Certolizumab Trough Levels and Antibodies in Crohn Disease: A Single-Center Experience

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Background: Certolizumab pegol (CZP) has been successfully used for the treatment of Crohn disease (CD); however, real-world data regarding the utility of CZP trough levels (CTLs) are lacking. We aimed to correlate CTL with CD outcomes and to determine frequency of CZP antibodies.

Methods: Retrospective evaluation of all CD patients on maintenance CZP with CTL obtained between 2016 and 2019. Outcomes included: median CTL, presence of anti-CZP antibodies, biochemical response (BR), clinical response (CR), radiologic response (RR), radiologic healing (RH), and mucosal healing (MH).

Results: Seventy-seven CD patients were included. Median CTL was 18.9 µg/mL (interquartile range, 7.6–35.4). Twenty-three patients (27.3%) had positive antibody levels, with lower median CTL compared to patients with no antibodies (0.0 vs 29.8; $P < 0.0001$). Median CTL levels were higher in patients with vs without CR (30.4 vs 10.3 µg/mL; $P = 0.0015$) and RR (29.6 vs 5.8 µg/mL; $P = 0.006$). CZP dosing at least every 2 weeks was associated with higher odds of achieving MH (odds ratio, 3.2; 95% confidence interval, 1.03–9.97). CTL resulted in change in clinical management in 62.7% of cases and presence of CMZ antibodies was associated with an odds ratio of 5.83 (95% confidence interval, 1.57–21.73) of change in management. Receiver operating characteristic curve and quartile analysis suggested that CTL >19 µg/mL is associated with increased rates of CR and RR.

Conclusions: Higher CTL was significantly associated with CR and RR. The rate of CZP antibodies was 27.3%. Our data suggest maintenance CTL of ≥19 µg/mL should be achieved in order to optimize outcomes in clinical practice.

Received for publications December 3, 2020; Editorial Decision January 26, 2021.

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Funding: None.

Conflict of Interest: Dr Edward V. Loftus has consulted for AbbVie, Allergan, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Calibr, Celgene, Celltrion Healthcare, Eli Lilly, Genentech, Gilead, Iterative Scopes, Janssen, Ono Pharma, Pfizer, Takeda, and UCB. Dr Loftus has received research support from Takeda, Janssen, AbbVie, UCB, Amgen, Pfizer, Celgene, Receptos, Genentech, Gilead, Robarts Clinical Trials, Theravance, and Bristol-Myers Squibb. He is a shareholder in Exact Sciences. Dr Sunanda Kane has consulted for Gilead, honorarium paid to Mayo Clinic. Dr John B. Kisiel is an inventor of intellectual property licensed to Exact Sciences (Madison, WI) and may receive royalties. Dr Konstantinos A. Papadakis is a stock shareholder in Amgen, Johnson and Johnson, Abbott Laboratories, and Medtronic. Dr David H. Bruining has consulted for Medtronics. Research support from Takeda and Medtronics. Dr Valérie Heron has served on the advisory board for Janssen, AbbVie, and Ferring and has served as a speaker for AbbVie and Pendopharm. The rest of the authors have no relevant disclosures.

Author Contribution: Guilherme Piovezani Ramos: original concept, study design, data abstraction, manuscript draft, review, and editing. Badr Al-Bawardy: study design, manuscript draft, and final revision. Manuel Bonfim Braga Neto: manuscript draft and final revision; Maria Alice V. Willrich, Adam C. Bledsoe, Kevin P. Quinn, and Valérie Heron: data abstraction, manuscript review, and editing. Amanda Johnson, Victor G. Chedid, Nayantara Coelho-Prabhu, John B. Kisiel, Konstantinos A. Papadakis, Darrell Pardi, Sunanda V. Kane, Laura Raffals, David H. Bruining, William A. Faubion, and William J. Tremaine: manuscript review and editing. William S. Harmsen: statistical analysis and critical review of the manuscript. Edward V. Loftus, Jr: original concept, study design, manuscript review, and final editing.

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doi: 10.1093/crocol/otab019
Published online 17 May 2021

Lay Summary

Measuring blood levels of certolizumab pegol may improve control of Crohn disease. One third of patients receiving this medication have developed antibodies against it, resulting in lower circulating drug levels. A level >19 µg/mL was associated with better treatment results.

