

# Infliximab Dosing Strategies and Predicted Trough Exposure in Children With Crohn Disease

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See “Time for Personalized Biologic Therapy: One Size Does Not Fit All” by Griffiths on page 666.

## ABSTRACT

**Objectives:** Standard infliximab maintenance dosing of 5 mg/kg every 8 weeks may be inadequate to consistently achieve sufficient drug exposure to minimize loss of response or treatment failure in pediatric Crohn disease (CD). We aimed to determine the predicted infliximab trough concentrations in children with CD during maintenance therapy and the percentage of patients achieving target trough concentration  $>3 \mu\text{g/mL}$ .

**Methods:** A Monte Carlo simulation analysis was constructed using a published population pharmacokinetic model based on data from 112 children in the REACH trial. We assessed maintenance dosing strategies of 5, 7.5, and 10 mg/kg at dosing intervals of every 4, 6, and 8 weeks for children that differed by age, weight, albumin level, and concomitant immunomodulator therapy.

**Results:** Based on the index case of a 10-year-old with CD receiving standard infliximab dosing with concomitant immunomodulator therapy, the median (interquartile range) simulated infliximab trough concentration at week 14 was 1.3 (0.5–2.7)  $\mu\text{g/mL}$  and 2.4 (1.0–4.8)  $\mu\text{g/mL}$  for albumin levels of 3 and 4 g/dL, respectively. Among 1000 simulated children in the model, trough concentration  $>3 \mu\text{g/mL}$  at week 14 was achieved 21% and 41% of the time for albumin levels of 3 and 4 g/dL, respectively.

**Conclusions:** Standard infliximab maintenance dosing in children with CD is predicted to frequently result in inadequate exposure, especially when albumin levels are low. Optimized dosing strategies for individual patients are needed to achieve sufficient drug exposure during infliximab maintenance therapy.

**Key Words:** children, Crohn disease, inflammatory bowel disease, infliximab, modeling, Monte Carlo simulation, pharmacokinetics

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## What Is Known

- Infliximab is a monoclonal antibody to tumor necrosis factor alpha and is the mainstay therapy for children with Crohn disease.
- Although effective, infliximab has a high loss of response rate at 1 year after beginning therapy, and there is increasing evidence that infliximab treatment failure is associated with trough concentrations  $<3 \mu\text{g/mL}$  during maintenance therapy.
- Children with lower albumin levels have higher infliximab clearance and lower drug exposures.

## What Is New

- We report the results of a Monte Carlo simulation analysis that implemented a published infliximab population pharmacokinetic model to examine infliximab dose-exposure relations in children with Crohn disease.
- With standard infliximab dosing of 5 mg/kg every 8 weeks, only 21% of patients with albumin of 3 g/dL and 41% of patients with albumin of 4 g/dL are predicted to achieve infliximab trough concentrations  $>3 \mu\text{g/mL}$ .
- Higher starting infliximab maintenance dosing strategies are needed in children with Crohn disease to consistently achieve a trough concentration  $>3 \mu\text{g/mL}$ .

Infliximab, a chimeric monoclonal antibody against tumor necrosis factor alpha, is the most commonly used biologic in the treatment of children with Crohn disease (CD). Standard infliximab dosing in children is 5 mg/kg at 0, 2, and 6 weeks during induction followed by maintenance doses of 5 mg/kg every 8 weeks (1–4). This dosing regimen is based on the original randomized controlled studies demonstrating efficacy of infliximab.

The REACH trial published in 2007 by Hyams et al (5) was a landmark study showing efficacy of infliximab in children for induction and maintenance of remission in moderate to severe CD. In this study of 112 children with CD, approximately 60% of the patients had clinical response or remission at 1 year. Clinical experience to date, however, shows frequent waning of effectiveness over time, and loss of response and/or need for dose modification has been reported in up to 50% of patients with CD by 54 weeks (5–7).

