A Population Physiologically−Based Pharmacokinetic Model to Characterize Antibody Disposition in Pediatrics and Evaluation of the Model using Infliximab

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The authors confirm that the Principal Investigators for this paper are Valentina Shakhnovich and Adam Frymoyer, and that they had direct clinical responsibility for patients.

Running head: Population Pediatric PBPK model for mAbs

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What is already known about this subject:

- There is no consensus on whether the PK of antibodies differ significantly between adults and children.
- PBPK models can provide mechanistic insight into age-dependent changes in the PK of drug molecules.

What this study adds:

- A pediatric PBPK model combined with population approaches has been developed to enable *a priori* prediction of antibody PK across different age groups, and characterization of interindividual variability in the clinical PK of antibodies in pediatrics.
- The PBPK model suggests that higher doses and/or more frequent dosing of infliximab than the FDA-labelled dosing regimen may be needed to achieve desired trough concentrations of the antibody in majority of pediatric patients.

ABSTRACT

Aims: In order to better predict the pharmacokinetics (PK) of antibodies in children, and to facilitate dose optimization of antibodies in pediatric patients, there is a need to develop systems PK models that integrate ontogeny related changes in human physiological parameters.

Methods: A population-based physiological-based PK (PBPK) model to characterize antibody PK in pediatrics has been developed, by incorporating age-related changes in body weight, organ weight, organ blood flow rate, and interstitial volumes in a previously published platform model. The model was further used to perform Monte Carlo simulations to investigate clearance vs. age and dose-exposure relationship for infliximab.

Results: By estimating only one parameter and associated interindividual variability, the model was able to characterize clinical PK of infliximab from two pediatric cohorts (n=141, 4-19 years) reasonably well. Model simulations demonstrated that only 50% of children reached desired trough concentrations when receiving FDA-labelled dosing regimen for infliximab, suggesting that higher doses and/or more frequent dosing are needed to achieve target trough concentrations of this antibody.

Conclusion: The pediatric PBPK model presented here can serve as a framework to characterize the PK of antibodies in pediatric patients. The model can also be applied to other protein therapeutics to advance precision medicine paradigm and optimize antibody dosing regimens in children.

INTRODUCTION

Determination of an optimal dosing regimen for monoclonal antibodies (mAbs) in pediatrics is challenging, due to limited clinical experience with these molecules. Often, the adult dosing regimen is extrapolated to pediatrics based on body weight (BW) or body surface area (BSA).[1] However, the validity of this practice remains in question since there is a lack of consensus regarding whether the pharmacokinetics (PK) of mAbs differ significantly between adults and children.[2] It is reported that infants and young children achieve a lower plasma exposure of mAbs compared to adults when the same BW-based doses are given, while BSA-based dosing may result in higher drug exposure in infants compared to adults.[2-4] The higher fraction of extracellular fluid volume and faster rate of extravasation in young children compared to adults may contribute to differences in mAb disposition between these two populations.[5] In addition, reported low expression levels of FcRn and relatively higher concentrations of endogenous IgG in infants,[6,7] may contribute to higher elimination of mAbs in children. Additional differences in organ composition between adults and children may also affect tissue PK of mAbs in these populations, despite the plasma PK being similar across different age groups.[1,8,9] As such, there is a need to develop systems PK models that can mathematically integrate physiological changes reported between adults and children, and help with *a priori* prediction of mAb PK in the plasma and site-of-action of pediatric population.

Physiologically-based pharmacokinetic (PBPK) models are widely used systems PK models to establish exposure-response relationships for drugs, and to facilitate the selection of safer and more effective dose in special populations like pediatrics. We have developed a platform PBPK model for mAbs in the past, which can characterize the PK of mAb in various preclinical species and humans reasonably well.[10] In this study, we have extended our platform PBPK model towards pediatrics, and evaluated the ability of this model to predict

the PK of mAb in different age groups. In order to accurately capture the dynamic changes in physiological properties that happen throughout the childhood, we have used a series of recently published comprehensive equations that describe the relationships between organ weight, blood flow and age.[11] We have also included a continuous relationship between age and interstitial volume fractions of adipose[12,13] and muscle tissues,[14] which has been previously reported to change between infants and adults.

