Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Infliximab in Pediatric Inflammatory Bowel Disease: A Systematic Review and Revised Dosing Considerations

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ABSTRACT

Objectives: Infliximab (IFX), a monoclonal antibody directed against tumor necrosis factor alpha is a potent treatment option for inflammatory bowel disease (IBD). Dosing regimens in children are extrapolated from adult data using a fixed, weight-based dose, which is often not adequate. While clinical trials have focused on safety and efficacy, there is limited data on pharmacokinetic characteristics and immunogenicity of IFX in children. The objective was to provide a systematic overview of current literature on pharmacokinetic and immunogenicity of IFX in children with IBD, to assess the validity of current adult to pediatric dosing extrapolation.

Methods: A literature search identified publications up to October 2018. Eligibility criteria were study population consisting of children and/or adolescents with IBD, report of IFX trough levels and/or antibodies-to IFX, full text article or abstract, article in English, and original data.

Results: Initial electronic search yielded 2360 potentially relevant articles, with 1831 remaining after removal of duplicates. An additional search yielded another 202 potentially relevant articles. Of the 2033 retrieved articles, 2000 articles were excluded based on title, abstract, or eligibility criteria. Clearance of IFX was increased in young children and children with extensive disease, leading to lower trough levels after extrapolated dosing of 5 mg/kg, antibodies-to IFX emergence, and subsequent reduced efficacy.

Conclusions: Adult to pediatric weight–based dosing extrapolation is often inadequate. We provide several considerations for optimal dosing of IFX in children and adolescents with IBD.

Key Words: inflammatory bowel disease, infliximab, pediatric, pharmacodynamics, pharmacokinetics

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What Is Known

- Current infliximab dosing in children with inflammatory bowel disease is extrapolated from adults (induction schedule of 5 mg/kg at week 0, 2, and 6 and subsequent q8 week maintenance infusions of 5 mg/kg).
- During maintenance treatment, infliximab treatment is aimed at reaching serum trough levels of 3 to 7 μg/mL, as associated with improved clinical outcome, reduction in inflammatory markers, and endoscopic remission in both pediatric and adult inflammatory bowel disease.
- Children and adolescents with extensive disease and high disease activity (such as acute severe ulcerative colitis) often have low serum albumin and increased infliximab clearance necessitating induction doses >5 mg/kg, aimed at reaching infliximab serum trough levels of 5 to 10 μg/mL at week 14.

What Is New

- Young children (younger than 11 years of age) have increased infliximab clearance and require a dose >5 mg/kg, or a dosing interval shorter than 8 weeks, aimed to reach and maintain adequate infliximab serum trough levels (>3 μg/mL).
- In case of infliximab monotherapy, a dose >5 mg/kg is often required to reach and maintain adequate infliximab serum trough levels.

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Tumor necrosis factor alpha (TNF-α) is a key inflammatory cytokine involved in various inflammatory pathways. TNF-α is detected in lesions in the intestine of patients with inflammatory bowel disease (IBD, Crohn disease [CD], and ulcerative colitis [UC]) (1) and has a pivotal role in IBD pathogenesis. Infliximab (IFX), a chimeric IgG1 monoclonal antibody (75% human, 25% murine), was developed in the early 1990s as the first anti-TNF-α biological agent. IFX is effective in refractory IBD and has been registered for use in children with CD and UC in 2007 and 2011, respectively (Supplemental Fig. 1, Supplemental Digital Content, *http://links.lww.com/MPG/B781*).

In adult literature increasing data suggest different therapeutic thresholds for IFX depending on the stage of therapy (induction vs established maintenance) and treatment goal (ie, clinical remission, endoscopic improvement) (2). Unfortunately similar target levels are not yet established in the pediatric population. In general both the administered dose of a monoclonal antibody and its clearance are important to achieve a certain target level.

In both children and adults with IBD, monoclonal antibodies often display highly variable and complex pharmacokinetic (PK) behavior with several factors influencing their clearance. IFX clearance in IBD can be influenced by disease-related factors such as disease severity (ie, local vs systemic inflammation), increased intestinal permeability due to inflammation, or increased proteatic activity and thus degradation of drug-TNF-α immune complexes in inflamed tissue. In addition, the presence of antibodies-to IFX (ATIs) and the use of concomitant immunomodulator (IM) are known to influence clearance of IFX. In IBD, age per se has not been established as an independent factor involved in IFX clearance. Goldman et al (3) have, however, previously reported a significant inverse association between age and IFX clearance in juvenile idiopathic arthritis patients. Children younger than 7 years of age had a 1.6-fold greater median clearance than children ages 7 years or older (0.008 vs 0.005 $L \cdot kg^{-1} \cdot day^{-1}$, respectively; $r^2 = 0.21$, $P < 0.001$).

Increased understanding of the variability of IFX clearance has gradually shifted the focus to proactive measurement of IFX trough levels (TLs) in children and adults also known as therapeutic drug monitoring (TDM). If age as an independent factor can potentially influence IFX clearance, it should be taken into account when administering IFX to younger patients with IBD. Current dosing in children is, however, weight based and originally extrapolated from adults as justified by several small studies suggesting initial similarity in PK between the different age groups (4–8). In adult IBD, TLs of 3 to 7 μg/mL are considered adequate and are associated with improved clinical outcome, reduction in inflammatory markers, and endoscopic remission (9–15) (Fig. 1).

After more than 10 years of clinical experience with IFX in pediatric IBD, there is reasonable doubt whether the linear adult-to-pediatric extrapolation and dosing advice is still valid. In practice, young children and children with severe acute colitis often need higher doses to reach adequate TLs and achieve and maintain clinical remission, as incorporated in the recent consensus-based European Crohn's and Colitis Organisation (ECCO)-European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guideline on acute severe UC (16,17).

We provide a systematic overview of the literature currently available on pharmacodynamics (PD), and immunogenicity of IFX in children and adolescents with IBD and assess the validity of current weight-based dosing schedules. Finally, we provide considerations for more optimal dosing of IFX in pediatric IBD.

METHODS

Search Strategy

A literature search was performed to identify all published studies that reported PK or PD data on IFX in children or adolescents with IBD. An initial systematic search of the following databases was performed up to February 12, 2016: Cochrane Central, Ovid MEDLINE, Embase, Web-of-Science, PubMed recent, and Google Scholar (see Appendix for detailed search strategy, published online). In addition, reference lists of review articles and selected articles were examined for additional eligible studies. An additional search was performed in Embase on October 18, 2018.

Inclusion and Exclusion Criteria

We included all studies (clinical trials, observational studies, and cohort studies) that fulfilled the following criteria: study population consisted of children or adolescents with IBD, report of IFX-TLs and/or ATIs, full text article or abstract available, article written in English, and original data available in article. Reviews, case reports, case series, meta-analyses, editorials, practical summaries or guidelines, and animal studies were excluded.

