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ORIGINAL RESEARCH ARTICLE

Infliximab Treatment Does Not Lead to Full TNF-α Inhibition: A Target-Mediated Drug Disposition Model

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Abstract

Background and Objective Infliximab, an anti-tumour necrosis factor (TNF)-α monoclonal antibody, has been approved in chronic inflammatory disease, including rheumatoid arthritis, Crohn's disease and ankylosing spondylitis. This study aimed to investigate and characterise target-mediated drug disposition of infliximab and antigen mass turnover during infliximab treatment.

Methods In this retrospective cohort of 186 patients treated with infliximab for rheumatoid arthritis, Crohn's disease or ankylosing spondylitis, trough infliximab concentrations were determined from samples collected between weeks 0 and 22 after treatment initiation. Target-mediated pharmacokinetics of infliximab was described using target-mediated drug disposition modelling. Target-mediated elimination parameters were determined for rheumatoid arthritis and Crohn's disease, assuming ankylosing spondylitis with no target-mediated elimination.

Results The quasi-equilibrium approximation of a target-mediated drug disposition model allowed a satisfactory description of infliximab concentration–time data. Estimated baseline TNF-α amounts were similar in Crohn's disease and rheumatoid arthritis ($R0 = 0.39$ vs 0.46 nM, respectively), but infliximab-TNF complex elimination was slower in Crohn's disease than in rheumatoid arthritis ($k_{int} = 0.024$ vs 0.061 day^{-1}, respectively). Terminal elimination half-lives were 13.5, 21.5 and 16.5 days for rheumatoid arthritis, Crohn's disease and ankylosing spondylitis, respectively. Estimated amounts of free target were close to baseline values before the next infusion suggesting that TNF-α inhibition may not be sustained over the entire dose interval.

Conclusions The present study is the first to quantify the influence of target antigen dynamics on infliximab pharmacokinetics. Target-mediated elimination of infliximab may be complex, involving a multi-scale turnover of TNF-α, especially in patients with Crohn's disease. Additional clinical studies are warranted to further evaluate and fine-tune dosing approaches to ensure sustained TNF-α inhibition.

1 Introduction

Infliximab is a chimeric IgG1 monoclonal antibody (mAb) that targets tumour necrosis factor (TNF-α). It was approved in chronic inflammatory rheumatisms such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis, and in inflammatory bowel diseases such as Crohn's disease (CD) and ulcerative colitis (UC). As for a majority of mAbs, infliximab has a high interindividual pharmacokinetic variability. Known factors of variability include body weight, sex and the presence of anti-drug antibodies [1].

Monoclonal antibodies bind to their target with high affinity, leading to the formation of mAb target complexes that are cleared by the immune system. This target-mediated elimination therefore increases with target levels and leads to decreased serum concentrations of unbound (active) mAbs. The joint kinetics of the mAb and the target antigen can be described using target-mediated drug disposition (TMDD) models. Infliximab pharmacokinetics was described in more than 30 studies [2], only a few of them investigated target-mediated pharmacokinetics of infliximab [3–7]. We previously showed that infliximab pharmacokinetics was influenced by the treated disease, with, for a given dose, lower infliximab concentrations in RA and CD than in AS. This might be due to TNF-α-mediated elimination of infliximab,

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Key Points

Previous studies reported differences in the pharmacokinetics of infliximab, an anti-tumour necrosis factor-α monoclonal antibody, between treated diseases, and other studies reported target-mediated pharmacokinetics. However, the link between these pharmacokinetic differences and the target antigen level has never been described.

The present study is the first to quantify the influence of target antigen dynamics on infliximab pharmacokinetics. It suggested that current infliximab dosing approaches may not sustain tumour necrosis factor-α inhibition over the entire dose interval, which nevertheless may not lead to a systematic loss of response.

The pharmacokinetics of infliximab appears complex, involving a multi-scale turnover of tumour necrosis factor-α and may explain, at least in part, the large disparity of previously reported pharmacokinetic parameter estimations.

as TNF-α blood concentrations are higher in UC and CD (27 and 16 pg/mL, respectively [8, 9]) than in RA (10.7 pg/mL [10]), and higher in RA than in AS (2.3 pg/mL [10]), with a very large interindividual variability.

However, TNF-α blood concentrations (approximately 0.0005 nM [8–10]) are negligible compared with infliximab trough concentrations (approximately 10–100 nM), suggesting a large and durable stoichiometric excess of infliximab. This observation leads to important issues. First, the large excess of infliximab would lead to a negligible target-mediated clearance, which is not in agreement with previous descriptions of infliximab target-mediated elimination [3–7]. Second, this excess would lead to a durable neutralisation of antigenic targets, which is not in agreement with the fact that infliximab concentrations associated with a good clinical response (approximately 20 nM [11]) are more than 10,000 fold higher than TNF-α blood concentrations [8–10]. Indeed, being an IgG, infliximab is distributed in almost all tissues and organs by transcytosis. This phenomenon is due to the neonatal Fc receptor, whose role is IgG transcytosis and protection against endogenous catabolism. Thus, TNF-α blood concentration may not be a good surrogate for the TNF-α total amount, i.e. the total amount of TNF-α targeted by infliximab may be much higher than its amount in blood.

In previous works, we described infliximab pharmacokinetics using a real-life database of patients treated with infliximab [12–14]. In the present study, we used this real-life database to develop a TMDD model quantifying free target and complex amounts and target-mediated elimination of infliximab in patients with RA and CD, taking patients with AS a reference.

