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Infliximab Pharmacokinetics are Influenced by Intravenous Immunoglobulin Administration in Patients with Kawasaki Disease

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ABSTRACT

Background Infliximab, a monoclonal antibody directed against tumor necrosis factor-α, is being evaluated as adjunctive therapy to intravenous immunoglobulin (IVIG) for treatment of young children with acute Kawasaki disease (KD).

Objective The aim of this study was to develop a population pharmacokinetic (PopPK) model for infliximab in children with KD and to evaluate the impact of covariates on infliximab disposition. Specifically, we wanted to investigate the effect of body weight and IVIG administration on pharmacokinetic parameters.

Methods In the current PopPK analysis, 70 subjects with median (interquartile range) age of 2.9 (1.3-4.4) years were included from two randomized controlled trials. Infliximab concentration-time data were best described by a two-compartment model with first-order elimination using NONMEM 7.3.

Results The clearance, volume of distribution of the central (V1) and peripheral (V2) compartment, and intercompartmental clearance estimates (95% confidence interval) from the PopPK analysis were 0.117 (0.091-0.134) L/day, 0.801 (0.545-0.960) L, 0.962 (0.733-1.759) L, and 0.692 (0.482-1.779) L/day, respectively. Allometric body weight was included on all parameters of the structural model and a covariate analysis revealed that administering infliximab after IVIG, as opposed to before, resulted in a 50% decrease in V2.

Conclusions Our study shows that the timing of infliximab administration relative to IVIG administration affects the disposition of the monoclonal antibody. These results may have important implications for other monoclonal antibodies administered in combination with IVIG for treating inflammatory diseases.

KEY POINTS

1. KD can cause life-threatening coronary artery aneurysms and is the leading cause of acquired heart disease in children. Infliximab is being evaluated as adjunctive therapy in acute KD because 10-20% of children are resistant to first-line IVIG therapy and this is the first report of a PopPK analysis of infliximab in children with acute KD.

2. When assessing the pharmacokinetics of infliximab in children with acute KD and evaluating the impact of covariates on infliximab disposition and dosing, we found that administering infliximab after IVIG, as opposed to before, results in a 50% decrease of V2.

3. Our study shows that timing of infliximab relative to IVIG administration affects the disposition of the biologic. As biologics are increasingly used in the treatment of inflammation-mediated diseases, data regarding impact and timing of IVIG administration on disposition of biologics is important.

1 INTRODUCTION

Kawasaki disease (KD), the leading cause of acquired heart disease in children, is a self-limited vasculitis of unknown cause and is typically diagnosed in children under the age of five. Symptoms consist of fever, strawberry tongue or erythematous cracked lips, rash, swollen extremities, cervical lymphadenopathy, oropharyngeal erythema, and injected conjunctivae. If left untreated, KD results in coronary artery aneurysms in up to 25% of children. The mainstay of treatment consists of high-dose intravenous immunoglobulin (IVIG) in combination with aspirin resulting in rapid improvement of clinical symptoms and a reduced incidence of coronary artery aneurysms in most children.(1) However, 10-20% of children with KD have persistence or recrudescence of fever following IVIG administration.(2) Since tumor necrosis factor-α (TNF) concentrations are elevated in the acute phase of KD and are highest in children who subsequently develop coronary artery aneurysms, this pro-inflammatory cytokine was proposed as a potential therapeutic target.(3, 4) Intensification of initial therapy with infliximab, a chimeric IgG1 anti-TNF monoclonal antibody, was shown to be safe and resulted in faster resolution of fever and fewer days of hospitalization.(5-7) These results were corroborated in a larger phase 3, randomized, double-blind, placebo-controlled trial in which 5 mg/kg infliximab intravenously (IV), in addition to standard therapy (IVIG 2 g/kg), led to fewer days of fever, decreased IVIG infusion reactions and a more rapid decrease in C-reactive protein and left anterior descending coronary artery (LAD) Z score as compared to treatment with IVIG alone.(8)

