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ORIGINAL ARTICLE

Quantitative relationship between infliximab exposure and inhibition of C-reactive protein synthesis to support inflammatory bowel disease management

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Aim: Quantitative and kinetic insights into the drug exposure-disease response relationship might enhance our knowledge on loss of response and support more effective monitoring of inflammatory activity by biomarkers in patients with inflammatory bowel disease (IBD) treated with infliximab (IFX). This study aimed to derive recommendations for dose adjustment and treatment optimisation based on mechanistic characterisation of the relationship between IFX serum concentration and C-reactive protein (CRP) concentration.

Methods: Data from an investigator-initiated trial included 121 patients with IBD during IFX maintenance treatment. Serum concentrations of IFX, antidrug antibodies (ADA), CRP, and disease-related covariates were determined at the mid-term and end of a dosing interval. Data were analysed using a pharmacometric nonlinear mixed-effects modelling approach. An IFX exposure-CRP model was generated and applied to evaluate dosing regimens to achieve CRP remission.

Results: The generated quantitative model showed that IFX has the potential to inhibit up to 72% (9% relative standard error [RSE]) of CRP synthesis in a patient. IFX concentration leading to 90% of the maximum CRP synthesis inhibition was 18.4 μg/mL (43% RSE). Presence of ADA was the most influential factor on IFX exposure. With standard dosing strategy, ≥55% of ADA+ patients experienced CRP non-remission. Shortening the dosing interval and co-therapy with immunomodulators were found to be the most beneficial strategies to maintain CRP remission.

Conclusions: With the generated model we could for the first time establish a robust relationship between IFX exposure and CRP synthesis inhibition, which could be utilised for treatment optimisation in IBD patients.

KEYWORDS

C-reactive protein remission, inflammatory bowel disease, infliximab dosing

The authors confirm that the Principal Investigator for this paper is Walter Reinisch and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

The inflammatory bowel diseases (IBDs), Crohn's disease and ulcerative colitis, comprise a complex variety of diseases characterised by chronic intestinal inflammation that may lead to irreversible damage and are associated with poor quality of life. While the control of IBDs has previously been of limited success, introduction of **antitumour necrosis factor α** (TNFα) monoclonal antibodies, such as infliximab (IFX), adalimumab and golimumab, brought about a notable advancement.[1] However, loss of response to the approved dosing regimen posits major challenges and introduced the need for Therapeutic Drug Monitoring (TDM), which finds clinical translations mostly with IFX.[1]

Furthermore, the choice of the most appropriate treatment target to be tackled and effective monitoring biomarkers in IBD is itself a complex task. Measures of clinical remission[2] are subjective and thus not appropriate for exploring exposure-response relationships of drugs, whereas the more objective assessment of endoscopic disease activity is less apt for long-term disease monitoring due to invasiveness. C-reactive protein (CRP) concentration has been found to be a suitable surrogate marker due to its correlation with endoscopy[3] and favourable kinetic behaviour.[4]

The relationship between serum concentrations of IFX and various disease outcomes has previously been investigated.[5–10] However, there is a lack of quantitative and kinetic knowledge of those relationships. A pharmacometric framework, using the quantitative pharmacokinetic/pharmacodynamics (PK/PD) population approach,[11] in comparison with a static relationship relating exposure and response only at fixed time points, describes the time course of both drug exposure and IBD activity, and additionally enables quantifying the variability between patients in the investigated population, and identifying and quantifying factors that impact drug exposure or disease activity.

The aim of this study was to derive recommendations for dose adjustment and treatment optimisation based on mechanistic and kinetic characterisation of the relationship between IFX dosing, IFX serum concentration and CRP concentration.

What is already known about this subject

- Clearance of infliximab (IFX) is subjected to high inter-individual variability, prompting the need for Therapeutic Drug Monitoring (TDM) to counteract loss-of-response in inflammatory bowel diseases (IBD).
- C-reactive protein (CRP) is routinely measured as a biomarker to monitor the activity of IBD.
- Quantitative and kinetic knowledge of the relationship between IFX exposure and disease response is scarce.

What this study adds

- A population pharmacokinetic/pharmacodynamic model describing the inhibitory effects of IFX on CRP synthesis was developed.
- High variability in IFX effect suggests that CRP monitoring should be included in the clinical decision making.
- Based on simulations from the model, dosing adjustments are suggested to support achieving continuous CRP remission.

2 | METHODS

2.1 | Study design

The data analysed in this study originated from an investigator-initiated trial performed at the University Hospital of the Medical University of Vienna. The study was conducted in accordance with ethical standards and was approved the institutional review board of the Medical University of Vienna. Written informed consent prior to inclusion was obtained from all patients.

Adult patients (n = 121) diagnosed with IBD (89 with Crohn's disease, 31 with ulcerative colitis (UC) and one patient with undetermined IBD type) in maintenance IFX treatment were included in the study, regardless of CRP concentration; patients with obvious conditions associated with increased CRP concentration (particularly infectious conditions) were excluded. The patients received IFX at absolute doses ranging from 100 to 1300 mg (median 400 mg; 1-11 mg/kg, median 5.6 mg/kg) at dosing intervals ranging from 3 to 12 weeks (median 8 weeks). Blood samples (n = 388) were taken at C_{min} (minimum or trough concentration) and at the middle of the dosing interval as part of Therapeutic Drug Monitoring in the period 2010-2012. Serum concentrations of IFX, antidrug antibodies (ADA), CRP, albumin and other relevant laboratory values were determined. In addition, potentially relevant patient-related (body weight, smoking status, sex), disease-related (diagnosis, disease duration as well as Harvey-Bradshaw index, number of surgeries, disease location, behaviour and age at diagnosis per Montreal classification for Crohn's disease and disease severity per Montreal classification for ulcerative colitis) and therapy-related (dosing, premedication with corticosteroids, co-therapy with immunomodulators) characteristics were recorded.

