

Pharmacokinetic-Pharmacodynamic Model of Vedolizumab for Targeting Endoscopic Remission in Patients With Crohn Disease: Posthoc Analysis of the LOVE-CD Study

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Background: Higher serum concentrations of vedolizumab have been associated with improved outcomes in inflammatory bowel disease. It is unclear how vedolizumab exposure is linked to endoscopic remission in Crohn disease (CD). We aimed to develop a pharmacokinetic-pharmacodynamic model linking vedolizumab exposure to endoscopic remission in CD.

Methods: Data were obtained from the first 110 patients participating in a phase 4 prospective multicenter trial (LOVE-CD; ClinicalTrials.gov identifier: NCT02646683), where vedolizumab was dosed at 300 mg every 8 weeks and serum concentrations and antibodies to vedolizumab were measured before each infusion. Concentration-time profiles were described by a 2-compartment model with parallel linear and nonlinear elimination. A first-order discrete-time Markov model was used to describe the relationship between pharmacokinetic exposure metrics and the probability of endoscopic remission (Simple Endoscopic Score for CD < 4).

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Results: Linear clearance was 0.215 L/d, and the volume of distribution of the central compartment was 4.92 L. Linear clearance was higher and vedolizumab exposure was lower in patients with lower serum albumin concentrations, in the presence of antibodies to vedolizumab, and in patients with previous exposure to other biologic therapy. A week 22 vedolizumab concentration of 20.0 mg/L was predicted to yield a 35% probability of achieving endoscopic remission at week 26. Model-based simulations suggested that endoscopic remission rates of 46.5% or 40.0% could be reached with every-4-weeks dosing in patients who were naïve or previously exposed to biologic therapy, respectively.

Conclusions: Model-informed dosing of vedolizumab in CD provides a foundation for future research aiming to maximize endoscopic remission rates.

Key Words: therapeutic drug monitoring, exposure-response, pharmacometrics, inflammatory bowel disease

Introduction

Vedolizumab is a humanized monoclonal antibody that binds the $\alpha 4\beta 7$ integrin and thus prevents the interaction of gut-homing lymphocytes with mucosal addressin cell adhesion molecule-1 in addition to changes in the innate immune system.^{1,2} Based on the results of the GEMINI program, it was approved for the treatment of patients with moderate to severe Crohn disease (CD) and ulcerative colitis (UC).³⁻⁵ A relationship between trough concentrations and clinical remission in CD was shown in the registration trial,⁶ and subsequent observational studies have also shown an association with endoscopic outcomes.^{7,8}

A population pharmacokinetic (PK) model was developed from the data accumulated during the clinical development program for CD and UC.⁹ The model identified low serum albumin concentrations and high body weight as covariates that lead to a clinically important increase in clearance. The pharmacodynamic (PD) model evaluated the percentage of mucosal addressin cell adhesion molecule-1 binding by lymphocytes, which has limited clinical value and provides little discriminative value because full saturation of the binding sites is achieved at vedolizumab serum concentrations as low as 1 mg/L—considerably lower than the concentrations found to be associated with favorable outcomes.^{7,8}

Concomitant clinical and endoscopic remission is the goal of contemporary management of CD.¹⁰ Rates of endoscopic remission in patients with CD rarely exceed 30%,^{11,12} and it remains unknown whether dosing escalation based on therapeutic drug monitoring could lead to higher rates of endoscopic remission. Although concentrations associated with endoscopic remission have been suggested in real-world studies,^{7,8,13} an integrated PK-PD model describing the relationship between dose, concentration, and outcome offers the opportunity of individualizing dosing based on patient characteristics and simulating intensified dosing regimens to assess the magnitude of increases in endoscopic remission rates.

In the phase 4 LOVE-CD study, patients with CD received vedolizumab at standard doses with serum concentration measurements before every infusion, together with endoscopic assessment at baseline, at week 26, and at week 52.¹² Our aim was to develop a PK-PD model linking vedolizumab dose and exposure to endoscopic remission from the LOVE-CD dataset. The model could be used to maximize endoscopic remission rates in patients with CD receiving vedolizumab.

MATERIALS AND METHODS

The LOVE-CD Trial

LOVE-CD was a phase 4 prospective open-label multicenter trial designed to assess endoscopic outcomes in patients with active CD treated with vedolizumab.¹² Briefly, 110 patients with active CD based on a CD Activity Index (CAI) score > 220 and the presence of mucosal ulceration at baseline

ileocolonoscopy received vedolizumab (300 mg) infusions at weeks 0, 2, and 6 and every 8 weeks thereafter through week 52. Patients received an additional infusion at week 10 if their CAI score had not decreased by at least 70 points. The trial was registered at EudraCT under 2014-005376-29 and at ClinicalTrials.gov under the identifier NCT02646683.