Although infliximab is administered by weight, a previous population pharmacokinetic (PopPK) analysis in pediatric and adult Crohn’s disease suggested

that dosing by weight may lead to underdosing in children or adults with low weight compared with adults of greater weight. This study, however, did not include children younger than 6 years of age, the most common age group to have KD.(9) In addition, infliximab is administered in combination with IVIG in children with KD, which may result in saturation of the neonatal Fc receptor (FcRn), potentially leading to increased clearance and/or impaired tissue distribution of the therapeutic antibody. FcRn has been shown to be important for IgG and albumin homeostasis as it protects these proteins from catabolism through the reticuloendothelial system, which partly explains their long half-lives.(10) Although the FcRn is non-saturable under physiologic conditions, it has been suggested that high doses of IgG (1-2 g/kg) may lead to substantial increases in the rate of elimination of exogenous and endogenous IgG by shunting IgG from the recycling pathway to the elimination pathway.(11)

Pharmacokinetics (PK) of infliximab in children with KD have been described by a non-compartmental analysis.(5) However, PopPK of infliximab in children with KD have not been described. Thus, by combining data from two randomized controlled trials, we sought to develop a PopPK model for infliximab in children with KD. In addition, we aimed to evaluate the impact of covariates on infliximab disposition, specifically investigating the effect of weight and IVIG administration on PK parameters.

2 METHODS

2.1 Data Assembly

Demographics, disease parameters and pharmacological data of patients receiving infliximab for the treatment of KD, originated from two multicenter, randomized, prospective clinical trial cohorts, totaling 70 subjects.(5, 8)

The study by Burns and colleagues recruited subjects with KD who were refractory to a first course of IVIG 2 g/kg given 48 hours to 7 days before being randomized to receive either study drug (infliximab 5 mg/kg at 1 mg/mL IV over 2 hours) or a second infusion of IVIG 2 g/kg. Time points of sampling for serum infliximab concentration assessment were: baseline (post-initial IVIG, pre-infliximab), 2 hours, 24 hours, day 7, day 14, and day 28 after administration of infliximab. In total, 12 subjects received study drug and 4 subjects crossed over to infliximab after failing to become afebrile after the second course of IVIG 2 g/kg and were included in the current PopPK analysis.

The study by Tremoulet and colleagues recruited subjects with KD who were randomized to receive either study drug (infliximab 5 mg/kg at 1 mg/mL IV over 2 hours) or to receive placebo (normal saline 5 mL/kg) as first line therapy. Immediately after administration of study drug or placebo, all subjects received IVIG 2 g/kg over the course of 10-12 hours. Time points of sampling for serum infliximab concentration assessment were: at baseline (prior to any treatment), 36 hours (24 hours after IVIG administration), day 14, and day 35 after administration of infliximab. Serum samples were available from a subset of 54 of 98 subjects who received study drug and were included in the current PopPK analysis.

In cases where the covariate value was not recorded at baseline or any time prior to baseline, the median value calculated from otherwise similar subjects in the population dataset was used. Serum infliximab concentration results with no recorded actual sample time were excluded from the analysis, as well as sample time records with no associated serum infliximab concentration.

All study protocols and consent forms were approved by institutional review boards or ethics committees at the study sites, and studies were conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki. All patients or legal guardians provided written informed consent or assent as appropriate before study participation.

2.2 Laboratory Analysis

In the study by Burns and colleagues, serum infliximab concentrations were measured by Janssen Biotech, Inc., formerly Centocor Biotech, Inc. using an in-house enzyme linked immunosorbent assay (ELISA) with a lower limit of detection of 0.10 µg/mL, as previously published.(12) In the study by Tremoulet and colleagues, serum infliximab concentrations were measured by the *Conformité Européenne* (CE)-marked RIDASCREEN® IFX Monitoring ELISA (R-Biopharm, Darmstadt, Germany) with a lower limit of quantification of 0.5 µg/mL, as previously published. (13, 14) Both assays were validated according to the United States Food and Drug Administration and/or the European Medicines Agency guidances and showed excellent agreement in a recent comparative study (intra-class correlation coefficient 0.960; 95% confidence interval 0.930 – 0.977).(15) Data below the limit of quantification were excluded from the analyses.