Concentrations of IFX were determined using the IDK monitor enzyme-linked immunosorbent assay (Immunodiagnostik AG, Bensheim, Germany[12]) and concentrations of ADA by a homogeneous liquid-phase mobility shift assay (Prometheus Anser ADA, Prometheus Laboratories Inc., San Diego, California, USA[13]), with a threshold for positive ADA (ie, lower limit of quantification) of 3.13 U/mL.

2.2 | PK/PD model development by pharmacometric analysis

Prior to PK/PD model development, statistical and graphical analyses were performed. Thereafter the data were analysed using the

nonlinear mixed-effects modelling approach.[14] For model development, the software tools NONMEM (version 7.3, ICON Plc, Ireland) and PsN (version 4.7.0) were employed, while R (version 3.3) and RStudio (version 1.1.447) were used for pre- and post-processing. The modelling process consisted of three main parts: (a) development of the base model characterising IFX PK, (b) covariate analysis aiming to identify patient-, disease- or therapy-specific factors significantly influencing IFX exposure and (c) development of a PK/PD model that quantifies the kinetic relationship between IFX exposure and disease activity as measured by CRP concentrations. The details of the modelling steps are given in the Supporting Information. Briefly, the crucial aspects were as follows:

a. The *base model* comprises a structural submodel that predicts the PK of IFX in a typical individual of the patient population and a statistical submodel which quantifies between- and within-patient variability in the PK profiles.
b. The *covariate model* enables identification of patient, disease or therapy factors that relevantly affect the PK profile, thus enabling individualisation of the IFX concentration-time profile according to these relevant factors.
c. In the course of *PK/PD model development*, the effect of IFX on CRP was implemented via sequential PK/PD modelling, ie, after the PK model including covariates was developed the IFX concentration predicted for each individual (based on the so-called empirical Bayesian estimates of the PK parameters) were used for PD model development.[15] To account for the time delay in changes of CRP concentration induced by IFX, indirect effect models were chosen.[15] The quality and predictive performance of the ultimate PK/PD model was assessed by a recommended approach, the prediction-corrected visual predictive check (n = 1000 simulations).[16]

2.3 | Assessment of standard dosing strategy

The developed PK/PD model was utilised to evaluate the current dosing strategy in terms of CRP remission (defined as CRP < 5 mg/L[17]) and this strategy was compared to potential alternative dosing strategies to select the most beneficial dosing approach(es). Stochastic simulations (n = 1000) were performed for a typical IBD patient and patients differing in the most influential covariate factors identified. As it has previously been shown that changing the dosing interval is superior to changes in administered dose with respect to adjustment of IFX exposure,[18] the standard dosing regimen (5 mg/kg at weeks 0, 2, 6 and every 8 weeks (q8w) afterwards) was compared to alternative dosing regimens that differed in dosing intervals. The investigations were focused on maintenance phase since no clinical data from the induction phase was available in the dataset underlying the developed model. Dosing intervals investigated ranged from every 4 (q4w) to every 12 weeks (q12w). For recommending alternative IFX dosing regimens, the time after IFX dosing when CRP concentration reached values ≥5 mg/L (CRP nonremission) was calculated for each regimen and compared for ADA+ and ADA– patients across the investigated dosing intervals in the presence and absence of co-therapy with immunomodulators.

3 | RESULTS

3.1 | PK/PD model development by pharmacometric analysis

The details of the model development process and outcomes are given in the Supporting Information. Altogether, 388 blood samples scattered over the entire dosing interval after IFX dosing from 121 patients were available for PK analysis (Table 1). Table 2 and Figure 1 give characteristics of measurements, demonstrating two sampling periods in this study: (a) from 2 to 6 weeks (mid-term) and (b) from 6 to 10 weeks (end of interval). The IFX concentration-time profiles were adequately characterised by the developed two-compartment PK model with linear elimination (Figure 2). Subsequently, four significant covariates (Supporting Information Figure S3) on clearance (CL) were identified: The development of ADA in a patient increased IFX CL by 97%, leading to an accelerated half-life and reduced exposure of IFX, whereas co-therapy with immunomodulators decreased IFX CL by 15.3%. Furthermore, low serum albumin concentration and high body weight were related to increased CL and thus decreased IFX exposure. Based on bootstrap (Supporting Information Figure S2), albumin concentration of 33 g/L was in almost 100% of cases related to increase in CL of >20% compared to the reference value. The extent of the effect of body weight was more modest, with both high (96 kg) and low (50 kg) values related to <20% change in CL compared to the reference value.

The developed PK model adequately described the measured IFX data (Supporting Information Figure S1). Volumes of distribution and intercompartmental exchange capacity values were in the range of typical PK parameters for monoclonal antibodies (mAbs; Supporting Information Table S1). Clearance in this study was 0.0126 L/h for the typical patient, having a body weight of 70 kg and serum albumin concentration of 43 g/L, that did not develop ADA and was not cotreated with immunomodulators. All covariates were considered time-varying, implying that CL changed over time with the covariates in each individual patient. Potential additional time-variance of CL on top of covariate effects could not be identified. From the covariates identified as significant, ADA presence had by far the highest impact: patients developing ADA (ADA+) revealed an approximately 2-fold higher CL compared to ADA– patients (Supporting Information Figure S2).

