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POSITION STATEMENT

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the therapeutic drug monitoring in pediatric inflammatory bowel disease

Lina M. Felipez[1] | **Sabina Ali**[2] | **Edwin F. de Zoeten**[3] | **Anne M. Griffiths**[4] | **Sandra C. Kim**[5] | **Ashish S. Patel**[6] | **Joel R. Rosh**[7] | **Jeremy Adler**[8,9]

[1]Nicklaus Children's Hospital, Miami, Florida, USA

[2]Benioff Children's Hospital, University of California at San Francisco, Oakland, California, USA

[3]Children's Hospital of Colorado Anschutz Medical Center, University of Colorado, Aurora, Colorado, USA

[4]The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[5]Cleveland Clinic Children's Hospital, Cleveland Clinic, Cleveland, Ohio, USA

[6]Phoenix Children's Hospital, Phoenix, Arizona, USA

[7]Cohen Children's Medical Center, Zucker School of Medicine, New Hyde Park, New York, USA

[8]C.S. Mott Children's Hospital, Michigan Medicine, Ann Arbor, Michigan, USA

[9]Susan B. Meister Child Health Evaluation and Research Center, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Inflammatory bowel diseases (IBD) require effective therapies to prevent morbidity and maintain quality of life. The introduction of biologic agents, beginning with monoclonal antibodies targeting tumor necrosis factor (TNF) alpha, has launched a new era of advancements that have markedly improved short- and long-term outcomes of Crohn's disease and ulcerative colitis. Along with these improvements, there have been challenges to address in optimizing use of biologic therapies in children with IBD. Young children may have rapid drug clearance, and growing children have changing medication needs related to changes in body size, metabolism, and development. For these and other reasons, one size (one dose) does not fit all. Therapeutic drug monitoring (TDM), which involves measurement of drug concentration in serum usually, typically at the predose trough, has emerged as a valuable tool for optimizing dosing and preventing pharmacokinetic failure. This society paper reviews the use of TDM, including target ranges during induction and maintenance therapy for anti-TNF agents and for emerging biologics. This report has been compiled by pediatric gastroenterologists on behalf of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition IBD committee after extensive review of the current literature. The purpose of this clinical position statement is to provide guidance to clinicians in the use of TDM to optimize the treatment of children with IBD.

CME module may be found at https://learnonline.naspghan.org/jpgn2

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Correspondence
Jeremy Adler, 2800 Plymouth Rd., NCRC Bldg 16, G029W, SPC 2800, Ann Arbor, MI 48109-2800, USA.
Email: jeradler@umich.edu

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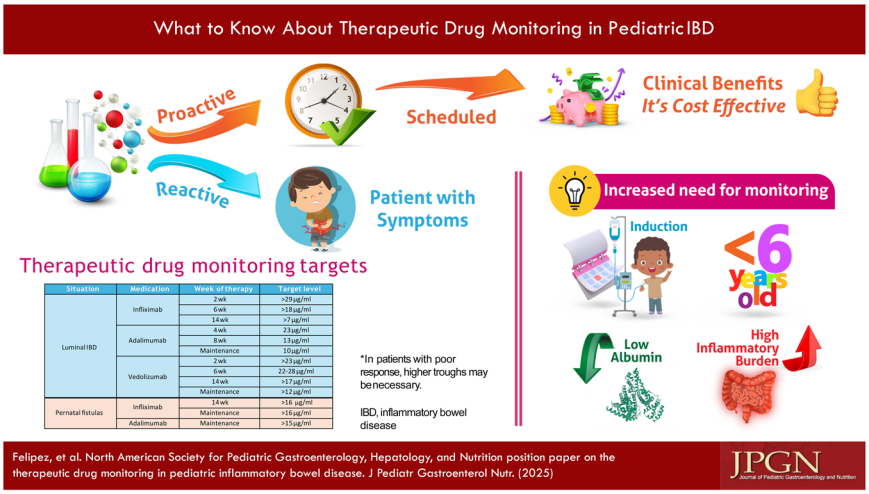

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antibody, dosing, pharmacokinetics, proactive monitoring, reactive monitoring

1 | INTRODUCTION

The therapeutic armamentarium for the inflammatory bowel diseases (IBD) is evolving rapidly, with recent regulatory approvals of several new oral small molecules (e.g., Janus kinase inhibitors and sphingosine-1-phosphate inhibitors) and biologic agents (anti-interleukin [IL]-23) for affected adults. Biologic therapies developed for IBD, and other immune-mediated disorders are large and complex molecules manufactured using recombinant DNA technology and designed to interact with the immune system in specific ways. The advent of target-specific biologic therapies, beginning more than 25 years ago with monoclonal antibodies against tumor necrosis factor alpha (anti-TNFα), ushered in a new era in the management of pediatric IBD. The greater efficacy of anti-TNFα medications compared to previously available therapies has allowed treatment targets to move beyond the control of symptoms and normalization of linear growth to facilitation of mucosal healing, and prevention of disease-associated complications.[1–6] For infliximab and adalimumab, multicenter clinical trials have established efficacy in achieving steroid-free remission in pediatric patients with luminal Crohn's disease (CD) and ulcerative colitis (UC), findings which have been further confirmed in real-world pediatric experience.[7–12]

Since the first introduction of anti-TNFα medications, much has been learned about how to optimize efficacy and sustain long-term therapeutic benefits. Sustained responsiveness to therapy is essential in children, given their long lives ahead, during which effective disease control will be needed. Therapeutic drug monitoring (TDM), which involves measuring serum levels (typically at trough), is increasingly used to optimize biologic therapy. This is especially important in growing children, where historically recommended doses were based on limited pharmacokinetic (PK) and pharmacodynamic (PD) data across the pediatric spectrum of age and body size. TDM has evolved from assessment of unsatisfactory response or loss of response to become a tool for proactively optimizing drug exposure to enhance the likelihood of achieving and maintaining clinical and endoscopic outcomes.

This position paper aims to address the role of TDM and optimal dosing strategies for biologic therapies used in treating pediatric IBD. The emphasis will be on

What is Known

- There is significant interindividual variation in clearance rates of biologic drugs in children with inflammatory bowel disease.
- Individualization of dosing is necessary depending on the degree of drug clearance and on the treatment target (e.g., symptom control vs. mucosal or transmural healing).
- Therapeutic drug monitoring (TDM) can aid in dose optimization of biologic medications used to treat inflammatory bowel disease.

What is New

- Summary of evidence for TDM targets in different pediatric inflammatory bowel disease states.
- Important gaps in the evidence remain for treating children with inflammatory bowel disease.

TABLE 1 Therapeutic drug monitoring targets.

