Positioning Biologic Therapies in the Management of Pediatric Inflammatory Bowel Disease

Jessica Breton, MD, Arthur Kastl, MD, Maire A. Conrad, MD, and Robert N. Baldassano, MD

Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Philadelphia; Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Corresponding author:
Dr Jessica Breton
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Department of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Roberts Center
2716 South Street
Philadelphia, PA 19146
Tel: (215) 590-7801
Fax: (267) 426-9001
E-mail: bretonj@email.chop.edu

Abstract: The incidence and prevalence of pediatric inflammatory bowel disease (IBD) are rising worldwide, with a steep increase in children under 5 years of age. Compared to adult IBD, pediatric IBD presents with a more severe, aggressive phenotype and unique complications, notably growth impairment. Treatment goals include achieving intestinal healing, reaching growth potential, and optimizing quality of life, all while limiting drug toxicities. In the last 2 decades, the advent of anti–tumor necrosis factor (TNF) α agents has significantly increased the potential to reach these goals. However, nonresponse or loss of response to anti-TNFα agents is still encountered in approximately one-third of patients. Although the development of novel biologic therapies has offered new alternatives in recent years, the use of these therapies in the pediatric setting has been limited due to delayed approval. This article summarizes the key evidence for biologic agents currently used in the treatment of pediatric IBD and discusses challenges and barriers unique to pediatric drug development.

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, progressive, and incurable inflammatory disorder of the gastrointestinal tract, with approximately 25% of patients presenting before 18 years of age.[1,2] While epidemiologic data suggest that the incidence of IBD may have stabilized among adults in North America, it has continued to rise in children, with the highest percentage increase observed among children under 5 years of age.[2,3] Importantly, this rising incidence has caused the pediatric prevalence of IBD to increase by 133% in the last decade in the United States, reaching 77 per 100,000 children in 2016.[2] Compared to adults, children with IBD are more likely to have extensive intestinal involvement and an aggressive disease course, in addition to experiencing different complications, such as growth impairment and delayed puberty.[4] The treatment of childhood-onset IBD also presents unique challenges,

Table 1. Biologics Currently Used in Pediatric Inflammatory Bowel Disease

Agent	Target	FDA Approval Year	Current Pediatric Guideline Indications	
			CD	UC
Infliximab	Chimeric monoclonal anti-TNFα	CD: 1998 (adult), 2006 (pediatric) UC: 2005 (adult), 2011 (pediatric)	Moderate to severe disease refractory to CS or an immunomodulator[14,15] First-line therapy use in CD patients judged at risk for progressive disease or in patients for whom CS could exacerbate underlying conditions[a,14,15]	Chronically active or CS-dependent UC, uncontrolled by 5-amino-salicylate and thiopurines[60]; acute severe colitis failing intravenous CS[43]
Adalimumab	Humanized monoclonal anti-TNFα	CD: 2007 (adult), 2012 (pediatric) UC: 2012 (adult)	Prophylactic therapy for preventing postoperative recurrence in high-risk patients[b,14,15]	Secondary loss of response to infliximab[60]
Vedolizumab	Humanized monoclonal anti-α4β7 integrin	CD: 2014 (adult) UC: 2014 (adult)	NA[c]	Second-line biologic therapy after anti-TNFα failure[60]
Ustekinumab	Humanized antibody to p40 subunit of IL-12/23	CD: 2016 (adult) UC: 2019 (adult)	Second-line biologic therapy after anti-TNFα failure[15]	NA[c]

CD, Crohn's disease; CS, corticosteroid; FDA, US Food and Drug Administration; IL, interleukin; NA, not applicable; TNF, tumor necrosis factor; UC, ulcerative colitis.

[a]Patients with extensive disease, deep colonic ulcerations, growth failure, perianal disease, or bone disease.

[b]Patients with extensive disease, short disease duration from diagnosis to surgery, long resected segment, penetrating disease, active disease beyond resection, perianal disease, or who smoke.

[c]Guideline recommendations for this pediatric indication are not yet available.

including limited therapeutic options with considerably fewer treatments approved by the US Food and Drug Administration (FDA). This landscape poses significant limitations for pediatric gastroenterologists and, by extension, is relevant for adult gastroenterologists as young patients transition into adult care.

Within the past 2 decades, the advent of anti–tumor necrosis factor (TNF) α agents has radically modified the management and disease course of IBD in both adults and children, resulting in greater remission and mucosal healing rates, fewer surgeries and hospitalizations, improved quality of life, and, notably for children, correction of growth failure.[5,6] Nevertheless, approximately one-third of patients are anti-TNFα primary nonresponders, and an additional 30% to 40% experience secondary loss of response.[7] In recent years, there has been a robust expansion of FDA-approved drugs for adult CD and UC, but there is significant lag time to approve these same drugs for children.[8]

This article evaluates the evidence for biologic agents currently used in the treatment of pediatric IBD after summarizing the previously published adult data. Key treatment attributes, efficacy, clinical pharmacology, and safety are reviewed. Finally, challenges and barriers unique to pediatric drug development are discussed.

Anti–Tumor Necrosis Factor α Agents

In children and adolescents, the anti-TNFα agents infliximab and adalimumab are currently the only biologics approved by the FDA for the treatment of pediatric IBD (Table 1). High-quality evidence for their efficacy and safety is accumulating and has shifted the treatment paradigm of pediatric IBD. However, controversies remain regarding their optimal use in this population, including indications as first-line therapies, therapeutic drug monitoring (TDM), combination therapy, and safety.

