Model-derived PK target threshold profile of ustekinumab therapeutic thresholds in inflammatory bowel diseases to guide precision dosing

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Background and Objectives

Inflammatory bowel diseases (IBD) are a group of chronic immune-mediated diseases affecting the gastrointestinal tract, causing debilitating symptoms such as persistent abdominal pain, diarrhoea, and fatigue and with negative influence on quality of life [1].

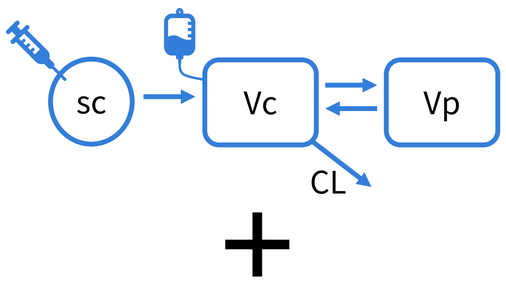
Ustekinumab (UST) is a mAb drug used to treat IBD. Since for UST an exposure-response relationship has been demonstrated, the lack of response in some patients might be due to suboptimal drug concentrations. Subsequently, TDM has been proposed [2].

TDM is performed by measuring the drug serum concentration (typically trough levels) at a specific timepoint and comparing to a pre-defined PK concentration threshold linking drug concentration to beneficial PD treatment outcome. Given the long dosing intervals of mAb drugs, this means that there is usually a **time lag of eight to twelve weeks** between TDM measurements and subsequent individual treatment optimisation.

This work aimed to provide the framework for a more **rapid UST treatment individualisation,** leveraging the knowledge from nonlinear mixed-effects (NLME) modelling to account for and leverage PK/PD targets from several studies at different timepoints simultaneously.

Methods

A two-compartment **NLME model** with 1st-order absorption and elimination was identified from literature [3].



PK/PD targets for reaching endoscopic remission with UST treatment for IBD were collected from literature (Table 1) [4-11].

Threshold concentrations was **weighted** based on number of patients involved in deriving them.

Table 1. PK/PD targets of UST concentration associated with endoscopic remission in IBD.

Week	Concentration [mg/L]	N patients	Reference
4	23.3	41	[5]
8	11.1	41	[5]
8	3.47	960	[4]
16	1.12	19	[6]
24	3.75	337	[7]
24	6.00	135	[8]
24	2.00	28	[9]
24	2.11	108	[10]
Maintenance (allocated: 24)	2.30	71	[11]
Maintenance (allocated: 24)	1.08	960	[4]

Maximum a posteriori (**MAP**) parameter value for CL was estimated fitting the PK/PD targets using the published model, for deriving the PK threshold profile.

Results

- Using the identified **NLME model** together with the **10 PK/PD targets** for reaching endoscopic remission, the **MAP** parameter value for CL was estimated to **0.182 L/day** (Table 2), for an UST clinical praxis dosing regimen of an intravenous induction loading dose of 390 mg followed by 90 mg subcutaneously every 8 weeks.
- From the **simulated UST concentration-time profile** (Figure 1), a **model-informed concentration threshold table** was generated for induction weeks 1-16 and maintenance therapy weeks 1-8 after dosing, increasing availability of the PK target profile for physicians without modelling experience (Table 3).

Results cont.