2 Methods

2.1 Data

The present study was conducted using concentration–time data from a retrospective cohort of 363 routine practice patients treated with infliximab between 2005 and 2012 in the Tours University Hospital (Tours, France). As part of the routine daily therapeutic drug monitoring of infliximab, blood samples were collected to measure infliximab trough concentrations. Individual results were interpreted, sent to the prescriber and discussed in clinical rounds. Infliximab concentrations were therefore not obtained specifically for this study and were already used in previous publications [12–18].

As described elsewhere [13, 14, 17], we assessed a subgroup of patients that met the following criteria to allow a robust estimation of pharmacokinetic parameters: patients with AS, RA and CD, for whom infliximab concentrations were available before the first infusion and at each visit and in whom no anti-drug antibodies were detected during the follow-up. As the number of patients with RA in this cohort subgroup was low (18 patients), we added patients who benefited from infliximab therapeutic drug monitoring between 2012 and 2019. Of the 85 patients with RA treated during this period, only five met the inclusion criteria. Finally, data were available for 186 patients, including 91, 23 and 72 patients with AS, RA and CD, respectively (Table 1).

Infliximab concentrations were measured using a validated enzyme-linked immunosorbent assay. Limit of detection and the lower and upper limits of quantitation were 0.031, 0.103 and 15 mg/L, respectively. This technique was shown to measure the concentrations of unbound infliximab [19].

2.2 Pharmacokinetic Analysis

2.2.1 Software

Concentration–time data were analysed using the nonlinear mixed-effects modelling software Monolix Suite 2019 (Lixoft®, Antony, France). A large number of iterations (1000 and 400 iteration kernels 1 and 2, respectively) and five Markov chains were used. The Fisher information matrix and objective function (− 2.likelihood) were computed using stochastic approximation and importance sampling, respectively. All parameters were estimated simultaneously.

2.2.2 Structural Model Design

We developed a TMDD model [20] with quasi-equilibrium (QE) approximation [21], accounting for the influence of TNF-α concentrations and turnover in patients with both RA and CD (Fig. 1). This approximation was the more effective method to describe our data (Electronic Supplementary Material [ESM]). We assumed negligible target-mediated elimination in patients with AS and that differences in infliximab pharmacokinetics between patients with RA or CD on the one hand, and patients with AS on the other hand, were only due to target antigens. Concentrations of TNF-α were not measured and thus considered as latent, which did not hamper TMDD parameter estimation. The QE model described total infliximab (i.e. unbound plus infliximab-TNF complexes) and total latent TNF-α (i.e. free targets plus complexes) as follows:

$$\frac{dC_T}{dt} = In(t) - k_e \cdot C - \frac{R_T \cdot k_{int} \cdot C}{K_D + C},$$

$$\frac{dR_T}{dt} = k_{in} - k_{out} \cdot R_T - \left(k_{int} - k_{out}\right) \cdot \frac{R_T \cdot C}{K_D + C},$$

$$C = \frac{1}{2}\left[\left(C_T - R_T - K_D\right) + \sqrt{\left(C_T - R_T - K_D\right)^2 - 4 \cdot K_D \cdot C_T}\right],$$

where $In(t)$ is the infliximab input function, C_T and R_T are total infliximab and total TNF-α concentrations, respectively, C is the unbound infliximab concentration, k_e is the elimination rate constant, k_{in} and k_{out} are TNF-α zero-order input and first-order output, respectively, R_0 is the baseline antigen mass, i.e. TNF-α concentration available for infliximab binding, with $R_T(0) = R_0 = k_{in}/k_{out}$, k_{int} is the infliximab-TNF-α complex destruction rate constant and K_D is the dissociation constant. The pharmacokinetic model was parameterised using volume (V) and clearance (CL).

Our model accounted for different TNF-α turnover and interaction with infliximab between patients with RA and CD. Model parameters were noted with "ra" and "cd" in the exponent for rheumatoid arthritis and Crohn's disease, respectively. The model was developed in four steps.

2.2.2.1 Step 1: TMDD Model in Patients with RA In RA, the TNF-α reservoir is considered as mainly circulating [22–24]. Several values of K_D^{ra} were previously reported: 0.027 nM [25], 1.93 nM [26] and 0.43 nM [27]. We performed several parameter estimations utilising all these values, and a value of 10 nM for a sensitivity analysis.

2.2.2.2 Step 2: TMDD Model in Patients with CD In CD, it is admitted that the TNF-α reservoir is both circulating and expressed on intestine inflammatory cells (monocytes, macrophages) [28–30]. Several values of K_D^{cd} were found in the literature and tested in our parameter estimation: 0.046 nM [31], 0.45 nM [32], 0.468 nM [25] and 5.9 nM [25], and a value of 10 nM for a sensitivity analysis.

2.2.2.3 Step 3: Simultaneous RA and CD TMDD Models K_D^{ra} and K_D^{cd} values that led to the best data fit in steps 1 and 2 were retained. In addition, early attempts showed a high correlation between k_{out}^{ra} and k_{out}^{cd} estimates. Therefore, we estimated only one value of the TNF-α elimination rate constant for both RA and CD.

2.2.2.4 Step 4: Covariate Selection Covariates [13] were added in the TMDD model designed in step 3.

2.2.3 Statistical Models

2.2.3.1 Interindividual and Error Models The statistical model of interindividual variability was exponential, with interindividual standard deviations fixed to 0 when the relative standard error and/or shrinkages were high. The error model was proportional.

