Population pharmacokinetics of infliximab in patients with inflammatory bowel disease

Buurman, D. J.; Maurer, J. M.; Keizer, R. J.; Kosterink, J. G. W.; Dijkstra, G.

Published in:
Alimentary Pharmacology & Therapeutics

DOI:
10.1111/apt.13299

Publication date:
2015

AP&T Alimentary Pharmacology and Therapeutics

Population pharmacokinetics of infliximab in patients with inflammatory bowel disease: potential implications for dosing in clinical practice

D. J. Buurman*[,1], J. M. Maurer[†,1], R. J. Keizer[‡], J. G. W. Kosterink[†,§] & G. Dijkstra*

*Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
[†]Department of Clinical Pharmacy and Pharmacology Groningen, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
[‡]Department of Bioengineering and Therapeutic Sciences, School of Pharmacy, University of California San Francisco, San Francisco, CA, USA.
[§]Section Pharmacotherapy and Pharmaceutical Care, Department of Pharmacy, University of Groningen, Groningen, The Netherlands.

Correspondence to:
Dr D. J. Buurman, Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands.
E-mail: d.buurman@umcg.nl

[1]Both authors share first authorship.

Publication data
Submitted 14 October 2014
First decision 12 November 2014
Resubmitted 11 May 2015
Accepted 9 June 2015
EV Pub Online 26 June 2015

This article was accepted for publication after full peer-review.

SUMMARY

Background
Infliximab (IFX) is effective in the treatment of inflammatory bowel diseases (IBD). Currently, IFX is administered at fixed doses and intervals; however, costs are high and optimisation is necessary. Several publications indicate that IFX should be dosed on trough levels ≥3.0 mg/L. For optimising IFX dosing, the use of a pharmacokinetic model is important. Population pharmacokinetics of IFX have been described earlier; however, these models were not used for dose optimising.

Aims
To develop a pharmacokinetic model for IFX in IBD patients that can be used for dose-optimisation of IFX and to predict serum trough levels in this population.

Methods
An observational retrospective study was performed in 42 IFX-treated IBD patients. Serum samples were drawn before infusion at $T = 0$, 2, 6, 14, 22 and 54 weeks and analysed for IFX and antibodies against IFX (ATI). Relevant covariates were recorded and a population pharmacokinetic model was developed.

Results
Individual plots created using the final model showed good correspondence between observed and model predicted values. Serum levels were influenced by ATI, disease activity, sex and albumin. Our results show that in patients without ATI target trough levels ≥3.0 mg/L can be achieved by increasing dosing intervals from 8 to 12 weeks combined with a dose increase. This results in a reduction of 33% in concomitant costs.

Conclusions
In IBD patients without ATI, trough level dosing based on longer intervals can reduce IFX therapy-related visits to the hospital with one-third. Trough level based dose intensification should always be justified by disease activity parameters.

Aliment Pharmacol Ther 2015; **42:** 529–539

doi:10.1111/apt.13299

INTRODUCTION

Infliximab (IFX), a chimeric mouse-human monoclonal antibody against tumour necrosis factor alpha (anti-TNF-α), has proven to be effective in the treatment of inflammatory bowel diseases (IBD), i.e. Crohn's disease (CD) and ulcerative colitis (UC) not responding to conventional therapy. IFX is effective in inducing and maintaining remission of luminal and fistulising CD and UC.[1–4] Anti-TNF-α agents are administered at fixed doses and fixed intervals derived from dose finding studies.[4, 5] Measuring IFX and anti-drug antibodies against IFX (ATI) levels is not common practice and until recently dose intensification was only based on clinical evaluation of the disease which appeared to be often inaccurate.[6–8]

In the literature, several studies demonstrated a relationship between IFX drug concentrations, the presence of ATI and clinical outcome.[9] Episodic IFX treatment in patients with CD has been associated with a higher rate of ATI as compared with scheduled maintenance therapy.[10] Patients on IFX therapy who develop ATI have a threefold higher increased risk of loss of response to therapy compared with those who do not develop ATIs.[11]

Several publications indicate that low IFX trough levels (variating from 2 to 3.5 mg/L) may increase the risk of flare of disease symptoms and inflammation. Low trough levels are associated with (clinical) parameters like high C-reactive protein (CRP) levels, male sex and higher albumin levels.[12–16] IFX levels ≥3 mg/L at the start of a maintenance regime appeared to be predictive for sustained response to IFX.[9, 17] It has also been demonstrated that the achievement of endoscopic healing requires even higher IFX trough levels.[18]

Therefore, therapeutic drug monitoring (TDM) based on IFX trough levels and anti-drug antibody level measurements has the potential to play an important role in the optimisation of anti-TNF-α treatment.[6, 19] Currently, several studies designed to dose IFX based on trough levels are ongoing. To be able to predict the IFX serum levels and optimise the IFX dose based on serum level, the use of a pharmacokinetic model is of great importance. Furthermore, the costs in IBD therapy are mainly driven by anti-TNF-α therapy and a strategy to optimise IFX therapy and avoid unnecessary treatment is desirable.[20]

The population pharmacokinetics (popPK) of IFX have been described earlier for patients with ankylosing spondylitis, rheumatoid arthritis and IBD.[21–23] However, these models were not used to predict serum trough levels or for dose optimising of IFX. In this article, we describe a retrospective study that was performed to develop a pharmacokinetic (PK) model for IFX in IBD patients in an out-patient setting that can be used for dose-optimisation of IFX and to predict serum trough levels in this population.

