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A Clinical Prediction Model to Determine Probability of Response to Certolizumab Pegol for Crohn's Disease

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Abstract

Background: Certolizumab pegol (CZP) is effective for moderately to severely active Crohn's disease (CD). Higher plasma concentrations are associated with better outcomes and increased drug clearance is the driver of subtherapeutic CZP concentrations.

Objective: We aimed to develop a prediction model incorporating CZP clearance and patient variables to allow estimation of the probability for remission prior to initiating therapy.

Methods: A population pharmacokinetic model estimated baseline CZP clearance in patients with CD from 9 phase 2 and 3 trials. Multivariable prediction models were developed and validated using the PRECISE 1 and PRECISE 2 datasets to identify candidate predictors for a composite remission outcome (Crohn's Disease Activity Index ≤150 and fecal calprotectin concentration ≤250 μg/g) at Weeks 6 or 26. An online clinical decision support tool (CDST) was developed.

Results: Baseline CZP clearance ≥0.5 L/day was associated with subtherapeutic Week 6 CZP plasma concentrations. Baseline weight (odds ratio [OR] 1.04; 95% confidence interval [CI] 1.02–1.07), calculated CZP clearance (OR 0.92; 0.87-0.96]), hematocrit (OR 2.55; 1.43–4.54), and FC (OR 0.66; 0.54–0.80) were associated with Week 6 remission. Baseline weight (OR 1.04; 1.02–1.07), calculated CZP clearance (OR 0.93; 0.88–0.97]), and PRO2 (OR 0.93; 0.87–0.99) were associated with Week 26 remission.

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Authors' contributions

PLCL, LG, ZW, AP, and NVC planned the study; PLCL, ZW, LG, and NVC conducted the study; ZW conducted statistical analysis; PLCL, ZW, LG, BGF, LMS, WJS, PSD, VJ, and NVC interpreted the data; PLCL, ZW, LMS, and NVC drafted the manuscript; all authors critically reviewed the manuscript and approved the final submitted draft.

Conclusions: Patients with CD with accelerated baseline CZP clearance are at risk of subtherapeutic CZP concentrations. Patient-level probabilities for a composite remission outcome can be predicted for patients with CD by entering commonly available patient- and disease-related factors into an online CDST (https://premedibd.com) incorporating CZP clearance.

Keywords

prediction model; Crohn's disease; certolizumab pegol

1 INTRODUCTION

Certolizumab pegol (CZP) is effective treatment for moderately to severely active Crohn's disease (CD) at approved subcutaneous doses of 400 mg on weeks 0, 2, and 4 (induction) and every 4 weeks thereafter (maintenance) [1,2]. Prior research has demonstrated a relationship between CZP drug exposure and outcomes, with higher plasma CZP concentrations associated with more favorable clinical, endoscopic, and biomarker-based (C-reactive protein [CRP], fecal calprotectin [FC] concentrations) disease outcomes [3]. Week 6 CZP serum concentrations ≥36 μg/mL, >44 μg/mL, and >48 μg /mL were associated with clinical remission (Crohn's Disease Activity Index (CDAI]< 150), FC concentration ≤250 μg/g (specificity 90.1%; sensitivity 27.4%; area under curve 0.711), and a composite outcome of CDAI ≤150 and FC ≤250 μg/g at Week 6, respectively [3]. Week 6 CZP serum concentrations were associated with the composite outcome of CDAI ≤150 and FC ≤250 μg/g at both Week 6 and Week 26 in multivariable analyses [3]. Therapeutic drug monitoring (TDM) with measurement of drug and anti-drug antibody concentrations has been proposed to be a valuable tool to optimize biologic therapy [4].

Patients with increased baseline drug clearance may be at risk for subtherapeutic CZP serum concentrations. The ability to calculate CZP clearance prior to initiation of therapy using baseline variables may facilitate the identification of patients with CD who are at risk for subtherapeutic CZP concentrations and those for whom therapeutic CZP concentrations may be achieved with approved dosing. A previously developed population pharmacokinetic (PK) model [5] that takes into account the time-varying nature of patient and disease characteristics and anti-CZP antibody concentration as a continuous variable, can be used to calculate baseline CZP clearance. Prediction models that consider baseline clinical variables and drug clearance may theoretically facilitate the identification of patients with CD likely to achieve various clinical, endoscopic, and biologic disease outcomes during CZP therapy, and aid clinical decision making.

