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Validation of PBPK-Based Translation to Predict Monoclonal Antibody Pharmacokinetics in Pediatric Populations

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PURPOSE

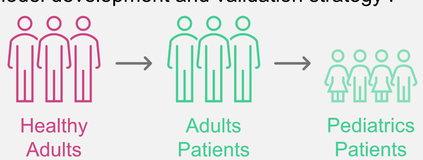
Accurate prediction of the pediatric dose is a necessity before conducting a clinical trial or using a drug product in standard clinical practices. For the pediatric population, safety and efficacy need to be considered for ethical reasons. The recommended doses of most of the therapeutic proteins, including monoclonal antibodies (mAbs), are extrapolated to pediatrics from adult doses based on body weight. This approach does not consider physiological and biochemical differences between children and adults. mAbs' underexposure, limiting its efficacy in this population, is therefore possible. Other methods are necessary to mechanistically predict pediatric doses. For small molecules, physiologically based pharmacokinetic (PBPK) models have been long used to predict pediatric dose based on age-related changes in the physiology and enzymes/transporters ontogeny

OBJECTIVE

This study aims to evaluate the ability of the PBPK model to predict pediatric exposure for mAbs

METHODS

- Two mAbs were used: **infliximab** (anti-TNF-alpha) and **bevacizumab** (anti-VEGF).
- PBPK models were built using the Biologics module within **GastroPlus**©.
- Vascular and lymphatic reflection coefficients, and endosomal elimination rate constant, were fitted to describe observed data in healthy subjects. All other model parameters were kept as default.
- For bevacizumab, target-mediated drug disposition (TMDD) was implemented in the model. Binding parameters and VGEF plasma concentrations were extracted from the literature.
- Model development and validation strategy :



RESULTS

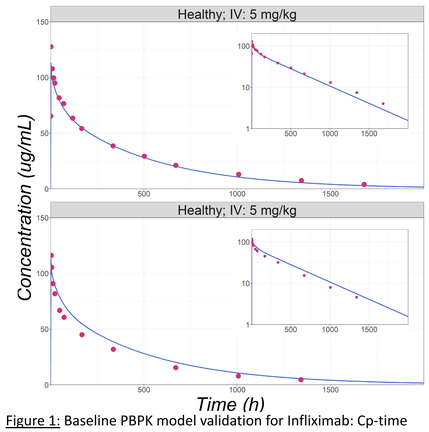


Figure 1: Baseline PBPK model validation for Infliximab: Cp-time profiles following IV administration in healthy adult subjects. Symbols are observed data and lines are simulated concentration-time courses

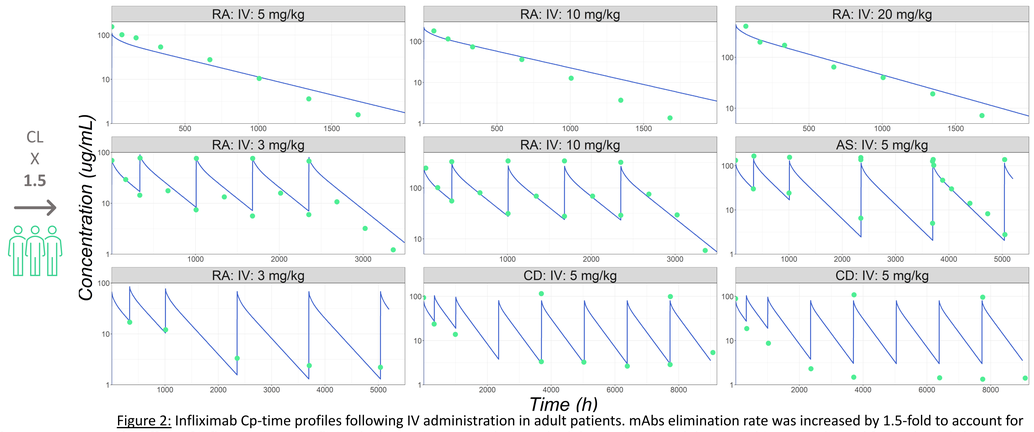


Figure 2: Infliximab Cp-time profiles following IV administration in adult patients. mAbs elimination rate was increased by 1.5-fold to account for the effect of inflammation on infliximab elimination. Dose, dosing schedules, and patients' demographic were adjusted for each study based on the published information. RA: rheumatoid arthritis; AS: ankylosing spondylitis; CD: Chron disease

