Model Based Approach to Inform Early Clinical Development for a Biologic

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Introduction / Objectives

A model-based approach combining all relevant information such as target biology, PK, potency and dose/concentration response curves from in vivo animal models is a useful tool to define the starting dose and the therapeutic concentration range for biologics. Integrating the knowledge about the mechanism of action, pharmacology, as well as the location, expression and turnover of the target is a key factor. In the example presented here, all the available knowledge and data was integrated in a model-based approach in order to inform the design of early clinical trials for a biologic under development for an inflammatory condition.

The objectives of this modelling exercise were:

- to determine the therapeutic concentration range
- to predict the dose range / regimen expected that results in clinical efficacy

PK/Target Turnover Model

The PK/target turnover model was built to simulate the anticipated target occupancy in plasma and lymph both in health and disease. The compound was assumed to partition into the lymph/spleen compartment where it either binds to the soluble or membrane-bound target. A population PK model was developed based on monkey data (NONMEM VI) and human PK parameter were obtained by allometric scaling. Figure 1 shows a schematic representation of the model. The model components were defined as follows:

- System Parameters:
  - ✓ Membrane target expression → in house in vitro and literature data
  - ✓ Soluble target expression → literature data
  - ✓ Half-life of membrane and soluble target → literature data
- Compound Parameters:
  - ✓ Antibody pharmacokinetics → allometric scaling from monkey PK
  - ✓ Distribution into lymph → literature data
  - ✓ Target binding affinity → in house in vitro data

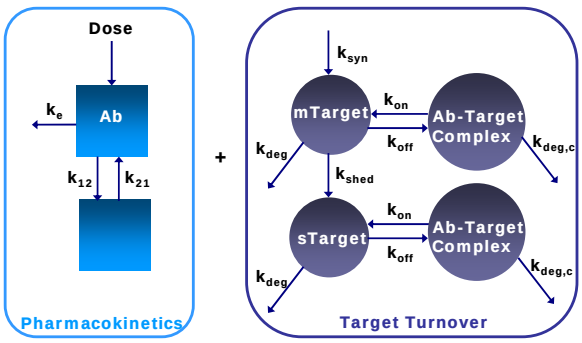


Figure 1. Schematic representation of the PK/target turnover model.

Simulations were performed for different dose levels / regimens using Berkeley Madonna v 8.3.14 to generate time profiles of antibody concentration in plasma and lymph, levels of free target in lymph and target occupancy in the lymph. Interindividual variability was included in the PK part of the model assuming the same variability as the one observed in clinical data from similar in house antibodies. Figure 2 shows as an example the outcome of one set of simulations at one dose level.

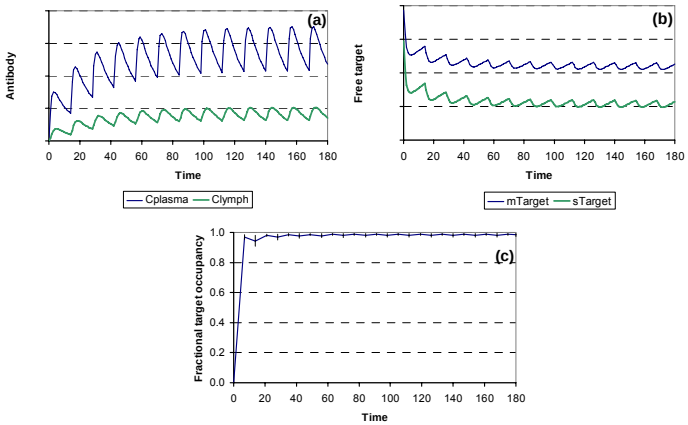
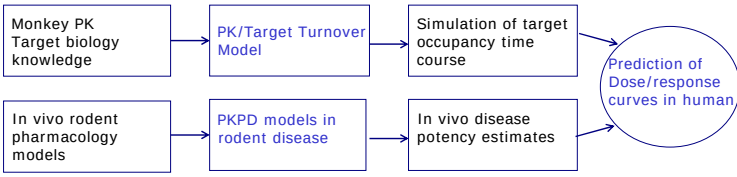


Figure 2. Simulations outcome at one dose level (median).a) Antibody concentration in plasma and lymph; b) free membrane-bound and soluble target; c) fractional target occupancy

Model-Based Strategy



PK/PD Rodent Disease Model

PK and PD data were collected in a rodent disease model experiment that involved prophylactic dosing. Mice received twice weekly chronic dosing of the antibody. Sparse PK sampling was obtained throughout the experiment. Three PD endpoints (PD1, PD2 and PD3) were measured at the end of the experiment. Population PK and PKPD modelling was performed using NONMEM VI.