Increasing evidence in adults and children has shown treatment failure may be resulting in part from low infliximab exposure. Several observational studies suggest that infliximab trough concentrations  $<3 \mu\text{g/mL}$  are associated with worse clinical outcomes based on higher disease activity indices and/or increased systemic

inflammation as measured by C-reactive protein (7–12). Dose optimization including dose escalation based on trough concentration monitoring has proved beneficial (10,13,14). In children with CD, trough concentrations achieved after standard infliximab maintenance dosing are not well characterized. Important predictors of infliximab drug clearance in children with CD have been identified with weight and serum albumin having the largest influence (15). For example, infliximab drug clearance is 25% higher in a child with a serum albumin of 3 mg/dL compared with 4 mg/dL. Even after accounting for known predictors in the pharmacokinetics of infliximab, large variation between children still, however, exists (15). Taken together, a 1-size fits all approach for infliximab dosing in children with CD may be inappropriate.

We hypothesize that standard infliximab maintenance dosing in children at 5 mg/kg every 8 weeks results in large variation in drug exposure and does not consistently achieve infliximab trough concentrations >3 µg/mL. As the initial step in evaluating this hypothesis, the objective of the present study was to evaluate predicted infliximab trough concentrations in children with CD during maintenance therapy including the percentage of patients achieving target trough concentration >3 µg/mL.

## METHODS

### Infliximab Pharmacokinetic Model

A published infliximab population pharmacokinetic model developed from 112 children in the REACH trial and 580 adults in the ACCENT I trial was implemented in the nonlinear mixed effects modeling software NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD) (15). In ACCENT I, serum infliximab concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) with a lower limit of detection of 0.1 µg/mL. The method for serum infliximab concentration determination in REACH was not reported. A 2-compartment model with first-order elimination was used to describe infliximab pharmacokinetics. Clearance (CL) was predicted by weight (WT, kg), serum albumin (ALB, g/dL), presence of antibodies to infliximab (ATI, yes/no), and concomitant immunomodulation therapy (IMM, yes/no). Sex had no impact on clearance. The equation for CL was as follows:

$$CL(\text{mL/kg/day}) = 5.42 \times \left(\frac{\text{WT}}{65 \text{ kg}}\right)^{-0.313} \times \left(\frac{\text{ALB}}{4.1 \text{ g/dL}}\right)^{-0.855} \\ \times (0.863)^{\text{IMM}} \times (1.292)^{\text{ATI}},$$

where IMM = 1 in patients receiving concomitant immunomodulation therapy and 0 in patients not receiving concomitant immunomodulation therapy; ATI = 1 in presence of antibodies to infliximab and 0 in patients without presence of antibodies to infliximab. Central and peripheral volumes of distribution ( $V_c$  and  $V_p$ ) were predicted by weight as given by the equations:

$$V_c(\text{mL/kg}) = 52.4 \times \left(\frac{\text{WT}}{65 \text{ kg}}\right)^{-0.233}$$

$$V_p(\text{mL/kg}) = 19.6 \times \left(\frac{\text{WT}}{65 \text{ kg}}\right)^{-0.588}$$

Intercompartmental clearance (Q) was constant (2.26 mL · kg<sup>-1</sup> · day<sup>-1</sup>). After accounting for known predictors, the remaining variation between children was described by an exponential error model for CL (% coefficient of variation [% CV] 25.4%),  $V_c$  (16.3%) and  $V_p$  (% CV 34.9%). Residual variability (a measure of the difference between the model predicted concentration for a patient and the observed concentration in that patient)

was captured using a combined proportional (% CV 27.5%) and additive error model (standard deviation [SD] ± 0.244 µg/mL).

### Monte Carlo Simulations

Using the published infliximab population pharmacokinetic model for children with CD, Monte Carlo simulation methods were applied in NONMEM 7.2 to understand infliximab dose-exposure relations in children with CD (16–18). Monte Carlo simulation is a technique that allows the incorporation of the underlying biological variation in a model. Via repeated sampling of simulated patients, the data reveal a range of possible outcomes (ie, infliximab trough concentrations) in a patient population, which can be used to determine the probability of a specific outcome (ie, probability of achieving trough concentration >3 µg/mL) (19). Furthermore, by using simulated data, a wide spectrum of clinical scenarios can be evaluated, which would not be feasible in an actual clinical trial in children.