MATERIALS AND METHODS

Study design

This study was an observational, retrospective, single-centre study of IFX-treated CD and UC patients in the years 2007–2012 conducted at the Gastroenterology department of the University Medical Center Groningen. The study population comprised patients who were treated with IFX infusion at week 0, 2, 6 as induction phase followed by a maintenance phase for at least 40 weeks in a dosage of 5 mg/kg every 8 weeks. Serum samples analysed for IFX trough levels were routinely collected before infusions at weeks 0, 2, 6, 14, 22 and 54. Samples at $t = 54$ were also analysed for ATI. Patient files were reviewed by an investigator and possible relevant covariates were recorded: clinical [Harvey–Bradshaw index (HBI),[24] Global physician scale (GPA), Mayo score, Montreal classification, extension of disease, disease duration, concomitant immunosuppressive drugs, prior IFX use, smoking, UC/CD, weight] and laboratory parameters (CRP, albumin, leucocytes). Data from the HBI were treated as continuous data. Of the initially identified possible covariates, only covariates for which values were available for at least half of the patients[21] were included in the statistical analysis. The results were divided in two periods: induction (week 0–6) and maintenance (week 14, 22 and 54).

Analysis of infliximab and ATI levels

To measure IFX trough and ATI levels, the samples were sent to the laboratory for monoclonal therapeutics, Sanquin Diagnostics, Amsterdam, The Netherlands.

IFX trough levels were measured using an in-house developed enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification was 0.002 mg/L. ATI levels were measured using a radioimmunoassay. Both methods are extensively described previously.[25–27]

Model development

A popPK model was developed incorporating the full dosing history and concentration measurements of all patients. A two-compartment model, also used in

literature, was used as starting model.[21–23, 28] Due to the small size of the study cohort, it was not attempted to re-evaluate the model structure for the PK model, but model parameters were re-estimated. After initial model fitting, visual inspections of concentration–time plots showed several potential outlying data points. Therefore, using conditional weighted residuals (CWRES) from the base model, data points with CWRES >3.5 [corresponding to values outside the 99.95% confidence interval (CI) for normally distributed data] were labelled as outlier and removed from the data set.

A stepwise covariate modelling (scm) procedure was implemented on the base model for the parameters 'clearance (CL)' and 'central volume of distribution (V_c)'. It was not attempted to estimate covariates on parameters describing peripheral distribution ['peripheral volume of distribution (V_p)' and 'inter-compartmental clearance (Q)'] as these could only be estimated with moderate precision. In the first 'forward' inclusion step of the scm, covariates were added to the base model in a stepwise fashion based on statistical significance ($P < 0.05$). In a second 'backward elimination' step, covariates were then removed from the final model obtained in the first step, if removal of the covariate did not result in a significantly ($P < 0.01$) worse fit. For both continuous and binary covariates, only linear models were considered. In the scm, continuous covariates were centred respective to the median value. For missing time-invariant covariates, the median covariate value was imputed, while for missing time-varying covariates the last known value was carried forward (LOCF), if any earlier observation was available for the individual. An effect of a covariate of less than 25% was deemed clinically irrelevant. Therefore, after the scm procedure, only covariates with a relative absolute effect size of >0.25 were retained in the full model. For continuous covariates, the relative effect was defined as the estimated coefficient multiplied by 2 s.d. of the covariate values in the patient population. A plot was implemented showing the effect of the statistically significant covariates on PK parameters, as well as the uncertainty around the estimate ('clinical relevance plot').

Final model evaluation was performed using a visual predictive check (VPC). Relative standard errors for the parameter estimates were obtained from the covariance step in NONMEM. For the final full model, a bootstrap analysis using 1000 samples was implemented to obtain nonparametric estimates of uncertainty in parameter estimates (95% CI).

Simulation

Monte Carlo simulations were implemented to study expected drug concentration profiles for a clinical patient population. Simulation results were stratified by covariates that were identified as significant/relevant in the covariate analysis. Simulations were performed for three dose levels (300, 400, 600 mg), for three dosing schedules in the maintenance phase (dosing every 8, 12 or 16 weeks) and using an initial loading phase (dosing at 0, 2, 6 weeks). Patients were assumed to be on steady state after three doses in the maintenance phase. Simulation of the HBI in patients was done using a parametric distribution. The current data best supported a log-normal distribution, with mean 1.96 and standard deviation 0.53 (both on log-scale).

Software

Models were implemented in NONMEM (version 7.2; ICON Development Solutions, Dubln Ireland), with Pirana, PsN and R/Xpose as modelling environment.[29] The first-order conditional estimation method with random effects interaction was used throughout the analysis. Data handling, generation of plots and simulations were performed using R (version 3.0.0 or higher, http://cran.r-project.org/).

Endpoints

The primary objective of this retrospective study was to develop a pharmacokinetic model for IFX in IBD patients that can be used to optimise IFX dosing in an out-patient setting.

RESULTS

Data from 42 individuals were available. All patients were still considered as responders to IFX therapy at $T = 54$ weeks and were in clinical remission. For most patients, six samples were available for analysis ($t = 0$ included), which resulted in a total of 188 IFX serum levels available for analysis. None of the IFX measurements were below the lower limit of quantification for the IFX assay. After initial model fitting, five measurements were identified as outliers and were removed from the data set. A summary of patient demographics and covariate values is shown in Table 1a and 1b. Median CRP levels at baseline and at week 54 were 5 mg/L (range 5–105) and 5 mg/L (range 5–38), $P = 0.138$ respectively. The median GPA score at was 2 (range 1–3) at baseline and 0 (range 0–2) at week 54. The HBI declined from median of 6 (range 3–24) at baseline to median of 2.5 (range 0–9) at week 54, $P < 0.001$. There

Table 1a | Patient demographics and covariates at baseline

Time-invariant	Median (range)/numbers in cat.	Missing	Time-varying	Median (range)	Missing
Weight (kg)	75 (51–145)	–	Albumin (g/L)	41 (33–50)	1
Age (year)	44 (19–80)	–	CRP (mg/L)	5.0 (5.0–105)	–
Smoking	31–/11+	–	Leucocytes ($\times 10^9$/L)	5.8 (2.6–16)	–
Sex	22 F/20 M	–	TNF-alfa (ng/L)	1191 (885–1667)	22
HBI	6 (3–24)	8			
GPA†	2 (1–3)				
Prior IFX use	40–/2+	–			
Disease type (UC/CD)	8/34	–			
Baseline medication					
Thiopurines	16–/26+	–			
Steroids	23–/19+	–			
Mesalazine	32–/10+	–			
Methotrexate	34–/8+	–			

† GPA = Global physician assessment score (0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease).

