Journal of Crohn's and Colitis, 2019, 1248–1256
doi:10.1093/ecco-jcc/jjz050
Advance Access publication March 1, 2019
Original Article

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Subcutaneous Absorption Contributes to Observed Interindividual Variability in Adalimumab Serum Concentrations in Crohn's Disease: A Prospective Multicentre Study

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Abstract

Background and Aim: Therapeutic drug monitoring is used to optimise adalimumab therapy in patients with Crohn's disease [CD]. However, the interindividual variability in drug absorption and the quantitative effect on drug clearance of anti-adalimumab antibodies [AAA], measured with a drug-resistant assay, are unclear. We aimed to characterise adalimumab population pharmacokinetics [PopPK] and identify determinants of interindividual variability in patients with CD.

Methods: In a prospective multicentre open-label cohort study in 28 patients with CD starting adalimumab therapy peak, intermediate, and trough serum samples were analysed for adalimumab and AAA concentrations using a drug resistant assay. Adalimumab concentration-time data were analysed by non-linear mixed effects modelling and were adequately described by a PopPK model with first-order absorption and one-compartment disposition with linear elimination. Clinical remission at Week 12 [W12] was defined as a Harvey-Bradshaw index ≤4.

Results: The absorption rate, volume of distribution, and clearance estimates of a typical patient were respectively 0.343 /day, 7.8 L, and 0.330 L/day. A 4-fold difference in the range of adalimumab concentrations was observed 7 days after the first dose and found to be inversely correlated with baseline lean body weight [LBW], soluble tumour necrosis factor [s-TNF], and s-TNF receptor-1 whereas positive AAA and higher LBW were found to be important predictors of accelerated clearance. An adalimumab concentration at W12 of >7.3 μg/mL was significantly associated with achieving clinical remission at W12.

Conclusion: Variability in subcutaneous drug absorption is an important contributor to the observed interindividual variability in adalimumab concentrations, in addition to drug clearance [ClinicalTrials.gov NCT02450513].

Key Words: Crohn's disease; adalimumab; pharmacokinetics; therapeutic drug monitoring; absorption rate

1. Introduction

Adalimumab, a fully human subcutaneously [SC] administered immunoglobulin G1 tumour necrosis factor-α [TNF-α] antagonist, is effective for inducing and maintaining clinical response and remission in patients with moderately-to-severely active Crohn's disease [CD].[1–4] A dose-response relationship was shown for adalimumab, as patients induced with 160 mg at Week 0 and 80 mg at Week 2 compared with those receiving 80/40 mg, 40/20 mg, or placebo, were more likely to achieve clinical remission at Week 4 [36%, 24%, 18%, and 12%, respectively].[2] Similarly, two pivotal studies showed that maintenance of clinical remission was achieved in a numerically higher proportion of patients treated with adalimumab 40 mg every week [EW] compared with 40 mg every other week [EOW], or placebo at Week 56 [45%, 40%, and 15%, for combined rates, respectively].[1,3] An observational cohort study in 168 CD patients with median follow-up of almost 2 years showed that discontinuation of adalimumab therapy because of loss of response to therapy was directly correlated with low adalimumab serum trough concentrations.[5] Antibodies to adalimumab [AAA] were detected in 9% of patients with a drug-sensitive AAA assay and 20% of patients with a drug-tolerant AAA assay, and were more frequently observed in patients who also had low adalimumab serum trough concentrations.[6] Specifically, a serum adalimumab trough concentration at Week 4 of <5 µg/mL and use of adalimumab monotherapy [i.e., not in combination with an immunomodulator] were associated with AAA formation.[6] So far, AAA have mainly been measured during maintenance therapy and at trough, yet little is known about the timing of AAA development, especially during induction therapy and their quantitative impact on pharmacokinetics.[7]

Several observational cohort studies found an association between adalimumab serum trough concentrations and clinically important outcomes such as clinical, biomarker endoscopic, and histological remission.[8–16] However, there is variability in the proposed cut-points, which can be partly attributed to limited data about quantitative adalimumab PK and whether adalimumab serum concentrations should be measured at peak, intermediate, or trough.[17,18] Indeed, SC administration of adalimumab is characterised by a slow absorption into the systemic circulation, with a time to peak serum drug concentration of 5 days and a bioavailability of 64%; however, little is known about the variability between subjects and factors influencing variability.[19] The concentration-time profile of adalimumab was evaluated quantitatively in several cohorts of patients with CD, yet only trough concentrations were available, which did not allow precise characterisation of the absorption phase.[20–22] Furthermore, in all studies a drug-sensitive AAA assay was used which may have underestimated the proportion of immunised patients and the quantitative effect of AAA on adalimumab clearance. Compartmental population PK analyses of adalimumab in patients with rheumatoid arthritis [RA] have been done previously.[23,24] However, these data may not be transferable to patients with CD, since clearance may be upregulated, as shown for infliximab where clearance was found to be 30% higher in patients with CD vs RA.[25,26]

The objectives of our prospective observational study with intense sampling were to develop a population PK model in patients with moderately-to-severely active CD starting adalimumab therapy, and to evaluate the impact of covariates on adalimumab disposition.

