



Q.Zhao^{1,2}, M.M.E Jongsma ², S.A. Vuijk² , B.C.M. de Winter^{1,2}, T.Preijers ^{1,2}, L. de Ridder ²

1 Rotterdam Clinical Pharmacometrics Group, Rotterdam, The Netherlands; 2 Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands; 3 Department of Paediatric Gastroenterology, Erasmus Medical Center/Sophia Children's Hospital, Rotterdam, the Netherlands

CONCLUSION

Pediatric inflammatory bowel disease (IBD) patients (≤10 years), demonstrated a higher infliximab (IFX) clearance (CL) than pediatric patients (>10 to <17 years) and adults, with albumin and CRP explaining the variability of CL. The differences obtained across the IFX assays did not affect overall drug exposure. To maintain trough concentrations above 5 mg/L in pediatric patients (≤10 years), a dosing interval of 4 weeks is required.

RATIONALE

Our previously published study indicated that approximately 72% of PIBD patients below 10 years old experience low trough concentrations and younger pediatric patients may require higher doses to attain similar target trough levels. Although population PK (popPK) analyses allow us to describe such physiological changes, no popPK analyses in pediatric IBD patients (≤10 years) have yet been published in literature. For measuring IFX concentrations in serum, multiple Enzyme-Linked Immunosorbent Assay (ELISA) assays have been established. While a general target trough level of >5 µg/mL is widely accepted across assays, inter-assay variability has been reported in research settings, suggesting that therapeutic interpretation may be influenced by the specific assay used.

AIM

As the currently published popPK analyses for IFX only included data obtained from a single ELISA assay and pediatric patients above 10 years old, this study aimed to investigate the popPK of IFX in pediatric IBD patients (≤10 years) and to assess the effect of different IFX assays on the accuracy of PK parameter estimation.

METHODS

- ❖ Clinical data: 104 very young pediatric (< 10 years old) with 2150 infliximab concentrations were obtained; 6 different ELISA assays were included.
- ❖ Evaluating the predictive performance of published popPK models

$$rMPE\ (\%) = \frac{1}{n} \sum_{i=1}^n \frac{C_{pred,i} - C_{obs,i}}{C_{obs,i}} \times 100(\%)$$
$$rRMSE\ (\%) = \sqrt{\frac{1}{n} \sum_{i=1}^n \left(\frac{C_{pred,i} - C_{obs,i}}{C_{obs,i}} \right)^2} \times 100(\%)$$

- ❖ Base model construction and covariate analysis (\$error block were stratified by ELISA assays; BLQ data is 12%, M3 method was used)
- ❖ CL were compared between young/old pediatric patients and adults.
- ❖ Evaluating the impact of multiple IFX assays (rMPE was obtained for each assay; post-hoc individual CL and AUC_{W6-14} were compared)
- ❖ Monte Carlo simulations were performed to explore alternative dosing strategies.

RESULTS

- 1.This study addresses the first population pharmacokinetic (popPK) analysis of infliximab administered to pediatric inflammatory bowel disease (IBD) patients <10 years of age.
2. The best performing published model showed values for rMPE and rRMSE were 33.73% and 1189.59%, which rendered all models inadequate for our study population.
- 3.Pediatric IBD patients (≤10 years) exhibit higher infliximab clearance (CL) than older children (>10 to < 17 years old) and adults.
- 4.Assessment of measured IFX concentrations using different IFX assays simultaneously demonstrated that differences across assays had no significant effect on drug exposure.
- 5.A dosing interval of 4 weeks is needed to maintain IFX trough concentrations above 5 mg/L in pediatric IBD patients (≤10 years).