Situation	Medication	Week of therapy	Target level (μg/mL)[a]
Luminal IBD	Infliximab	2 weeks	>29
		6 weeks	>18
		14 weeks	>7
	Adalimumab	4 weeks	23
		8 weeks	13
		Maintenance	10
	Vedolizumab	2 weeks	>23
		6 weeks	22–28
		14 weeks	>17
		Maintenance	>12
Perianal fistulas	Infliximab	14 week	>16
		Maintenance	>16
	Adalimumab	Maintenance	>15
VEO-IBD	Infliximab	2 weeks	>23
		6 weeks	>16

Abbreviations: IBD, inflammatory bowel disease; VEO, very early onset.
[a]Patients with poor response troughs higher may be necessary.

anti-TNFα medications, which have the most robust data, but data relevant to newer medications will also be included as available. Throughout the paper, we will summarize available evidence for TDM targets (see Table 1). Summary recommendations are derived from the literature review and agreed upon by consensus of the authors. The optimal timing of TDM is not yet clear. For example, should TDM be checked before the 3rd and/or 4th doses? Nevertheless, we have documented recommended target levels at each timepoint for which data exist as a reference for clinicians.

1.1 | Methods

This report has been compiled by pediatric gastroenterologists on behalf of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) IBD committee after extensive review of the current literature, using PubMed and Google Scholar to identify all peer-reviewed manuscripts. Searches included relevant keywords and free text including medications by name, "therapeutic drug monitoring," "trough," "monitoring," "antidrug antibodies," "loss of response," "pharmacokinetics," "pharmacodynamics," and "immunogenicity." The author's expertise, strength of the evidence, sample size, and statistical significance were assessed for each paper. No formal grading of the quality of evidence, or voting on specific statements was done. However, all authors reviewed all sections of this manuscript, and all agreed with the final statements and language as published.

1.2 | What is TDM?

TDM refers to measuring the concentration of a drug or its metabolites to enable individualized dose adjustments with the aim of optimizing efficacy. TDM can also be performed with or without concomitant measurement of antidrug antibody (ADA) levels.[13] TDM can be used during induction or maintenance therapy. TDM can be "proactive" and performed at a predesignated point in time, or "reactive" when a patient develops symptoms. Proactive TDM during induction (referred to as "induction TDM") is important because patients commonly have active disease, with resulting increased drug clearance, putting them at greater risk of inadequate drug exposure, early development of antidrug antibodies, and treatment failure.[14]

Primary nonresponse to any drug may occur for PK or pharmacodynamic (PD) (i.e., mechanistic) reasons.[13] TDM is performed with the aim of preventing primary PK-related treatment failure. In anti-TNFα therapy, several studies have shown an association between higher induction anti-TNFα drug concentrations and favorable therapeutic outcomes. For example, higher infliximab concentrations at Weeks 6 and 14 are associated with subsequent higher rates of steroid-free remission.[15,16] For both Infliximab and adalimumab, suboptimal Week 14 drug concentrations are associated with increased risk of development of ADA and low drug concentrations, in turn adversely affecting durability of response.[17]

Development of ADA can be associated with increased drug clearance, greater likelihood of treatment failure, and increased risk of antibody-mediated reaction.[18,19] For low-level ADA, these risks can be mitigated with either dose escalation or the addition of concomitant immunomodulators. Low-level antibodies may be transient and may resolve after these measures.[18,20] However, for patients with high-level ADA, such measures are generally ineffective, and switching to a different medication within the same class is generally warranted.[18] In the case of low-level ADA, early detection is beneficial, as it enables early identification of patients, before developing high-level antibodies or to becoming symptomatic. This provides an opportunity for dose escalation, and possible prevention of worsening ADA development and loss of efficacy or reaction.[17,20,21]

For patients receiving anti-TNFα maintenance therapy, most published data focuses on the use of reactive TDM in the setting of secondary loss of response. The use of reactive TDM provides information which may aid in treatment decision-making to determine whether a patient is more likely to respond to

dose-escalation of the same medication, switching in class to another anti-TNFα medication, or switching out of class to an agent with a different mechanism of action. Reactive TDM has demonstrable clinical benefits and is cost-effective, and has been endorsed by multiple international consensus guidelines.[22–24]

In contrast to reactive TDM, proactive TDM is performed to ensure ongoing adequate dosing, and not to investigate poor response to therapy. Assa et al. conducted an open-label prospective randomized trial of proactive TDM among children with CD treated with adalimumab.[21] All patients responding to standard induction regimen were randomized to proactive versus reactive TDM every 8 weeks beginning at Week 4. Patients randomized to proactive TDM with adalimumab regimen intensification for any level <5 μg/mL were nearly twice as likely to achieve sustained corticosteroid-free remission by Week 72 compared to those who underwent reactive TDM (82% vs. 48%; $p = 0.002$). This corresponds to a number needed to treat of 3, meaning for every three patients who undergo proactive TDM, one additional patient will achieve sustained remission compared to without proactive TDM. Importantly, decline in fecal calprotectin was also greater among those managed with proactive TDM. Proactive TDM has also been evaluated in the real-world setting of implementing a practice-wide protocol. In a single center prospective observational cohort, Zitomersky et al. found ongoing intermittent TDM during maintenance infliximab therapy enabled identification of patients with low serum infliximab levels or presence or antidrug antibodies, facilitating dose optimization,.[25] In a multicenter retrospective study, Ali et al. reported greater longevity of anti-TNF therapy among children with proactive TDM, where 60% fewer discontinued the medication for loss of efficacy compared to those without proactive TDM. Lyles et al. further reported on the results of a prospective quality improvement initiative in which, after measurement of induction TDM, per protocol all patients being treated with anti-TNFα medications had TDM measured yearly starting in 2014.[26] They found that 59% of patients in the postimplementation timeframe who underwent proactive TDM had sustained steroid-free clinical remission compared to 42% of patients treated before implementation of routine proactive TDM ($p = 0.003$). They further found that the development of ADA was 55% less common if proactive TDM was done. These findings are notably different from those found in randomized controlled studies of proactive TDM in adults with IBD. The reasons for this have not been explored, but the inadequacy of calculating dosing based on weight rather than body surface area (BSA) in younger children is likely to play a role, as is rapid drug clearance in younger patients and rapid growth of older patients.[27–29] However, despite weaker findings of proactive TDM in adults, there is evidence proactive TDM may be cost-effective even in adult patients.[30] In a systematic review of studies evaluating cost, Marquez-Megias et al.[31] found that a strategy of proactive TDM is cost-effective, and possibly cost-saving. Wu et al. subsequently conducted an evaluation of infliximab TDM prospectively evaluated across Australia among all adults with IBD.[32] To our knowledge, prospective cost-effectiveness studies have not yet been evaluated in pediatrics. However, given the unambiguous improved outcomes with proactive TDM in prospective pediatric studies, proactive TDM is likely to be cost-effective in children.[33–35] This was recently supported by a Markov simulation modeling study in pediatrics which found proactive TDM to be more cost-effective than reactive TDM.[36]

2 | ANTITUMOR NECROSIS AGENTS

The "biologic era" for IBD commenced with the US Food and Drug Administration (FDA) approval of infliximab for the treatment of moderate–severe CD in adults in 1998. Optimization of this type of therapy continues to be an active area of research. Notably, more than 25 years after infliximab was first approved, a recent systematic review concluded that there are insufficient PK studies in pediatric IBD and that this precludes full extrapolation from adult dosing studies.[1] However, there is important clinical experience and high-quality evidence supporting treating pediatric IBD with anti-TNFα agents.