Efficacy in Crohn's Disease

Anti-TNFα therapy has been extensively studied in double-blinded, randomized, controlled trials (RCTs) in adults, demonstrating efficacy and safety in both induction and maintenance of remission.[9,10] In pediatric patients, there is high-quality evidence from trials involving open-label induction and randomized, dose-ranging maintenance therapy, with none of these trials being placebo-controlled (Table 2).[11-15] The majority of these RCTs were conducted with children who had previously been refractory to nonbiologic therapies and were on concomitant immunomodulators. Nonetheless, even in

Table 2. Randomized, Controlled Trials in Pediatric IBD Assessing the Efficacy of Anti-TNFα Therapies

Study (Authors); Agent	Study Design	Patients (N) and IBD Type	Combination With IM	Efficacy Endpoints		Post Hoc Analysis Key Findings
				Clinical Response	Clinical Remission	
REACH (Hyams et al[11]); IFX	Responders randomized at week 10: every 8 weeks vs every 12 weeks	Total CD patients: 112 At week 10: 99	100%	**Induction (Week 10)**		Rapid and sustained improvement in perianal disease[b,70] Improvement in biomarkers of bone formation[25]
				88.4%	58.9%	
				Maintenance (Week 52)		
				Every 8 weeks: 63.5%	Every 8 weeks: 55.8%	
				Every 12 weeks: 33.3%[a]	Every 12 weeks: 23.5%[a]	
GFHGNP (Ruemmele et al[12]); IFX	Responders randomized at week 10: every 8 weeks vs on-demand basis[c]	Total CD patients: 40 At week 10: 34	100%	**Induction (Week 10)**		NA
				NA	85%	
				Maintenance (Week 60)		
				NA	Every 8 weeks: 83% On demand: 61%[a]	
T72 (Hyams et al[41]); IFX	Responders randomized at week 8: every 8 weeks vs every 12 weeks	Total UC patients: 60 At week 4: 45	53%	**Induction (Week 8)**		PUCAI was no less predictive of sustained remission than mucosal healing at week 8[37]
				73.3%	33.3%	
				Maintenance (Week 52)		
				NA	Every 8 weeks: 38.1% Every 12 weeks: 18.2%	
IMAgINE-1 (Hyams et al[13]); ADA	Responders randomized at week 4: HD vs LD	Total CD patients: 188 At week 4: 155	62%	**Maintenance (Week 26)**		Week 26 clinical remission: TL,[57] 11.3 µg/mL vs NR, 10.5 µg/mL[a] Clinical remission associated with higher postescalation TL[66] (pre-escalation, 9.8 µg/mL; postescalation, 21.0 µg/mL) No benefit of combination therapy in terms of clinical remission[76] Fistula closure[b] associated with higher TL[67] (10.0 µg/mL vs 6.1 µg/mL)
				HD: 59.1% LD: 48.4%	HD: 38.7% LD: 28.4%	
				HD IFX-naive: 47.6%	HD IFX-naive: 16.7%	
				HD IFX-exposed: 68.6%	HD IFX-exposed: 56.9%	
				Maintenance (Week 52)		
				HD: 41.9% LD: 28.4%[a]	HD: 33.5% LD: 23.2%	
				HD IFX-naive: 26.2%	HD IFX-naive: 19.0%	
				HD IFX-exposed: 54.9%	HD IFX-exposed: 45.1%[a]	
PAILOT (Assa et al[16]); ADA	Responders randomized at week 4: proactive TDM vs reactive TDM	Total CD patients: 82 At week 4: 78	44%	**Induction (Week 4)**		No benefit of combination therapy in terms of clinical remission[77]
				95%	NA	
				Maintenance (Week 72)		
				NA	Proactive TDM: 82% Reactive TDM: 48%[a]	

ADA, adalimumab; CD, Crohn's disease; HD, high dose; IBD, inflammatory bowel disease; IFX, infliximab; IM, immunomodulator; LD, low dose; NA, not applicable; NR, nonresponders; PUCAI, Pediatric Ulcerative Colitis Activity Index; TDM, therapeutic drug monitoring; TL, trough level; TNF, tumor necrosis factor; UC, ulcerative colitis.

[a]$P<.05$, between 2 interval/dosing arms.

[b]Pediatric Crohn's Disease Activity Index Perirectal subscore was used to assess perianal symptom activity and therapeutic response.

[c]IFX infusions were only repeated if the patient showed signs of a relapse (eg, Harvey-Bradshaw Index >5, incomplete fistula closure, fistula reopening).

these refractory populations, the clinical remission rate with infliximab ranged between 59% and 85%, and was sustained at 1 year in 56% to 83% of those who responded to standard induction treatment.[11,12] The IMAgINE-1 trial was a double-blinded RCT assessing dose-ranging maintenance therapy with adalimumab after open-label, weight-adjusted induction therapy, and included both infliximab-naive patients and patients who had failed infliximab (44%).[13] In patients responding to induction, clinical remission occurred in 38.7% and 33.5% at weeks 26 and 52, respectively, with no significant difference between the high- and low-dose groups. Importantly, a significantly higher remission rate among infliximab-exposed patients was shown when compared to infliximab-naive patients at both weeks 26 and 52 (56.9% vs 16.7% and 45.1% vs 19.0%, respectively).[13] Likewise, in the recently published PAILOT trial,[16] which only included children naive to anti-TNFα agents, rates of clinical remission after adalimumab induction (48%-82%) were higher than rates reported in the IMAgINE-1 trial.[13] These results are consistent with observations from previous adult trials[9,10] and underscore the importance of optimization and treatment durability with the first biologic agent.