Key Words: therapeutic drug monitoring, inflammatory bowel disease, Crohn disease, certolizumab pegol

INTRODUCTION

Inflammatory bowel diseases (IBDs), encompassing Crohn disease (CD) and ulcerative colitis, are chronic inflammatory conditions that can result in impairment of quality of life, frequent hospitalizations, and the need for surgery. The treatment goals of IBD include, but are not limited to, corticosteroid-free clinical remission and mucosal healing (MH).[1] The advent of biologic therapies has revolutionized the management of IBD. However, a significant proportion of IBD patients will lose response to biologics, which include anti-tumor necrosis factor (anti-TNF) agents, anti-integrins, or anti-interleukins. For example, the annual rate of loss of response to infliximab has been estimated to be as high as 12%.[2] This loss of response can be attributed to either pharmacodynamic factors (such as alternate inflammatory pathway) or pharmacokinetics (such as low drug levels).[3] Therapeutic drug monitoring (TDM) has been employed to address the pharmacokinetics of loss of response. It allows for measurement of drug level and detection of antidrug antibodies (ADAs). TDM has become an integral part of IBD management. Societal guidelines and consensus statements have endorsed TDM compared to empiric dose escalation.[4,5] Overwhelming evidence exists to support the correlation between infliximab and adalimumab drug levels with clinical remission, inflammatory marker normalization, and MH.[6–11]

Certolizumab pegol (CZP) is a humanized anti-TNF biologic that was approved by the FDA in 2008 for the treatment of CD. Early pivotal clinical trials have demonstrated its efficacy and safety in CD.[12,13] The long-term effectiveness of CZP has also been demonstrated in multiple subsequent trials and case series.[14–16] The real-world clinical impact of measuring the trough serum levels of CZP is less understood than with other anti-TNF agents such as infliximab and adalimumab. Post hoc analysis of the endoscopic mucosal Improvement in patients with active CD treated with CZP (MUSIC) trial showed that higher trough levels of CZP were associated with endoscopic response and remission.[17] The American Gastroenterology Guidelines on TDM in IBD recommended a CZP threshold maintenance level of ≥20 µg/mL.[4] This level was obtained from pooled analysis of 9 trials compromising >2000 patients. Nevertheless, real-world clinical data regarding the utility of CZP trough levels (CTLs) and correlation with clinical and endoscopic findings remain lacking. Furthermore, even though the presence of anti-TNF ADA has been shown to result in lower serum drug levels, data on the impact of anti-CZP drug antibodies on serum levels are lacking.[18–20]

This study aims to determine: (1) the median CTL and frequency of anti-CZP ADA in a group of CD patients treated with CZP in clinical practice; (2) the correlation of CTL with C-reactive protein (CRP), symptom response, MH, and radiologic healing (RH); and (3) the change in clinical management based on CTL.

MATERIALS AND METHODS

Inclusion Criteria and Data Abstraction

We performed a retrospective evaluation of all CD patients treated with CZP at Mayo Clinic in Rochester, Minnesota, between October 2016 and October 2019. CD patients on maintenance therapy with CZP who had CTL assessed were included in the study. Patients on induction therapy with CZP (ie, within 4 weeks of initiation) or in whom CTL were not obtained during maintenance were excluded from the study. Patients completed induction with CZP and received maintenance dosing of either 400 mg subcutaneously every 4 weeks or 200 mg every 2 weeks. Data were abstracted for demographics, smoking status, and IBD disease and management details. Data on previous biologic use (infliximab, adalimumab, CZP, vedolizumab, natalizumab, ustekinumab) and previous surgeries were collected. History of ADA development was obtained and defined as either presence of laboratory findings or comments in clinical notes mentioning prior history of ADA. Current use of combination therapy (azathioprine, 6-mercaptoprine, or methotrexate) and corticosteroid therapy (prednisone and budesonide) was noted. Endoscopic data were collected if performed within 3 months of the CTL. CRP data were collected if it was performed within 30 days of the CTL.

CTL was measured using automated enzyme-linked immunosorbent assay (ELISA) using reagents from Theradiag (Croissy Beaubourg, France) at the reference laboratory InformTX (Phoenix, AZ) for both the drug quantitation and a simultaneous evaluation for anti-CZP antibodies. The ELISA assay used for CZP concentration has an upper limit of quantitation of 84 µg/mL. For anti-CZP antibodies, the analytical measurable range of the ELISA ranges from 10 to 160 AU/mL in a drug-sensitive approach. Results below this range are reported as negative, or antibodies not detected. Any detectable signal is considered positive for antibodies-to-CZP (antibodies detected).