2.1 | Mechanism of action

TNFα is a pro-inflammatory cytokine implicated in the etiopathogenesis of IBD, among other systemic inflammatory and autoimmune diseases. TNFα is produced by T-lymphocytes, macrophages, dendritic cells, and fibroblasts. The precursor form of TNFα transmembrane (tmTNF), is activated through TNFα converting enzyme (TACE) to soluble TNFα (sTNF), which impacts inflammatory pathways through TNFα receptors (expressed in all human tissue). TNFα plays a critical role in the regulation of inflammatory responses through its pleiotropic effect on different immune and nonimmune cells including macrophage activation, Paneth cell death, intestinal epithelial cell apoptosis, T-cell apoptosis, neoangiogenesis, and matrix metalloproteinase tissue inhibition, the dysregulation of which leads to the development of chronic inflammatory disease.[37,38]

Multiple anti-TNFα agents have efficacy for the treatment of chronic inflammatory and autoimmune disease. The primary mode of action is through neutralization of sTNF and tmTNF as well as induction of

apoptosis.[17,39] Although all anti-TNFα agents are able to neutralize sTNF, there may be differences in the intrinsic binding properties to sTNF and to neutralization via TNFα receptors.[38]

Anti-TNFα agents for IBD therapy can be categorized in the following forms: monoclonal IgG1 antibody agents (mAb) against human TNFα (infliximab, adalimumab, and golimumab) and fragment antigen-binding (Fab') region of anti-TNFα mAb (certolizumab). However, certolizumab, while potentially less immunogenic, is generally not as efficacious in CD compared to infliximab or adalimumab, and development of this agent for pediatric approval has been disbanded.[40]

2.2 | PKs and PDs

PK relates to how the body metabolizes and clears a medication, while PD relates to what the drug does to the body. Anti-TNFα therapy is currently available as an intravenous (IV) infusion or as a subcutaneous (SC) injection and the method of administration has a direct effect on drug absorption. IV administration allows for rapid and reliable absorption while the SC route undergoes lymphatic transport leading to variable rates of absorption.[17,41] As a class, anti-TNFα elimination is largely due to intracellular clearance through the reticuloendothelial system with little contribution from renal or biliary clearance due to the large size of these proteins.[42,43] While the full catabolism of anti-TNFα monoclonal antibodies is not yet known, immunogenicity with antibody-mediated clearance and fecal loss from severely inflamed bowel are each associated with accelerated drug clearance.[44,45]

Patient characteristics including age, sex, weight, serum albumin, concomitant immune modifying therapies and ADA levels all affect the PK of anti-TNFα medications.[1,46] Notably, young age is frequently associated with more rapid drug clearance and decreased serum trough drug levels especially when dosing is based upon body weight as opposed to BSA.[1,27–29,47–49] Hypoalbuminemia has consistently been found to be associated with fecal drug loss and increased drug clearance.[15,50] In addition, inflammatory burden is associated with variable and often increased anti-TNFα medication clearance.[7,41] In each of these settings, increased drug clearance is associated with poor treatment efficacy and increased immunogenicity.[1,7,15,41,44,45,47,48,50] In addition to immunogenicity, which is associated with early drug clearance, there have been data to suggest that carriage of HLA-DQA1*05 is a risk factor for the development of antidrug antibodies.[23,51,52] This immunogenicity can be reduced by administration of concomitant immunomodulators or by attentive use of proactive TDM including during the induction period.[46,53]

Primary or (rarely) secondary PD nonresponse or loss of response to anti-TNFα therapy may also occur, due to disease processes that are not driven by TNFα.[1,54–57] There may be different subtypes of IBD which primarily involve other inflammatory pathways.[58] Genetic polymorphisms may also contribute to variable response to anti-TNFα medications.[59]

2.3 | Anti-TNFα dosing and monitoring targets

2.3.1 | Inflammatory disease

Historically, anti-TNFα target trough levels were defined in adults with CD treated with infliximab where a trough level >5 μg/mL was associated with improved clinical response compared to those with lower trough levels.[22] The results were based on retrospective medical record review where the outcome of clinical response was loosely defined as improvement in symptoms without dose escalation or starting corticosteroids. No children were included in this study. In the intervening years, it has become clear that different target trough levels are needed during induction versus maintenance phase, with different endpoints (e.g., symptom resolution vs. endoscopic healing), and with different phenotypes of disease (e.g., perianal fistulizing vs. nonperianal CD).[60] Pediatric studies have also determined adult infliximab targets are insufficient. In a prospective pediatric study, which used a similar clinical outcome measure, Stein et al. determined that serum infliximab trough levels >9 μg/mL at 10 weeks of therapy were associated with improved clinical outcomes by 12 months.[46,61,62]

In a prospective pediatric study, Clarkston et al. found that a trough level of 29 μg/mL at 2 weeks is required to achieve both clinical and biologic response. Patients with lower trough levels had 13-fold greater odds of clinical nonresponse. Additionally, a trough of 18 μg/mL at 6 weeks was associated with improved response. Patients with lower trough levels had sixfold greater odds of clinical nonresponse. They also observed that patients who did not achieve a trough >5–7 μg/mL by 14 weeks of therapy had a 21-fold increase in the odds of clinical nonresponse.[62] The study further determined that hypoalbuminemia and greater disease burden were associated with lower likelihood of achieving this target trough level with standard induction dosing. Lyles et al. prospectively implemented a practice-wide policy of proactive TDM, targeting a trough level of 5 μg/mL. They found that patients were twice as likely achieve sustained clinical remission and an 80% less likely to develop antidrug antibodies after implementing this proactive TDM policy.[26]

Rinawi et al. also prospectively evaluated children with CD initiating adalimumab.[63] They found a minimum adalimumab level of 22.5 μg/mL at Week 4 and

12.5 μg/mL at Week 8 were associated with higher likelihood of clinical remission including normalization of fecal calprotectin and c-reactive protein at Week 24 without escalation to weekly dosing. A much lower adalimumab trough level (5 μg/mL) was utilized as a threshold to trigger regimen intensification in both the previously mentioned PAILOT randomized trial by Assa et al.[21] Kim et al. also prospectively evaluated pediatric patients with CD, and found an adalimumab level of 8.2 μg/mL during maintenance therapy was associated with improved mucosal healing, while levels above 10 μg/mL were associated with maintenance of remission over 3 years.[64]

When a patient is found to have a subtherapeutic anti-TNFα trough level, the total medication dose should be increased in proportion to the magnitude of how low trough level is below the target. There is evidence to suggest that shortening the dosing interval is more effective at raising the serum level than increasing the dose, similar to the approach of raising the trough level of other medications.[65] However, dose intensification may also be needed, particularly if shortening of the interval has already been done, or if a greater increase in serum level is needed. In addition, if the serum level is extremely low or undetectable, then full re-induction is warranted in addition to dose escalation.[66]

As a practice point, TDM is routinely recommended at the end of induction for most patients. We recommend obtaining TDM earlier during induction in at-risk populations, including younger age children, those with hypoalbuminemia, and those with increased inflammatory burden.

