Development of a mechanistic absorption model for a monoclonal antibody administered subcutaneously

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INTRODUCTION

The number of commercially available biological drugs and in particular monoclonal antibodies is strongly increasing.

- Despite several persistent challenges (formulation conditions, immunogenicity, incomplete bioavailability), the subcutaneous route is of increasing interest.
- Intravenous and subcutaneous data of a humanized IgG1 were obtained from a phase I study.

OBJECTIVE

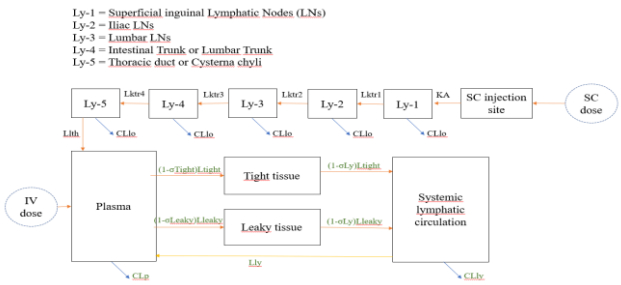
- **Implementation in a minimal PBPK model of a mechanistic model of subcutaneous absorption for monoclonal antibodies (mAbs) following administration in the abdomen.**

METHODS

A minimal PBPK (mPBPK) model was constructed using Nonmem version 7.4.

- The model was developed and validated based on observed clinical data from 33 patients, including 15 IV infusion and 18 SC administrations.
- Tissues are classified into two collective compartments (tight and leaky) considering permeabilities.
- Several transit compartments mimicking a relevant physiological pathway (i.e lymph nodes and flows) for the abdominal area have been added between the SC injection site and the plasma compartment.
- The pre-systemic clearance CLlo from lymph nodes was estimated to be close to zero and therefore negligible, so bioavailability was assumed to be 100%.

Figure 1: Schematic representation of transit compartments towards the systemic circulation after SC injection in abdomen



RESULTS

Table 1: Final parameters for the IV and SC model

Parameters	Estimations	RSE (%)	Shrinkage (%)
σ tight	0.95	16	
σ leaky	0.37	23	18
LKTR (L/Day)	3.4	52	40
CLly (L/Day)	0.67	27	26
Vp (L)	5.2	6.9	21
CLp FIX (L/day)	0.4		
KA (L/day)	0.0036	14	35
Sd FIX (ηLKTR)	1.9		
Sd (η σleaky)	1.7	22	
Sd (ηCLly)	1.1	27	
Sd (ηVp)	0.28	44	
Sd (ηKA)	0.49	48	
Sd (εprop)	0.16	5	

RESULTS (continued)

- The mPBPK model could describe adequately the observed data following IV and SC administration.
- Identifiability problems appeared after sensitivity analysis, therefore only two transit constants could be estimated.
- Values in agreement with published data were found for the different transit constants and absorption parameters.
- As shown by the diagnostic plots, the model correctly predicts the observations over the dose range (1,3.5 and 12 mg for IV administration and 12, 36 and 60 mg for SC administration.)

Figure 2: Conditional weighted residuals as a function of time (left) and population predicted concentrations (right) for the final model

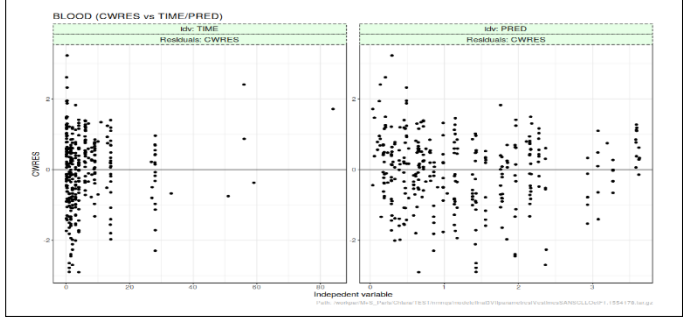
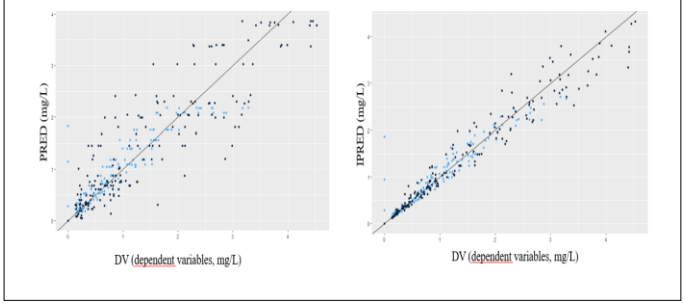


Figure 3: Population (left) and individual (right) predicted concentrations versus observed ones for the final model (IV in blue and SC in black)



DISCUSSION

- This is the first mPBPK model, to our knowledge, that has incorporated lymph nodes as transit compartments.
- The model successfully estimated the transit constants obtained after subcutaneous injection in the abdomen.

CONCLUSIONS

- **Simulations showed that transit constants, and therefore transit rate, impact pharmacokinetics metrics (Tmax and Cmax), suggesting that dosing adjustment could be performed in individuals with altered lymphatic drainage.**

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