Table 1. Parameter estimates for the base model, final model and bootstrap analysis of IFX in pediatric IBD patients ≤ 10 years old.								
Parameters	Base model estimates			Final model estimates			Bootstrap of the final model	
	Estimate	RSE (%)	Shr. (%)	Estimate	RSE (%)	Shr. (%)	Median	95% CI
Population PK parameter								
CL (L/day/65kg)	0.804	11%		0.779	7%		0.775	0.615 - 0.943
V ₁ (L/65kg)	17.6	17%		17.2	16%		17.1	10.831 - 23.629
V ₂ (L/65kg)	1.21 (FIX)			1.21 (FIX)			1.21 (FIX)	
Q (L/day/65kg)	0.0697 (FIX)			0.0697 (FIX)			0.0697 (FIX)	
Inter-individual variability								
CL (%CV)	46.3%	10%	14%	41.1%	12%	15%	39.8%	26.88% - 52.35%
Covariate relationships								
ALB on CL				-0.758	32%		-0.754	-1.270 - -0.246
CRP on CL				0.0545	36%		0.0541	0.016 - 0.093
Residual unexplained variability								
Prop. RUV for Sanquin	0.927	33%	42%	0.951	27%	33%	0.941	0.387 - 1.516
Prop. RUV for Immundiagnostik	0.805	11%	16%	0.781	9%	14%	0.777	0.603 - 0.959
Prop. RUV for Caltag	0.665	8%	13%	0.617	9%	10%	0.617	0.509 - 0.724
Prop. RUV for Matrix biotek	0.525	18%	6%	0.591	20%	6%	0.584	0.320 - 0.862
Prop. RUV for Shomron Ben-Horin	0.902	25%	27%	0.889	25%	25%	0.848	0.088 - 1.690
Prop. RUV for Promonitor	1.11	35%	12%	0.914	31%	11%	0.861	-0.021 - 1.848

IFX: infliximab; IBD: inflammatory bowel disease; RSE: relative standard error; Shr.: shrinkage; CI: confidence interval; CL: clearance; V₁: volume distribution for central compartment; V₂: volume distribution for peripheral compartment; Q: inter-compartmental clearance; ALB: albumin; CRP: C-reactive protein; RUV: residual unexplained variability; CV: coefficient of variation; Prop.: proportional error.

Table 2. Infliximab PK parameters comparison between pediatric IBD patients (≤10 years old) and pediatric IBD patients (>10 and < 17 years old).							
	Refined model	Chung et al. (2023)	Fasanmade et al. (2011)	Bauman et al. (2019)	Xiong et al. (2021)	Susana et al. (2024)	Colman et al. (2017)
Population	Young children	Old children	Young and old children	Old children	Old children	Young and old children	Old children
Age (years)	Median (range), 8.2 (1.2~10.0)	Median (IQR), 12.7 (10.1, 14.6)	Median (range), 13 (6~17)	Mean ±SD, 14.5 ±3.6	Mean ±SD, 13 ±3.7	Median (range), 13 (1-16)	Median (IQR), 14.0 (11.1, 16.0)
Number of patients	104	85	112	135	78	30	128
Covariate relationships on CL	ALB, CRP	ALB, CRP, SEX, ATI	ALB, ATI, IMM	ALB, ATI, ESR	ALB, ESR, CD64, ATI	ESR, ALB, FC	ALB, ESR
CL	0.779 L/day/65kg	0.299 L/day/37.4kg	0.353 L/day/65kg	0.293 L/h/65kg	0.331 L/day/65kg	0.158 L/day/46.4kg	0.0151 L/day/65kg
V1	17.2 L/65kg	3.3 L/37.4kg	3.5 L/65kg	3.52 L/65kg	2.97 L/65kg	0.6750 L/46.4 kg	4.44L L/65kg
V2	1.21 L/65kg	1.21 L/37.4kg	1.898 L/65kg	1.9 L/65kg	2.84 L/65kg	1.19 L/46.4 kg	1.94 L/65kg
Q	0.0697 L/day/65kg	0.0697 L/day/37.4kg	0.299 L/day	0.229 L/day/65kg (fixed)	0.229 L/day/65kg (fixed)	0.0696 L/day/46.4kg	0.229 L/day

PK: pharmacokinetics; IBD: inflammatory bowel disease; CL: clearance; V₁: volume of distribution for central compartment; V₂: volume of distribution for peripheral compartment; Q: inter-compartment clearance; ALB: albumin; CRP: C-reactive protein; ATI: antibody to infliximab; IMM: immunomodulatory; ESR: Erythrocyte Sedimentation Rate; CD64: Fc gamma receptor I; FC:feecal.