Outcomes

Primary outcomes included median CTL in the cohort and presence of anti-CZP ADA. Secondary outcomes

were based on median CTL associated with: biochemical response (BR), defined as CRP <8 mg/dL; radiologic response (RR), defined as improvement per radiology impression on CT enterography and/or MR enterography; RH, defined as absence of inflammation on CT enterography and/or MR enterography imaging; clinical response (CR), defined as improvement in reported symptoms; and MH, defined as absence of mucosal ulcers in CD. RR and RH were defined based on objective criteria previously described.[21] Deep remission (DR) was defined as achieving both MH and CR.

Statistical Analysis

Descriptive statistics were summarized with medians and ranges for continuous variables and as frequencies and percentages for categorical variables. The correlations between CTL and albumin as well as body mass index (BMI) were estimated using the Spearman rank correlation. *R* values were interpreted based on previously established guidelines.[22] Logistic regression models were used to assess univariate associations between CTL (dependent variable) and patient characteristics (independent variables). Results were reported as odds ratio (OR) and 95% confidence interval (CI). Receiver operator characteristic (ROC) curves were displayed for the outcomes of CR and RR for the measurement variable of CTL. Cut-points for CTL for each of these 3 outcomes were reported, choosing cut-points to maximize the sum of sensitivity and specificity. The area under the ROC curve was reported for CTL. *P* values less than 0.05 were considered statistically significant. Analyses were done using SAS version 9.4 (SAS Institute, Inc., Cary, NC), and figures were generated using R (version 3.6.2).[23]

Ethical Considerations

The study protocol was approved by the Mayo Clinic Institutional Review Board (IRB # 17-001945).

RESULTS

Baseline Characteristics

A total of 77 CD patients were included in the study. The median age was 40 years (interquartile range, 33–56) and 58.4% were females. CZP was administered every 4 weeks in 57.1% of the cohort (n = 44) and every 2 weeks in 42.9% (n = 33). Table 1 summarizes baseline characteristics including disease phenotype, prior medications, previous surgeries, and CZP dosing.

CTL and Antibodies

The overall median CTL was 18.9 µg/mL (interquartile range, 7.6–35.4). In patients receiving CZP every 2 weeks the median level was 28.7 vs 13.4 µg/mL in every 4 weeks ($P = 0.12$). A small correlation between CTL and albumin levels was noted ($r = 0.23$, $P = 0.15$). Conversely, CTL had a small inverse correlation with BMI ($r = -0.20$, $P = 0.08$).

TABLE 1. Demographic, Disease, and Therapy Characteristics

	Entire Cohort (n = 77)
Age, years	40 (33–56)
Female	45 (58.4%)
BMI, kg/m^2	25 (22–29)
Albumin level, g/dL	4.2 (3.6–4.3)
Smoking	7 (9.1%)
Disease duration, years	16 (9–28)
CD phenotype	
Terminal ileum	9 (11.7%)
Colon	12 (15.6%)
Ileocolonic	52 (67.5%)
Upper GI	4 (5.2%)
Inflammatory	22 (28.6%)
Stricturing	20 (26%)
Penetrating	35 (45.4%)
Perianal disease	33 (42.8%)
CZP dosing	
Every 4 weeks or more	44 (57.1%)
Every 2 weeks or less	33 (42.9%)
Concomitant IMM therapy	23 (29.9%)
History of intestinal surgery	52 (67.5%)
History of prior biologic use	60 (77.9%)
History of ADAs	11 (14.3%)

Data are given as n (%) or median (interquartile ranges).

Twenty-one patients (27.3%) had positive antibody levels (Table 2). The presence of antibodies was associated with a lower median CTL compared to patients with no antibodies (0.0 vs 29.8; $P < 0.0001$). The differences in median CTL (29.4 vs 14.4 µg/mL; $P = 0.19$) and anti-CZP antibody development (17.4% vs 31.5%; $P = 0.20$) between patients with and without concomitant immunomodulator (IMM) were not statistically significant (Fig. 1). The highest concentration of CZP at which an anti-CZP was found to be positive was 5.7 µg/mL in patients without an IMM, and 43.3 µg/mL in patients with IMM. Even though the majority of the cohort had been on other biologics prior to CZP (60/77) only 18% (11/60) had history of prior ADA. Neither prior biologic ($P = 0.46$) nor ADA ($P = 0.40$) history were associated with CZP antibody development.