Plasma concentrations of soluble TNF receptor (sTNFR)-1 were measured as a proxy for soluble TNF (16) using Quantikine ELISA Human TNF RI Immunoassay (R&D system, Minneapolis, MN) per manufacturer's instructions.

2.3 Population Pharmacokinetic Model Development

Non-linear mixed-effects modelling software (NONMEM version 7.3) was used to analyze the data. During development, the PopPK models were assessed for appropriateness using conventional criteria, including convergence status, likelihood ratio test, parameter precision, assessment of goodness-of-fit. A model was accepted only if it converged with a successful covariance step.

The structural PK model component was established first. The base model consisted of a 2-compartment PK model with first-order elimination parameterized in terms of estimated clearance (CL), volume of distribution of the central compartment (V1), inter-compartmental clearance (Q), and volume of distribution of the peripheral compartment (V2) (ADVAN4, TRANS4) using the FOCE-I fitting subroutine. Allometric body weight was included on all parameters (CL, V1, Q, and V2) of the structural model. Covariance of CL, V1, Q, and V2 was accounted for using a full omega block structure. This base model was found to adequately describe the observed serum infliximab concentration-time data.

Then, the stochastic model (e.g. inter-individual variability model component and the residual error model component), was introduced. Inter-individual variability was included on CL, V1, and V2. The differences between model-predicted and observed concentrations were assessed with a constant coefficient of variation proportional error model.

Next, the covariate model component was introduced, which describes the influence of fixed effects (e.g., demographic factors and baseline laboratory values) on PK parameters. The covariate analysis was performed using baseline values that were normalized to the population median value. Demographic covariates for the PopPK

dataset were: age (years), body weight (kg), sex, race (White, African American, Asian, and other), C-reactive protein (mg/dL), white blood cell count (x10^9/L), days of illness at enrollment, and sequence of IVIG before or after infliximab administration.

Continuous covariates, such as albumin concentration, were modelled using the general equation:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} cov_i^{\theta i} \ ,$$

where *TVP* represents the typical value of the model-predicted PK parameter, for example, CL, for the 'typical' individual with covariate value(s) cov_i; P_{pop} represents the population central tendency for the PK parameter *TVP*; cov_i represents the individual value for the covariate normalized to a reference value; and θ_i represents a scale factor relating the covariate to the structural parameter.

Categorical covariates, such as sex, were modelled using the general equation:

$$TVP = P_{pop} \cdot \prod_{i=1}^{n} (1 + cov_i \cdot \theta_i) \ ,$$

where cov_i is fixed to 1 for the test subgroup (e.g. females) and θ_i represents a scale factor relating the covariate to the structural parameter.

Covariate analysis was performed by examining the influence of each covariate alone on the base model. The resulting single, nested covariate models were ranked by the *p*-value for the likelihood ratio test comparison with the base model. Covariates with a $p < 0.01$ (≥6.64 reduction in the minimum objective function value reported in NONMEM) were considered in more detail and pooled into the full multivariable model assessment. The full model was subjected to a backward elimination process, where each covariate was eliminated using $p = 0.001$ for the likelihood ratio test comparison. Removal of a covariate was considered significant at $p < 0.001$, i.e., only covariates

associated with an increase of at least 10.83 in objective function value were retained in the model.

