Quantitative Approach to Predicting Human Pharmacokinetics of Monoclonal Antibody (DSP-mAbX) from Preclinical Data

M-44

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Introduction

DSP-mAbX is a full human monoclonal antibody targeted to a cell surface antigen. The cross-reactivity of DSP-mAbX to the target antigen in human and monkey has already been confirmed. Here, a quantitative translation of DSP-mAbX in vitro and in vivo pharmacology from cynomolgus monkeys to humans is presented. This approach is useful to guide the selection of a safe starting dose for Phase 1 clinical trials based on levels of target occupancy.

Objectives

・To construct the TMDD model of DSP-mAbX pharmacokinetics and time profile of target occupancy using monkey data.

・To develop a mechanistic approach to predicting human pharmacokinetics from in-vitro data and in-vivo non-human primate PK data based on the construct of a TMDD model.

・To predict a safe starting dose of DSP-mAbX in human.

Methods

A TMDD model was developed from the data shown below [1-3].

Data

・In vivo PK/PD study

- Animals: cynomolgus monkeys (n=39)
- Test substance: DSP-mAbX (monoclonal antibody)
- Administration route: IV
- Dose: 0.01, 0.1, 1, 5, 15, 150 mg/kg
- Sample collection: Plasma and Blood
- Analysis
  - ・ECL immunoassay (DSP-mAbX plasma concentration)
  - ・FACS cell based assay (target occupancy)
  - ・Immunogenicity assay (anti-drug antibody)
- Data point exclusion was based on ADA positivity.

・In vitro binding assay

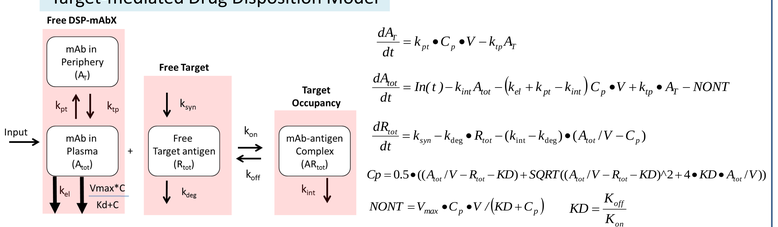
- Antigen: monkey and human target protein
- Antibody: DSP-mAbX
- Analysis: Surface plasmon resonance (Kon and Koff value)

PK Modeling

・Non-linear mixed effects modeling approach with NONMEM VII (ADVAN13)

・Models were evaluated using objective function values, mechanistic plausibility of parameters and performance in visual predictive checks (VPC).

Target-mediated Drug Disposition Model



$$\frac{dA_T}{dt} = k_{pt} \bullet C_p \bullet V - k_{tp} A_T$$

$$\frac{dA_{tot}}{dt} = In(t) - k_{int} A_{tot} - \left(k_{el} + k_{pt} - k_{int}\right) C_p \bullet V + k_{tp} \bullet A_T - NONT$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg} \bullet R_{tot} - \left(k_{int} - k_{deg}\right) \bullet \left(A_{tot}/V - C_p\right)$$

$$Cp = 0.5 \bullet ((A_{tot}/V - R_{tot} - KD) + SQRT((A_{tot}/V - R_{tot} - KD)\text{^}2 + 4 \bullet KD \bullet A_{tot}/V))$$

$$NONT = V_{max} \bullet C_p \bullet V / \left(KD + C_p\right) \qquad KD = \frac{K_{off}}{K_{on}}$$

Abbreviations

Ksyn, zero-order synthesis rate constant; kint, internalization rate constant; KD, dissociation constant (Koff/Kon); kpt, First-order plasma-to-tissue distribution rate constant; ktp, First-order tissue-to-plasma distribution rate constant; kel, elimination rate constant; NONT, elimination rate by non-specific targets.

Results

PK/PD studies in cynomolgus monkeys

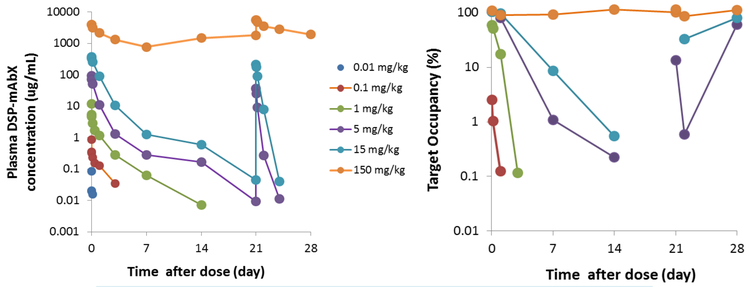


FIGURE 1. Observed Monkey PK/PD Profiles of DSP-mAbX

・A total of 39 monkeys received increasing doses of DSP-mAbX and exhibited non-linear exposure more than dose-proportional (**FIGURE 1**).