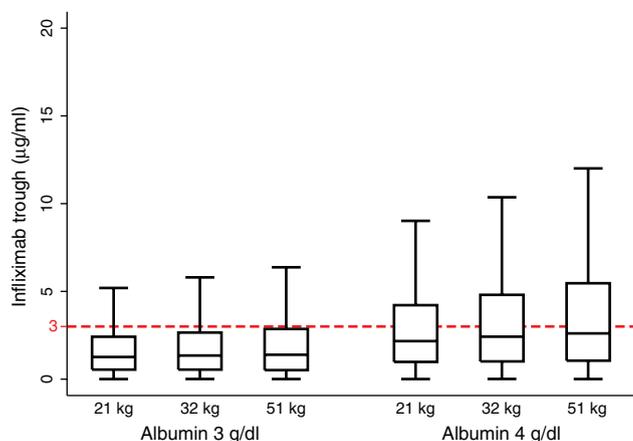
In the present analysis, we evaluated infliximab maintenance dosing strategies of 5, 7.5, and 10 mg/kg at dosing intervals of every 4, 6, and 8 weeks in children with CD. Clinically relevant predictors of infliximab pharmacokinetics (ie, weight, albumin, and concomitant immunomodulator status) were examined (Table 1). A weight of 21, 32, and 51 kg were chosen based on ~CDC 50% weight-for-age for a 6-, 10-, or 14-year-old, respectively. Albumin of 3 and 4 g/dL are common levels reported in children with CD (15,20). For a given Monte Carlo simulation (n = 1000 simulated children with CD), the maintenance dosing regimen and patient type (ie, weight, albumin, and concomitant immunomodulator therapy status) were fixed. Monte Carlo simulations were then repeatedly conducted, in which only 1 predictor was varied between simulations. All possible combinations of dosing regimen, weight, albumin, and concomitant immunomodulator therapy status were evaluated resulting in 108 unique Monte Carlo simulations. This systematic and in-depth sensitivity analysis allowed an examination of the effect of each predictor on trough concentration achievement for a given dosing regimen.

For each Monte Carlo simulation, infliximab trough concentrations were then analyzed before the second or third maintenance dose depending on the dosing interval, specifically trough concentrations before the maintenance dose at week 12 (if dosing interval every 6 weeks) or week 14 (if dosing interval every 4 or 8 weeks). In addition, the percentage of children that achieved a trough concentration >3 µg/mL was calculated at the above time points for each infliximab dosing regimen and patient type. Target trough concentrations of >3 µg/mL were chosen based on previous reports noting an association with treatment response (7–12). Statistical analyses of the data and figure productions were performed using STATA 13 (StataCorp LP, College Station, TX).

TABLE 1. Model inputs for Monte Carlo simulations

|                                |
|--------------------------------|
| Infliximab maintenance regimen |
| Dose: 5, 7.5, or 10 mg/kg      |
| Interval: every 4, 6, or 8 wk  |
| Weight*                        |
| 21, 32, and 51 kg              |
| Albumin                        |
| 3 or 4 g/dL                    |
| Concomitant immunomodulator    |
| Yes or no                      |
| Infliximab antibodies          |
| Assumed not present            |

\*Weights represent ~CDC 50% weight-for-age for a 6-, 10-, or 14-year-old, respectively.



**FIGURE 1.** Predicted infliximab trough concentrations ( $\mu\text{g}/\text{mL}$ ) by weight and albumin level at standard maintenance dosing of 5 mg/kg every 8 weeks. Each box plot represents trough concentrations at week 14 from 1000 simulated children with CD on concomitant immunomodulator therapy. Dashed line references target trough concentrations of 3  $\mu\text{g}/\text{mL}$ . CD = Crohn disease.