After all covariates that did not meet the criteria for retention were eliminated, the final model was evaluated for model performance. For a visual predictive check, infliximab serum concentrations were simulated 1000 times with dose and covariate data used in the model development data set, using the same sampling times. The simulated and observed data were then compared graphically. Non-parametric bootstrap replicates of the final PK model (N=1000) were generated to evaluate parameter precision. Runs that converged successfully were used to generate median and 95% CIs of the model parameters and impact of the covariates on these parameters. Simulations were conducted with Berkeley Madonna software (Version 8.2).

2.4 Statistical Analyses

In a subsequent analysis, our aim was to identify factors that influence early (36 hour) infliximab exposure specifically, as this time window is believed to be critical to treat patients with acute KD. Because of the overall small sample size, stringent inclusion criteria for covariates in the PopPK model ($p < 0.001$) and the 36-hour infliximab serum concentration being highly dependent on several PK parameters, we wanted to minimize the risk of a type-2 error. Hence, we conducted a multivariable logistic regression to identify covariates associated with the infliximab serum concentration at 36 hours in a subset of patients, for whom additional variables were available: age at onset of KD, sex, body weight, illness day at initial treatment, IVIG resistance, white blood cell count, absolute band count, erythrocyte sedimentation rate,

C-reactive protein, hemoglobin Z score normalized for age, platelet count, albumin, alanine aminotransferase, gamma-glutamyl transferase, baseline sTNFR1 levels, baseline LAD and right coronary artery (RCA) Z score, ΔZ score (baseline – 5 weeks) of both LAD and RCA, and maximum Z score. Factors not significant at the 0.05 level were removed from the model by backwards elimination. The analysis was performed using IBM SPSS Statistics version 22.0 for Windows (IBM, Chicago, IL). Graphical presentation of data was conducted with GraphPad Prism (Version 7.0) (GraphPad Software, San Diego, CA).

3 RESULTS

3.1 Pharmacokinetic Analysis Data Set

The final PK analysis data set consisted of 70 subjects with 175 infliximab concentrations, or an average of 2.5 concentrations per patient. Patients' demographic and clinical characteristics at baseline are shown in Table 1. The median (interquartile range, IQR) age was 2.9 (1.3-4.4) years, the median (IQR) body weight was 14.0 (10.0-18.2) kg and most patients were White (64.3%).

3.2 Population Pharmacokinetic Modelling Results

The PopPK parameter estimates of the final model for a typical KD patient with body weight of 14 kg were for CL = 0.117 L/day, V1 = 0.801 L, Q = 0.692 L/day, and V2 = 0.962 L (Table 2). Infliximab exhibited an inter-individual variability for CL, V1, and V2 of respectively 36.5%, 30.4%, and 16.3%. Shrinkage on CL, V1, and V2 were respectively 25.5%, 17.1%, and 28.0% while the epsilon shrinkage was 25.6%. The

acceptable shrinkage on CL, V1, and V2 implied that individual variance estimates of these parameters would be reliable.

The allometric relationships between the PK parameters of infliximab and weight changes were considered in the structural model by multiplying the PK parameters with weight, exponentiated by a factor of 0.75 for CL and Q, and a factor of 1 for V1 and V2. Following the stepwise covariate selection process, only the sequence of IVIG administration before or after 5 mg/kg infliximab IV was found to be associated with V2. More specifically, administering IVIG before infliximab resulted in an almost 50% reduction of V2 in comparison to administrating IVIG after infliximab.

The equations for the final model were as follows:

$$CL = 0.117\ L/day \cdot \left(\frac{WT}{14\ kg}\right)^{0.75},$$

$$V1 = 0.801\ L \cdot \left(\frac{WT}{14\ kg}\right)^{1},$$

$$V2 = 0.962\ L \cdot \left(\frac{WT}{14\ kg}\right)^{1} \cdot (1 + IVGF \cdot -0.497),$$

$$Q = 0.692\ L/day \cdot \left(\frac{WT}{14\ kg}\right)^{0.75},$$

where *WT* = body weight, and *IVGF* = 1 for patients who received an IVIG infusion first, before the infliximab infusion.