This study aimed to identify patients prior to initiation of CZP therapy who were likely to have adequate drug exposure when administered indicated doses of CZP, using a population PK approach [5] to calculate baseline CZP clearance, to develop and validate prediction models using baseline variables (e.g., demographic, clinical, biochemical, pharmacologic) to estimate the probability of a patient achieving a composite remission endpoint (CDAI ≤150 and FC ≤250 μg/g) at either Week 6 (induction) or Week 26 (maintenance), and to develop an online tool to aid decision making for clinicians considering CZP as treatment for moderately to severely active CD.

2 MATERIALS AND METHODS

2.1 Data assembly

Data used to identify patients with CD likely to have adequate drug exposure based on baseline clearance of CZP were available from nine randomized, controlled, phase 2 and 3 CZP trials (N=2,157), as previously described [5].

For development and validation of prediction models, data required to calculate a composite remission outcome defined as a CDAI score ≤150 and FC concentration ≤250 μg/g at Weeks 6 or 26 were available for patients with active CD (defined as a CDAI score ≥220) who were previously included in the PRECISE 1 [1] (NCT00152490; n=328) and PRECISE 2 [2] (NCT00152425; n=636) phase 3 multi-national, multi-center double-blind placebo-controlled parallel group trials and who received treatment with CZP. In PRECISE 1, patients were randomized to subcutaneous treatment with 400 mg of CZP or placebo at weeks 0, 2, and 4 and then every 4 weeks. In PRECISE 2, patients received open-label subcutaneous treatment with 400 mg CZP at weeks 0, 2, and 4. Patients with a response to CZP at Week 6 (n=427) were randomized to treatment with 400 mg CZP or placebo every 4 weeks. Patients in both trials were followed until Week 26.

2.2 Certolizumab clearance and association with effective certolizumab concentrations

Apparent baseline CZP clearance (CL/F) was estimated based on a formula developed in a previously described population PK model, [5] with adjustment in consideration of the characteristics of patients who had not yet initiated CZP therapy, namely, removal of a time weighting factor and an assumption for the absence of anti-CZP antibodies. The revised formula was as follows:

$$CL/F = 0.527 \times (BW/70)^{0.496} \times (CRP/8)^{0.0657} \times 1.07^{SEX} \times (ALBU/40)^{-0.919}$$

where BW represents body weight (kg), CRP represents serum C-reactive protein concentration (mg/L), SEX represents gender (male=0, female=1) and ALBU represents serum albumin concentration (g/L).

Baseline CZP clearance was compared between patients who achieved observed Week 6 CZP plasma concentrations previously associated with meaningful clinical (>36 μg/mL for CDAI ≤150), biologic (>44 μg/mL for FC ≤250 μg/g), and composite clinical and biologic (>48 μg/mL for CDAI ≤150 and FC ≤250 μg/g) outcomes at Week 6. Receiver operating characteristic (ROC) curve analysis identified baseline CZP clearance thresholds associated with effective CZP plasma concentrations at Week 6.

2.3 Development and validation of prediction models

Prediction models were developed using the PRECISE 2 dataset to identify candidate predictors for the composite remission endpoint at Week 6 or Week 26. Candidate predictors considered for inclusion were selected based on potential availability, plausibility, and interpretability in clinical practice, in addition to calculated baseline CZP clearance. Data for

all 636 patients treated with CZP induction therapy were used for development of the Week 6 model, whereas data for patients treated with CZP for both the induction and maintenance phases of the PRECISE 2 trial (n=427) were used for development of the Week 26 model.

Internal validation of the models was performed using a bootstrap resampling method with 2,000 replications of the PRECISE2 and the combined PRECISE 1 and 2 datasets. External validation assessed the generalizability of the internally validated model using the PRECISE 1 dataset.

2.4 Statistical analysis

Baseline CZP clearance (median and interquartile range) and the characteristics of the patients whose data were utilized for model development were summarized descriptively.