・The TMDD model was fit to the available data. Its parameter estimates and GOF were shown in **TABLE1 and FIGURE 2**.

TABLE 1. Parameter estimates and relative standard error for final model

Parameter (unit)	Estimated Monkey Parameter	Relative standard error(%)
CL (L/day)	0.0664	46.6
V (L)	0.288	38.2
kpt (1/day)	0.47	29.4
ktp (1/day)	0.643	17.2
Vmax (nM/day)	967	80.3
Km (nM)	826	81.4
KD (nM)	96.5, 132.2	FIXED
Kdeg (1/day)	62.7	139
Kint (1/day)	161	130

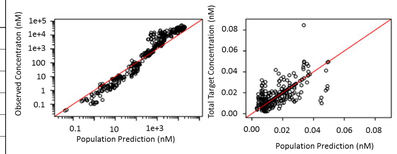


FIGURE 2. Goodness-of-Fit of final model

Human PK/PD prediction

・Human PK/PD parameters were predicted using the scaling exponent based on the empirical approach[2][4]. V_{max}, Km, K_{deg}, K_{int} and R0 were assumed to be the same as the cynomolgus monkeys' parameters. Human parameters were shown in **TABLE2**.

TABLE 2. Predicted human PK/PD parameters

Parameter (unit)	Estimated Monkey Parameter	Predicted Human Parameter	Exponent (b)
PK Parameters			
CL (L/day)	0.0664	1.18	0.96
V (L)	0.288	5.76	1
kpt (1/day)	0.47	0.222	-0.25
ktp (1/day)	0.643	0.304	-0.25
PD Parameters			
Vmax (nM/day)	967	967	ns
Km (nM)	826	826	ns
KD (nM)	96.5, 132.2	145.3	-
Kdeg (1/day)	62.7	62.7	ns
Kint (1/day)	161	161	ns
baseline receptor concentration, R0 (nM)	0.0217	0.0217	ns

ns = not scaled, KD = Koff/Kon from *in vitro* measurements in each species

Results

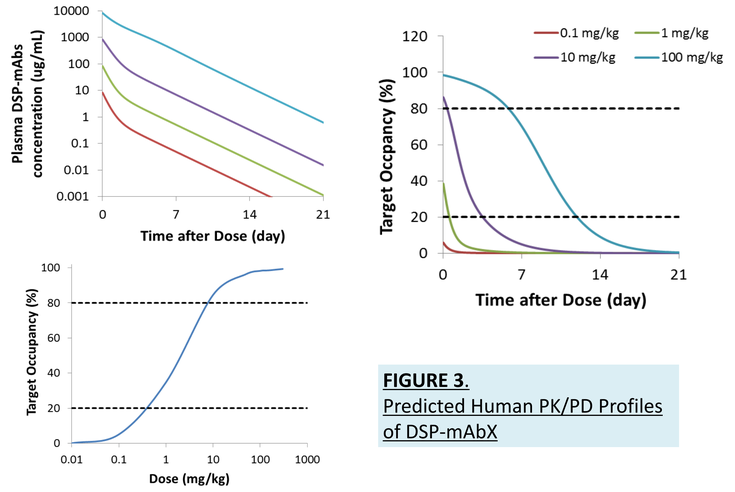


FIGURE 3. Predicted Human PK/PD Profiles of DSP-mAbX

・Human PK/PD profiles were predicted using the monkey data and the scaling exponent (**FIGURE 3**).

・Dosing between 0.1 and 0.5 mg/kg is predicted to achieve 10-20% target occupancy in accordance with the Minimal Anticipated Biological Effect Level (MABEL). Dosing at 10 mg/kg is predicted to achieve target occupancy > 80% in humans.

Conclusion

・A two-compartment model with non-linear and target-mediated drug disposition for DSP-mAbX PK in cynomolgus monkey was developed. The estimated parameters were scaled to predict human PK/PD.

・The developed model aided in selection of a safe starting dose and a pharmacological relevant dose escalation strategy of DSP-mAbx in humans.

・Incorporating target kinetics into a PK model to be used for interspecies scaling is a sensible approach for human PK/PD prediction. We plan to rebuild the TMDD model in human data. Future analysis should include a population modeling-based approach on larger datasets to estimate inter-individual variability for model parameters.

References

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