

Covariate analysis of infliximab in Crohn's disease using available pharmacokinetic models as prior

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Background and Objectives

A substantial proportion of patients with Crohn's disease lose response to the monoclonal antibody infliximab (IFX) [1]. In some patients, maintenance IFX therapy induces an immune reaction and development of anti-drug antibodies (ADAs). ADAs have been associated with increased drug clearance (CL), acute infusion reactions and loss of response. ADAs developed in different individuals differ in terms of affinity to IFX, abundance, biologic effect (neutralising/non-

neutralising) and persistence of the immune reaction. To date, the ADA impact on IFX CL is often assessed as a binary covariate. This study aimed to elaborate the PK model of IFX in Crohn's disease exploiting the prior knowledge from two published population pharmacokinetic (PK) models [2,3] to further assess covariates affecting CL with a focus on the implementation of ADAs.

Methods

- Data originated from a 20-week investigator-initiated clinical study of Crohn's disease patients with secondary treatment failure to IFX [4]. The present study included 66 patients receiving treatment interventions. IFX and ADA samples were collected at weeks 0, 12 and 20 (all $\sim C_{min}$). Two assays were used to quantify total and free ADA concentrations: homogenous mobility shift assay (HMSA) [5] and reporter gene assay (RGA) [6], respectively.
- Log-transformed IFX data was analysed with a nonlinear mixed-effects approach in NONMEM 7.3. A likelihood based approach (M3) was used to account for samples below the lower limit of quantification [7].
- The two population PK models available in literature (Eq. 1, A and B) were re-parameterised and normalised to a body weight of 65 kg (Eq. 1, C) for comparability.

$$\begin{aligned}
 \text{[A]} \quad CL_{BW} &= 5.42 \cdot \left(\frac{BW}{65}\right)^{-0.313} \cdot \left(\frac{sAlb}{41}\right)^{-0.855} \cdot (1.292)^{ADA} \cdot (0.863)^{IMM} \cdot \exp(\eta_1) \text{ mL/day/kg} \\
 V1_{BW} &= 52.4 \cdot \left(\frac{BW}{65}\right)^{-0.233} \cdot \exp(\eta_2) \text{ mL/kg} \\
 Q_{BW} &= 2.26 \text{ mL/day/kg} \\
 V2_{BW} &= 19.6 \cdot \left(\frac{BW}{65}\right)^{-0.588} \cdot \exp(\eta_3) \text{ mL/kg} \\
 \text{[B]} \quad k_e &= 0.049 \cdot \left(\frac{hsCRP}{2.2}\right)^{0.055} \cdot (1.15)^{FCGR3A:V/V} \cdot \exp(\eta_1) \text{ day}^{-1} \\
 Vd_{BW} &= 0.087 \text{ mL/kg} \\
 \text{[C]} \quad \theta &= \theta_{BW} \cdot BW = \theta_{65kg} \cdot 65 \cdot \left(\frac{BW}{65}\right) \\
 CL_{65kg} &= k_e \cdot Vd_{65kg}
 \end{aligned}$$

Eq. 1. [A]: 2-compartment model with body weight (BW), serum albumin (sAlb), anti-drug antibody status (ADA) and concomitant immunosuppressives (IMM) implemented on CL and BW implemented on V1 and V2. [B]: 1-compartment model with high-sensitivity C-reactive protein (hsCRP) and FCGR3A genotype (FCGR3A:V/V) implemented on k_e ; and BW linearly on Vd. [C]: Normalisation to 65 kg BW.

- Based on structure and parameter values of the prior-models, further covariate analysis were performed on CL:
 - Yes/No on patient level ('ADA+ patient') - fractional change
 - Yes/No on sample level ('ADA+ sample') - fractional change
 - Continuous covariate ('ADA concentration') - linear function
- Other covariates, after being screened for clinical plausibility and by graphical analysis (CL vs covariate), were evaluated in a stepwise inclusion ($p=0.05$) and exclusion ($p=0.01$) procedure.