The concentration of CRP was determined in 339 blood samples. The graphical analysis indicated that there was a strong relation between IFX and CRP concentrations (Figure 3): CRP increased with decreasing IFX concentration (Figure 3A). Using the IFX threshold concentrations described in the literature (3 and 7 μg/mL), this trend was also clearly visible on stratification into three groups: IFX underexposed, within the target range and overexposed (Figure 3B). This was confirmed by statistical comparison: the relationship between

TABLE 1 Summary of patient characteristics at the time of first study day

Categorical characteristics	Number of patients (%)
Sex (n = 121)	
Male	62 (51.2)
Female	59 (48.8)
Smoking (n = 118)	
Nonsmoker	41 (34.7)
Smoker	46 (39.0)
Ex-smoker	31 (26.3)
Diagnosis (n = 121)	
Crohn's disease	88 (72.7)
Ulcerative colitis	32 (26.4)
Indeterminable IBD	1 (0.9)
Age at diagnosis of Crohn's disease (n = 88)	
≤16 years	11 (12.5)
17-40 years	65 (73.9)
>40 years	12 (13.6)
Crohn's disease location (n = 88)	
Ileal	10 (11.3)
Colonic	21 (23.9)
Ileocolonic	57 (64.8)
Crohn's disease behaviour (n = 87)	
Nonstricturing, nonpenetrating	30 (34.5)
Stricturing	25 (28.7)
Penetrating	32 (36.8)
Ulcerative colitis severity (n = 32)	
Mild	2 (6.25)
Moderate	9 (28.1)
Severe	21 (65.6)
Number of surgeries (n = 118)	
0	85 (72.0)
1	20 (17.0)
2	10 (8.5)
3	3 (2.5)
Continuous characteristics	**Median (minimum, maximum)**
Body weight (kg)	70 (47, 115)
Height (cm)	171 (155, 190)
Body mass index (kg/m^2)	23.2 (14.5, 41.7)

IBD, irritable bowel disease.

IFX and disease activity measures was highest for CRP (Spearman's rank correlation: 2×10^{-10}, 2×10^{-5} and 0.003 for CRP, albumin and Harvey-Bradshaw index, respectively). Correlation between CRP and serum albumin concentrations was significant ($P < 10^{-10}$), contrary to the correlation between CRP and Harvey-Bradshaw index ($P > .1$).

Leveraging mechanistic knowledge on the immunological CRP kinetics, an inhibition of CRP synthesis by IFX exposure was assumed and realised in the PK/PD model.[4] To explore a potential difference in CD and UC subpopulation regarding serum CRP concentrations, multiple approaches were undertaken: the exploratory analysis prior to modelling identified no difference in CRP concentration range after first or previous dose between CD and UC, the relation between IFX and CRP was statistically significant (P value $<10^{-4}$) in both subpopulations and during model development no effect of IBD type was identified on baseline CRP and/or drug efficacy (IC_{50}). The PK/PD model that adequately described (Supporting Information Figure S4) the relationship between IFX exposure and CRP concentration comprised an indirect response E_{max} model (Figure 2) that accounted for time delay in CRP change induced by IFX. The degradation rate constant of CRP was fixed to correspond to a reported half-life of 19 hours (0.0365 h^{-1}) to avoid identification issues.[20] The generated quantitative and kinetic model showed that IFX has the potential to inhibit up to 72% of CRP synthesis in a patient (Figure 4A). IFX concentration leading to 50% of the maximum CRP synthesis inhibition was 2.04 μg/mL and IFX concentration leading to 90% of the maximum CRP synthesis inhibition was 18.4 μg/mL. The time point when these values were reached was naturally dependent on covariates defining the PK profile, as demonstrated in Figure 4B. The baseline CRP concentration could be estimated to be 6.32 mg/L for the typical individual, with high between-patient variability (coefficient of variation; CV) of 115% CV (5^{th}-95^{th} percentile range based on 1000 simulations: 1.50-28.4 mg/L). Similarly, between-patient variability in IFX concentration leading to half-maximum effect was found to be very high (209% CV; Figure 4C,D). None of the investigated covariates (eg diagnosis, sex, smoking status, age at diagnosis, Crohn's disease behaviour, Crohn's disease location, Montreal classification of ulcerative colitis severity, number of surgeries, baseline body weight, time since diagnosis at first IFX infusion) explained a significant part of the variability.

3.2 | Assessment of standard dosing strategy

To evaluate the standard and alternative dosing regimens, simulations were performed for a typical patient for nine different dosing intervals (q4w-q12w). Figure 5A shows the distribution of time to loss of CRP remission (CRP > 5 mg/L) for ADA+ and ADA– patients with (upper panel) and without (lower panel) co-therapy with immunomodulators in dependence of the dosing interval. The numbers below the boxes show the number of patients that experienced CRP > 5 mg/L at any point during a dosing interval: With the standard dosing regimen in the maintenance phase (q8w), more than half of ADA+ patients experience CRP nonremission, regardless of immunomodulator use. However, co-therapy with immunomodulators significantly decreased the proportion of patients experiencing CRP nonremission from 74% to 55%. In Figure 5B, median times to loss of CRP remission per dosing interval were extracted. To increase the number of patients that accomplish CRP remission over the whole dosing interval, a dosing

TABLE 2 Summary of blood samples (n_{total} = 388, $n_{mid\text{-}interval}$ = 202, $n_{end\text{-}interval}$ = 177) characteristics

Categorical characteristics	Number of total samples (%)	Number of mid-interval samples (%)	Number of trough samples (%)
Concomitant therapy with immunomodulators			
Yes	68 (17.5)	31 (15.3)	25 (14.0)
No	320 (82.5)	172 (84.7)	154 (86.0)
Antidrug antibodies			
Yes	82 (21.1)	41 (20.3)	41 (23.2)
No	306 (78.9)	161 (79.7)	136 (76.8)
Continuous characteristics	Median (minimum, maximum)	Median (minimum, maximum)	Median (minimum, maximum)
Absolute dose administered [mg]	400 (100, 1,300)	…	…
Concentration of IFX (μg/mL) (n = 388)	8.30 (0.10, 53.5)	13.8 (0.10,52.0)	4.30 (0.10, 24.0)
Concentration of CRP (mg/L) (n = 339)	2.70 (0.20, 120)	2.80 (0.20,120)	2.35 (2.00, 50.8)
Concentration of Alb (g/L) (n = 312)	42.9 (25.3, 51.6)	43.0 (25.3, 50.8)	42.7 (25.8, 51.6)
Harvey-Bradshaw index (n = 236)	2 (0, 19)	2 (0, 18)	2 (0, 19)

Note. Mid-interval samples were defined as samples taken between week 2 and week 6 after dose, end-of-interval (trough) samples were defined as samples taken between week 6 and week 10 after dose.
Abbreviations: Alb, serum albumin; CRP, C-reactive protein; IFX, infliximab.