2.2.3.2 Influence of Covariates The categorical covariates (CAT) were sex (SX), underlying disease (DIS = RA or CD vs AS), methotrexate cotreatment (MTX) and age ≤ 15 years (AGE ≤ 15). These covariates were tested in the one-compartment and the QE models. The influence of CAT on a given parameter was implemented as: $\ln\left(\theta_{TV}\right) = \ln\left(\theta_{CAT=0}\right) + \beta_{CAT=1}$, where θ_{TV} is the typical value of structural parameter θ, $\theta_{CAT} = 0$ is the value of θ for the reference category and $\beta_{CAT} = 1$ is the parameter leading to the value for the other category. The continuous covariate was body weight (BW), which was centred on its median and implemented using a power model.

Table 1 Summary of patients' characteristics

Characteristics	Patients ($N = 186$)
Starting dose (mg)	300 (250–400)
Body weight (kg)	65 (54–77)
Age (years)	39 (28–49)
Sex (female/male)	69 (37)
Disease	
Ankylosing spondylitis	91 (49)
Rheumatoid arthritis	72 (39)
Crohn's diease	23 (12)
Methotrexate cotreatment in rheumatoid arthritis	11 (28)
Age ≤ 15 years in Crohn's disease	15 (22)

Results are given either as median (interquartile range) or as n (%)

2.2.3.3 Covariate Selection We implemented the influence of BW, SX, MTX and AGE ≤ 15 on *V* and CL. In addition, as MTX acts as an anti-inflammatory drug, it may decrease TNF-α concentrations. Thus, during step 3, the influence of MTX was implemented on R_0^{ra} and compared to MTX on CL. Because we suspected an association of age with TNF-α concentrations, the influence of AGE ≤ 15 was implemented on R_0^{cd} and was compared to AGE ≤ 15 on V_D. Values of R_0 with MTX and AGE ≤ 15 covariates were implemented as follows:

$$R_{0,AGE15}^{cd} = R_0^{cd} \cdot e^{-\beta_{AGE} \cdot AGE15},$$

$$R_{0,MTX}^{ra} = R_0^{ra} \cdot e^{-\beta_{MTX} \cdot MTX},$$

where R_0^{ra} is the reference value of antigen mass (without MTX and age > 15 years), and β_{AGE} and β_{MTX} are parameters leading to the value if age ≤ 15 years and with MTX cotreatment, respectively.

2.2.4 Model Evaluation

2.2.4.1 Model Comparison Structural models were compared using Akaike's information criterion (AIC), which combines the − 2 ln-likelihood and the number of parameters to be estimated. For each relationship, the model with the lowest AIC was chosen. The − 2 ln-likelihood of the interindividual, residual and covariate models were compared using the likelihood ratio test; the difference in − 2 ln-likelihood (ΔLL) between two models was assumed to follow a χ^2 distribution.

The influence of potential covariates on structural parameters was assessed in two steps: (1) a univariate step in which the influence of each covariate on structural parameters associated with interindividual variability was tested separately from the others. Covariates showing a significant influence ($\alpha < 0.1$) were kept for the (2) multivariate step, in which a forward-backward stepwise selection process was made. In the forward stepwise, covariates showing a significant association with pharmacokinetic parameters ($\alpha < 0.05$) were added individually to the base model. In the backward stepwise, covariates whose removal resulted in a statistically significant re-increase ($\alpha < 0.02$) were kept in the final model.

2.2.4.2 Model Goodness of Fit Target-mediated drug disposition models were evaluated graphically using goodness-of-fit diagnostic plots: observed vs population predicted and individual predicted fitted concentrations; population and individual weighted residuals vs population predictions and individual predictions, respectively. Visual predictive checks and normalised prediction distribution errors were also performed by simulating 1000 replicates using both fixed-effect and random-effect final parameters.

2.2.5 Model-Based Simulations

The typical parameter values of the final model were used to simulate typical profiles of unbound infliximab concentrations for AS, RA and CD, and total target (R_T) and free/baseline target ratio (R_F/R_0) in time for RA and CD. The simulated dosing regimen was 300 mg at weeks 0, 2, 6 and 14. Simulated profiles corresponded to population parameter estimates, i.e. for a female subject aged > 15 years with median BW and not co-treated with MTX. In addition, we simulated these profiles for a patient with RA with MTX cotreatment, as well as for a patient with CD aged ≤ 15 years. Terminal elimination half-lives ($T½_R$) were derived from terminal elimination slopes.

3 Results

3.1 Base Model

Infliximab concentration–time data were satisfactorily described by the QE model (ESM). In patients with RA, the best K_D^{ra} value was 0.43 nM [27]. Other values led to an increase in AIC; k_{int}^{ra} estimate was sensitive to the fixed K_D^{ra} value (Table 2). In patients with CD, the best K_D^{cd} value was 0.45 nM [32]. Lower values led to an increase in AIC, whereas upper values led to unlikely k_{out}^{cd} estimates, corresponding to TNF-α elimination half-lives ($\ln(2)/k_{out}$) of 17–26 h, much higher than what was previously reported in the literature [33–36] (0.1–1.7 h, depending on species and TNF-α amounts, Table 2).

Estimating a unique k_{out} value for both RA and CD did not decrease model performances (model 3 vs 4, ΔAIC = 0.37, Table 3), and avoided a correlation between both k_{out} estimates. The QE model led to a better description of concentration–time data than the simple one-compartment model, which supports our assumption of TNF-mediated pharmacokinetics: reductions in AIC were 7.94 and 18.98 between base and final one-compartment vs TMDD models, respectively (ESM).