Data Extraction and Quality Assessment

Titles and abstracts found through the search strategy were evaluated by 2 independent reviewers (D.A.W. and M.E.J.) for potential eligibility, using predefined criteria as described above. Full articles and abstracts were included when inclusion criteria were met. Systematic review was performed according to the PRISMA guidelines (18). Quality assessment was not performed due to study heterogeneity. Any disagreements were resolved by discussion. Key questions were formulated according to the "PICO" method. P [population]: in pediatric patients with IBD, is; I [intervention]: weight-based IFXdosing according to extrapolation from adults (so 5 mg/kg); C [comparison]: compared to dosing in real-life clinical practice; O [outcome]: effective and safe in reaching adequate IFX TLs and inducing and maintaining clinical and/or endoscopic response and remission. The following data were retrieved from published reports: study population, design of study, dose and dosing interval of IFX, TLs, type of assay used, concentration of ATI, disease outcome, and concomitant (IM) treatment.

Definition of Standard Infliximab Treatment

IFX is administered intravenously in a weight-based dose in both pediatric and adult patients. In pediatric IBD, similar to adult IBD, recommended use of IFX indicates a dosing schedule of 5 mg/kg as an induction regimen (infusions at weeks 0, 2, and 6) followed by a maintenance regimen of 5 mg/kg every 8 weeks in case of clinical response. IFX therapy can be intensified by increasing the dose, shortening the interval between infusions, or both if clinical response is lost over time. The different assays to measure IFX concentration and ATI status in serum are discussed in the Supplemental content. In Supplemental Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B781*), the assay used is listed per individual study.

RESULTS

The electronic search yielded 2558 potentially relevant articles. An additional 11 articles were identified from reference lists in review articles (19–24). After removal of duplicates, 2033

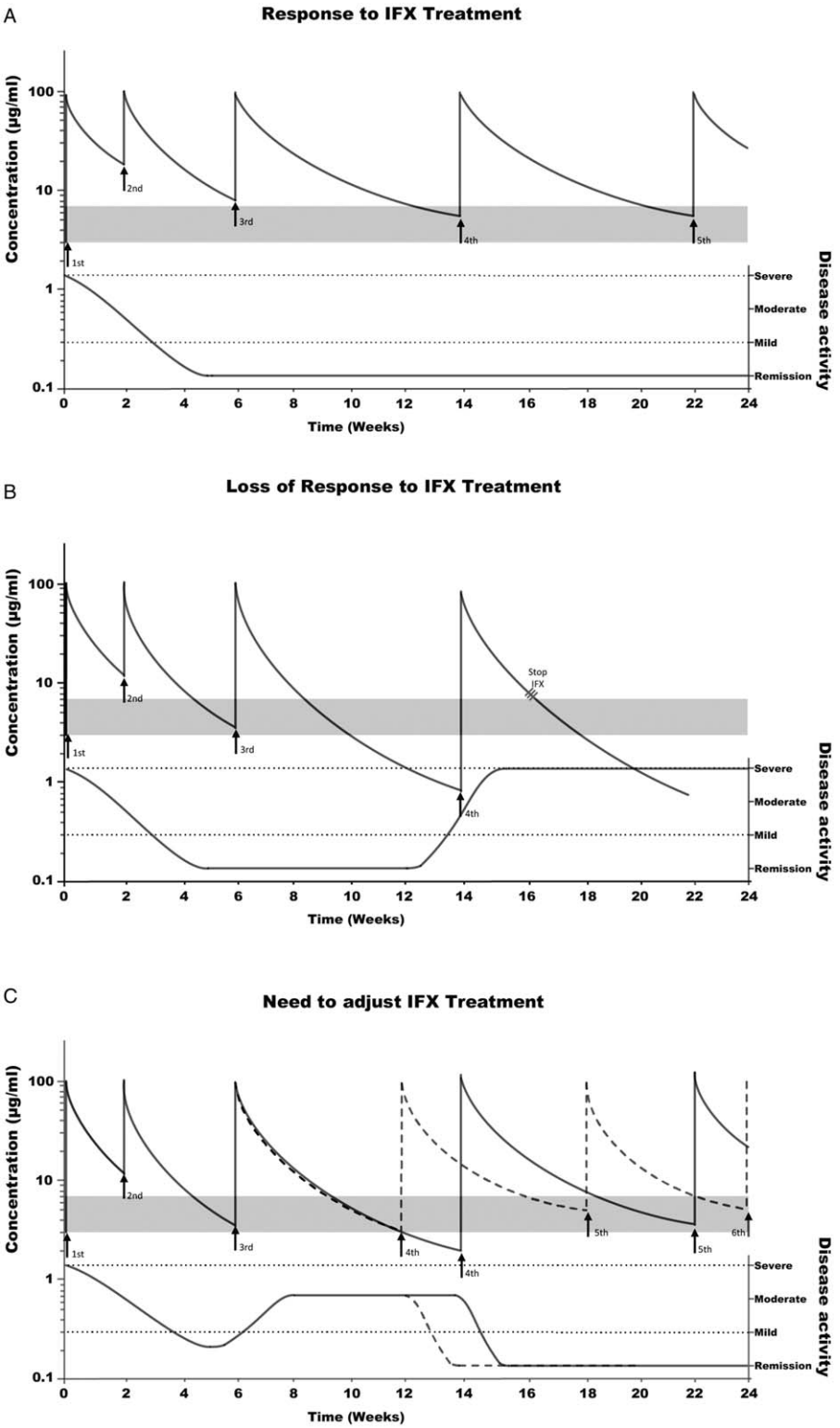

FIGURE 1. Three hypothetical clinical scenarios and their influence on IFX pharmacokinetic (PK). Three hypothetical clinical scenarios and their influence on IFX PK in patients with inflammatory bowel disease (IBD) with expected response in clinical disease activity during induction and maintenance until week 24. IFX concentration is given on a log scale. The grey area indicates the therapeutic window between 3 and 7 μg/mL. IFX concentrations <3 μg/mL are associated with increases of clinical disease scores and the inflammatory marker C-reactive protein (82). IFX concentrations >3 μg/mL are associated with sustained response (13), decrease in disease activity (83), and decrease in risk of treatment failure (11). Disease activity is divided in remission, mild, moderate, and severe disease activity. Each arrow represents an IFX infusion. Response to IFX