Differences in baseline clearance values between patients who achieved or did not achieve CZP concentration thresholds (i.e., 36 μg/mL, 44 μg/mL, and 48 μg/mL) previously found to be associated with various clinical, biologic, and composite clinical and biologic outcomes were evaluated using the Mann-Whitney test. The cut points of baseline CZP clearance associated with CZP serum concentrations of 36 μg/mL, 44 μg/mL, and 48 μg/mL at Week 6 were identified to maximize the product of sensitivity and specificity as described by Liu et al [6].

For model development, univariable logistic regression analysis was used to identify candidate predictors ($p<0.25$) for multivariable analyses. Multivariable logistic regression analysis was used to identify candidate predictors for the composite remission endpoint at either Week 6 or Week 26. The final model was developed with Akaike information criterion (AIC) selection for removal of candidate predictors. The final model included statistically significant ($p<0.05$) predictors in multivariate regression.

Model performance was assessed in terms of overall prediction errors (the amount of variance explained by the model; assessed by Nagelkerke R^2 [range, 0 (the index does not explain any of the observed variation) to 1 (the index perfectly explains the observed variation)] and Brier score [range, 0 to 1, with lower scores denoting less error]), predictive accuracy assessed by discrimination (the ability to differentiate the binary outcome of remission, quantified by the area under the ROC curve), and calibration (the agreement between predicted and observed probabilities; examined graphically using a calibration curve obtained with bootstrapping of 2,000 replicates based on nonparametric smoother, and measured by Hosmer-Lemeshow goodness of fit test [test values with p values greater than 0.05 indicate adequate model fit], calibration slope, and intercept).

For internal model validation, Efron's optimism bootstrap method with 2,000 replicates of the PRECISE 2 and the combined PRECISE 1 and 2 datasets was used to correct for performance measure optimism (over-fitting). Final predictors were those most frequently included in models obtained from the 2,000 bootstrap replicates, with the lowest AIC and $p<0.05$. External model validation was carried out using performance metrics and graphical assessments as previously described for internal model validation using the PRECISE 1

dataset. Final model fit and optimism were assessed using the bootstrap resampling method previously described.

A clinical decision support tool (CDST) to calculate the probability for achieving the composite remission outcome at Week 6 or Week 26 in individual patients prior to initiation of CZP therapy was developed using a nomogram approach [7] and subsequently incorporated into an online calculator.

Statistical analyses were performed with SAS® (SAS, Toronto, Canada).

3 RESULTS

3.1 Certolizumab clearance and association with effective certolizumab concentrations

Baseline CZP clearance was significantly higher in patients not achieving effective Week 6 CZP plasma concentration thresholds of 36 μg/mL, 44 μg/mL, and 48 μg/mL compared to patients who achieved these thresholds (Figure 1 and Supplementary Table 1). Associated ROC curves are shown in Supplementary Figure 1. Baseline CZP clearance ≥0.5 L/day, observed in 60% (1,256/2,098) of the patients whose data were included in this analysis, was associated with subtherapeutic Week 6 CZP plasma concentrations (Table 1).

3.2 Prediction models

The baseline characteristics and demographics of the patients whose data were utilized in the development and validation of the Week 6 and Week 26 models are shown in Supplementary Table 2.

A total of 73% (466/636) of patients whose data were utilized for Week 6 model development achieved the composite remission outcome at Week 6 compared to 19% (120/636) who did not achieve the outcome (data were missing for 8% [50/636] of patients). A total of 9% (38/427) of patients whose data were utilized for Week 26 model development achieved the composite remission outcome at Week 26 compared to 80% (341/427) who did not achieve the outcome (data were missing for 11% [48/427] of patients).

The results of univariable and multivariable logistic regression analysis of baseline factors predictive of the composite remission endpoint at Week 6 and Week 26 for patients with CD treated with CZP are shown in Table 2 and Table 3, respectively. In multivariable analysis, baseline weight (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02, 1.07), calculated CZP clearance (OR 0.92, 95% CI 0.87, 0.96), hematocrit (OR 2.55, 95% CI 1.43, 4.54), and FC (OR 0.66, 95% CI 0.54, 0.80) were associated with achieving the composite remission outcome at Week 6, with apparent area under the curves (95% CI) of 0.83 (0.80, 0.87), 0.80 (0.76, 0.83), and 0.70 (0.59, 0.81) for the derivation (PRECISE 2 dataset), internal (PRECISE 1 and 2 datasets), and external (PRECISE 1) validation models, respectively. Optimism-corrected area under the curves were 0.83 and 0.79 for the internal validation models (PRECISE 2 and PRECISE 1 and 2, respectively) and 0.72 for the external validation model.