2. Methods

2.1. Study design, participants, and outcomes

This was a prospective observational multicentre study conducted at the University Hospitals Leuven, Leuven, Belgium, and AZ Delta, Roeselare, Belgium, with a primary objective to develop a population PK model for adalimumab in patients with Crohn's disease. Patients with moderately-to-severely active CD, naïve for TNF antagonists and starting adalimumab therapy as per discretion of the treating physician, were eligible for the study. Participants received adalimumab SC at a dose of 160 mg at Week [W] 0, 80 mg at W2, 40 mg at W4, and every other week [EOW] thereafter. Patients were not on a concomitant immunomodulator [azathioprine, 6-mercaptopurine, or methotrexate]. Serum samples were collected before and 2 h after first injection, intermediate at Weeks 1 and 3, and before injection at Weeks 2, 4, and 12. Clinical remission was defined by a Harvey-Bradshaw index [HBI] of ≤4 and assessed at Weeks 0, 4, and 12. Serum albumin was measured at Week 0 and high-sensitivity C-reactive protein was measured at Weeks 0, 4, and 12 as part of routine clinical care. Biologic remission was defined by a C-reactive protein concentration of <5 mg/L.

The study protocol was reviewed and approved by the Institutional Review Board [S53297] and by the Federal Agency for Medicines and Health Products [EudraCT: 2011-004632-54] and registered on ClinicalTrials.gov [NCT02450513]. All participants provided written informed consent.

2.2. Laboratory analysis

An in-house developed TNF-coated enzyme-linked immunosorbent assay [ELISA] was used to measure adalimumab serum concentrations from 0.2 to 22.5 µg/mL.[27] An in-house developed drug-resistant AAA assay was applied for accurate quantification of AAA with concentrations up to 25 µg/mL calibrator equivalents. The assay has a lower limit of detection and a lower limit of quantification of 0.77 and 3.61 µg/mL equivalents, respectively.[28] This assay is specific to AAA detection and remains accurate for quantification in the presence of adalimumab up to 50 µg/mL.

Soluble TNF [s-TNF] and soluble TNF receptor-1 [s-TNFR-1] were measured in serum samples using the Proinflammatory Panel 1 [human TNF] Kit and the Human TNF-RI Ultra-Sensitive Kit, respectively [Meso Scale Discovery, USA] according to manufacturer's instructions.

2.3. Pharmacokinetic modelling

Adalimumab serum concentration-time data were analysed using non-linear mixed-effects modelling software [NONMEM 7.3]. For this assessment, a log-transform both sides [LTBS] approach was used, and therefore the adalimumab serum concentrations used for modelling were natural logarithm [Ln] transformed. PopPK models were assessed for appropriateness using conventional criteria, including convergence status, likelihood ratio test, parameter precision, and assessment of goodness-of-fit. A model was accepted only if it converged with a successful covariance step.

First the structural PopPK model component was established, consisting of a first-order absorption and one-compartment disposition with first-order elimination, and was parameterised in terms of estimated absorption [K_A], apparent volume of distribution [V/F], and apparent clearance [CL/F] [ADVAN2, TRANS2] using the FOCE-I fitting subroutine. This base model was

found to adequately describe the observed serum adalimumab concentration-time data.

Second, the stochastic model was introduced to describe the interindividual variability model component and the residual error model component. Interindividual variability was included on K_A, V/F, and CL/F, and covariance of these parameters was accounted for using a full omega block structure. Because an LTBS approach was used, the differences between model-predicted and observed concentrations were modelled with a constant coefficient of variation proportional error model [additive on the log scale]. This approach allows simulations to be conducted without the model producing negative concentration values, and has a beneficial effect on stabilising model performance.

Third, the covariate model component was introduced to describe the influence of fixed effects [e.g., demographic factors and baseline laboratory values] on PK parameters. The covariate analysis was performed using baseline values that were normalised to the population median value. Tested covariates for the PopPK dataset were: age [years], sex, body weight [kg], body mass index [kg/m^2], body surface area [m^2], lean body weight [kg], albumin [g/dL], C-reactive protein [mg/dL], haemoglobin [g/dL], HBI, s-TNF [pg/mL], s-TNFR-1 [ng/mL], and time-varying AAA [µg/mL equivalents]. Body surface area [BSA] was estimated using the following formula[29]:

$$\text{BSA } [\text{m}^2] = \text{Body Weight}^{0.425} \ [\text{kg}] \cdot \text{Height}^{0.725} \ [\text{cm}] \cdot 0.007184,$$

lean body weight [LBW] was estimated using the following equations[30]:

$$\text{For men}: \ \text{LBW } [\text{kg}] = (0.32810 \cdot \text{Body Weight } [\text{kg}]) + (0.33929 \cdot \text{Height } [\text{cm}]) - 29.5336$$

