Translational PK of bevacizumab between monkey and human using PBPK modeling

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Introduction

- PBPK modeling is increasingly used in Model Informed Drug Development (MIDD) of small molecules but its application to development of monoclonal antibodies (mAbs) is recent
- The objective of this study was to develop a translational mAbs PBPK modeling approach based on bevacizumab data from the literature to better support use of MIDD in mAbs development

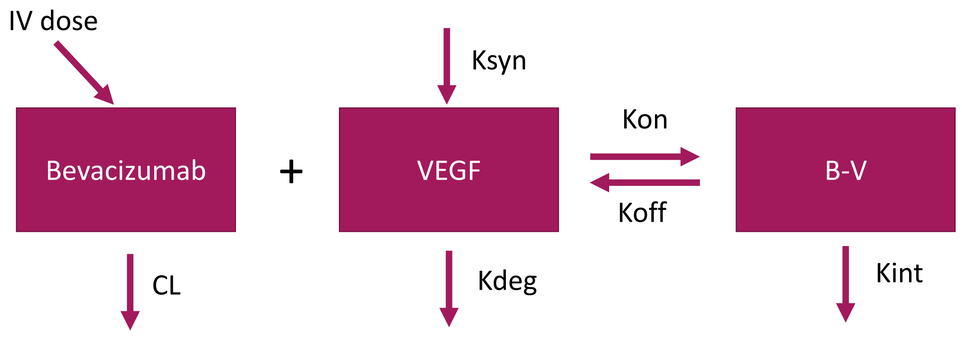

Figure 1 : TMDD model for interaction of bevacizumab with its target VEGF

Methods

A full PBPK model for mAbs was developed using digitalized PK data of bevacizumab and Xtend-bevacizumab (bevacizumab with higher FcRn affinity) [1,2,3,4,5,6,7,8,9,10] in PK-Sim® and MoBi® (OSPS) software.

The model includes the target-mediated drug disposition (TMDD) phenomenon due to the interaction of bevacizumab with its target (VEGF). The model was built based on monkey data and refined at each step of a theoretical drug development :

1 – Model building in cynomolgus monkey (bevacizumab)

2 – Validation (a) and refinement (b) in cynomolgus with Xtend-bevacizumab

3 – Prediction of HV PK (a), then refinement with the data (b)

4 – Prediction of adult cancer patients PK (a), then refinement with the data (b)

5 – Prediction of PK in pediatric patients

At each step, the model-predicted AUC and Cmax were compared with the observed values.

Parameters	Description of parameters	(1) Cynomolgus Model fitting	(2a) Cynomolgus Xtendbeva Model Prediction	(2b) Cynomolgus Xtendbeva Model fitting	(3a) Human HV Model Prediction	(3b) Human HV Model fitting	(4a) Human patients Model Prediction	(4b) Human patients Model fitting	(5) Pediatric Model Prediction
		Cynomolgus data		Cynomolgus data (xtend)		HV data		Adult patients data	Pediatric patients data
Kd-FcRn (nmol/L)	Equilibrium dissociation constant of bevacizumab to FcRn	Fitted value : 0.45	11-fold lower than bevacizumab [10] : 0.041	Same	2-fold higher than monkey [15] : 0.9	Fitted value : 0.94	Same	Same	Same
Kdeg (1/min)	Degradation rate constant of VEGF (1st order)	No TMDD				Fitted value : $1.2x10^{-4}$	Same	Same	Same value as adult
Kint (1/min)	Internalization rate constant of B-V (1st order)	No TMDD				Fitted value [16] : $3.35x10^{-5}$	Same	Same	Same
Kd-target (nmol/L)	Equilibrium dissociation constant of bevacizumab to VEGF	Human physiological value [14] : 0.058	Same	Same	Same	Same	Same	Same	Same
Koff-target (1/s)	Constant of dissociation rate of B-V (1st order)	No TMDD				In-vitro value [14] : $3.1x10^{-5}$	Same	Same	Same
Conc VEGF (nmol/L)	Concentration of VEGF	0.3	Same	Same	Between 0 and 3 [11]	Fitted value : 0.3	10-fold higher than HV [11,12,13] : 3	Fitted value : 3.86	Same value as adult