Interindividual variances of V and CL were estimable, while those of all other structural parameters had to be fixed to 0. All model parameters were estimated with good accuracy (Table 4). Diagnostic plots were obtained from the final QE model (ESM), which showed a good agreement between observed and predicted infliximab concentrations. Individual-weighted residuals, normalised prediction distribution errors and VPCs showed no obvious bias or model misspecification.

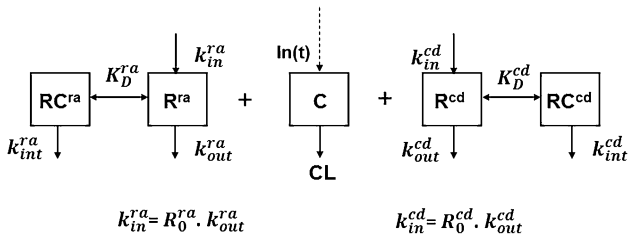

Fig. 1 Target-mediated drug disposition with quasi-equilibrium approximation. Base parameters are estimated for rheumatoid arthritis, Crohn's disease and ankylosing spondylitis, the latter being used as a reference, while target-mediated drug disposition parameters are estimated for rheumatoid arthritis (*left*, "s" exponent) and Crohn's disease (*right*, "m" exponent). *CL* (endogenous) clearance, *In(t)* infliximab input function, K_D dissociation constant, k_{in} zero-order unbound target production rate constant, k_{int} infliximab-TNF complex elimination rate constant, k_{out} first-order destruction rate constant, R_0 baseline TNF-α amount, *TNF* tumour necrosis factor, *V* volume of distribution

3.2 Covariate Selection

Both *V* and CL increased with body weight (BW) and were higher in male than in female patients (Table 4). Young age (AGE ≤ 15 years) in patients with CD and MTX cotreatment (MTX) in patients with RA led to decreased *V* and CL, respectively. The association of MTX was stronger with R_0^{ra} (model 7 vs 5 ΔLL = − 8.15) than with CL (model 6 vs 5 ΔLL = − 5.67), which suggests an effect of MTX on the TNF-α amount rather than on infliximab elimination. Methotrexate cotreatment was associated with a value of R_0^{ra} decreased to 14% the value without cotreatment. The influence of young age on R_0^{cd} (model 8, ΔLL = − 17.24) was stronger than that on V (model 7, ΔLL = − 8.13). Similarly to the influence of MTX, this suggests an influence of age on antigen mass rather than on infliximab elimination (Table 3). In our cohort, young patients with CD (aged ≤ 15 years) had an R_0^{cd} value of 3% of that of adults (Table 4). The final QE model included influences of MTX and age on R_0^{ra} and R_0^{cd}, respectively (model 17, Tables 3 and 4).

3.3 Model-Based Simulations

Simulations of typical unbound infliximab concentrations, total target amounts and the R_F/R_0 ratio in time showed substantial differences between diseases (Fig. 2A). In RA and CD, infliximab input was followed by a dramatic increase in total target amounts, with a maximum increase of 130- and 220-fold from the initial value in RA and CD, respectively. Despite comparable baseline target amounts, different k_{int} values led to different kinetics of total target and R_F/R_0 ratios between RA and CD. Indeed, target occupancy is higher and more delayed in RA than in CD despite a lower total target amount in RA than in CD. These differences in k_{int} values led to altered unbound infliximab kinetics: $T½_R$ was lower in RA (13.5 days) and higher in CD (21.5 days) compared with AS (16.5 days). Furthermore, R_F/R_0 ratios returned to almost 1 before infliximab infusion at steady state, suggesting that infliximab does not provide a sufficient target inhibition. In patients with RA, MTX cotreatment led to total target amounts divided by almost 7 and an increased terminal *T½* (15.5 days, Fig. 2B). In patients with CD, young patients (aged ≤ 15 years) had total target amounts divided by 26 and a pharmacokinetic profile almost identical to AS (Fig. 2C).

4 Discussion

To our knowledge, this is the first study that investigated the influence of total antigen mass on infliximab pharmacokinetics in both patients with RA and CD. We used a QE TMDD model and it suggests that the differences in infliximab pharmacokinetics between RA and CD were explained by TMDD. This model not only captured the effect of disease on infliximab pharmacokinetics, but also was able to provide an estimation of the total antigen amount available for infliximab binding.

Among therapeutic mAbs, infliximab is the one that pharmacokinetics was the most extensively studied using compartmental modelling, with 32 publications till today, most of them dealing with, at least in part, inflammatory bowel diseases (24 publications). The influence of the target antigen was suggested in nine studies [1, 37], in which increased inflammatory activity was associated with higher CL. Infliximab target-mediated pharmacokinetics was investigated in five studies: one measuring blood TNF-α concentrations in individual UC data [3], whereas four were made without TNF-α concentration measurements [4–7]. Our k_{int} estimates are comparable to values reported by these studies, except for Berends et al, who reported a higher value (0.98 day^{-1}). This may be explained by the fact that their study specifically focused on blood TNF-α concentrations as a target.

