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PERSPECTIVE

Allometric Considerations on Proteins Administered Intravitreally to Children

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Therapeutic proteins administered into the intravitreal (IVT) chamber of the eye have become the treatment option of choice for several ocular disorders. The understanding of ocular and systemic pharmacokinetics (PK) as well as pharmacodynamics (PD) is still developing. Here, we present a perspective on current knowledge and knowledge gaps as well as an allometric framework to extrapolate exposure in the vitreous and systemic circulation to children focusing on relative changes in clearance.

GENERAL PHARMACOKINETICS

The most prominent class of IVT administered protein drugs antagonize the vascular endothelial growth factor (anti-VEGFs) and are approved to treat various retinal vascular diseases with macular edema. Although these indications are generally not of relevance in children, based on the mode-of-action, anti-VEGFs are investigated in alternative ophthalmological pediatric indications as early as in preterm neonates suffering from retinopathy of prematurity (ROP). Originally, anti-VEGFs have been developed as angiogenesis inhibitors in oncological indications, where the administration route is intravenous (i.v.).

The complex PK is governed by target binding, target turnover, and redistribution from different tissues, diverse clearance mechanisms of relevance for proteins, most of which have to be considered for the vitreous as well as the systemic circulation, with different relevance for different doses. Vitreous sampling is generally not possible in humans. Although systemic PK data is available after both i.v. and IVT administration,[1] bioanalytical methods limit information especially for IVT; for example, due to lower limits of quantification or because of interactions of drug with endogenous target challenging the accurate quantification of free vs. bound drug. The i.v. treatment regimens for patients with cancer generally use higher doses than IVT regimens and are not studied in cross-over design to properly assess bioavailability. Thus, there are important knowledge gaps in the PK understanding of IVT administered proteins.

PHARMACOMETRIC SCALING APPROACHES

General knowledge regarding protein PK and PD in children has been summarized at different occasions, Edlund *et al.*[2] have recently provided a comprehensive review focusing on monoclonal antibodies.

Pharmacometric techniques have become standard to support pediatric development with model-based extrapolation and interpolation techniques to inform studies, especially with respect to dosing and sampling before clinical trial conduct, and to analyze data upon availability, respectively. Although extrapolation of efficacy and safety is preferred, often only extrapolation of PK can be informed and, if the exposure response relationship can be assumed to be independent of age, extrapolated PK may serve as a surrogate to support clinical trial decision making.

Population PK can be used to estimate exposure based on sparse samples and interpolate results. Underlying compartmental models are also frequently used for extrapolation using allometric scaling techniques, and have also been considered for protein therapeutics, see below. Physiologically based PK models are increasingly considered for pediatric extrapolation. Here, the separation of drug and system parameters promises a better integration of independent information. However, complex models introduce parameters that are sensitive but largely uninformed along the age-scale for IVT administered proteins, including diverse permeabilities or different clearance pathways dependent on FcRn or target expression.

VITREAL EXPOSURE

Spandau[3] commented on optimal dosage for intravitreal bevacizumab for ROP using geometric considerations of the eye and estimated that the volume of a premature infant eye is about one-third of the volume of the adult eye and that, consequently, a dose reduction by a factor of ~3 may be appropriate.

This would imply that eye volume changes linearly translate into vitreous exposure changes. Latter seems logical when considering maximal exposure (peak plasma concentration ($C_{max}^{vitreous}$)) largely determined by the initial volume of distribution given by the vitreous volume. Assuming that administered doses of anti-VEGFs generally by far exceed vitreous target concentrations, it is considered that the PD effects are not driven by maximal vitreal drug concentration. Rather integral exposure (area under the curve ($AUC^{vitreous}$)) or the length above a certain threshold are considered

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driving PD. Thereby, higher doses translate primarily into prolongation of effects, similar to higher binding affinity.[4]