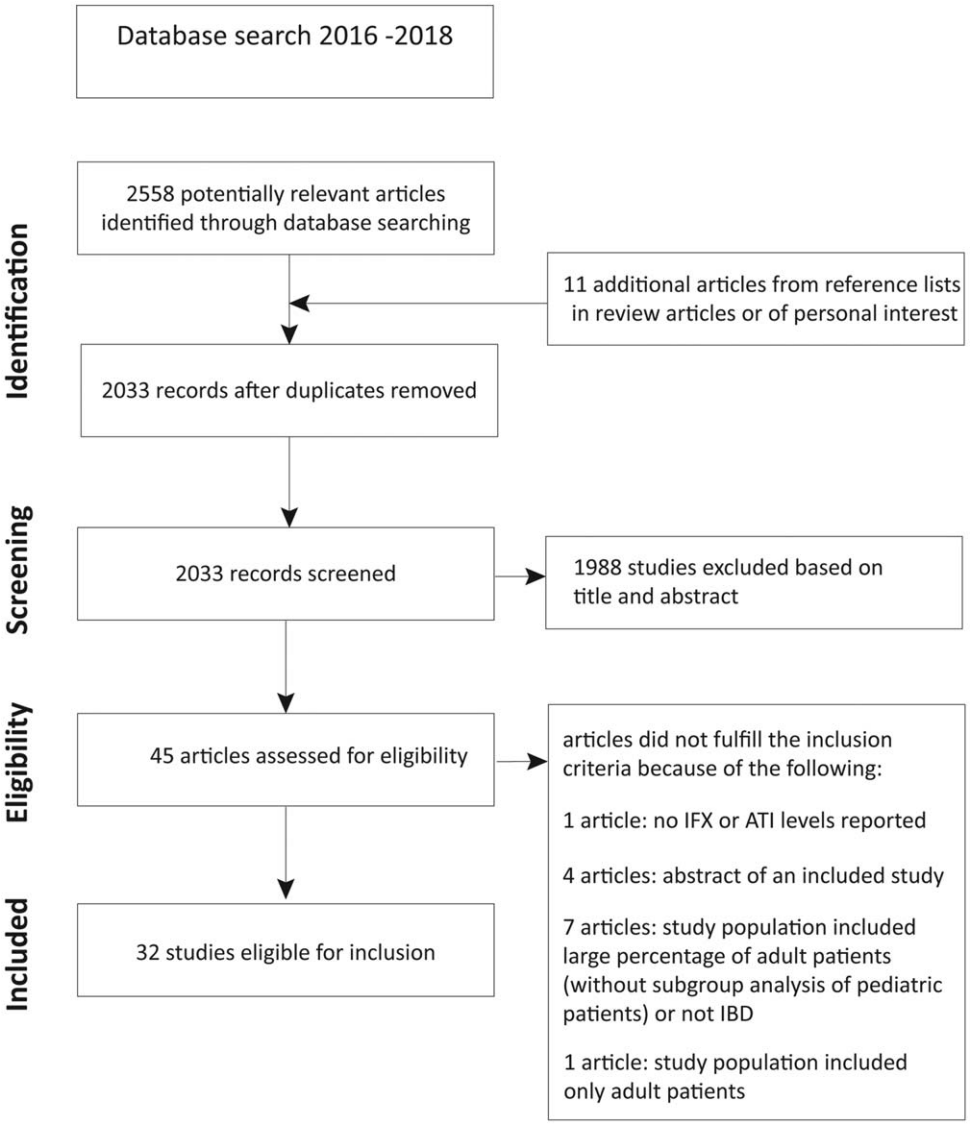

FIGURE 2. Study selection and exclusion stages PRISMA flow diagram of study selection and exclusion stages. ATI = antibodies-to IFX; IBD = inflammatory bowel disease; IFX = infliximab.

records remained, of which 1988 articles were excluded on the basis of title or abstract. A total of 45 articles were retrieved for detailed assessment (Fig. 2) of which 13 did not meet our inclusion criteria, resulting in a total of 32 articles for review.

Of the 32 studies that were selected, 23 were full text manuscripts and 9 were abstracts. Regarding study design, 4 were randomized controlled trials (7,25–27), 2 were cross-sectional studies (28,29), and 26 were cohort studies, of which 14 were retrospective (23,30–42), 11 were prospective (19–21,24,43–49), and 1 partially retrospective and prospective (22) as listed in Supplemental Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B781*).

Study Population

In total 2386 patients were reported in the 32 included studies. Ten of these studies included CD patients only, whereas 2 focused exclusively on patients with UC. Most included patients

treatment: (A) a normal PK pattern in a patient responding to IFX treatment. IFX concentration remains above the therapeutic range minimum of 3 μg/mL and leads to a decrease in clinical disease activity. Loss of Response to IFX treatment: (B) a PK pattern in a patient with antibodies-to IFX (ATI) formation shortly after the induction phase. IFX concentration decreases below the therapeutic range minimum of 3 μg/mL because of higher clearance due to ATI formation. Clinical disease activity decreases initially, but increases after ATIs are formed. When ATIs are detected using analytical assays, IFX treatment is stopped. Need to adjust IFX treatment: (C) an expected PK pattern in patients with factors that might decrease IFX concentration such as young age, high disease severity, low albumin, or low body weight. Adjustment of dose (continued line) or interval (interrupted line) increases IFX concentration above therapeutic minimum of 3 μg/mL. Clinical disease activity increases after initial response. IFX treatment adjustment leads to regain of response and less disease activity. IFX = infliximab.

had CD phenotype (n = 1763; 74%) followed by UC (n = 382; 16%) and IBD-unclassified (n = 19; 1%). Three included studies did not specify the ratio of disease phenotype (n = 222 patients; 9%).

Dose and Dosing Schedules

The majority of studies listed in Supplemental Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B781*) used a standard dosing regimen of 5 mg/kg as established in adult trials in CD (ie, ACCENT I (5), ACCENT II (5,50), and SONIC trials (51)) or UC (ie, ACT 1 (6) and ACT 2 (52)), except for 5 studies where higher doses were used (20,26,29,32,44). One study reported on pediatric patients treated with an IFX biosimilar (41).

Pharmacokinetics

Induction Phase

Median IFX serum levels during induction phase (of infusion at week 0, 2, and 6) were reported in several studies at different timepoints and levels ranged from 19.3 μg/mL (week 2), 10.9 to 14.5 μg/mL (week 6), 17.6 μg/mL (weeks 2 and 6 combined), 27 to 29 μg/mL (week 8), 16.80 μg/mL (week 10), and 5.9 μg/mL (weeks 11–14), with 5 mg/kg dosing (20,25–27,30,41,43,49).

Maintenance Phase

During maintenance median serum TLs ranged from 1.9 to 11.8 μg/mL, with IFX doses ranging between 5 and 15 mg/kg administered in 5- to 12-week intervals (19,20,25,27,37,39–44,46). Higher dose and shorter dosing interval led to higher TLs (25,28). Mean serum levels also increased with increasing IFX dose (4.0, 40.2, and 88.6 μg/mL, 1 week after a single dose of 1, 5, and 10 mg/kg IFX, respectively) (26). The respective areas under the curve (mean ± SD) for the respective doses were 3192 ± 1790; 23,852 ± 9792; and 58,216 ± 21,118 μg/mL · h. Several studies reported on IFX-TLs but did not specify when these were measured; IFX-TLs in these studies ranged from 1.8 to 13.6 μg/mL (23,29,35).

