A Population Pharmacokinetic and Exposure–Response Model of Golimumab for Targeting Endoscopic Remission in Patients With Ulcerative Colitis

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Background: Unlike other anti-tumor necrosis factor alpha antibodies, golimumab does not deliver on its promise of effectiveness for treating patients with ulcerative colitis. We investigated the value of therapeutic drug monitoring for optimizing golimumab therapy.

Methods: We analyzed the golimumab pharmacokinetics data of 56 patients with moderate to severe ulcerative colitis. Induction and maintenance golimumab concentrations (296 venipuncture, 414 serum) were used to develop a population pharmacokinetic model. Exposure–response relationships were analyzed using the data of 40/56 patients with available endoscopy data. Receiver operating characteristic curve analysis was performed, and an exposure–response Markov model was developed, linking golimumab exposure to probabilities of transitioning between Mayo endoscopic subscore (MES) states from baseline to week (w)14.

Results: Golimumab pharmacokinetics was best described by a 2-compartment model with linear absorption and elimination. Antibodies to golimumab and previous biological therapy reduced golimumab exposure. Still, interindividual pharmacokinetic variability (IIV_{PK}) remained largely unexplained. Endoscopic remission (ER; $MES_{w14} \leq 1$) was achieved in 14/40 (35%) patients. Golimumab serum trough concentration thresholds of 7.4 mg/L (w6) and 3.2 mg/L (w14) predicted ER at w14 (positive predictive values [pv+] 83% and 91%, pv- 82% and 67%, respectively). The 3.2-mg/L target predicted 38% and 44% chances of achieving ER in patients with $MES_{baseline}$ of 3 and 2, respectively.

Conclusions: Personalized, model-based induction dosing aiming at here-established target concentrations may account for IIV_{PK} and thus provide patients with more equal chances of achieving ER. As <50% of patients attained the exposure targets, higher golimumab induction dosing requires investigation to secure its future in clinical practice.

Key Words: monoclonal antibodies, therapeutic drug monitoring, personalized medicine, exposure response, population pharmacokinetics–pharmacodynamics

INTRODUCTION

Golimumab is a fully human immunoglobulin G1 monoclonal antibody that inhibits tumor necrosis factor alpha (TNF α).¹ Based on the integrated phase 2b/3 Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT) studies, golimumab was approved for

the treatment of adults with moderate to severe ulcerative colitis (UC) who have not responded adequately to or cannot use conventional therapies.^{2–4} The PURSUIT-SC study showed that subcutaneous golimumab administration safely induces clinical response, clinical remission, and endoscopic remission and increases quality of life at week 6 in larger percentages of

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patients than placebo.³ The PURSUIT-M study showed that golimumab was able to maintain the initially induced clinical response and achieve clinical remission and endoscopic remission at both weeks 30 and 54 of therapy.⁴

In PURSUIT, golimumab serum concentrations as early as week 2 were higher among patients achieving clinical response and endoscopic remission at week 6.⁵ Adedokun et al. identified optimal golimumab serum concentration thresholds at weeks 2, 4, and 6 of 8.9 mg/L, 7.4 mg/L, and 2.5 mg/L, respectively, as desirable targets for attainment of an optimal clinical outcome rate in the population. In a small observational “real-world” study, Detrez et al. reported higher golimumab serum concentrations at week 6 among patients achieving partial clinical response.⁶ An optimal week 6 golimumab serum concentration threshold of 2.6 mg/L was identified. Therapeutic drug monitoring (TDM) may be used for targeting these thresholds.

Although symptom resolution and control were the primary therapeutic goals in PURSUIT, treatment goals have evolved in recent years, now largely focusing on endoscopic healing.⁷ Indirect evidence supports the idea that early endoscopic healing is associated with improved long-term clinical outcomes, corticosteroid discontinuation, and lower risk of colectomy.^{7,8} To date, no optimal golimumab serum concentration thresholds have been established for targeting endoscopic remission.

Patients in the PURSUIT studies were biologically naïve, which undermines the relevance of these studies for real-world clinical practice, where patients have often been pre-exposed to infliximab and/or adalimumab. Evidence is growing that the efficacy of biological therapies is inferior in patients who were previously treated with biologicals as compared with those who are biologically naïve.⁹ For this reason, confirmatory data on the effectiveness of golimumab in the real-world setting are needed.