Large proteins are primarily cleared toward the aqueous humor, where diffusion in the vitreous toward the posterior chamber in the front of the eye is considered rate limiting. Based on the semi-mechanistic model by Schmitt,[5] the elimination rate constant (k) is proportional to $(D^*A)/d^*V$, with the diffusion coefficient (D), the cross-section area (A), the length of diffusion path (d), and volume of distribution given by the vitreous volume (V). Whereas D is independent of the radius of the vitreous chamber (r), A, d, and V scale with the r^2, r, and r^3, respectively. It follows that k is proportional to r^{-2}, half-life is proportional to 1/k (i.e., r^2 or $V^{2/3}$), and clearance is proportional k^*V, which is proportional to r, or $V^{1/3}$. These considerations are related to and in line with those of Hutton-Smith and colleagues.[6]

Figure 1 shows the scaling of the vitreous volume with the different allometric exponents according to the above considerations. These can be directly translated into dose adaptions required to match adult maximal (light green diamonds) or integral exposure (dark green triangles). As can be seen, higher doses than indicated by linear scaling based on the vitreous volume will be required to match integral vitreal exposure and a dose reduction by a factor of three in preterm neonates will yield reduced integral exposure.

The above considerations assume a geometric similarity of the adult and pediatric eye, such as a constant relation of vitreous to total eye volume (for the volume estimations), or that A is scaling with r^2 (for the scaling of k). The considerations also assume that clearance into the posterior chamber is rate-limiting across age, and factors, such as permeation across the back of the eye tissue, of relevance for small molecules, or convection within the vitreous can be neglected.

SYSTEMIC EXPOSURE

The fraction of drug that becomes available in the systemic circulation after intravitreal clearance is primarily considered in the context of safety and may serve as an indirect means of estimating ocular PK (e.g., when flip-flop kinetics is assumed). Allometric scaling of clearance based on bodyweight (BW) is frequently applied to extrapolate systemic clearance or exposure, especially for small molecules. Although an allometric exponent of 0.75 for scaling clearance is often motivated or promoted with physiological considerations on the liver or general metabolic function, smaller and larger exponents, depending on the compound, have been shown to describe data better.[7]

Alternatively, especially for the very young, maturation functions have been suggested in combination with a fixed exponent of 0.75, to reflect clearance maturation as was also suggested for palivizumab,[8] one of the proteins comparatively well studied in children. The approach is common for small molecules where some processes, such as certain metabolizing enzyme activities, only develop after term. However, compartmental models, including maturation functions, do not properly separate blood flow, permeation, and intrinsic clearance processes, and maturation functions derived for one compound lump these parameters and may, therefore, not translate to other compounds.

Without specific data or knowledge, an exponent of 0.75 may still be considered the best choice for extrapolation,