Our R_0 estimates were 100-fold greater than circulating TNF-α concentrations: in RA and CD, R_0^s and R_0^m were 0.39 and 0.46 nM, respectively, while circulating TNF-α concentrations were approximately 0.0003 nM in RA [10, 38] and 0.0004 in CD [8, 9]. Therefore, our model may have captured the influence of the target antigen located outside the bloodstream but still able to interact with infliximab, this part of TNF-α available for infliximab binding being the largest. This tissular TNF-α may explain the apparent lack of association between circulating TNF-α concentrations and the infliximab concentration–response relationship. In RA, this could explain the controversial association of circulating TNF-α concentrations and clinical response [39, 40]. In inflammatory bowel diseases, this could explain the large difference in k_{int} estimates between Berends et al. [3] and our

Table 2 Selection of fixed dissociation constant values

Parameter	Unit	Rheumatoid arthritis					Crohn's disease					
		1 comp disease	High K_D	Kim et al. [26]	Chen et al. [27]	Kaymakcalan et al. [25]	1 comp disease	Scallon et al. [31]	Scallon et al. [32]	Kaymakcalan et al. [25] transfected	Kaymakcalan et al. [25] activated	High K_D
K_D	nM	–	10*	1.93*	**0.43***	0.027*	–	0.046*	**0.45***	0.468*	5.9*	10*
V	L	6.2	6.3	6.3	**6.2**	6.2	6.2	6.2	**6.2**	6.2	6.1	6.1
CL	$L \cdot day^{-1}$	0.26	0.26	0.26	**0.26**	0.27	0.22	0.27	**0.27**	0.27	0.27	0.27
R_0	nM	–	0.515	0.227	**0.432**	0.462	–	0.0252	**0.223**	0.225	2.670	4.5
k_{out}	day^{-1}	–	5.83	11.7	**4.41**	4.44	–	86.4	**10.3**	10.1	0.953	0.62
k_{int}	day^{-1}	–	0.335	0.174	**0.0385**	0.0373	–	0.0183	**0.0197**	0.0196	0.0202	0.0214
− 2LL	–	3050.24	3050.61	3050.59	**3048.16**	3048.22	4178.74	4172.65	**4172.58**	4172.64	4172.87	4173.14
AIC	–	3064.24	3068.61	3068.59	**3066.16**	3066.22	4194.74	4190.65	**4190.58**	4190.64	4190.87	4191.14

Bold symbols correspond to K_D values that led to best concentration-time data description

Estimated pharmacokinetic parameters for each fixed dissociation constant (K_D) value. Models were 1 compartment with diseases (RA, CD) accounted as covariates, high K_D where K_D was fixed at 10 nM; other K_D values were obtained in Kim et al. [26], Chen et al. [27], Kaymakcalan et al. [25], Scallon et al. [31] and Scallon et al. [32]. From Kaymakcalan et al., a "transfected" value was obtained from Sp2/0 myeloma cells transfected with a gene expressing a mutant form of human TNF, whereas an "activated" value was obtained from human PBMC activated with diverse compounds [32]

− 2LL − 2 ln-likelihood, *AIC* Akaike's information criterion, *CL* clearance, k_{int} infliximab-TNF complex elimination rate constant, k_{out} unbound target elimination rate constant, *PBMC*, R_0 baseline TNF-α amount, *TNF* tumour necrosis factor, *V* volume of distribution

Table 3 Comparison of target-mediated drug disposition models

Model number	Base model	Covariates			− 2LL	AIC
		Disease	WT, CL	MTX, AGE ≤ 15		
1	QSS				4559.55	4581.55
2	QSS, $k^{s}_{out} = k^{m}_{out}$				4560.55	4580.55
3	QE				4560.85	4581.85
4	QE, $k^{s}_{out} = k^{m}_{out}$				4562.48	4581.48
5	QE, $k^{s}_{out} = k^{m}_{out}$		WT and SEX on *V* and CL		4498.76	4526.76
6	QE, $k^{s}_{out} = k^{m}_{out}$		WT and SEX on *V* and CL	MTX on CL	4493.09	4523.09
7	QE, $k^{s}_{out} = k^{m}_{out}$		WT and SEX on *V* and CL	MTX on R^{s}_{0}	4490.61	4522.61
8	QE, $k^{s}_{out} = k^{m}_{out}$		WT and SEX on *V* and CL	AGE ≤ 15 on *V*	4490.63	4520.63
9	QE, $k^{s}_{out} = k^{m}_{out}$		WT and SEX on *V* and CL	AGE ≤ 15 on R^{m}_{0}	4481.52	4513.52
10	QE, $k^{s}_{out} = k^{m}_{out}$		WT and SEX on *V* and CL	MTX on CL, AGE ≤ 15 on *V*	4485.13	4517.13
11	QE, $k^{s}_{out} = k^{m}_{out}$		WT and SEX on *V* and CL	MTX on R^{s}_{0}, AGE ≤ 15 on R^{m}_{0}	4475.78	4507.78

2LL − 2 ln-likelihood, *AGE < 15* age below 15 years in CD, *AIC* Akaike's information criterion, *CD* Crohn's disease, *CL* clearance, k_{out} unbound target elimination rate constant, "*m*" and "*s*" stand for "membrane" for CD and "serum" for rheumatoid arthritis, respectively, *MTX* methotrexate cotreatment in rheumatoid arthritis, *QE* quasi-equilibrium approximation, *QSS* quasi-steady-state approximation, R_0 baseline TNF-α amount, *RA* rheumatoid arthritis, *TNF* tumour necrosis factor, *V* volume of distribution, *WT* body weight

study (0.98 vs 0.024 day^{-1}). Indeed, these authors may have quantified a "fast" target-mediated, involving circulating TNF-α concentrations [3], while we and others quantified a "slow" target-mediated component of elimination [4–6], involving a whole TNF-α amount.