$$\text{For women}: \ \text{LBW } [\text{kg}] = (0.29569 \cdot \text{Body Weight } [\text{kg}]) + (0.41813 \cdot \text{Height } [\text{cm}]) - 43.2933$$

and continuous covariates, such as albumin concentration, were modelled using the general equation:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} cov_i^{\theta i},$$

where TVP represents the typical value of the model-predicted PK parameter, for example, V/F, for the 'typical' individual with covariate value[s] cov_i; P_{pop} represents the population central tendency for the PK parameter TVP; cov_i represents the individual value for the covariate normalised to a reference value; and θ_i represents a scale factor relating the covariate to the structural parameter.

Categorical covariates, such as sex, were modelled using the general equation:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} (1 + cov_i \cdot \theta_i),$$

where cov_i is fixed to 1 for the test subgroup [e.g., females] and θ_i represents a scale factor relating the covariate to the structural parameter.

Covariate analysis was performed by examining the influence of each covariate alone on the base model. The resulting single, nested covariate models were ranked by the p-value for the likelihood ratio test comparison with the base model. Covariates with a p <0.01 [≥6.64 reduction in the minimum objective function value] were considered in more detail and pooled into the full multivariable model assessment. The full model was subjected to a backward elimination process, where each covariate was eliminated using p = 0.001 for the likelihood ratio test comparison. Removal of a covariate was considered significant at p <0.001, i.e., only covariates associated with an increase of at least 10.83 in objective function value were retained in the model.

After all covariates that did not meet the criteria for retention were eliminated, the final model was evaluated for model performance. For a visual predictive check, adalimumab serum concentrations were simulated 1000 times with dose and covariate data used in the model development dataset, using the same sampling times. The simulated and observed data were then compared graphically. Non-parametric bootstrap replicates of the final PK model [N = 1000] were generated to evaluate parameter precision. Runs that converged successfully were used to generate median and 95% confidence intervals [CIs] of the model parameters and impact of the covariates on these parameters.

Sample records with missing adalimumab serum concentration data were excluded from the analysis, as well as adalimumab serum concentrations with no recorded actual sample time. Observations with an adalimumab concentration below the limit of quantification [BLQ] of the analytical assay were changed to one-half of the lower limit of quantification throughout the dataset, and the M3 method was used for these BLQ observations.[31] The last observation carried forward method was used for missing covariates.

2.4. Statistical analysis

Variables not normally distributed were presented as median [interquartile range, IQR]. The t test and Mann-Whitney test were used for the comparison of respectively normally and not normally distributed variables. The correlation of normally and not normally distributed variables was expressed using the Pearson and Spearman correlation coefficient, respectively. A p-value of <0.05 was considered significant. Receiver operating characteristic [ROC] curve analysis was performed to identify an adalimumab serum concentration threshold that corresponded clinical remission with Youden index, which maximises both sensitivity and specificity of the ROC curve.[32] GraphPad Prism 8 [San Diego, CA, USA] was used as statistical software.

3. Results

3.1. Patients and outcomes

The final analysis data set consisted of a cohort of 28 patients with CD, with 185 analysable records. Patient demographics and clinical characteristics at baseline are shown in Table 1. The median [interquartile range, IQR] age was 37 years [30–49] and 53.7% were female. Most patients were in active disease at baseline with a median [IQR] HBI score of 7 [4–12] and C-reactive protein of 8.0 mg/L [2.1–22.0]. By W12, clinical remission was observed in 19/28 patients [67.9%]. Of the patients with HBI >4 at baseline, 13/21 patients [61.9%] achieved clinical remission by W12. By W12, biologic remission was observed in 20/28 patients [71.4%]. Of the patients with C-reactive protein ≥5 mg/L at baseline, 10/18 patients [55.6%] achieved biologic remission by W12. AAA were detected in 5/28 patients [17.9%], as early as W2 in one patient, and median concentration of AAA by W12 was 1.8 µg/mL equivalents. Of those who developed AAA, 3/5 patients were in clinical remission at W12.

Table 1. Patient demographics and clinical characteristics at study enrolment of all 28 included Crohn's disease patients.