## RESULTS

### Standard Infliximab Dosing

Infliximab trough concentrations were highly dependent on albumin level (Fig. 1). For example, at standard maintenance dosing of 5 mg/kg every 8 weeks in simulated children with a weight of 32 kg receiving concomitant immunomodulator therapy, the median (IQR) predicted infliximab trough concentration at week 14 was 1.3 (0.5–2.7)  $\mu\text{g}/\text{mL}$  and 2.4 (1.0–4.8)  $\mu\text{g}/\text{mL}$  for albumin levels of 3 and 4 g/dL, respectively. The impact of weight on trough concentration was small and likely not clinically relevant at standard maintenance dosing (Fig. 1). For example, the median (IQR) simulated infliximab trough concentration at week 14 in children with albumin 4 g/dL receiving concomitant immunomodulator therapy was 2.1 (1.0–4.2)  $\mu\text{g}/\text{mL}$ , 2.4 (1.0–4.8)  $\mu\text{g}/\text{mL}$ , and 2.6 (1.1–5.5)  $\mu\text{g}/\text{mL}$  for weights of 21, 32, and 51 kg, respectively. At albumin 3 g/dL (when infliximab clearance is predicted to be high), the impact of weight on trough concentration became negligible with a median (IQR) trough concentration of 1.3 (0.5–2.4)  $\mu\text{g}/\text{mL}$ , 1.3 (0.5–2.7)  $\mu\text{g}/\text{mL}$ , and 1.4 (0.5–2.9)  $\mu\text{g}/\text{mL}$  for weights of 21, 32, and 51 kg, respectively.

Target trough concentrations  $>3 \mu\text{g}/\text{mL}$  were not consistently achieved at standard maintenance dosing of 5 mg/kg every 8 weeks across simulated children of different weight and albumin (Table 2). For example, among 1000 children with a weight of 32 kg in the simulated model receiving standard maintenance dosing, a trough concentration  $>3 \mu\text{g}/\text{mL}$  was achieved at week 14 in only 21% and 41% of the time for albumin levels of 3 and 4 g/dL, respectively.

### Optimized Infliximab Dosing Strategies

Higher infliximab dose amounts (ie, 7.5 or 10 mg/kg) and/or shorter dosing intervals (ie, every 4 or every 6 weeks) increased the predicted trough concentration exposure. Figure 2 shows the impact of maintenance dosing strategy on predicted infliximab trough concentrations by albumin level in children with a weight of 32 kg. Overall, shortening the dosing interval had a larger impact on trough concentration than increasing the dose amount. At an albumin level of 3 g/dL and weight of 32 kg, a dose increase from the standard infliximab maintenance dosing of 5 mg/kg every 8 weeks to 7.5 mg/kg every 8 weeks resulted in a median trough concentration at week 14 of 1.9 (0.8–4.0)  $\mu\text{g}/\text{mL}$  (compared with 1.3 (0.5–2.7)  $\mu\text{g}/\text{mL}$  with standard maintenance dosing). If the dose was increased to 10 mg/kg every 8 weeks, the median trough concentration at week 14 was 2.6 (1.0–5.2)  $\mu\text{g}/\text{mL}$ . Maintaining the dose at 5 mg/kg but shortening the interval to every 6 weeks resulted in a median trough concentration of 2.5 (1.2–4.7)  $\mu\text{g}/\text{mL}$ . Similar trends in trough concentration and dosing strategy were seen for children with weights of 21 and 52 kg (supplementary Table S1, <http://links.lww.com/MPG/A614>).