Only 3 studies described the biological half-life of IFX, which is 9 to 11 days in 5 mg/kg dosing in both CD and UC (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B781*) (7,25,26). Hadigan et al (26) reported that biological half-life of IFX increased (4.8, 9.3, and 9.5 days) with dose of IFX administered (for 1, 5, and 10 mg/kg doses, respectively).

Pharmacokinetics in Young Children

Articles were also reviewed on PK data for children younger than 10 years of age, in agreement with the Paris classification (category A1a). Eleven articles included IFX-TLs of children within this age range. None of the articles presented PK data specifically on these young children. One article specified the number of patients younger than 10 years of age (n = 13, all patients with CD) (49). One article reported an IFX-TL of 7.1 μg/mL for patients 6 to 11 years of age (25).

Factors Associated With Pharmacokinetics

Proposed factors likely associated with IFX PK in IBD were age, weight, dose, presence of ATI, concomitant IM use, inflammation, clearance, and albumin (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B781*). TLs were consistently lower in younger pediatric patients with IBD (25,29,37,43). Age was positively associated with IFX-TL in 1 study (β estimate = 0.31, $P = 0.04$; mean age 18.5 ± 4.4 years) (29). Week 6 TL was lower in patients with UC aged 6 to 11 years compared to patients aged 12 to 17 years (7.1 vs 15.3 μg/mL) (25). IFX-TLs were an estimated 4 to 17 μg/mL for a 100 mg dose (n = 5), 5 to 40 μg/mL for a 200 mg dose (n = 9), and 24 to 49 μg/mL for a 300 mg dose (n = 3) (43). Authors only reported total doses and related IFX-TL levels, but as all patients received 5 mg/kg, it can be deducted that patients receiving the lower doses were the youngest. Young children with lower body weight had significantly lower TLs at week 2 ($P < 0.001$) and week 6 ($P = 0.0445$). This also suggests lower exposures in younger children while receiving body weight normalized doses. Finally, median IFX-TL was statistically higher for patients above the age of 17 years ($P = 0.010$) (37).

Several studies reported that TLs were inversely correlated with inflammatory markers such as fecal calprotectin (43,44,48), C-reactive protein (CRP) (19,29,40,42,44,46,48), and erythrocyte sedimentation rate (32,40,42,48). In addition, serum albumin levels and body weight are associated with IFX-TLs: children with lower TLs had lower serum albumin levels and weighed less than children with high TLs (25,39,40,42,44,48).

In adults, concomitant IM therapy is known to increase IFX-TLs. We found conflicting data in children and adolescents. Most studies addressed combination IFX + IM treatment (such as thiopurines, corticosteroids, and methotrexate) Concomitant IM treatment varied between 10.8% and 100% of patients within included studies (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B781*). Ten studies examined the association between IM use and IFX-TLs (25,28,29,32,33,35,40,42,44,46). Recently Chi et al (29) reported that, after adjusting for covariates such as age, body mass index, CRP, and erythrocyte sedimentation rate, mean IFX-TLs were significantly higher in combination treatment (17.0 ± 1.3 μg/mL) versus initial IFX monotherapy (11.5 ± 2.1 μg/mL). In all other studies, use of IM when starting IFX treatment (25,44,46) or IM use at the time of TL measurement (28,32,33,35,40,42,44) did not result in higher TLs. Singh et al (46) reported higher TLs in patients who received an IM during start of IFX treatment compared to no IM at week 14 (6.8 vs 3.1 μg/mL; $P = 0.14$) and week 54 (7.6 vs 3.45 μg/mL; $P = 0.29$), but this difference was not statistically significant. Importantly, patients with TLs ≥3 μg/mL were using concomitant IM more often compared to patients who had TLs <3 μg/mL (94% vs 79%; $P = 0.06$) (28). Taken together, concomitant IM treatment seems to increase IFX levels, as in adults.

ATI prevalence between 0% and 47% was reported while actual concentrations of ATI were reported in 11 studies (19,20,23,25,28,30,31,38,41,42,44). The units used to express ATI concentration were not uniform, probably because of the use of different assays within these studies. Candon et al (30) reported that compared to moderate ATI titers (1:100–1:2000), high ATI titers (1:4000–1:8000) were more often associated with infusion reactions. Time until ATI formation varied greatly within our reviewed articles (7,21,22,30,32,33,36,38,39,43). In some studies, ATI were detected already during the induction phase with the earliest report before the second infusion (21,22,30,33,43). In most studies, ATI were detected during maintenance phase with the latest ATI detection occurring 4.6 years after start of IFX (32).

IM combination therapy seems related to a lower risk of ATI formation (22,28,29,31,38,46). Miele et al (31) reported that IM use protected against high titers of ATI and possibly ATI formation. Schatz et al (22) reported that in 4 patients with low ATI titers, ATI disappeared after IFX dose escalation or reintroduction of azathioprine. Singh et al (46) reported an association between IM use before week 14, and the lower number of patients positive for ATI after 1 year of IFX therapy. Zitomersky et al (28) reported that

previous IM use, but not IM use at time of IFX measurement, correlated with lower concentrations of ATI. Chi et al (29) reported that in multivariate analysis patients currently on combination therapy had a lower risk of detectable ATI (9.5%) compared with those on monotherapy (20.0%) in multivariate analysis (OR 0.3; 95% CI, 0.1–0.7; $P < 0.01$). Finally, Kansen et al (38) reported that children receiving IFX monotherapy had a lower chance of remaining ATI free at 12, 24, and 36 months after start of IFX compared to children with continuous IM combination therapy (72.6%, 57.7%, and 48.1% compared to 93.4%, 91%, and 91%, respectively). Taken together, data suggest a protective role for IM combination therapy against immunogenicity of IFX, by lowering the risk of ATI formation.

Several studies reported an inverse relationship between ATI and TLs (20,21,28,37,48). One study reported that TLs measured at week 14 may have a predictive value for occurrence of ATI at week 54 after start of IFX (21). Emergence of ATIs was associated with loss of response (22,30,33,34,37,38), duration of therapy (39,49), and progression to surgery (28). There was no apparent association between patient age and ATI prevalence (24,31), although Miele et al suggested a protective role for young age in the formation of ATI. This association was, however, not statistically significant in the limited number of patients examined (n = 34).

Clinical Outcome: Pharmacodynamics

In adults, multiple studies have been conducted on the relationship between IFX-TLs and clinical outcome. Currently there is, however, no well-defined optimal threshold for IFX-TL. In their guideline on TDM in adults with IBD, the American Gastroenterological Association suggests an IFX-TL of ≥5 μg/mL during maintenance as a beneficial threshold based on the proportion of patients not in remission compared to other thresholds (IFX-TL ≥1 μg/mL, 25% not in remission; ≥3 μg/mL, 15% not in remission; ≥5 μg/mL, 8% not in remission; ≥7 or ≥10 μg/mL, 4% not in remission) (53,54). A cross-sectional retrospective study in patients with CD with perianal fistulas by Yarur et al (55) reported that an IFX-TL ≥10.1 μg/mL may improve outcome, specifically increasing the chance of achieving fistula healing ($P = 0.012$). In addition, an IFX-TL <10.1 μg/mL was associated with lack of mucosal healing ($P = 0.01$).