In multivariable analysis, baseline weight (OR 1.04, 95% CI 1.02, 1.07), calculated CZP clearance (OR 0.93, 95% CI 0.88, 0.97), and Patient-reported outcome-2 (PRO2) [8] (OR 0.93, 95% CI 0.87, 0.99) were associated with achieving the composite remission outcome at Week 26, with apparent area under the curves (95% CI) of 0.71 (0.63, 0.79), 0.72 (0.66, 0.77), and 0.71 (0.63, 0.79) for the derivation (PRECISE 2 dataset), internal (PRECISE 1 and 2 datasets), and external (PRECISE 1) validation models, respectively. Optimism-corrected area under the curves were 0.69 and 0.71 for the internal validation models (PRECISE 2 and PRECISE 1 and 2, respectively) and 0.72 for the external validation model. A summary of the performance of the Week 6 and Week 26 models in the derivation and validation datasets is shown in Supplementary Table 3. Furthermore, although variables correlated with CZP clearance were included in the multivariate regression models in addition to CZP clearance, only moderate correlation between the variables in the multivariable regression models was observed suggesting a low potential for multicollinearity (data not shown).

3.3 Online calculator

An online calculator for prediction of the probability of the composite remission outcome at Week 6 or Week 26 prior to initiating CZP therapy for patients with CD was developed based on the prediction models (https://premedibd.com). As baseline CZP clearance was found to be a significant covariate for both Week 6 and Week 26 models, the model equation for the baseline CZP clearance (as described in the methods) was integrated as a component of the model and calculated directly upon entering body weight, baseline CRP concentration, sex, and baseline albumin concentration, and for individual patients, avoiding the need to calculate clearance independently. Predicted patient-level probabilities (including 95% CI) of the composite remission outcome during induction (Week 6) or maintenance (Week 26) prior to initiation CZP therapy are calculated automatically for patients with CD upon entering commonly available patient- and disease-related factors at baseline (i.e., sex, albumin concentration, CRP concentration, body weight, FC concentration, and hematocrit for Week 6 predictions and sex, albumin, CRP concentration, body weight, abdominal pain [mild, moderate, severe], and stool frequency [number of liquid or very soft stools] for Week 26 predictions).

4 DISCUSSION

We have demonstrated that patients with CD with accelerated baseline CZP clearance (≥0.5 L/day) are at risk for subtherapeutic CZP concentrations at Week 6. Clearance can be calculated using baseline clinical variables prior to initiation of CZP therapy and allow for identification of patients for whom therapeutic CZP concentrations may be achieved with approved dosing. We also confirmed that baseline CZP clearance is clinically and statistically predictive of response to therapy, developed models with good predictive value for a composite outcome of remission, and validated the models in an independent patient cohort. These models formed the basis for development of a CDST to calculate the probability of achieving a composite remission outcome at Week 6 or 26 in patients with CD based on baseline CZP clearance and patient- and disease-related factors, prior to initiation of CZP therapy.

Prediction models can help to personalize treatment decisions based upon probability of response (Figure 2). Therapeutic drug monitoring can be implemented in patients at risk for accelerated CZP clearance (i.e., with a “low” probability of response to therapy) to confirm therapeutic drug exposure and potentially increase the likelihood of treatment success. The potential utility of prediction models for this purpose is highlighted in the results of the SERENE UC trial [9]. In this phase 3 controlled trial, no difference in clinical remission rates at Week 8 were observed between patients who were randomized to treatment with higher induction doses of adalimumab (160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6) and those who were randomized to standard induction doses (160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg at Weeks 4 and 6). Although there was no overall benefit of higher adalimumab doses in the trial, the results suggest that methods to proactively identify patients who might benefit from TDM or tight monitoring (i.e., those at risk for accelerated clearance or “low” probability for response) are needed to avoid over- or under-treatment and improve patient outcomes.