The ability of the pediatric PBPK model to predict the PK of mAbs was evaluated using clinical PK data of infliximab (IFX). In order to capture the inter-individual variability (IIV) observed in the clinical PK of mAbs, the PBPK model was further evolved to account for the variability in the key PK parameters.[10] In fact, such population PBPK modelling approach[15] has been applied towards adults,[16] but no such application exist for pediatric population yet. After establishing the population PBPK model, Monte Carlo simulations were used to critically evaluate how well different IFX dosing regimens commonly used in the clinical care achieve target IFX trough concentrations in children. Our simulations suggest that more intense dosing regimen may be needed to achieve the targeted trough concentrations of IFX in majority of the pediatric patients.

METHODS

Clinical Dataset for Model Validation

Clinical PK of IFX was obtained from two cross-sectional cohorts of children receiving intravenous IFX as part of routine clinical care at either the Children's Mercy Kansas City Infusion Center (cohort 1, IRB#14100454) or Lucile Packard Children's Hospital Stanford University (cohort 2, protocol# 44562). Both studies were approved by the local Institutional Review Board with waiver of consent. Patient demographics (**Table 1**) were comparable between the two cohorts. The details of the two cohorts are provided in Supplementary materials.

PBPK Model Structure and Physiological Parameters

A detailed structure (**Figure 1**) for the mAb PBPK model has been described in our previous publication.[10]

Mathematical equations describing the continuous relationships between age and BW, organ weight, and blood flow rate were obtained from our recent publication[11] and incorporated into the PBPK model (**Tables S1-S4**). As physiological properties are continuously changing within the pediatric age range, time-varying nature of physiology for each patient was accounted for using **equation 1**.

$$Age_i = Age_i^{ini} + time \quad (1)$$

Above, Age_i is the actual age of *i* patient and Age_i^{ini} is the initial age when this patient entered the study. Thus, we were able to derive the physiological parameters based on an individuals' age, BW and sex, which were changed for each patient in real-time. Mathematical equations (**equation 2**) that describe the change in fractional ratio of interstitial volume over total tissue volume (f_{IS}¿as a function of age were derived from published data.[8]

$$f_{IS} = a \cdot e^{b \cdot AGE} (2)$$

Above, *a* is 0.358 and 0.466 and *b* is -0.0459 and -0.0542 for muscle and fat, respectively. For all tissues across all ages, lymph flow was assumed to be 0.2% of plasma flow for a given tissue,[17] and endosomal volume be 0.5% of total tissue volume.[18]

PBPK Model Fitting and Parameter Estimation

IFX PK data from two cohorts were simultaneously fitted with the PBPK model. Data were censored if observed concentrations were below the LLOQ or above the ULOQ. The censoring interval for LLOQ and ULOQ were 0-0.5 ug/mL and 40-150 ug/mL, respectively. Most of the drug-specific parameters were taken from the previous publication[19] and assumed to be the same across the age range (**Table S5**). Only degradation rate of IgG that is unbound to FcRn (K_{deg} ¿ was estimated with Stochastic Approximation Expectation Maximization (SAEM) algorithm in Monolix (2019R2). K_{deg} was assumed to be lognormally distributed, and was characterized using the following equation:

$$K_{degi} = K_{degpop} \cdot \exp(\eta_i)$$

Above, $K_{degi}$and K_{degpop} are individual and typical values of population parameters, and η_i denotes the IIV random effects, which is normally distributed with a mean of 0 and a variance of ω^2_{Kdegi}. The tested residual error models included additive, proportional, and combined error models. Model qualification was guided by the precision of parameter estimates, goodness-of-fit (GOF) plots, % shrinkage, and visual predictive check (VPC) plots. Albumin levels, immunomodulator use (azathioprine, 6-mercaptopurine or methotrexate), C-reactive protein (CRP) levels, type of disease (IBD, JIA, uveitis), and study-type (cohort 1 vs 2) were tested as covariates on the K_{deg}, as these parameters have been previously reported to influence the PK of IFX.[20-26] Statistical tests were made using Pearson's correlation or ANOVA and Wald test, where *P* value <0.05 was considered statistically significant.