In the PURSUIT-SC and PURSUIT-M studies, golimumab serum concentrations were measured in blood samples collected predominantly at trough. This relatively sparse sampling scheme may not be sufficient to adequately describe the golimumab population pharmacokinetics.¹⁰ To allow more flexibility in sample collection for building an adequate population pharmacokinetic model, a dried blood spot (DBS) sampling technique has been developed and analytically validated for the quantification of golimumab.¹¹

In the current work, we evaluated the role of TDM of golimumab for targeting endoscopic healing in real-world clinical practice. Therefore, we developed a population pharmacokinetic model and an exposure–response model to describe the golimumab dose–exposure and exposure–response relationship, respectively, and to potentially facilitate model-based dose optimization for targeting the established exposure and response targets.

METHODS

Study Population

Adult patients with a confirmed diagnosis of UC at 2 tertiary hospitals receiving golimumab between November 2015

and September 2017 were included. The study designs and patient inclusion criteria for these studies have been previously described.^{6,11,12} Study 1 was a prospective study performed at the University Hospitals Leuven, Belgium, including 10 adult patients with UC on golimumab therapy, 5 starting induction therapy and 5 on maintenance therapy.¹¹ Study 2 was a retrospective study, also performed at the University Hospitals Leuven, Belgium, including 21 patients starting golimumab therapy.⁶ Study 3 was a retrospective study performed at the University Medical Centre Ljubljana, Slovenia, including 24 patients starting golimumab therapy.¹² After publication of the original studies, an additional 3 and 3 patients were included in studies 2 and 3. As 5 patients were included in both study 1 and study 2, our pooled data analysis included a total of 56 patients.

Dosing Scheme

Golimumab was administered subcutaneously, after a 2-dose induction regimen with fixed doses of 200 mg at baseline (day 0) and 100 mg 14 days later. Maintenance therapy followed body weight–based stratified dosing at 4-week intervals from week 6 (day 42) onwards, involving 50-mg doses for patients weighing <80 kg and 100-mg doses for patients weighing ≥80 kg. Patients who had an inadequate response upon induction therapy received 100-mg maintenance doses, irrespective of body weight.

Sampling Scheme

In study 1, capillary DBS samples were collected after a rich sampling scheme (Table 1; Supplementary Fig. 1).¹¹ In study 2, peripheral venous serum samples were taken at days 7, 14, 28, 42, and 98.⁶ In study 3, peripheral venous serum samples were taken at days 3, 7, 14, 21, 28, 42, 70, 98, 182, 266, 280, 308, and 350.¹² DBS eluates and serum samples were stored at –20°C, under which condition immunoglobulin G has been shown to be stable for up to 25 years.¹³

Analytical Methods

Golimumab concentrations in serum and DBS were determined by a validated enzyme-linked immunosorbent assay (ELISA).^{6,11} The lowest quantifiable concentration was 0.1 mg/L. Antibodies to golimumab (ATG) were quantified in serum samples using a validated drug-tolerant ELISA.⁶ The lowest quantifiable concentration was 25 ng/mL equivalents of monoclonal antibody to golimumab 159B8. Given the relative drug tolerance of the ATG assay, ATG were only quantified in samples with a golimumab concentration of ≤4.0 mg/L.

Efficacy Evaluation

Endoscopic remission was defined as going from a baseline Mayo endoscopic subscore of 2 (moderate disease) or 3 (severe disease) to a subscore of 0 (inactive disease) or 1 (mild disease) at week 14 (day 98).

