID2 and 25–50 μg/ml in EXXELERATE (**Figure 1**).

Quartile analysis

The relationship between CZP plasma concentration quartiles and DAS28(CRP) LDA/remission outcomes was analyzed at weeks 12 and 24 (**Figure 2**). At week 24, there was evidence of an association between CZP concentration and DAS28(CRP) LDA in both RAPID1/RAPID2 (*P* = 0.0098) and EXXELERATE data sets (*P* = 0.0483), with the highest proportion of patients achieving LDA for CZP plasma concentrations > 26.1 μg/ml in RAPID1/RAPID2 and > 50.4 μg/ml in EXXELERATE. A numerically greater proportion of patients with CZP concentrations above the upper quartile (Q3) achieved DAS28(CRP) LDA compared with those with concentrations below the lower quartile (Q1) (**Figure 2b**). Similar trends were observed at week 12, although the association was weaker (RAPID1/RAPID2: *P* = 0.0177; EXXELERATE: *P* = 0.1579) (**Figure 2a**). The exposure–response relationship was less consistent for DAS28(CRP) remission at both timepoints, although differences between CZP concentrations > Q3 and < Q1 were

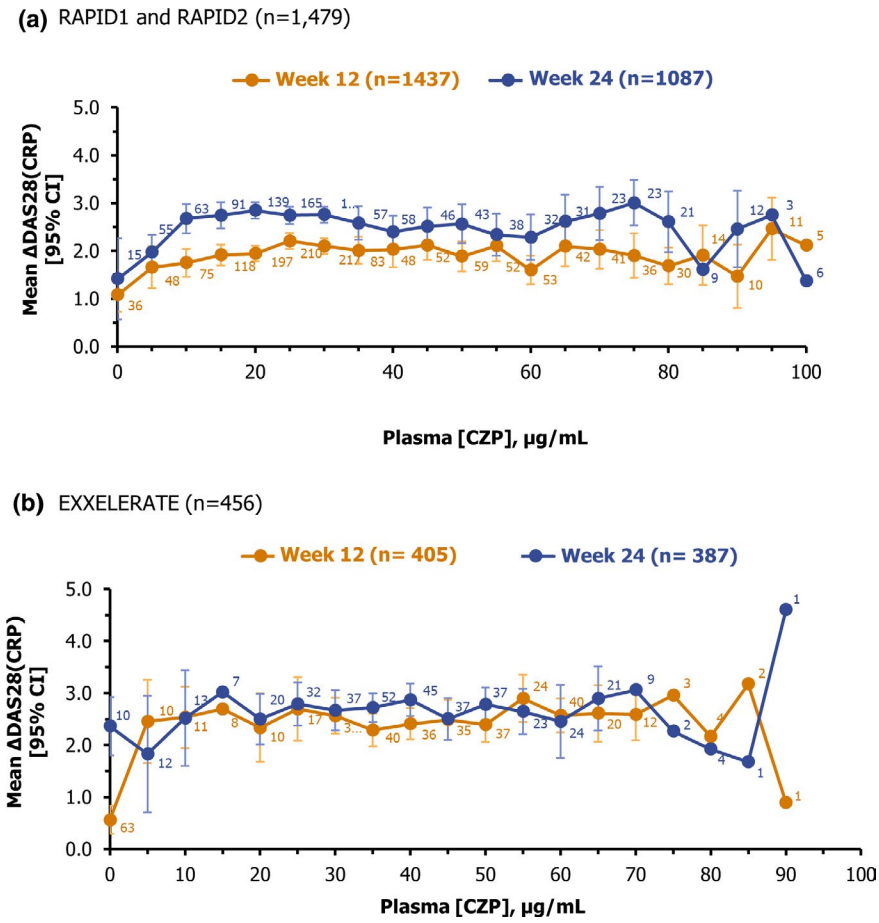

Figure 1 Exposure–response curve of CZP vs. change from baseline in DAS28(CRP) at weeks 12 and 24. (**a**) RAPID1 and RAPID2 (*n* = 1,479). (**b**) EXXELERATE (n = 456). Patients' CZP concentrations were grouped to the nearest 5 μg/ml; the number of patients is shown next to each data point. Error bars correspond to 95% confidence intervals. For data points corresponding to < 10 patients, confidence intervals are not shown. Patients with CZP concentration > 100 μg/ml were excluded from the analysis (RAPID1 and RAPID2 only; excluded patients: 26 of 1,438 at week 12 and 22 of 1,087 at week 24). CI, confidence interval; CZP, certolizumab pegol; ΔDAS28(CRP), change from baseline in Disease Activity Score 28-joint assessment with C-reactive protein.