Several pediatric studies related TLs to clinical outcome (Table 1). More than half of the studies demonstrated a significant association between high IFX-TLs and beneficial clinical outcome (21,25,32,34,37,39,40,42,46,47,49). High TLs were associated with high rates of clinical response (92.9%), clinical remission (64.3%), and mucosal healing (92.9%), although the authors did not specify a cut-off for TLs (25). Two studies did suggest optimal cut-off IFX thresholds for ongoing IFX therapy at 12 months (49) (IFX-TL ≥9.10 μg/mL at week 10) and deep remission (clinical remission with normal CRP) at week 54 (21) (IFX-TL ≥5.5 μg/mL at week 14).

Van Hoeve et al (42) reported that median TLs during maintenance treatment were significantly higher in children in clinical, biological, and endoscopic remission compared to patients not in remission. Two studies reported that week 14 TLs may have predictive value for clinical remission without dose intensification during maintenance or deep remission (clinical remission with normal CRP) (21,46). Hofmekler et al (37) defined clinical outcome as the need for dose optimization and reported that 37% of children who required dose optimization had low TLs during maintenance (<3 μg/mL). Stein et al (49) reported that children who were still on IFX treatment after 12 months had higher 10-week median TLs compared to patients who had stopped IFX treatment. El-Matary et al reported a significant correlation between higher TLs at week 14 and healing of fistulizing perianal CD at week 24. At week 14 IFX-TL in patients with CD with healed fistulae or fistulae in the process of healing (ie, decrease or cessation of fistula drainage) was significantly higher compared to the nonresponsive perianal CD group (12.7 vs 5.4 μg/mL; $P = 0.02$) (47). In summary, data suggest an association between high TLs and beneficial clinical outcome. Only 2 pediatric studies suggested IFX-TL thresholds for optimal outcome.

DISCUSSION

In this review, we investigated the literature currently available on IFX PK and immunogenicity in children and adolescents with IBD. In 2015 to 2016, position papers from the ESPGHAN, the ECCO, and the global Pediatric IBD Network emphasized the importance of assessing PK, PD, and safety in the pediatric IBD population (56,57). We demonstrate that there are insufficient PK studies in pediatric IBD, and that the available studies were conducted in only a limited number of patients. Consequently there is not enough evidence to support adult-to-pediatric extrapolation concerning IFX dosing.

Historically, clinical trials in children and adolescents were initiated long after approval of IFX for adults (Supplemental Fig. 1, Supplemental Digital Content, *http://links.lww.com/MPG/B781*). At that time, PK and PD were assumed to be similar for all age groups, resulting in all-age weight-based dosing. Not only body weight, but also growth and maturity, disease extent, serum albumin levels, and formation of ATIs are all, however, important in the systemic disposition of IFX (58–60).

In general, the optimal therapeutic thresholds for IFX remain very much the subject of investigation. The optimal threshold can vary because of per-patient differences in phase of therapy, disease activity, and/or treatment goal. For instance, the American Gastroenterological Association suggested an optimal threshold of ≥5 μg/mL during maintenance in all patients with IBD based on proportion of patients not in remission (53,54). If the goal is to achieve fistula healing an IFX-TL ≥10.1 μg/mL has been suggested. An IFX-TL <10.1 μg/mL was associated with lack of mucosal healing (55).

In our reviewed articles, 2 studies suggested optimal cut-off IFX thresholds, that is, for ongoing IFX therapy at 12 months (49) (IFX-TL ≥9.10 μg/mL at week 10) and for deep remission (clinical remission with normal CRP) at week 54 (21) (IFX-TL ≥5.5 μg/mL at week 14). Recently, data from a large prospective cohort study by Kennedy et al (2) known as the personalized anti-TNF therapy in CD study (PANTS) was published in the *Lancet* in which the authors included both adult (n = 1391; 86.4%) and pediatric (n = 219; 13.6%) patients with CD treated with IFX. Interestingly, these data support a higher target IFX concentration than previously thought, both during induction and maintenance (30–35 μg/mL at week 6 for week 14 remission and 7 μg/mL at week 14 for week 54 remission, respectively). Continued prospective cohort research on IFX TLs in relation to clinical outcome will provide more well-defined recommendations in the future.

It is known from adult IBD literature that IFX clearance is associated with disease severity (10,61,62). The extent and severity of mucosal inflammation in children with IBD is reflected by the clinical need for dose escalation in this population, to achieve increased IFX serum concentrations above the therapeutic lower threshold (63). Hypothetically, these patients may benefit from higher initial IFX dosing during induction for maintenance of adequate IFX serum concentrations and thus IFX treatment (Fig. 1C). To maintain response children and adolescents with IBD more often require dose escalation or interval shortening in the first year of IFX treatment compared to adults (50%–57% vs 23%–46%, respectively) (7,64–66). In addition to the need for higher dosing in case of increased clearance in acute severe

TABLE 1. Pharmacodynamics: infliximab concentration and clinical response in the pediatric population by treatment phase