Table 1b | Baseline immunosuppressive medication, dose and duration expressed as median (range)

Medication	Number of subjects	Dose (mg)	Duration (months)
Azathioprine	20	150 (50–300)	25 (3–360)
Mercaptopurine	6	88 (75–100)	5 (1–13)
Methotrexate	8	15 (12.5–25)	9 (1–72)
Budesonide	11	6 (3–9)	7 (1–108)
Prednisolone	5	30 (10–50)	1 (1–7)
5-aminosalicylic acid	10	3550 (3000–4000)	12 (3–204)
Baseline: no medication	4	–	–
Baseline: mono therapy	20	–	–
Baseline: combination therapy	18	–	–

were no significant differences between HBI, CRP and albumin between males and females and between smokers and nonsmokers.

IFX trough and ATI levels. Figure 1 and Table 2 show a summary of the measured IFX trough levels. All patients had detectable IFX trough levels; however, a large inter-individual variation was observed. In the induction phase, 77% of the female and 95% of the male patients had an IFX trough level ≥3 mg/L after three infusions which decreased to 46% in the female and 30% in the male patients at $T = 54$ weeks in the maintenance phase. Two patients had developed ATI at week 54. Median IFX concentrations at week 2 and week 54 were 34 (range 4–62) and 3 (range 0–25), $P < 0.001$ respectively. There was a significant correlation for CRP at baseline and IFX trough level at week 2 ($R = 0.408$, $P = 0.010$), but not for IFX trough level at week 54. There was no significant difference in IFX trough levels at week 2 and 54 between smokers and nonsmokers.

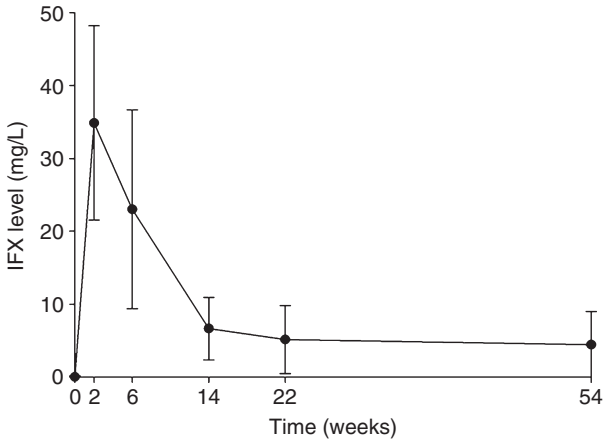

Figure 1 | Summary of IFX trough levels based on the available serum samples of 42 patients (mean ± s.d.).

Model development. Reasonably good fit was obtained with the base model. Even when using the parameter estimates from Fasanmade *et al.*[23] but re-estimating only

residual error magnitude, the estimates for the residual error components were lower than reported in the original publication, and evaluation of individual plots revealed reasonable fit. However, re-estimation of the model parameters of the base model resulted in a very significant improvement in fit ($P < 0.001$). Parameters were estimates with good precision (%) as is shown in Table 3. Especially the parameters describing drug distribution were considerably different from those reported by Fasanmade *et al.*[23] A 40% increase in CL in the maintenance phase was observed compared to the induction phase. There was no significant difference in CL between patients with UC and CD (34 vs. 42%).

Covariate model. Treatment period was implemented manually as a covariate before implementation of the scm, and showed a significant improvement in fit ($P < 0.001$). In the forward step of the scm, four additional covariates were identified as statistically significant [ATI, SEX and albumin (ALB) on CL, and HBI on volume of distribution (V)], which were also retained in the model during the backward elimination step. The covariate effect sizes could be estimated with reasonable precision (11–35%). The largest relative effect size was found for ATI on CL, as can be seen in Figure 2. In contrast with other popPK studies for monoclonal antibodies,[21–23, 28] we did not find a relationship between bodyweight and CL or V. In fact the model showed worse fit when any of the earlier reported relationships for weight were implemented in the model. The sex of the patient was found to be a significant predictor in our study. The CL for male patients was estimated to be 35% higher than in females, a finding which has also been reported by others.[13]

Albumin was found to be a significant predictor of PK, having a negative effect on CL, which corroborates findings by others. However, in our analysis, we found the effect to have only a small clinical relevance, i.e. lower than our defined threshold of 25% relative magnitude, and the bootstrap analysis also showed that the confidence interval included 0. The covariate was therefore removed from the model.

