Towards understanding the loss of response to infliximab in patients with inflammatory bowel disease: A population PK modelling approach

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Background

- Infliximab (IFX) is an anti-tumour necrosis factor α monoclonal antibody used to treat inflammatory bowel disease (IBD)
- In up to 60% of patients loss of response (LOR) develops over time [1]
- LOR has been related to low IFX plasma concentrations [1]

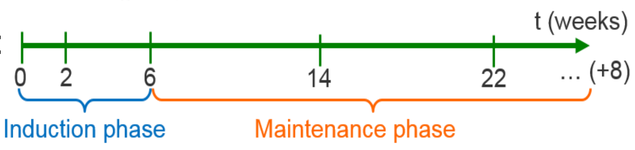
Objectives

- The aim of the study is to investigate the impact of patient and disease characteristics on IFX exposure in order to identify the subpopulations at risk of therapy failure and provide a tool for improvement of IFX therapy in patients with IBD.

Methods

Study design

- Investigator initiated trial (Medical University of Vienna)
- Therapeutic drug monitoring (TDM) data: 122 IBD patients (s. Tab. 1 and Fig. 2)
- Dosing schedule:



- Median (range) dose: 400 mg (100-1300) ~ 5.6 mg/kg (1.2-10.8)
- Median (range) time since last dose of the available plasma samples: 5.57 weeks (0.57 – 12.4; s. Fig. 1)

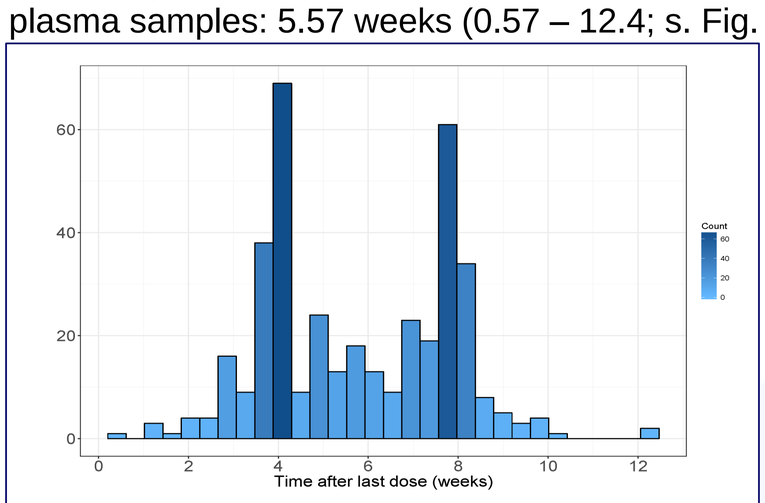


Figure 1. Distribution of samples per time since last dose.

Table 1. Summary of patient characteristics ($n_{patients}$ = 122).

Categorical patient characteristic	Number of patients (%)
Sex (n=122)	
Male	63 (51.6)
Female	59 (48.4)
Diagnosis (n=122)	
Crohn's disease (CD)	90 (73.8)
Ulcerative colitis (UC)	31 (25.4)
Indeterminable	1 (0.8)
Age at diagnosis of CD (n=89)	
≤ 16 years	11 (12.3)
17-40 years	66 (74.2)
> 40 years	12 (13.5)
Crohn's disease location (n=89)	
Ileal	10 (11.2)
Colonic	21 (23.6)
Ileocolonic	58 (65.2)
Concomitant therapy with immunomodulators (n = 122)	
Yes *	23 (18.8)
No	99 (81.1)
Smoking (n=119)	
Non-smoker	41 (34.4)
Current smoker	46 (38.7)
Ex-smoker	32 (26.9)

Continuous patient characteristic [unit]	Median (min, max)
Body weight [kg]	70 (47-115)
Height [cm]	171 (155; 190)
Body mass index [kg/m²]	23.2 (14.5; 41.7)