TABLE 1. Data Summary

Parameter	Study 1	Study 2	Study 3	Pooled
No. patients (%)	10 (18)	19 (34)	27 (48)	56 (100)
Baseline demographics				
Sex, female, No. (%)	6 (60)	9 (47)	15 (56)	30 (54)
Age, median (IQR), y	35 (24–54)	45 (31–53)	45 (39–55)	45 (33–54)
Weight, median (IQR), kg	74 (60–80)	71 (65–76)	75 (65–87)	72 (64–82)
Fat-free mass, median (IQR), kg	45 (39–59)	47 (42–57)	50 (43–60)	47 (41–58)
Previous biological therapy, No. (%)	1 (10)	8 (42)	2 (7)	11 (20)
Infliximab, No. (%)	0 (0)	5 (26)	0 (0)	5 (9)
Adalimumab, No. (%)	1 (10)	3 (16)	2 (7)	6 (11)
Reason stop previous biological therapy				
Primary nonresponse, No. (%)	1 (10)	1 (5)	0 (0)	2 (4)
Loss of response, No. (%)	0 (0)	5 (26)	1 (4)	6 (11)
Intolerance, No. (%)	0 (0)	2 (11)	1 (4)	3 (5)
Current smokers, No. (%)	2 (20)	0 (0)	2 (7)	4 (7)
Serology at baseline				
C-reactive protein, median (IQR), mg/L	3.8 (0.5–5.4)	4.8 (1.2–22.1)	5.0 (5.0–6.5)	5.0 (4.6–8.8)
Albumin, median (IQR), g/L	43.0 (41.8–44.9)	42.1 (39.8–44.8)	43.0 (41.5–45.0)	43.0 (40.9–45.0)
Alkaline phosphatase, median (IQR), U/L	66.5 (60.2–80.8)	69.0 (57.0–90.5)	69.0 (58.5–72.0)	69.0 (58.0–81.5)
Concomitant medication				
Mesalazine, No. (%)	7 (70)	9 (47)	0 (0)	16 (29)
Azathioprine, No. (%)	0 (0)	2 (11)	8 (30)	10 (18)
Corticosteroids, No. (%)	3 (30)	9 (47)	10 (37)	22 (39)
Sampling				
Samples available, No. (%)	376 (53)	148 (21)	186 (26)	710 (100)
Venipuncture, No. (%)	80 (21)	148 (100)	186 (100)	414 (58)
Dried blood spot, No. (%)	296 (79)	0 (0)	0 (0)	296 (42)
No. samples per patient, median (range)	40 (31–64)	4 (2–13)	8 (3–13)	7 (2–64)
Samples with undetectable golimumab, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Samples with antibodies to golimumab, No. (%)	12 (3.5)	1 (1)	2 (1)	15 (2)
Patients with antibodies to golimumab, No. (%)	5 (50)	1 (5)	1 (4)	7 (13)
Endoscopy				
Baseline Mayo endoscopic subscore, 0:1:2:3:NA, No. (%)	0:2:5:3:0 (0:20:50:30:0)	0:0:7:12:0 (0:0:37:63:0)	0:3:7:10:7 (0:11:26:37:26)	0:5:19:25:7 (0:9:34:45:13)
Postinduction Mayo endoscopic subscore, 0:1:2:3:NA, No. (%)	3:1:2:3:1 (30:10:20:30:10)	1:2:6:8:2 (5:11:32:42:11)	10:3:6:5:3 (37:11:22:19:11)	14:6:14:16:6 (25:11:25:29:11)
Endoscopic remission, yes:no:NA, No. (%)	3:5:2 (30:50:20)	3:14:2 (16:74:11)	8:7:12 (30:26:44)	14:26:16 (25:46:29)

Population Pharmacokinetic and Exposure–Response Model Development and Evaluation

Population modeling was performed in NONMEM (version 7.4; Icon Development Solutions, Ellicott City, MD, USA) with a GNU Fortran 95 compiler and the Perl-Speaks-NONMEM (PsN; version 4.7.0) toolkit and Pirana (version 2.9.7).

Population pharmacokinetic model

Different structural models were fitted to the golimumab pharmacokinetic data employing first-order conditional estimation with interaction and subroutine ADVAN6. Models were fitted simultaneously to serum and DBS concentrations by estimation of a population conversion factor that related individually predicted serum and DBS concentrations.¹⁴ Based on visual

inspection of the data and a literature review, a pharmacokinetic model was developed starting from a 1-compartment model with linear absorption and elimination.^{10, 15–19} The most parsimonious model was withheld based on model fit evaluations using standard goodness-of-fit diagnostics (residual and simulation-based plots), convergence of the minimization criteria, physiological plausibility, precision of the parameter estimates, and a drop in the objective function value (OFV) of at least 3.84 ($P \leq 0.050$, 1 degree of freedom). All structural model parameters were assumed to be log-normally distributed. Two levels of random effects were estimated: interindividual variability and residual variability. Additive and/or proportional residual error models were explored separately for serum and DBS concentrations. Eta and epsilon shrinkage values $\leq 20\%$ were considered acceptable.²⁰

Correlations between covariates and pharmacokinetic parameters were considered in the covariate model to explain interindividual variability in the golimumab pharmacokinetics. The impact of ATG on golimumab clearance was evaluated using a time-invariant approach (dichotomous 0 or 1 indicating absence or presence of ATG at the patient level [ATG_{patient}]) and time-varying approaches (dichotomous at the sample level [ATG_{sample}], persistent upon initial detection [ATG_{onset}], and transient upon later confirmed disappearance [ATG_{transient}]). The patients' fat-free mass was predicted using the semimechanistic model developed by Janmahasatian et al.²¹ Baseline serum albumin, C-reactive protein, and alkaline phosphatase concentrations were evaluated. Also, the Mayo endoscopic subscore at baseline, previous biological therapy, and concurrent treatment with corticosteroids, mesalazine, and azathioprine were evaluated.