For V, a significant and clinically relevant effect was found for the HBI at baseline, a higher value resulting in lower values of V. The final full model was thus defined as:

$$CL_i = CL_{pop} \cdot 1.345^{SEX} \cdot 1.722^{ATI} \cdot 1.40^{PERIOD} \quad (1)$$

$$V_i = V_{pop} \cdot 0.964 \cdot (HBI - 6) \quad (2)$$

Table 2 | Percentage of patients with IFX trough levels above 2.0 mg/L

Week	No of samples	Sex	% ≥2.0 mg/L
0	42	Male	0
		Female	0
2	42	Male	100
		Female	100
6	40	Male	95
		Female	82
14	41	Male	75
		Female	91
22	42	Male	70
		Female	77
54	32	Male	55
		Female	64

Table 3 | Parameter estimates for final population kinetic model of IFX

Parameter	Parameter	Estimate (precision)mate (RSE%)	Unit	Range
CL	Clearance	0.199 (6%)	L/day	(0.161–0.228)
V_{cc}	Central volume of distribution	4.94 (10%)	L	(3.030–5.800)
Q	Inter-compartmental clearance	0.0618 (23%)	L/day	(0.038–0.104)
V_p	Volume of peripheral compartment	3.13 (32%)	L	(1.360–5.940)
ω_{CL}	BSV in CL	18.0% (18%)		(7.7–27%)
ω_{Vc}	BSV in V_c	17.1% (31%)		(1.5–33%)
σ_{prop}	Proportional error magnitude	21.7% (30%)		(8.0–32%)
σ_{add}	Additive error magnitude	0.98 (18%)	mg/L	(0.61–1.54%)
θ_{period}	Increase of CL in maintenance phase	+40% (11%)		(15–94%)
θ_{ATI}	Effect of ATI on CL	+72% (35%)		(24–136%)
θ_{sex}	Effect of sex on CL	+35% (34%)		(12–59%)
Θ_{HBI}	Effect of HBI on V	−3.6 (28%)	HBI point^{-1}	(−7.5–−0.4)

BSV, between-subject variability.

in which SEX is defined as 0 for males and 1 for females, ATI is 0/1 for the presence of antibodies against IFX, and PERIOD is 0 for induction phase and 1 for the maintenance phase, HBI is the HBI at baseline.

Individual plots created using the final full model showed good correspondence between observed and model predicted values, as can be seen in Figure 3 which compares the population prediction with the observed IFX concentrations for a few randomly selected patients. Goodness-of-fit plots of conditional weighted residuals vs. time and predictions and of individual predictions vs. observations revealed no trends, indicating an unbiased model fit (data not shown). Shrinkage in empirical Bayes estimates (EBEs) was only 3% for inter-individual random effects in CL and V, and 11% for the residual errors. The visual predictive check (Figure 4) for the full model indicated that the model was able to describe the population mean PK profile as well as the between-subject variability adequately, as all observed quantiles (5%, 50%, 95%) were contained within their respective prediction interval in every bin.

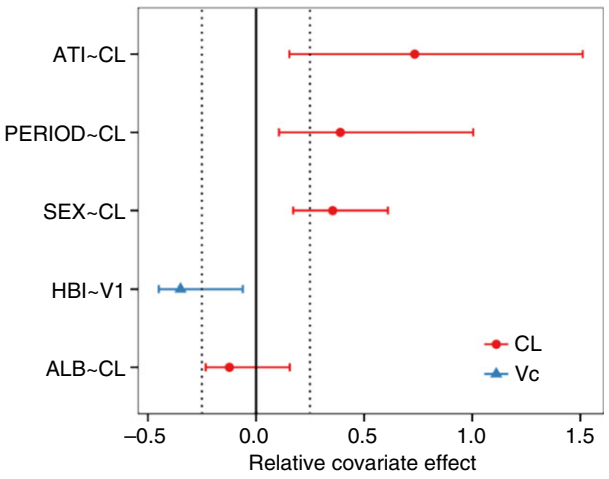

Figure 2 | Plot of estimated effect magnitude on CL and *V* with the horizontal lines indicating the 95% CI around the estimated effect magnitude (dot). The dotted lines indicate the pre-specified clinical (ir-)relevance criterium. For continuous covariates, the relative effect was defined as the estimated coefficient multiplied by 2 s.d. of the covariate values in the patient population.

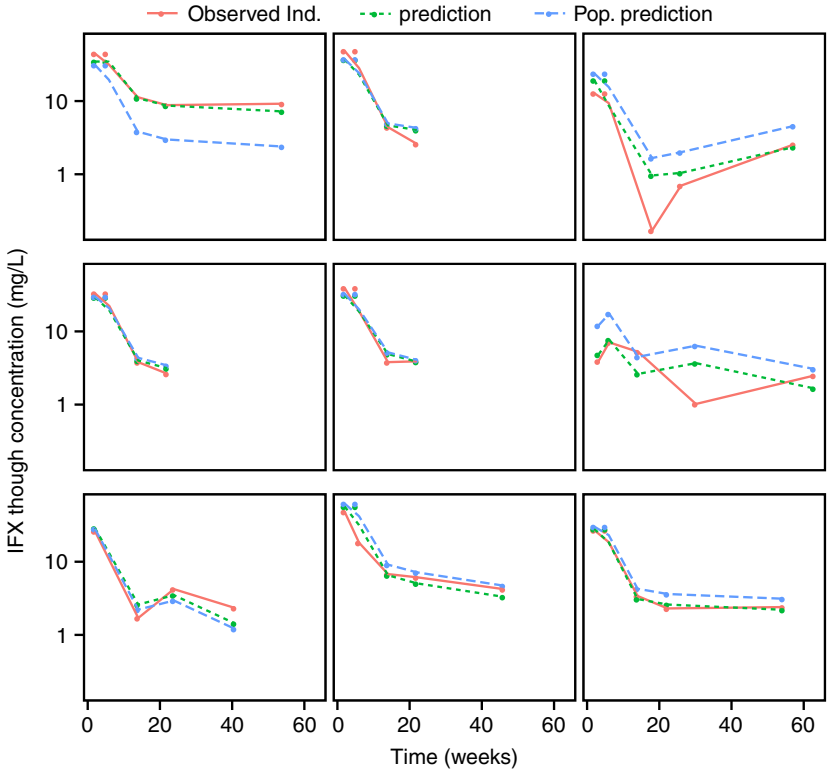

Figure 3 | Model predictions (both population and individual) and observations plotted for nine representative patients. Note that for the predictions not the continuous time course is shown, but only the expected trough concentrations.