- PK model:
  - ✓ Sparse PK data were combined with rich PK data from a separate single dose experiment.
  - ✓ Two compartment model with first order absorption and elimination.
  - ✓ Interindividual variability only on CL and a proportional error model used.
- PKPD model:
  - ✓ AUC during the last week of the PD experiment was computed for each animal to be used as the exposure parameter (AUC_{7days})
  - ✓ An inhibitory E_{max} model was used to relate the AUC_{7days} to each PD variables:

$$PD = BASE + E_0 \cdot \left(1 - \frac{E_{max} \cdot AUC_{7days}^{\gamma}}{AUC50_{7days}^{\gamma} + AUC_{7days}^{\gamma}}\right)$$

where BASE represents the PD endpoint value for the saline group (no challenge, no treatment); E_0 represents the PD endpoint value for the placebo group (challenge, no treatment); E_{max} is the maximum inhibitory effect; AUC_{7days} is the AUC during the last 7 days of treatment; $AUC50_{7days}$ is the AUC_{7days} that produces half of the maximum effect; and is the sigmoidicity factor.

Figure 3 shows the visual predictive checks for the PKPD models of the three PD endpoints evaluated. E_{max} was only estimated for PD3 and it was fixed to 1 for PD1 and PD3. Interindividual variability was only estimated for E_0.

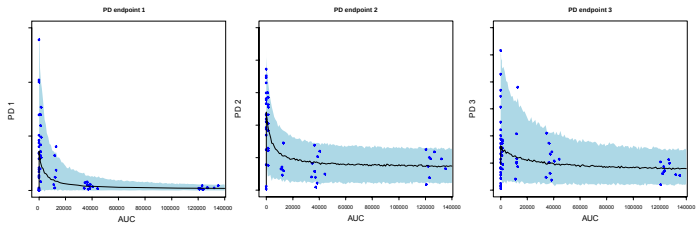


Figure 3. VPC for the three PD endpoints. Solid line represents the median prediction; blue area represents the 5th and 95th percentile prediction interval.

Translation to human & Conclusions

The target occupancy and the PKPD models results were integrated to predict the dose window that would translate into a meaningful pharmacological response in the clinical setting:

- efficacious exposure range: estimated AUC50 for PD1, PD2 and PD3 from the rodent disease model were used to compute the AUC resulting in 20% to 90% of the maximum effect and a human/mouse potency correction factor was applied.
- efficacious dose range/regimen: the predicted human PK parameters were used to calculate the corresponding human dose levels for the defined efficacious exposure range.
- % of effect/steady state target occupancy curves vs. dose were generated for dosing regimens QxW, QyW and QzW and results are displayed in Figure 4.

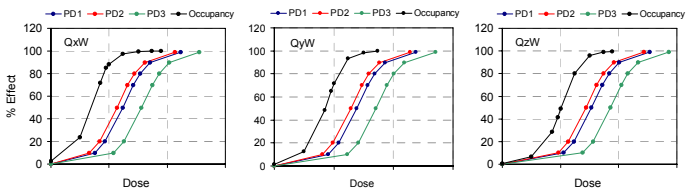


Figure 4. Simulated dose-response profiles for target occupancy in lymph and the 3 PD endpoints for dose regimens QxW,QyW and QzW.

- The combination of the two modelling approaches, target binding & PKPD of disease endpoints showed that a high target binding level is required before relevant downstream pharmacological effects can be observed.
- The integration of all in vitro, preclinical in vivo and available literature data as well as the understanding of the mechanism of action and the disease allowed through modelling and simulation to define the dose levels / regimen to be evaluated during early clinical development of the compound.

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