Monte Carlo Simulation

The pediatric PBPK model with the estimated value for K_{deg} was used in the mlxR package (version 4.0) in R software to simulate plasma and tissue PK profiles of IFX in 0-20 years old male and female children. The simulations accounted for IIV of K_{deg} without residual variability. For each dosing regimens in each age and sex group, we simulated the concentrations every 1 hr for 1000 patients for at least 8 doses to ensure reaching the steady-state. BW for the simulated patients in each age group were randomly sampled, assuming they were lognormally distributed, using the mean values and standard deviation reported from Centers for the Disease Control and Prevention (CDC).[27] We simulated five doses (5, 7.5, 10, 12, and 15 mg/kg) with different frequencies [every 4 wk (Q4W), every 6 wk (Q6W), and every 8wk (Q8W)]. The median, 5th and 95th percentiles were determined based on 1000 individual simulations, and 90% confidence intervals (CI) were derived using R software. Based on our clinical experience and published literature,[28] we examined IFX target trough concentrations of 3, 5, 7, and 16 ug/mL. Percentage of patients who achieved the target trough concentration for each of the different dosing regimens were calculated.

We also investigated the age vs. area under concentration-time curve (AUC) and age vs. clearance relationships for IFX. We calculated the AUC during one dosing interval at steady-state (AUC_{ss}) for each 1000 simulated patient, and calculated the median, 5th and 95th percentiles, and derived 90% CI for each age and sex group. Clearance and BW-normalized clearance were calculated by dividing dose (mg) or BW-based dose (mg/kg) by AUC_{ss}. The predicted AUC_{ss}, clearance, and BW-normalized clearance in different age groups were compared with clinically observed data reported in the literature.[20,29-33]

RESULTS

The PBPK model was able to characterize the PK of IFX from the two cohorts, with ages ranging from 4 to 19 years and BW ranging from 14.2 to 138 kg, reasonably well **(Figure 2)**. The K_{deg} was estimated with good precision [relative standard error (RSE) = 3.62%] and the optimized typical value of K_{deg} for IFX was 44.6 h^{-1}, which was slightly higher than previously published typical value for a mAb (15.3 h^{-1}).[19] The estimated IIV of K_{deg} was 33.6% (RSE = 8.62%) and shrinkage was 4.19%. A proportional error model best described the residual variability with an estimate of 32.3% (RSE = 10.4%). Covariate analysis demonstrated no statistically significant predictors of K_{deg} in the PBPK model using Pearson's correlation tests/ANOVA and Wald tests (**Table S6)**. In addition, no significant patterns were observed in the plots of predicted versus observed concentration when stratified by weight, sex, dosing regimens, and all covariates (**Figure S1-4**). No patterns were observed in delta plot for each covariate (**Figure S5**). As such, no covariates were included in the final population PBPK model.

Figure 2a shows the simulated plasma PK profiles of IFX in comparison with the PK of a nonspecific mAb in a 5-year-old child, at an FDA-approved dosing regimen of IFX in children (i.e., 5mg/kg Q8W). **Figure 2b** shows the simulated plasma PK profile of IFX from **Figure 2a** with 90% CI, which accounts for the IIV. The model predictions for several representative patients, across different age groups, disease types, and dosing regimens, along with their observed data, are shown in **Figure 2c-f**. The model was able to predict the PK of IFX across age, sex, dosing regimens, treatment indication (i.e., induction versus maintenance), and disease type, reasonably well.

Figure 3a shows the predicted versus observed concentrations of IFX. Before accounting for IIV stemming from K_{deg}, 70% of predictions were within 2-fold of the observed data,

whereas, after accounting for IIV stemming from K_{deg}, more than 99% of predictions were within 2-fold of the observed concentrations, as shown in **Figure 3b**. **Figure 3c-3f** shows the plots of population weighted residuals (WRES) and individual WRES with respect to the time and prediction, demonstrating that the points were scattered evenly around the horizontal zero-line without any pattern.

Figure 4 shows the median and 90% CI for clearance, BW-normalized clearance, and AUC_{ss} in children from 0 to 20 years of age, based on population simulation results. The PBPK model-predicted PK parameters were similar to the parameter values reported in different clinical studies (**Figure 4**). Although total clearance (mL/day) increased with age, BW-normalized clearance (mL/day/kg) and AUC_{ss} remained steady from 0 to 20 years of age, suggesting no significant change in systemic clearance or drug exposure during childhood growth and development.