PK and PD Data

Serum samples for the quantification of vedolizumab and antibodies to vedolizumab (ATV) were collected before infusion at every study visit. Vedolizumab concentrations were measured using an immunoassay with rabbit ATV to capture vedolizumab and rabbit anti-vedolizumab F(ab')₂ fragments, as previously described (Sanquin Laboratories, Amsterdam, the Netherlands).¹⁴ The lower limit of quantification in serum was 0.100 mg/L, and interassay precision and accuracy were 1% to 4% and 87% to 115%, respectively. The ATV were measured using a drug-sensitive assay as described previously.^{15,16}

Ileocolonoscopies were performed at baseline, week 26, and week 52. The Simple Endoscopic Score for CD (SES-CD) was used to assess disease activity.¹⁷ Video recordings of the procedures were assessed by 4 expert central readers unaware of the study visit sequence and clinical information. Scores given by the central readers were used unless there was considerable discrepancy between central reader scoring and site reader scoring, when recordings underwent additional adjudication as described elsewhere.¹² Endoscopic remission was defined as SES-CD < 4 at weeks 26 and 52. Patients who discontinued the trial before the end of the study period were considered dropouts; a proportion of these patients underwent exit ileocolonoscopy upon discontinuing the trial.

Model Development, Evaluation, and Selection

PK model

The structural model was based on a previously published 2-compartment model with parallel linear and nonlinear elimination ([Supplementary Fig. 1](#)).⁹ Parameters for which the current dataset was unlikely to be sufficiently informative (peripheral compartment volume of distribution, intercompartmental clearance, Michaelis-Menten constant, maximum elimination rate) were not re-estimated but were fixed to estimates from the previously published model. The most parsimonious model was withheld based on standard goodness-of-fit plots, successful minimization, the precision of parameter estimates, the condition number, and a decrease in the objective function value (OFV) of at least 3.84 points ($P < 0.05$, 1 degree of freedom, nested models). Model parameters were added to the random-effects model (eg, interindividual and interoccasion variability). Two occasions were defined: induction (up to the week 14 dose) and maintenance (from week 14 onward). Fixed-effects parameters were assumed to be log-normally distributed,

and patient-specific random effects were assumed to be normally distributed with a mean of zero and a variance of omega. Additive, proportional, and combined additive-proportional error models were explored to describe residual error.

Time-varying covariates included albumin, CDAI, C-reactive protein, ATV (as a dichotomous variable), body weight, and fat-free mass.¹⁸ Time-constant covariates included sex, age, SES-CD at baseline, previous exposure to anti-tumor necrosis factor (TNF) agents, corticosteroid treatment at baseline, and immunomodulator (thiopurine or methotrexate) treatment at baseline. Covariates with correlation coefficients > 0.30 were not simultaneously included as potential predictors. Covariates were identified using forward addition (decrease in OFV ≥ 6.63 points, $\alpha = 0.01$, 1 degree of freedom) followed by backward elimination (increase in OFV ≥ 10.8 points, $\alpha = 0.001$, 1 degree of freedom). Covariate effects were only tested on PK parameters with η -shrinkage < 20%.¹⁹ Parameterization as a power function with centering on medians and linear parameterization was tested for continuous covariates.

PD model

A sequential PK-PD analysis method was used. Empirical Bayes posthoc estimates of individual parameters from the PK model were used to construct individual concentration-time profiles. Different exposure metrics (individual predicted concentrations at weeks 2, 6, and 22; area under the concentration-time curve from week 0 to week 2, week 0 to week 6, week 0 to week 22) were compared as input fitted to the same PD model. A first-order Markov model was developed to link vedolizumab exposure to endoscopic remission (Supplementary Fig. 1). Exposure was used to predict transition probabilities between no endoscopic remission (0), endoscopic remission (1), and dropout (2). If patients left the study and underwent an exit endoscopy before week 26, then the endoscopic outcome was imputed for week 26 and dropout was imputed for week 52. Random effects around transition probabilities were not included in the model. The contribution of vedolizumab exposure to transition probabilities was modeled using a maximum effect function. Based on a literature search, the maximum effect was set at 70% because higher endoscopic remission rates are clinically implausible—a proportion of patients with CD do not respond to treatment even with high exposure.⁸ In addition, the effect of time on transition probabilities was evaluated. The Laplacian method was used to approximate the marginal likelihood.

Model Evaluation

Models were evaluated using OFV comparisons, precision of parameter estimates, goodness-of-fit plots, and a prediction-corrected visual predictive check plot (n = 1000 simulated replicates of the original dataset). Standard errors for parameter estimates were obtained from the covariance step. We obtained 95% confidence intervals for model parameter estimates using bootstrapping (n = 2000 bootstraps).