Study	Text	N	Disease	Clinical endpoints	IFX-TL related to clinical response	IFX PK data	Study findings
Induction							
Adedokun et al (25)	FT	60	IBD, UC only	Clinical response at week 8 Clinical remission at week 8 (PUCAI/Mayo) Mucosal healing at week 8 (Mayo endoscopy subscore)	Yes	Induction: Age: week 6 TL lower in patients aged 6–11 years vs 12–17 years (7.1 vs 15.3 μg/mL) Maintenance: 8-week infusions: 1.9 μg/mL 12-week infusions: 0.8 μg/mL	IFX-TL: high IFX-TL associated with increased efficacy specifically clinical response, clinical remission, and mucosal healing (no *P* value)
El-Matary et al (47)	FT	27	IBD, Crohn only	Disease phenotype (healing of fistulizing perianal CD [PCD] at week 24)	Yes	Induction: median pre-fourth dose IFX-TL in the group with healed fistulae or fistulae in the process of healing was 12.7 μg/mL (IQR; 6.6–15.5) compared with 5.4 μg/mL (2.7–8.4) in the nonresponsive perianal CD disease group ($P = 0.02$).	IFX-TL: Significant correlation between IFX-TLs at week 14 and healing of fistulizing perianal CD at week 24 ($r = 0.65$; $P = 0.0002$). IFX-TL was a good predictor of fistula healing 24 weeks after start of IFX treatment (OR, 1.2; 95% CI, 1.004–1.29; $P = 0.04$).
Hadigan et al (26)	A	21	IBD, Crohn only	Clinical disease score Disease phenotype Clinical response (weeks 4 and 8) Clinical remission (weeks 4 and 8) Adverse IFX reactions	No	Serum IFX concentration after one IFX infusion proportional to dose; 4.0, 40.2, 88.6 μg/mL at week 1 following the infusion for 1, 5, and 10 mg/kg	IFX-TL: Association with clinical parameters not examined. At weeks 4 and 8, respectively clinical response was achieved in 65% and 90%, and clinical remission was achieved in 25% and 38%.
Rosenthal et al (21)	A	38	IBD	Primary nonresponse Clinical remission (CR) (week 54) based on disease score and absence of dose or frequency intensification before week 54 Deep remission CR with normal CRP Sustained Durable remission CR at every maintenance infusion (week 14–54)	Yes	NR	IFX-TL: week 14 IFX-TL associated with week 54 clinical remission ($P = 0.009$), deep remission ($P = 0.009$), and clinical remission at every maintenance infusion ($P = 0.04$). Optimal cut off IFX-TL at week 14 to predict deep remission was 5.5 μg/mL ($P = 0.01$).
Maintenance							
Burgess et al (41)	FT	60	IBD, Crohn only	Clinical response	Yes	Induction: median IFX-TL postinduction was 8.4 μg/mL (week 6 median = 10.9 μg/mL; weeks 11–14 median 5.9 μg/mL) Maintenance: significantly lower than median IFX-TL of patients postinduction (4.0 μg/mL; $P < 0.001$).	IFX-TL: median IFX-TL significantly lower in patients in relapse compared to remission (3.0 vs 5.2 μg/mL; $P < 0.001$). IFX-TL <3 μg/mL; in 31/63 (49%) patients in relapse vs 30/143 (21%) patients in remission ($P < 0.001$). IFX-TL >7 μg/mL; in 7/63 (11%) patients in relapse vs 46/143 (32%) patients in remission ($P < 0.001$)
Cardile et al (19)	A	15	IBD	Clinical disease score Adverse IFX reactions	No	Maintenance: 5.5 μg/mL (range 0.1–14.9). No difference between CD and UC (2.5 vs 3.2 μg/mL; $P = 0.6$).	IFX-TL: No significant association between clinical score and TL (no *P*-value)

Study	Text	N	Disease	Clinical endpoints	IFX-TL related to clinical response	IFX PK data	Study findings
Chi et al (29)	FT	223	IBD	Clinical disease score	Unclear	Overall, mean IFX-TL of all patients was 13.6 μg/mL (SD ± 11.1)	IFX-TL: Cutoff of ≥3.5 for sustained durable response was taken from literature by authors. IFX-TL <3.5 μg/mL less common in IM therapy patients compared to current IFX monotherapy patients (8.3% (7/84) vs 27.3% (38/139); adjusted OR 0.13; 95% CI, 0.04–0.39; $P < 0.01$).
Choi et al (34)	FT	39	IBD	Clinical response during maintenance treatment Clinical remission (PCDAI/PUCAI <10) or poor response Regained response after dose intensification	Yes	Maintenance: IFX-TLs in patients in clinical remission group (n = 16; median, 3.99 μg/mL; IQR, 0.30–21.96). IFX-TL in patients with poor response group (n = 23; median, 0.88 μg/mL; IQR, 0.00–6.80) ($P = 0.002$).	IFX-TL: Significant difference in IFX-TLs between patients in clinical remission compared to patients who had poor response to treatment (n = 16; median 3.99 μg/mL; IQR 0.30–21.96 vs n = 23; median 0.88 μg/mL; IQR 0.00–6.80; $P = 0.002$). Seventeen patients (17/21, 80.9%) from poor response group regained response after dose intensification, with increase of IFX-TLs (median 7.76 μg/mL; IQR 1.96–20.00).
Hoekman et al (44)	FT	39	IBD	Clinical disease activity (short PCDAI/PCDAI/PUCAI) Clinical remission (PCDAI/PUCAI <10)	No	Maintenance: In cross-sectional analysis median IFX-TL was 3.5 μg/mL, 38% lower and 23% higher than therapeutic range of 3–7 μg/mL	IFX-TL: No difference in median TL between patients in remission or active disease (3.5 vs 2.3 μg/mL). Actual clinical scores did not correlate with TL ($P = 0.95$)
Hofmekler et al (37) 2017	FT	129	IBD	Clinical outcome (defined as requiring dose optimization)	Unclear	Maintenance: serum IFX was detected in 212 samples (88.0%) with a median level of 11.8 μg/mL (IQR 5.9–17.7). Patients receiving a dose of 5 mg/kg at Q6 week interval exhibited significantly higher IFX level than Q8 week interval (9.8 μg/mL (4.6–15.9) vs 5.6 μg/mL (2.9–11.4); $P = 0.009$.	IFX-TL: study did not specifically examine symptomatic loss of response, but demonstrated that IFX-TLs were low in 48 of 129 (37.2%) children who required dose optimization based on serum IFX levels <3 mg/mL during maintenance (no P value).
Minar et al (32)	FT	72	IBD, Crohn only	Disease phenotype Clinical disease score (PGA) Clinical remission (PGA was quiescent between >6 and <9 months from TDM-led intensification) Primary non response (no improvement of symptoms during IFX induction) Secondary loss of response (worsening of gastrointestinal symptoms following initial clinical response to IFX induction)	Yes	Maintenance: concentrations reported only in subselection of 55 patients (see Table 1). IFX concentrations were also determined mid-interval, in-between infusions	IFX-TL: inflammatory CD patients had higher median TL than penetrating/stricturing CD patients (5.2 vs 3.6 μg/mL; $P < 0.05$)
Minar et al (45)	A	37	IBD, Crohn only	Disease phenotype Steroid-free remission IFX failure	No	NR	IFX-TL: trend for lower IFX-TL in IFX failure patients compared to those remaining in remission (mean 1.6 μg/mL (SD 1.3) vs mean 3.5 μg/mL (SD 3.5); $P = 0.1$)