3.3 Pharmacokinetic Model Evaluation

Goodness-of-fit plots of the final model are shown in Supplementary Figure S1. Diagnostic plots for the final PopPK model are shown in Supplementary Figures S2-S4. There was no apparent bias or obvious model misspecification in these diagnostic plots, suggesting that the model adequately described the serum infliximab concentration-time data.

A total of 1000 non-parametric unstratified bootstrap replicates were generated for the final PK model. Of those, 806 (80.6%) converged successfully and were used to generate the 95% confidence intervals (CIs) for the model parameters and the impact of the covariates on these parameters (Table 2). The visual predictive check of the final model for all data showed that the model provides a good description of the data (Supplementary Figure S5).

3.4 Simulations of Impact of IVIG on Infliximab Disposition

Simulations in a typical patient with body weight of 14 kg receiving one dose of 5 mg/kg infliximab IV, showed 16.0% and 30.5% higher serum infliximab concentrations at 24 and 48 hours in patients receiving infliximab after IVIG, compared to those receiving infliximab before IVIG (Figure 1). Similarly, early infliximab exposure, as represented by the area under the concentration curve in the first week after infliximab administration ($AUC_{D0\text{-}D7}$), was 22.1% higher in patients receiving infliximab after IVIG, compared to those receiving infliximab before IVIG (Figure 1).

Dose simulations in a typical patient with body weight of 14 kg showed that a dose of 7.5 mg/kg infliximab results in slightly higher early infliximab exposure if infliximab is administered before IVIG, compared to a dose of 5 mg/kg infliximab IV administered after IVIG (Figure 2).

3.5 Impact of soluble TNF receptor (sTNFR)-1 on Infliximab Disposition

From the study by Tremoulet and colleagues, sTNFR-1 concentrations were measured in banked plasma from 95 KD patients (44 randomized to placebo and 51 to infliximab) at baseline with a median (IQR) of 2.7 (2.0 – 3.8) ng/mL. Baseline sTNFR-1 concentrations were significantly lower in patients with normal (<2.5) vs. abnormal

(≥2.5) maximum LAD or right coronary artery Z score (2.5 ng/ml vs. 3.2 ng/mL, respectively, P = 0.026) (Figure 3). Multivariable logistic regression was carried out to identify covariates associated with early infliximab serum concentrations at 36 hours after the infliximab infusion (24 hours after the IVIG infusion). Results of the univariable analysis are shown in Supplementary Table S1. The final multivariable model showed that lower 36-hour serum infliximab concentrations were associated with lower baseline body weight, higher baseline sTNFR-1 concentration and higher baseline LAD Z score (Table 3).

4 DISCUSSION

Here, we conducted a PopPK analysis for infliximab in children with KD, the leading cause of acquired heart disease in children. The concentration-time profile was adequately described by a two-compartment model with first-order elimination parameterized in terms of estimated clearance, volume of distribution of the central compartment, inter-compartmental clearance, and volume of distribution of the peripheral compartment. Estimates from the PopPK analysis for a typical KD patient with 14 kg body weight were (normalized by weight) CL = 0.117 L/day (8.36 mL/kg/day), V1 = 0.801 L (57.2 mL/kg), V2 = 0.962 L (68.7 mL/kg), and 0.692 L/day (49.4 mL/kg/day), respectively. Previously, a PopPK analysis for infliximab was conducted in pediatric patients with Crohn's disease (CD) with parameter estimates calculated to be respectively 5.43 mL/kg/day, 54.2 mL/kg, 29.2 mL/kg, and 3.52 mL/kg/day, which were comparable to the adult patient population with CD.(9) Differences with the current PopPK analysis in parameter estimates may result from a different disease indication,

single vs. multiple dosing (CD), younger vs. older age (median 2.9 years (KD) vs. 13 years (CD) with no CD patients <6 years), lower vs. higher body weight (median 14 kg (KD) vs. 42 kg (CD)), different study design, and sampling.