Age, years	37 [30–49]
Sex, male, *n* [%]	13 [46.4]
Disease location, *n* [%][a]	
Ileal disease [L1]	12 [42.9]
Colonic disease [L2]	6 [21.4]
Ileocolonic disease [L3]	10 [35.7]
Upper GI involvement [L4]	2 [7.1]
Disease behaviour, *n* [%][a]	
Inflammatory [B1]	17 [60.7]
Stricturing [B2]	10 [35.7]
Penetrating [B3]	1 [3.6]
Perianal disease [p]	4 [14.3]
Active perianal fistulae, *n* [%]	1 [3.6]
Previous ileocolonic resection, *n* [%]	6 [21.4]
Smoking status, *n* [%]	
Active smoking	7 [25]
Previously smoking	7 [25]
Never smoked	14 [50]
Body weight [kg]	66.0 [55.3–73.0]
Body mass index [kg/m^2]	22.6 [19.1–24.3]
Body surface area [m^2]	1.8 [1.6–1.9]
Lean body weight [kg]	47.8 [43.6–54.7]
Serum albumin [g/dL]	39.9 [36.4–43.7]
C-reactive protein [mg/L]	8.0 [2.1–22.0]
Haemoglobin [g/dL]	13.2 [12.0–14.4]
Harvey-Bradshaw index	7 [4–12]
Soluble tumour necrosis factor [pg/mL]	0.68 [0.49–0.93]
Soluble tumour necrosis factor receptor-1 [ng/mL]	2.63 [2.04–3.16]
Concomitant corticosteroids, yes:no:n/a	12:15:2 [39:54:7]

Data are median [interquartile range] or *n* [%]
GI, gastrointestinal; n/a: not available.
[a]Following Montreal classification.[42]

3.2. Pharmacokinetics

Two h following administration of 160 mg adalimumab, 18/26 patients [69%] had a detectable adalimumab serum concentration and the overall median [IQR] concentration was 0.6 [0.2–1.2] µg/mL. At 7 days after the first dose, the median [IQR] adalimumab serum concentration was 13.5 [10.5–19.2] µg/mL, with an almost 4-fold difference between the lowest [7.2 µg/mL] and the highest [26.8 µg/mL] concentration. An inverse correlation was observed between adalimumab serum concentration at Day 7 and the following variables at baseline: LBW [r = -0.558; p = 0.003], s-TNF [r = -0.512; p = 0.007], and s-TNFR-1 [r = -0.486; p = 0.012] [Figure 1].

The PopPK parameter estimates for adalimumab of the final model for a typical patient were for K_A = 0.343 /day, V/F = 7.8 L, and CL/F = 0.330 L/day [Table 2]. Adalimumab exhibited an interindividual variability for K_A, V/F, and CL/F of, respectively 103.9%, 35.6%, and 32.6%. Shrinkage on K_A, V/F, and CL/F were respectively, 6.3%, 26.7%, and 6.5%, implying that individual variance estimates of these parameters would be reliable. Covariate analysis showed that adalimumab CL/F increased for a typical patient with CD from 0.330 L/day to 0.525 L/day when becoming AAA-positive. Adalimumab CL/F also increased by LBW from 62.8 to 140.8% of the median value over the 5th to 95th percentile of the LBW range [38.7–58.3 kg].

3.3. PopPK model evaluation

Prediction-based diagnostic plots show the goodness-of-fit of the observed and the model predicted adalimumab serum concentration data [Figure 2]. A visual predictive check of the final PopPK model for all data shows no apparent bias or obvious mis-specification, suggesting that the model adequately described the adalimumab serum concentration-time data [Figure 3]. A total of 1000 non-parametric unstratified bootstrap replicates were generated for the final PK model. Of those, 718 [71.8%] converged successfully and were used to generate the 95% confidence intervals [CIs] for the model parameters and the impact of the covariates on these parameters [Table 2].

3.4. Exposure-response relationship

The median [IQR] adalimumab serum concentration at W12 was 10.4 [8.7–12.3] µg/mL in patients who were in remission at W12 compared with 5.7 [2.4–7.6] µg/mL in those who were not in remission at W12 [p = 0.008] [Figure 4]. Including only patients with HBI >4 at baseline, a ROC curve analysis identified an adalimumab serum concentration threshold of at least 7.3 µg/mL to be associated with clinical remission at W12 [sensitivity 75%, specificity 91.7%, area under ROC curve 0.81, p = 0.02] [Figure 5].

At W12, an inverse correlation was found between adalimumab serum trough concentration and s-TNF [r = -0.473; p = 0.015]. Furthermore, a significant decrease of median s-TNR-1 concentration from baseline to W12 was observed [W0: 2.63 to W12: 2.39; p = 0.020] across all patients.

4. Discussion

Here we developed a PopPK model for adalimumab in patients with CD, and found that the adalimumab concentration-time profile was adequately described by a model with first-order absorption and one-compartment disposition with linear elimination. Because of intense sampling at intermediate, peak, and trough time points, we could describe the interindividual variability in drug absorption and observed an almost 4-fold difference in the range of adalimumab concentrations at Day 7 after the first administration of 160 mg. These findings indicate that variability in subcutaneous drug absorption contributes to the observed interindividual variability in adalimumab concentration, in addition to drug clearance.

