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# A Target-Mediated Drug Disposition model for infliximab in patients with Ulcerative Colitis

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## Background

**Ulcerative Colitis (UC)** is an inflammatory bowel disease (IBD) affecting the colon and rectum of the gastrointestinal tract. **Infliximab (IFX)** is an intravenously administered **monoclonal antibody (mAb)** directed against the pro-inflammatory cytokine tumor necrosis factor (TNF). **Target-mediated drug disposition (TMDD)** is reported for mAbs meaning that the pharmacokinetics of mAbs are affected because of their high target affinity [1,2]. **The objective of this study is to characterize the pharmacokinetics of IFX in patients with UC**.

## Methods

- Prospective cohort study
- 20 patients, anti-TNF naive, UC
- IFX (5 mg/kg): week 0, 2 and 6
- IFX, antibodies-to-IFX (ATIs) and TNF serum concentrations were measured
- NONMEM (FOCE+I): A population pharmacokinetic model was developed to describe pharmacokinetics of IFX. Next, a TMDD was developed to describe the target-dependent pharmacokinetics of IFX.

## Results

**PK model**

- A two-compartment model best described the concentration-time profiles of IFX.
- As a binary covariate the formation of ATIs increased clearance 2.3-fold. Patients with low albumin serum concentrations exhibited higher clearance.

$$CL = 0.396 \times (^{ALB}/_{38})^{-1.07} \times (2.3 \times ATI)$$

**TMDD model**

- In the TMDD model (figure 1 and 2), estimates for BMAX and KD were 0.0983 nM and 1550 nM, respectively. Estimated TMDD parameters of the preliminary TMDD model were within the expected range.

*Table 1: PK and TMDD parameter estimates*

| | PK model | TMDD model |
|---|---|---|
| Parameter | Estimate (RSE) | Estimate (RSE) |
| CL (L/day) | 0.396 (7%) | 0.451 (5%) |
| Vc (L) | 3.2 (5%) | 3.04 (5%) |
| Vp (L) | 1.8 (28%) | 1.83 (22%) |
| Q (L/day) | 0.344 (37%) | 0.293 (25%) |
| ATI-CL | 2.3 (18%) | 1.27 (19%) |
| ALB-CL | -1.07 (33%) | -2.01 (13%) |
| IIV – CL (%) | 29.6 (18%) | - |
| IIV – Vc (%) | 21.4 (16%) | - |
| IIV – Vp (%) | 59.7 (22%) | - |
| Additive error | 0.208 (14%) | 0.352 (10%) |
| Bmax (nM) | - | 0.0983 (5%) |
| Kd (nM) | - | 1550 (5%) |
| Kon ((nmol/L)$^{-1}$/day) | - | 106000 (20%) |
| Kdeg (day$^{-1}$) | - | 0.086 (21%) |
| Kint (day$^{-1}$) | - | 0 (-) |

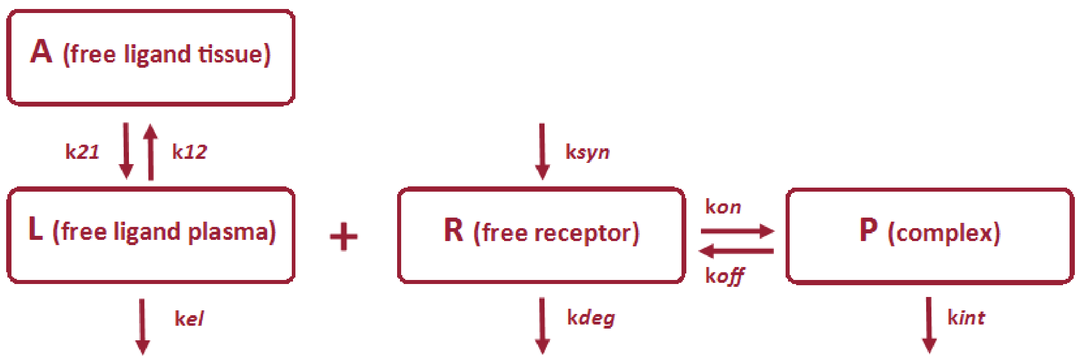


*Figure 1: Schematic TMDD model. Ksyn and kdeg represent the synthesis and degradation rate of R, respectively. Bmax represents the baseline of R (ksyn/kdeg). Kon and koff are the association and dissociation rate constants (kd=koff/kon) and kint is the internalization rate constant of the complex.*

