Model-based comparison of mAb clearance in pediatric populations

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Motivation & Objectives

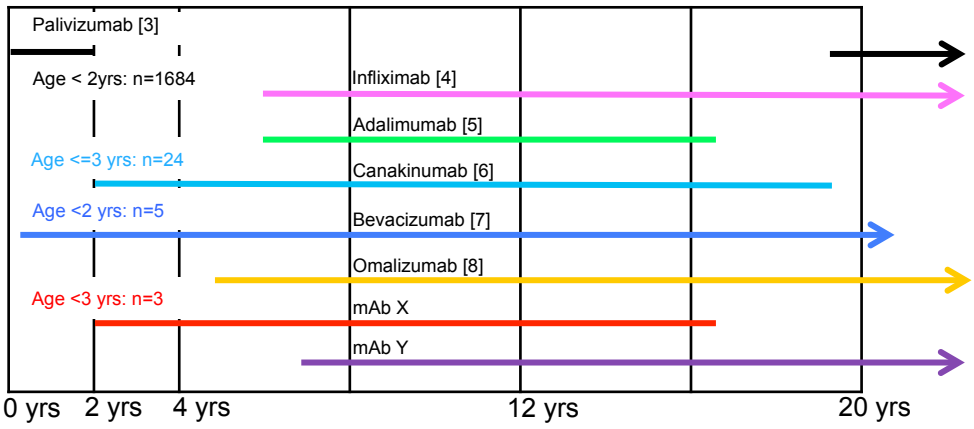
Health authorities demand the early use of predictive models to support pediatric drug development. So far, few models to predict monoclonal antibody (mAb) pharmacokinetics (PK) in children have been used. However, no comparison of the model-based predictions across age exists.

The **objective** of this study was to quantitatively compare age-dependency of clearance (mean and spread) using the available models.

Data & Models

We reviewed literature on POP-PK models involving pediatric populations (including individuals < 12 years of age). Target-independent clearance (CL) was compared using these models by linking the reported covariates (typically body weight (BW) and albumin concentration (Alb)) to postnatal age (PNA), e.g., using WHO/CDC growth charts [1] and reported ontogeny of albumin concentration [2].

Age range of investigated study populations



Comparison of unspecific clearance, case examples

Current POP-PK models mainly include purely body weight-based scaling methods. Only for Palivizumab, an explicit age-based 'maturation' function was used [3].

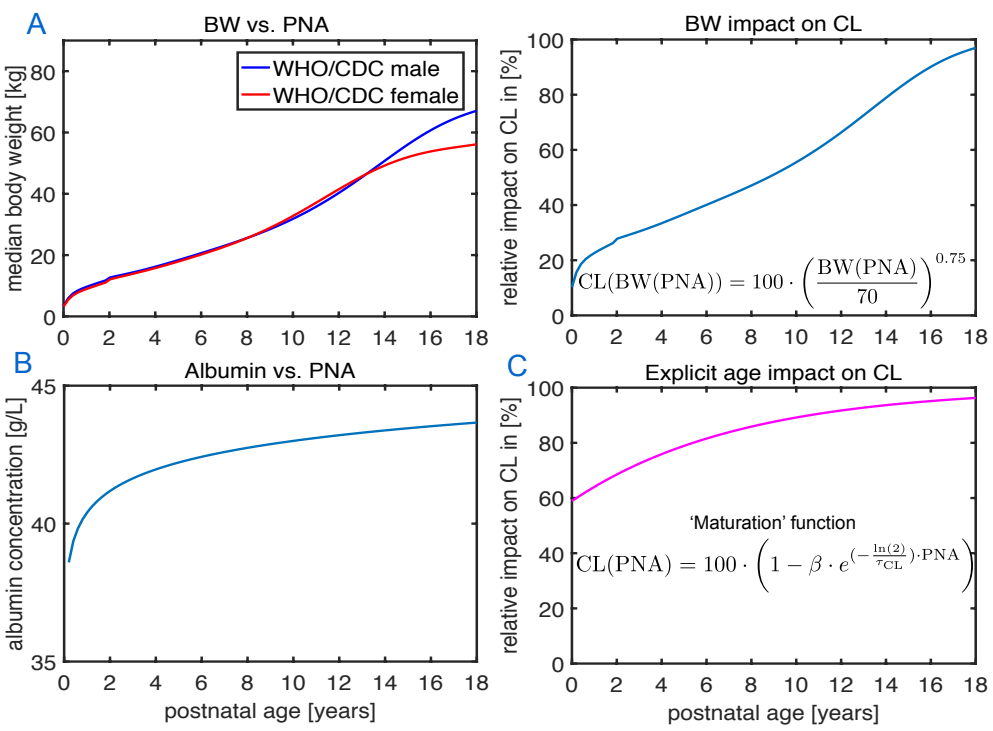
- Palivizumab [3]