Simulations

The models were used to simulate 3 dosing regimens with 2000 patients per regimen:

1. 300 mg at weeks 0, 2, 6, 14, and 22 (“per label”)
2. 300 mg at weeks 0, 2, 6, 10, 14, and 22 (“per label with additional week 10 infusion”)
3. 300 mg at weeks 0, 2, 6, 10, 14, 18, and 22 (“every 4 weeks after induction”)

Continuous covariates were sampled from the original dataset; within each dosing regimen simulation, 1000 patients had been previously exposed to anti-TNF agents.

Software

Population PK and PD analyses were performed in NONMEM (version 7.4; ICON Development Solutions, Gaithersburg, MD) from the interface software Pirana (version 2.9.4; Certara Inc., Princeton, NJ). Data visualization, model management, and evaluation were done using the Perl-speaks-NONMEM (PsN, version 4.6.0) toolkit, and R (version 3.4.1) using the *tidyverse* collection of packages.²⁰ NONMEM control streams are available in the Appendix.

Ethical Considerations

The study protocol was approved by the institutional review board at each study site, and all patients provided written informed consent before inclusion in the study. The study was conducted in accordance with good clinical practice and the principles of the Declaration of Helsinki.

RESULTS

Study Population

The study included 108/110 (98%) patients enrolled in the LOVE-CD trial who had at least 1 serum sample with detectable vedolizumab (Table 1). The single sample with a vedolizumab concentration below the limit of quantification was excluded from further analysis. Seventy-six patients completed week 26 of the study, and 74 of these 76 patients underwent the week 26 endoscopy. Sixty-three patients completed week 52, and 61 of these 63 patients had an endoscopic assessment at that time point. Fourteen patients of 34 early withdrawals before week 26 underwent an exit endoscopy at a median time point of 22.5 weeks. One patient of 11 early withdrawals between weeks 26 and 52 underwent an early withdrawal endoscopy, which was performed at week 28.

PK Model

A 2-compartment model with parallel linear and nonlinear elimination fit the data well. Interindividual and interoccasion variability were estimated for linear clearance (CL_L ; Table 2). Residual variability was described with a combined additive and proportional error model. Equation 1 shows how the vedolizumab CL_L of patient i at time j ($CL_{L,i,j}$) was increased in the presence of ATV and with low albumin (ALB) and as decreased in patients who had not been previously exposed to anti-TNF agents ($TNFNAIVE$):

$$CL_{L,i,j} = \theta_{CL_L} \times (1 - 0.020 \times (ALB_{i,j} - 41)) \times (1.89)^{ATV_{i,j}} \times (0.755)^{TNFNAIVE_i} \times e^{\eta_{1,i} + FLAG(1)\eta_{2,i} + FLAG(2)\eta_{3,i}} \quad (1)$$

θ_{CL_L} is the typical population clearance for a patient with albumin 41 g/L without ATV and previously exposed to anti-TNF agents, η_1 is the interindividual variability of CL_L , η_2 and η_3 are the interoccasion variability (FLAG[1], FLAG[2]) of CL_L , $ATV_{i,j}$ equals 1 if ATV were positive at

Table 1. Patient Characteristics

Variable	Value
Number of patients,* n	108
Demographics at baseline	
Women, n (%)	75 (69)
Age, median (IQR), y	36 (28-46)
Weight, median (IQR), kg	71 (61-82)
Fat-free mass, median (IQR), kg	47 (40-56)
Disease duration, median (IQR), y	9 (5-16)
CDAI score, median (IQR)	261 (238-312)
Previous exposure to anti-TNF agents, n (%)	96 (89)
Biochemistry at baseline	
Albumin, median (IQR), g/L	41 (38-43)
C-reactive protein, median (IQR), mg/L	8.7 (3.3-21.7)
Concomitant medication at baseline	
Corticosteroids, n (%)	44 (41)
Immunomodulators, n (%)	22 (20)
Endoscopy at baseline	
SES-CD, median (IQR)	12 (7-17)
Disease location, ileal:colonic:ileocolonic, n (%)	26:32:50 (24:30:46)
Vedolizumab treatment and antidrug antibodies	
Available samples, n	737
Samples with undetectable vedolizumab, n (%)	1 (0.1)
Patients with ATV, n (%)	4 (3.7)
Patients with ATV on more than one occasion, n (%)	2 (1.9)
Samples with ATV, n (%)	10 (1.4)
Additional infusion at week 10	68 (63)
Endoscopic remission during the study	
At week 26, n (%)	36 (33)
At week 52, n (%)	40 (37)