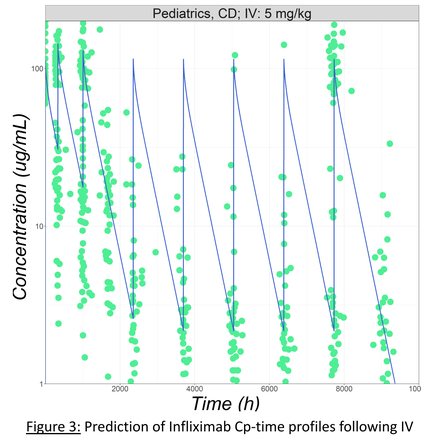


Figure 3: Prediction of Infliximab Cp-time profiles following IV administration in pediatric patients affected by Chron disease. CD: Chron disease

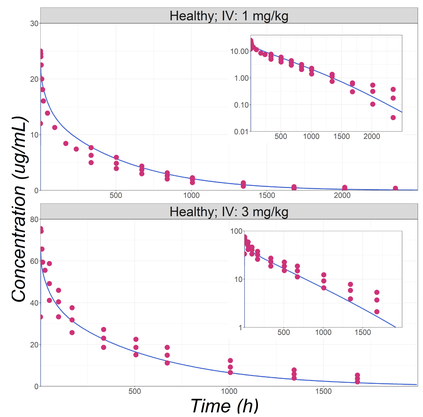


Figure 4: Baseline PBPK model validation for bevacizumab: Cp-time profiles following IV administration in healthy adult subjects. Symbols are observed data and lines are simulated concentration-time courses

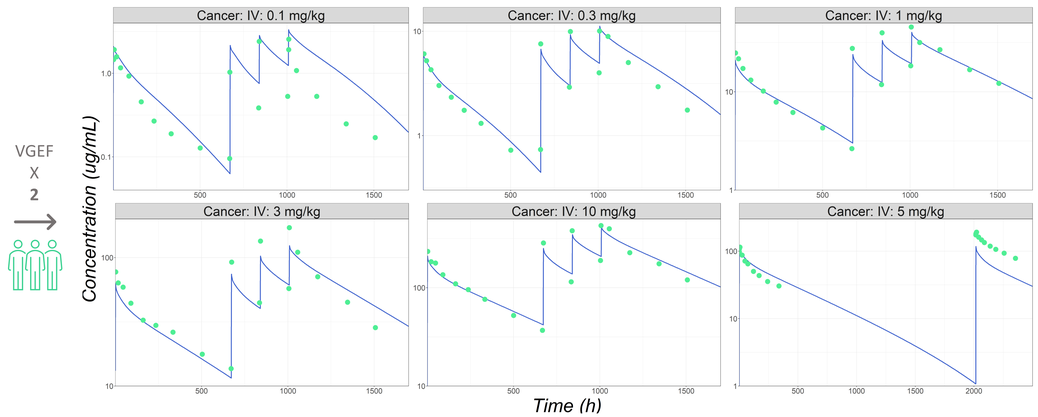


Figure 5: Infliximab Cp-time profiles following IV administration in adult cancer patients. Circulating VEGF concentration was increased by 2-fold to account for the effect of cancer disease on VEGF production. Dose, dosing schedules, and patients' demographic were adjusted for each study based on the published information.

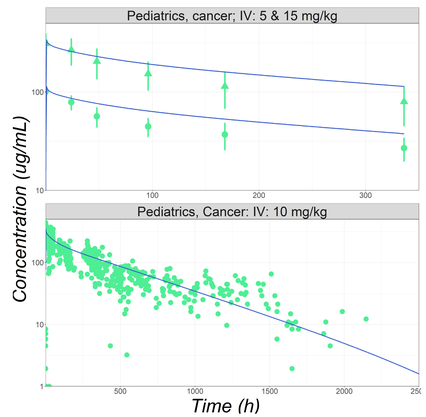


Figure 6: Prediction of bevacizumab Cp-time profiles following IV administration in pediatric cancer patients. In the top panel, circles & triangles represent 5 and 15 mg/kg doses, respectively.

CONCLUSIONS

- PBPK models allowed an accurate prediction of the observed data in the pediatric population for two mAbs: infliximab and bevacizumab.
- For both mAbs, one of the PBPK model parameters was adjusted to account for disease conditions prior to performing the pediatric extrapolation (endosomal clearance for infliximab and circulating VGEF concentration for bevacizumab)
- The accurate pediatric extrapolation outcomes for these mAbs represent an important step in the validation process of the extrapolation method used to predict biologics' exposure in this population using PBPK models.

PhinC Development

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