Even if our k_{int} values are similar to those previously reported for infliximab [4–6], these values are substantially lower than what was reported across all antibodies (1.5 day^{-1} in median) [1]. Indeed, increased k_{int} values correspond to an increased elimination of mAb-target complexes, and therefore a sharper nonlinear elimination shape. Conversely, low k_{int} values correspond to a disappearance of this nonlinearity, as well as a longer terminal *T½*. These elimination features are even more pronounced for high or low R_0 values, respectively [41].

In addition, we found a lower value of k_{int} for CD (k^{cd}_{int} = 0.024 day^{-1}) than for RA (k^{ra}_{int} = 0.061 day^{-1}), which suggests that the infliximab-TNF complex elimination is slower for CD than for RA. As the proportion of cell-expressed TNF-α is higher in CD than in RA [22–24, 28, 30], the CL complexes may be lower after the binding of infliximab to cell-expressed TNF-α than to circulating TNF-α. This difference in k_{int} values is consistent with previous publications, which report shorter terminal *T½* in RA than CD (inter-publication median Tt = 9.7 vs 13.7 days [2]). As a result, if elimination *T½* is unchanged over time in patients with AS (16.5 days), elimination *T½* in both RA and CD changes over time because of target-mediated elimination, and tends towards 13.5 and 21.5 days, respectively. Interestingly, terminal estimation *T½* is very variable across publications, varying from 9.3 days [42] to 16.0 days [43] in RA (four publications) and from 9.7 days [3] to 51.5 days [44] in CD. Of note, four publications in patients with inflammatory bowel disease reported a terminal *T½* of more than 20 days [2]. This disparity may be due to data paucity, even more so because terminal *T½* varies across time.

The slow elimination of complexes compared with those of other mAbs [37] indicates a large retention of TNF-α by infliximab, even larger in CD than in RA. Indeed, our model shows a dramatic increase of the total amount of targets during infliximab treatment (up to 220-fold and 130-fold for CD and RA, respectively). Furthermore, this retention explains the higher terminal T½ in CD than in RA. An increase in the total target amount has already been observed and explained for mAbs in general [1, 37, 45], as well as for infliximab in particular [3]. This is due to an elimination *T½* of unbound TNF-α (1.7 h in the present study) that is much shorter than the elimination *T½* of unbound infliximab (17 days). As unbound infliximab, infliximab-TNF complexes are recycled by the neonatal Fc receptor, which leads to a decrease in the global elimination of TNF-α and therefore to an increase in the total TNF-α amount.

For treatment with mAbs, it is considered that the relevant dosing regime is associated with sufficient target inhibition [46]. Therefore, we evaluated the free/baseline target ratio (R_F/R_0) during infliximab treatment. We observed that R_F/R_0 was decreased to almost 0 after the first administration, but this ratio returns to almost 1 before the fourth injection of infliximab, which suggests a lack of sustained TNF-α inhibition during the between-infusion interval. A similar result was reported by Berends et al. in patients with UC treated with infliximab: free soluble TNF-α returned to two-thirds of its baseline concentration 1 month after the last dose [3].

Table 4 Model parameter estimates

Parameter	Unit	Model			
		QE base		QE final	
		Estimate	RSE%	Estimate	RSE%
V	L	5.9	4.3	5.6	4.2
CL	L·day^{-1}	0.26	3.3	0.24	3.9
K_D^s	nM	0.43	(fixed)	0.43	(fixed)
R_0^s	nM	0.29	45	0.39	23
K_{int}^s	day^{-1}	0.047	29	0.061	18
K_D^m	nM	0.45	(fixed)	0.45	(fixed)
R_0^m	nM	0.32	28.4	0.46	9.2
K_{int}^m	day^{-1}	0.020	15	0.024	19
k_{out}	day^{-1}	8.7	32	10.5	17
RA_CL	–	–	–	–	–
CD_V	–	–	–	–	–
CD_CL	–	–	–	–	–
BW_V	–	–	–	0.40	29
SEX_V	–	–	–	0.21	30
BW_CL	–	–	–	0.44	23
SEX_CL	–	–	–	0.24	23
MTX_CL	–	–	–	–	–
AGE < 15_V	–	–	–	–	–
MTX_R_0^s	–	–	–	1.96	31
AGE < 15_R_0^m	–	–	–	3.37	29
ω_V	–	0.23	18	0.21	18
ω_{CL}	–	0.34	6.8	0.31	6.8
σ_{prop}	–	0.31	3.7	0.29	3.6
− 2LL	–	4562.48	–	4475.78	–
AIC	–	4581.48	–	4507.78	–

Parameters were obtained from base (with disease accounted as RA and CD covariates) and final one-compartment models, and from base and final QE models

− 2LL −2 ln-likelihood, *AGE < 15* age below 15 years in CD, *AIC* Akaike's information criterion, *CD* Crohn's disease, *CL* clearance, k_{int} infliximab-TNF complex elimination rate constant, k_{out} unbound target elimination rate constant, *MTX* methotrexate cotreatment in rheumatoid arthritis, *"m"* and *"s"* stand for "membrane", for CD and "serum" for rheumatoid arthritis, respectively, *QE* quasi-equilibrium approximation, *QSS* quasi-steady-state approximation, R_0 baseline TNF-α amount, *RA* rheumatoid arthritis, *RSE* relative standard error, *TNF* tumor necrosis factor, *V* volume of distribution, *WT* body weight, ω interindividual standard deviation, σ_{prop} proportional error standard deviation

However, as no systematic loss of response at this time was reported, a full blockade of TNF may not be necessary to reach a clinically relevant response. It can moreover be hypothesised that the effect of infliximab is related to its binding to a deep TNF-α compartment, e.g. TNF-α expressed at the cell surface (monocytes, macrophages) in RA [24] and in CD [29, 30]. The kinetics of this deep compartment may differ from that estimated in the present study, and could not be detected in our data. Therefore, additional clinical studies would be needed, where inflammatory cells would be counted repeatedly in time.