There is accumulating evidence that mucosal healing is associated with better outcomes, providing the foundational evidence for achieving deep remission as the ultimate target in IBD.[6] While initial pediatric trials focused on clinical remission, a few observational and retrospective studies have subsequently demonstrated endoscopic healing rates varying between 22% and 42% at 3 to 12 months after treatment initiation.[17-21] Additionally, a greater likelihood of achieving mucosal healing at 1 year was shown with the use of anti-TNFα agents as first-line therapy in luminal CD as compared to escalation therapy in 2 pediatric retrospective cohorts,[20,21] similar to findings in previously published adult data. These findings, therefore, suggest the superiority of a top-down therapeutic approach in achieving deep remission in pediatric CD.

Linear growth failure is a frequent complication of CD in prepubescent children and represents an important therapeutic target that must be achieved early in the disease so that irreversible sequelae can be mitigated. This concept is best demonstrated by Walters and colleagues in a secondary analysis of data from the large RISK observational cohort.[5] In this study, a significantly greater rate of clinical remission and linear growth normalization was shown at 1 year in newly diagnosed CD patients treated with anti-TNFα therapy within the first 3 months after diagnosis compared to patients treated with an immunomodulator only (85.3% vs 60.3%; relative risk, 1.41; P=.0017). Several additional studies,[11-13,22-25] including the landmark REACH trial,[11] have shown the efficacy

of anti-TNFα therapy at facilitating catch-up growth, further supporting its use as first-line therapy in children presenting with linear growth failure.

Finally, little data have demonstrated the long-term efficacy and treatment durability of anti-TNFα therapy beyond 1 year in the pediatric CD population. Overall, the 1- and 3-year sustained durable remission rates have been reported to be 50% to 80% and 40% to 70%, respectively, with stabilization occurring beyond 2 years of treatment.[24,26-30] As previously assessed in an adult systematic review and meta-analysis,[7] the main reason for discontinuation is secondary loss of response. Retrospective pediatric cohorts have shown a variable recaptured response rate of 37% to 75% with dose intensification.[11,30,31] These findings, therefore, emphasize the need for effective and optimized long-term treatment strategies for pediatric patients, where avoidance of secondary loss of response is of utmost importance.

Efficacy in Ulcerative Colitis

Key adult RCTs, systematic reviews, and meta-analyses have highlighted the efficacy of infliximab and adalimumab in inducing clinical remission and mucosal healing and reducing the need for colectomies in patients with chronically active UC.[32,33] To date, infliximab is the only anti-TNFα agent approved by the FDA in pediatric UC (Table 1). Evidence for its use comes mainly from adult clinical trials and pediatric retrospective and observational cohort studies,[30,34-40] with only 1 published RCT,[41] resulting in FDA approval for this indication. In this RCT, 73% of children with moderate to severe UC responded to a standard induction protocol of infliximab, and 38% maintained clinical remission at 1 year.[41] Mucosal healing was achieved in more than two-thirds of patients at week 8. Long-term efficacy of infliximab in UC has also been demonstrated, with retrospective studies reporting sustained durable remission in 40% of patients for a mean period of 2 years.[30,42] It should be noted, however, that the majority of these studies only included ambulatory patients. Thus, these numbers may not be applicable to hospitalized patients with corticosteroid-refractory acute severe colitis, defined in children by a Pediatric UC Activity Index score of 65 or higher,[43] and for whom only infliximab is used as salvage therapy.

Importantly, a relationship between the increased use of anti-TNFα agents and the reduction of surgery risk for children with UC has been suggested,[34-38] with the exception of 1 retrospective study in hospitalized patients with acute severe colitis.[39] These contradictory results may be related to the heterogeneity of the studied populations (hospitalized vs ambulatory), disease severity (acute vs chronically active), and infliximab dosing regimens, all of which may impact drug clearance and, thus, true drug

exposure. Indeed, the dosing optimization likely plays a critical role in hospitalized patients with acute severe colitis, for whom drug clearance is increased from high TNFα burden, panconic involvement, and hypoalbuminemia.[44,45] To this end, intensified induction regimens, with doses of infliximab up to 10 mg/kg and increased frequency in an effort to achieve adequate drug exposure, are highlighted in the recent guidelines from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)[43] and a retrospective study by Church and colleagues.[40] This study reported higher clinical remission rates and a lower colectomy rate at 1 year with intensified induction (mean induction dose >7 mg/kg or interval <5 weeks between doses 1 and 3), as compared to standard dosing (hazard ratio, 3.2; *P*=.02).[40] These findings strongly justify both intensified dosing and early measures of pharmacokinetics to maximize efficacy and possibly mitigate disease complications.

The efficacy and safety profiles of adalimumab for induction and maintenance therapy in moderate to severe active UC have been shown in the landmark adult ULTRA trials[46,47] and subsequently reiterated in systematic reviews and meta-analyses,[9,33] with better results seen in anti-TNFα–naive patients. Pediatric evidence regarding adalimumab in UC remains scarce, and is limited to 2 small retrospective studies in patients experiencing secondary loss of response to infliximab.[30,31] In these 2 studies, response to anti-TNFα therapy was recaptured in 55% to 80% of patients, with clinical remission maintained for a median follow-up of 2 years.[30,31] While these results appear promising, data from ongoing clinical trials including biologically naive patients may provide further supportive evidence.

Risk Stratification in Crohn's Disease
Recent inception cohort studies in pediatric IBD have highlighted baseline phenotyping of patients to predict the severity of their disease course and help identify who will benefit the most from early biologic treatment.[48-50]

Results from the RISK observational study provide some of the highest-quality data supporting the early use of anti-TNFα therapy in children with CD at risk for severe disease progression.[48] In this multicenter, propensity-matched, inception cohort, 913 children with inflammatory, nonstricturing CD at disease onset were enrolled and prospectively followed for complications and response to therapies. Early anti-TNFα therapy use (started within the first 3 months after diagnosis) led to a substantial reduction in penetrating, but not fibrostenotic, complications. A risk stratification model found that African-American race as well as anti–*Saccharomyces cerevisiae* antibodies and bacterial flagellin (anti-CBir1) were all associated with disease complications. Additional

predictors for disease progression were found when studying the microbial communities and intestinal gene expression.

