Target-mediated drug disposition model of ustekinumab in patients with ulcerative colitis

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Background

- Inflammatory Bowel Disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic and relapsing inflammation of the gastrointestinal tract.[1]
- Ustekinumab is a human IgG monoclonal antibody, indicated for the treatment of adult patients with moderately to severely active Crohn's disease (2016) and ulcerative colitis (2019).[2]
- Pharmacokinetic studies of ustekinumab in ulcerative colitis are limited; however, evidence from Crohn's disease supports target-mediated drug disposition (TMDD).[3]

Objectives

- To evaluate the pharmacokinetics of ustekinumab in patients with ulcerative colitis with an emphasis on identifying and characterizing nonlinear kinetics.

Patients and Methods

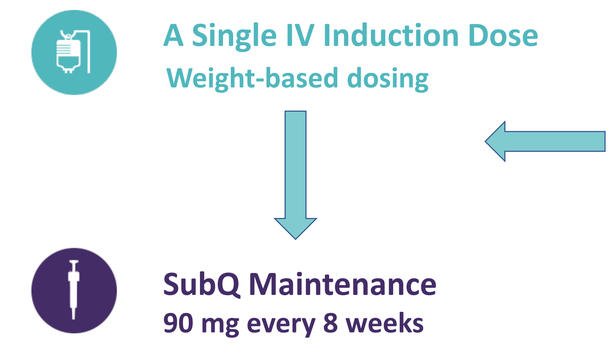
Baseline characteristics

- 35 patients with ulcerative colitis
- Prospective observational study

Table I: Patients' characteristics at baseline (n=35)

Characteristic	Value
Women, n (%)	16 (46)
Age at UST initiation, years, median (IQR)	40 (33-52)
Weight, kg, median (IQR)	81 (68-92)
Height, cm, median (IQR)	173 (169-181)
Body mass index, kg/m^2, median (IQR)	26 (23-29)
Intravenous ustekinumab dose, n (%)	
260 mg	2 (5.7)
390 mg	19 (54.3)
520 mg	13 (37.1)
800 mg	1 (2.9)
Serum albumin, g/L, median (IQR)	42 (39-46)
C-reactive protein, mg/L, median (IQR)	5 (5-11)
Fecal calprotectin (n=30), mg/kg, median (IQR)	278 (104-500)
Smoking status, n (%)	
active smoking	3 (8.6)
previously smoking	4 (11.4)
never smoked	28 (80)
Disease duration, years, median (IQR)	6 (3-8)
Previous biological therapy, n (%)	21 (60.0)
previous anti-TNF exposure	13 (37.1)
previous vedolizumab exposure	16 (45.7)
previous anti-TNF and vedolizumab exposure	8 (22.9)
Mayo endoscopic score, n (%)	
2 (moderate disease)	14 (40)
3 (severe disease)	13 (37.1)
score not available	8 (22.9)
IBDQ score (n=17), median (IQR)	125 (103-182)

Ustekinumab Dosing



Body weight	Induction dose
≤55 kg	260 mg
> 55 to ≤ 85 kg	390 mg
> 85 kg	520 mg

Study design

- 11 PK samples/patient

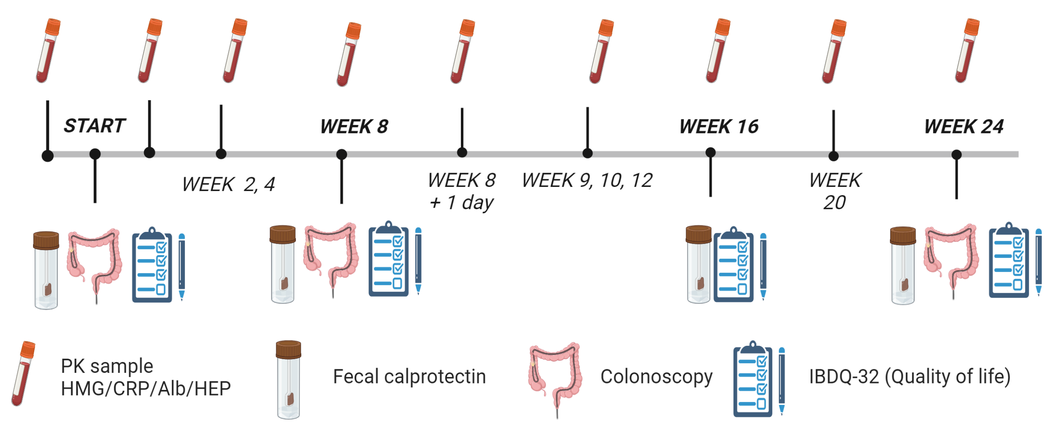


Figure 1: Study design

MODELING:

- NONMEM 7.5[4]
- First Order Conditional Estimation with Interaction (FOCE-I)
- 1 and 2 compartment (CMT) structural models + inclusion of nonlinear elimination models

TESTED NONLINEAR ELIMINATION MODELS:

- Time-dependent elimination rate approximated by exponential decrease in clearance (EXP_CL_decay) [5]
- Concentration-dependent (Michaelis-Menten type) elimination (MM type) [5]
- Irreversible binding of rituximab to latent target with no description of target turnover (IB_L0)[5]
- Target-mediated elimination with irreversible binding of rituximab to latent target and zero-order antigen input (IB_turnover)[5]
- Quasi-equilibrium (QE) approximation of the full TMDD model (QE)[6,7]
- Extended QE TMDD – distribution compartment for target [3]

Results

Table II: Comparison of different non-linear elimination models

Model (IIV on CL, Vc, F)	**OFV**	**AIC**
2-CMT	2470.36	2492.36
2-CMT + EXP_CL_DECAY	2456.50	2482.50
2-CMT + MM type	2470.36	2496.36
2-CMT + IB_L0	2470.36	2496.36
2-CMT + IB_turnover	2459.85	2487.85
2-CMT + QE_TMDD	**2446.50**	**2476.50**
2-CMT + QE_extended	2440.32	2476.32

Figure 1: Final model: QE TMDD model

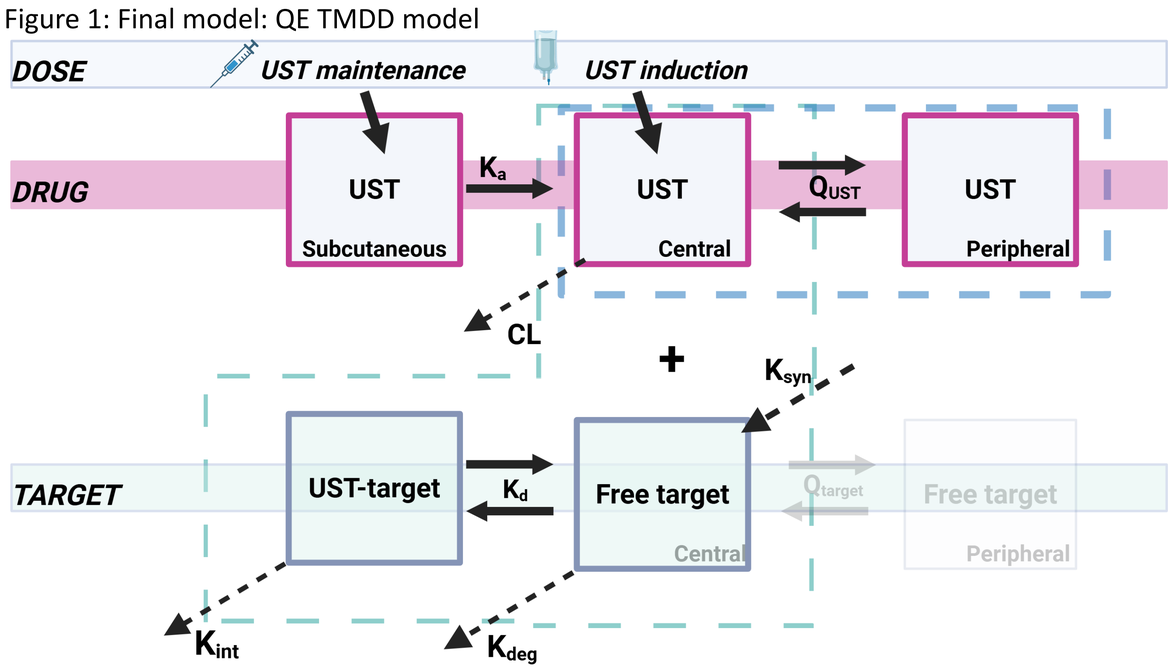


Table II: Model parametrization

Parameter (Units)	**Value (% RSE)**	**Variability**	**Value (% RSE)**
K_a (day^{-1})	0.293 (9)	Interindividual variability	
CL (L/day)	0.182 (12)	IIV CL (%, CV)	47 (33)
V_c (L)	2.77 (7)	IIV Vc (%, CV)	10.6 (107)
V_p (L)	1.01 (23)	IIV F (%, CV)	115.3 (67)
Q (L/day)	0.686 (24)	Residual variability	
F (%)	84.8 (8)	Additive RUV (nmol/L)	1.28 (28)
k_{syn} (nmol/(L × day))	21.2 (25)	Proportional RUV (%)	22.2 (4)
k_{deg}(day^{-1})	950.4 (51)		
K_d (nmol/L)	0.0185 (41)		
k_{int} (day^{-1})	0.0152 (27)		

Conclusion

- 2-compartment quasi-equilibrium TMDD model best describes ustekinumab PK in patients with ulcerative colitis.

Future improvements

- Identify and incorporate important covariates into the model.
- Develop a population pharmacokinetic-pharmacodynamic (PK-PD) model of UST in patients with ulcerative colitis.
- Use popPK-PD model to predict treatment outcome (e.g. clinical, biochemical, endoscopic, quality of life remission).

References

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