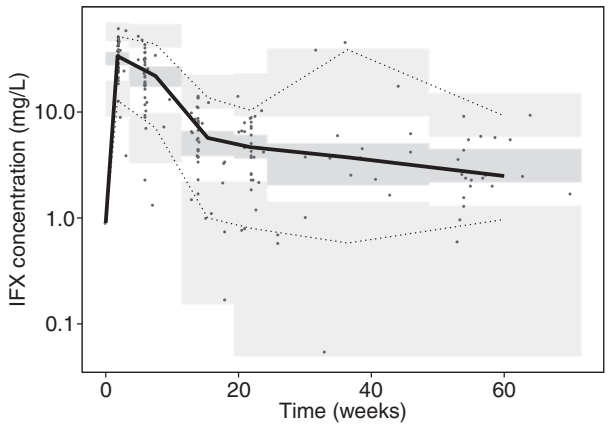

Figure 4 | Visual predictive check of final model. The solid line indicates the observed median values per time interval, while the dotted lines indicate the observed 5th and 95th percentile of the observed data. The shaded areas represent the prediction interval for the median (dark grey), and the 5th and 95th percentile (light grey).

Simulation. The expected time course of IFX concentrations (in a patient population similar to our cohort) is shown in Figure 5, assuming every 8-week dosing in the maintenance phase. This shows that at 400 mg or 600 mg, the majority of patients that do not show ATI are expected to have trough concentrations higher than 3 mg/L.[9, 17] However, a majority of patients (either male or female) that do show ATI are expected to experience trough concentrations below the threshold.

Results from the simulation studying dosing regimens with longer dosing intervals are summarised in Figure 6, which shows the expected distribution of trough levels for different dosing regimens, stratified by dose and patient characteristic, indicating that dosing every 16 weeks invariably results in the majority of patients showing trough concentrations lower than the threshold, even in those patients not showing ATI. Dosing every 12 weeks shows improved profiles, i.e. in patients who do not show ATI, this regime is expected to result in adequate levels in most patients. Table 4 summarises the fractions of patients that are expected to have trough levels under the 3 mg/L threshold.

DISCUSSIONS

Our study resulted in several interesting findings not reported in earlier PK analyses of IFX. A PK model was developed and considerably higher CL was observed during the maintenance phase compared with the induction phase, and the HBI was identified as a predictor of V.

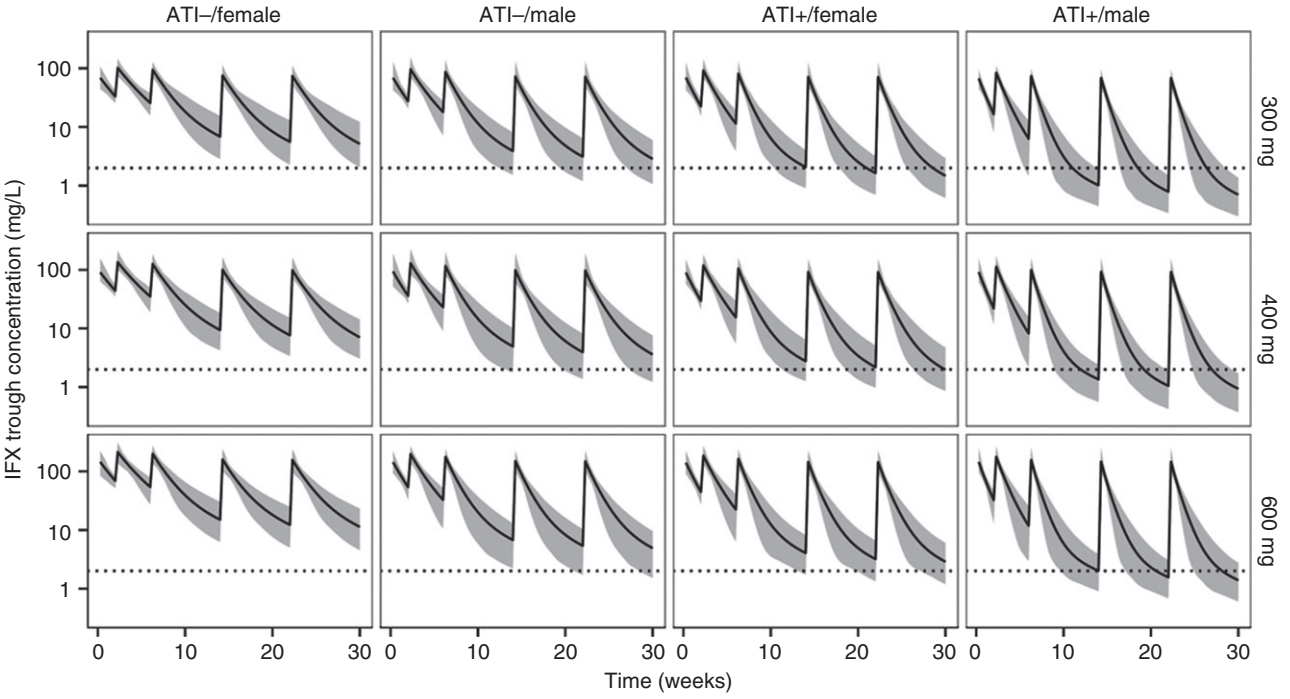

Figure 5 | Monte Carlo simulation of patient population for 'every 8-week' dosing, stratified by dose level and covariates, ATI and SEX. The horizontal dashed line shows the minimum trough level aim (3.0 mg/L).