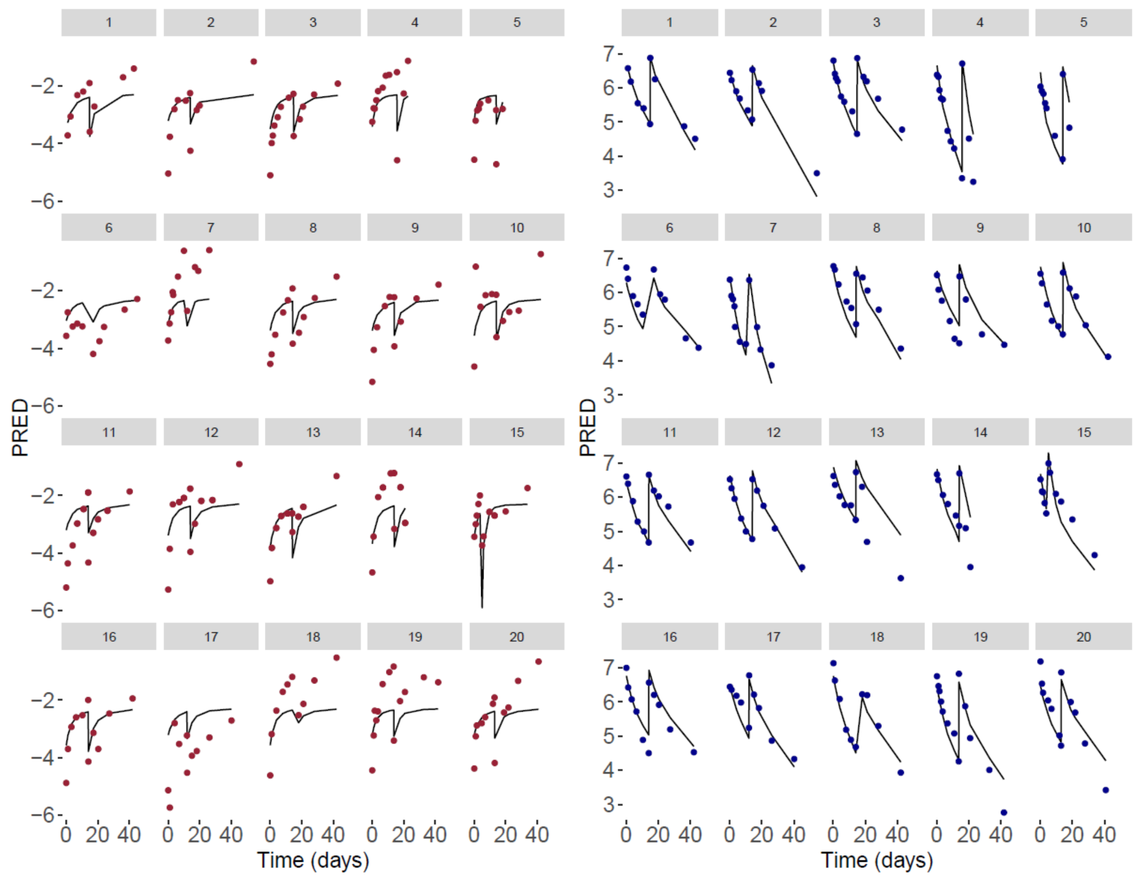


*Figure 2: Predicted TNF vs. observed TNF (left), Predicted IFX vs. observed IFX (right) . Lines represent predicted concentrations, dots represent observed concentrations*

References:

[1] Dua P, Hawkins E, van der Graaf P. A Tutorial on Target-Mediated Drug Disposition (TMDD) Models. CPT Pharmacometrics Syst Pharmacol. 2015;4(6):324–37.

[2] Gibiansky L, Gibiansky E. Target-mediated drug disposition model: approximations, identifiability of model parameters and applications to the population pharmacokinetic-pharmacodynamic modeling of biologics. Expert Opin Drug Metab Toxicol. 2009;5(7):803–12.

## Conclusions

The formation of ATIs and low serum albumin levels increased clearance. A preliminary TMDD model was developed to describe the target-dependent pharmacokinetics of IFX. The TMDD model will be further developed.