Study	Text	N	Disease	Clinical endpoints	IFX-TL related to clinical response	IFX PK data	Study findings
Rolandsdotter et al (40)	FT	45	IBD	Clinical response Clinical remission (based on disease activity score, CRP, and ESR)	Yes	Maintenance: mean IFX-TL was 5.2 μg/mL, median IFX-TL 4.5 μg/mL (range from <0.2 to 21)	IFX-TL: significantly higher mean IFX-TL in samples taken during remission compared to active disease (7.2 vs 4.5 μg/mL; $P < 0.05$). No significant difference between patients with active disease compared to patients in remission in dose-interval (days) (mean 43.0 days vs mean 42.7 days, respectively; $P = 0.88$), nor in mean dose of IFX (6.4 vs 6.5 mg/kg, respectively; $P = 0.76$).
Van Hoeve et al (42)	FT	52	IBD	Clinical remission (PCDAI/PUCAI <10) Biological remission (CRP ≤5 mg/L in combination with an ESR ≤20 mm/h, in patients with elevated inflammatory markers at the start of IFX therapy only) Combined clinical and biological remission (see criteria above) Endoscopic remission (absence of ulcerations on endoscopy)	Yes	Maintenance: median IFX-TL was 5.0 [3.2–7.3] μg/mL	IFX-TL: during maintenance, significantly higher median IFX-TL in children in different types of remission compared to lack of response. Clinical remission compared to lack of response (5.4 μg/mL [3.8–8.0] vs 4.2 μg/mL [2.6–6.7]; $P < 0.0001$), biological remission compared to lack of response (5.2 μg/mL [3.7–7.7] vs 4.2 μg/mL [2.6–6.5]; $P < 0.0001$), combined clinical and biological remission compared to lack of response (5.7 μg/mL [4.0–8.2] vs 4 μg/mL [2.7–6.8]; $P < 0.0001$), and endoscopic remission compared to lack of response (6.5 μg/mL [4.2–9.5] vs 3.2 μg/mL [2.3–5.6]; $P = 0.001$). Similar results on endoscopic remission versus no remission based on diagnosis [CD vs UC]: in CD patients 6.5 μg/mL [3.8–9.6] vs 3.7 μg/mL [2.7–4.9]; $P = 0.012$; in UC patients 6.2 μg/mL [4.5–9.3] vs 4.8 μg/mL [2.5–7.1]; $P = 0.037$.
Induction and maintenance							
Mehrotra et al (27)	A	60	IBD, UC only	Clinical response (week 8) Clinical remission (week 54)	No	Induction: adult UC clinical trial data (not specified) was used for comparison. Week 8 median IFX serum concentrations were similar between children and adults (29 vs 33 lg/mL). Steady-state TLs in pediatric patients were slightly lower compared to adults (1.9 vs 2.5 lg/mL).	IFX-TL: clinical response was similar for pediatric and adult patients (70%) despite slightly lower median serum concentrations in children compared to adults at week 8 (29 vs 33 lg/mL) and during maintenance (1.9 vs 2.5 lg/mL). Similar remission rates at week 54 in adults compared to children and adolescents (35% vs 38%) after 5 mg/kg dose every 8 weeks.

Study	Text	N	Disease	Clinical endpoints	IFX-TL related to clinical response	IFX PK data	Study findings
Merras-Salmio and Kolho (39)	FT	146	IBD	Clinical outcome (remission with IFX withdrawn, ongoing IFX therapy, no efficacy/loss of initial efficacy with IFX discontinued, or adverse effects)	Yes	Induction: median IFX-TL after induction therapy was 8.0 mg/L. Maintenance: median IFX-TL was lower at 2.8 mg/L. Significantly lower IFX-TLs in CD compared to patients with UC (respective medians 2.6 and 4.4 mg/L, $P < 0.0.001$).	IFX-TL: substantially higher median IFX-TLs in patients with either remission or ongoing therapy, compared to patients with no or loss of efficacy (3.7 mg/L [1.8–5.4] vs 1.2 mg/L [0.03–4.4], respectively; $P = 0.01$).
Singh et al (46)	FT	58	IBD	Clinical disease score Clinical remission (CR) based on disease score Persistent remission (PR) (week 54) CR without dose intensification Sustained durable remission (SDR) PR from week 14 through week 54 (SDR14) or from week 22 through week 54 (SDR22) Primary nonresponders patients who stopped IFX before the first maintenance infusion (week 14). Early termination patients who entered maintenance phase at week 14, but stopped IFX therapy before week 54 end point.	Yes	Induction: median [IQR] IFX-TL at week 14 was 5.1 [3.1–7.5] μg/mL Maintenance: median [IQR] IFX-TL at week 54 was 5.2 [3.7–9.1] μg/mL	IFX-TL: significant difference in median IFX-TL at week 14 in patients with persistent remission compared to no persistent remission (4.7 vs 2.6 μg/mL; $P = 0.03$). Higher week 14 median IFX-TLs in patients in persistent remission from week 22 through 54 compared to patients not in persistent remission (5.1 vs 3.0 μg/mL; $P = 0.04$)
Stein et al (49)	FT	77	IBD, Crohn only	Clinical disease score (PCDAI) Clinical response (ongoing IFX therapy at 12 mo)	Yes	Induction: median (IQR) IFX-TL at week 10: 16.80 μg/mL (9.00–35.00) Maintenance: 6 months 3.80 μg/mL* (0.90–7.90), and 12 months: 5.85 μg/mL**(1.05–11.05) after start of IFX. (Excluding 8 (*) and 17 (**) patients off of IFX at time of respective measurement)	IFX-TL: ongoing IFX therapy at 12 months was associated with higher 10-week median IFX-TLs (20.40 μg/mL; [IQR 11.20–35.00] vs 8.70 μg/mL; IQR 0.90–16.90; $P = 0.01$). Suggested best cutoff value for week 10 IFX-TL was ≥9.10 μg/mL.

A = abstract; CD = Crohn disease; CI = confidence interval; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FT = full text; IBD = inflammatory bowel disease; IFX-TL = infliximab trough level; IQR = interquartile range; NR = not reported; OR = odds ratio; PCDAI = Pediatric Crohn Disease Activity Index; PGA = physician global assessment; PK = pharmacokinetic; PUCAI = Pediatric Ulcerative Colitis Activity Index; UC = ulcerative colitis.

pediatric UC, current ECCO-ESPGHAN guidelines also advise to aim for higher TLs (5–10 μg/mL) during maintenance treatment and thus suggest an IFX intensified induction dose (dosing between 5 and 10 mg/kg is suggested). In addition, the authors suggest TDM of IFX-TLs during induction to maximize efficacy (16).

Despite the lack of evidence in IBD, we suspect that IFX clearance is inversely related to age (ie, higher clearance in younger children) similar to findings by Goldman et al (3) in patients with juvenile idiopathic arthritis. TLs increase with dose and the IFX level profile in children shows a pattern similar to adults during induction and maintenance (Fig. 1A) (4,7,8). Several pediatric studies, however, reported TLs below the therapeutic range with a standard 5 mg/kg dose at an 8-week interval (25,27). Four studies comparing different age groups showed TLs to be lower in younger children with IBD compared to adolescents (25,29,37,43).

Data suggest that there is an association between young age and a decrease in IFX exposure, that is, in a pediatric patient with IBD receiving standard treatment IFX-TLs are lower compared to an adult patient with IBD with similar disease burden. It would be interesting to determine at what age pediatric PK and adult PK begin to show more resemblance. Unfortunately current available data do not yet enable us to answer this question. It is important to acknowledge that the aforementioned association between younger age and increased clearance might be an oversimplification. Because younger children tend to have more colitis with extensive disease, disease severity (ie, extent and location) may be a confounding factor.