*Two patients were excluded from the dataset because no serum samples for quantifying vedolizumab were collected. IQR indicates interquartile range.

time j , and $TNFNAIVE_i$ equals 1 if patient i had not previously been exposed to anti-TNF agents. We found that CL_L increased with lower albumin (+ 26%, from 41 g/L to 28 g/L), in the presence of antibodies to vedolizumab (+ 89% compared to no antibodies), and in patients previously exposed to biologics (+ 25% compared to no prior exposure). Compared to the interindividual variability of CL_L in the base model (32.1%), the 3 covariates explained an additional 5.9% of the interindividual variability in vedolizumab clearance (Table 2). The goodness-of-fit plots showed that the model described the observed data adequately (Supplementary Fig. 2). The prediction-corrected visual predictive check showed good agreement between simulated and observed data but some underprediction of concentrations during late maintenance beyond week 38 (Fig. 1).

PD Model

The first-order Markov model described patients' transitions between endoscopic remission, no endoscopic remission, and dropout at baseline to the state at weeks 26 and 52.

Individual predicted vedolizumab concentrations at week 22 were the best exposure metric to predict endoscopic remission at week 26 (Supplementary Table 1). Higher concentrations increased the probability of achieving endoscopic remission, and the model was further improved by incorporating the effect of time on the probability of dropping without achieving endoscopic remission; the probability increased with elapsing time. The model adequately predicted the probability of endoscopic remission (Fig. 2). At a week 22 individual-predicted vedolizumab concentration of 20.0 mg/L, a patient had a 35% probability of achieving endoscopic remission at week 26.

Simulations

The median predicted probability of endoscopic remission increased with intensified dosing, reaching a difference of 19.8 percentage points between the "per label" regimen without a week 10 infusion and "every 4 weeks after induction" in patients who had taken anti-TNF agents and 17.4 percentage points between these 2 regimens in patients who were anti-TNF-naïve (Table 3). Conservatively estimating that all patients would receive a week 10 infusion in addition to the "per label" regimen, a clinical study would require a total of 268 (134 per study arm) patients who had taken anti-TNF agents or 468 patients who were anti-TNF-naïve (234 per study arm) to show the superiority of the "every 4 weeks after induction" regimen for endoscopic remission (significance level 5%, power 80%, 1:1 randomization).

Discussion

We report the development of the first population PK-PD model that links vedolizumab dose, vedolizumab exposure, and endoscopic remission in patients with CD. Covariates associated with increased clearance were low albumin concentrations, previous exposure to TNF antagonists, and the presence of ATV. The model could be used to individualize dosing with the aim of maximizing rates of endoscopic remission.

The values of the vedolizumab PK parameters (CL_L and central compartment volume of distribution) in our model are slightly higher than in the model developed by Rosario, Dirks, et al.⁹ This finding could reflect differences in patient characteristics (higher proportion of patients exposed to anti-TNF agents in LOVE-CD) and sampling schedules. Contrary to previous work, we identified a clinically important impact of ATV on CL_L . This observation could be the consequence of a relatively higher proportion of patients with persistently present antidrug antibodies (2 out of the 4 patients with detected antibodies; 50%) compared to the registration trial, where they were detected on 2 or more consecutive occasions in 3/33 (9%) patients with ATV.⁴ Note that the relatively high persistence of antidrug antibodies may have overestimated the effect in our dataset. Furthermore, the presence of antidrug antibodies was modeled as a time-constant effect in previous work,⁹ thereby potentially blurring the different consequences of transient and persistent ATV. Recently, serum samples from GEMINI were reassessed for antidrug antibodies using a drug-tolerant assay, revealing an increased prevalence of immunogenicity.²¹ The previously developed population PK model was updated with these new findings, and the presence of antidrug antibodies was estimated to increase clearance by 10%, although no distinction between

Table 2. Base and Final Model Parameter Estimates. Fixed Estimates in the Pharmacokinetic Model Were Derived from the Rosario et al. (2015) Model