Risk Stratification in Ulcerative Colitis
The PROTECT trial was a multicenter inception cohort designed to study the natural history of children who were newly diagnosed with UC and who were initially treated with mesalamine or corticosteroids, with further therapy escalation guided by the Pediatric UC Activity Index.[49,50] In this study of 428 children, corticosteroid-free remission at weeks 12 and 52 on mesalamine was achieved in 34% and 38% of patients, respectively, with those presenting with mild disease at diagnosis being more likely to remain on mesalamine (49% vs 30%). The strongest predictor for corticosteroid-free remission at weeks 12 and 52 was induction of clinical remission by week 4, highlighting the importance of prompt treatment decision-making early in the course of the disease. Over 1 year, approximately half of the patients required escalation to an immunomodulator or anti-TNFα therapy, and 6% underwent colectomy. Predictors of escalation to anti-TNFα therapy were low vitamin D level, anemia, and decreased rectal biopsy eosinophil count at presentation. Importantly, specific gut microbial community and intestinal gene expression signatures were found to improve the prediction to escalate to a biologic therapy.

Together, these studies demonstrate the need to individualize therapeutic choices based on risk factors for severe disease course and treatment goals, rather than using a broad one-size-fits-all step-up approach. Future risk stratification studies and RCTs validating the aforementioned key clinical and biological predictors will help to develop more personalized treatment approaches with the potential to alter the natural history of pediatric IBD.

Clinical Pharmacology
Therapeutic Drug Monitoring TDM refers to the measurement of drug and antidrug antibody serum concentrations to guide clinical decision-making and achieve specific treatment goals.[51] Along with several adult studies,[52-54] a few pediatric cohort studies and post hoc analyses of RCTs, summarized in a recent review by Carman and colleagues, have demonstrated the positive exposure-response relationship between anti-TNFα concentrations and clinical and biological outcomes.[55] Inversely, lower drug levels have been associated with drug antibody formation and, consequently, greater likelihood of loss of response.[7,55-57] Collectively, these studies have supported the clinical use of TDM to achieve the highest possible response and increase drug retention.

However, the superiority of proactive vs reactive TDM is still under debate.[51,58] Currently, societal

guidelines support the role of reactive TDM-based dose optimization at the time of loss of response.[15,43,59,60] Nevertheless, reactive TDM-based management does not take into account the substantial inter- and intraindividual variability in drug clearance, which can be influenced by antidrug antibody status, concomitant immunosuppressant use, body weight (obesity), sex (male), extent and severity of bowel disease, C-reactive protein, serum albumin, and TNF burden (acting as an antigen sink).[45,61] To this end, proactive TDM may allow individualized dosing adjustment and may potentially lead to higher rates of remission, fewer IBD-related complications, lower rates of immunogenicity, and better drug retention.[51] Key pediatric observational prospective studies[62-65] and a post hoc analysis[66] have provided further evidence for the utility of proactive TDM during maintenance therapy, showing positive associations between adequate drug exposure and sustained durable remission, mucosal healing, and drug retention. In a recent pediatric prospective CD cohort, the benefit of proactive TDM during induction was also demonstrated with infliximab concentrations greater than 18 μg/L at infusion 3 (week 6) being strongly associated with clinical and biological response and infliximab levels greater than 5 μg/L at the start of maintenance.[65] Additionally, use of TDM to maintain a higher trough level (TL) has been associated with greater likelihood of fistula closure in adult and pediatric patients with perianal fistulizing disease.[67-70]

Recently, Assa and colleagues provided additional evidence suggesting the superiority of proactive over reactive TDM in PAILOT, the first pediatric RCT.[16] In this study, a higher proportion of patients in the proactive arm achieved the primary endpoint of sustained corticosteroid-free clinical remission, defined as a Pediatric CD Activity Index score of less than 10 at all visits (82% vs 48%; P=.002), in addition to a fecal calprotectin level of less than 150 μg/g (47% vs 22%; P=.02). Dose intensification was required in almost 90% of the proactive group in order to achieve a modest trough threshold of 5 μg/mL. Furthermore, in line with recent adult data[71] and a post hoc analysis of the IMAgINE-1 trial,[57,66] a maintenance TL above 10.0 μg/mL was associated with a higher rate of clinical remission. Overall, this is the first proactive TDM RCT in the pediatric and adult literature achieving its primary endpoint.[72,73]

TDM is a key component of managing IBD patients on anti-TNFα therapy. While reactive TDM of anti-TNFα agents has been adopted by societal guidelines, there is an increasing body of literature to support the benefit of proactive TDM, particularly in pediatric populations.

Combination Therapy Vs Monotherapy The potential benefit of combination therapy was first demonstrated in the landmark SONIC trial,[74] which showed higher rates of clinical and endoscopic remission with use of infliximab in combination with a thiopurine (57% vs 44%; P=.02). The reason for the improved efficacy with combination therapy remains unclear but may be related to a synergistic effect between the 2 agents or the achievement of higher biologic concentration due to antidrug antibody suppression and decreased drug clearance.[74]

