Towards a comprehensive PK/PD model of infliximab in inflammatory bowel diseases, with support of prior knowledge

Ana-Marija Grisic (1,2), Alexander Eser (3), Wilhelm Huisinga (4), Walter Reinisch (3), Charlotte Kloft (1)

(1) Dept. of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Germany,
(2) Graduate Research Training program PharMetrX, Germany,
(3) Dept. for Gastroenterology and Hepatology, Medical University of Vienna, Austria,
(4) Institute of Mathematics, Universitaet Potsdam, Germany

Background

- Up to 60% of inflammatory bowel disease (IBD) patients experience loss of response (LOR) to infliximab (IFX)
- LOR is related to low IFX plasma concentrations [1]
- PK/PD model would empower therapeutic drug monitoring

Objectives

- To analyse the dose-concentration-effect (CRP) relation of IFX in IBD in order to gain more insight into the underlying mechanisms and enable better tailoring of the treatment to improve chances of therapy success

Methods

- Investigator-initiated therapeutic drug monitoring trial
- $n_{patients}$ = 121
- Median (range) dose: 400 mg (100-1300 mg)
- Sparse sampling (s. Fig. 1A) ➔ demands frequentist prior
- Software: R (3.4.1), RStudio (1.1.447), NONMEM (7.3.0), PsN (4.2.0) and Pirana (2.9.4)

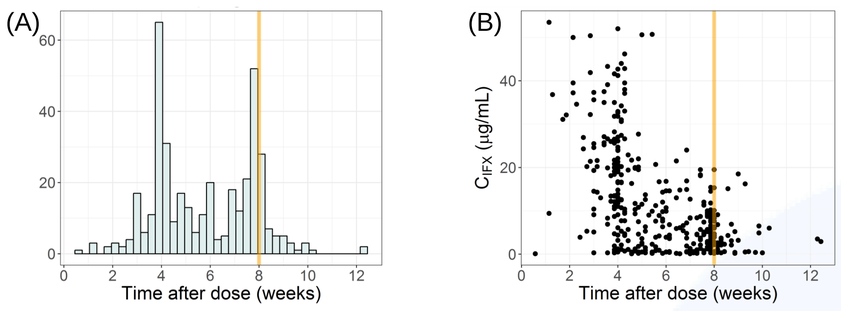

Figure 1. PK data: (A) Distribution of sampling times; (B) IFX concentration over time since last dose. Yellow line represents time of C_{min} for standard dosing interval (q8w).

PK and PD data, and modelling approach

- $n_{PK\ observations}$ = 388 (s. Fig. 1B)
- Prior PK model: Fasanmade et al. [2]
- Biomarker: C-reactive protein concentration (C_{CRP})
- $n_{PD\ observations}$ = 339 (s. Fig. 2)
- Indirect drug effect model with synthesis inhibition (Fig. 3)
- Prior PD model: Ternant et al. [3]
- Sequential PKPD analysis

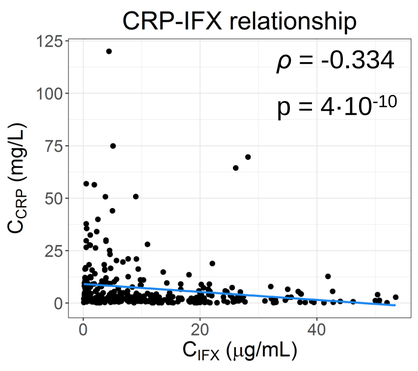

Figure 2. Exposure-response relationship: CRP concentration at different IFX concentration.

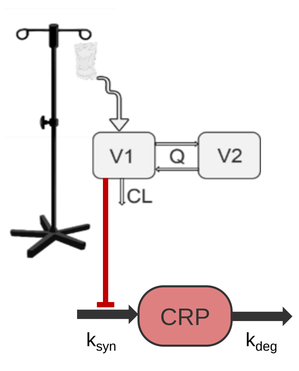

Figure 3. Graphical PK/PD model.