In addition to routine proactive monitoring of patients with inflammatory disease, there is evidence for differential drug clearance during an exacerbation of disease.[67–69] In a retrospective analysis of four cohorts of adults with CD, Wright et al. found patients with active disease on endoscopy had 30% greater adalimumab clearance than those with in endoscopically inactive disease.[70] In a prospective observational adult IBD cohort, Petitcollin et al. found wide variation in infliximab clearance between individuals, which varied with disease activity.[71] Magro et al. conducted a prospective observational PK study which demonstrated increased disease activity is associated with greater infliximab clearance and greater risk of disease progression.[72] Taken together, these and other studies support the need for reactive TDM during active disease. They also indicate greater drug exposure is likely needed during active disease to achieve the above outlined drug trough targets. During active disease, additional reactive TDM is recommended to evaluate the reason for active disease and to enable dose adjustment to achieve therapeutic drub levels.

For inflammatory CD and nonsevere UC, the strongest evidence for TDM is during anti-TNFα induction, and we recommend targeting infliximab concentrations of at least 29 μg/mL at Week 2, 18 μg/mL at Week 6, 9 μg/mL at Week 10, and 7 μg/mL at Week 14. For adalimumab, we recommend targeting 23 μg/mL at Week 4 and 13 μg/mL at Week 8 of induction, and 10 μg/mL during maintenance therapy. Based on prospective randomized trial evidence, we recommend proactive TDM during maintenance every 6–12 months until such time as the optimal frequency of monitoring during maintenance is elucidated.

2.3.2 | Acute severe UC (ASUC)

Perhaps the most well-documented setting in which intensified dosing of anti-TNF-α therapy is needed is in patients with ASUC. ASUC is associated with a high degree of morbidity and historically led to colectomy for the majority of children in the prebiologic era (58% by 1 year. and 61% by 6 years).[73,74] With the introduction of infliximab as rescue therapy, the rate of colectomy has decreased significantly for children and adults with UC.[75–78]

Accelerated infliximab clearance is well documented in ASUC and has contributed to high rates of treatment failure.[79] In severe colitis, gastrointestinal protein loss is increased due to epithelial barrier dysfunction.[80] There also may be increased burden of TNF-α itself.[81] Regardless of the pathophysiology, there is substantial evidence that intensified dosing improves drug levels.[82] This was demonstrated in a retrospective study of adults with UC, in which patients with ASUC on average had approximately half the infliximab trough levels at Day 14 of treatment compared to those with moderately severe UC, despite similar dosing patterns.[83]

Rapid infliximab clearance in acute UC can be overcome with accelerated dosing. In a retrospective study, adults with acute steroid refractory UC, who received an extra infliximab infusion during induction had 89% reduced hazard of colectomy by 30 days compared to standard induction dosing Weeks 0, 2, and 6.[84] Govani et al. also found that an accelerated infusion schedule including an extra dose before Week 2 was associated with reduced likelihood of early colectomy.[85]

Other studies addressed target infliximab trough levels. Papamichael et al. found that infliximab concentration <16.5 μg/mL at Week 2 after induction was an independent predictor of colectomy[86] and in a post hoc analysis of data from ACT-1 and ACT-2 trials ($n = 728$), serum infliximab levels of >41 μg/mL at Week 8 of induction were associated with improved clinical response (sensitivity 63%, specificity 62%, positive predictive value 80%).[87] Gordon et al. recommend targeting infliximab concentrations for adults with UC of at least 20–25 μg/mL at Week 2, 15–20 μg/mL at Week

6, and 7–10 μg/mL at Week 14.[24,88] Together these studies suggest that rapid infliximab clearance in ASUC may be overcome by increased anti-TNF-α medication delivery.

There is growing pediatric evidence supporting the management of ASUC with accelerated infliximab dosing.[89] In a retrospective study, Church et al. evaluated 125 pediatric patients with ASUC.[90] They compared infliximab dosing of 5 mg/kg Weeks 0, 2, and 6 with "intensified" dosing, defined as induction dose ≥7 mg/kg and/or an interval ≤5 weeks between the 1st and 3rd doses. Among children with steroid-refractory UC, those treated with intensified infliximab dosing had a threefold higher likelihood of achieving remission and 60% reduced risk of colectomy compared to standard dosing. Importantly, this was despite the intensified treatment group being sicker at baseline than those treated with standard dosing. One-year outcomes were also superior in a recent Canadian multicenter prospective cohort study of children hospitalized at time of diagnosis with steroid-refractory ASUC, and in whom infliximab was intensified.[91] Infliximab use may have been associated with reduced colectomy rates, although the relationship with infliximab dosing was difficult to discern due to confounding by disease severity. Whaley et al. conducted a prospective study of infliximab PK in pediatric patients with ASUC.[92] They found that patients with high infliximab clearance by Day 3 had a 50-fold increased hazard of colectomy. Despite having small sample size, the well-designed prospective study demonstrated how strongly rapid infliximab clearance is associated with treatment response in ASUC, confirming prior clinical observations.

The best current evidence indicates pediatric patients with ASUC should be routinely treated with infliximab induction, often requiring doses greater than 10 mg/kg. In patients with a partial improvement after the first infliximab infusion, consider giving an additional infliximab infusion of at least 10 mg/kg as early as Day 3–5 to bolster the serum infliximab level and improve the likelihood of response.

2.3.3 | Perianal fistula

Management of perianal fistulas associated with pediatric CD requires a medical-surgical multidisciplinary approach that includes careful assessment, drainage of purulence through the placement of drains/setons, and follow-up imaging.[93–95] Anti-TNF-α medications have the strongest evidence for improved perianal fistula healing.[96] However, despite improvement over other medical therapies, outcomes of perianal fistulizing complications remain poor. Bouguen et al. reported on a multicenter retrospective study of adults with perianal fistulizing CD.[97] They found that infliximab 5 mg/kg at Weeks 0, 2, 6, and every 8 weeks resulted in closure of at least one fistula tract by 1 year in 33% of patients. Fewer patients had complete healing, and only 46% of those had sustained fistula closure. Dupont-Lucas et al. reported a retrospective study of pediatric patients with perianal fistulas from the GETAID group.[98] Among 101 patients treated with standard induction infliximab dosing, 53 (52%) had response, defined as cessation of drainage and resolution of pain. In this study, 42% of those patients with improvement underwent dose intensification within the first year of treatment.