The stepwise covariate modeling approach consisted of a forward addition procedure (decrease in OFV ≥ 6.64 , $P \leq 0.010$; chi-square distribution, 1 degree of freedom) and a backward elimination procedure (increase in OFV ≥ 10.8 , P value ≤ 0.001 ; chi-square distribution, 1 degree of freedom).

Exposure–response model

Pharmacokinetic and exposure–response modeling were performed sequentially. The individual predicted golimumab

serum concentrations and cumulative areas under the golimumab concentration–time curve at days 14, 28, 42, and 98 were obtained from the empirical Bayesian estimates and individual dosing histories during estimation of the parameters of the final pharmacokinetic model. A Markov model then was implemented to explore the relationship between these golimumab exposure metrics and the probability of achieving endoscopic remission at day 98 (Fig. 1). The golimumab exposure metrics were modeled to affect the transition probabilities between Mayo endoscopic subscores of 3, 2, and combined 1 and 0 (representing endoscopic remission). A detailed description of the exposure–response model is given by Dreesen et al.²²

Model evaluation

The goodness of fit of the pharmacokinetic model was assessed using plots of the observed vs population- and individual-predicted golimumab serum concentrations and plots of conditional weighted residuals vs population-predicted golimumab serum concentrations and time. Final pharmacokinetic model evaluation was performed using a prediction-corrected visual predictive check (pcVPC) by 1000 simulated data sets. Shark plots were generated to investigate how the OFV differences between the base and the final pharmacokinetic and exposure–response models are distributed across individuals. Standard errors for the parameter estimates were obtained from the covariance step. As the bootstrap is limited in use due to the unbalanced sampling design of the study, sampling importance resampling (SIR) was adopted for parameter uncertainty estimation.²³ Pharmacokinetic stochastic simulations were performed ($n = 1000$) using Berkeley Madonna (version 8.318; Berkeley Madonna Inc., University of California, Berkeley, CA, USA).

Statistical Analyses

Data from the 3 studies were imported in R (version 3.5.1; R Foundation for Statistical Computing, R Core Team, Vienna, Austria) for data wrangling, visualization, and statistical analyses.²⁴ Graphics were generated using the ggplot2

FIGURE 1. Schematic representation of the golimumab exposure–response Markov model. The 3 observed states and 6 transitions were described using 4 parameters: the baseline proportions of patients with Mayo endoscopic subscores of 3 and 2 (ie, $P_{3, \text{baseline}}$ and $P_{2, \text{baseline}}$) and the transition probabilities corresponding to going from a baseline Mayo endoscopic subscore of 3 to 2 (ie, $P_{3 \rightarrow 2}$) and from 2 to 1 or 0 (ie, $P_{2 \rightarrow 1,0}$). All other transition probabilities are implicit: $P_{3 \rightarrow 3} = 1 - P_{3 \rightarrow 2}$, $P_{2 \rightarrow 3} = 1 - P_{3 \rightarrow 2}$, $P_{2 \rightarrow 2} = 1 - P_{2 \rightarrow 1,0}$, and $P_{1,0 \rightarrow 2} = 1 - P_{2 \rightarrow 1,0}$.

package in RStudio (version 1.1.383; R Studio, Inc., RStudio Team, Boston, MA, USA).²⁵

Descriptive statistics were stated as percentages for discrete variables and as median (interquartile range) for continuous variables. ATG and biomarker concentrations below the limit of quantification were replaced with the limit of quantification. Golimumab serum concentrations below the limit of quantification were replaced with the limit of quantification for statistical analyses other than population modeling. Available case analysis was implemented to deal with missing endoscopy data. The Fisher exact test was used for the analysis of discrete variables. The Wilcoxon signed rank test was used for analysis of paired measurements. Unpaired data were analyzed with the Wilcoxon rank sum test. Diagnostic performance was assessed with receiver operating characteristic curve (ROC) analysis. A therapeutic threshold value was selected using the Youden *J* statistic.²⁶ Generalized linear model selection was performed by heuristic searches using the *glmulti* R function based on the lowest small-sample corrected Akaike Information Criterion.²⁷ A 2-sided *P* value ≤ 0.050 denoted statistical significance.

ETHICAL CONSIDERATIONS

The studies were approved by the local Ethics Committee of the University Hospitals Leuven (study 1: B322201630705/S59372; and study 2: B322201213950/S53684) and the Republic of Slovenia National Medical Ethics Committee (study 3: 0120-013/2016-2). The prospective study (study 1) is registered at ClinicalTrials.gov with identifier NCT02910375. All studies were conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients provided written informed consent before study participation.

