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Human Pharmacokinetics Prediction for Trastuzumab Using Scaling and Two-Compartment Modeling with B-hFcRn Mice PK Data

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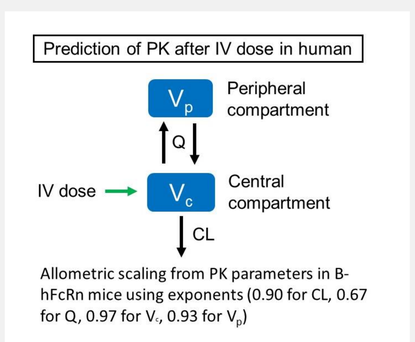
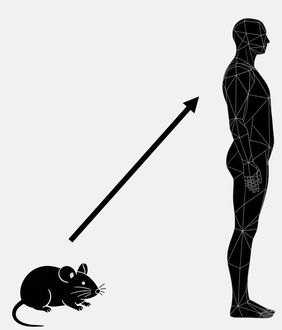
PURPOSE

Biocytogen humanized neonatal Fc receptor mice (B-hFcRn mice) offer an alternative model for Tg32 mice in pharmacokinetic study of biologics; however, differences between B-hFcRn and Tg32 mice raise uncertainties about whether data from B-hFcRn mice can reliably predict human pharmacokinetics.

METHOD(S)

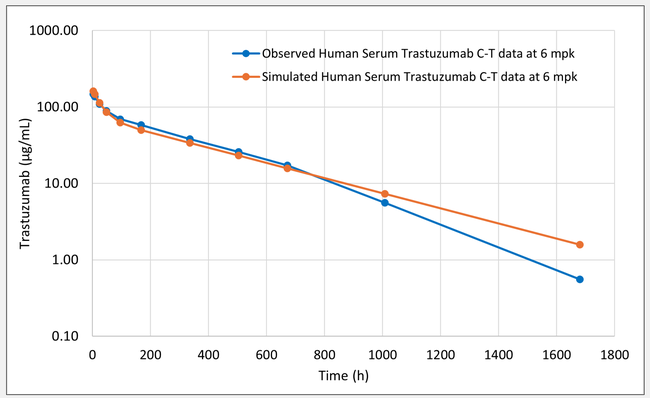
Serum drug concentrations were measured using enzyme-linked immunosorbent assay (ELISA) in B-hFcRn mice following a single intravenous dose of 10 mg/kg Trastuzumab over 504 hours. Using allometric scaling, clearance (CL), intercompartmental clearance (Q), central volume of distribution (Vc), and peripheral volume of distribution (Vp) were extrapolated to humans. Additionally, the species-invariant time method (Dedrick Plot) was applied to predict human pharmacokinetic profiles. Pharmacokinetic parameters (CL, Q, Vc, and Vp) were calculated using a two-compartment model and scaled to human.





RESULT(S)

- The extrapolated pharmacokinetic parameters and concentration-time curves for humans showed accurate predictions within a 1.5-fold error.
- The concentration-time curve for a single 6 mg/kg dose of Trastuzumab was accurately forecasted up to approximately 200 hours in the mono-exponential elimination phase using the Dedrick Plot method.
- Using the two-compartment model, the human concentration-time curve was predicted, accurately reflecting up to 1006 hours post-administration, including both mono-exponential and bi-exponential elimination phases.



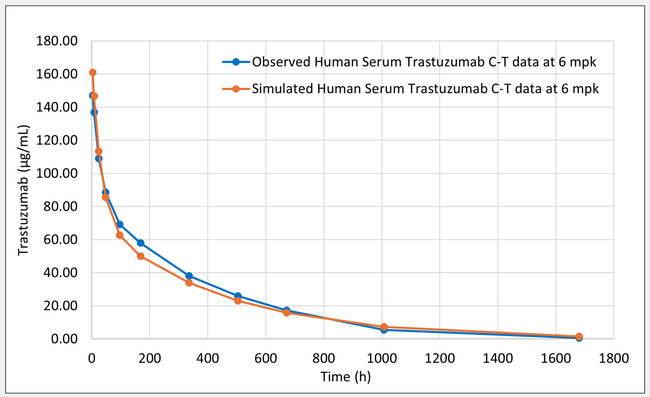


Figure 1. Observed and simulated concentration-time profiles in humans after a single 6 mg/kg dose of Trastuzumab, simulated using the two-compartment model.

CONCLUSION(S)

These findings demonstrate the ability to accurately predict human pharmacokinetics for Trastuzumab using preclinical data from B-hFcRn mice, showcasing the potential of this approach for early drug development and translational research.

REFERENCES

[1] Haraya, Kenta et al. “Prediction of human pharmacokinetics of Fc-engineered therapeutic monoclonal antibodies using human FcRn transgenic mice.” mAbs vol. 17,1 (2025): 2484443.
[2] Yin, Donghua et al. “A randomized phase 1 pharmacokinetic trial comparing the potential biosimilar PF-05280014 with trastuzumab in healthy volunteers (REFLECTIONS B327-01).” British journal of clinical pharmacology vol. 78,6 (2014): 1281-90.