Ideal CTL Threshold

Higher CTL was associated with CR ($P = 0015$) and RR ($P = 0.006$). Quartile CZP analysis per outcome is summarized in Table 3. Associations between CTL and MH ($P = 0.38$) or RH ($P = 0.10$) were not statistically significant. For every 1 µg/mL increase in CTL, the odds of CR increased by 4.5% (OR, 1.045; 95% CI, 1.02–1.07) and RR by 6.7% (OR, 1.067; 95%

TABLE 2. CTLs and Clinical Outcomes

	Entire Cohort (n = 77)
CZP levels, µg/mL	18.9 (7.6–35.4)
Positive CZP antibody	21 (27.3%)
CRP, mg/L	8.9 (3.5–22.4)*
MH on endoscopy	20/51 (39.2%)
RH	14/46 (30.4%)
RR	22/45 (48.9%)
CR	39/77 (50.6%)
DR	15/51 (29.4%)
Change in management based on level	47 (61.0%)
Increased dose	18 (23.4%)
IMM added	2 (2.6%)
Drug discontinued	27 (35.0%)

MH, mucosal healing; RH, radiologic healing; RR, radiologic response; CR, clinical response; DR, deep remission.
Data are given as n (%) or median (interquartile ranges).
*CRP data were available in 57 patients.

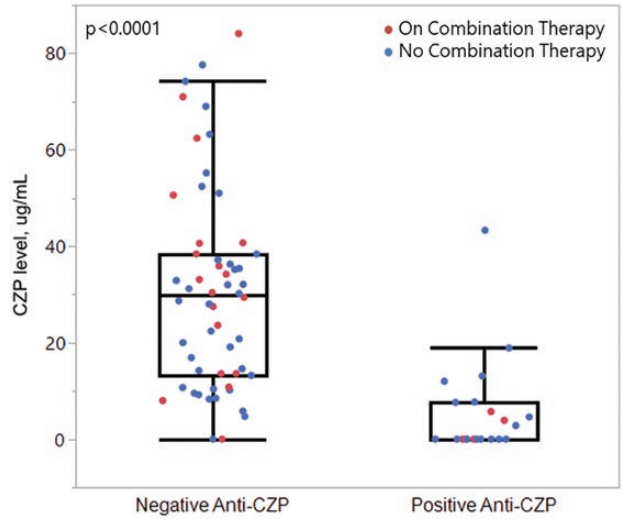

FIGURE 1. CTLs and anticertolizumab antibodies. Box plots comparing CTL between patients who developed or not anti-CZP antibodies ($P > 0.0001$). Boxes reflect median and outlier ranges. Scattered dots represent patients in each group receiving (red) or not (blue) combination therapy with IMMs. No statistically significant difference was seen on CTL ($P = 0.19$) and anti-CZP antibody development ($P = 0.20$) comparing patients with and without IMM use.

CI, 1.02–1.12). As demonstrated in Figure 2, the ROC curve demonstrated that CTL predicted CR with an area under the curve of 0.73 (95% CI, 0.62–0.84). Similar results were seen with CTL and RR with an area under the curve of 0.83 (95% CI, 0.71–0.95). The following cut-points to maximize the sum of sensitivity and specificity were identified for each outcome: CR, 18.9 µg/mL, sensitivity 69.2% and specificity 71.1%; and RR, 10.8 µg/mL, sensitivity 81.8% and specificity 73.9%.

CTL and Clinical Management

Biochemical response data were available in 57 patients (65%). Patients with a CRP ≤3 mg/dL had a numerically higher but nonsignificant median CTL of 33.2 µg/mL compared to 10.8 µg/mL in those with a higher CRP ($P = 0.07$). CRP and clinical outcomes are summarized in Table 2.

CR was obtained from clinical notes in all patients in the cohort. CR was achieved in 50.6% of the cohort (Fig. 3A). Median CTL was significantly higher in patients who achieved CR as compared to those that did not (30.4 vs 10.3 µg/mL; $P = 0.0015$). Greater than or equal to the median CTL (19 µg/mL) was associated with an OR of 5.5 (95% CI, 2.08–14.67) of achieving CR, whereas the presence of anti-CZP antibodies was associated with a 80% reduction in the odds of achieving CR (OR, 0.20; 95% CI, 0.06–0.63) (Table 4). CTL resulted in a change in clinical management in 61% of cases ($P = 0.0002$): increase in dose frequency (n = 18), addition of an IMM (n = 2), and discontinuation of CZP (n = 27). The presence of anti-CZP antibodies was associated with an OR of 5.6 ($P = 0.01$) for change in management. Greater than or equal to median CTL was associated with a 92% reduction of odds of changes in clinical management (OR, 0.08; $P < 0.0001$) (Table 4). Univariate analyses per outcome are summarized in Supplementary Table 1.

