Prediction of target-mediated PK profile of Bevacizumab in cancer patients using PBPK modeling

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Background

- Monoclonal antibodies (mAbs) exhibit complex disposition features compared to conventional small-molecule drugs. One of the significant factors affecting their disposition is the selective binding to their target and the localization of the target (e.g., circulating or membrane-bound)
- PBPK models are a useful approach used during all phases of drug product development due to their ability to scale pharmacokinetic (PK) predictions between species and populations.
- The mAbs' PBPK models can be used to predict the sufficient dose allowing a targeted receptor occupancy. However, significant efforts remain to fully develop and validate PBPK models to support mAbs drug development.

Aim & Objectives

This study aimed to support GastroPlus© Biologic module development by:

A. Propose improvements of the Biologic module capacities based on literature analysis
B. Define the model structure for mAbs targeting circulating antigens
C. Validate the new PBPK model using one case study:

Bevacizumab directed against the soluble target VEGF: PK prediction of bevacizumab in cancer patients using a PBPK model previously validated in healthy subjects.

Material & Methods

PBPK models development steps

Model development

- Bevacizumab drug parameters and affinity with FcRn and target VEGF
- Soluble antigen amounts and Physiological parameters

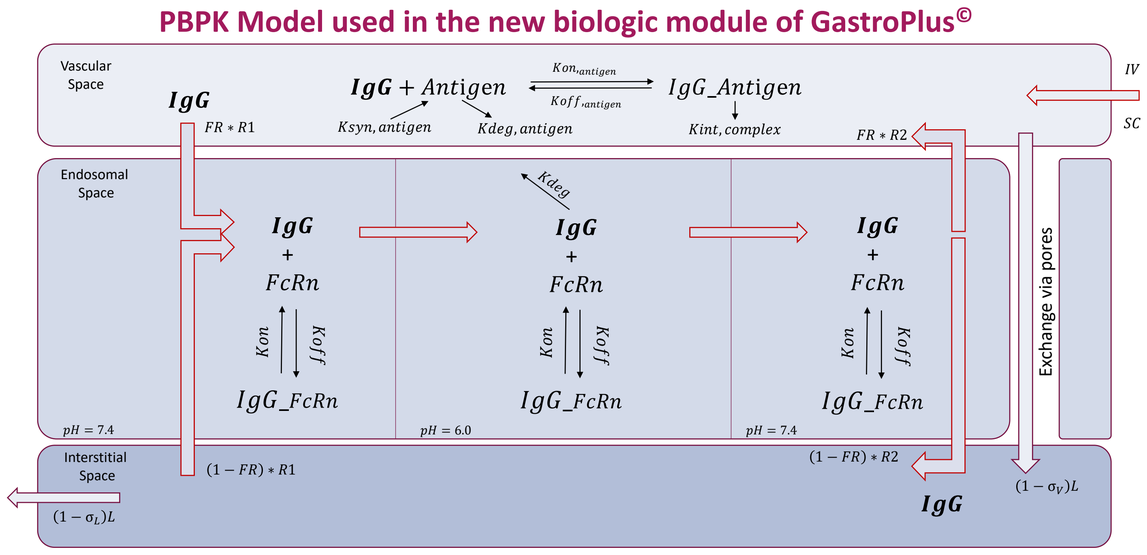
Model verification

- Simulations and optimization of the TMDD mechanism after i.v. bolus dosing in healthy subjects (0.5mg/kg)
- Validation of Pharmacokinetics after i.v. infusion dosing in healthy subjects with PK datasets from literature (1mg/kg) within two-fold

Model application

- Model simulations after i.v. infusion dosing in cancer patients changing the amount of VEGF in blood compartments

