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.



Healthy Subjects





Cancer Patients



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. \checkmark 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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