CTL and Mucosal Healing

MH data were available in 51 patients (66.2% of cohort). MH was achieved in 39.2% of patients. Median CTL was 27.8 and 12.0 µg/mL in patients with and without MH, respectively ($P = 0.38$) (Fig. 3B). CZP dosing every 2 weeks or more frequently was associated with MH (OR, 3.51; 95% CI, 1.07–11.59) (Table 4). DR, defined as achieving both MH and CR, was present in 29.4% (15/51) of the cohort. No statistically significant difference was seen comparing CTL in patients that achieved or not DR (28.0 vs 11.4; $P = 0.27$).

CTL and Radiologic Findings

Radiologic findings were available in 46 patients (59.7%). One patient had no prior imaging exam for RR comparison. RR was achieved in 48.9% and RH was achieved in 30.4% of the cohort. Median CTL levels were significantly higher in patients with RR compared to those without RR (29.6 vs 5.8 µg/mL; $P = 0.006$). The same difference was not statistically significant in patients with RH or not (29.6 vs 10.3 µg/mL; $P = 0.10$) (Fig. 3C, D). Table 4 summarizes predictors positively and negatively impacting the odds of achieving RR. Male gender was associated with an 87% reduction in the odds of achieving RH and 81% reduction in achieving RR (Table 4). Other predictors associated with reduced odds of achieving RR included: age >40 years (OR, 0.25; 95% CI, 0.07–0.86), above the median (19 µg/mL) CTL (OR, 10.18; 95% CI, 2.5–41.39), and presence of anti-CZP antibodies (OR, 0.19; 95% CI, 0.04–0.80).

TABLE 3. CTL Quartile Analysis per Outcome

% (No. Patients)	Q1 (<7.5 µg/mL)	Q2 (7.51–19.0)	Q3 (19.01–35.4)	Q4 (>35.4)	*P*
CR	31.6 (6/19)	30.0 (6/20)	68.4 (13/19)	73.7 (14/19)	0.0080*
Changes in management	89.5 (17/19)	85 (17/20)	36.8 (7/19)	31.6 (6/19)	0.0003*
MH	25.0 (3/12)	37.5 (6/16)	53.8 (7/13)	40.0 (4/10)	0.5454
RH	7.7 (1/13)	30.8 (4/13)	45.5 (5/11)	44.4 (4/9)	0.2427
RR	7.7 (1/13)	46.2 (6/13)	72.7 (8/11)	87.5 (7/8)	0.0115*

*$P < 0.05$.
CR, clinical response; MH, mucosal healing; RH, radiographic healing; and RR, radiographic response.