* On at least one occasion

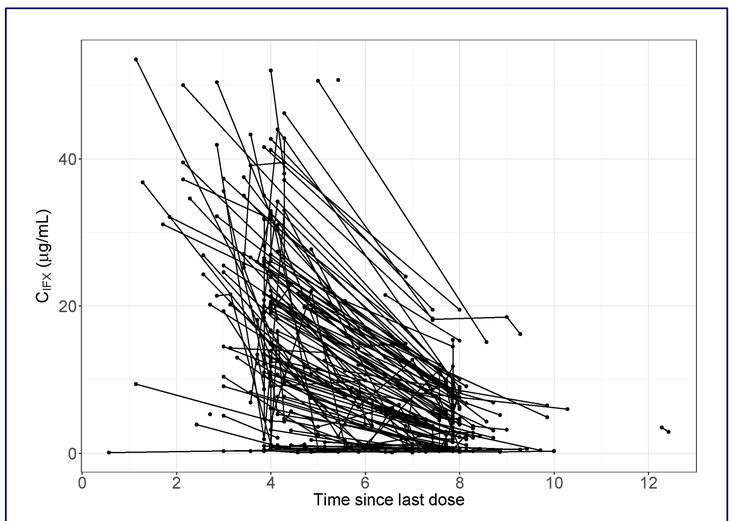


Figure 2. Concentration-time plot of the available sparse PK data.

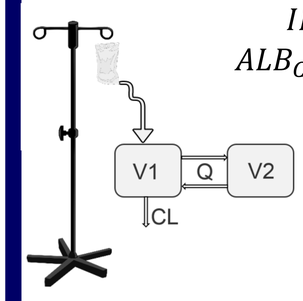
Modelling of the IFX PK

- Nonlinear mixed effect modelling approach (NONMEM 7.3, PsN 4.4, Pirana 2.9.4, R 3.2.4, Rstudio 1.0.143)
- Sparse data ➔ the frequentist prior approach using a published model as a prior [2] with the assumption of normal and inverse-Wishart distribution for fixed- and random-effect parameters, respectively

Results

- A 2-CMT model with linear elimination adequately described IFX PK in the study population (s. Tab 2), as demonstrated by visual predictive check (s. Fig. 3)

$$CL = CL_{pop} \cdot ADA_{CL} \cdot HBI_{CL} \cdot IMM_{CL} \cdot ALB_{CL} \cdot BW_{CL} \cdot e^{\eta(CL)}$$
$$ADA_{CL} = (1 + \theta_{ADA\_CL} \cdot ADA)$$
$$HBI_{CL} = (1 + \theta_{HBI\_CL} \cdot HBI)$$
$$IMM_{CL} = (1 + \theta_{IMM\_CL} \cdot IMM)$$
$$ALB_{CL} = (1 + \theta_{ALB\_CL} \cdot (ALB - 38.6))$$
$$BW_{CL} = \left(\frac{BW}{70}\right)^{\theta_{BW\_CL}}$$
$$V_1 = V_{1,pop}$$
$$V_2 = V_{2,pop}$$
$$Q = Q_{pop}$$



- Nonlinear CL component was negligible
- Due to the data sparseness (high η-shrinkage for IIV of V_1 and V_2) covariate analysis was performed exclusively on CL
- The most influential covariate was ADA status, indicating ~2 times higher CL in presence of ADA
- Inclusion of all significant covariates reduced IIV by ~23 % (from 52.8%CV to 40.8%CV)

Table 2. Parameter estimates of the PK model supported by prior information and utilised prior estimates.