RESULTS

Data Source

A total of 56 adult patients with UC were included for the population pharmacokinetic model building (Table 1). Golimumab serum concentrations were obtained from 710 blood samples (296 DBS samples and 414 peripheral venipuncture samples) (Supplementary Fig. 1). None of the samples had a golimumab serum concentration below the limit of quantification. Still, ATG were detected in 15/710 samples (2%) from 7/56 patients (13%) using the drug-tolerant assay. Eleven patients (20%) had previously been treated with another biological (infliximab or adalimumab).

Population Pharmacokinetic Analysis

Base model

The data were best described by a 2-compartment model with linear absorption and elimination (Table 2). Including interindividual variability on the apparent linear clearance (CL/F),

on the apparent volume of distribution in the central compartment (V_c/F), and on the apparent volume of distribution in the peripheral compartment (V_p/F) significantly improved the model fit. The η -shrinkage of the empirical Bayesian estimates of the interindividual random effects was 3%, 13%, and 18% for CL/F, V_c/F , and V_p/F , respectively. The residual error was best described using combined additive and proportional error models for venipuncture and DBS samples separately. The ϵ -shrinkage was 7%.

Covariate analysis and final model

From the univariate analysis, CL/F was shown to be significantly higher when ATG were present, when albumin was lower, and when the patient was previously treated with another biological ($P < 0.0001$, $P = 0.019$, and $P = 0.028$, respectively) (Supplementary Table 1). V_p/F was significantly higher in patients who had previously been treated with another biological ($P < 0.0001$). After stepwise forward addition and backward elimination, ATG and previous biological therapy were found to correlate significantly with CL/F and V_p/F , respectively, and thus remained in the final model. The apparent golimumab clearance and volume of distribution in the peripheral compartment were estimated in the final model from the following equations:

$$CL/F = (0.417 \times ATG0) + (0.545 \times ATG1) \times e^{0.278} \quad (1)$$

$$V_p/F = (3.85 \times PREV0) + (15.3 \times PREV1) \times e^{1.77}$$

where either dummy variable ATG0 (ATG absent) or ATG1 (ATG present) took the value 1 and, similarly, PREV0 (no previous biological therapy) or PREV1 (previous biological therapy) took the value 1, whereas the other dummy variable remained at the initialized value of 0. Golimumab clearance was 31% higher when ATG had been detected. Patients who had received previous biological therapy had a 4.0-fold higher volume of distribution in the peripheral compartment. Previous biological therapy and detection of ATG were not correlated (phi coefficient of correlation, 0.08; $P = 0.614$). Body weight was not identified as a significant covariate in our analysis.

Evaluation of the final model

The goodness-of-fit plots showed that the model described the observed data adequately (Supplementary Fig. 2). The pcVPC showed a good predictive capacity of the model (Fig. 2). The median and 95% confidence intervals (CIs) obtained from SIR are reported in Table 2. Twenty-nine (52%) patients had a decrease in the OFV with the final model vs the base model (Supplementary Fig. 3A). The simulated effects of ATG and previous biological therapy on the golimumab pharmacokinetics are shown in Figure 3. The unexplained interindividual variability remained high after the introduction of the 2 covariates (57% and 221% for CL/F and V_p/F , respectively).

TABLE 2. Golimumab Population Pharmacokinetic and Pharmacodynamic Parameter Estimates