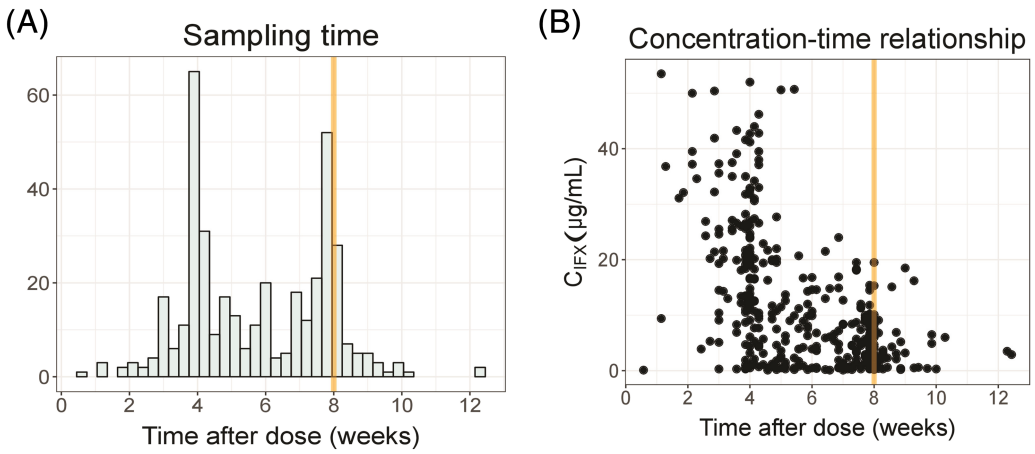

FIGURE 1 Overview of available measurements of infliximab (IFX) concentration in the investigated patient population. (A) Distribution of sampling times over dosing interval. The samples were mainly taken at C_{min} (trough) levels and at the middle of the dosing interval. The different dosing intervals arose from clinical decisions. (B) Concentration of IFX over time after last dose. Note that the dataset informs only the later phase of the concentration-time profile. The vertical orange line designates the standard dosing interval of 8 weeks (q8w). C_{IFX}, measured IFX concentration

interval shorter than the standard regimen would be required in both ADA+ and ADA− patient subpopulations: To this end, in the absence of co-therapy with immunomodulators, dosing intervals superior to q8w would be q7w and q5w for ADA− and ADA+ patients, respectively (Figure 5B). Furthermore, co-therapy with immunomodulators obliviates the need for dosing interval reduction in ADA− patients and shortens the needed dosing interval to q6w in ADA+ patients.

4 | DISCUSSION

To the best of the authors' knowledge, this is the first time that a population model that characterises the relationship of IFX PK to CRP concentration as a time-varying variable in IBD has been reported: This analysis characterised IFX exposure and its inhibition of CRP synthesis, and thereby enabled quantification of relevant PK and PD parameters, including variability in IFX exposure and response in the population. Patients who develop ADA and have low albumin, high BW and/or are not co-treated with immunomodulators were identified as subpopulations vulnerable to IFX underexposure. Furthermore, the model-based investigations indicate that shortening of the standard maintenance phase dosing interval dependent on ADA status should be considered to increase the number of patients maintaining CRP remission.

Despite its long presence in IBD management, therapy with IFX still faces challenges calling for further optimisation, from immunogenicity, to variable induction drug response, to loss of response to the therapy over time. The relationship between IFX exposure and CRP

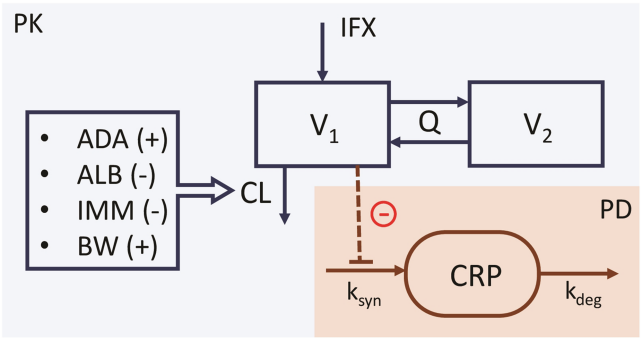

FIGURE 2 Graphical representation of the final pharmacokinetic/pharmacodynamics (PK/PD) model. Infliximab (IFX) PK is described by a two-compartment model with linear elimination. Antidrug antibody status, serum albumin concentration, co-therapy with immunomodulators and body weight were identified to impact the drug clearance (CL). The effect of IFX on C-reactive protein (CRP) was best characterised via the indirect drug effect modelling approach, whereby the plasma concentration of IFX was related to inhibition of CRP synthesis. ADA, antidrug antibodies; ALB, serum albumin concentration; BW, body weight; CL, clearance; CRP, C-reactive protein; IFX, infliximab; IMM, co-therapy with immunomodulators; k_{deg}, rate constant of CRP degradation; k_{syn}, rate constant of CRP synthesis; Q, intercompartmental exchange capacity; V_1, volume of central compartment; V_2, volume of peripheral compartment

concentration has so far not been characterised in a quantitative and mechanism-based way. Pharmacometric approaches enable a quantitative, kinetic and mechanistic insight into the underlying PK and PD/immunological pathways to be obtained. The developed models can be used to support clinical decisions as part of TDM, advocated by several national societies for the maintenance period of anti-TNFα therapy.