Parameter	Estimate (% RSE) (shrinkage)	Estimate (% RSE) (shrinkage)	Bootstrapped Estimate (95% CI)
PK model	Base model (OFV = 3156.2)	Final model (OFV = 3065.1)	
CL _L (L/d)	0.211 (4)	0.215 (3)	0.214 (0.201-0.229)
Albumin on CL _L	—	-0.020 (29)	-0.021 (-0.031 to -0.011)
Antidrug antibodies on CL _L	—	1.89 (26)	1.86 (1.05-3.10)
No previous biologic exposure on CL _L	—	0.755 (9)	0.767 (0.65-0.91)
V1 (L)	5.01 (4)	4.92 (4)	4.92 (4.54-5.33)
V2 (L)	1.65 FIX	1.65 FIX	—
Q (L/d)	0.12 FIX	0.12 FIX	—
Km (mg/L)	0.964 FIX	0.964 FIX	—
Vm (mg/d)	0.265 FIX	0.265 FIX	—
Interindividual variability (CV %)			
CL _L (%)	32.1 (20) (8)	26.2 (22) (11)	25.5 (19.7-30.8)
Interoccasion variability (CV %)			
CL _L (%)	17.0 (35) (41)	15.2 (41) (40)	14.5 (8.4-20.2)
Additive error (mg/L)	0.608 (45)	0.469 (63)	0.411 (0.104-1.579)
Proportional error (%)	0.234 (8)	0.189 (8)	0.179 (0.148-0.211)
Markov model	Base model (OFV = 1,240,377)	Final model (OFV = 1,240,339)	
E _{max01} (%)	24.1 (13)	70 FIX	—
EC _{50,01} (mg/L)	—	20.0 (23)	19.6 (11.9-29.4)
E _{max02} (%)	32.5 (15)	1 FIX	—
ET _{50,02} (days)	—	515 (21)	514 (358-745)
E _{max10} (%)	10.0 (49)	1 FIX	—
EC _{50,10} (mg/L)	—	1.78 (55)	1.56 (0.36-3.62)
E _{max12} (%)	2.8 (98)	1 FIX	—
EC _{50,12} (mg/L)	—	0.47 (94)	0.70 (0.36-3.62)

Fixed estimates in the PK model were derived from Rosario et al.⁹ The coefficient of variation was calculated as the square root of variance. CI indicates confidence interval; CV, coefficient of variation; EC₅₀, concentration at half-maximal effect; E_{max}, maximum drug effect; FIX, fixed estimate; Km, Michaelis-Menten constant; OFV, objective function value; Q, intercompartmental clearance; RSE, relative standard error; V1, central compartment volume of distribution; V2, peripheral compartment volume of distribution; Vm, maximum elimination rate.

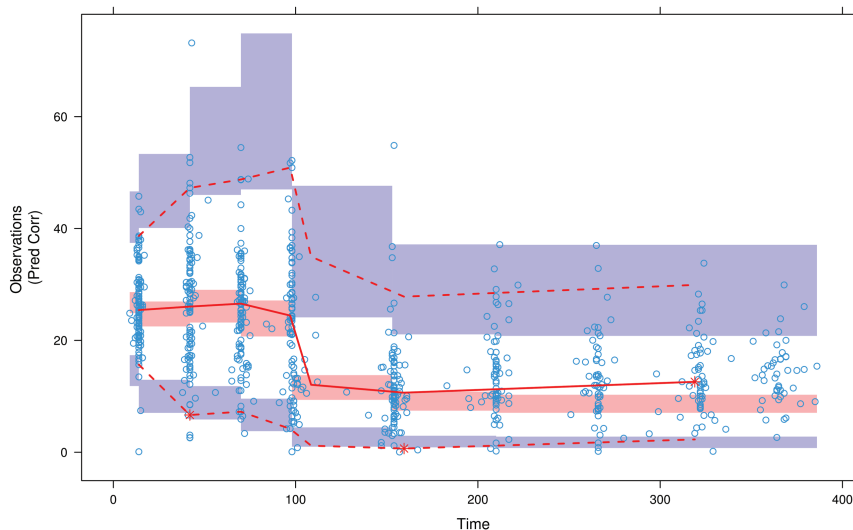


Figure 1. Prediction-corrected visual predictive check of the final population PK model. Observed vedolizumab concentrations are represented by empty blue circles. The solid line connects the observed median prediction-corrected vedolizumab serum concentrations (mg/L) per bin. The dashed lines connect the fifth and 95th percentiles of the prediction-corrected observations. Shaded areas denote the 95% confidence interval of the median, fifth, and 95th percentiles of the simulated values (n = 1000).