Parameter	Base Model	Final Model		
	Estimate (%RSE) [%Shrinkage]	Estimate (%RSE) [%Shrinkage]	SIR Estimate (SIR 95% CI)	SIR Deviation, %
Pharmacokinetic model	OFV 957.9	OFV 922.6		
Typical values				
k_a , d ⁻¹	0.473 (15)	0.495 (15)	0.501 (0.417 to 0.596)	+1.21
CL/F, L/d	0.442 (8)	–	to	–
When no ATG	–	0.417 (9)	0.413 (0.370 to 0.464)	–0.96
When ATG	–	0.545 (11)	0.541 (0.464 to 0.627)	–0.73
V_c /F, L	8.64 (8)	8.82 (8)	8.88 (7.79 to 9.83)	+0.68
Q/F, L/d	0.430 (25)	0.469 (20)	0.461 (0.368 to 0.587)	–1.71
V_p /F, L	4.48 (35)	–	to	–
When no PREV	–	3.85 (43)	3.93 (3.03 to 5.18)	+2.08
When PREV	–	15.3 (43)	15.2 (8.48 to 31.0)	–0.65
Dried blood spot-to-venipuncture conversion factor	4.09 (3)	4.14 (3)	4.14 (3.95 to 4.34)	0.00
Interindividual variability				
CL, %	58.7 (12) [3]	56.6 (13) [4]	57.1 (45.0 to 71.8)	+0.88
V_c /F, %	29.4 (15) [13]	28.3 (16) [14]	28.6 (22.4 to 36.1)	+1.06
V_p /F, %	169.0 (17) [18]	220.7 (22) [21]	240.4 (133.7 to 419.8)	+8.93
Corr(CL/F- V_c /F), %	38.1 (39)	37.9 (43)	37.2 (13.7 to 64.1)	–1.85
Corr(CL/F- V_p /F), %	–39.9 (45)	–43.0 (31)	–43.5 (–64.1 to –16.8)	+1.16
Corr(V_c /F- V_p /F), %	58.5 (24)	48.6 (32)	48.3 (21.6 to 72.5)	–0.62
Residual errors				
Venipuncture				
Proportional error, %	2.43 (19) [7]	2.62 (20) [7]	2.61 (1.74 to 3.66)	–0.38
Additive error, mg/L	0.976 (28) [7]	0.874 (34) [7]	0.886 (0.650 to 1.117)	+1.37
Dried blood spot				
Proportional error, %	5.38 (19) [7]	6.00 (6) [7]	6.04 (4.79 to 7.17)	+0.67
Additive error, mg/L	0.134 (97) [7]	0.059 (104) [7]	0.060 (0.025 to 0.136)	+1.69
Exposure–response model	OFV 143.0	OFV 121.5		
$C_{98,50}^{3 \rightarrow 2}$, mg/L	–	0.5 (48)	0.5 (0.2 to 1.0)	0.00
$C_{98,50}^{2 \rightarrow 1,0}$, mg/L	–	4.1 (36)	4.2 (2.0 to 8.1)	+2.44

Hill's coefficients were fixed to 1 in the exposure–response model.

Abbreviations: –, not applicable; $C_{98,50}^{3 \rightarrow 2}$, predicted golimumab serum trough concentration at day 98 (C_{98}) corresponding to a 50% probability of going from a Mayo endoscopic subscore of 3 to 2; $C_{98,50}^{2 \rightarrow 1,0}$, predicted golimumab serum trough concentration at day 98 (C_{98}) corresponding to a 50% probability of going from a Mayo endoscopic subscore of 2 to 1 or 0; Corr, correlation; k_a , absorption rate constant; PREV, previous biological therapy; Q/F, apparent intercompartmental clearance; RSE, relative standard error.

Exposure–Response Analysis

A total of 40/56 patients (71%) underwent endoscopies both at baseline and at week 14 with evaluation of the Mayo endoscopic subscore. Endoscopic remission was achieved in 14/40 patients (35%) (Supplementary Fig. 4). These patients had higher observed and model-predicted golimumab serum trough concentrations from week 4 onwards (Supplementary Table 2). A golimumab serum trough concentration threshold at week 6 of 7.4 mg/L was identified to predict endoscopic remission at week 14, with a

positive predictive value of 83% and a negative predictive value of 82% (Fig. 4). In addition, the estimated area under the golimumab concentration–time curve from week 0 to week 6 was higher when endoscopic remission was achieved ($P = 0.015$) (Supplementary Table 2).

The predicted golimumab serum trough concentration at week 14 was identified as the best predictor of endoscopic remission (lowest OFV) (Table 2). Thirty-two (80%) patients had a decrease in the OFV with the final model vs the base model (Supplementary Fig. 3B). The different exposure metrics were

FIGURE 2. Prediction-corrected visual predictive check. The solid line connects the observed median prediction-corrected golimumab concentrations per bin. The dashed lines connect the fifth and 95th percentiles of the prediction-corrected observations. The light and dark shaded areas indicate the 90% prediction intervals of the fifth and 95th percentiles and the median, respectively, of the simulated data ($n = 1000$). The observed prediction-corrected golimumab concentrations are represented by open circles.

FIGURE 3. Simulated golimumab serum concentration–time profiles demonstrating the impact of previous biological therapy and antibodies to golimumab on golimumab exposure after standard induction and 100-mg maintenance dosage regimen. Data represent the median and 95% prediction interval of 1000 simulated patients.