The PopPK parameter estimates for adalimumab of the final model for a typical Crohn's disease patient were for K_A = 0.343 /day, V/F = 7.8 L, and CL/F = 0.330 L/day. The apparent clearance was found to be similar to previously published PopPK models for adalimumab, where CL/F for a typical patient was estimated to be 0.42 L/day by Ternant *et al.* and 0.32 L/day by Berends *et al.*[20,21] However, the estimates for K_A were found to be similar but lower [0.15 /day and 0.2 /day] and different for V/F [13.5 L and 4.07 L] in the models by, respectively, Ternant *et al.* and Berends *et al.* These differences may be attributed to differences in sampling regimen, as the previous models were built using sparse sampling, mostly at trough, which may not allow precise estimation of parameter estimates for absorption and apparent volume of distribution, typically requiring sampling at peak and intermediate time points. Nor does sparse sampling allow characterisation of the interindividual variability of these parameters. Here we observed a strong correlation between baseline LBW, s-TNF, and s-TNFR-1 and Day 7 adalimumab serum concentrations. Although poorly understood, absorption of biologics is believed to be mainly through the lymphatic system, with an important role for the neonatal Fc receptor.[33] Our findings for adalimumab are consistent with previous observations that absorption is inversely correlated with different size measures, which can be explained by hypodermis thickness increasing with body weight.[34]

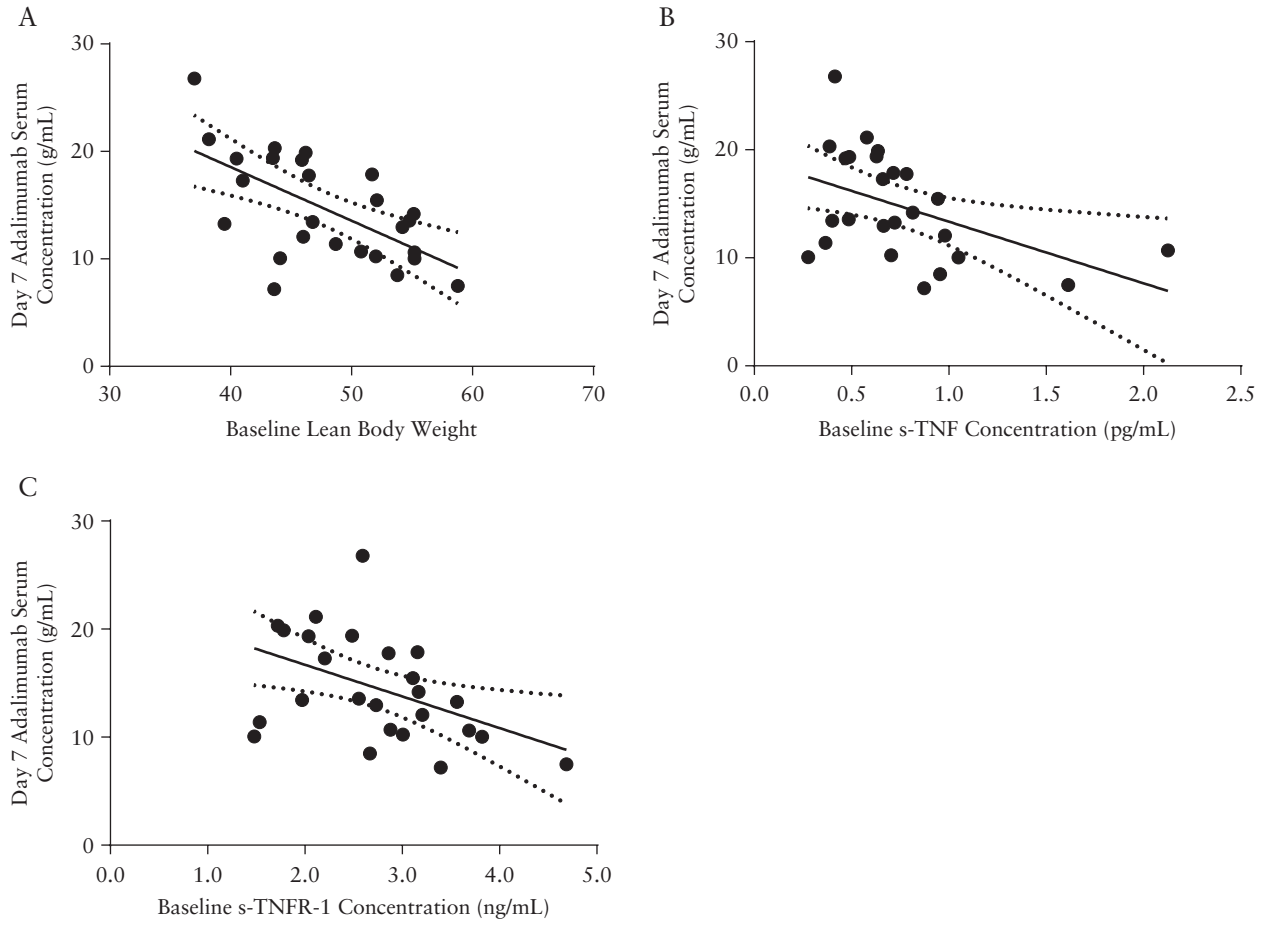

Figure 1. Correlation between adalimumab serum concentration at Day 7 and [A] baseline lean body weight [Spearman r = -0.558; $p = 0.003$], [B] baseline soluble tumour necrosis factor [Spearman r = -0.512; $p = 0.007$], and [C] baseline soluble tumour necrosis factor receptor 1[Spearman r = -0.486; $p = 0.012$]. Full line represents linear regression and dotted lines represent 95% confidence bands.