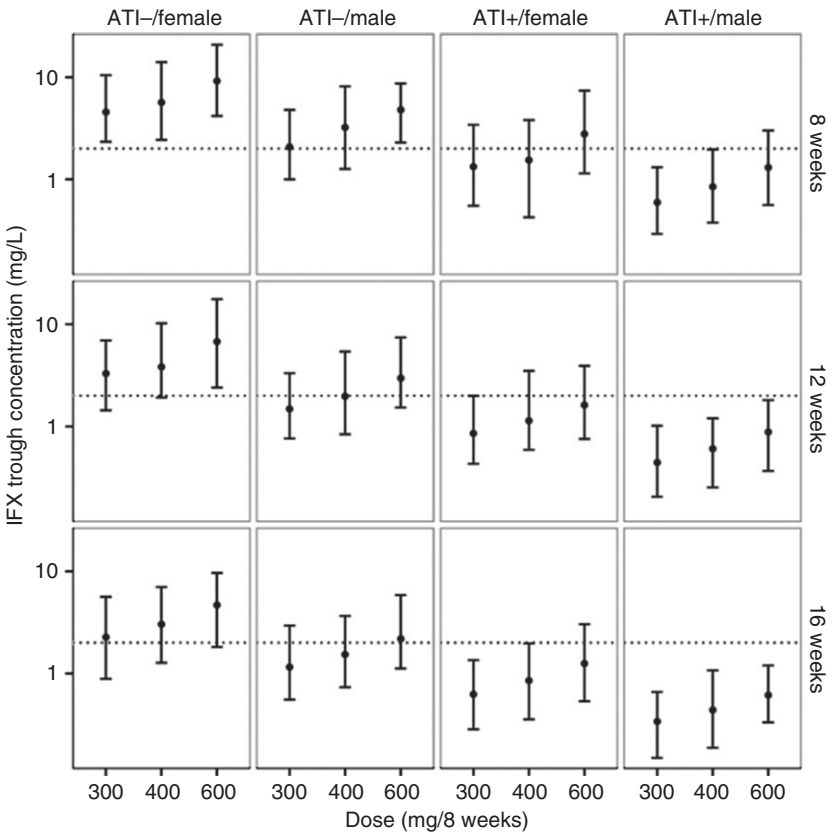

Figure 6 | Monte Carlo simulation of patient population for 8-, 12- and 16-week dosing, stratified by covariate. The horizontal dashed line shows the minimum trough level aim of ≥3.0 mg/L.

Table 4 | Expected fraction of patient population below 3.0 mg/L at $T = 54$ weeks, calculated by simulation. Dosing scenarios where expected fraction of patients under 3 mg/L is lower than 20% are bold

Dose interval	Sex	ATI	300 mg*	400 mg*	600 mg*
q8 weeks	Female	–	**14%**	**8%**	**0%**
		+	51%	48%	40%
	Male	–	42%	33%	**14%**
		+	53%	53%	52%
q12 weeks	Female	–	32%	**19%**	**9%**
		+	53%	52%	49%
	Male	–	49%	44%	31%
		+	53%	53%	53%
q16 weeks	Female	–	42%	31%	**12%**
		+	53%	53%	52%
	Male	–	52%	49%	42%
		+	53%	53%	53%

* Dosing per 8 weeks, so 300 mg = 450 mg for q12 and 600 mg for q16 regimens.

Simulations from the developed model showed that dosing every 12 weeks instead of every 8 weeks can be considered in IFX treatment of patients with IBD, but only in those who do not show ATI. Considering the high percentage of patient in remission with trough levels ≤3.0 mg/L, dose intensification or modification in dose intervals should always be combined with clinical and/or endoscopic disease activity parameters

Despite years of experience with the use of IFX in treatment of patients with IBD several questions still remain unanswered. These questions include which patient demographics or biomarkers are predictive of pharmacokinetics, whether PK is different between the induction and maintenance phase, and whether a longer dosing interval can result in similar adequate trough levels and similar effectiveness. Furthermore, observational studies showed that approximately 25–40% of the patients experienced loss of response over time.[30] In some studies, it was demonstrated that these patients would require an increase in dose or decrease in infusion interval.[31, 32] Katz *et al.* concluded that dose intensification leads to a response in 47% of CD patients who lost response to standard IFX dose, but concluded that halving the infusion intervals is probably not superior to dose-doubling.[33] Kopylov *et al.* showed that shortening the dosing interval to 6 weeks appears to be at least as effective as doubling the dose to 10 mg/kg.[34] The conclusions of these studies were drawn without TDM and based on clinical parameters. Therefore, the question remains which role TDM can play in optimisation of IFX treatment.

To be able to perform adequate TDM, a PK model was developed based on models published earlier for IFX.[21–23, 28] Although this was a relatively small study, sufficient data were available to allow the development of a population PK model that could be used with confidence to perform simulations of several dosing regimens.

Not all findings from the model building process were consistent with reports from previous studies. Except for the volume of distribution,[35] the main PK parameters were significantly different from those reported by others, especially those describing distribution to peripheral tissue. This may be attributed, e.g. to differences in patient populations or different sampling schemes. Therefore, it was attempted to re-estimate all PK parameters, including Q and V2, and the bootstrap analysis confirmed that most PK parameters could be estimated with reasonable precision (all <35%). However, it must be noted that for the simulation of expected trough levels, the distribution process is not the most important component, as trough samples are always taken in the "elimination phase" of the drug.