In a previous non-compartmental analysis of infliximab PK in patients with KD (i.e., a subset of the patients included in the current study), clearance and volume of distribution were found to be 3.36 mL/kg/day and 67 mL/kg, respectively.(5) In comparison, the median (IQR) empiric Bayesian post-hoc estimates (normalized by weight) that were obtained with the final PopPK model in the current analysis, for the same subset of patients, were: 7.63 (5.52-15.19) mL/kg/day and 88.75 (66.49-121.95) mL/kg, respectively. Although the volume of distribution is comparable across both analyses, the parameter estimate for clearance is two-fold higher in the PopPK analysis. The clearance may have been underestimated in the non-compartmental analysis because sparse serum sampling may have led to an over estimation of the true AUC.

Here, the availability of data from two randomized, controlled clinical trials with different designs allowed for comparing the effect of administrating infliximab before or after IVIG. In the study by Burns and colleagues, infliximab was given after IVIG administration, as a secondary therapy in patients who were IVIG-resistant.(5) In the study by Tremoulet and colleagues, infliximab was given before IVIG administration, as an addition to standard therapy.(8) Fc gamma receptors (FcγR) and FcRn play an important role in the homeostasis of endogenous immunoglobulins and therapeutic monoclonal antibodies through regulation of the elimination and recycling pathways, respectively, which are non-saturable under physiologic conditions.(17) In addition to affecting clearance, studies *in vitro* showed that FcRn actively transports IgG in a bi-

directional manner: apical to basolateral and basolateral to apical direction.(18) As high doses of immunoglobulin (IVIG 1-2 g/kg) may saturate FcRn (11), administrating IVIG may have an effect on the distribution of endogenous and therapeutic proteins. Indeed, here the covariate analysis showed that if infliximab is administered after IVIG, the volume of distribution of the peripheral compartment is reduced by almost 50%. Consequently, this may be a reflection of lower penetration of drug into the peripheral compartment and higher serum infliximab concentrations. These findings may also be applicable to an adult patient population and in patients with comorbidities requiring treatment with a therapeutic monoclonal antibody in combination with IVIG. For example, patients with chronic inflammatory illnesses (e.g. rheumatoid arthritis, CD, and ulcerative colitis) may require specific anti-inflammatory therapy in combination with IVIG for the treatment of autoimmune encephalitis.(19)

Depending on whether the primary mechanism of action of infliximab is mediated through systemic exposure or penetration into the peripheral (i.e. tissue) compartment, the sequence of IVIG administration should be taken into account and the infliximab dose adjusted accordingly. For the treatment of KD, it is unclear whether serum or tissue infliximab concentrations are more important. However, since the difference in coronary artery LAD Z score between baseline and 2 weeks is larger in infliximab-treated compared to IVIG-treated children indicating that infliximab may be protective against the development of coronary artery aneurysms (8), penetration of drug into the tissue compartment may be more important. One might expect that since TNF (52 kDa) is only present in pg/mL concentrations in the serum vs. µg/mL concentrations of infliximab (~150 kDa), all free soluble and transmembrane TNF on the surface of

circulating white blood cells (respectively sTNF and tmTNF) in serum would be complexed by infliximab and neutralized shortly after the infusion. However, we found that circulating levels of sTNFR-1 are higher in subjects with elevated coronary artery Z scores suggesting that production of TNF in these patients may exceed the binding capacity of infliximab at the 5 mg/kg dose used. This may also be the case for tmTNF in tissue, where the ratio of TNF to infliximab may be even higher than in the serum. Here, we show in a multivariable logistic regression that a higher degree of inflammation at baseline, reflected by higher sTNFR-1 concentrations (a proxy for TNF (16)) and higher LAD Z scores, is associated with lower serum infliximab concentrations at 36 hours. Interestingly, observations in rheumatoid arthritis and inflammatory bowel disease point towards a similar inverse correlation between pre-treatment objective markers of disease activity (i.e. C-reactive protein) and subsequent subtherapeutic infliximab trough concentrations, leading to worse outcomes.(20, 21) A similar relationship between infliximab exposure and response to therapy in pediatric and adult patients with inflammatory bowel disease has recently been reviewed.(22)