$$\mathrm{CL(PNA)} = \mathrm{CL_{pop}} \cdot \left(\frac{\mathrm{BW(PNA)}}{70}\right)^{0.75} \cdot \left(1 - \beta \cdot e^{\left(-\frac{\ln(2)}{\tau_{\mathrm{CL}}}\right)\cdot \mathrm{PNA}}\right) \cdot e^{\eta_{\mathrm{CL}}}$$

- Bevacizumab [7]

$$\mathrm{CL(PNA)} = \mathrm{CL_{pop}} \cdot \left(\frac{\mathrm{BW(PNA)}}{70}\right)^{0.75} \cdot \left(\frac{\mathrm{Alb(PNA)}}{39}\right)^{-0.3} \cdot 1.11(male) \cdot e^{\eta_{\mathrm{CL}}}$$

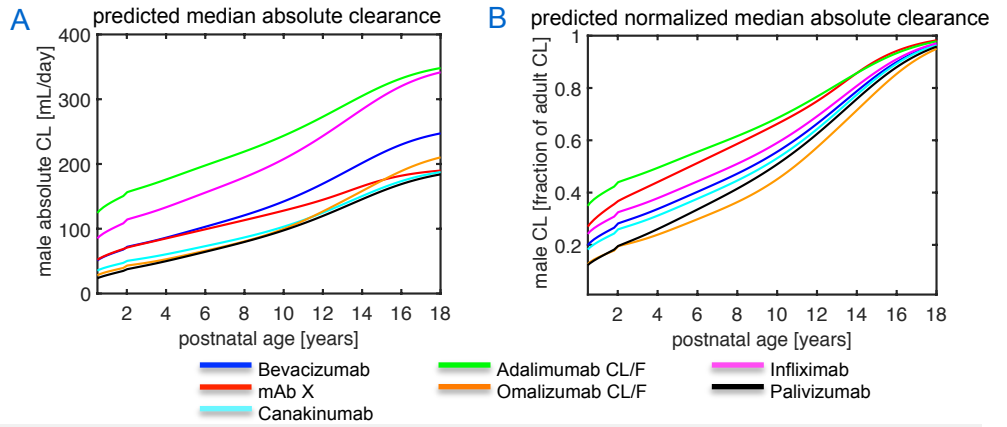
How to compare the different models?



A. To predict weight-dependency of CL across age, we make use of the reported BW vs.postnatal age relationship from WHO/CDC growth charts.
B. Known ontogeny of albumin concentration is used to predict the impact of albumin on CL.
C. 'Maturation' of CL (used to predict PK of palivizumab in infants) is described by an empirical covariate model that considers age in addition to body weight effects.