Table 2. Adalimumab PK parameter estimates of final population PK model for a typical patient[a] with CD.

Parameter	NONMEM		Bootstrap[b]	
	Estimate	SEE [%]	Median	95% CI
Ka [/day]	0.343	0.1	0.381	0.237–0.541
V/F [L]	7.80	0.07	8.34	6.91–9.68
CL/F [L/day]	0.330	0.02	0.331	0.288–0.386
AAA on CL	1.59	18.1	1.65	0.88–2.33
LBW on CL	1.97	0.5	1.49	-0.069 to 2.73
IIV [%CV]				
Ka	103.9	1.1	94.1	68.3–1.22
V/F	35.6	0.02	28.3	14.1–42.3
CL/F	32.6	0.06	31.9	21.6–43.6
Correlation between Ka and V/F	0.402	0.04	0.200	-0.590 to 0.711
Correlation between Ka and CL/F	-0.576	0.2	-0.397	-0.842 to 0.174
Correlation between V/F and CL/F	-0.340	0.06	0.188	-0.681 to 0.933
Residual error				
Proportional error [%] [additive on the Ln scale]	-16.6	0.07	-15.5	-0.192 to -0.122

PK, pharmacokinetics; CD, Crohn's disease; NONMEM, non-linear mixed-effects modelling; SE, standard error of estimate; CI, confidence interval; AAA, anti-adalimumab antibodies; LBW, lean body weight; IIV, interindividual variability; Ln, natural logarithm.

[a]Represents a patient with covariate values equal to the median of the population.

[b]Calculated from 1000 bootstrap replicates.

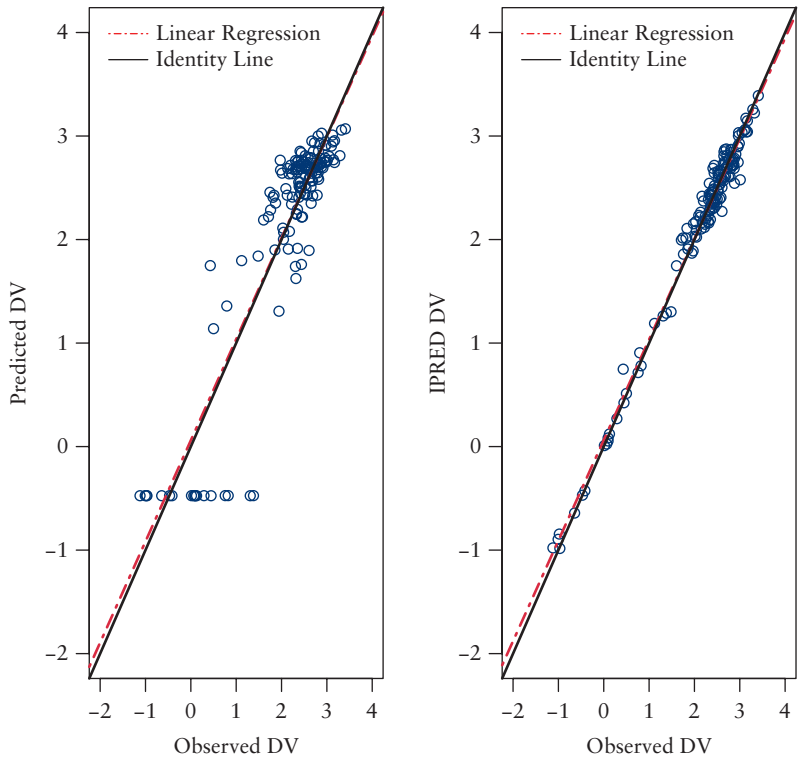

Figure 2. Goodness-of-fit plots of final model. Predicted DV vs Observed DV [left] and Individual Predicted [IPRED] DV vs Observed DV [right]. DV, dependent variable. Adalimumab concentrations [μg/mL] are natural logarithm [Ln] transformed.