Results

- The PK models showed good parameter agreement, both when compared internally (Table 1) as well as with general PK traits of the monoclonal antibody drug class [8].
- The resulting prior-model was a 2-compartment model using the transformed estimates from the Fasanmade model for V1, V2 and Q.
- All structural parameters were scaled allometrically with body weight (fixed exponents).
- Typical CLs were assumed to represent the mean of the population and other covariate relations originally included in the models were removed.
- Due to the sparse data situation, V1, V2 and Q as well as their IIVs were fixed during further model development. CL and IIV for CL were implemented using the PRIOR functionality using 2 priors (re-parametrised CL estimates, Table 1).

Table 1. Original and re-parametrised parameter estimates

Parameter	Original estimate	Re-parametrised estimate
<i>Fasanmade et al.</i>		
CL	5.42 mL/day/kg	0.352 L/day
V1	52.4 mL/kg	3.41 L
Q	2.26 mL/day/kg	0.147 L/day
V2	19.6 mL/kg	1.27 L
IIV CL	30.7 %	
IIV V1	12.6 %	
IIV V2	55.3 %	
<i>Ternant et al.</i>		
k_e	0.049 day ⁻¹ (k_e)	0.277 L/day (CL)
Vd	0.087 L/kg	5.66 L
IIV k_e	37 %	
V1 + V2 = 4.68 L		

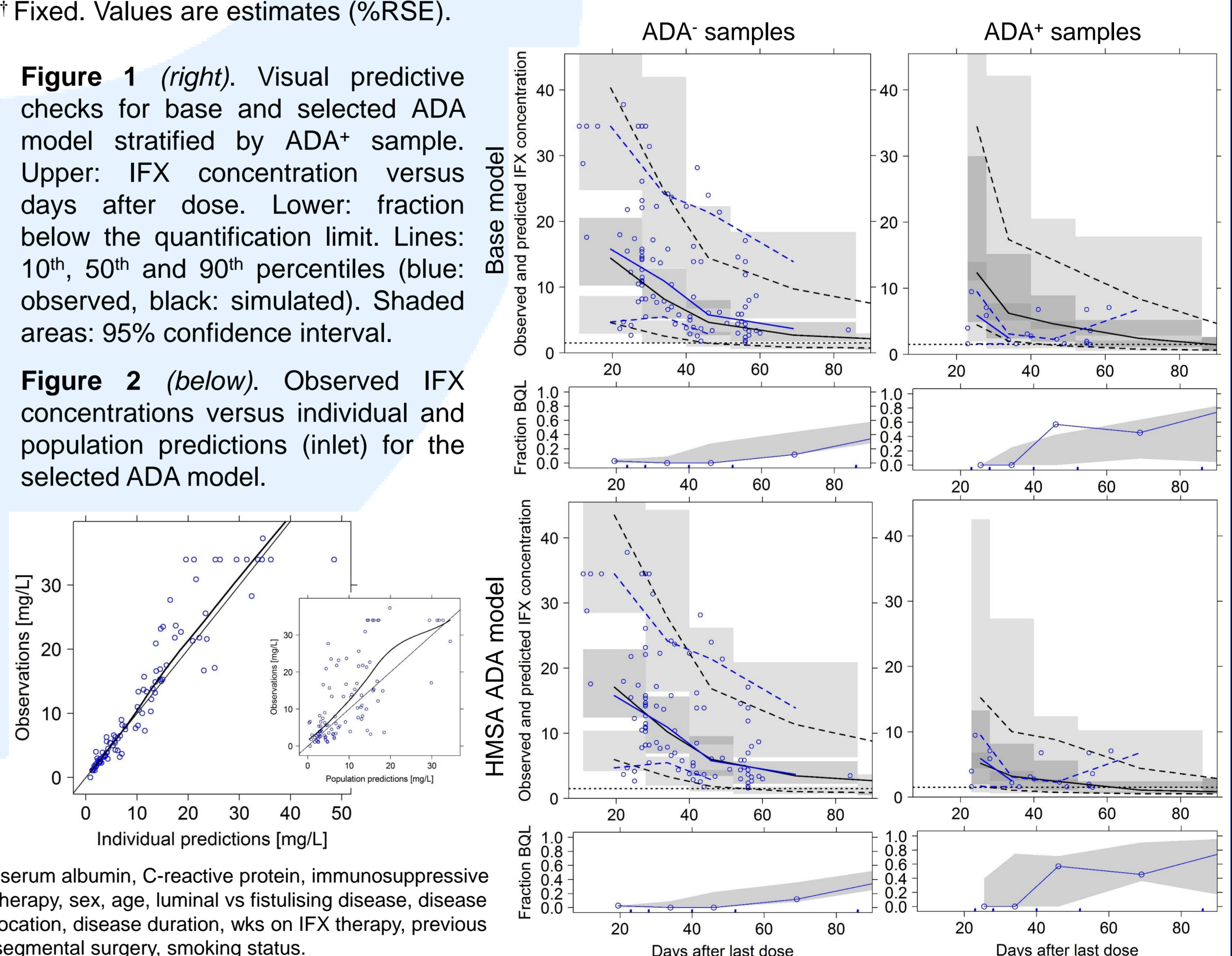
Results (cont.)