Results: Final PK/PD model

$$V_{1,i} = V_1 \cdot e^{\eta_{V1}}$$
$$Q_i = Q$$
$$V_{2,i} = V_2 \cdot e^{\eta_{V2}}$$
$$CL_i = CL \cdot ADA_{CL} \cdot sAlb_{CL} \cdot BW_{CL} \cdot IMM_{CL} \cdot e^{\eta_{CL}}$$
$$ADA_{CL} = 1 + \theta_{ADA\_CL} \cdot ADA$$
$$sAlb_{CL} = \left(\frac{sAlb}{43\ g/L}\right)^{\theta_{sAlb\_CL}}$$
$$BW_{CL} = \left(\frac{BW}{70\ kg}\right)^{\theta_{BW\_CL}}$$
$$IMM_{CL} = \theta_{IMM\_CL}{}^{IMM}$$
$$Y_{ij} = X_{ij} + \left(Y_{ij} \cdot \varepsilon_{prop.} + \varepsilon_{add.}\right) \cdot e^{\eta_{\varepsilon}}$$

ADA : Anti-drug antibodies
BW : Body weight
IMM : Co-therapy with immunomodulators
sAlb : Serum albumin concentration

Table 1. Final PK model parameters.

Parameter (unit)	Estimate (RSE%)
V_1 (L)	3.67 FIX [2]
Q (L/d)	0.161 FIX [2]
V_2 (L)	0.956 (11)
CL (L/d)	0.262 (3)
θ_{ADA_CL}	0.972 (4)
θ_{sAlb_CL}	-1.17 (21)
θ_{BW_CL}	0.356 (41)
θ_{IMM_CL}	0.847 (5)
η_{V1} (CV%)	12.8 FIX [2]
η_{V2} (CV%)	55.3 FIX [2]
η_{CL} (CV%)	34.9 (8)
η_{ε} (CV%)	22.2 (18)
$\varepsilon_{prop.}$ (CV%)	24.0 (7)
$\varepsilon_{add.}$ (SD)	0.478 (21)

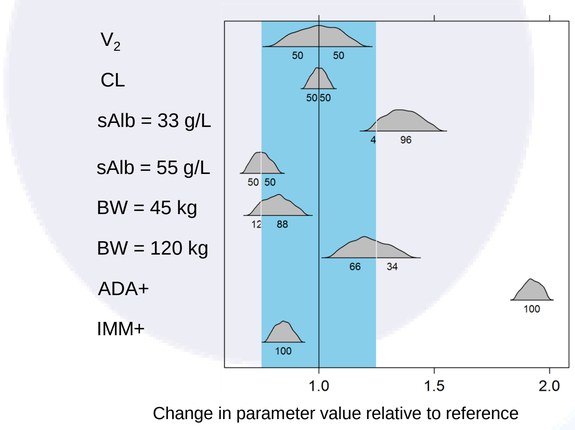

Figure 4. Clinical inference of covariates

$$\frac{dCRP}{dt} = k_{syn} \cdot \frac{I_{max} \cdot C_{IFX}}{IC_{50} + C_{IFX}} - k_{deg} \cdot C_{CRP}(t)$$

Table 2. Final PD parameters.

Parameter (unit)	Estimate (RSE%)
$C_{CRP,baseline}$(mg/dL)	0.632 (17)
k_{deg} (1/h)	0.0365 FIX [3]
IC_{50} (mg/L)	2.04 (43)
I_{max}	0.719 (9)
η_{IC50} (CV%)	208.9 (42) [3]
$\eta_{CRP,baseline}$ (CV%)	115.2 (15) [3]
$\sigma_{prop.}$ (CV%)	65.3 (4)