Davidov et al. conducted a retrospective study of adults with perianal fistulizing CD at two referral centers.[99] They found among the 36 patients included, 69% had an initial symptomatic response by 14 weeks. The median infliximab trough levels of responders were higher than nonresponders by threefold and fivefold at Weeks 2 and 6, respectively, suggesting a substantially higher dosing target may be needed for perianal fistula healing. Yarur et al. conducted a similar retrospective study in a multicenter population of adult patients with perianal fistulas treated with infliximab.[100] They found 54% achieved fistula healing, and found those with healing had higher serum infliximab levels than those without healing (median 15.8 vs. 4.4 μg/mL). Endoscopic analysis was also performed to determine mucosal healing and internal "closure" as well as external closure. With this higher standard, they found only 25% had fistula closure with infliximab levels ≤10 μg/mL, 42% had closure with trough levels 10.1–20.1 μg/mL, and 48% had perianal fistula closure with infliximab trough levels above 20.2 μg/mL. Plevris et al. performed another retrospective cross-sectional study of adults with perianal fistulizing CD, evaluating both infliximab and adalimumab.[101] For adalimumab, median level associated with fistula closure was 14.8 μg/mL compared to 5.7 μg/mL for those without fistula closure. Papamichael et al. performed a multicenter retrospective study of perianal fistula healing, again finding higher median adalimumab levels among patients who achieved fistula healing compared to nonhealing (12.9 vs. 6.1 μg/mL).[102]

Only one study that we are aware of evaluated perianal fistula healing confirmed by cross-sectional imaging. DeGregorio et al. evaluated outcomes of anti-TNFα therapy in a retrospective study using the Van Assche Index.[103] In this study, they confirmed that patients with magnetic resonance imaging (MRI) evidence of healing had higher adalimumab levels (median 9.8 vs. 6.2 μg/mL) and infliximab levels (median 7.4 vs. 3.9 μg/mL) than those without healing. Limited prospective data exists. Papamichael et al. performed a post hoc analysis of prospective data collected from the ACCENT-II trial.[86] They also found higher infliximab levels were associated with improved healing. They defined composite healing as symptomatic resolution and normalization of CRP, finding

healing occurred at 14 weeks among 20% of patients with infliximab level <8.7 μg/mL, and 48% with infliximab levels ≥8.7 μg/mL.

El-Matary et al. performed a pediatric study evaluating a prospective multicenter inception cohort of children with CD treated with infliximab.[104] In this study, 85 children who developed perianal fistulas had available infliximab levels. The authors found that by 24 weeks of therapy, 52% of patients had achieved fistula healing. The median infliximab trough before the 4th dose in patients with clinical improvement was 12.7 μg/mL compared to 5.4 μg/mL in nonresponders. No data on healing of the fistula tract was available. Singer et al. conducted a single center retrospective study of perianal fistula healing in pediatric patients with CD.[95] They found that anti-TNFα therapy coupled with TDM performed after induction before 6 months after initiating therapy was associated with 78% increased likelihood of perianal fistula healing over anti-TNFα therapy without TDM and dose adjustment after induction.

Overall, there is less evidence to support adalimumab use over infliximab for treatment of perianal fistulas. It is possible that adalimumab may have lower efficacy for perianal fistula.[105] However, it is unclear if this is inherent to adalimumab, or if it relates to less frequent TDM or less frequent dose escalation in practice. TDM is less commonly performed for adalimumab than for infliximab in practice.[26,106] In both infliximab and adalimumab, high drug levels are associated with greater likelihood of perianal fistula healing. However, it is difficult to determine if dose escalation itself improves healing. Castaño-Milla et al. reported a retrospective study of anti-TNFα naïve adults with perianal fistulas.[107] They noted that 33% of patients achieved fistula closure only after dose escalation. Another multicenter study evaluated the association between dose escalation and perianal fistula healing.[108] They found dose escalation of both infliximab and adalimumab were associated with improved perianal fistula healing. Maas et al. found that the poorer response among adalimumab-treated patients was associated with less frequent dose escalation and lower serum levels than among infliximab-treated patients.[105]

The best evidence currently available supports anti-TNFα therapy in combination with abscess/fistula drainage procedures and close monitoring with imaging. Targeting higher infliximab and adalimumab troughs is associated with improved healing. Exact trough targets may be different depending on perianal fistula complexity. We recommend an infliximab induction trough >16 μg/mL at Week 14, as higher levels in induction increase the likelihood of fistula closure. Induction targets for adalimumab are not available. Maintenance trough levels of >16 μg/mL for infliximab and >15 μg/mL for adalimumab are recommended as initial targets. However, in patients with nonhealing fistulas, higher troughs >20 μg/mL may be necessary.

2.3.4 | Very early onset IBD (VEO-IBD)

VEO-IBD is defined as disease onset under 6 years of age. Patients diagnosed before the age of 2 years are classified as infantile-onset IBD and they carry the highest risk for monogenic disorders, including primary immune dysregulation, which may not respond to traditional IBD medications. Benchimol et al. showed that the incidence of VEO-IBD has been increasing over the past three decades.[109] VEO-IBD most commonly presents with predominantly colonic disease, and in the case of monogenic disease, may have a more severe course of disease.[27,110]

There are no medications approved by the FDA for treating children less than 6 years of age. Currently, anti-TNFα agents are the most commonly used biologic therapy to treat VEO-IBD.[27] The response of VEO-IBD to anti-TNFα medications may be variable.[111,112] As noted above, some of this may be due to inadequate dosing versus rapid drug clearance in young children.[27–29] Patients with VEO-IBD have the lowest weight, making them the most susceptible to underdosing. Bramuzzo et al. found that patients who weigh less than 40 kg have about 40% less drug exposure per body weight than children >40 kg.[111] Stallard et al. demonstrated that higher infliximab doses based on BSA of 200 mg/m^2 with close monitoring of TDM are needed for young children with IBD.[29] Assa et al. found on average, target infliximab concentrations >23 μg/mL were needed before the second induction infusion, >16 μg/mL before the third infusion and >10 μg/mL at maintenance to induce and maintain remission in patients with infantile-onset IBD.[113] While there are observational studies describing efficacy safety of adalimumab in VEO-IBD, we found no reports of dosing or TDM in this age group.[114]

The best evidence currently available supports intensified dosing of anti-TNFα therapy at 200 mg/m^2 in VEO-IBD with close TDM. Targeting infliximab concentrations of a minimum of >23 μg/mL before the second infusion, >16 μg/mL before the third infusion, but higher levels are likely needed if inadequate response. However, in patients with poor response troughs higher than this may be necessary. Future studies in patients with VEO-IBD, perhaps exploring dosing based upon BSA and re-examining TDM targets, are needed to guide optimization of anti-TNFα therapy.

2.4 | Prevention of immunogenicity

Immunogenicity is the ability of a foreign substance, such as an antigen or drug, to provoke an immune response in the body. In anti-TNFα therapy, immunogenicity is central

to the loss of response to the drug. Avoidance of immunogenicity is one of the keys to durable therapy and long-term steroid free remission. In the pivotal REFINE study on immunogenicity in pediatric IBD, Coleman et al. found that antibodies to infliximab were detected in 68% of patients in the cohort, and starting dose under 7.5 mg/kg was one of the strongest predictors of developing antidrug antibodies.[46] They also found that infliximab dose escalation for patients with low-level antibodies led to antibody clearance, and prevented loss of response in 38% of patients. However, in the COMBINE trial, a prospective randomized trial of anti-TNFα therapy plus either methotrexate versus placebo, ADA development was considerably lower than reported in the REFINE cohort for both infliximab (21% with methotrexate, 47% monotherapy) and adalimumab (15% with methotrexate, 34% monotherapy).[106] The reason for this discrepancy may be related to the assay used.