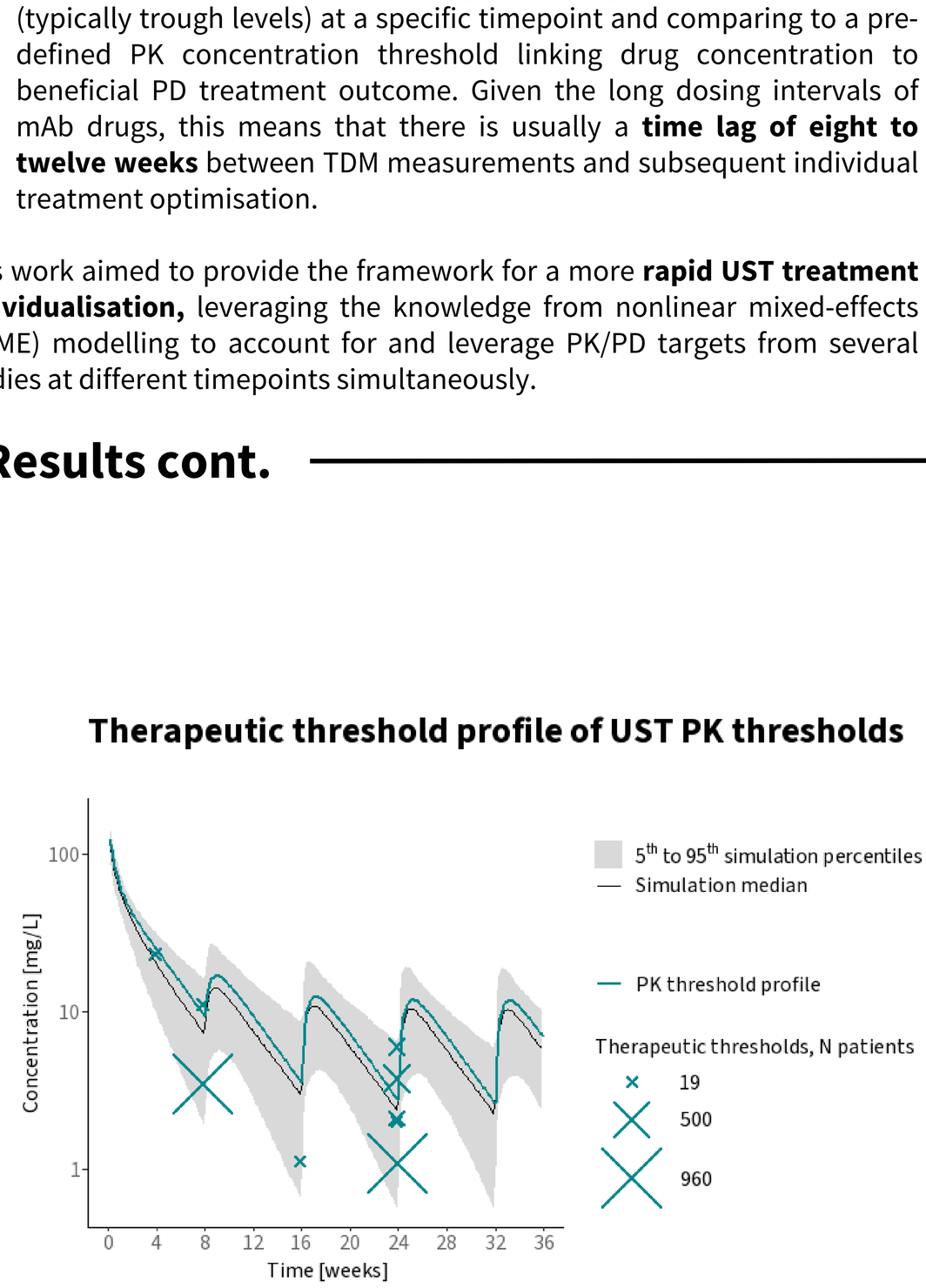


Figure 1. Simulated target concentration-time threshold profile based on 10 therapeutic thresholds plotted together with the thresholds and stochastic simulations using model published by O.J. Adedokun et al. (2022) [3, 4-11].

Table 2. Model parameters for UST therapeutic target profile

Parameter [unit]	Value
Ka [d^{-1}]	0.181
F [%]	78.2
$CL_{MAP\ threshold\ profile}$ [L/d]	0.182
Vc [L]	2.75
Vp [L]	1.88
Q [L/day]	0.287

Table 3. Model-informed therapeutic thresholds for the clinical praxis dosing regimen of 390 mg intravenous loading dose followed by 90 mg subcutaneously every 8 weeks.

Induction therapy		Maintenance (q8w)	
Week	*Target concentration [mg/L]*	*Week*	*Target concentration [mg/L]*
2	37.2	1	10.8
4	21.2	2	9.56
6	12.5	3	7.58
8 (pre-dose)	7.37	4	5.87
10	12.7	5	4.52
12	7.70	6	3.47
14	4.55	7	2.67
16 (pre-dose)	2.69	8 (pre-dose)	2.06

Conclusions

This work leverages the knowledge from NLME modelling to **account for** and **average** PK/PD targets from several studies at **different timepoints**. A complete concentration-time profile for induction and maintenance dosing every 8 weeks was derived from 10 published PK/PD targets and a published NLME model.

A framework is provided for more **rapid treatment individualisation** by **enabling TDM sampling** of UST treatment against IBD **at any point** during the dosing interval. By using the model-based threshold time profile, **dosing optimisation** to secure drug levels associated with endoscopic remission is facilitated.

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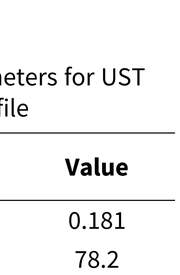
IBD: Inflammatory bowel diseases
mAb: Monoclonal antibody
MAP: Maximum a posteriori
NLME: Nonlinear mixed-effects
PK/PD: Pharmacokinetic/pharmacodynamic
TDM: Therapeutic Drug Monitoring
UST: Ustekinumab



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