FIGURE 4. The kernel density plot represents the distributions of predicted golimumab serum trough concentrations at week 6 in patients who achieved endoscopic remission at week 14 (green) and those who did not (red). The vertical line indicates the threshold of 7.4 mg/L, established using Youden's J statistic. The numbers of true positive (TP), false positive (FP), true negative (TN), and false negative (FN) patients for this threshold are indicated, as are the sensitivity (se), specificity (sp), positive predictive value (ppv), negative predictive value (npv), positive likelihood ratio (+lr), and negative likelihood ratio (-lr). The receiver operating characteristics curve. The gray shaded area represents the 95% confidence interval of the specificity based on 2000 bootstrap replicates.

highly correlated (Spearman's $\rho > 0.5$) (Supplementary Fig. 5). Following the label-recommended induction dosing scheme, a week 14 golimumab serum trough concentration of 3.2 mg/L was estimated to yield 41% of patients attaining endoscopic remission (Fig. 5). Similarly, targeting a week 6 golimumab serum trough concentration of 7.4 mg/L predicted 44% of patients attaining endoscopic remission (data not shown). Only 11/40 (28%) and 18/40 (45%) patients in our cohort reached these week 6 and 14 serum trough concentration targets, with negative predictive values of 82% and 67%, respectively (Supplementary Table 2).

Predictors of Response

A Mayo endoscopic subscore of 3, a lower serum albumin at baseline, and concurrent treatment with corticosteroids were identified as the most important predictors compromising an individual's probability of achieving endoscopic remission (Supplementary Table 3, Supplementary Fig. 6).

DISCUSSION

This is the first real-world population pharmacokinetic-pharmacodynamic study of golimumab in adult patients with UC. The pooled golimumab serum concentration-time data of 56 patients were adequately described by a 2-compartment

model with first-order absorption and elimination. The availability of a validated DBS micro-sampling method facilitated frequent sampling while limiting the patient burden, thereby aiding the identification of the peripheral compartment, which was not identified by Xu et al., who relied on the relatively sparse sample collection from the PURSUIT and GO-KIDS programs.¹⁰ As DBS can be self-collected by the patient, requires no centrifugation, and can be transported at room temperature, it is a convenient field work substitute for serum sampling in clinical studies.¹¹

The estimated values of the golimumab pharmacokinetic parameters are generally consistent with those reported in literature.^{10, 15, 18, 19} The DBS-to-venipuncture conversion factor estimated from the model was $4.1\% \pm 3\%$ and was similar to that obtained from the regression analysis by Detrez et al.¹¹ ATG and previous biological therapy were found to increase the golimumab apparent clearance and the volume of distribution in the peripheral compartment, respectively. Despite the statistical significance of the covariate effects on the golimumab pharmacokinetics, the remaining unexplained interindividual variability remains large, opposing a priori dose stratification.

In the study by Xu et al., the presence of ATG increased golimumab clearance by 21%, which is less than the 31% in

FIGURE 5. Goodness of fit of the exposure–response model. Observed (tiles) fractions of patients attaining postinduction Mayo endoscopic subscores of 3 (red), 2 (yellow), and ≤ 1 (green) and predicted (lines) fractions of patients attaining postinduction Mayo endoscopic subscores of 3 (red) and >1 (green) as a function of the predicted golimumab serum trough concentration at week 14 (4 quantiles). Gray numbers indicate the number of patients in each bin.

our study.¹⁰ However, they used a drug-sensitive ATG assay, whereas we applied a drug-tolerant ATG assay.^{6,19} Nonetheless, the effect of ATG on golimumab clearance cannot be compared because different calibrators were used, different strategies were used for sample selection, and other modeling approaches were used (see the “Methods” section).^{28,29} Although Xu et al. classified patients as ATG positive or negative depending on the detection of ATG at any visit (time-constant approach), we considered a time-varying approach, where patients were ATG positive once ATG were detected, until later proof of the absence of ATG. Taking into account the transiency in ATG detection resulted in the largest drop in OFV in the univariate analysis.

Although often suggested, we have now confirmed that previous biological therapy negatively affects the golimumab pharmacokinetics, and thereby also the response.⁹ Our findings demonstrate the importance of inclusion of these patients in future clinical drug development programs. Although the 200/100-mg and 400/200-mg induction schemes resulted in similar proportions of biologically naïve PURSUIT-SC patients attaining the efficacy end points, patients previously treated with another biological may benefit from higher induction dosing.³ There is currently no biological reason for the larger volume of distribution in the peripheral compartment in patients previously

treated with another biological, but this may be explained by a larger in-tissue TNF α load or protein-losing enteropathy.^{30,31} None of the available variables in our cohort correlated with previous biological therapy (all $P > 0.050$, data not shown). Further studies are needed to investigate the underlying mechanism in detail.

Unlike the model of Xu et al., body weight was not an influential covariate of the golimumab pharmacokinetics in our analysis.¹⁰ This may be explained by the relatively limited variability in body weights in our cohort, as compared with the cohort of Xu et al., which also included pediatric data. In addition, we did not identify the effects of comedication and serum albumin.