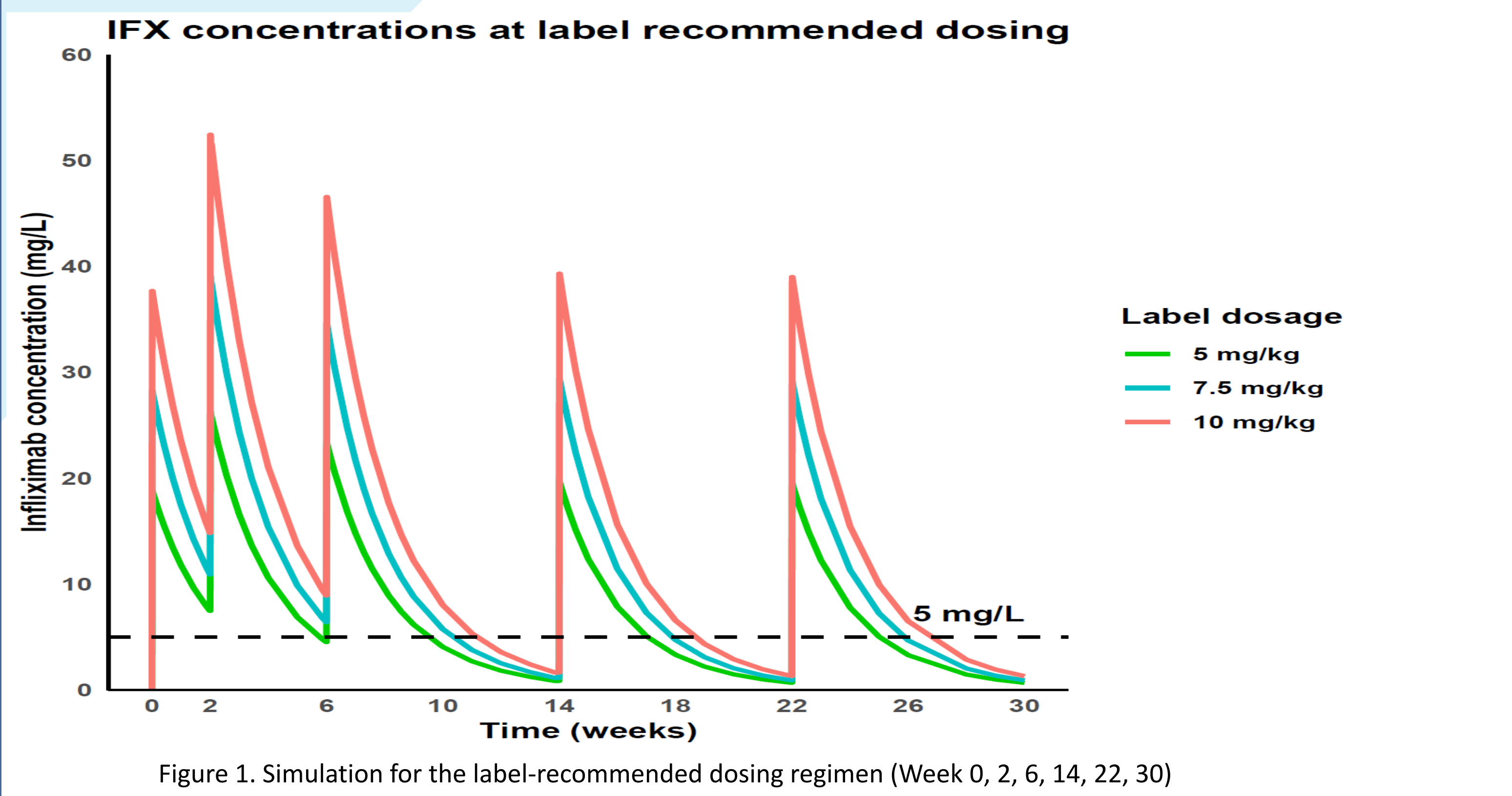


Table 3. Comparison for IFX prediction error, individual CL and calculated AUC _{week6-14} by different IFX assays.				
Assay A	Assay B	P-value (pairwise Wilcoxon test)		
		PE	Individual CL	AUC _{week6-14}
Immundiagnostik	Sanquin	0.26	0.03	0.80
Immundiagnostik	Promonitor	0.06	0.08	0.70
Immundiagnostik	Caltag	0.84	0.35	0.85
Immundiagnostik	Shomron Ben-Horin	<0.05	0.05	0.87
Immundiagnostik	Matrix biotek	0.89	0.16	0.39
Sanquin	Promonitor	0.64	0.94	0.89
Sanquin	Caltag	0.22	0.13	0.66
Sanquin	Shomron Ben-Horin	0.86	0.98	0.93
Sanquin	Matrix biotek	0.53	0.97	0.55
Promonitor	Caltag	0.06	0.26	0.56
Promonitor	Shomron Ben-Horin	0.91	0.97	0.83
Promonitor	Matrix biotek	0.18	0.84	0.64
Caltag	Shomron Ben-Horin	<0.05	0.23	0.72
Caltag	Matrix biotek	0.86	0.37	0.30
Shomron Ben-Horin	Matrix biotek	0.08	0.82	0.49

IFX: infliximab; PE: prediction error; CL: clearance; AUC_{week6-14}: area under the curve between week 6 -14.