The covariate modelling procedure identified several statistically significant. Some of these were expected *a priori,* but not all. The relationship identified in other studies between CL and patient weight was not found in our analysis. Most likely we did not find such a relationship in our study because the patients in our data set only spanned a limited range of weight (90% CI between 60 and 100, with a few outliers >100 kg). Other studies contained wider ranges of weights, some also including data from children. To illustrate, the relationship identified in Ref. 23 predicted only a difference of 5.6% in CL for patients with weights ranging between 60 kg and 100 kg, so it is unlikely that this effect would have been identified in our cohort.

The sex of the patient was a significant predictor of PK in our study, with CL 35% higher in males than in females, which was found in a previous studies as well and of similar magnitude.[23]

Our analysis did identify a relationship between albumin levels (at baseline) and CL. However, similar to weight, our population showed only a moderate amount of variability in albumin levels, in which the interquartile difference would only result in an 8.3% difference in CL according to the relationship in Ref. 23, which was likely too low a signal to be detected in our cohort.

In our cohort only two patients showed ATI, but the effect was still found to be significant. Due to the limited number of patients with ATI, probably due to the fact all subjects had concomitant medication for IBD treatment, the effect must be interpreted with some caution. However, ATI were also identified in other popPK reports as relevant predictor of PK. The effect that was found in our statistical analysis confirmed our expectations, but it is the magnitude of the effect that may require further study in a larger population. In a study by Fasanmade,[23] an effect of ATI was also identified, although it was found to be lower (29.2% vs. 72%, but within the 95% CI of our current estimate).

Finally, we identified the HBI as significant covariate on *V*, i.e. a higher HBI was correlated with a lower *V*. The HBI is a measure of disease state used in the diagnosis of Crohn's disease, and includes parameters like the general well-being of the patient, the presence of abdominal pain and the number of stools per day. An effect of HBI on PK parameters has not been reported before, but to our knowledge, HBI has also never been tested as possible covariate in reported popPK analyses. Disease activity could influence effectiveness of biologicals such as IFX by increased utilisation or faecal losses due to mucosal ulcerations. We did not include faecal calprotectin as a covariate in our analysis because in most patients this parameter was not measured routinely during this retrospective study. The statistical significance and clinical relevance of disease activity (HBI or another disease activity score with or without a faecal marker such as calprotectin) need to be confirmed in a prospective study in a larger patient population.

The simulations from our model predict lower trough levels in patients who develop ATI. Our simulations show that almost all of these patients will have a trough level below 3 mg/L, when dosed at 400 mg. In our data set, we had only two patients who developed ATI (on 400 and 500 mg), and these patients showed trough levels in the range of 0.58–2.02 mg/L during the maintenance phase, corroborating our prediction that these patients are likely to show ineffective trough concentrations. In these patients, a dose increase (or a decrease in the dosing interval) is warranted when disease activity is still present. However, switching to another anti-TNF antibody is probably more cost-effective.[36]

Our simulations also showed that for patients without ATI, it may be considered to dose every 12 weeks instead of every 8 weeks: at dose relative to 400 mg/8 weeks, this is expected to result in adequate dose levels (>3 mg/L) for a majority of female patients (83% at 12 weeks vs. 94% at 8 weeks), while at 600 mg/8 weeks, >99% of patients are expected to show concentrations above the threshold. Unfortunately, for male patients, our simulations predict that dosing every 12 weeks will

result in about half of the population experiencing too low trough concentrations. If dosed at an even longer time interval (every 16 weeks), the majority of patients without ATI, either male (50–72%) or female (5–39%), are expected to show trough levels <3 mg/L even if dosed at 600 mg, rendering this dosing schedule infeasible in clinical practice.

Dosing every 12 weeks instead of every 8 weeks will reduce concomitant costs to IFX therapy (laboratory, nurses, out-patient clinic, etc) with 33% for each patient treated according to this strategy. However, these aspects of therapy represent a minor part of the total costs in IBD patients.[20] More important is the fact that patients have to visit the hospital for IFX-related therapy only four times a year instead of six times. This is more convenient for the patients but also creates more capacity in the hospital which can be used for other purposes.

Anti-TNF-α therapy is expensive and therefore it is important to optimise the use of it. TDM can be used to optimise dosing regimens in patients with low, but also with high IFX levels, to obtain a cost-effective treatment. In this study, all patients had detectable IFX trough levels and good clinical response with a significant decline of HBI, with many patients below a score of 4. However, at $t = 54$ weeks, only 46% of female and 30% of the male patients had IFX trough levels of >3.0 mg/L. Unfortunately, more accurate disease activity parameters such as endoscopy or faecal calprotectin were not available for most patients. It is tempting to speculate that these patients in remission with low trough levels would be good candidates for a stopping strategy. Therefore, trough level dosing should always be combined with clinical and/or endoscopic disease activity parameters to avoid unnecessary dose intensification.

CONCLUSIONS

The developed pharmacokinetic model could be used to optimise TDM of IFX in IBD patients, but it needs to be confirmed in a prospective clinical trial. Simulations from the model show that dosing every 12 weeks can be considered in the treatment of patients with IBD with IFX, but only in those who do not show ATI. This strategy reduces IFX therapy-related visits to the hospital with one-third. Considering the high percentage of patients in remission with trough levels ≤3.0 mg/L, dose intensification or modification in dose intervals should always be combined with clinical and/or endoscopic disease activity parameters.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: All authors have contributed significantly to the submitted work. Buurman, Maurer and Keizer conducted the analysis. Buurman, Maurer, Keizer, Kosterink and Dijkstra wrote the manuscript. Buurman, Maurer, Keizer, Kosterink and Dijkstra were responsible for the conception and design of the study. All authors contributed to the drafting of the manuscript and revised it critically for important intellectual content.