Treatment goals in CD currently include both clinical (resolution of abdominal pain and diarrhea or altered bowel habits) and endoscopic (resolution of ulceration) outcomes [10]. Endoscopic remission and deep remission (defined as the absence of mucosal ulceration and CDAI <150), are consistently associated with better long-term outcomes [11], however, the ability to undertake repeated endoscopic assessment to determine response to therapy and patient acceptance of invasive procedures are limitations of this strategy. Inflammatory biomarkers, such as FC concentration, might be useful to detect residual intestinal inflammation and facilitate patient monitoring. Indeed, stool concentrations of FC correlate well with the presence and degree of mucosal inflammation in CD and might be useful surrogates to identify patients at risk for poor outcomes [12–15]. A FC concentration >250 μg/g was associated with the presence of large ulcers and concentrations ≤250 μg/g predicted endoscopic remission [12]. Furthermore, a treatment algorithm based on concentrations of FC and CRP to monitor inflammatory activity and clinical symptoms (tight control) led to superior outcomes compared with an algorithm based on clinical management alone in patients with early CD [16]. In this study, a higher proportion of patients in the biomarker and tight control group achieved mucosal healing (Crohn’s Disease Index of Severity [CDEIS] <4) and no deep ulcers on endoscopy, deep remission (CDAI <150 and CDEIS <4 and no deep ulcers, draining fistula, or prednisone use for 8 weeks or more), biological remission (FC <250 μg/g, CRP <5 mg/L, and CDEIS <4), and steroid-free remission (CDAI <150 with no prednisone for 8 weeks), compared to patients managed based on symptoms alone. In addition, fewer CD-related hospitalizations occurred in the tight control arm (13.2 vs. 28.0 events/100 patient-years; p=0.021). Finally, Plevris et al [17] showed that normalization of FC within the first 12 months of CD diagnosis was associated with a significantly lower risk of disease progression. In this study, FC <250 μg/g was used as proxy to measure mucosal healing and was associated with a reduced risk of future surgery, disease progression, and future hospitalization.

This study has both strengths and weaknesses. The models were developed and validated using high-quality data from randomized controlled trials and were also externally validated. Model components are/can be routinely collected in clinical practice. These baseline factors can easily be incorporated into the freely accessible online calculator developed as part of

this study to calculate the predicted patient-level probability of achieving the composite remission outcome during induction or maintenance therapy *prior* to initiation of CZP therapy. Importantly, in contrast to other biologic agents, prior exposure to anti-tumor necrosis factor-alpha therapy was not identified as a predictor for outcomes assessed in this study for reasons that are unknown. Finally, our study supports the importance of drug clearance to predict important outcomes for patients with CD.

A weakness of our study is that the models were not developed to predict endoscopic healing, a treatment target recommended in current guidelines. Definitive evidence for the adequacy of FC concentrations as a surrogate for this outcome is not currently available. A recent systematic review and validation of published prediction models concluded that avoiding ileocolonoscopies based on these models or individual biomarkers (FC and CRP) was not yet justified due to insufficient certainty to predict endoscopic healing [18]. Additional prospective data are needed to assess the value of FC concentration as a surrogate for endoscopy. Moreover, laboratory assays were conducted as part of the original clinical trials. Although results from these assays are correlated with assays that are available in a clinical diagnostic setting, the methods used to quantify FC and CRP in clinical practice may vary from those used in the original clinical trials. Furthermore, PRO2 (calculated as the weighted sum of patient-reported abdominal pain and stool frequency scores [each averaged over 7 days]) was identified as a predictor for the composite outcome of remission in the Week 26 model. Because this calculation may be practically difficult in clinical practice, an alternative metric of using values collected at a single time point (e.g., at the baseline clinic visit) requires further validation. Finally, while the models were externally validated in a robust clinical trial dataset, validation in the clinical setting has not yet been undertaken. The freely available online clinical decision support tool may help to provide real-world evidence to assess the clinical utility and validity of the models to predict remission.

5 CONCLUSION

In conclusion, consistent with data for other biologics [19], we have confirmed that CZP clearance is a significant covariate associated with response to therapy. Prediction models developed and validated in this study that include CZP clearance may help to identify patients who are likely to respond to CZP prior to initiation of therapy and facilitate a more personalized approach to the treatment of CD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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UCB Pharma conducted the original clinical trials, provided funding for the study, and participated in the review of this report.