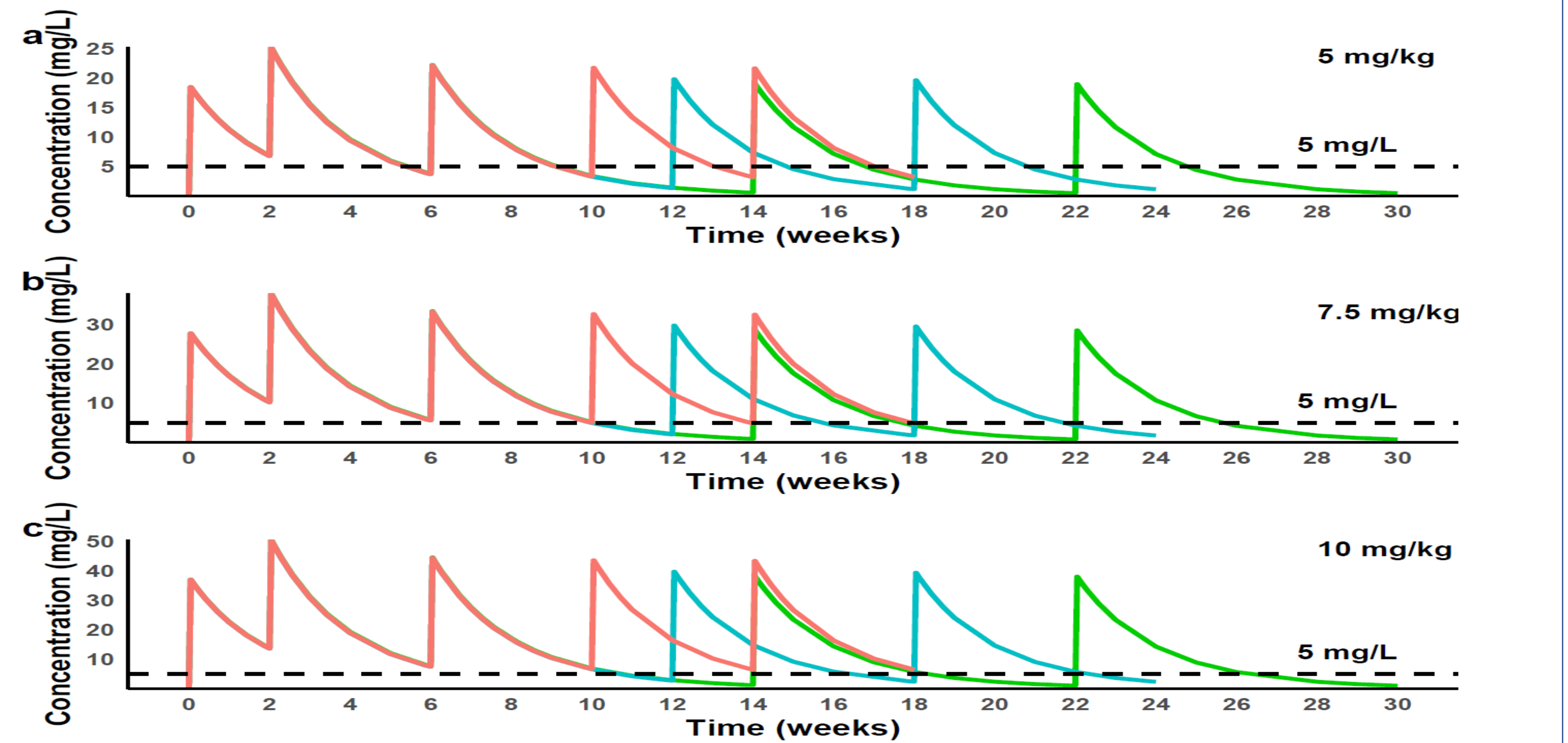


Figure 2. Simulation for the 5-year-old pediatric IBD patients receiving different dosing strategies. a) the dosage is 5 mg/kg; b) the dosage is 7.5 mg/kg; c) the dosage is 10 mg/kg.