The results from the multivariable regression analysis are complementary to the PopPK model, as the former specifically investigates variables that influence early serum infliximab concentrations, a time window believed to be critical when treating patients with acute KD. Given that children with KD who develop coronary artery aneurysms have higher concentrations of TNF (3, 4), exposure to higher concentrations of infliximab in those patients may lead to a better response, as observed in patients with CD.(23) Furthermore, our results indicate that patients with low body weight may be at increased risk of underdosing, as the results from the multivariable model confirm

that allometric scaling for CL in the PopPK model is appropriate given that patients with lower body weight at baseline have lower serum infliximab concentrations at 36 hours, regardless of weight based dosing. A national clinical trial comparing the effectiveness of infliximab vs. a second IVIG infusion for KD patients with recurrent fever after their initial IVIG treatment is currently in progress and infliximab is dosed at 10 mg/kg (NCT03065244). This will afford an opportunity to further test our PK model predictions.

We recognize both strengths and limitations to our work. Even though the impact of IVIG administration on infliximab PK was not evaluated in the same study and could not be evaluated longitudinally, this is the only PK model created for patients treated with both a therapeutic monoclonal antibody and high-dose IVIG. As the use of biologics increases in the treatment of KD as well as other inflammation-mediated diseases, data regarding the impact and timing of IVIG administration on concentrations and distribution of biologics becomes increasingly important. A limitation of our work is the relatively small sample size and sparse sampling, although the PopPK model described the infliximab concentration-time data well and no apparent bias or obvious model misspecification was observed. A limitation of the model is that we have no way of directly assessing infliximab concentrations or effects at the site of interest, in the coronary arteries, nor can we experimentally determine the relative importance of serum vs. tissue infliximab concentrations.

To conclude, our study shows that the timing of infliximab administration relative to IVIG administration affects the disposition of the monoclonal antibody and that KD patients with evidence of coronary artery damage have higher concentrations of plasma s-TNFR1 and may benefit from higher doses of infliximab. As use of therapeutic

monoclonal antibody therapy becomes more common in inflammatory diseases that are also treated with IVIG, consideration must be given to the potential impact of saturation of the FcγR and FcRn on the concentration and distribution of the expensive, targeted monoclonal antibody therapy.

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AUTHOR CONTRIBUTIONS

NVC wrote manuscript; NVC, AHT, and JCB designed research; NVC, JO, CS, AHT, and JCB performed research; NVC, JO, CS, BMB, EVC, AHT, and JCB analyzed data; JO, CS, BMB, EVC, AHT, and JCB critically revised the manuscript for important

intellectual content. All authors approved the final version of the article, including the authorship list.

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FIGURE LEGENDS

Figure 1. Simulations (n=1000) of average ± standard deviation infliximab serum concentrations in a typical KD patient of 14 kg after 5 mg/kg infliximab IV administration, before or after IVIG administration.

Figure 2. Simulations of infliximab serum concentrations in a typical KD patient of 14 kg for 5 mg/kg, 7.5 mg/kg or 10 mg/kg infliximab IV administration before or after IVIG administration.

Figure 3. Baseline, pre-treatment serum concentrations of soluble tumor necrosis factor-α receptor (sTNFR)-1 in Kawasaki disease patients with normal (<2.5) and abnormal (≥2.5) maximum left anterior descending or right coronary artery Z scores. Box plots and whiskers represent the median, interquartile range, and 5^{th} and 95^{th} percentile. Outliers are shown as individual symbols.