The PBPK mode was also used to predict the percentage of children that achieves the target trough concentrations at different, commonly used, dosing regimens. The results from this analysis are summarized in **Table 2**. Of note, here we present results based on simulations conducted for 10-year-old males. However, the percentages were similar for children between 0-20 years and for both males and females (data not shown), and the information summarized in **Table 2** is applicable to children in general. We found that when receiving FDA-labelled 5 mg/kg Q8W regimen, only 30% and 50% of children achieved a trough concentration >5 ug/mL and >3 ug/mL, respectively. More intense dosing strategies (e.g., doses ≥10 mg/kg and/or drug frequency ≤Q6W) were required to achieve concentrations >5 ug/mL in >80% of patients. For higher target trough concentration (e.g., >7 ug/mL), more frequent dosing was more efficient in achieving target trough concentrations than dose escalation (i.e., mg/kg). For example, 10 mg/kg Q6W and 10 mg/kg Q4W dosing regimens resulted in >90% of children achieving trough concentrations >7 ug/mL and >16 ug/mL, respectively.

DISCUSSION

Whether the PK of mAbs in children is different from adults remains unclear. However, it is known that children have marked variability in the PK of mAb such as IFX, and target trough concentration achievement in children frequently requires higher IFX dosing for IBD, JIA, and uveitis.[34,35] To investigate if there are any physiological bases for observing the differences in the PK of mAb between the adults and pediatrics, and to develop a mathematical model that can characterize population PK of mAbs in pediatrics, we have extended our previously established platform PBPK model for mAbs towards pediatrics.[10] We have also evaluated the ability of this model to characterize the clinical PK of IFX (a prototype drug) in different age groups, across different BW, sex, disease types, and dosing regimen. In the future, we hope to apply our model to other mAbs commonly prescribed to children, in order to advance the field of pediatric precision therapeutics and optimize mAb dosing strategies for children.

While several population PK models of IFX have been published, PBPK models offer the potential opportunity to provide more mechanistic insight into age-dependent changes in the PK of mAb. In addition, two pediatric PBPK models of mAbs have been published recently.[36,37] However, these models do not estimate IIV in the PK mAbs based on observed individual data. To our knowledge, this is the first study that combines a pediatric PBPK model with population approaches, which allow the model to account for the dynamic changes in the physiology of children along with the IIV observed in the physiological parameters. This is an important feature of the model considering the variability in the PK data from pediatric populations and availability of only sparse data.[15] This approach allowed us to characterize the IIV in the clinical PK of model mAb IFX, following estimation of just one physiological parameter and associated variability. The PBPK model was able to well-

capture the IFX PK data across different ages, weights, and sex, and the estimated CV% of K_{deg} indicated high variability in the elimination parameter between pediatric patients.

We have incorporated a series of published equations that describe physiological parameters and age relationships into the PBPK model,[11] allowing us to account for real-time growth and maturation of the individuals throughout the time course of drug exposure. This time-variant PBPK model is especially relevant for chronic disorders that start in childhood and continue through adulthood (e.g., IBD, JIA, uveitis).[38] Age-dependent changes in interstitial volumes of adipose[12,13] and muscle[14] were also incorporated into the PBPK model. However, such information is not available for other tissues. It is important to note that this is a key parameter, since tissue interstitial volume directly determines the interstitial concentrations at the site-of-action. To evaluate the effect of this parameter, we further simulated tissue PK profiles of the mAb in 1 month, 1, 2, 5,10, and 15 years old children, as shown in **Figure S6**. We observed that the PK profiles of mAb in fat and muscle were significantly different among different age groups, and the PK was not always parallel to the plasma PK profiles. However, for other tissues that did not have age-dependent changes in interstitial volume, the PK profiles were similar across different age groups and parallel to the plasma PK profiles. As such, more information about age-dependent changes in tissue composition is needed to better understand tissue PK of mAbs in pediatrics.[5]

While this model serves as a foundation for the development of a platform pediatric PBPK model for mAbs, there are many other physiological parameters that could change with age that are not accounted for in this model, since there is no robust quantitative information that can facilitate mathematical characterization of the continuous changes in these parameters with age. Edginton et al.[39] have reported that extravasation rate of mAb is approximately 3 times higher in neonates than in adults, and organ capillary density follows a U-shaped relationship as a function of age. Both of these age-dependent changes in physiology can

affect mAb convection from plasma to interstitial space, and may be relevant to pediatric PBPK model. Lymphatic tissue has also been reported to change with age,[40] but specific lymph flow rate data in pediatrics is not available yet. Therefore, here we have assumed that pediatric lymph flow is proportional to the regional blood flow, and set it as 0.2% of the plasma flow[17] (i.e. similar to the adults). Other studies have set lymph flow as 2 to 2.6-fold higher in neonates than in adults based on allometry scaling from adult data[37] or animal studies,[39,41] highlighting the differences in PBPK approaches due to the gaps in the availability of pediatric physiological data. Of note, while the lymph flow is not a highly sensitive parameter when it comes to plasma PK of mAbs, changes in this parameter can lead to significant changes in tissue PK of mAbs, which is hard to measure in the clinic.