Of note, in CD, R_F/R_0 increases toward a value > 100% before stabilising towards 100%. This unexpected phenomenon might be due to the fact that, in CD, k_{int} (0.024 day^{-1}) is inferior to the unbound infliximab elimination rate constant (k_e = CL/V = 0.042 day^{-1}), which is not the case for RA (k_{int} = 0.061 day^{-1}). Indeed, this phenomenon was observed by simulations of several sets of parameters with k_e being set inferior, equal or superior to k_{int} (data not shown). Nevertheless, this phenomenon shall have to be investigated in more detail, which is beyond the scope of the present study.

We previously reported a decreased CL in patients with RA treated with MTX [13, 42], which suggested that the anti-inflammatory activity of MTX could decrease the TNF-α amount and/or the immunosuppressive activity of MTX could decrease the risk of developing anti-drug antibodies, both mechanisms leading to increased infliximab concentrations. In the present study, MTX cotreatment was more strongly associated with decreased R_0^{ra} than CL, suggesting a clear effect of MTX on the target amount; MTX would decrease TNF-α concentrations by more than six-fold, which results in increased infliximab concentrations and terminal $T½$ (15.6 days). In addition, the fact that MTX does not alter infliximab pharmacokinetics in patients with AS may be due to a negligible amount of systemic TNF-α in these patients [47]. Moreover, in our previous study on these data [13], we found a decreased V in patients aged ≤ 15 years that was never reported before [1]. Similarly to MTX, age ≤ 15 years was more strongly associated with decreased R_0^{cd} than V, suggesting that patients aged ≤ 15 years presented with much lower target amounts, independently from body weight. This effect was associated with infliximab concentrations and terminal $T½$ comparable to patients with AS. Nevertheless, no such effect was documented in previous publications of infliximab pharmacokinetics where children were included (six publications). It is possible that this effect concerns only our cohort and cannot be generalised, but it may be easily investigated in other patient cohorts that included children [48–50].

Our study has limitations. First, our model was developed using trough concentrations, which precluded the identification of the peripheral compartment, as one third of previous infliximab pharmacokinetic modelling publications. Second, this study necessitated the fixing of K_D values for both RA and CD. Even if several values were found in the literature, attempted and compared, there may still remain a risk of misspecification, leading to biased values for TMDD parameter estimates. Third, we assumed the absence of target-mediated elimination in these patients and that differences between patients with RA/CD and AS were due to the target antigen only. Nevertheless, this assumption appears sustainable, as the nonlinear elimination shape of infliximab