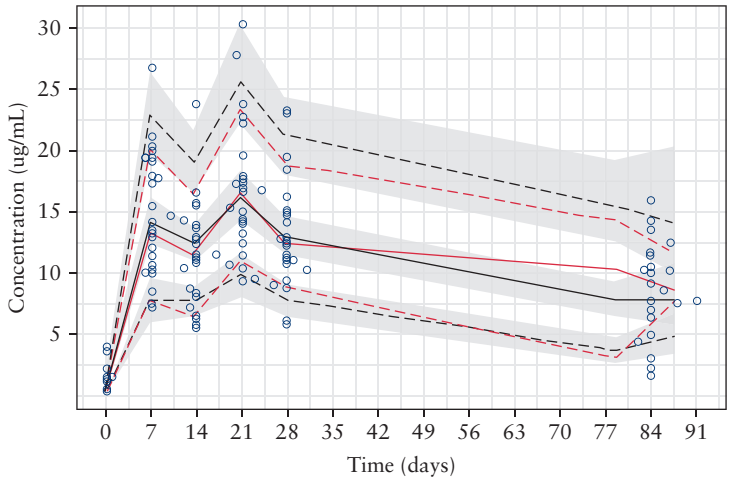

Figure 3. Visual predictive check of the final model. The solid red line represents the median, and the lower and upper dashed red lines represent the 10th and 90th percentile, respectively, of the observed data, represented by blue circles. The solid black line represents the median of the predicted data, and the lower and upper dashed black lines represent the 10th and 90th percentile of simulated data, respectively, with grey shades denoting the 90% confidence intervals.

The observed inverse correlation between baseline serum TNF and Day 7 adalimumab concentration may reflect target mediated drug disposition.[35]

Covariate analysis identified LBW and AAA to explain part of the interindividual variability in CL/F, with a residual unexplained variability of 32.6%. By using a drug-resistant AAA assay, we were able to detect AAA in one patient as early as W2. When patients became AAA-positive, CL/F increased 1.6-fold, reducing the adalimumab half-life from 16.4 days in a typical patient to 10.3 days in a patient positive for AAA. LBW had a similarly important influence on adalimumab CL/F, as we found the adalimumab half-life to vary from 26.1 days to 11.6 days over the 5th to 95th percentile of the LBW range [38.7–58.3 kg]. Although baseline s-TNF was not found to be predictive of adalimumab CL/F, we did observe a significant inverse correlation between s-TNF and adalimumab serum trough concentration at W12, which in addition to our observations at Day 7, may further indicate accelerated drug clearance because of target-mediated drug disposition.

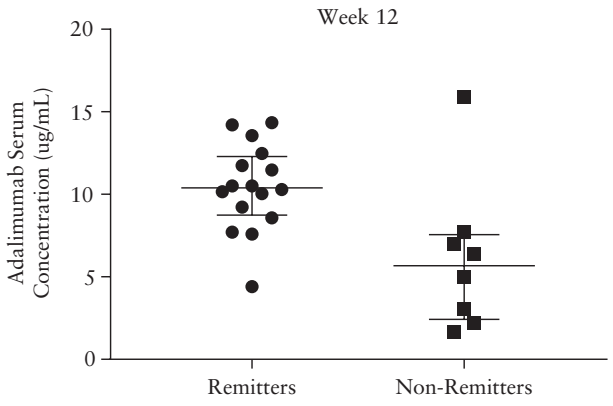

Figure 4. Median with interquartile range adalimumab serum concentration [µg/mL] in patients who were in remission vs those who were not at Week 12 [$p = 0.008$].

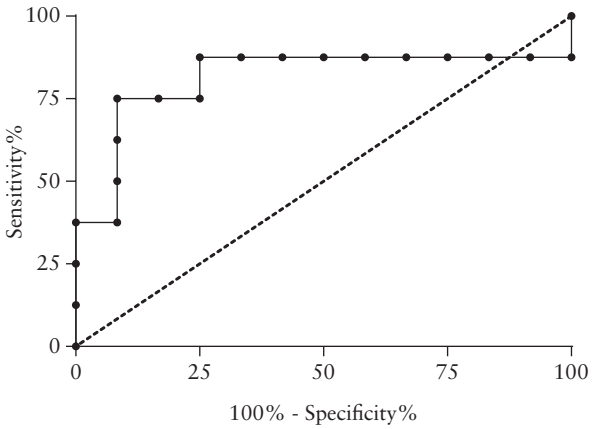

Figure 5. Receiver operating characteristic [ROC] curve of Week 12 adalimumab serum concentration and Week 12 clinical remission.

Of importance, we found that the increased adalimumab CL because of increased LBW and/or AAA positivity is clinically relevant. Indeed, adalimumab serum concentrations were associated with outcomes, and an adalimumab serum trough concentration ≥7.3 µg/mL at W12 was associated with achieving clinical remission at W12. This threshold adds further prospective evidence to the proposed threshold of ≥7.5 ± 1 µg/mL for therapeutic drug monitoring to optimise therapy with adalimumab.[36,37] Although not observed in our cohort, others have found earlier time points to be associated with clinically important outcomes at W12.[38] The adalimumab peak to trough ratio was found to be 1.3 at steady state in a typical patient, indicating that adalimumab serum peak and trough concentrations should not be used interchangeably for therapeutic drug monitoring. Therefore, adalimumab serum concentrations should be measured at the same time point as the threshold that is being applied, which is typically at trough.