Table 2 Summary of observed CZP plasma concentrations

			CZP concentration (μg/ml)	
Study	**Week**	***n***	**Geometric mean**	**Median (IQR)**
RAPID1 + RAPID2	12	1,482	27.3	28.8 (20.3–48.6)
	24	1,122	27.1	28.5 (19.4–45.7)
EXXELERATE	12	424	34.0	42.4 (31.2–56.8)
	24	343	31.9	38.4 (28.0–50.4)

CZP, certolizumab pegol; IQR, interquartile range.

still observed. The strongest association was observed in the EXXELERATE data set (week 12: $P = 0.0185$; week 24: $P = 0.0112$) (**Figure 2c,d**).

ROC analyses

EXXELERATE data showed similar AUROC values (varying between 0.54 and 0.59) for CZP concentration across all tested conditions; that is, DAS28(CRP) LDA and remission at weeks 12 and 24. CZP concentration thresholds of at least 28.0 μg/ml (sensitivity: 86.0%; specificity: 20.2%) at week 12 and 23.2 μg/ml (sensitivity: 89.6%; specificity: 19.7%) at week 24 were associated with achievement of DAS28(CRP) remission at these timepoints (**Table 3** and **Figure S1**). CZP thresholds of 30.4 μg/ml (sensitivity: 80.0%; specificity: 24.2%) at week 12 and 17.6 μg/ml (sensitivity: 93.3%; specificity: 17.0%) at week 24 were associated with achievement of DAS28(CRP) LDA. As indicated by the negative predictive values (**Table 3**), ~ 50% of patients with CZP concentrations below the reported cutoff values for DAS28(CRP) LDA did not achieve this outcome (week 12: 47.4%; week 24: 55.9%).