Conflicts of interest

PLCL, **LG**, and **ZW** are employees of Alimentiv, Inc. (formerly Robarts Clinical Trials, Inc.); **BGF** has received grant/research support from AbbVie Inc., Amgen Inc., AstraZeneca/MedImmune Ltd., Atlantic Pharmaceuticals Ltd., Boehringer-Ingelheim, Celgene Corporation, Celltech, Genentech Inc/Hoffmann-La Roche Ltd., Gilead

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Availability of data and material

The data underlying this article are available in the article and in its online supplementary material.

ABBREVIATIONS:

AIC	akaike information criterion
BW	body weight
CD	Crohn's Disease

CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Index of Severity
CDST	clinical decision support tool
CRP	c-reactive protein
CZP	certolizumab pegol
FC	fecal calprotectin
PK	pharmacokinetic
ROC	receiver operating characteristic
TDM	therapeutic drug monitoring

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KEY POINTS:

Higher plasma certolizumab pegol (CZP) concentrations are associated with more favorable Crohn's disease outcomes.

Accelerated baseline CZP clearance (≥0.5 L/day) was associated with subtherapeutic CZP concentrations.

Valid prediction models that utilize CZP clearance and commonly available patient-and disease-related factors to calculate the probability of a composite remission outcome prior to initiation of CZP therapy are now available online.

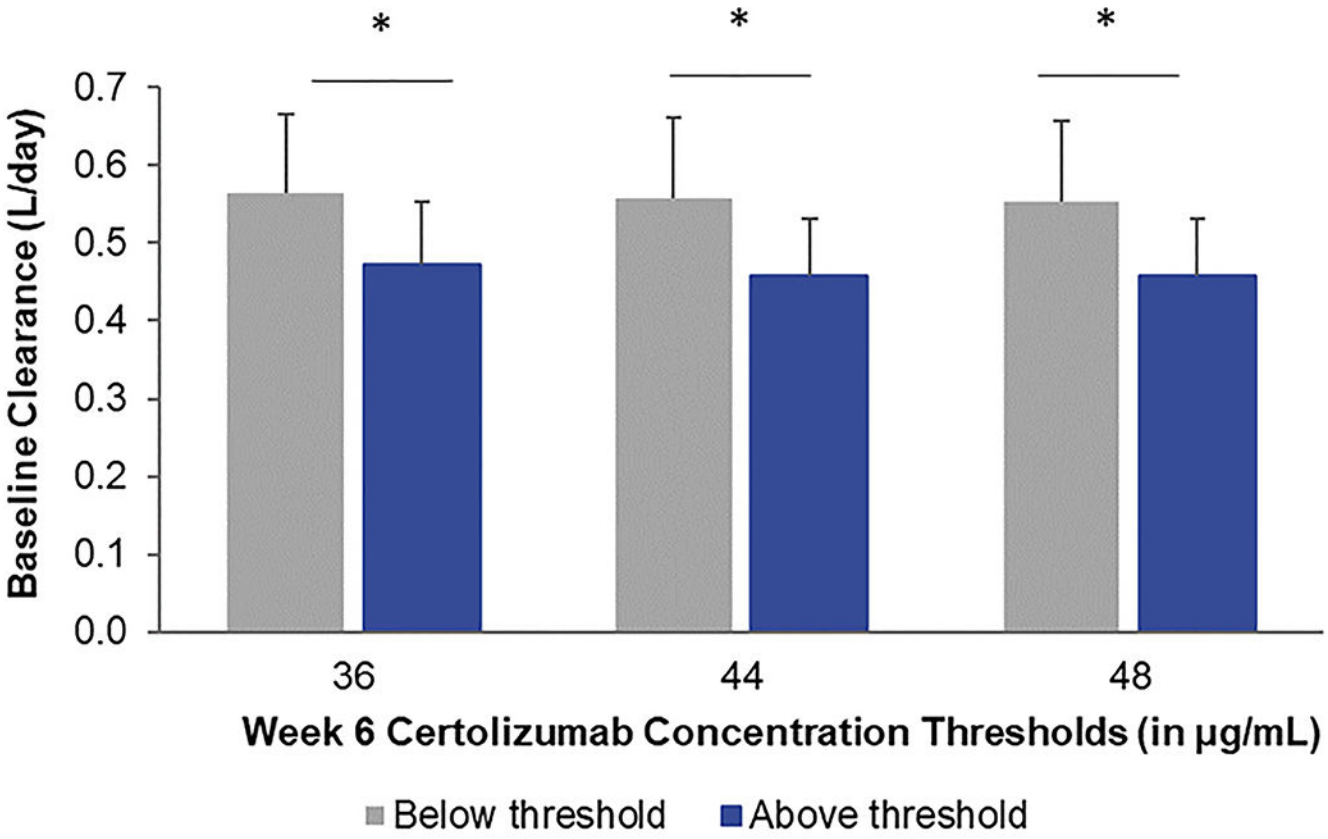
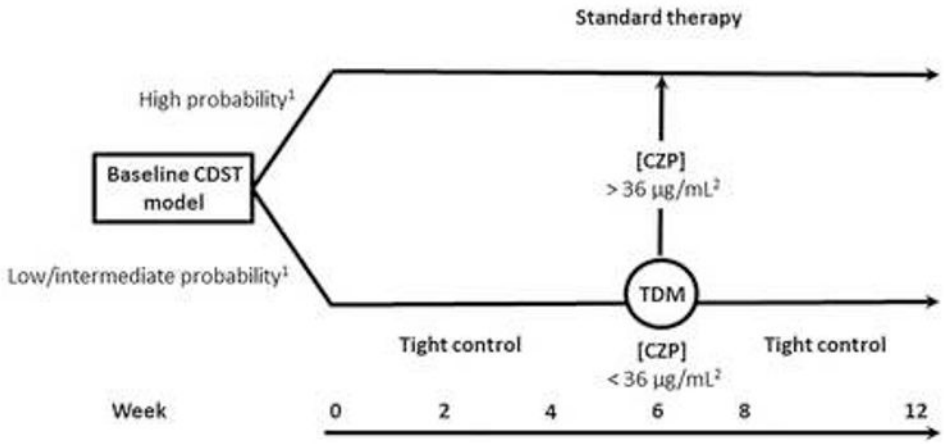