- All implementations of the ADA covariate improved the fit of the base model (Table 2). The HMSA ADA concentration caused the highest drop in OFV as well as the best improvement in predictive performance (GOF plots and VPCs). The implementation largely corrected for the slight over-prediction of concentrations in ADA+ samples and under-prediction of the ADA- samples as seen in the base model (Figure 1).
- No other candidate covariate was found significant.†

Table 2. Parameter estimates from base model and different ADA covariate models. Values in grey columns are based on ADA information from the HMSA and the white columns are based on RGA.

Parameter	Base model	ADA+ patient	ADA+ sample	ADA concentration	ADA+ patient	ADA+ sample	ADA concentration
OFV	-414	-442	-444	-447	-422	-424	-441
Δ OFV (base)		-28.1	-29.9	-33.6	-7.66	-9.75	-26.9
CL, L/day	0.318 (4.7)	0.265 (6.0)	0.275 (5.4)	0.289 (5.0)	0.304 (4.8)	0.299 (5.3)	0.306 (2.3)
V1, L	3.41†						
Q, L/day	0.147†						
V2, L	1.27†						
ADA impact		0.700 (25)	0.451 (24)	0.0138 (24)	0.538 (45)	0.301 (38)	0.0474 (64)
IIV CL, CV%	32.9 (3.3)	32.2 (3.3)	32.6 (3.3)	32.4 (3.3)	32.7 (3.4)	32.7 (3.4)	32.6 (2.6)
IIV V1, CV%	12.6†						
IIV V2, CV%	55.3†						
Prop error, %	50.6 (7.8)	47.9 (10.4)	47.2 (8.6)	43.5 (10.9)	50.7 (11)	51.5 (11)	47.2 (8.6)

† Fixed. Values are estimates (%RSE).



Conclusions and Perspectives

- Based on data from an investigator-initiated clinical study and two published PK models we confirmed and elaborated the impact of ADAs on IFX CL. The total ADA concentration (HMSA) improved the predictive performance the most.
- No other covariate was found significant, potentially as a result of the low patient number in this dataset. Although not identified here, sAlb, for example, may still be a covariate to consider as it recently was confirmed in a population model for inflammatory bowel diseases [9].
- The developed PK model will be used to investigate the PK/PD relationship of IFX in CD, aiming to identify the effective therapeutic range.

References:

- [1] Gisbert, Panes. Am J Gastroenterol 104:760 (2009), [2] Fasanmade et al. Clin Ther. 33:946 (2011), [3] Ternant et al. Clin Pharmacokinet 54:551 (2015), [4] Steenholdt et al. Gut 63:919 (2014), [5] Wang et al. J Immunol Methods 382:177 (2012), [6] Lallemand et al. J Immunol Methods 373:229 (2011), [7] Beal. J Pharmacokinet Pharmacodyn 28:481 (2001), [8] Dirks et al. Clin Pharmacokinet 49:633 (2010), [9] Dotan et al. Inflamm Bowel Dis 20:2247 (2014)



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