Concomitant therapy with an immunomodulator can reduce drug clearance leading to higher drug concentrations and also decrease risk of development of anti-drug antibodies. Due to the long-term risk of thiopurines, the North American pediatric community have focused on anti-TNFα monotherapy with drug level optimization or administration of low dose once weekly oral methotrexate as an alternate immunomodulator. The REFINE cohort supports this approach and suggest that early therapeutic drug exposure (starting dose >7.5 mg/kg) and timely detection of immunogenicity are paramount to sustain therapeutic response and long-term durability.[46] The COMBINE pragmatic randomized study of anti-TNFα monotherapy versus dual therapy demonstrated the addition of low-dose oral methotrexate was associated with a lower rate of ADA development and anti-TNFα drug discontinuation, especially for adalimumab more than infliximab.[106] The reason for this difference between adalimumab and infliximab was not explored in the study, but it is noteworthy that patients on adalimumab underwent TDM less often and were more likely to have received on-label (and therefore lower) dosing than those treated with infliximab.[115]

In a prospective observational cohort that included children, the personalized anti-TNF therapy in CD study (PANTS), Kennedy et al. found patients who achieved an infliximab level of 7 μg/mL or adalimumab trough level of 12 μg/mL by Week 14 were less likely to develop antidrug antibodies and more likely to remain on therapy at 1 year.[17] Specifically pediatric studies have also indicated higher adalimumab levels are associated with lower risk of immunogenicity, although a specific trough level has not been defined.[21,26,63]

Dose optimization and proactive TDM have also been shown to reduce the immunogenicity of infliximab and adalimumab in pediatric IBD. In the practice-wide, study of implementation study described above, yearly proactive TDM was associated with 55% reduced risk of developing antidrug antibodies.[26] The PAILOT trial, which compared proactive versus reactive TDM, found no added benefit of concomitant immunomodulator, suggesting that TDM may obviate the need for concomitant therapy.[116] However, the equivalence of concomitant therapy and TDM has not been adequately evaluated. Stallard et al. also found that infliximab doses based on BSA of 200 mg/m^2 with close TDM monitoring was associated with reduced ADA development among younger/lighter children.[29] BSA based dosing is preferable due to the nonlinear relationship between weight and BSA; children weighing less than 40 kg are systematically underdosed if prescribed standard adult weight-based doses.[29]

The best available evidence for preventing immunogenicity supports initiating therapy with infliximab doses greater than 8 mg/kg, and in the case of hypoalbuminemia, doses greater than 10 mg/kg. For children <40 kg, doses of 200 mg/m^2 are more appropriate. At Week 14, targeting an infliximab trough >7 μg/mL, and an adalimumab trough >12 μg/mL is associated with lower risk of immunogenicity. TDM during induction and proactively thereafter is recommended to identify low serum levels and enable dose optimization to improve treatment outcomes and treatment longevity. The optimal timing and frequency of proactive monitoring during maintenance has yet to be determined. Concomitant immunomodulator use can also help reduce immunogenicity. However, it remains unclear whether TDM may obviate the need for concomitant therapy.

It is important to note that intensive anti-TNFα dosing strategies are not experimental. The initial doses of infliximab and adalimumab approved by the United States Food and Drug Administration (FDA) routinely lead to under-treatment, poor outcomes, and treatment discontinuation.[60,117] There is a rich, corroborated, and verified evidence-base to support the safety and efficacy of high-dose therapy anti-TNFα therapy when clinically indicated, especially as supported by TDM.[50,62,65,100,101,103,118]

2.4.1 | ADAs

In patients who develop ADA, the magnitude of antibody development has bearing on the response to treatment.[18,20] In a retrospective study of adults with IBD, Yanai et al. determined that patients with low levels of ADA to infliximab ≤9 μg/mL equivalent and ADA to adalimumab <4 μg/mL equivalent were both associated with increased likelihood of response to dose escalation compared to patients with higher ADA levels.[18]

3 | VEDOLIZUMAB

Vedolizumab is a monoclonal antibody that targets the α4β7 integrin and is FDA approved for the treatment of adult patients with moderate–severe CD and UC. Recommended dosing of vedolizumab is 300 mg IV

at Weeks 0, 2, and 6 followed by every 8 weeks maintenance in adults. In pediatrics, while there is not yet an FDA-approved indication, published experience has utilized 200 mg/m^2 dosing up to the adult dose of 300 mg with the same dosing intervals as in adults.[119–121]

3.1 | Mechanism of action

Integrins play a critical role in homing of immune cells into different compartments of the body. The α4β7 integrin is specifically a lymphocyte homing receptor that can bind to two ligands, mucosal vascular addressing cell adhesion molecule-1 (MAdCAM-1) and vascular cell adhesion molecule-1 (VCAM-1) and leads to leukocyte homing and retention in the intestines. α4β7 is expressed on T and B cells and has been associated with T cell trafficking to the intestine.[122] Vedolizumab is the first anti-integrin to specifically target α4β7. Due to its intestine-specific properties and decreased systemic effects this therapy is attractive for use in pediatrics.[123]

3.2 | PKs and PDs

Dosing of vedolizumab in adults is generally nonweight-based, while there is more variability in PK among children and individuals under 30 kg.[124] Following IV administration, vedolizumab rapidly saturates circulating α4β7 receptors and the drug is eliminated in a linear fashion.[125] Similar to anti-TNFα agents, increased body mass index (BMI) and decreased albumin are associated with more rapid clearance and lower serum drug levels.[126,127] This suggests that in the setting of hypoalbuminemia higher doses or more frequent dosing of vedolizumab may be needed. In addition to inflammatory burden, there may be fecal microbial predictors of response as higher levels of fecal butyrate may indicate better mucosal integrity and predict slower clearance and early clinical vedolizumab response.[127,128] In the absence of a true PK:PD correlation, clinical markers of disease severity and partial response that is lost by 8 weeks may help guide the decision to shorten the dosing interval.

3.3 | Vedolizumab dosing and monitoring targets

3.3.1 | Inflammatory disease

Vedolizumab exhibits primarily linear clearance in adults and older children with both CD and UC.[126] The GEMINI I and II studies assessed two maintenance dosing regimens in adults including every 4 weeks and every 8 weeks and did not find significant differences between these regimens.[129,130] However, long-term follow-up study demonstrated changing to 4-week interval dosing resulted in improved outcomes for a subset of patients who had failure to respond to standard dosing in the original trial.[131] The HUBBLE trial of vedolizumab PK in children demonstrated relatively lower vedolizumab trough levels in children <30 kg.[124] This was also seen in a cohort of children with anti-TNF-refractory IBD, 90% of whom required vedolizumab dose escalation after initial dosing of 6 mg/kg every 8 weeks after induction.[121] Atia et al. reported on a multicenter prospective pediatric cohort, where they found children under 30 kg required vedolizumab doses of 200 mg/m^2 or 10 mg/kg.[119]

Vedolizumab therapy is attractive for use in pediatrics due to its intestinal specificity, and low immunogenicity. There remain questions in pediatric IBD care as to the role of clearance, although assessment of other biologics suggest that the PKs and PDs of biologic medications are very similar when comparing adults to older children. Little evidence is available for the use of vedolizumab in specific disease subgroups.