PBPK Model used in the new biologic module of GastroPlus©



Results

Healthy Subjects

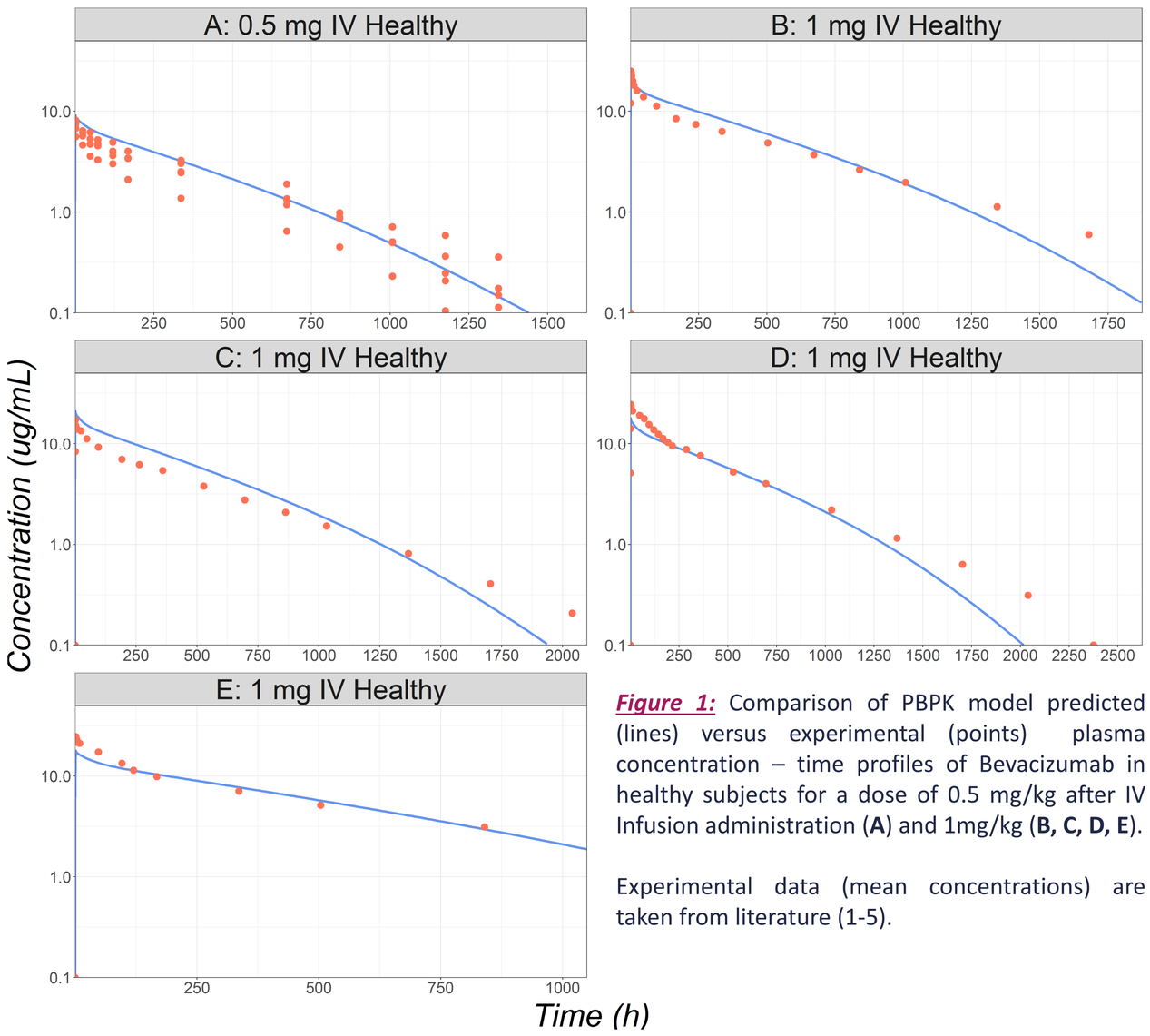


Figure 1: Comparison of PBPK model predicted (lines) versus experimental (points) plasma concentration – time profiles of Bevacizumab in healthy subjects for a dose of 0.5 mg/kg after IV Infusion administration (**A**) and 1mg/kg (**B, C, D, E**).

Experimental data (mean concentrations) are taken from literature (1-5).