A post hoc analysis of the SONIC trial found that among patients with similar serum trough concentrations of infliximab, combination therapy was not significantly more effective than infliximab alone.[75] Although the use of combination therapy was associated with a lower risk of immunogenicity, no significant difference in rates of clinical remission between combination therapy and monotherapy was demonstrated. Similarly, in the pediatric setting, 2 post hoc analyses of the IMAgINE-1 (56% biologically naive) and PAILOT (100% biologically naive) RCTs showed no additional benefit of combination therapy in terms of adalimumab pharmacokinetics, prevention of immunogenicity, or efficacy.[76,77] Therefore, whether proactive TDM with monotherapy is equal to or better than the use of combination therapy as a strategy to improve the pharmacokinetic and treatment durability of anti-TNFα therapy remains in question. In a pediatric prospective study of 77 children with CD starting infliximab therapy (55% monotherapy), Stein and colleagues suggested the benefit of individualized dosing adjustment using proactive TDM at week 10.[64] Patients who remained on infliximab at 1 year had a higher median week 10 infliximab TL, as compared with patients who discontinued infliximab (20.4 μg/mL vs 8.7 μg/mL; P=.01),[64] regardless of use of combination therapy. Subsequently, Lega and colleagues demonstrated in an adult cohort that early proactive optimization of infliximab monotherapy at week 10 was as effective as combination therapy at sustaining therapeutic TL and clinical remission at 1 year.[78]

Until further pediatric data are available, the benefits of using combination therapy should be balanced with the potential for higher rates of adverse events such as infection, malignancy, and toxicity.[79,80] In pediatric IBD, the use of combination therapy may be appropriate in children who exhibit a higher risk of disease complication, children with immunogenic loss of response to previous anti-TNFα therapy, or children who may benefit from the synergistic effect between the 2 agents.[80] This decision should take into account additional individual factors for which a higher risk of malignancies and infections has been suggested (eg, risk of hepatosplenic lymphoma in young men and lymphoproliferative disorder in patients naive to Epstein-Barr virus [EBV] who were exposed to thiopurines).[81-83] Finally, withdrawal of immunomodulators after 6 months in patients achieving therapeutic

drug levels has been advocated as the optimum time to achieve long-term benefits.[15,60,84]

Safety

By virtue of the central role of TNFα in macrophage activation, neutrophil recruitment, and formation of granulomas, anti-TNFα therapy use has been linked to an increased risk of infection.[85] Based on a meta-analysis of 65 pediatric studies (9516 patient years of follow-up [PYF]), the rate of serious infections in children with IBD exposed to anti-TNFα agents has been suggested to be significantly lower than the rate in adults.[86] This risk has been estimated to be 3.5 per 100 patient years (PYs) and similar to that of children receiving immunomodulator monotherapy.[86] Notably, the rate of serious infections associated with anti-TNFα agents represents half the rate of serious infections for children receiving corticosteroids (7.3/100 PYs).[86] Additionally, a higher risk of infections has been reported in the adult and pediatric literature when using anti-TNFα therapy in combination with an immunomodulator or corticosteroid.[79,86,87]

Prevention and surveillance should be key elements in the management of patients on any immunosuppressive therapy, and care should be guided by the latest pediatric evidence-based recommendations.[88] Finally, while immunosuppressive therapies may increase the risk of infections, it is also essential to remember that underlying active disease, malnutrition, and complications, including surgeries, also predispose patients with IBD to infections.[88]

Prior reports have raised concerns for an increased risk of lymphoproliferative disorders (eg, EBV-associated lymphomas or hepatosplenic T-cell lymphomas) with IBD-related immunosuppressive therapies, most notably thiopurines and anti-TNFα therapies. However, these initial data were largely limited to case series or retrospective studies with small sample sizes and short durations of follow-up. The most robust evidence in regard to malignancy risk in children with IBD exposed to anti-TNFα therapy comes from the DEVELOP registry,[82] an ongoing prospective safety registry for pediatric IBD that includes both patients exposed and never exposed to infliximab. In 5766 patients (24,543 PYF; median, 4.5 years/patient), there were 15 patients with malignancy events. Thirteen were exposed to thiopurines (10 with infliximab, 3 to thiopurine only), 1 to infliximab only, and 1 to neither biologics nor thiopurines. Comparison with rates from healthy controls indicated a standardized incidence rate for malignancy of 2.43 (95% CI, 1.29-4.15) for thiopurine exposure (with or without biologic exposure), but no significant increase in neoplasia with infliximab exposure in the absence of thiopurine exposure (standardized incidence rate, 1.49; 95% CI, 0.04-8.28). Of note, 5 cases of hemophagocytic lymphocytic histiocytosis were reported, all with viral infection (EBV or cytomegalovirus) in patients only exposed to thiopurine. No case of hepatosplenic T-cell lymphoma was reported during this study period. Overall, while the risk for malignancies appears low across the available pediatric literature,[79,82,86] the average length of treatment exposure and follow-up reported in those studies is short in comparison to real-world experience, and, therefore, pediatric patients should continue to be monitored closely as more safety data accumulate over time.

Very–Early-Onset Inflammatory Bowel Disease

An emerging population of children younger than 6 years of age with IBD represents a unique form of disease, termed very–early-onset IBD (VEO-IBD), which is phenotypically and genetically distinct from older-onset IBD. VEO-IBD can be associated with increased disease severity and poor responsiveness to conventional therapies. As such, this population subset may require different treatment strategies.[89] Thus far, there are only retrospective evaluations of these patients on anti-TNFα therapies. These reports have demonstrated higher rates of anti-TNFα failure in VEO-IBD than in older-onset IBD, during both induction and maintenance phases, with overall shorter duration of therapy due to failure to reach and sustain clinical remission.[90-92]

In addition, there have been reports that younger children require dose optimization more commonly than older children, which may also impact failure rates.[93] Future prospective studies evaluating the role of proactive TDM and use of different dosing strategies are needed. Due to the possibility of poor response or durability of anti-TNFα therapies, additional consideration should be taken in the diagnostic evaluation of these patients, many of whom likely have different drivers of disease and require thorough immunologic and genetic workup.[94] This evaluation can help determine if alternative targeted therapeutics would be more likely to be beneficial earlier in the treatment strategy.