Parameter [unit]	Estimate (RSE, %) [shrinkage, %]	Prior model estimate [2]
CL_{pop} [L/d]	0.288 (4)	-
$V_{1,pop}[L]$	3.66 (1)	3.67
Q_{pop} [L/d]	0.173 (8)	0.158
$V_{2,pop}[L]$	1.30 (4)	1.37
θ_{ADA_CL}	0.863 (10)	-
θ_{HBI_CL}	0.0303 (31)	-
θ_{IMM_CL}	-0.174 (23)	-
θ_{ALB_CL}	-0.0163 (32)	-
θ_{BW_CL}	0.412 (34)	-
ω_{CL} [%CV]	40.8 (7) [6]	-
σ_{prop} [%CV]	31.5 (5) [13]	-
σ_{add} [SD, $^{\mu g}/_{mL}$]	0.543 (20) [13]	-

ADA: anti-drug antibodies; ALB: serum albumin concentration; BW: body weight; CV%: coefficient of variation; HBI: Harvey-Bradshaw index; IMM: concomitant therapy with immunomodulators; SD: standard deviation.

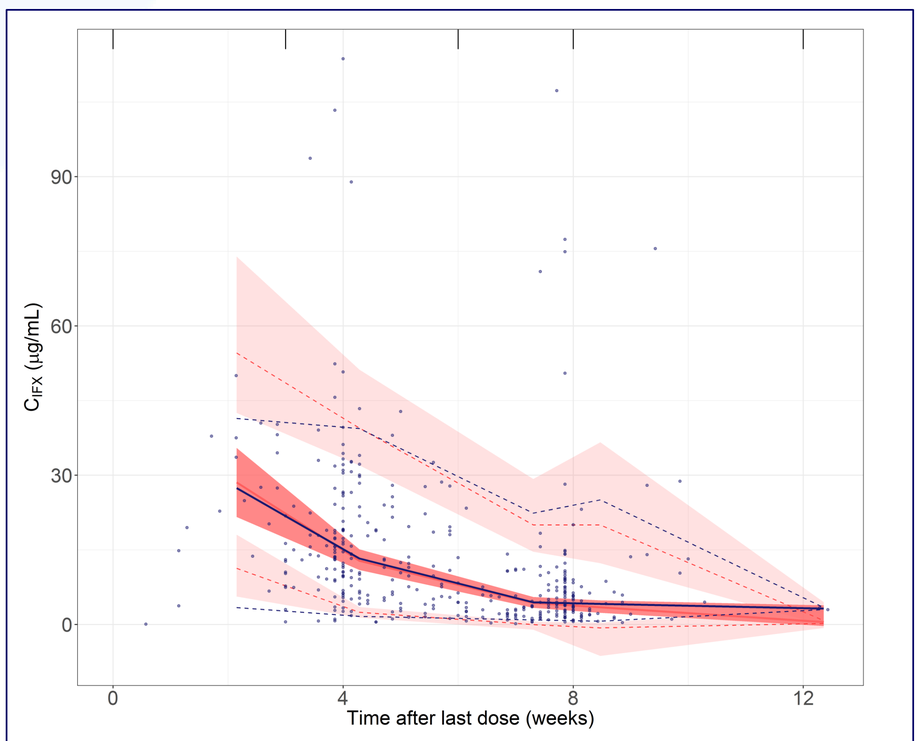


Figure 3. Prediction-corrected visual predictive check (pcVPC) for PK model. Blue dots: observed IFX concentrations; blue lines: median (solid) and 5th and 95th percentiles (dashed) of observations; red lines: median (solid) and 5th and 95th percentiles (dashed) of the simulations; red shaded areas: 90% confidence intervals of the median (dark) and around quantiles (light) of the simulations.

Conclusions and future perspectives

- Using the frequentist prior approach enabled adequate description of IFX PK from the sparse TDM data
- In addition to ADA status, disease activity (serum albumin concentration and disease activity index), body weight and use of immunomodulators have significant influence on CL
- As a next step the developed PK model will be linked with the PD data in order to combine the available knowledge in a PKPD model that is to contribute to rational use of IFX in treatment of IBD

References:

[1] MG Ward et al. Aliment. Pharmacol. Ther. (2017)
[2] AA Fasanmade et al. Clin. Ther. 33: 946-964 (2011)

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