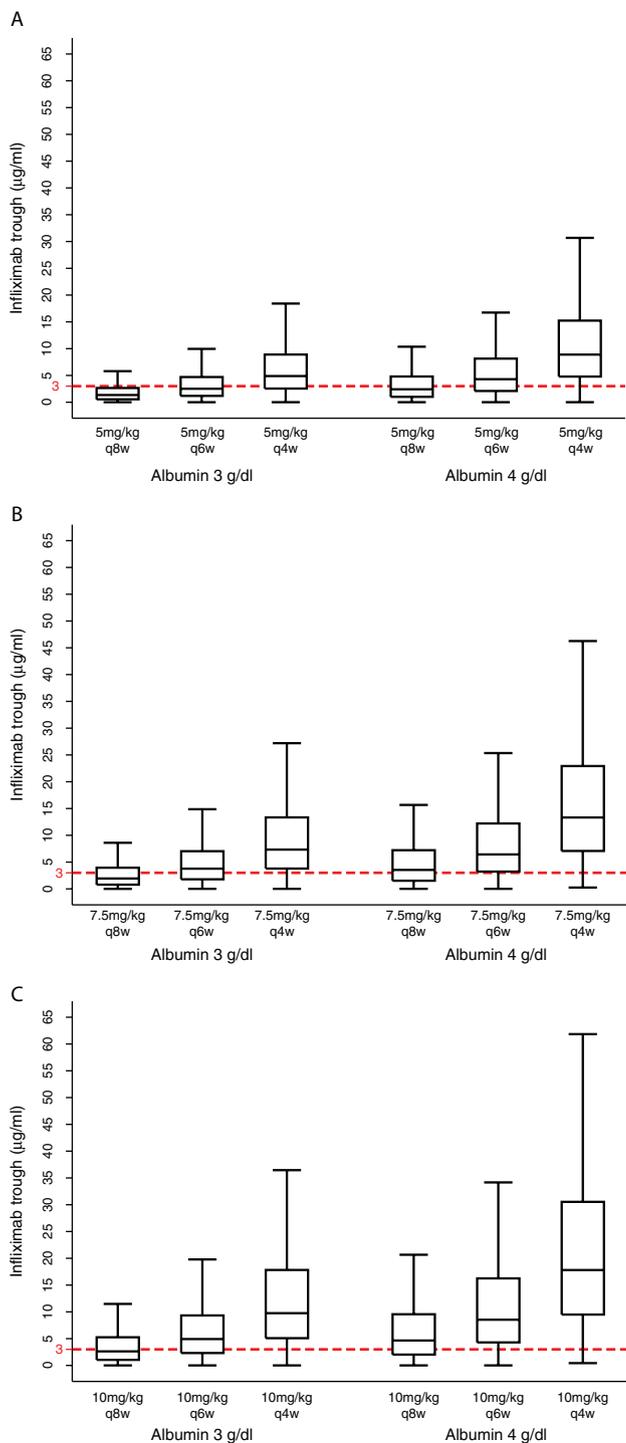
The percentage of children predicted to achieve a target trough concentration  $>3 \mu\text{g}/\text{mL}$  for the different dosing strategies is shown by weight and albumin in Table 2. Overall, more aggressive dosing is predicted to be needed to consistently achieve a trough concentration  $>3 \mu\text{g}/\text{mL}$  in children with CD. The “optimized” dosing strategies predicted to achieve a trough concentration of  $>3 \mu\text{g}/\text{mL}$  in at least 80% of children with a weight of 32 kg were as follows: 7.5 or 10 mg/kg every 4 weeks for albumin levels of 3 g/dL, and 5 mg/kg every 4 weeks or 10 mg/kg every 6 weeks for albumin levels of 4 g/dL (Fig. 3). Similar “optimized” dosing strategies were predicted for children with weights of 21 and 52 kg.

For patients not on concomitant immunomodulators, infliximab exposures were slightly lower overall because of a predicted  $\sim 14\%$  faster drug clearance. The same trends and relations were, however, seen, and the optimized dosing strategy predicted to achieve a trough concentration of  $>3 \mu\text{g}/\text{mL}$  in at least 80% of