BW vs. PNA relationship and ontogeny of albumin concentration from healthy subjects

Results: Comparison of age-dependency of mAb unspecific clearance based on available POP-PK models

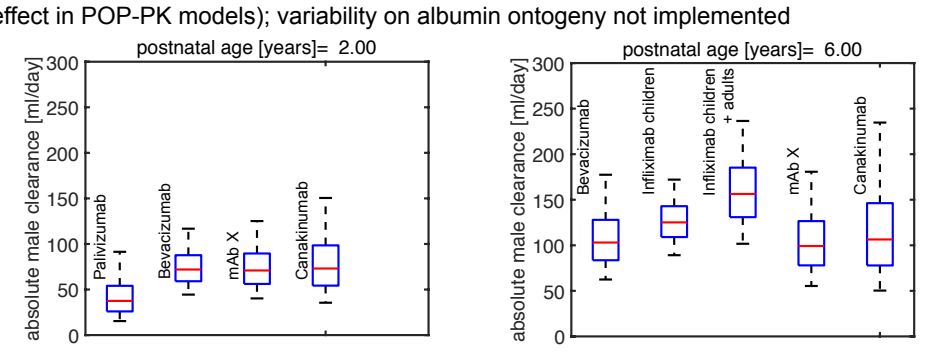


A. Pronounced differences in the trend of absolute CL across age are visible between the investigated mAbs.
B. Absolute CL was normalized to CL of an 18 year-old subject. Not only differences in the overall trend, but also differences at a specific age are visible between different mAbs, e.g., at 2 years of age, CL varies up to a factor 2.

Potential reasons for the differences: (i) different models used to predict CL; (ii) disease effects; (iii) different study populations.

Comparison of clearance including inter-individual variability (IIV)

IIV is based on variability of BW across age [1] and on IIV on CL (between-patient random effect in POP-PK models); variability on albumin ontogeny not implemented



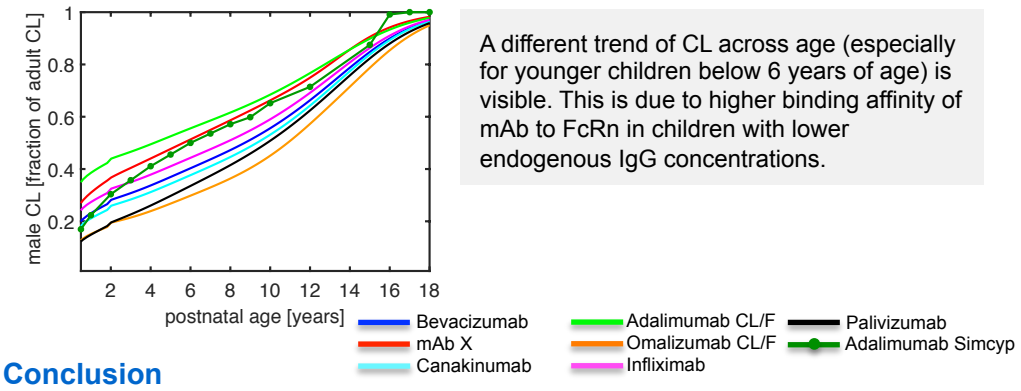
Increasing IIV with age depends on increasing variability of BW across PNA. IIV between the mAbs is highly dependent on study population (random effect). Lower median for palivizumab could be related to explicit age effect. Lower median CL of infliximab in children is related to comedication and lower incidence of anti-drug antibodies.

Implemented features in commercial PBPK software to predict mAb PK in pediatric populations

	Implemented IgG ontogeny	Implemented FcRn ontogeny
PK-Sim® (V 7.0)	yes	no
SimCyp® (V15 R1)	yes	no
Gastroplus® 9.0	no	no

The concentrations of the neonatal Fc receptor (FcRn) and of endogenous IgG are important factors that determine the unspecific CL of mAbs. All models consider explicity/implicitly the competition between endogenous IgG and therapeutic mAbs for binding to FcRn.

Case example PBPK (Simcyp®): Predicted normalized median absolute CL including Simcyp®-predicted Adalimumab target-independent CL



A different trend of CL across age (especially for younger children below 6 years of age) is visible. This is due to higher binding affinity of mAb to FcRn in children with lower endogenous IgG concentrations.

Conclusion

It remains to be elucidated within further research whether differences in age dependency of CL between mAbs are related to a bias in assessment due to usually sparse data below 6 years of age (except Palivizumab) or due to effects of disease and study population. Detailed knowledge on maturation processes, e.g., FcRn ontogeny, IgG catabolic clearance are needed to increase confidence using PBPK models.

References

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