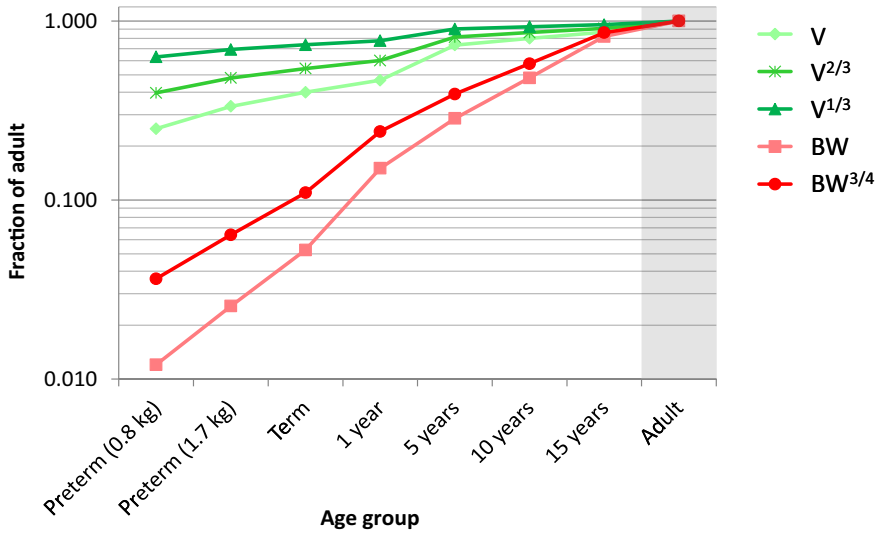

Figure 1 Age groups on the x-axis and fraction relative to adult values on the y-axis. Vitreous volume (V) is scaled in three scenarios distinguished by their allometric exponents. According to considerations described in the text, the scenario with the exponent 1 (light green diamonds) predicts 1/peak plasma concentration ($C_{max}^{vitreous}$) for constant doses, as well as dose adaptions required to achieve a constant $C_{max}^{vitreous}$; the scenario with the exponent 2/3 (green crosses) predicts intravitreal half-life time changes; the scenario with the exponent 1/3 (dark green triangles) predicts changes in intravitreal clearance and 1/area under the curve ($AUC^{vitreous}$) for constant doses, as well as dose adaptions required to achieve a constant $AUC^{vitreous}$. Bodyweight (BW) is scaled in two scenarios distinguished by their allometric exponents to indicate two scenarios for predicting systemic clearance, corresponding to $1/AUC^{plasma}$, as well as required dose adaptions to achieve a constant AUC^{plasma}. Based on data from the International Commission on Radiological Protection,[10] with an adult fraction V of 1/3 for 1.7 kg preterm neonates as estimated by Spandau[3] (corresponding to a birthweight around gestational age week 32) and V of 1/4 as assumed for 0.8 kg preterm neonates.

whereas an exponent of 1 may be considered conservative with respect to potential safety concerns. As indicated in **Figure 1**, clearance is predicted to become smaller with the higher exponent (red lines), extrapolating smaller doses for equivalent exposure. Exponents larger than 1 have been described for small molecules, however, there it has also been described that some metabolizing pathways are basically absent at term and only start developing upon birth. Although data are very limited for protein clearance pathways in children, involved degradation pathways include proteolytic mechanism conserved from yeast to man and it may be assumed that there is some level of constitutive clearance activity, including activity also in the developing fetus.

Interestingly, data for IVT bevacizumab[9] in patients with ROP show half-lives comparable to those observed in adults,[1] indicating a BW-based allometric exponent for clearance close to 1, when also the volume of distribution is assumed to scale with that exponent. This exponent also describes data for palivizumab reasonably well without an additional maturation function. Although more PK data will be required to better quantify and generalize these considerations, the examples support the notion that clearance pathways are active in preterm neonates.

DISCUSSION

The allometric functions for vitreal and systemic exposure shown in **Figure 1** also highlight a general challenge: whereas eye volume increases up to a factor of 3 or 4 from premature infants to adults, BW increases up to a factor of 100. Thus, pediatric IVT doses adjusted to provide vitreal exposures equivalent to adult exposures with approved doses for ophthalmologic indications will lead to increased systemic exposure in children compared to adults. Alternatively, IVT doses adjusted to provide equivalent systemic exposure will lead to decreased vitreous exposure with the potential of being subtherapeutic.

However, taking aflibercept as the anti-VEGF example with the highest binding affinity and best durability, it is not only approved for ophthalmologic indications (Eylea) but, as ziv-aflibercept in a different formulation with, for example, higher osmolarity, also in oncology (Zaltrap). The Zaltrap doses recommended in adult oncology indications are 4 mg/kg administered as an i.v. infusion, whereas Eylea doses recommended for adult ophthalmology indications are 2 mg administered IVT indicating a large safety margin for ophthalmologic indications. In this case and according to the above considerations, pediatric IVT doses extrapolated to match adult vitreal exposure would lead to systemic exposures above those extrapolated for recommended IVT doses but below those extrapolated for recommended i.v. doses. As with many therapeutic interventions in higher risk subjects, potential risks have to be evaluated against promised benefits.

The presented concepts relate to PK and may be carried forward to target binding as the primary mode-of-action in different adult and pediatric indications and may be extended to consider small molecules. Clinical end points may differ, however, and translation of efficacy across diseases and ages involving unknowns may also differ. Although more pediatric data will amass in the years to come, differences in study design, limited patient numbers, and sparsity of data collected are all inherent when evaluating investigational medications in children. Generally, presented concepts may be proven to be false, but then also offer a framework to interpret data beyond size-based effects considered here.

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