By using a drug-resistant AAA assay that can accurately detect AAA in the presence of up to 50 µg/mL, we were able to characterise the early onset of AAA. We found an immunogenicity rate of 17.9% by W12, which is similar to previous findings in patients with Crohn's disease[6] and rheumatoid arthritis.[39] Although predictive of adalimumab serum concentrations [significant covariate of adalimumab CL/F], by W12 3/5 patients [60%] who were AAA-positive were in clinical remission. These findings are similar to the observations for infliximab that not all anti-drug antibodies detected with drug-tolerant/resistant assays are clinically relevant, and that typically high-concentration persisting antibodies require a switch of therapy.[40] Interestingly, in the recent Poetic Study in 98 patients with CD starting adalimumab therapy, an association was observed between AAA during induction and primary non-response [odds ratio = 5.4, 95% confidence interval: 1.6–17.8, $p = 0.005$], further underscoring the importance of measuring AAA.[41]

Our study has both strengths and weaknesses. The limited sample size may have resulted in decreased power to detect covariates associated with adalimumab pharmacokinetics. However, prospective collection of data and intense serum sampling, both during induction and maintenance therapy, allowed development of a comprehensive PopPK model that adequately described the adalimumab concentration-time profile and allowed characterisation of IIV of K_A, V/F, and CL/F, and estimation of these parameters with good precision. A further limitation of our study is the absence of endoscopic outcomes or other objective markers of inflammation [e.g., faecal calprotectin]; however, a clinical scoring index was used to prospectively assess disease activity.

In conclusion, we developed the first population pharmacokinetic model of adalimumab in patients with CD based on intense sampling, allowing quantitative description of the absorption rate and apparent volume of distribution and clearance. Using a drug-resistant AAA assay, we found that AAA in addition to LBW have a clinically significant impact on adalimumab clearance. Specifically, we found an adalimumab serum trough concentration at W12 of at least 7.3 µg/mL to be significantly associated with achieving clinical remission at W12. When applying therapeutic drug monitoring in clinical practice, serum peak and trough adalimumab concentrations should not be used interchangeably because of a peak-to-trough ratio of 1.3. Future studies should focus on optimising drug exposure, aiming to increase efficacy of adalimumab in patients with CD.

Funding

NVC holds a Research Scholar Award [RSA] from the American Gastroenterological Association [AGA]. The work was in part supported by a TBM grant T003716N of the Research Foundation—Flanders [FWO], Belgium. SB gratefully acknowledges the financial support of the China Scholarship Council. GVA, MF, and SV are senior clinical researchers of the Research Foundation—Flanders [FWO], Belgium.

Conflict of Interest

NVC received a research grant from R-Biopharm, Takeda, and UCB and consultancy fees from Janssen, Pfizer, Progenity, Prometheus, Takeda, and UCB outside of the submitted work. FB received research grants from Abbvie, Chiesi, Ipsen, Roche, and speakers and consultancy fees from Abbvie, Cellgene, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, Vifor. SB, ED, and GC declare no conflict of interest. GVA received financial support for research from Abbott and Ferring Pharmaceuticals, consultancy fees from PDL BioPharma, UCB Pharma, Sanofi-Aventis, Abbott, Abbvie, Ferring, Novartis, Biogen Idec, Janssen Biologics, NovoNordisk, Zealand Pharma A/S, Millenium/Takeda, Shire, Novartis, Bristol Mayer Squibb, and lecture fees from Janssen, MSD, and Abbott. MF reports research grant: Janssen, Takeda; consultancy: Abbvie, Boehringer-Ingelheim, Ferring, Janssen, Mitsubishi Tanabe, MSD, Pfizer; speaker's fee: Abbvie, Boehringer-Ingelheim, Chiesi, Ferring, Janssen, Lamepro, Mitsubishi Tanabe, MSD, Pfizer, Tramedico, Tillotts, Zeria. SV has received grant support from AbbVie, MSD, J&J, Pfizer, and Takeda; received speaker fees from AbbVie, MSD, Takeda, Ferring, Dr Falk Pharma, Hospira, Pfizer Inc., and Tillots; and served as a consultant for AbbVie, MSD, Takeda,

Ferring, Genentech/Roche, Shire, Pfizer Inc., Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. AG received financial support for research from Pfizer, MSD & Takeda; lecture fees from MSD, Janssen Biologicals, Pfizer, Takeda, Novartis, and Abbvie; consultancy fees from Takeda. KU Leuven holds a license agreement with R-biopharm, apDia, and Merck.

Acknowledgments

The authors are grateful to the patients who were willing to participate in this study and for their support in the research on inflammatory bowel disease.

Author Contributions

NVC performed the research and wrote the paper, NVC, FB, SB, ED, GC, GVA, MF, SV, and AG collected and analysed the data, NVC, FB, SV, and AG designed the research study, SB, ED, GVA, MF, SV, and AG reviewed the paper for important intellectual content. All authors reviewed the paper and approved the final version of the article, including the authorship list.

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