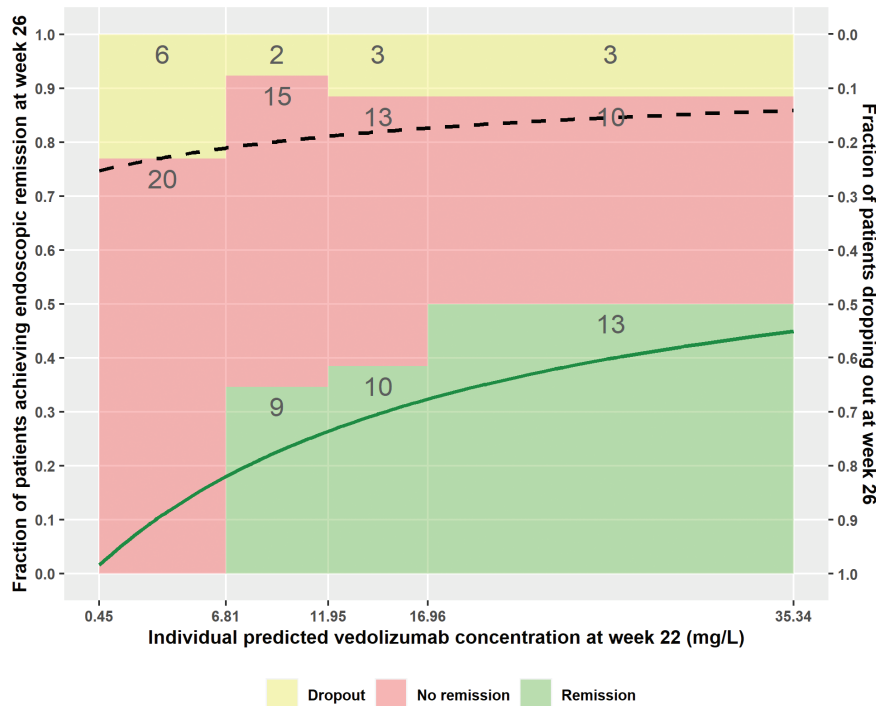


Figure 2. Goodness-of-fit plots for the Markov model. Observed (tiles) and predicted (lines) of patients achieving endoscopic remission (full line) or dropping out (dashed line) at week 26 as a function of individual predicted vedolizumab concentrations at week 22. Numbers indicate the number of patients in each quantile. Only patients with a SES-CD > 3 at baseline are shown (n = 106).

Table 3. Simulated Median Predicted Probabilities (with 95% Bootstrapped CI) of Achieving Endoscopic Remission at Week 26 With Different Dosing Regimens

Dosing regimen	Anti-TNF-naïve	Anti-TNF-experienced
	Median Predicted Probability of Endoscopic Remission (95% bootstrapped CI)	
300 mg at weeks 0, 2, 6, 14, 22	29.1% (21.2%-36.1%)	20.2% (13.6%-27.0%)
300 mg at weeks 0, 2, 6, 10, 14, 22	33.9% (26.3%-40.9%)	24.2% (16.0%-32.4%)
300 mg at weeks 0, 2, 6, 10, 14, 18, 22	46.5% (41.1%-50.6%)	40.0% (33.5%-45.2%)

transient and persistently present antibodies was made. This estimate is nonetheless within the 95% confidence interval of our estimate. On balance, the impact of ATV is small at the population level because of the low rate of immunogenicity, but it is significant in the rare patient with persistent antidrug antibodies.

Lower rates of endoscopic remission in patients previously exposed to biologics were observed in patients treated with vedolizumab,^{22, 23} although a unifying mechanistic explanation is still lacking. Rosario et al⁹ identified a 4% increase in CL_L with prior anti-TNF exposure, which was judged to be clinically insignificant. In a Belgian study, patients with CD and prior treatment with TNF antagonists had lower vedolizumab serum concentrations compared to patients receiving vedolizumab as a first-line biologic.²³ Although prior treatment with TNF antagonists could also be regarded as a proxy for more aggressive disease behavior or higher disease activity, this factor seemed to be independent of other disease activity markers in the abovementioned study. A small study highlighted differences in exosomes, extracellular nanovesicles, in patients with inflammatory bowel disease,

stratified by previous TNF antagonist exposure.²⁴ Increased sequestration of vedolizumab within the exosomes of patients exposed to anti-TNF agents was observed, which could interfere with therapeutic efficacy.

Albumin concentrations were found to be negatively associated with clearance, which is an almost universal finding in monoclonal antibodies used in inflammatory bowel disease,^{9, 25, 26} potentially reflecting protein-losing enteropathy whereby large amounts of serum proteins, including monoclonal antibodies, are lost through the diseased intestinal surface as a result of higher disease activity.²⁷ We did not find an effect of weight on clearance, which may have been related to the narrower range in body weight in LOVE-CD compared to GEMINI, where a clinically significant effect became apparent at a body weight > 120 kg.⁹ After incorporating covariate effects, we found that interindividual variability in clearance remained largely unexplained, as has also been observed with other monoclonal antibodies used in inflammatory bowel disease.^{25, 26, 28-30} Consequently, Bayesian forecasting (a posteriori prediction) rather than a priori dose stratification will be re-

quired if one uses the model for precision dosing. We noted an underestimation of concentrations in late maintenance (beyond week 38), a potential consequence of adopting parameters of nonlinear clearance that we were unable to estimate independently directly from the previously published model,⁹ which may be an overestimate for our dataset.