Biosimilar Agents

A biosimilar agent resembles the original biologic in terms of molecular structure and efficacy, but by definition is not a generic form. From a regulatory standpoint, once a biosimilar has been shown to be equivalent for 1 clinical indication, extrapolation of efficacy to other clinical indications is accepted.[95] In 2016, the FDA recommended that CT-P13 (Celltrion), a biosimilar to infliximab, be approved for its rheumatologic conditions and, by extension, for adult and pediatric UC and CD.[96] This occurred despite no RCTs studying CT-P13 in IBD, and, indeed, there are limited data regarding the

Table 3. Summary of Main Studies Related to Vedolizumab Efficacy in Pediatric IBD

Study Authors and Type	Patients (N) and IBD Type	Combination With IM	Anti-TNFα Exposure	Efficacy Endpoints		Other Key Findings
				Clinical Response	Clinical Remission	
Singh et al[114] Retrospective multicenter study	N=52 CD: 58% UC/IBD-U: 42%	29%	90%	**Week 14**		UC/IBD-U was more likely than CD to be in clinical remission at weeks 14 and 22 Week 6 clinical remission was predictive of week 14 clinical remission
				NA	CD: 42% UC/IBD-U: 76%	
				Week 22		
				NA	CD: 33% UC/IBD-U: 71%	
Conrad et al[112] Prospective single-center study	N=21 CD: 76% UC/IBD-U: 24%	43%	100%	**Week 14**		1-year sustained response rate was 80%
				CD: 47% UC/IBD-U: 75%	CD: 25% UC/IBD-U: 40%	
				Week 22		
				CD: 60% UC/IBD-U: 50%	CD: 31% UC/IBD-U: 40%	
Ledder et al[116] Retrospective multicenter study	N=64 CD: 64% UC/IBD-U: 36%	67%	100%	**Week 14**		Mucosal healing rate (week 14): CD, 17%; UC/IBD-U, 15%
				NA	CD: 14% UC/IBD-U: 37%	
				Week 22		
				NA	CD: 19% UC/IBD-U: 34%	
Jossen et al[115] Retrospective single-center study	N=68 CD: 49% UC/IBD-U: 51%	NA	53%	**Week 49**		Endoscopic and histologic remission rates were 51% and 42%, respectively Anti-TNFα exposure negatively impacted clinical and endoscopic remission
				NA	CD: 48% UC/IBD-U: 57%	

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease–unclassified; IM, immunomodulator; NA, not applicable; TNF, tumor necrosis factor; UC, ulcerative colitis.

bioequivalence of this compound in IBD.[97] The decision to switch is often based on an economic evaluation, which might not involve patients, parents, or physicians in the decision-making process. While a comprehensive review of biosimilar development, regulatory requirements, clinical outcomes, and perspectives is beyond the scope of this article, it is important to note that the Crohn's & Colitis Foundation cautions against interchangeability until further evidence regarding safety, efficacy, and immunogenicity has been gathered.[98]

Other Biologic Agents Used in Pediatrics

In the search to enlarge the therapeutic armamentarium, newer biologics, namely vedolizumab (Entyvio, Takeda) and ustekinumab (Stelara, Janssen), have shown

effectiveness in both UC and CD and were recently granted FDA approval, although only in adults. In pediatric practice, off-label use of these biologics has been increasing, and evidence from real-world cohort studies is growing.

Vedolizumab

Efficacy Vedolizumab is a humanized anti-α4β7 integrin receptor molecule that inhibits lymphocyte trafficking to the gut by interfering with the ability of the lymphocytes to bind to mucosal addressin cell adhesion molecule-1 (MAdCAM-1).[99] Since 2013, 3 landmark phase 3 adult GEMINI trials and their extension phases, several real-life cohort studies, and 2 systematic reviews and meta-analyses have confirmed the efficacy and safety of vedolizumab in treating patients with UC and luminal CD and the induction of mucosal healing.[100-107] Nevertheless, while overall effectiveness has been demonstrated irrespective of anti-TNFα treatment history,[100-102] post hoc analyses have revealed a delayed response in addition to an overall lower rate of clinical and endoscopic remission in anti-TNFα–exposed patients.[108,109] A suggested physiologic mechanism for these observed differences has included downregulation of MAdCAM-1 by anti-TNFα therapy.[110] However, it is noteworthy that anti-TNFα–exposed populations have also typically represented a more refractory disease phenotype. These observations further raise the question of whether or not vedolizumab could be used more effectively as first-line therapy in the treatment algorithm for moderate to severe UC, a topic that has recently been investigated in the VARSITY trial comparing vedolizumab and adalimumab in the treatment of active UC in adults.[111] In this study, clinical remission at week 52 occurred in a significantly higher percentage of patients who received vedolizumab than in patients who received adalimumab (31.3% vs 22.5%), as did endoscopic improvement (39.7% vs 27.7%). These results suggest a shift in the therapeutic approach of IBD, positioning anti-adhesion molecules as an option for first-line therapy to achieve the best outcomes. Longitudinal studies will help further determine the true impact of this alternative biologic on disease course and rates of colectomy.