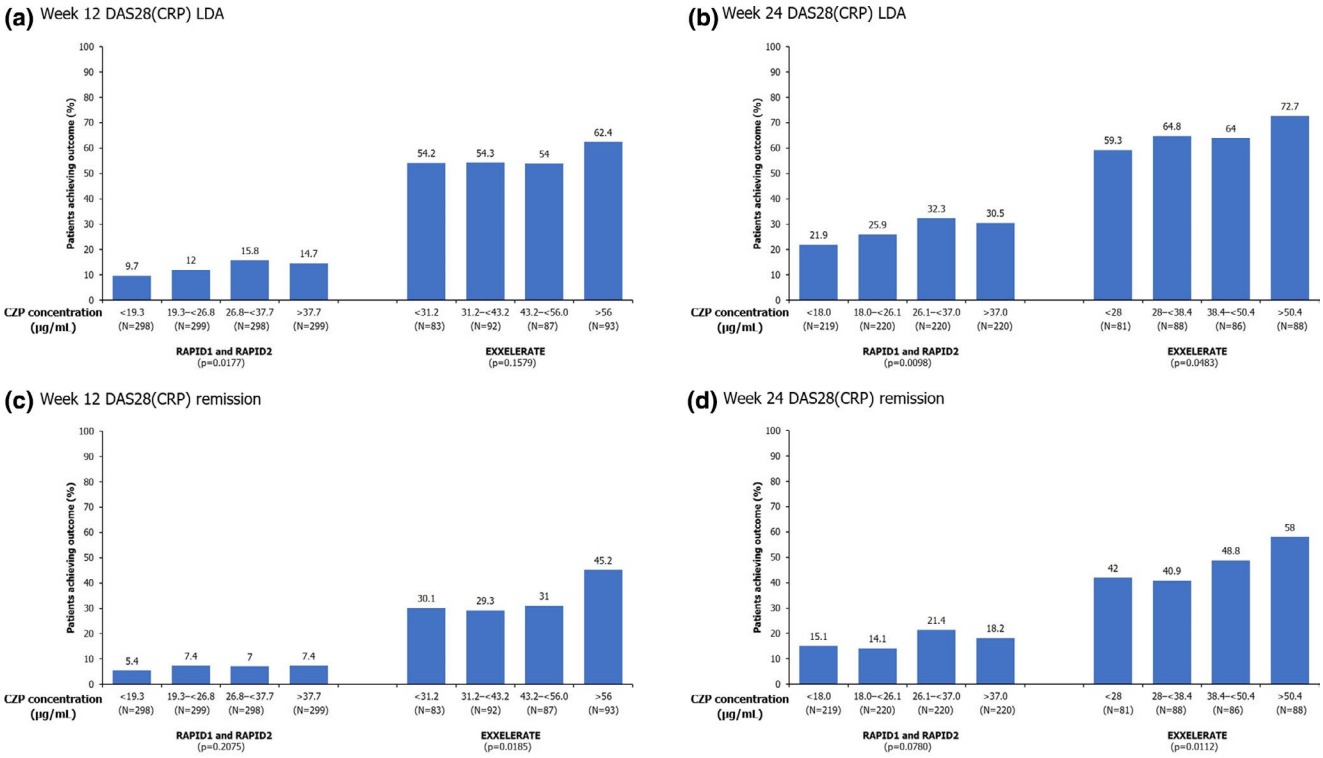

Figure 2 CZP concentration quartile analyses of DAS28(CRP) remission or LDA. (**a**) Week 12 DAS28(CRP) LDA. (**b**) Week 24 DAS28(CRP) LDA. (**c**) Week 12 DAS28(CRP) remission. (**d**) Week 24 DAS28(CRP) remission. Patients were grouped according to CZP concentration (µg/ml) quartile, as detailed on the *X* axis. Note that disease activity in the original EXXELERATE publication was reported as DAS28(ESR).[45] CZP, certolizumab pegol; DAS28(CRP), Disease Activity Score 28-joint assessment with C-reactive protein; ESR, erythrocyte sedimentation rate; LDA, low disease activity.

Table 3 Summary of ROC analyses in EXXELERATE (CZP-randomized patients)

Outcome	Week	AUROC (95% CI)	CZP cutoff point[a] (µg/ml)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
DAS28(CRP) remission	12	0.58 (0.51–0.64)	28.0	86.0	20.2	36.4	73.0
DAS28(CRP) LDA	12	0.54 (0.47– 0.60)	30.4	80.0	24.2	58.6	47.4
DAS28(CRP) remission	24	0.59 (0.53– 0.65)	23.2	89.6	19.7	51.2	66.7
DAS28(CRP) LDA	24	0.57 (0.51– 0.64)	17.6	93.3	17.0	69.2	55.9

Data shown are for CZP-randomized patients only.
AUROC, area under the receiver operating characteristic curve; CI, confidence interval; CZP, certolizumab pegol; DAS28(CRP), Disease Activity Score in 28 joints with C-reactive protein; LDA, low disease activity; ROC, receiver operating characteristic.
[a]CZP concentration linked to the highest Youden index value associated with ≥ 80% sensitivity.

Similarly, ~ 70% of patients with CZP concentrations below the cutoff values for DAS28(CRP) remission did not achieve this outcome (week 12: 73.0%; week 24: 66.7%).