Cancer Patients

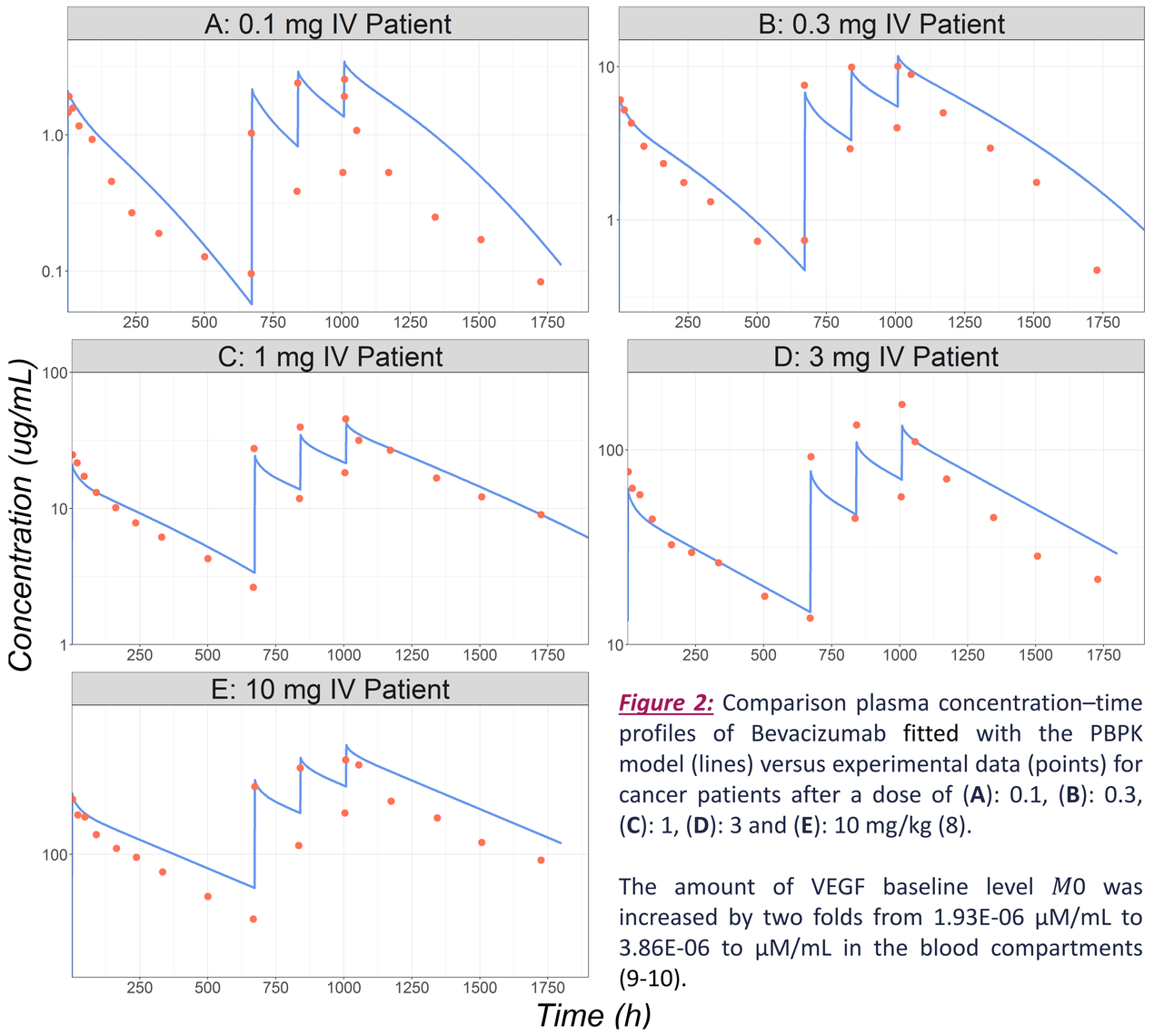


Figure 2: Comparison plasma concentration–time profiles of Bevacizumab fitted with the PBPK model (lines) versus experimental data (points) for cancer patients after a dose of (**A**): 0.1, (**B**): 0.3, (**C**): 1, (**D**): 3 and (**E**): 10 mg/kg (8).

The amount of VEGF baseline level $M0$ was increased by two folds from 1.93E-06 µM/mL to 3.86E-06 to µM/mL in the blood compartments (9-10).