Sixty-five percent of the patients in our cohort did not achieve endoscopic remission at week 14, as compared with the 58% of patients not achieving endoscopic remission at week 6 in PURSUIT-SC.³ Patients with endoscopic remission were found to have higher golimumab exposure. By performing ROC analysis, as was also done by Adedokun et al., we identified a golimumab serum trough concentration threshold of 7.4 mg/L at week 6, which is much higher than the previously suggested 2.5 mg/L for targeting clinical response.⁵ Only 28% of the patients in our study attained the 7.4-mg/L target, suggesting the potential benefits of intensified golimumab induction dosing. In addition, the poor prognosis when below this

threshold (17% endoscopic remission) and the good prognosis when above this threshold (82% endoscopic remission) support a role for TDM for targeting this threshold. Similarly, we identified a golimumab serum concentration threshold at week 4 of 11.4 mg/L, which is again higher than the 7.4-mg/L threshold for clinical response proposed by Adedokun et al.⁵

Our exposure–response model was informed by individual predicted golimumab serum concentrations or cumulative areas under the golimumab concentration–time curves at days 28, 42, and 98 after the start of induction therapy. These exposure metrics informed the probabilities of transitioning from (i) a baseline Mayo endoscopic subscore of 3 to a subscore of 2 at week 14 and (ii) a baseline Mayo endoscopic subscore of 2 to a subscore ≤ 1 at week 14. The OFV dropped with 21.5 points from the null model, where transition probabilities were estimated by chance alone, to the model informed by the individual predicted golimumab serum trough concentration at week 14, which supports a role for exposure optimization by means of TDM.

Our population pharmacokinetic and exposure–response models allow dose selection for targeting a certain golimumab exposure and the associated probability of endoscopic remission. However, as the interindividual variability remains largely unexplained, Bayesian methodology can be used for better estimating the individual patients' model parameters. Therefore, early sampling is required, which may be facilitated by DBS or another validated micro-sampling technique (eg, volumetric absorptive micro-sampling), and implementation of the model in a dedicated TDM software tool is a requisite.

As opposed to the currently used “one dose fits all” approach, our suggested “one exposure fits all” approach gives all patients a more equal chance of achieving endoscopic remission. Model-based golimumab dose optimization thus provides a more justifiable approach for facilitating the decision on drug continuation. However, in patient populations with higher proportions of patients previously treated with biologicals, higher doses will be needed, as these patients need more drug to achieve the same exposure. In addition, in a population consisting of more patients with a baseline Mayo endoscopic subscore of 3, higher doses are needed, as more patients need additional exposure for transitioning from subscore of 3 to 2.

The results of our analyses must be interpreted carefully. First, the sample size of the study was relatively small as compared with the PURSUIT studies. Although rich sampling resulted in high precision of parameter estimates, 56 patients seemed to be insufficient for detecting previously identified effects of serum albumin and body weight. Second, our model assumes time-invariant pharmacokinetics (apart from the ATG effect), although it has been shown that the infliximab pharmacokinetics can change with disease activity.³² Future studies should consider evaluating time-varying serum albumin for capturing the negative effect of the inflammatory burden on golimumab exposure. Third, our population pharmacokinetic model was built using data from patients who all received the

standard golimumab induction therapy. Therefore, our model does not support interval shortening and dose escalations, resulting in a golimumab exposure outside the range observed in this study. Fourth, the golimumab assay used by Xu et al. detected significantly lower concentrations as compared with the assay used in our study.²⁹ Despite an excellent correlation between both assays, one cannot directly compare measurements and should thus be careful when comparing therapeutic thresholds between the studies. Also, the ATG assay comparison was inconclusive.²⁹ Furthermore, no ATG were detected within the first 14 weeks of therapy, but this might be biased by our sample selection strategy (see the “Methods”). Finally, the currently available dose strengths of 50 mg and 100 mg limited the flexibility of golimumab dose individualization. Dose-adjustable delivery systems may be cost-effective in the future, but most urgent is the need for repeating the PURSUIT-SC study including patients in whom previous biological therapy has failed, similar to what was done in the vedolizumab GEMINI-3 and ustekinumab UNITI-2 studies.^{33, 34}

CONCLUSIONS

To conclude, the results of our study support a role for model-based TDM during golimumab induction therapy. Higher golimumab exposure needs to be targeted for achieving endoscopic remission as compared with clinical outcomes. With the currently approved induction dosing, only 25% and 43% of patients reached the proposed 7.4-mg/L and 3.2-mg/L serum trough concentration targets at days 42 and 98, respectively, suggesting underexposure in a substantial proportion of patients. Prospective trials are urged, as poor response to standard golimumab induction therapy compromises its future use in clinical practice.

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