The first part of this analysis characterised the PK of IFX in IBD patients on maintenance phase treatment, including evaluation of factors that significantly contribute to the variability in IFX PK. In our analysis, the covariates that significantly impacted CL in the investigated population were ADA status, co-therapy with immunomodulators, serum albumin concentration and body weight. Previously published IFX PK models show a high level of agreement with respect to identified covariates (eg, body size, disease activity markers, ADA, co-medication) and our findings are also in good agreement with these reports.[21–29] In contrast to most of the previously developed models, all covariates in the present analysis were implemented as time-varying variables, thus implying a realistic change of IFX CL over time relative to the covariate values in individual patients. By incorporating the change over time in covariate values (in contrast to baseline covariate values only), more information from a covariate-parameter relationship from the data is used.

Mechanistically, the development of ADA affects both the PK and IFX effects. ADA molecules binding to active sites of the IFX molecule hinder its efficacy by disabling binding to its target, TNFα. Furthermore, the IFX-ADA complexes formed are promptly cleared from blood, contributing to higher CL of IFX.[30] Despite differences in assays available for ADA detection/quantification, especially the lower limit of quantification, resulting in varying definitions of ADA positivity in different analyses, ADA have consistently been found to impact IFX CL. The assay used in this study quantified total (both drug-bound and unbound) ADA concentration, with a cut-off for ADA positivity of 3.13 U/mL. In this analysis, an approximately 2-fold higher IFX CL was found in patients who developed ADA compared to patients who did not. The ADA status was, however, not found to impact the drug efficacy in our model. Another important factor that influences IFX CL is serum albumin concentration, as confirmed by our analysis as well. Serum albumin is likely related to IFX CL via two mechanisms: (a) as a marker of disease state and increased protein turnover in inflammation and (b) as a marker of the neonatal Fc-receptor (FcRn) activity (lower albumin concentration indicative of lower FcRn activity, resulting in higher IFX CL), potentially explaining why albumin was the disease activity marker predictive of IFX CL

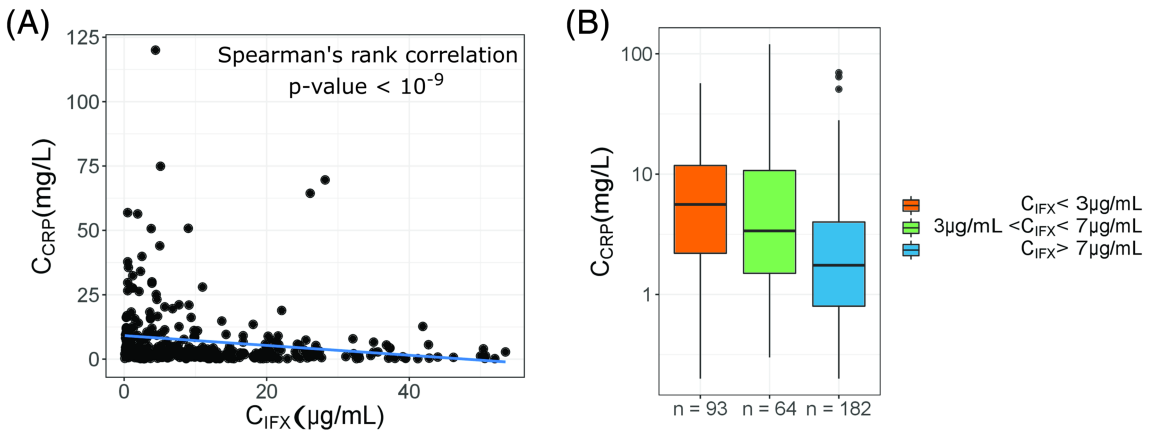

FIGURE 3 Relation between infliximab (IFX) exposure (ie, plasma concentration) and C-reactive protein (CRP) concentration. (A) Concentration of CRP over IFX concentration. The blue line represents linear regression. (B) Simplified comparison of the IFX-CRP relationship. Concentrations of IFX were stratified in three groups: ≤3 µg/mL, between 3 and 7 µg/mL, and >7 µg/mL.[19] The numbers indicate the number of observations each group comprises. A decrease in CRP concentration from the group with lowest IFX exposure to the group with highest is observed. C_{CRP}, measured CRP concentration; C_{IFX}, measured IFX concentration