Pediatric evidence is currently limited to small, prospective, observational[112] and retrospective studies,[113-115] as well as long-term, open-label, follow-up data reports (Table 3).[116] Using an adapted dosing of 5 mg/kg up to 300 mg, these combined pediatric studies have reported week 14 and 22 clinical remission rates to be 37% to 76% and 34% to 71%, respectively, in a heterogeneous patient population.[112-116] Similar to what is seen in adult cohorts, remission rates have been numerically higher in UC as compared to CD and in anti-TNFα–naive

children compared to patients with prior exposure. In a recently published retrospective cohort, vedolizumab was also shown to induce mucosal healing (composite score of endoscopic and histologic remission) at a rate of 38%.[115]

The favorable risk-benefit profile makes vedolizumab an ideal therapeutic choice for pediatric IBD. However, an important limitation is its delayed onset of action, for which corticosteroid use as bridge therapy is often necessary in this population that is already at increased risk of growth failure and bone loss. Recently, Hamel and colleagues published their small, single-center experience of using concomitant tacrolimus between anti-TNFα withdrawal to vedolizumab maintenance as a corticosteroid-sparing bridge therapy in moderate to severe IBD.[117] Future larger-scale studies evaluating tacrolimus as a bridge therapy during induction for severe colitis are needed to confirm these promising results.

Clinical Pharmacology To date, there are no published pediatric studies assessing vedolizumab TDM, but an exposure-efficacy relationship has been suggested. In a post hoc analysis of the GEMINI trials,[118] trough concentrations at week 6 greater than 17 μg/mL for UC and greater than 16 μg/mL for CD were associated with a higher likelihood of achieving clinical remission.[118] High body mass index and more severe disease at initiation of therapy reflected by low baseline albumin and anemia levels and high C-reactive protein levels were associated with lower vedolizumab serum levels and worse therapeutic outcomes. Using propensity score–based case-matching analysis from GEMINI 1 and adjusting for confounders affecting drug clearance, a potential target TL for vedolizumab concentrations in patients with UC was identified.[119] The proposed concentrations were 37.1 μg/mL, 18.4 μg/mL, and 12.7 μg/mL at weeks 6 and 14 and during maintenance treatment, respectively. A positive correlation between a higher TL and mucosal healing has also been reported in a GEMINI 1 post hoc analysis, with UC patients having steady-state trough concentrations in the upper quartiles (quartiles 2-4, TL >19 μg/mL) being more likely to achieve deep remission at week 52.[120] Similar dose-efficacy relationships in CD have been shown in real-world cohort studies.[121,122] Additionally, histologic remission, a distinct treatment target for which growing evidence is suggesting better clinical outcomes, was recently shown to be associated with a TL greater than 25 μg/mL during maintenance therapy.[123]

Importantly, in contrast to anti-TNFα therapy where immunogenicity has been associated with accelerated drug clearance and loss of response, immunogenicity of vedolizumab appears to be low (<5%) and mostly transient, with less than 1% of patients having persistent drug

antibodies.[124] These findings likely explain the observed lack of additional benefit with combination therapy. Future prospective studies evaluating the mechanisms underlying primary nonresponse and loss of response to vedolizumab as well as the impact of dose optimization are needed before positioning drug monitoring in the therapeutic algorithm of vedolizumab.[125]

Safety Safety data regarding use of vedolizumab in children are limited. In the largest multicenter case series of 64 children, the Pediatric IBD Porto Group of ESPGHAN reported no serious adverse events at a median follow-up of 24 weeks.[116] Future data from the currently enrolling prospective multicenter VEDOKIDS cohort study will help to further define the risk-benefit profile of vedolizumab in pediatric IBD.[126] Pooled data from adult clinical trials and real-world observational studies have reported no increase in serious adverse events, serious infections, or malignancies, therefore supporting the notion that gut-selective biologics are safe, and perhaps safer than anti-TNFα agents.[127,128] In a systematic review of vedolizumab-exposed patients (N=3979) with follow-up ranging from 10 weeks to 46 months, the risks for treatment-related serious adverse events and severe infections were 20 per 100 PYs (<8%) and 7.4 per 100 PYs (<0.6%), respectively, with no reported cases of progressive multifocal leukoencephalopathy.[127] Risk of infusion-related reactions was less than 5%. Moreover, the recently published results from the open-label extension study GEMINI-LTS (total of 5670 PYs) confirmed no increased risk of malignancies with vedolizumab exposure.[128] Theoretical concerns for an increased risk of perioperative complications, including wound dehiscence and infections secondary to inhibition of lymphocyte trafficking, have been raised with vedolizumab. While initial small adult and pediatric retrospective studies may support these concerns,[129-132] recent systematic reviews and meta-analyses have not detected an increased risk of postoperative complications compared to either preoperative anti-TNFα therapy or no prior biologic therapy.[133,134] Overall, given its favorable long-term risk-benefit profile, vedolizumab may be a safe alternative in patients for whom it might be best to avoid systematic immunosuppression, including those predisposed to infection and/or malignancy.

Ustekinumab
Efficacy Ustekinumab, a human monoclonal antibody targeting the common p40 subunit of interleukin (IL) 12 and IL-23, has demonstrated clinical efficacy in the phase 2 CERTIFI and phase 3 UNITI trials for induction and maintenance of remission in adult CD.[135-137] Endoscopic healing has also been reported in a post hoc analysis of

the UNITI trials.[138] Moreover, accumulating data suggest efficacy of ustekinumab in treating refractory perianal fistulizing CD.[139,140] Finally, new data for the use of anti–IL-12/23 have been emerging for UC from the phase 3 UNIFI trial.[141,142]

Off-label use of ustekinumab in the pediatric population is increasing. However, evidence for its efficacy and safety in this age group is limited to 3 observational cohort studies in children with CD refractory to anti-TNFα therapies[143-145] and an ongoing large randomized trial[146] (Table 4). Recently, Dayan and colleagues highlighted increased efficacy among biologic-naive patients compared to biologic-exposed patients (90% vs 50%; *P*=.03) in an observational study including 52 children and young adults (38 children, 81% with CD).[143] Fusillo and colleagues, in a preliminary analysis of a prospective cohort of 20 pediatric biologic-exposed patients, including 16 with CD, described clinical response in 52% of patients at week 6 and 45% at a median follow-up of 26 weeks.[145] Similar long-term outcomes at 12 months were reported in a separate retrospective cohort of 44 pediatric patients.[144] Overall, these results suggest that ustekinumab is efficacious in pediatric patients with IBD, but larger cohort studies will be required to validate the efficacy, safety profile, and optimized dosing regimen in this population.