DISCUSSION

Maintaining patients with immune-mediated inflammatory diseases in LDA or remission is becoming an increasingly realistic target. Our findings indicate that monitoring plasma CZP concentration may help to guide treatment strategies and potentially achieve better clinical outcomes for some patients. Based on data from three clinical trials of CZP, drug concentrations measured in plasma using two different assays were used to characterize the exposure–response relationship of CZP in patients with RA. These data included a large data set pooled across two RCTs (RAPID1 and RAPID2) and their respective OLEs, measured with the enzyme-linked immunoassay developed in-house by the sponsor, and a data set from the EXXELERATE study, measured with the commercial LISA-TRACKER CZP assay.[41–45]

The exposure–response curves and quartile analyses indicate that there may be an association between CZP concentration and DAS28(CRP) outcomes. CZP plasma concentrations below Q1 generally corresponded to smaller improvements in DAS28(CRP) from baseline (especially at CZP concentrations of < 10 µg/ml) and a lower proportion

of patients achieving DAS28(CRP) LDA and remission compared with patients with CZP concentrations in the upper quartile. A plateau effect was observed at higher CZP concentrations, but the maximum concentration associated with therapeutic benefit was not defined here; this would require the analysis of safety data in addition to efficacy outcomes, which was beyond the objective of this study. Future studies could employ methodologies such as population pharmacokinetic–pharmacodynamic analyses to further investigate the relationship between plasma CZP concentrations and disease activity in patients with RA. Furthermore, across the three studies, some patients had undetectable plasma CZP levels at weeks 12 and 24, which may reflect the presence of neutralizing ADAb. However, examination of immunogenicity was not within the scope of this analysis.

Based on the ROC analysis of EXXELERATE data (measured with the LISA-TRACKER assay), CZP concentrations ≥ 28.0 μg/ml at week 12 were associated with a greater likelihood of achieving DAS28(CRP) LDA and remission outcomes. At week 24, CZP concentrations ≥ 17.6 μg/ml were associated with LDA/remission outcomes. The lower thresholds observed for CZP at week 24 suggest that the effect of the loading dose (CZP 400 mg at weeks 0, 2, and 4, leading to higher trough concentrations) was still detected at week 12. The cutoff value associated with an increased likelihood of DAS28(CRP) LDA/remission outcomes at week 12 falls within the range of CZP concentrations that were most frequently recorded in patients in the EXXELERATE trial (25–50 μg/ml). Furthermore, these cutoff values are also in line with recent data from the Norwegian Antirheumatic Drug Register (NOR-DMARD)—based on a cohort of 110 patients with axSpA and another cohort of 81 patients with RA, serum CZP concentrations ≥ 20 μg/ml in both indications were associated with greater improvements in disease activity at 3 months of treatment.[49,50]

Although drug concentration assessment is widely recommended in the treatment of CD,[37,38] in rheumatology, there is still a lack of guidance on the drug-specific anti-TNF concentrations needed to achieve specific clinical targets.[39] Current treatment guidelines in RA recommend that patients who fail to respond to one anti-TNF be switched either to another anti-TNF drug or to an alternative biologic agent with a different mechanism of action.[51,52] However, several studies examining the exposure–response relationship of infliximab,[1,12–15,53–56] adalimumab,[3,11,15] and etanercept,[7,9] have demonstrated that good responders tend to have significantly higher plasma drug concentrations than nonresponders and moderate responders. Moreover, findings from recent studies in patients with axSpA, PsA, and RA suggest that failure to respond to anti-TNFs may be at least partially linked to immunogenicity.[53,57–59] This evidence supports the argument that the clinical effect of anti-TNFs may be concentration-dependent for some patients, and therefore some nonresponders who have subtherapeutic drug concentrations may benefit from a change in dose rather than an immediate switch to a different biologic. If patients have low drug concentrations, it is important to examine potentially relevant factors, such as compliance to treatment and, possibly, the presence of ADAb, among other factors.[60]

Drug dosing to achieve a defined target concentration should be performed in the context of each patient's individual circumstances. The present analysis did not adjust for factors other than CZP plasma concentration that may affect response to CZP treatment. However, previous studies using data from phase III and IV trials of CZP in patients with RA have shown that factors such as early nonresponse to treatment and comorbidities can decrease the likelihood of achieving therapeutic response.[61–63] Therefore, these and other patient characteristics, such as disease activity, concomitant immunosuppressive medications, as well as expected individual therapeutic aims (including prevention of flares, improved disease control, or remission), must be considered collectively when planning to adjust drug dosing to achieve a specific clinical effect.[64]