There are studies that also support that hematopoietic cells are involved in the homeostasis of mAb due to the expression and function of FcRn in these cells.[42,43] In the current PBPK model, however, only endothelial cells are assumed to express the FcRn. Since it is reported that hematopoietic cell concentrations at birth are about 2-fold higher than in adults and decline with age,[39,44] incorporating age-dependent mAb homeostasis via hematopoietic cells may be included in the pediatric PBPK model to refine it further.[39] Endogenous mAb can also compete with exogenous mAb for FcRn in the endosomal compartment.[45] The ontogeny of endogenous mAb has been reported previously, with the overall endogenous mAb concentration reaching 50% of the adult level by the end of the first year of life.[37] In addition, increased mAb clearance has been observed in patients with higher endogenous mAb burden associated with disease status.[46] While the current PBPK model did not account for the contribution of endogenous mAb, age-dependent and/or disease-related changes in endogenous mAb in the endosomal compartment can be easily included in the model. It is important to note that since all the PK data used in this investigation came from 4 year or older children, any model misspecification issues related to this assumption may not have

been noticeable during our analysis. Similarly, due to the paucity of data and lack of consistency in reported ontogeny related changes in FcRn expression[6,7] in animals and human,[47] here we have not incorporated age related changes in FcRn expression in the PBPK model. Hardiansyah et al.[48] used a minimal PBPK model to analyse the relationship between age, weight, and FcRn concentration, suggesting that FcRn expression was inversely proportional to age. However, other studies have conversely reported FcRn expression to increase with age until the end of puberty.[6,7] Ultimately, more studies are needed for quantitative measurement of FcRn in pediatric organs before incorporation of this data into the PBPK model. As such, several assumptions had to be made during the development of our PBPK model, due to the limited physiologic information available for paediatrics. However, since the model presented here is a platform model, it can be easily updated to account for any new information as it becomes available.

When IFX binds to its soluble target, tumour necrosis factor-α (TNF-α), the mAb-target complex can be eliminated by antibody-dependent cellular phagocytosis via Fcγ receptors,[3,49] in addition to the pathway of nonspecific cellular uptake followed by lysosomal degradation. We thus optimized K_{deg} value specific to IFX to characterize this additional elimination of IFX-target complex in the PBPK model. Since there is no evidence that the process of cellular uptake and mAb-FcRn interaction were different between IFX and a typical mAb, the values of CL_{up} and FcRn interaction-related parameters for IFX were set to be the same as typical mAbs, and fixed in the PBPK model. As prior clinical studies reported IFX to display linear PK when it is given at doses that are commonly used in clinical practice,[50] we did not include target-mediated drug disposition (TMDD) in the current PBPK model. Additionally, it has been previously reported that a wide range of TNF-α levels (0.1-100 pM) had minimal effect on IFX clearance according to sensitivity analysis.[37] For mAbs other than IFX, where targets

play important roles in drug disposition, one would need to incorporate soluble or membrane target into the platform pediatric PBPK model presented herein.

Anti-drug antibodies (ADA) may affect PK and pharmacodynamics (PD) of mAbs, but several factors such as limitations in ADA quantification, relative rarity of immunogenicity in clinical trials, and yet to be characterized tissue distribution of ADA-mAb complexes, make it challenging to incorporate ADA into physiologically-based PK/PD models.[51] Corresponding to the clinical observations that approximately 7-10% of patients develop ADA during maintenance therapy,[52] 11% of patients in our dataset developed ADA. Only half of these patients had detectable IFX concentrations and, as such, it was felt that the current dataset provided limited information about ADA and IFX PK relationship. However, data below LLOQ (primarily from patients with ADA) or above ULOQ were treated as interval censored data, in attempt to be comprehensive and include this relevant information into the PBPK model.