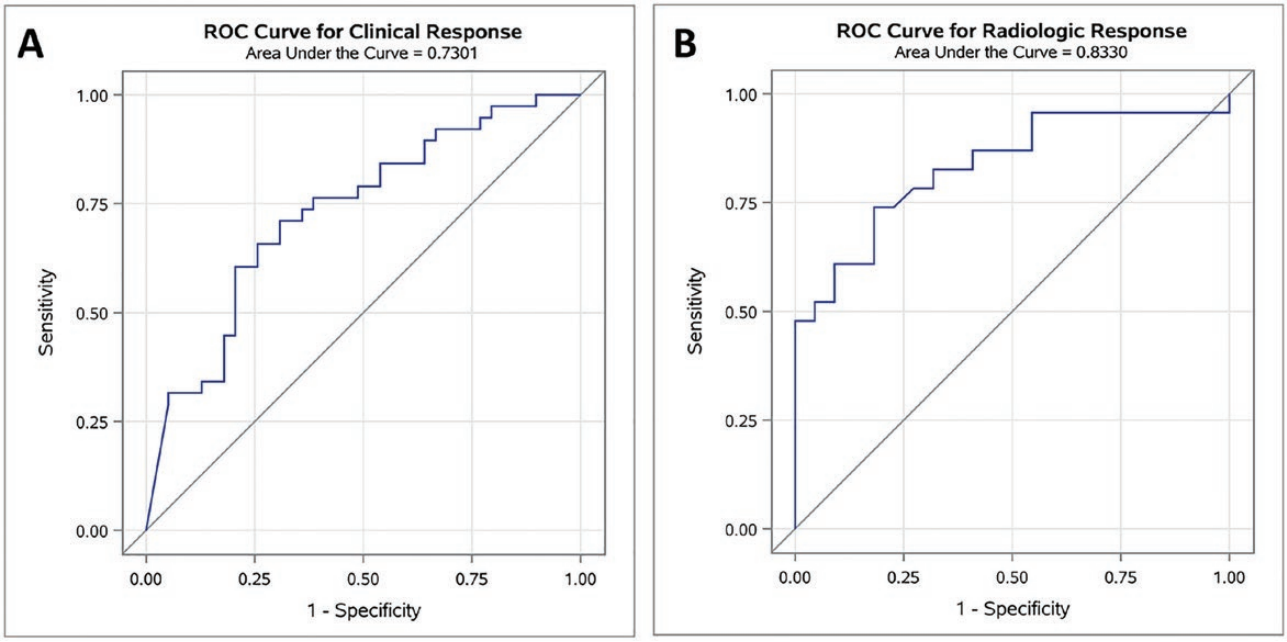

FIGURE 2. Ideal CTL threshold. ROC curve correlating CTLs with clinical response (A) and radiologic response (B).

DISCUSSION

In this real-world single-center experience of the use of TDM in clinical practice among patients with CD treated with CZP, the median CTL was 18.9 µg/mL, and 27.3% of patients had anti-CZP antibodies. Our results demonstrated that higher CTL was significantly associated with CR and RR. Conversely, lower CTL resulted in changes in clinical management in 61% of cases, with the presence of anti-CZP antibodies significantly increasing the odds (OR, 5.6) of changes occurring. While patients with receiving CZP dosing at least every 2 weeks had a higher odds of achieving MH, the presence of anti-CZP antibodies negatively impacted the odds of achieving CR and RR. Ideal CTL cutoffs varied with outcomes assessed, with levels of 18.9 and 10.8 µg/mL, associated with maximized sensitivity and specificity of achieving, respectively, CR and RR, CR. This was congruent with quartile analysis showing patients with CTL between 19.1–35.4 and those >35.4 µg/mL had significantly higher rates of CR, RH, and RR.

The use of TDM has been associated with better clinical and endoscopic outcomes of anti-TNF therapy.[24,25] This approach allows for more proactive optimization of medical therapy through recognition of suboptimal drug levels or treatment failure. Even though studies on the use of infliximab and adalimumab TDM are abundant, data on CZP TDM remain scarce and mostly consist of post hoc analyses.[17] Several factors have been reported to directly impact serum levels of biologics used for the treatment of IBD.[7,8,26] In the present cohort, a small inverse relation between BMI ($r = -0.22$) was seen with CTL. Even though no statistical significant difference was seen on median CTL among patients receiving different CZP doses, this factor was important determinant in those achieving MH, and should be taken into account in future studies. We also found