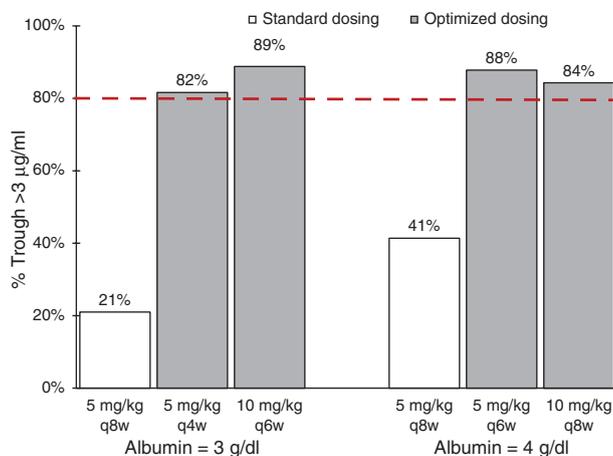
**TABLE 2.** Percentage of children with CD on concomitant immunomodulator therapy predicted to achieve target infliximab trough concentrations  $>3 \mu\text{g}/\text{mL}$  at week 12 of 14 of maintenance therapy by weight, albumin, and dosing regimen

| Weight, kg | Albumin, mg/dL | Maintenance dosing regimen |       |       |           |       |       |          |       |       |
|------------|----------------|----------------------------|-------|-------|-----------|-------|-------|----------|-------|-------|
|            |                | 5 mg/kg                    |       |       | 7.5 mg/kg |       |       | 10 mg/kg |       |       |
|            |                | q 8 w                      | q 6 w | q 4 w | q 8 w     | q 6 w | q 4 w | q 8 w    | q 6 w | q 4 w |
| 21         | 3              | 17                         | 37    | 62    | 31        | 54    | 77    | 43       | 65    | 85    |
|            | 4              | 37                         | 59    | 84    | 53        | 73    | 92    | 65       | 82    | 95    |
| 32         | 3              | 21                         | 43    | 69    | 35        | 59    | 82    | 46       | 69    | 89    |
|            | 4              | 41                         | 64    | 88    | 57        | 77    | 94    | 65       | 84    | 97    |
| 51         | 3              | 23                         | 48    | 76    | 38        | 62    | 87    | 48       | 71    | 92    |
|            | 4              | 44                         | 69    | 92    | 58        | 80    | 96    | 67       | 86    | 98    |

CD = Crohn disease. Dosing interval expressed in weeks (w). Weight represents  $\sim$ CDC 50% weight-for-age for a 6-, 10-, or 14-year-old, respectively.



**FIGURE 2.** Predicted infliximab trough concentrations ( $\mu\text{g/mL}$ ) by albumin level during maintenance therapy at the following doses: A, 5 mg/kg; B, 7.5 mg/kg; and C, 10 mg/kg given every 4, 6, or 8 weeks (q4w, q6w, q8w). Each box plot represents trough concentrations at week 12 or 14 from 1000 simulated children with CD on concomitant immunomodulator therapy and weighing 32 kg. Dashed line references target trough concentrations of 3  $\mu\text{g/mL}$ . CD = Crohn disease.



**FIGURE 3.** Percentage of children predicted to achieve a trough concentration  $>3 \mu\text{g/mL}$  after standard and optimized infliximab maintenance dosing strategies. Optimized dosing strategies were selected based on achievement of a trough concentration  $>3 \mu\text{g/mL}$  in  $>80\%$  of 1000 simulated children with CD on concomitant immunomodulator therapy and weighing 32 kg. Dosing intervals were every 4, 6, or 8 weeks (ie, q4w, q6w, q8w). CD = Crohn disease.

children were similar across albumin levels and weight (supplementary Tables S2 and S3, <http://links.lww.com/MPG/A614>).

### DISCUSSION

Using a published population pharmacokinetic model that was based on data from 112 patients with CD in the REACH trial, we constructed a Monte Carlo simulation analysis of hypothetical children with CD. We found that standard infliximab maintenance dosing of 5 mg/kg every 8 weeks is predicted to frequently result in trough concentrations  $<3 \mu\text{g/mL}$  in children with CD with an albumin 4 g/dL or less.