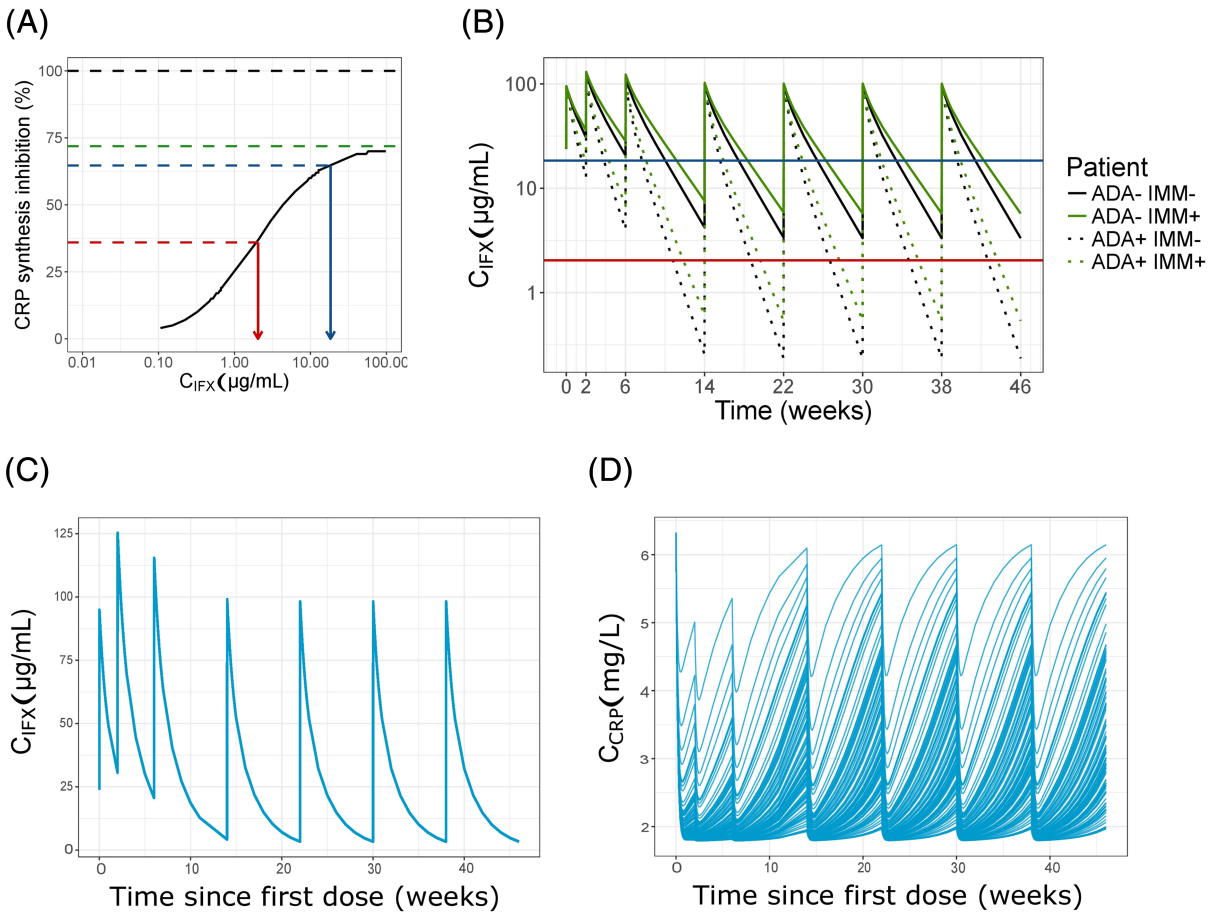

FIGURE 4 Illustration of infliximab (IFX) concentration (C_{IFX})-effect (C-reactive protein [CRP] synthesis inhibition)-time relationships. (A) IFX exposure-CRP synthesis inhibition curve and IFX potency. Red and blue arrows designate the IFX concentrations corresponding to 90% (18.4 µg/mL) and 50% (2.04 µg/mL) of the maximum CRP synthesis inhibition effect of ~72% (dashed green line), respectively. (B) Time after dose when IFX concentration falls below the 90% (blue line) and 50% (red line) effect concentrations for ADA– (solid lines) and ADA+ (dotted lines) patients without (black lines) and with (green lines) immunomodulator co-therapy. (C) and (D) Visualisation of high unexplained between-patient variability in IFX concentrations leading to a half-maximum effect on CRP concentration (IC_{50} value). Stochastic simulations were performed whereby variability in IC_{50} was considered. (C) IFX concentration-time profile in a reference individual. (D) Corresponding potential CRP concentration profiles. The plot demonstrates that due to high between-patient variability that could not be explained with any covariates, even for a patient with a known PK profile and baseline CRP concentration it is not possible to predict a single corresponding CRP profile, but rather a (rather wide) range of potential CRP profiles. ADA, antidrug antibodies; C_{CRP}, measured CRP concentration; C_{IFX}, measured IFX concentration; IMM, co-therapy with immunomodulators

rather than CRP. Furthermore, our analysis revealed a direct relationship between body weight and IFX CL, as well as an inverse relationship between co-therapy with immunomodulators and CL (see below). This analysis also investigated the potential impact of other covariates (eg, disease, sex), but none of them had a significant effect on CL. Given the similar proportion of male and female patients, our results suggest that dosing recommendations for both sexes must not be different.

Of the myriad measures used to assess activity of IBD, biomarkers currently represent adjunctive treatment targets primarily aimed for disease monitoring.[31] This study focused on CRP due to its favourable characteristics: (a) correlation with endoscopy,[3] (b) high sensitivity and short half-life ($t_{½}$ = approximately 19 h), and (c) well-known kinetic behaviour that does not differ between healthy and diseased individuals.[4]

One of the aims of this work was to investigate the PK/PD relationship between IFX exposure and IBD activity measures. In this analysis, disease activity measures were CRP and serum albumin concentrations, and the Harvey-Bradshaw index for patients with Crohn's disease. For UC, disease severity was assessed according to the Montreal classification and disease activity by the partial Mayo score; however, due to the low number of patients with UC, subanalyses in this group were not performed. As TNFα is the main initiator of immunological cascade resulting in CRP synthesis, lower levels of TNFα lead to lower CRP synthesis (Figure 2). Since IFX does not inhibit CRP synthesis directly, a certain time-delay between maximum IFX exposure and maximum inhibition of CRP synthesis is expected. In the PK/PD model, this time-delay was incorporated as IFX inhibition of CRP synthesis via the indirect response modelling approach. The model estimated that up to approximately 72% of