Monte Carlo simulations allowed us to account for IIV in K_{deg} and predict a range of concentrations for different pediatric ages and for various dosing regimens. The predicted systemic exposure (AUC_{ss}) and clearance, along with 90% CI, for patients of 0-20 years provided insight into whether linear adult-to pediatric extrapolation is appropriate and whether same BW-based dosing strategies can be applied to the entire pediatric age range. Although total clearance (mL/day) of IFX increased with age, when normalized by BW, clearance per kg remained unchanged across different age groups. This corresponded to the clinical observations that weigh-normalized IFX clearance in young patients (including infants with Kawasaki disease) was similar to the clearance in adult patients with RA,[29,53-55] and agreed with statements that clearance of most mAbs were comparable between adults and pediatrics after adjusting for body size.[56,57] However, our finding contradicted some review articles which concluded that most mAbs show a higher BW-normalized clearance in

pediatrics than in adults.[1,58] One reason for this discrepancy may be that the youngest patient in our dataset was only 4 years of age and data from younger children are needed to validate our simulated observations.

Of paramount importance to clinicians are the results from our population PBPK simulation. Using the standard FDA-labelled 5 mg/kg Q8W dosing of IFX, the majority of patients fall far below trough concentration of 5-16 ug/mL, which are considered to be adequate for IBD treatment,[59] associated with improved clinical outcomes based on clinical trial results,[60-62] recommended by clinical guideline,[63] and desired based on our own clinical experience. Our simulations also showed that higher doses and/or shorter dosing intervals are needed to achieve target troughs for paediatrics (Table 2).[59,64] This finding corresponded well with previous publications that have used population PK approach for dose optimization of IFX in children.[28,61]

In summary, here we have developed a population PBPK model to characterize pediatric PK of mAbs. Age related changes in BW, organ weight, and organ blood flow rate were incorporated into the PBPK model, along with the changes in interstitial volumes of adipose and muscle. The model was used to characterize clinical PK of IFX by estimating just one model parameter and associated IIV. The PBPK model was further used to simulate age vs. clearance and dose-exposure relationship for IFX. Our results suggest that more intense dosing regimen may be needed to achieve the targeted trough concentrations of IFX in majority of the pediatric patients.

CONFLICT OF INTEREST

RSF reports no conflicts of interest related to this work.

MLB reports no conflicts of interest related to this work.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Patient Demographics

Characteristic	Cohort 1 (N = 93)	Cohort 2 (N = 48)	All (N = 141)
Age			
Mean (SD)	14.7 (3.84)	14.4 (3.50)	14.6 (3.72)
Median (range)	16.0 (4.0-19.0)	15.0 (6.2-19.0)	15.0 (4.0-19.0)
Female sex, no. (%)	41 (44.1)	22 (45.8)	63 (44.7)
Weight, kg			
Mean (SD)	58.7 (23.2)	50.2 (17.1)	55.8 (21.6)
Median (range)	54.5 (14.2-138)	52.8 (21.0-87.7)	54.0 (14.2-138)
Diagnosis, no. (%)			
IBD	69 (74.2)	48 (100)	117 (83.0)
JIA	16 (17.2)	0	16 (11.3)
Uveitis	8 (8.60)	0	8 (5.67)
Treatment with induction, no. (%)	0	19 (39.6)	19 (13.5)
Use of immunomodulator, no. (%)	39 (41.9)	43 (89.6)	82 (58.2)
Dosing regimen			
< 5 mg/kg, no./no. total (%)	2/93 (2.06)	5/48 (10.2)	7/141 (4.79)
Q4W, no.	1	2	3
Q5-7W, no.	1	0	1
Q8W, no.	0	2	2
> Q8W, no.	0	1	1
5-7.5 mg/kg, no./no. total (%)	33/93 (34.0)	26/48 (53.1)	59/141 (40.4)
Q4W, no.	4	4	8
Q5-7W, no.	13	9	22
Q8W, no.	16	11	27
> Q8W, no.	0	2	2
7.5-10 mg/kg, no./no. total (%)	38/93 (39.2)	11/48 (22.4)	49/141 (33.6)
Q4W, no.	17	1	18
Q5-7W, no.	17	7	24
Q8W, no.	4	3	7
10-12.5 mg/kg, no./no. total (%)	20/93 (20.6)	6/48 (12.2)	26/141 (17.8)
Q4W, no.	12	1	13
Q5-7W, no.	4	4	8
>12.5 mg/kg, no./no. total (%)	4/93 (4.12)	1/48 (2.04)	5/141 (3.42)
Q4W, no.	3	1	4
Q5-7W, no.	1	0	1
Albumin (g/dL)			
Mean (SD)	4.31 (0.512)	3.51 (0.561)	4.03 (0.645)
Median (range)	4.30 (3.1-7.7)	3.60 (2.3-4.7)	4.10 (2.3-7.7)
CRP > 10 mg/dL, no. (%)	1 (1.08) [a]	15 (31.3)	16 (11.4)
ADA detectable, no. (%)	6 (6.45)	4 (8.33)	10 (7.09)

[a] Data were not available for 13 patients. IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; CRP, C-creatinine protein; ADA, anti-drug antibodies.