Fig. 1.

Mean baseline CZP clearance values in patients who did or did not achieve effective Week 6 CZP concentration thresholds (*p<0.0001; error bars=standard deviation)



[1]Predicted probabilities may be interpreted subjectively as low/intermediate/high by clinicians and patients
[2]Threshold concentrations associated with CDAI ≤ 150 and FC ≤ 250 µg/g at Week 6 as reported in *Vande Casteele N, et al. Aliment Pharmacol Ther* 2018; 47:229-237.

Legend	
CDAI	Crohn's Disease Activity Index
CDST	Clinical decision support tool to determine probability of response to therapy
[CZP]	Certolizumab plasma concentration
FC	Fecal calprotectin
Standard therapy	Consider standard therapy
TDM	Therapeutic drug monitoring of [CZP]
Tight control	Consider dose optimization/tight monitoring/combination therapy and/or other therapies

Fig. 2.

Theoretical algorithm for individualizing treatment decisions based on probability of response prior to initiation of certolizumab therapy

Table 1.

Summary of receiver operating characteristic curve analysis of baseline CZP clearance and effective Week 6 CZP concentration thresholds

Week 6 plasma CZP concentration threshold (μg/mL)	Baseline CZP clearance threshold (L/day)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC at cut point (%)	PLR*	NLR*
<36	>0.504	70.3	70.7	85.1	49.9	70.5	2.40	0.42
<44	>0.504	68.1	76.9	91.2	40.5	72.5	2.95	0.42
<48	>0.495	69.3	71.3	91.8	33.4	70.3	2.42	0.43

* For achieving concentration threshold

AUROC, area under the receiver operating curve; CZP, certolizumab pegol; PLR, positive likelihood ratio; PPV, positive predictive value; NLR, negative likelihood ratio; NPV, negative predictive value.

Table 2.

Uni- and multivariable analysis of baseline factors predictive of a composite remission endpoint at Week 6 in CZP-treated patients.