In general, as with other biologic therapies, a higher serum vedolizumab concentration is associated with higher likelihood of treatment response. Typically, this is assessed by correlation with endoscopic remission and/or clinical improvement. Multiple studies identified that in patients with IBD (either UC or CD) early trough levels at Week 2[132] with a cut off of >23.2 μg/mL or Week 6[133,134] with a cut off of above 22–28 μg/mL or at Week 14[135]) above 16.55 μg/mL predicted a higher likelihood of sustained response over the first year. In regard to clinical remission one study identified that corticosteroid free, clinical and biochemical remission was correlated to higher trough vedolizumab concentration.[136] Overall, a systematic review and meta-analysis of five studies performed by Singh et al., identified that in UC, vedolizumab trough levels were consistently higher in patients who achieved clinical or endoscopic remission, although in this same study this correlation was not found in patients with CD.[137] There was no increase in adverse events noted in patients that had higher trough levels and this was supported by a small study by Sengupta et al.[138] These data suggest that there are valid reasons for increasing the dosing frequency of vedolizumab, most importantly to improve clinical, endoscopic remission in patients who have partial vedolizumab response.

Multiple studies have identified the role of vedolizumab trough levels during induction as a tool to suggest likelihood of clinical remission at 14 weeks and 52 weeks postinitiation of therapy but there is less of an understanding of the role of TDM during maintenance therapy. One of the larger studies ($N = 258$) to evaluate this question was performed by Ungaro et al., which evaluated adults and children with IBD being treated with vedolizumab.[136] This study demonstrated that patients in clinical,

biochemical, corticosteroid free and endoscopic remission had higher vedolizumab trough levels during maintenance therapy. The authors recommended a maintenance trough level above 11.5 μg/mL to increase the likelihood of remission, although no guidance was provided on frequency of monitoring. Recently, the TUMMY study was performed to determine the association between vedolizumab trough levels and clinical or biochemical remission during the maintenance phase of therapy (>14 weeks).[139] In this study of 159 patients with IBD, there was an association of vedolizumab trough levels with biochemical remission but not clinical remission. Notably, drug level may have been related to the actual state of the disease itself, as patients with greater inflammation had more rapid drug clearance leading to lower vedolizumab levels. Nevertheless, further studies are needed to define the relationship between maintenance trough levels and remission especially in the pediatric population.

The best available evidence supports TDM during induction. Targeting vedolizumab levels concentrations of a minimum of >23 μg/mL at Week 2, 22–28 μg/mL at Week 6, and above 17 μg/mL at Week 14. There may be benefit for proactive monitoring with a maintenance trough target of >12 μg/mL. Future pediatric studies are needed to guide optimization of vedolizumab therapy and TDM guidance.

3.3.2 | ASUC

To date, no randomized controlled trials have investigated the use of vedolizumab for the treatment of ASUC. This is due to the realization that remission onset is relatively slow with vedolizumab compared to other currently available therapies despite good responses identified in the GEMINI I trial in the subpopulation of patients with ASUC. There have been trials using calcineurin inhibitors (tacrolimus or cyclosporin) as a bridge to vedolizumab therapy allowing time for the vedolizumab to take effect thus identifying a method to use this medication for ASUC. A meta-analysis of these small studies suggests that an average of 65%–69% of the patients were able to avoid colectomy with this strategy.[140] These studies did not address in a prospective manner the dosing regimen that would be optimal in this setting.

In the opinion of the authors, vedolizumab does not have a role as primary therapy in ASUC.

3.3.3 | Perianal fistula

Another special circumstance that is seen in the use of anti-TNF medications is the treatment of perianal CD. Assessment of the use of vedolizumab in this population began in the GEMINI 2 Study where 153 patients had fistulizing CD and it was determined that of those patients treated with vedolizumab 31% achieved fistula closure by Week 52 compared to 11% treated with placebo.[141] In this study, trough levels did not appear to affect closure rate. In the ENTERPRISE study, which was a randomized, double-blind, phase 4 trial evaluating two vedolizumab IV dosing regimens in 32 patients with fistulizing CD, which was stopped early due to poor enrollment, they found that 43%–53% achieved a greater than 50% decrease in draining fistulae and 100% closure at Week 30.[142] However, they found no difference in vedolizumab serum levels in responders compared to nonresponders at any of the study timepoints. Finally, in a multicenter cohort study of 151 patient with perianal fistulae treated with vedolizumab they found a very low rate of successful closure near 22%, which was affected by the high rate of discontinuation of therapy (68%) by Week 33.[143] These data together suggest that further studies are needed to determine the role of vedolizumab in perianal fistulae but at this time there is no data to suggest increased doses or frequency would be beneficial.

We cannot make recommendations for TDM targets of vedolizumab due to an absence of evidence for an association between vedolizumab levels and perianal fistula healing.

3.3.4 | VEO-IBD

As noted above, frequently there are greater concentrations of biologic required for patients in the category of very early onset IBD (<6 years old), children under 30 kg require vedolizumab doses of 200 mg/m^2 or 10 mg/kg. As with most IBD medications for this population, studies are few and far between and provide mostly recommendations based on clinical expertise or studies with small numbers. With that understanding, vedolizumab is an attractive therapy for this population due to its mechanism of action as well as its low side effect profile. The only published study is a retrospective analysis of 16 patients with VEOIBD where there was a noted clinical response in 56% of the patients at the 4th dose of vedolizumab. Further studies are required to assess the safety and efficacy in this population.[144]

Further studies are required to assess the efficacy and safety of vedolizumab in this population. For now, we tentatively recommend using the same TDM targets for vedolizumab as in older children with inflammatory disease outlined above.

3.4 | Prevention of immunogenicity

Vedolizumab immunogenicity has been determined to be low in randomized controlled trials. Fewer than 5% of patients test positive for antivedolizumab antibodies

in at least one sample at any time but fewer than 1% of patients develop a persistently positive anti-vedolizumab antibody.[129,130,145] Development of anti-vedolizumab antibodies, however, is associated with increased drug clearance. In a retrospective study of 9356 patients antivedolizumab antibodies arose in 2.9% of patient and these antibodies were associated with lower vedolizumab levels compared to patients without detectable antivedolizumab antibodies.[146] In addition, there was no significant effect of the use of immunomodulators in combination with vedolizumab on the development of antivedolizumab antibodies.[129,130] Immunogenicity of vedolizumab in pediatric patients has not been evaluated.

4 | ANTI-IL AGENTS

IL cytokines serve as communicators for immune-signaling. Specifically, IL-12 and IL-23 are involved with pro-inflammatory signaling.