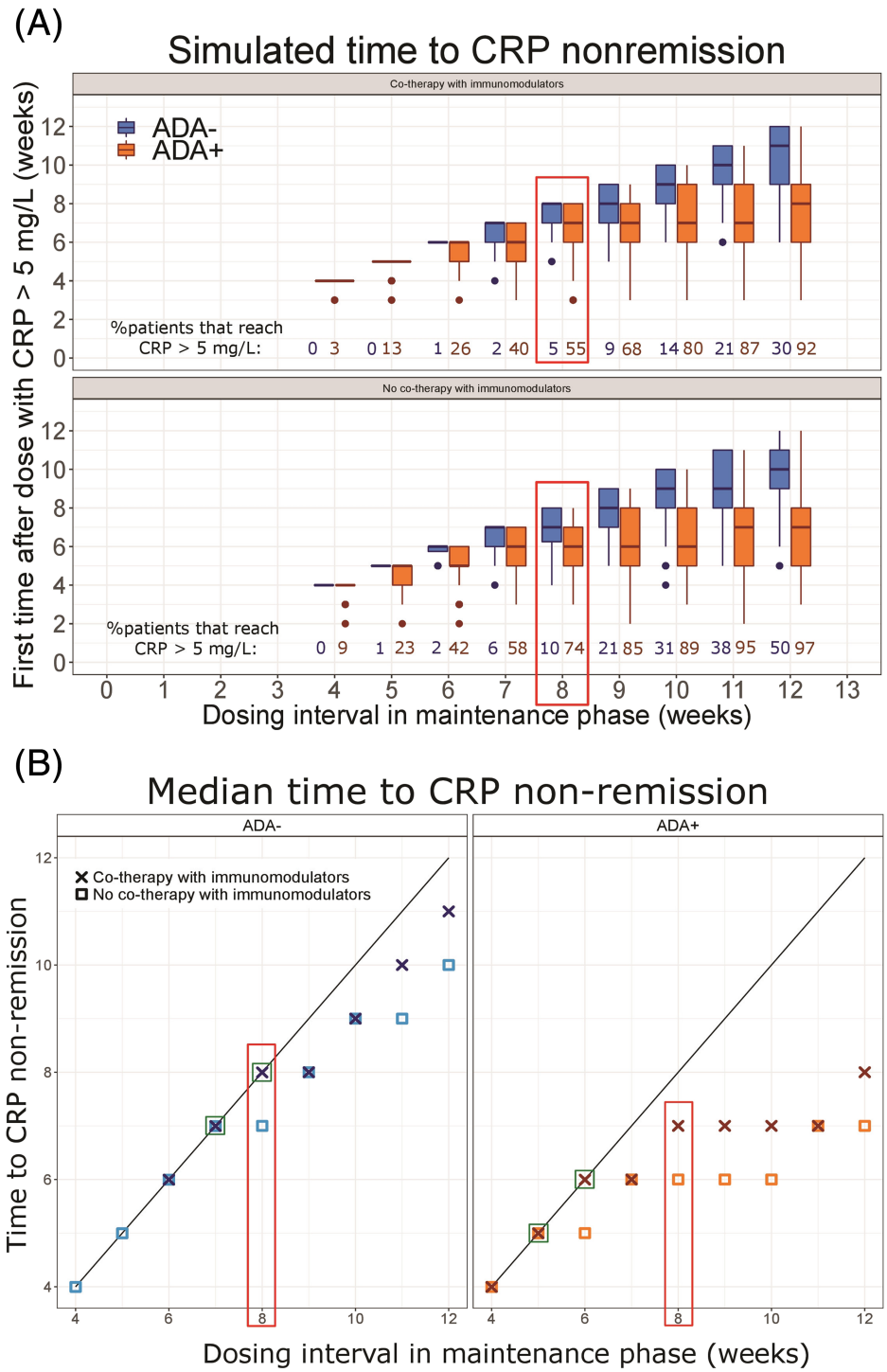

FIGURE 5 Evaluation of the standard and alternative infliximab (IFX) dosing regimens with respect to C-reactive protein (CRP) suppression via stochastic simulations (n = 1000) of patients that differ only in antidrug antibody status. For the simulations, variability in the PK submodel parameters was considered. (a) Distribution of time points in the weeks after the fifth dose when CRP concentration reached 5 mg/L (CRP nonremission) as box-whisker plot over simulated IFX dosing intervals, stratified by antidrug antibody (ADA) status and co-therapy with immunomodulators. Note that the virtual patients that do not experience CRP concentrations above 5 mg/L (ie, without loss of CRP remission) are not included in the plot. Proportions of patients experiencing CRP nonremission (shown below each box) are higher in cases of ADA development and absence of co-therapy with immunomodulators. (b) Simplification showing only the median time after the fifth dose when CRP concentration reached CRP nonremission stratified by ADA development and immunomodulatory co-therapy. In the presence of co-therapy with immunomodulators, the standard IFX dosing interval of every 8 weeks (q8w) corresponds to median time to CRP nonremission in ADA– patients, whereas for ADA+ patients reduction to q6w is to be recommended. In the absence of co-therapy with immunomodulators, for ADA– patients a dosing interval of q7w corresponds to the median time to CRP nonremission, whereas for ADA+ patients further reduction to a dosing interval of q5w should be preferred. Red frame, standard IFX dosing regimen every 8 weeks

CRP synthesis can be inhibited by IFX (Figure 4A). In other words, the IFX effect is saturable and CRP synthesis cannot be 100% inhibited by IFX: Regardless of how high IFX concentrations are achieved within an individual, approximately a quarter of CRP synthesis cannot be inhibited. This finding, now quantified, is in good accordance with previous knowledge, since TNFα is not the only immunological initiator of CRP synthesis.[4] Concentration of IFX leading to half-maximum effect was 2.04 μg/mL, which approximately corresponds to PK targets previously described in the literature.[19] The corresponding IFX concentration leading to 90% of the maximum effect was 18.4 μg/mL. As, depending on their covariates, different patients might have different PK profiles, the time after a dose when IFX concentration falls below an effective level might differ as well. This is illustrated in Figure 4B: a typical ADA− patient drops below the 90% effect IFX concentration before week 4 in the absence of co-therapy with immunomodulators and after week 4 in the presence of the co-therapy. The IFX concentration never falls below the 50% effect concentration in this subpopulation. In contrast, ADA+ patients fall below the 90% effect concentration threshold around week 2, regardless of immunomodulators use, ie, approximately or more than 2x faster than the ADA− patient. Thus, in ADA+ patients the 90% effect concentration is achieved during only one quarter of the dosing interval. The beneficial co-therapy with immunomodulators, however, delays crossing the 50% effect concentration threshold in ADA+ patients from 5 to 6 weeks. From the clinical perspective, a very important finding of this analysis is the high between-patient variability in IC_{50} value of IFX for the effect on CRP (∼209% CV). One hypothesis to explain the identified high between-patient variability in IC_{50} is the fact that CRP is a far downstream biomarker with respect to IFX binding to TNFα. A similar finding was recently obtained for faecal calprotectin in a report of an IFX-faecal calprotectin PK/PD model.[32] This indicates that there is a potentially high individual difference in effect (ie, inhibition of CRP synthesis) among patients even in cases of the same IFX exposure (Figure 4C,D). Practically, this implies that monitoring of disease activity measures, such as CRP concentration, might be advantageous over solely monitoring IFX concentration. Further investigations in the direction of identifying covariates that contribute to this high variability are warranted.