Univariable			Multivariable			
Baseline variable	**Odds ratio (95% CI)**	**P value**	**Estimate***	**SE**	**Odds ratio (95% CI)**	**P value**
Calculated CZP clearance	0.94 (0.92, 0.96)	<.0001	−0.087	0.024	0.92 (0.87, 0.96)	0.0003
Weight	1.02 (1.01, 1.03)	<.0001	0.042	0.012	1.04 (1.02, 1.07)	0.0005
Hematocrit[a] (normal vs. low)	5.9 (3.6, 9.67)	<.0001	0.93	0.29	2.55 (1.43, 4.54)	0.0015
FC concentration (log scale)	0.5 (0.43, 0.58)	<.0001	−0.42	0.099	0.66 (0.54, 0.80)	<.0001
CRP concentration (log scale)	0.41(0.33, 0.51)	<.0001				
Albumin concentrations	1.26 (1.18, 1.34)	<.0001				
Age	1.03 (1.01, 1.05)	0.0013				
Prior anti-TNF therapy (yes)	0.53 (0.32, 0.88)	0.014				
Prior IBD surgery (yes)	1.6 (1.06, 2.43)	0.027				
Stool frequency	0.93 (0.87, 1.01)	0.078				
Use of immunosuppressants (yes)	0.7 (0.46, 1.06)	0.091				
PRO2[b]	0.98 (0.94, 1.01)	0.1552				
Use of corticosteroids (yes)	0.74 (0.49, 1.14)	0.1733				
Sex	0.87 (0.58, 1.3)	0.4913				
Disease duration	1 (0.98, .03)	0.7938				
Current smoker	0.99 (0.65, 1.52)	0.9764				

CI, confidence interval; CRP, C-reactive protein; CZP, certolizumab pegol; FC, fecal calprotectin; IBD, inflammatory bowel disease; PRO, patient-reported outcome; SE, standard error; TNF, tumor necrosis factor.

*Intercept estimate for the model=1.76

[a]Hematocrit values were considered “low” when less than 0.38 for females or less than 0.42 for males; values were considered “normal” if above these thresholds.

[b]PRO2 = 2 x average of 7-day number of liquid or very soft stools + 5 x average of 7-day abdominal pain (0=none, 1=mild,2=moderate, 3=severe).

Table 3.

Uni- and multivariable analysis of baseline factors predictive of a composite remission endpoint at Week 26 in CZP-treated patients.

	Univariable		Multivariable			
Baseline variable	**Odds ratio (95% CI)**	**P value**	**Estimate***	**SE**	**Odds ratio (95% CI)**	**P value**
Calculated CZP clearance	0.97 (0.93, 1)	0.0405	−0.077	0.025	0.93 (0.88, 0.97)	0.0017
Weight	1.02 (1, 1.03)	0.0874	0.044	0.013	1.04 (1.02, 1.07)	0.0008
PRO2[a]	0.94 (0.88, 0.99)	0.0337	−0.071	0.033	0.93 (0.87, 0.99)	0.0334
FC concentration (log scale)	0.67 (0.54, 0.84)	0.0004				
CRP concentration (log scale)	0.56 (0.41, 0.78)	0.0005				
Albumin concentration	1.11 (1.01, 1.2)	0.0155				
Hematocrit[b] (normal vs. low)	2.04 (1.02, 4.08)	0.0444				
Stool frequency	0.87 (0.76, 1)	0.0528				
Current smoker (yes)	0.53 (0.24, 1.2)	0.1264				
Sex	0.65 (0.33, 1.3)	0.2264				
Prior anti-TNF Therapy (yes)	0.64 (0.28, 1.44)	0.2826				
Use of immunosuppressants (yes)	0.69 (0.34, 1.4)	0.3099				
Disease duration	0.98 (0.93, 1.02)	0.3175				
Age	1.01 (0.98, 1.04)	0.3796				
Use of corticosteroids (yes)	0.89 (0.44, 1.8)	0.7397				
Prior IBD Surgery (yes)	0.98 (0.47, 2.06)	0.9612				

CI, confidence interval; CRP, C-reactive protein; CZP, certolizumab pegol; FC, fecal calprotectin; IBD, inflammatory bowel disease; PRO, patient-reported outcome; SE, standard error; TNF, tumor necrosis factor.

*Intercept estimate for the model=0.023

[a]PRO2 = 2 x average of 7-day number of liquid or very soft stools + 5 x average of 7-day abdominal pain (0=none, 1=mild,2=moderate, 3=severe).

[b]Hematocrit values were considered “low” when less than 0.38 for females or less than 0.42 for males; values were considered “normal” if above these thresholds.