4.1 | Mechanism of action

The initial therapeutic target developed in IBD was the p40 subunit that was common to both of these cytokines. The first anti-IL-12/23 drug available was ustekinumab, which uses a monoclonal antibody against the p40 subunit. Subsequently, selective IL-23 inhibitors that selectively block the p19 subunit unique to IL-23 have been developed. These agents include risankizumab, which is now FDA approved for the treatment of adult CD and UC, and mirikizumab and guselkumab, which are both FDA approved for treatment of UC and CD in adults. Sparing the IL-12 pathway preserves Th1 responses that has been shown beneficial for host immunity and malignancy surveillance.[147]

4.2 | PK and PDs

The serum level of ustekinumab rises in a dose-proportional manner following the IV induction dose. This has been shown to be the case in both CD and UC.[148,149] The mean serum concentration reaches steady state by the second maintenance dose irrespective of prior biologic exposure, or disease state in adults.[150] Similar to other biologics, serum level is decreased when there is a higher patient BMI, lower serum albumin, and increased inflammatory burden. Race-based differences in ustekinumab have also been described (Asian vs. non-Asian).[150] The PK of ustekinumab demonstrated in adults with IBD are similar for pediatric patients weighing >40 kg, but this was not the case for patients less than 30 kg in the industry-sponsored phase 1 trial, leading to recommendations for BSA-based dosing in younger, lighter patients.[150,151]

While early trial data showed a clear relationship between serum level and response, a variety of target trough levels have been proposed.[148,152] Consequently, the role of TDM continues to be less clear for ustekinumab than is the case for anti-TNFα therapy.[153] There is literature supporting the shortening of the dosing interval in both pediatric and adult patients who are experiencing a partial clinical response to standard dosing.[154,155] For those who have lost response, there is evidence supporting giving a single repeat IV induction dose.[156]

4.3 | Ustekinumab dosing and monitoring targets

4.3.1 | Inflammatory disease

Ustekinumab is approved for the treatment of adults with moderate–severe CD and UC.[151,157] Children over 40 kg can follow the adult weight-tiered IV induction dosing regimen approximating 6 mg/kg (260 mg if weighing 40 kg to less than 55 kg; 390 mg if 55 kg to less than 85 kg; 520 mg if over 85 kg). Based on PK data accrued in the pediatric phase 1 trial, the current and ongoing phase 3 pediatric CD clinical trial is employing BSA-based induction dosing of 250 mg/m^2 for children weighing less than 40 kg. Week 8 ustekinumab levels measured in a prospective multicenter Canadian study have corroborated this dosing. For maintenance therapy, Rosh et al. evaluated 90 mg every 8 weeks for patients over ≥40 kg, and 2 mg/kg for patients <40 kg, but this strategy resulted in low serum ustekinumab concentrations in children <40 kg.[151] More recently, the GETAID group published findings of a study in which they used 90 mg every 8 weeks for maintenance dosing regardless of weight. This dosing resulted in >60% of patients achieving steroid free clinical remission by 52 weeks.[158]

The interpatient variability provides some support for the practice of TDM, utilizing a trough measurement to determine the need to adjust dose or dosing interval. Recommended trough level to achieve mucosal healing is greater than 4.5 μg/mL,[152] and may require every 4-week dosing to achieve. Dayan et al., in a real-world pediatric cohort, reported a 90% steroid-free remission in biologic naïve patients at 1 year.[159] Interestingly, there was no significant difference in the trough levels between patients on or off steroids at 1 year. Other studies suggest at Week 2 a target level of >28–32 μg/mL, at Week 4 >19 μg/mL, and at Week 8 >7 μg/mL.[152,160] Other studies have found different trough cut-offs to be associated with mucosal healing.[161–163] Whether this relates to different assays or different disease behavior remains to be determined.

Future studies in Pediatric IBD are needed to guide optimization of ustekinumab therapy and the role of TDM. For now, based on currently available evidence, we tentatively recommend targeting ustekinumab concentrations of at least 28 µg/mL at Week 2, a level of at least 19 µg/mL at Week 4, at least 7 µg/mL at Week 8.

4.3.2 | ASUC

There are no published studies which have evaluated ustekinumab for use in ASUC.

4.4 | Perianal CD

There are adult data that suggest ustekinumab may be effective in treating perianal fistulizing disease. Chapuis-Biron described the GETAID population of adults, where 207 patients with perianal fistulas were treated with ustekinumab, 27% achieved fistula closure, and 33% were able to have setons successfully removed.[164] However, in a systematic review, Attauabi et al. found only 17% of patients had fistula closure after 52 weeks of ustekinumab therapy.[165] However, no study has evaluated ustekinumab TDM and perianal fistula healing.

4.4.1 | VEO-IBD

There is also scant evidence on the use of ustekinumab in VEO-IBD, none of which addresses TDM.[166]

4.5 | Prevention of immunogenicity

In the UNITI trials, ustekinumab use was associated with adverse events and serious adverse events in similar frequency to placebo.[167] The rate of ADA formation in long-term follow-up was very low (2.3% in IM-UNITI) which is considerably lower when compared to the rates of antibodies seen in the TNFα antagonist immunogenicity profiles. Therefore, monotherapy of ustekinumab is the common practice. A similarly low rate of antidrug antibodies was seen in the long-term extension study in pediatric CD.[168]

5 | CONCLUSION

TDM has emerged as a valuable tool in the management of pediatric IBD. This position paper highlights the importance of utilizing TDM to optimize treatment outcomes, and personalize therapies for pediatric patients living with IBD, especially when anti-TNFα therapy is used. By measuring drug levels during induction and maintenance therapy, clinicians can proactively tailor how to dose biologic agents and adjust treatment strategies based on individual patient characteristics (including disease severity and clinical response). TDM provides a comprehensive approach to guide clinical decision-making, ensuring that children with IBD receive the most effective treatment and preserve long-term treatment efficacy. This NASPGHAN position paper should also serve to document that high-dose therapy, especially guided by TDM, is evidence-based standard of care. As our understanding of the PKs and PDs of IBD medications continues to grow, the role of TDM will continue to be clarified. Further research and collaboration between clinicians and researchers are needed to refine TDM guidelines and expand its application in pediatric IBD care.

CONFLICT OF INTEREST STATEMENT

Anne M. Griffiths: Abbvie (advisory board member, speaker, investigator-initiated research funding); Alimentiv (speaker); Amgen (consultant); Janssen (advisory board member, speaker); Lilly (consultant); Pfizer (consultant); Takeda (speaker). Jeremy Adler: Janssen Research & Development (research funding). Joel R. Rosh: Advisor/Consultant: Abbvie, BMS, Janssen, Lilly, Pharmacosmos, Pfizer; Educational Grant: GI Health Foundation. The remaining authors declare no conflict of interest.

ORCID

Lina M. Felipez https://orcid.org/0009-0002-2382-1058
Sabina Ali https://orcid.org/0000-0002-5887-5454
Edwin F. de Zoeten https://orcid.org/0000-0002-0946-9759
Anne M. Griffiths https://orcid.org/0000-0001-8623-4665
Sandra C. Kim https://orcid.org/0009-0005-3302-7589
Ashish S. Patel https://orcid.org/0000-0002-4435-2644
Joel R. Rosh https://orcid.org/0009-0003-5108-3950
Jeremy Adler https://orcid.org/0000-0002-4857-6098

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