Reported prevalence of ATI in the pediatric population is comparable to adult data as reviewed by Lichtenstein et al (67). ATI formation increases IFX clearance, thereby lowering TLs and IFX efficacy. The potential effects of ATI formation on PK and clinical disease activity are schematically represented in Figure 1B. On the contrary, achieving higher IFX-TLs by increasing IFX dose or dosing interval can potentially prevent ATI formation (Table 2), because in adults both prolonged low IFX-TLs and low IFX-TLs at week 14 may precede ATI formation (68,69). Similarly to adult data, Rosenthal et al (21) reported an inverse association between IFX-TL at week 14 and ATIs at week 54 ($P = 0.003$) in pediatric patients with IBD. Several studies reported a reduction of ATI formation and ATI concentration with concomitant IM therapy, and an increase of IFX-TL. Interestingly, van Hoeve et al (42) did report a significant clinical and biological benefit from combination therapy.

Other factors in children and adolescents associated with low TLs were low albumin, low body weight, and high inflammatory markers (19,25,29,32,39,40,43,44,46,48). These are all factors that could potentially lead to increased clearance, as shown in adults (25,44,70). In older children, median biological half-life (6,7,25) and overall clearance (71) of IFX are reported to be similar to the adult population. In summary age, albumin, body weight, and the presence of inflammatory markers all seem associated with IFX clearance within the pediatric IBD population.

The strength of this systematic review is that it consists of a comprehensive overview of articles with original data on IFX PK and PD in children and adolescents. Several pediatric studies observed an association between IFX exposure and clinical response, similar to studies in adults. In addition, IFX-TLs were related with multiple factors including disease severity, age, presence of ATI, and clearance. Taken together, there is enough evidence to suggest that a proportion of pediatric patients will not achieve adequate IFX-TLs using weight-based dosing, but rather would benefit from individualized dosing which could result in a higher dose and/or shorter dosing interval. PK effects of therapy adjustment can be monitored by frequent measurement of IFX-TLs, also known as TDM. Figure 1C schematically represents the hypothetical PK profile of IFX in relation to clinical disease activity for patients that require adjustment of initial standard IFX treatment. Although analytical tests to determine IFX concentrations or ATIs are not standardized, several authors have reported good correlation between enzyme-linked immuno sorbent assays (ELISA), and electro-chemiluminescence immunoassays (ECLIA) and ELISA from different manufacturers (72–74). A greater greater understanding of how to interpret IFX PK data from different assays will improve comparability of their respective results. At present, efforts are also focusing on developing new assays that can improve on the speed of current assays used in TDM by measuring IFX concentrations or ATIs in dry blood spots or whole blood instead of serum. One such new assay using fiber optic surface plasmon resonance technology seems to generate data comparable to current ELISA assays (75). Novel assays could potentially speed up the TDM process from a current 2 hours to 1.5 days minimum to 20 minutes. More and more, proactive TDM is incorporated in clinical care to optimize treatment in the pediatric population. The possibility of point-of-care TDM by the development of new techniques, could benefit patients, and decision making by treating physicians.

Limitations of the current systematic review concern the limited number of small studies in children and their variable design and lack of standardization in measurement of IFX and ATI concentration. An accurate quantification and comparison of ATI concentration between studies is most difficult since ELISA assays do not detect ATIs in the presence of IFX. Care needs to be taken when comparing IFX-TLs and ATI levels. The small sample size of most studies (<n = 100 in 25/32 studies) make statistical analyses less reliable and complicate any comparison with adult PK data, as derived from larger patient samples. Despite these limitations the reported associations between IFX-TL and ATIs, and disease severity, disease extent, (prior) IM use, inflammatory markers, albumin, body weight, and age are still relevant. Although most

TABLE 2. Dosing and drug monitoring considerations for clinicians treating children and adolescents with infliximab

- Maintaining adequate IFX serum trough levels above the therapeutic lower limit of 3 μg/mL in children and adolescents is important for clinical efficacy of IFX and may also protect against the formation of antibodies-to-infliximab (ATIs).
- Treatment with concomitant immunomodulatory (IM) therapy during the induction phase of IFX treatment is advised, to prevent the formation of ATIs, and to increase the IFX serum concentration in children and adolescents.
- In case of IFX monotherapy in children and adolescents, a dose >5 mg/kg or a shortening of interval between IFX infusions might be required to reach and maintain adequate IFX serum trough levels above the therapeutic lower limit of 3 μg/mL. Frequent trough level measurement (therapeutic drug monitoring) is advised
- Young children (<11 years of age) are more likely to require a dose >5 mg/kg IFX or a shortening of interval between IFX infusions to reach and maintain adequate IFX serum trough levels above the therapeutic lower limit of 3 μg/mL. Frequent trough level measurement (therapeutic drug monitoring) is advised
- In children and adolescents with high disease severity (such as severe acute colitis), an initial dose >5 mg/kg IFX or a shortening of interval between IFX infusions should be considered to reach adequate IFX serum concentrations. Recent guidelines suggest that the therapeutic window in these patients is possibly between 5 and 10 μg/mL.
- In children and adolescents with low albumin concentrations, an initial dose >5 mg/kg IFX or a shortening of interval between IFX infusions should be considered to reach adequate IFX serum concentrations above the therapeutic lower limit of 3 μg/mL.

IFX = infliximab.

factors show trends similar to the adult population, there are unique differences such as the association between low TLs and young age and the more frequent occurrence of therapy escalation in children and adolescents with IBD.

Examining these distinctive factors will prove helpful in clarifying PK and PD differences in children and adolescents compared to adults. Large prospective cohort studies such as the recent PANTS study (2) have the potential to clarify these and other important questions regarding IFX PK, PD, and safety going forward. On the basis of this review, we propose several considerations for more optimal dosing of IFX in the pediatric population (Table 2).

CONCLUSIONS

In summary, literature with data on IFX PK or immunogenicity in children and adolescents is limited. From the included studies in this review, we conclude that current practice of extrapolation from adult experience to pediatric treatment is not valid. Currently, pediatric PK studies are too few and also lack statistical power to prove similarity of PK and PD between children and adolescents, and adults. Available literature shows increased IFX clearance specifically in young children and children with more severe disease. Especially in these cases, loss of response and/or need for frequent therapy adjustment is common when adult-extrapolated, weight-based dosing is used. Patients with increased clearance will need higher dosing of IFX to reach ''standard'' TLs (3–7 μg/mL). In addition, recent ECCO-ESPGHAN guidelines recommend aiming at higher IFX-TLs (5–10 μg/mL) in severe acute UC patients, while stressing the importance of TDM. To further improve therapeutic strategies in the pediatric population utilizing IFX, or any other newly developed biological drug, easy-to-use dashboard systems that combine data from existing PK models with patient information acquired from TDM and patient factors, can help to further optimize individual IFX dosing. Well-designed studies on the PK properties in the pediatric population, as well as implementation of proactive TDM can contribute to the advancement of these dashboard systems and improve on individualized therapeutic strategies in the future.

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