In our data, no long-term inhibitory effect of IFX on CRP was observed, ie, stopping IFX therapy leads to increase in disease activity, regardless of the time after IFX therapy initiation. Contrarily, clinical experience suggests that some patients will remain in a state of remission even if IFX therapy is ceased after a certain period.[33,34] In our data, samples were collected from a large number of patients, but spread over different ranges of time after first dose and with a relatively short follow-up time. This might contribute to the lack of identification of long-term disease suppression. If long-term data is available and this cumulative IFX effect was identified, it could be added to the PK/PD model.

We acknowledge that our study has certain limitations. As sampling in the first weeks of the dosing interval is scarce, the dataset informs only the later phase of the IFX concentration-time profile. This limitation manifests itself through the fact that the central volume of distribution and intercompartmental exchange capacity could not be estimated from the data alone, in contrast to clearance and peripheral volume of distribution. The frequentist prior approach enabled this limitation of the real-world clinical data situation to be overcome.[35] While the sampling scheme (ie, two samples per dosing interval) resulted in appreciable ranges of all variables (eg, IFX, CRP, ALB, covariates) due to the TDM nature of the dataset, the CRP concentration at the time of the first IFX infusion was not available for most patients. Our generated model, however, was able to estimate the plausible baseline CRP value very precisely. In addition, measurement of further factors, eg, genotyping and assessment of faecal loss of IFX, CRP and albumin, would enable investigation of their potential effect on the PK and PK/PD. For instance, besides the two known mechanisms of the albumin-IFX relationship (ie, the inverse relationship between serum albumin concentration and IBD activity, and the shared PK pathways of albumin and IFX, especially the FcRn salvage pathway), faecal loss might be an additional contributor. Finally, limitations of CRP as a disease marker (eg, lack of specificity) have to be acknowledged; investigation of additional disease markers would add to this knowledge and help further inform the choice of the most appropriate marker. This was accounted for in the developed PK/PD model by a finding of maximum CRP synthesis inhibition lower than 100%, whereby non-TNFα inducers of CRP synthesis are implied. Altogether, the heterogeneity of the patient population (covering broad ranges of the measured values) and the informative sampling time points (including an additional sample to the one taken just before the next IFX dose, i.e. trough) enabled the described IFX exposure-response relationship to be captured.

Pharmacometric nonlinear mixed-effects modelling analysis of PK/PD relationships enables characterisation of the analysed patient population over time in a continuous manner, at the same time providing insight into the variability between patients and relevant covariates. One of the advantages of this modelling approach is that after successful model development and evaluation, the model can be employed to test different hypotheses via simulations. This is illustrated by the in silico substudy we carried out. As the presence of ADA was found to lead to a very high influence on IFX CL and thus IFX exposure, we investigated how this impact reflects on CRP. To this end, simulations were performed for ADA+ and ADA− virtual IBD patients to assess different dosing intervals (q4w-q12w) and the impact of co-therapy with immunomodulators. The desired target was defined as CRP concentration <5 mg/L over the whole dosing interval (CRP remission). To assess the target attainment, simulations (n = 1000) were performed for each investigated dosing interval and (a) the percentage of patients with undesired outcome, ie, that reach CRP > 5 mg/L (CRP nonremission) and (b) the time after the fifth dose when the CRP concentration crossed and exceeded the target value were recorded. As shown in Figure 5A, when a standard dosing regimen (q8w) was simulated without co-therapy with immunomodulators, 10% of ADA− and as much as 74% of ADA+ patientsexperienced CRP values higher than 5 mg/L. These

proportions were lower in the presence of immunomodulators (5% and 55% for ADA− and ADA+ patients, respectively). The median time to loss of CRP remission (Figure 5B) suggests that ADA− patients accomplish continuous CRP remission with standard dosing interval q8w when they are co-treated with immunomodulators. On the other hand, in ADA+ patients a reduction of dosing interval would be required to q5w and q6w in the absence and presence of immunomodulators co-therapy, respectively.

In this study, we report the first PK/PD model relating IFX exposure to inhibition of CRP synthesis in IBD patients. Increased CL of IFX was related to development of ADA, low serum albumin, high body weight and absence of co-therapy with immunomodulators. The developed PK/PD model identified high variability in effect on CRP for the same IFX exposure, which could not be explained with evaluated covariates, suggesting individual CRP measurements should be monitored and included in the decision of a patient's dosing regimen. Based on simulations from the developed PK/PD model, concrete ADA status- and immunomodulatory co-therapy-dependent dosing adjustments of current standard dosing strategies are suggested to support achieving continuous CRP remission in these patients. Finally, the developed model enables simulation of any type of dosing regimen change (eg, dose change) and provides a framework for development of a dashboard system[28] that could directly support therapeutic decision making, with respect to achieving both IFX and CRP targets.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[36]

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CONTRIBUTORS

A.E. and W.R. conceived and designed the study and provided the data for the analysis. A.M.G. conducted the analysis and drafted the manuscript. C.K. and W.H. provided methodological support. All authors were involved in interpretation of results and critical revision of the manuscript. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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