Substantial increase in either dose amount or frequency is required to achieve adequate drug exposure at week 14, as evidenced by only 21% or 41% of children achieving trough concentrations  $>3 \mu\text{g/mL}$  if albumin levels were 3 g/dL or 4 g/dL, respectively. Optimized dosing strategies based on patients' albumin level appear to predictably achieve more adequate drug exposure during maintenance infliximab therapy. More personalized infliximab dosing based on albumin level has also been suggested in adults (21).

The clinical relevance of our findings is that inadequate drug exposure is highly associated with the formation of antibodies to infliximab, resulting in loss of response or treatment failure (22,23). Clinical studies in adults demonstrate improved infliximab efficacy when infliximab trough concentrations are consistently  $>3 \mu\text{g/mL}$  (8–12). Although the optimal trough concentration target in children is not well defined, a prospective observational cohort study in children with inflammatory bowel disease suggested even higher trough concentrations (ie,  $>4 \mu\text{g/mL}$ ) may be necessary (7). In clinical practice, children with CD often present with moderate to severe disease phenotype and high systemic inflammatory burden. Low albumin levels are frequently observed as part of the constellation of clinical signs in pediatric CD (15,24,25). As such, higher starting infliximab maintenance dosing strategies are likely warranted in children with CD and albumin of 4 g/dL or less to consistently achieve infliximab trough concentrations  $>3 \mu\text{g/mL}$ .

Our analysis highlights an important consideration in pediatric CD management in light of present movement toward personalized medicine. Available data suggest that there is large

variation of infliximab pharmacokinetics in children with inflammatory bowel disease (15). Therefore, individualizing therapeutic strategies for biologics such as infliximab are necessary, especially considering the overall impact on the value of IBD care that biologics use represents (26). In addition, based on our findings, we highlight the need for future studies evaluating the value of therapeutic drug monitoring in pediatric IBD management because many different strategies are available and presently used in clinical practice without standardization. Individualization of infliximab dosing in pediatric IBD requires formal assessment and detailed considerations for different disease phenotypes, patient-specific characteristics, and cost-effectiveness.

We acknowledge that the limitation of our analysis is the use of simulated data. The population pharmacokinetic model implemented was, however, established from 112 children with CD receiving infliximab as part of the REACH trial and 580 adults with CD receiving infliximab as part of the ACCENT I trial. No difference in infliximab pharmacokinetics was identified between children and adults during the population pharmacokinetic model development (15), and therefore the final model combining children and adult data was implemented. Population pharmacokinetic models are powerful tools that can help understand variation in exposure in a patient population (16–18); consequently, our analysis was able to capture the variability in infliximab pharmacokinetics seen between children with CD. Of course, caution is warranted in generalizing our results to patients falling outside the inclusion criteria for REACH or ACCENT I (eg, children younger than 6 years). Although we examined several different weights and serum albumins in our simulations, we were not able to portray the true variation and distribution of these characteristics seen in children with CD. In addition, the impact of severe malnourishment and obesity on infliximab pharmacokinetics and dose needs could not be examined because of limitations in the underlying pharmacokinetic model and remains unknown. Nonetheless, our results are in agreement with a recent clinical report by Hoekman et al of infliximab trough concentrations in children with CD (20). In those receiving infliximab 5 mg/kg every 8 weeks, 44% (n = 10/23) had a trough concentration <3 µg/mL (Daniel Hoekman, personal communication, October 9, 2015). Furthermore, by using already available pediatric CD pharmacokinetic data, we were able to gain insight into potential infliximab dose optimization strategies based on patient-specific clinical data and achieved trough concentrations. Prospective clinical pharmacokinetic data on infliximab dosing strategies and trough concentration achievement in children with CD will be necessary to confirm our findings.

In conclusion, our study supports the clinical rationale to optimize infliximab dosing in pediatric CD. To consistently achieve a trough concentration >3 µg/mL during maintenance therapy, higher infliximab doses and/or shorter dosing intervals are needed, especially when albumin levels are low. Future studies are needed to validate optimized biologic dosing strategies in children with IBD.

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