One of the strengths of the present study was the use of a large and comprehensive data set of CZP clinical studies. Analysis of the exposure–response relationship of anti-TNFs requires large data sets, the availability of standardized, validated assays, and controlled timing of blood sampling. This was the case here and in a previous exposure–response analysis performed on data from nine clinical trials of CZP in patients with CD, where CZP concentration was measured with the same sponsor assay used in the RAPID1 and RAPID2 studies, and a similar ROC analysis approach was used to define the CZP concentration thresholds associated with clinically important outcomes.[31] In addition, the fact that the EXXELERATE trial included an adalimumab comparator arm allowed us to further validate the approach used to define the CZP concentration thresholds in RA. Because the potential therapeutic range of adalimumab concentration in RA has been suggested in previous work,[11] the ROC analysis was also performed on EXXELERATE adalimumab data, providing similar results to those previously published (data not shown).

However, there were limitations to this study. First, CZP measurements given by the sponsor's ELISA for RAPID1/RAPID2 samples were, on average, ~ 25–30% lower than CZP measurements given by the LISA-TRACKER assay for EXXELERATE samples. This discrepancy may be due to intrinsic differences between the two assays; for instance, although the sponsor's ELISA uses an anti-human kappa light-chain antibody to detect CZP, the commercial LISA-TRACKER assay uses an anti-PEG antibody. Notably, the proportion of patients achieving LDA or remission outcomes at weeks 12 and 24 was higher for the EXXELERATE cohort analyzed here than for the RAPID1/RAPID2 population. Differences in study design may account for this finding—in EXXELERATE, patients who did not achieve DAS28-erythrocyte sedimentation rate (DAS28(ESR)) LDA (DAS28(ESR) ≤3.2) or a DAS28(ESR) reduction from baseline ≥ 1.2 after 12 weeks of CZP treatment were switched to adalimumab, and were therefore not included in the present analysis.[41,43,45] This may also explain why the exposure–response curves for EXXELERATE at weeks 12 and 24 had a similar plateau level in terms of change from baseline in DAS28(CRP) (**Figure 1b**), whereas the magnitude of DAS28(CRP)

improvement in RAPID1/RAPID2 was noticeably lower at week 12 compared with week 24 (**Figure 1a**). Finally, although our results suggest a possible exposure–response relationship for CZP, the current *post hoc* analysis did not allow for the evaluation of causality.

Although CZP concentrations associated with an increased likelihood of achieving DAS28(CRP) LDA and remission outcomes were identified in this study, it is important to highlight that the specificity levels for these values were low (< 25%). The use of these thresholds may contribute to identifying patients who are unlikely to respond to treatment, but a large proportion of nonresponders may still be missed using this method.

In the RAPID1, RAPID2, and EXXELERATE studies, CZP concentrations were measured in plasma. However, it may be easier and more reliable to measure CZP concentration in serum samples, to avoid potential interference from other blood proteins, such as clotting factors. Until recently, measuring drug concentrations was a time-consuming process, which limited the utility of such data for therapeutic decision making.[40] Recent technological advances may offer the possibility to assess drug concentrations in a matter of minutes, instead of weeks, using rapid assays at point of care.[65–67] This will allow clinicians to decide whether to modify or optimize treatment within a much shorter timeframe, and for a fraction of the cost of currently available assays, potentially improving the accessibility and implementation of TDM in clinical practice.[68]

In conclusion, the trends in CZP exposure–response described in this study suggest that further investigation into this relationship may provide clinicians with an additional tool for the approach to optimal treatment of patients with RA. Although an optimal therapeutic range will ultimately depend on patients' disease characteristics and desired clinical goals, the results of this study indicate that CZP concentrations ≥ 28.0 μg/ml at week 12 and ≥ 17.6 μg/ml at week 24 may be associated with a greater likelihood of achieving LDA/remission outcomes. Although confirmatory studies are warranted to define the optimal CZP therapeutic range at these timepoints, our findings indicate that CZP concentrations may be associated with improvement of disease activity.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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