Shortening the dosing interval of vedolizumab has shown promising results for clinical remission,³¹ yet data on endoscopic improvement remain scarce. Interpretation is further confounded by the fact that patients in the available studies did not undergo endoscopy before dose escalation: it is possible they had already achieved endoscopic remission despite the presence of symptoms and mildly elevated biomarkers. This research question is being addressed in the second, ongoing part of the LOVE-CD study. A recent multicentric study in which paired measurements of vedolizumab serum concentrations were made before and after dose escalation showed that patients with higher serum concentrations *before* escalation were more likely to respond clinically and endoscopically, tentatively suggesting that PD was the main underlying mechanism and that PK only reflects underlying disease activity.³² An additional recent study reported broadly similar findings, acknowledging that low serum trough concentrations alone do not account for the outcome of dose escalation.³³

The dilemma of treatment intensification is expected to be resolved by the recently completed ENTERPRET study (ClinicalTrials.gov identifier: NCT03029143) in patients with UC. In this study, patients with week 5 serum concentrations < 50 mg/L were randomized to standard dosing or to 1 of 2 experimental dosing regimens: vedolizumab 600 mg at week 6 followed by vedolizumab 300 mg every 4 weeks, or vedolizumab 600 mg every 4 weeks from week 6 onward. Doses were withheld in case vedolizumab trough concentrations during experimental treatment exceeded 90 mg/L. Recent reports of dosing interval prolongation^{34, 35} without loss of remission may not be applicable to this context, because they included patients mostly in remission with a median treatment duration longer than 5 years. Simulations based on our model suggest that higher rates of endoscopic remission than currently observed may be achieved through intensified dosing, potentially reaching 46.5% in patients naïve to anti-TNF agents. Nonetheless, it should be emphasized that intensified dosing regimens were not studied in the first part of the LOVE-CD study that is reported here and that simulations should be regarded as hypothesis-generating for future research. Further information about the exposure-response relationship of vedolizumab will accumulate with the introduction of subcutaneous dosing, where exposure is generally higher than with intravenous dosing.³⁶

Rates of endoscopic remission in CD are consistently lower than in UC.^{7, 8, 23} Meaningful differences in vedolizumab PK between the 2 diseases have not been shown yet. Conceivably, higher vedolizumab concentrations may be required to achieve endoscopic remission in CD than in UC. Trough concentrations associated with endoscopic remission in the current study were considerably higher than observed by other authors^{7, 13}: Aside from differences in study populations, endoscopic videos in LOVE-CD were evaluated by blinded central readers, an approach known to decrease endoscopic remission rates in comparison to local readers.

Limitations of the current study should be acknowledged. Extrapolation from the LOVE-CD patient population should be performed with care: The study was begun early after the regulatory approval of vedolizumab, resulting in the inclusion of a majority of patients with refractory CD experienced with biologics, which is not necessarily the case in contemporary cohorts of patients treated with vedolizumab. The suitability of our model should be further evaluated in patients naïve to biologics. Furthermore, PK sampling in the study was only performed at trough. Finally, the results of our simulations should be interpreted bearing in mind that intensified dosing regimens were not studied directly in LOVE-CD. These findings should therefore be used to inform potential future studies rather than daily clinical practice.

Conclusions

We have developed the first PK-PD model of vedolizumab to target endoscopic remission in CD. Higher vedolizumab exposure may be needed to achieve endoscopic remission. Patients previously treated with anti-TNF agents and those with low serum albumin concentrations are more likely to have insufficient vedolizumab exposure. Prospective trials of intensified vedolizumab dosing regimens may be warranted to assess strategies to maximize rates of endoscopic remission.

Supplementary Data

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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Appendix