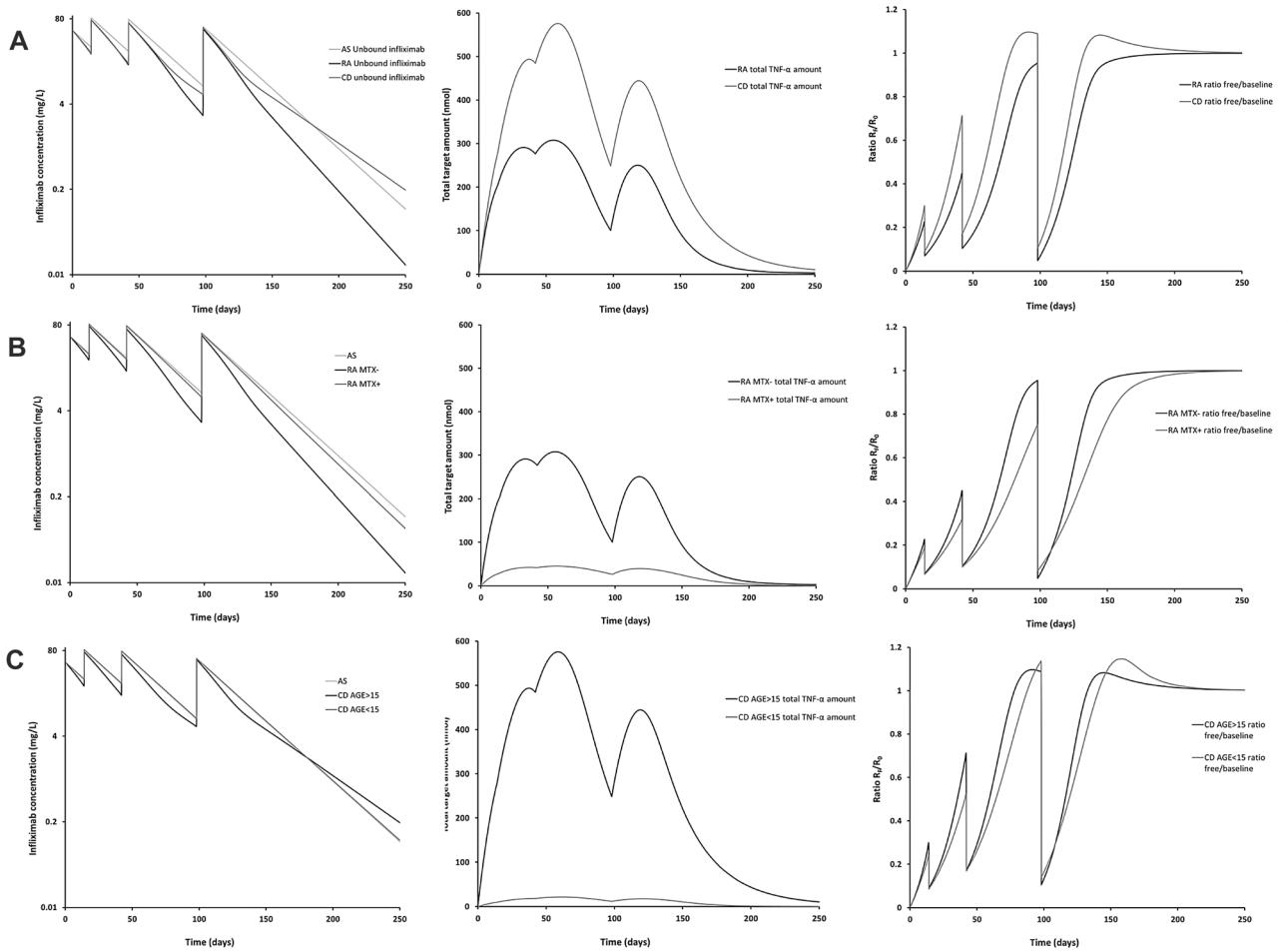

Fig. 2 Simulated typical profiles of unbound infliximab concentration–time (*left*), total tumor necrosis factor (TNF)-α (unbound plus bound to infliximab) amount (*middle*) and TNF-α unbound/baseline ratio (*right*). No TNF-α total amount or ratio was simulated for ankylosing spondylitis (AS) because it was assumed to have no target-mediated drug disposition. Simulated profiles were made for: **A** a female subject with age > 15 years and no methotrexate cotreatment. *Black*, *dark grey* and *light grey lines* represent rheumatoid arthritis, Crohn's disease and AS profiles, respectively; **B** rheumatoid arthritis, comparing a female subject with no methotrexate (*dark grey line*) vs methotrexate cotreatment (*black line*); concentration–time profile for AS is represented as a reference; **C** Crohn's disease, comparing a female subject with age ≤ 15 years (*dark grey line*) vs age > 15 years (*black line*); concentration–time profile for AS is represented as a reference

could have been detected in patients with AS [47, 51]. Taken together, these three limits may have led to biased R_0 and k_{int} estimations, which should be considered with caution. Fourth, we were not able to estimate interindividual variances of TMDD parameters. This prevented us simulating the interindividual distribution of infliximab concentrations, and notably quantifying the influence of target amounts on these. Fifth, TMDD in RA and CD was assessed in comparison with patients with AS. Sixth, no target measurements were available (circulating cell-expressed TNF-α) precluding a clear interpretation of our estimates of target amounts. Nevertheless, it seems that the turnover of TNF-α is complex, with several levels of expression (circulating inflammatory cells, joints, organs) that cannot be described with simple TMDD models. As such, investigating infliximab target-mediated elimination of cell-expressed TNF-α is expected to further enhance our understanding of infliximab concentration–response relationships.

5 Conclusions

This is the first study to report that inter-disease differences in infliximab pharmacokinetics may be explained by TMDD. In this "real-life" cohort, we were able to show a subtle but observable nonlinear component of infliximab elimination in patients with RA as well as in patients with CD. Target-mediated elimination of infliximab may be complex,

involving a multi-scale turnover of TNF-α, especially in patients with CD. Additional clinical studies are warranted to further evaluate and fine tune dosing approaches to ensure sustained TNF-α inhibition across inflammatory diseases. Ideally, these studies will include dense sampling strategies [3, 47], with infliximab concentration using a unique measurement technique.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40262-021-01057-3.

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Declarations

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Conflict of interest David Ternant acted as a consultant and has given lectures on behalf of his institution for Amgen, Sanofi, Boehringer-Ingelheim and Novartis. Marc Pfister is a part-time consultant at Certara, outside the submitted work. Denis Mulleman has acted as a consultant and given lectures on behalf of his institution for Pfizer, Novartis and Grifols; he has been invited to attend an international congress by Janssen-Cilag. His institution received grants for research from the non-governmental organisation Lions Club Tours Val de France. Laurence Picon has acted as a consultant for Abbvie, Janssen-Cilag, Pfizer and Takeda, outside the submitted work. Stephanie Willot has given lectures to Abbvie, outside the submitted work. Theodora Bejan-Angoulvant reports support for travel to congresses from Servier and BMS, outside the submitted work. She has given lectures on behalf of her institution to Amgen and Sanofi, outside the submitted work. Gilles Paintaud has received grants for his research team from Roche Pharma, Chugai, Pfizer, Novartis and Sanofi-Genzyme. Olivier le Tilly, Christophe Passot, Thierry Lecomte and Gilbert Koch have no conflicts of interest that are directly relevant to the content of this article.

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Consent to participate Informed consent was not sought in this retrospective analysis of routine patients, which is in accordance with institutional guidelines.

Consent for publication Not applicable.

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Code availability The code is available on request to the corresponding author.

Author contributions DT designed the research, analysed the data, interpreted the results and wrote the manuscript. MP, GP and GK participated in the data analysis and interpretation of the results and reviewed the manuscript. OT contributed to the data analysis and interpretation of the results and reviewed the manuscript. DM, LP, SW CP and TL participated in the data acquisition and reviewed the manuscript.

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