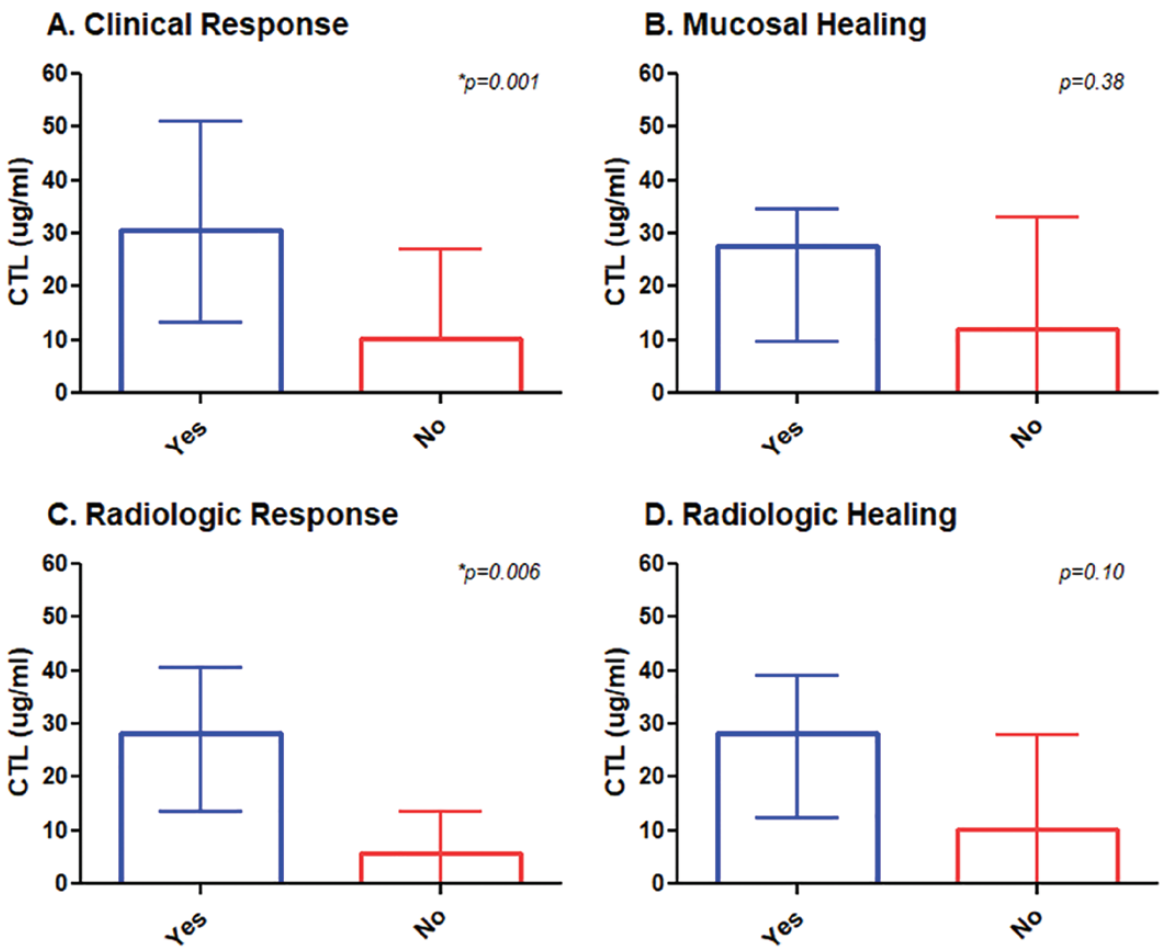

FIGURE 3. CTLs and clinical outcomes. Median CTL and interquartile ranges (IQRs) in patients with and without CR (A), MH (B), RR (C), and RH (D).

that higher levels of CZP were associated with higher rates of clinical and radiographic responses. This is in agreement with previous data describing the inverse association of CTL with the CD activity index and CRP.[27] We describe a novel observation that higher drug levels also correlate with radiographic response. In our cohort, patients who achieved RR or RH had higher CTL when compared to those who did not. This is of relevance with increased use of noninvasive testing to objectively monitor disease activity and response. Unfortunately, data on calprotectin were not readily available in most patients and therefore was not included in this study, but this should be considered in future investigations.

Notably, the presence of anti-CZP antibodies, seen in a third of the cohort, was a determinant factor to decrease the odds of achieving all assessed outcomes, in addition to increasing the odds of changes in clinical management. The rate of 27.7% of ADA formation seen in our cohort mirrors rates of other anti-TNF medications and is considerably higher when compared to other biologic classes, such as vedolizumab.[26,28] Conversely, in a cohort of rheumatoid arthritis patients, a lower rate (6.1%) of anti-CZP antibodies was reported.[29] Disease- and patient-specific features, along with different assays used for testing make it difficult to compare different ADA rates between studies. Nonetheless, further studies could explore a pathophysiologic aspect of IBD, such as drug elimination via the gastrointestinal tract that could potentially sensitize mucosal immune cells and, therefore, increase the immunogenicity of anti-TNF medications.[30] Mechanistically, the presence of anti-TNF ADA results in lower serum drug levels.[18–20] In this study, patients with confirmed anti-CZP antibodies had lower CTL when compared to those without antibodies (0.6 vs 29.8; $P < 0.0001$). Patients receiving concomitant IMM therapy, known to prevent antibody formation, also had a trend toward higher CTL (29.4 vs 14.4; $P = 0.25$) when compared to those receiving CZP monotherapy. In contrast, it was notable that CTL greater than the median (19 µg/mL) demonstrated the opposite effect by increasing the odds of achieving RH, RR, CR and decreasing the odds of changes in clinical management. Interestingly, in our cohort, history of ADA or prior biologic use was not associated with anti-CZP antibody development.