Population pharmacokinetic model

\$PROBLEM PopPK analysis of vedolizumab in LOVE-CD

```

;-----
$INPUT DROP ID DROP TIME TAD AMT RATE DV ADA EVID MDV GENDER WEIGHT ALBUMIN TNFNAIVE CRP
CDAI AGE SESCD FFM CS IMM OCC
;-----
$DATA template_vedolizumab_run007.csv IGNORE=I
;-----
$SUBROUTINES ADVAN6 TOL=6
;-----
$MODEL COMP(CENTRAL,DEFDOSE,DEFOBS)
COMP(PERIPH)
;-----
$PK
;-----
FLAG1=0
FLAG2=0

IF(TNFNAIVE.EQ.1) FLAG1 = 1
IF(ADA.EQ.1) FLAG2 = 1

FLAG3=0
FLAG4=0

IF(OCC.EQ.1) FLAG3 = 1
IF(OCC.EQ.2) FLAG4 = 1

TVCL = THETA(3) * (1 + (ALBUMIN - 41)*THETA(9)) * THETA(10)**FLAG1 * THETA(11)**FLAG2
CL = TVCL * EXP(ETA(1) + ETA(3) * FLAG3 + ETA(4) * FLAG4) ; [L/day]

TVV1 = THETA(4) ; [L]
V1 = TVV1 * EXP(ETA(2))

TVQ = THETA(5)
Q = TVQ
TVV2 = THETA(6)
V2 = TVV2
TVKM = THETA(7)
KM = TVKM ; [mg/L]

TVVM = THETA(8) ; [mg/day]
VM = TVVM

S1 = V1
K10 = CL/V1
K12 = Q/V1
K21 = Q/V2
;-----
$DES
C1 = A(1) / S1
DADT(1) = K21*A(2)-A(1)*K12-K10*A(1) - VM * C1 / (KM + C1)
DADT(2) = K12*A(1)-K21*A(2)
;-----

$THETA
(0.3) ;1 RUV Add.
(0, 0.121) ;2 RUV Prop.
(0, 0.140) ;3 CL
(0, 8) ;4 V1
(0.12 FIX) ;5 Q
(1.65 FIX) ;6 V2

```

```
(0.964 FIX)          ;7 KM
(0.265 FIX)          ;8 VM
(-0.03)              ;9 ALBUMIN on CL
(0.75)               ;10 TNFNAIVE on CL
(2.5)                ;11 ADA on CL
;-----
```

```
$OMEGA
0.12                 ;IIV-CLL
0.03                 ;IIV-V1
$OMEGA BLOCK(1) 0.05; iov
$OMEGA BLOCK(1) SAME
;-----
```

```
$$SIGMA
1 FIX ;residual variability (do not change!)
$error
;-----
```

```
IPRED = F
      W = SQRT(THETA(1)**2 + IPRED*IPRED*THETA(2)**2)
      IF(W.EQ.0) W = 1
IRES = DV-IPRED
IWRES = IRES/W
Y = IPRED + W*EPS(1)
;-----
```

```
$EST METHOD=1 INTERACTION MAXEVAL=9999 SIG=3 PRINT=5 NOABORT POSTHOC
$COV
;-----
```

Pharmacodynamic model

\$PROBLEM PD analysis of vedolizumab in LOVE-CD

```
$INPUT ID DROP VISIT IPRED2 IPRED6 IPRED22 CAUC2 CAUC6 CAUC22 ENDREM=DV PREV
```

```
$DATA data_MM.csv IGNORE=@
```

```
$PRED
DAYS=(VISIT*7)+0.01
; ----- transitions from score 0 -----
; 0 --> 1
EMAX01 = THETA(1) + ETA(1)
EC5001 = THETA(2)
P01 = EMAX01 - EMAX01*(1-(IPRED22/(EC5001+IPRED22)))
; 0 --> 2
EMAX02 = THETA(3)
ET5002 = THETA(4)
P02 = EMAX02 - EMAX02*(1-(DAYS/(ET5002+DAYS)))
; 0 --> 0
P00 = 1 - P01 - P02
;----- transitions from score 1 -----
; 1 --> 0
P10 = THETA(5)

; 1 --> 2
P12 = THETA(6)

; 1 --> 1
P11 = 1 - P10 - P12
;----- transition fractions -----
IF (PREV.EQ.0.AND.DV.EQ.1) Y = P01
IF (PREV.EQ.1.AND.DV.EQ.0) Y = P10
```

```
IF (PREV.EQ.0.AND.DV.EQ.2) Y = P02*(1-P01)
IF (PREV.EQ.1.AND.DV.EQ.2) Y = P12*(1-P10)
IF (PREV.EQ.0.AND.DV.EQ.0) Y = 1 - P01 - P02*(1-P01)
IF (PREV.EQ.1.AND.DV.EQ.1) Y = 1 - P10 - P12*(1-P10)
```

```
$THETA
```

```
0.7 FIX      ; EMAX01
(0,40)      ; EC5001
1 FIX       ; EMAX02
(0, 364)    ; ET5002
(0, 0.05, 1) ; P10
(0, 0.1, 1) ; P12
```

```
$OMEGA
```

```
0 FIX; ETA(1)
```

```
$COV PRINT=E MATRIX=S
```

```
$ESTIMATION METHOD=COND LAPLACE LIKE MAX=9999 MSFO=msf55
```

```
$TABLE ID VISIT ENDREM IPRED2 IPRED6 IPRED22 CAUC2 CAUC6 CAUC22 Y P01 P02 P00 P10 P12 P11 NOPRINT
ONEHEADER FILE=sdtab85
```