Iterative process

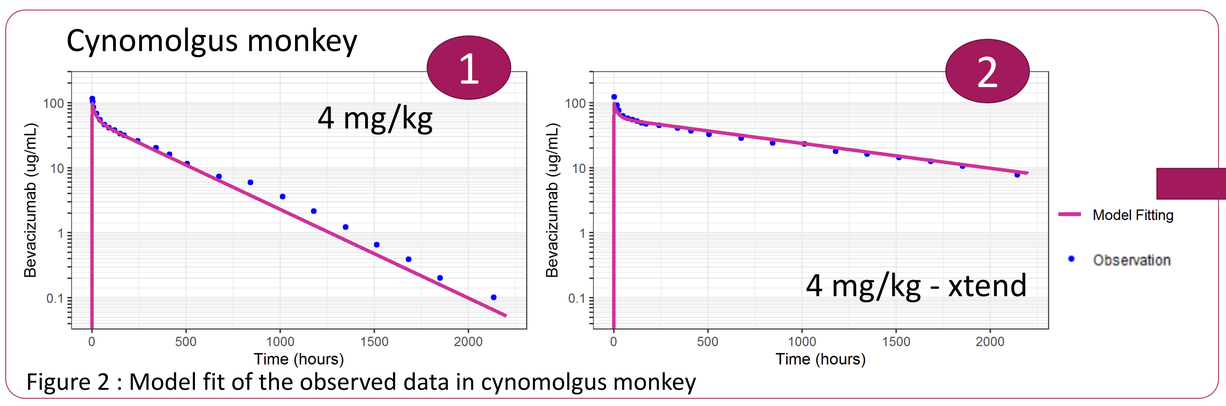

Figure 2 : Model fit of the observed data in cynomolgus monkey

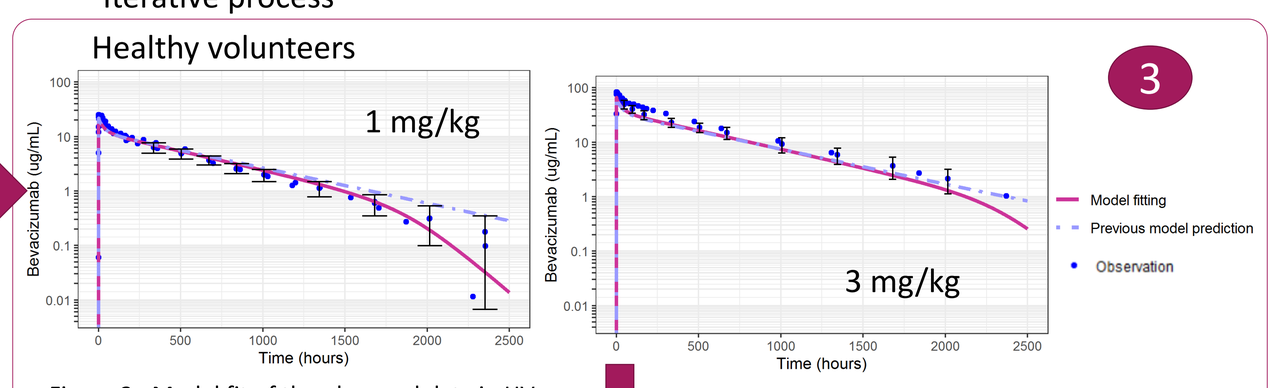

Figure 3 : Model fit of the observed data in HV

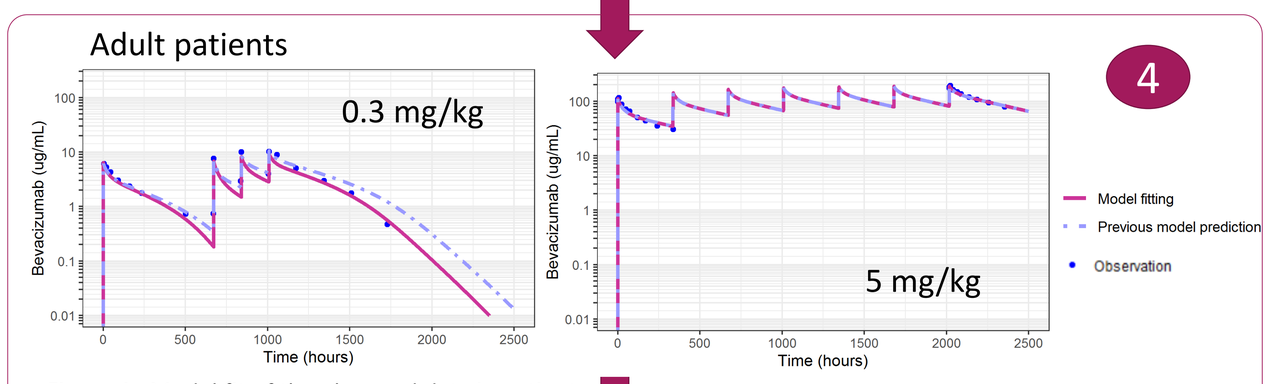

Figure 4 : Model fit of the observed data in patients

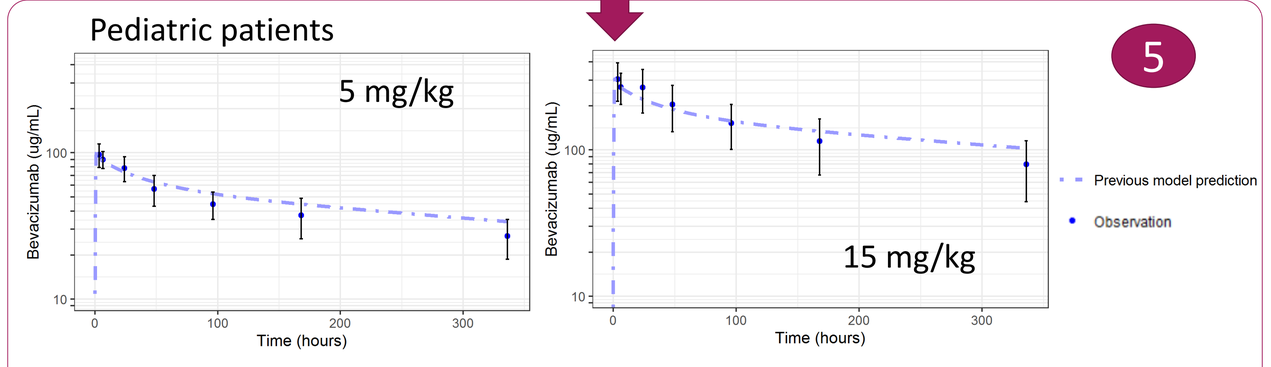

Figure 5 : Model fit of the observed data in pediatric patients

Validation of the model

Figure 6 : Observed versus model-predicted AUC and Cmax of bevacizumab.

Conclusion

- The full PBPK model with TMDD describing interaction of bevacizumab with its soluble target (VEGF) was successfully developed using PK-Sim® and MoBi®
- The model was satisfactorily applied for inter-species (from monkey to human) and inter-molecules (from bevacizumab to Xtend-bevacizumab) PK translation.
- All model-predicted AUC and Cmax were within 2-fold of the observed values.

→ This work is a first step to generalize the use of full PBPK models for mAbs PK translation and optimization.

References

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