TABLE 4. Predictors of CR, MH, RR, and Healing Within 30 Days of CTL

Parameter	OR (95% CI)	*P*
CR		
CTL ≥19 µg/mL	5.52 (2.08–14.67)	0.0006
Presence of CMZ antibody	0.20 (0.06–0.63)	0.0059
Change in management		
CTL ≥19 µg/mL	0.08 (0.02–0.24)	<0.0001
Presence of CZP antibody	5.59 (1.48–21.12)	0.0112
MH		
CMZ dosing every ≤2 weeks	3.5 (1.07–11.59)	0.039
CMZ dosing every ≥3 weeks	1.0 (reference)	
RH		
Male gender	0.13 (0.02–0.68)	0.015
RR		
Male gender	0.19 (0.05–0.70)	0.012
Age >40 years	0.25 (0.07–0.86)	0.028
CZP level ≥19 µg/mL	10.18 (2.5–41.39)	0.0012
Presence of CZP antibody	0.13 (0.02–0.69)	0.016

Data are given as OR (95% CI) unless denoted otherwise. Supplementary Table 1 summarizes all univariate analyses performed.

Current available guidelines describe 20 µg/mL as the goal CTL target. A separate expert consensus from the US agreed on 15 µg/mL as the ideal cutoff, while a European consensus suggested an even lower target at 10 µg/mL.[31,32] Our data demonstrated that ideal CTL cutoffs may vary depending on which outcomes are assessed. For example, CTL as low as 10.8 µg/mL were associated with improvement in radiologic findings (RR), whereas correlation with complete resolution of symptoms (CR) was only seen with CTL of 18.9 µg/mL. Given the limited sample size, we were not able to analyze the ideal CTL cutoff correlating with MH, currently defined as gold standard outcome in many clinical trials. In a prior study on CTL, clinical remission (confirmed by CRP, calprotectin, and CD activity index) was seen with levels as high as 44–48 µg/mL at week 6 postinduction.[27] In our cohort, patients who achieved RH and MH had a median CTL of >29 µg/mL, suggesting that even higher levels may indeed be necessary to obtain resolution of intestinal inflammation. Furthermore, quartile CTL analysis demonstrates that the majority of patients with CTL between 19–35.4 and >35.4 µg/mL were significantly more likely to achieve CR, RH, and RR. The same trend, with no statistical significance was seen with MH, whereas patients in the lower quartiles (<7.5 and 7.5–19 µg/mL) were more frequently seen to have changes in clinical management. Therefore, based on our data, we would argue that maintenance levels of at least 19 µg/mL would be ideal to maximize the chances of achieving clinical outcomes including CR, RR, RH, and ultimately MH.

Our study has limitations. First, the sample size, restricted to a single referral center, prevents us from broader analysis of factors capable of interfering with CTL. Furthermore, the retrospective design limited our ability to obtain data on all outcomes of interest. More importantly, this is only a snapshot in time and an optimal study design should longitudinally evaluate how fluctuations on CTL may impact disease course. For instance, this design prevented us from assessing the pharmacokinetics of different CZP dosing regimens in the overall drug levels, which can ultimately be important in achieving therapeutic concentrations. Even though our radiologic assessments were based on previously established criteria, interobserver variability can play a role in differences seen with RR and RH.[21] Nonetheless, our study strengths are significant. This is the largest real-world cohort monitoring CTL and correlating to clinical outcomes. Also, obtaining data on a single highly specialized clinical center with standardized diagnostic protocols ensure credibility to the data extracted. Lastly, we demonstrated the novel association between CTL and radiologic outcomes, currently being substantially used in practice as a surrogate assessment for mucosal inflammation and disease monitoring.

CONCLUSIONS

We describe the first real-world cross-sectional experience with CTL and CD clinical outcomes. While the presence of ADA is frequent and associated with poorer outcomes, higher CTL directly correlate with CR, RR, RH, and MH. CTL of at least 19 µg/mL should be sought in order to optimize outcomes in clinical practice. Further studies should focus on assessing prospectively how changes on TDM reflect different disease activity states. Lastly, exploring mechanisms leading to the development of ADA, not restricted to CZP, could reveal new strategies to optimize drug levels and, consequently, improve clinical outcomes.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

ACKNOWLEDGMENTS

All authors have read and agree with the final version of the manuscript.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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