Table 2. Percentage of pediatrics predicted to achieve target infliximab trough concentrations by dosing regimen

	Percentage (%) achieved target C_{trough}			
	> 3 ug/mL	**> 5 ug/mL**	**> 7 ug/mL**	**> 16 ug/mL**
5 mg/kg				
Q8W	73.7	50.8	30.1	2.80
Q6W	94.1	82.8	66.3	16.7
Q4W	99.8	98.7	95.9	60.1
7.5 mg/kg				
Q8W	87.2	68.7	53.9	13.5
Q6W	97.9	92.6	85.0	38.9
Q4W	100	99.6	98.7	85.0
10 mg/kg				
Q8W	91.9	80.8	66.7	23.0
Q6W	98.8	96.7	91.3	58.1
Q4W	100	99.8	99.6	93.3
12.5 mg/kg				
Q8W	94.4	87.0	76.0	34.6
Q6W	99.4	97.9	95.4	70.2
Q4W	100	100	99.8	96.7
15 mg/kg				
Q8W	96.6	89.4	82.9	46.4
Q6W	99.6	98.7	97.0	79.5
Q4W	100	100	99.8	98.0

Percentages were calculated based on the results of 1000 simulations in 10-year-old male populations accounting for inter-individual variability and without residual error.

FIGURE LEGENDS

Figure 1. (A) Structure of the whole-body platform PBPK model of mAb in pediatrics. All organs are represented by a rectangular compartment and connected in an anatomical manner with blood flow (*solid arrows*) and lymphatic flow (*dashed arrows*). Organ weights and organ blood flow rates in each organ is a function of age, body weight, and sex. **(B)** Structure of the organ level PBPK model of mAb in pediatrics. Each organ within the model, except blood and lymph node, is divided into plasma, blood cell, endosomal, interstitial and cellular sub-compartments. Drug-specific parameters were fixed and taken from a previous publication (**Table S1**) and only degradation rate of FcRn unbound IgG (K_{deg} ¿ was estimated accounting for inter-individual variability.

Figure 2. (A) Comparison of plasma PK profiles of a typical antibody and infliximab. Figure displays simulated plasma PK profiles of a typical antibody and infliximab in a 5-year-old male (weight 18.3 kg) after receiving infliximab 5 mg/kg at weeks 0, 2 and 6 and then every 8 wks. **(B)** Population simulation of infliximab plasma PK profiles. Simulated infliximab plasma PK profiles in the 5-year-old male pediatric population (weight 18.3 kg, CV 14.5%) accounting for inter-individual variability of K_{deg}. The black line represents the median, and the shaded area represents the 90% CI. (**C-F**) Represent predicted and observed infliximab plasma PK profiles in pediatrics for different ages, sex, and treatment indications (i.e., induction vs. maintenance). Figure displays individual prediction (*solid lines*) and observed infliximab concentration (*solid dots*) for (**C**) 4-7 years every 4 wks maintenance therapy; (**D**) 8-12 years every 4-8 wks maintenance therapy; (**E**) 13-20 years every 5-8 wks maintenance therapy; (**E**) 15 years induction therapy.

Figure 3. Diagnostic plots. The plots of population (A) and individual (B) prediction versus observed concentration along with the identity line (*solid line*) and 2-fold boundary lines

(*dashed lines*) stratified by different age groups. The plots of population (C) and individual (D) weighted residuals versus time since first dose, and population (E) and individual (F) weighted residuals versus observations, along with spline interpolation (*blue lines*).

Figure 4. Relationships between age and PK parameters. The plots display PBPK model simulated values of (**A**) total clearance (mL/day), (**B**) body weight normalized clearance (mL/day/kg), and (**C**) $AUC_{0\text{-}tau}$ at steady state for infliximab in 0-20 years old subjects, superimposed over the published data collected from [20,29-31] (red circles). The black line and the shaded area represent the median and the 90% CI, respectively.