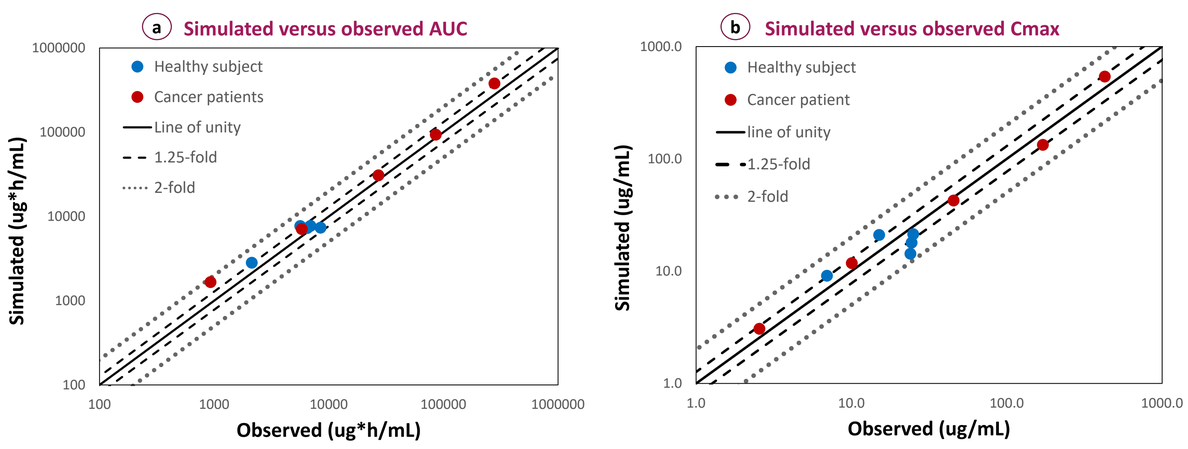


Figure 3: PBPK model validation plots for Cmax and AUC ratios : (**a**): AUC ratios, (**b**): Cmax ratios.

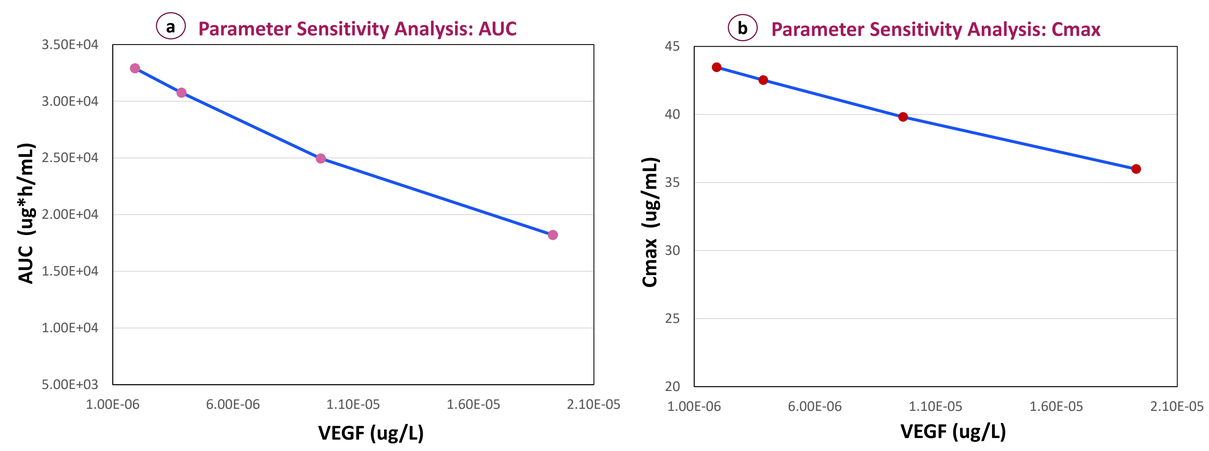


Figure 4: Analysis of the sensitivity of model parameters to different amounts of VEGF using factors 2, 5, and 10 in cancer patient (**a**): AUC , (**b**)**:** Cmax.

Conclusion

- ✓ The PBPK model developed for Anti-VEGF Bevacizumab mAb predicted reasonably well the PK in cancer patients from the PK of healthy subjects.
- ✓ This model was used to validate a beta version of GastroPlus© including the expression of soluble antigen targets in the blood compartment.

References

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