All authors have read and approved the manuscript.

ACKNOWLEDGEMENTS

Declaration of personal and funding interests: None.

REFERENCES

1. Van Assche G, Dignass A, Reinisch W, *et al.* The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis* 2010; **4**: 63–101.
2. Stange EF, Travis SP, Vermeire S, *et al.* European evidence-based Consensus on the diagnosis and management of ulcerative colitis: Definitions and diagnosis. *J Crohns Colitis* 2008; **2**: 1–23.
3. Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541–9.
4. Rutgeerts P, Sandborn WJ, Feagan BG, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462–76.
5. Targan SR, Hanauer SB, van Deventer SJ, *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337**: 1029–35.
6. Vande Casteele N, Ballet V, Van Assche G, Rutgeerts P, Vermeire S, Gils A. Early serial trough and antidrug antibody level measurements predict clinical outcome of infliximab and adalimumab treatment. *Gut* 2012; **61**: 321; author reply 322.
7. Ben-Horin S, Yavzori M, Katz L, *et al.* The immunogenic part of infliximab is the F(ab')2, but measuring antibodies to the intact infliximab molecule is more clinically useful. *Gut* 2011; **60**: 41–8.
8. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut* 2010; **59**: 49–54.
9. Levesque BG, Greenberg GR, Zou G, *et al.* A prospective cohort study to determine the relationship between serum infliximab concentration and efficacy in patients with luminal Crohn's disease. *Aliment Pharmacol Ther* 2014; **39**: 1126–35.

10. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1248–54.
11. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol* 2013; **108**: 40–7; quiz 48.
12. Cornillie F, Hanauer S, Diamond R, *et al.* Postinductionserum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut* 2014; **63**: 1721–7.
13. Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther* 2010; **48**: 297–308.
14. Reinisch W, Wang Y, Oddens BJ, Link R. C-reactive protein, an indicator for maintained response or remission to infliximab in patients with Crohn's disease: a post-hoc analysis from ACCENT I. *Aliment Pharmacol Ther* 2012; **35**: 568–76.
15. Vande Casteele N, Khanna R, Levesque BG, *et al.* The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. *Gut.* 2014 Oct 21. [Epub ahead of print].
16. Paul S, Del Tedesco E, Marotte H, *et al.* Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis* 2013; **19**: 2568–76.
17. Bortlik M, Duricova D, Malickova K, *et al.* Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. *J Crohns Colitis* 2013; **7**: 736–43.
18. Imaeda H, Bamba S, Takahashi K, *et al.* Relationship between serum infliximab trough levels and endoscopic activities in patients with Crohn's disease under scheduled maintenance treatment. *J Gastroenterol* 2014; **49**: 674–82.
19. van de Casteele N. 1159 results on the optimisation phase of the prospective controlled trough level adapted infliximab treatment (TAXIT) Trial. *Gastroenterology* 2012; **5**: 211–2.
20. van der Valk ME, Mangen MJ, Leenders M, *et al.* Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: results from the COIN study. *Gut* 2014; **63**: 72–9.
21. Ternant D, Aubourg A, Magdelaine-Beuzelin C, *et al.* Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit* 2008; **30**: 523–9.
22. Fasanmade AA, Adedokun OJ, Blank M, Zhou H, Davis HM. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. *Clin Ther* 2011; **33**: 946–64.
23. Fasanmade AA, Adedokun OJ, Ford J, *et al.* Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol* 2009; **65**: 1211–28.
24. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980; **1**: 514.
25. Jamnitski A, Bartelds GM, Nurmohamed MT, *et al.* The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept. *Ann Rheum Dis* 2011; **70**: 284–8.
26. van Kuijk AW, de Groot M, Stapel SO, Dijkmans BA, Wolbink GJ, Tak PP. Relationship between the clinical response to adalimumab treatment and serum levels of adalimumab and anti-adalimumab antibodies in patients with psoriatic arthritis. *Ann Rheum Dis* 2010; **69**: 624–5.
27. Vande Casteele N, Buurman DJ, Sturkenboom MG, *et al.* Detection of infliximab levels and anti-infliximab antibodies: a comparison of three different assays. *Aliment Pharmacol Ther* 2012; **36**: 765–71.
28. Xu Z, Seitz K, Fasanmade A, *et al.* Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. *J Clin Pharmacol* 2008; **48**: 681–95.
29. Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. *CPT Pharmacometrics Syst Pharmacol* 2013; **2**: e50.
30. Schnitzler F, Fidder H, Ferrante M, *et al.* Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut* 2009; **58**: 492–500.
31. Regueiro M, Siemanowski B, Kip KE, Plevy S. Infliximab dose intensification in Crohn's disease. *Inflamm Bowel Dis* 2007; **13**: 1093–9.
32. Gisbert JP, Panes J. Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. *Am J Gastroenterol* 2009; **104**: 760–7.
33. Katz L, Gisbert JP, Manoogian B, *et al.* Doubling the infliximab dose versus halving the infusion intervals in Crohn's disease patients with loss of response. *Inflamm Bowel Dis* 2012; **11**: 2020–33.
34. Kopylov U, Mantzaris GJ, Katsanos KH, *et al.* The efficacy of shortening the dosing interval to once every six weeks in Crohn's patients losing response to maintenance dose of infliximab. *Aliment Pharmacol Ther* 2011 Feb; **33**: 349–57.
35. Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet* 2010; **49**: 493–507.
36. Vande Casteele N, Gils A, Singh S, *et al.* Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol* 2013; **108**: 962–71.