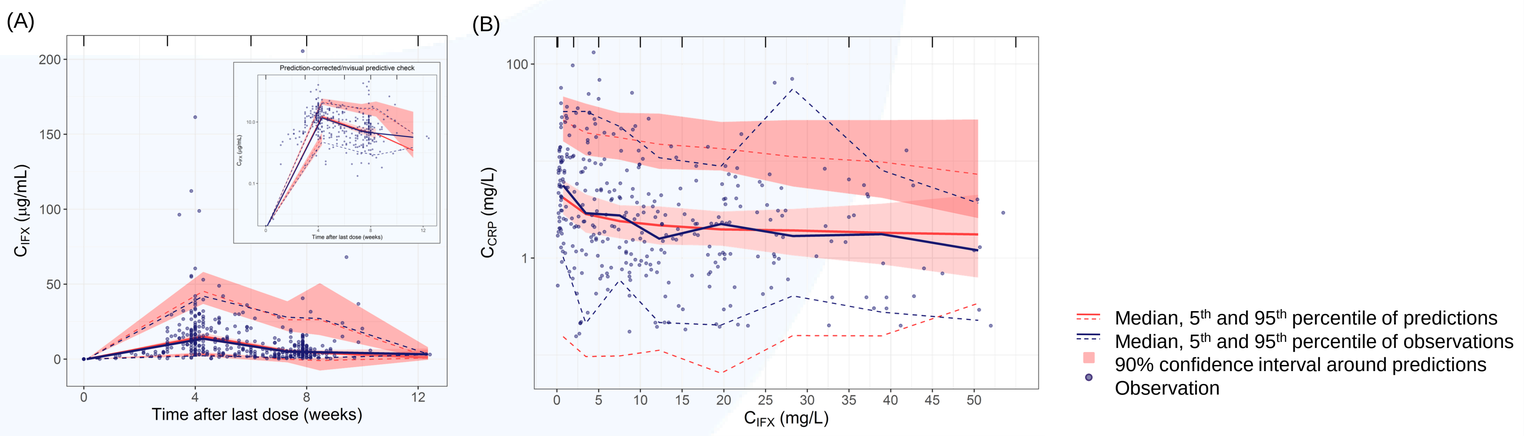

Figure 5. PK (A) and PKPD (B) model evaluation: pcVPC (n_{sim} = 1000).

Impact of exposure variability on response: Case of ADAs

- Effect of ADA presence ("ADA+") on CRP (incl. IIV in PK)

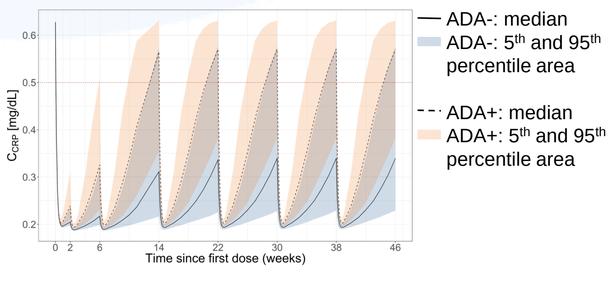

Figure 6. Typical response profile for a patient (BW = 70kg, sAlb = 43 g/L, IMM-) without (blue) and with (orange) ADAs with IFX dose of 5 mg/kg, standard induction phase and q8w maintenance phase.

➔ Sources of IIV in C_{IFX} reflect on C_{CRP}

- Dosing interval reduction was previously found to be superior to dose amount intensification [4]

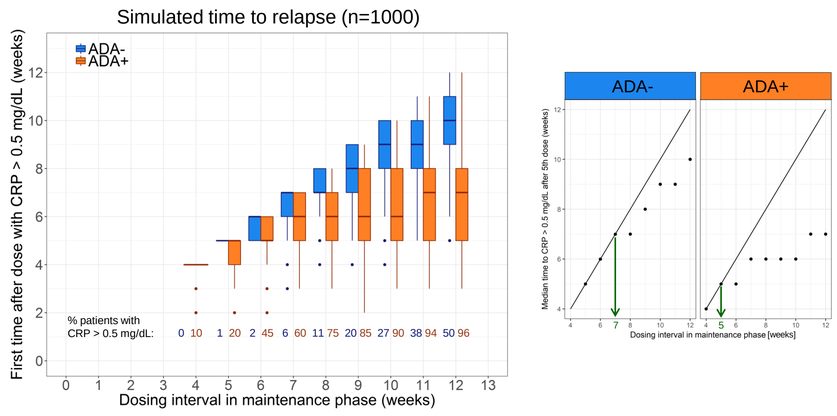

Figure 7. Simulated response (n=1000): Time since 5th dose to CRP > 0.5 mg/dL (BW = 70kg, sAlb = 43 g/L, IMM-).

- Simulated dosing intervals: q4w-q12w (dose = 5 mg/kg, standard induction phase)

➔ ADA- patients: q7w; ADA+ patients: q5w

Conclusions & future perspectives

- The PK/PD model relating IFX concentration to the inhibition of CRP production with support of prior information described the data well
- Subpopulations at risk: IMM-, ADA+, high disease activity and high BW
- Simulations of alternative therapy strategies (i.e. dosing intervals): For ADA- patients "q7w" and for ADA+ "q5w" are more appropriate dosing intervals than the current standard "q8w" regimen
- Outlook: Model extension to account for other PD data

References:

[1] A. Hemperly, N. Vande Casteele. Clin. Pharmcokinet. (2018).
[2] A.A. Fasanmade et al. Clin. Ther. (2011).
[3] D. Ternant et al. Br. J. Clin. Pharmacol. (2015).
[4] H. Andersson et al. American Conference of Pharmacometrics. (2014).

For additional information, please contact:
Ana-Marija Grišić,
MSc (Pharm), PhD Student
ana-marija.grisic@fu-berlin.de

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