Clinical Pharmacology Compared to infliximab, the immunogenicity of ustekinumab is remarkably low, with antibody formation reported in only 0.7% of patients by week 36 and in 2.3% by 1 year.[147] Although data regarding TDM remain scarce, a recent study of phase 3 adult CD data showed that trough concentrations of 0.8 μg/mL or greater were associated with maintenance of clinical remission in a higher proportion of patients than in patients with lower trough concentrations. Additionally, unlike anti-TNFα agents, concentrations of ustekinumab did not seem to be affected by cotreatment with immunomodulators.[147,148]

Safety While long-term safety data for ustekinumab are limited in IBD, safety data from psoriasis and psoriatic arthritis registries underscore no increased risk of serious infection, malignancy, or mortality.[149] Data from clinical trials in adult IBD demonstrated a similarly favorable safety profile.[135-137]

Future Interleukin Inhibitors Although the efficacy and safety of ustekinumab are well-established in IBD, it remains unclear whether modulation of the IL-12 axis adds potential risk related to the role of IL-12 in host defense mechanisms. Hence, selectively blocking IL-23(p19) might offer important differentiation in

Table 4. Summary of Main Studies Related to Ustekinumab Efficacy in Pediatric IBD

Study Authors and Type	Patients (N) and IBD Type	Combination With IM	Anti-TNFα Exposure	Efficacy Endpoints	
				Clinical Response	Clinical Remission
Dayan et al[143] Prospective cohort study	N=52 (38 <18 years) CD: 81% UC/IBD-U: 19%	23%	81%	**Week 52**	
				NA	CD: 60% UC/IBD-U: 50%
Chavannes et al[144] Prospective cohort study	N=44 CD: 100%	29.5%	100%	**Week 52**	
				47.8%	38.6%
Fusillo et al[145] Prospective cohort study	n=25 (week 6) n=20 (week >26) CD: 80% UC/IBD-U: 20%	52%	100%	**Week 6[a]**	
				52%	24%[a]
				Week >26[a]	
				45%	40%

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease–unclassified; IM, immunomodulator; NA, not applicable; TNF, tumor necrosis factor; UC, ulcerative colitis.

[a]For both CD and UC/IBD-U combined.

efficacy, safety, and dosing. The current biologic development pipeline includes 3 monoclonal antibodies directed against IL-23(p19): brazikumab (AstraZeneca), risankizumab (AbbVie), and mirikizumab (Eli Lilly), all of which are in active IBD clinical trials. Mirikizumab is the only agent in this family that has parallel pediatric arms to the adult trials at this time.[150]

Facilitating Clinical Drug Trials for Children With Inflammatory Bowel Disease

Conducting clinical drug trials in the pediatric IBD setting presents several challenges that include the relatively small eligible population, greater reluctance from parents to enroll children in trials due to concerns for potential side effects and invasive procedures, ethical issues of subjecting sick children to placebo, fear of subtherapeutic dosing of IBD drugs, and required long pre-enrollment washout periods.[8,151] Consequently, pediatric therapies have faced long delays in approval, and this time lag has led to extensive off-label use of drugs, often without clear guidance and appropriate dosing. This is particularly concerning because extrapolation from dose-finding adult studies has often been shown to be too low in real-world experience.[63,90,152] While stakeholders agree on the critical need to expedite drug development for pediatric IBD, the optimal trial design for assessing novel therapies is still a

subject of debate among pediatric IBD experts, pharmaceutical companies, regulatory agencies, and the patient and family community.[151]

In order to address this need, a group of international pediatric IBD experts (Pediatric Inflammatory Bowel Disease Network) recently published a consensus process on how to facilitate pediatric IBD clinical drug designs.[8] Key points include acceptance of extrapolation of efficacy from adult data and real-world safety data, requirements for pharmacokinetic and/or pharmacodynamic studies in children of all age groups prior to adult approval, consideration for higher dosing per kilogram (or use of body surface area–based dosing) in children weighing less than 30 kg, and improved feasibility for successful RCTs by way of adapted small sample size, reduced number of invasive procedures, and minimized washout period prior to inclusion. Hopefully, once in practice, these novel approaches to pediatric IBD drug development will help expedite drug approval and enlarge the therapeutic armamentarium for this vulnerable population.

Conclusion

In the last decade, a significantly increased number of children with IBD have been treated with biologic drugs. Anti-TNFα agents have revolutionized the management of IBD, positively modifying the natural disease history in

children. Importantly, inception cohort studies of pediatric CD and UC (RISK and PROTECT, respectively) have highlighted the variable course of disease and necessity of adopting an individualized approach with early use of biologic therapy in patients at risk of severe disease progression. Moreover, newer categories of biologic drugs (ie, anti-integrin, anti-IL) that have shown efficacy and safety in the adult population may also be the new horizon of IBD treatment in children. The landscape of IBD treatment is widening rapidly; however, few medications have a registered pediatric indication. Important barriers to drug approval in this vulnerable population have been identified, and solutions to optimize clinical trial design for emerging and existing therapies in pediatrics have been proposed by international societies. There is a need for collaboration among pediatric IBD experts as well as among physicians, patients and families, research organizations, and the pharmaceutical industry to facilitate global drug development and advancement in pediatric IBD.

References

1. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3(7):390-407.
2. Ye Y, Manne S, Treem WR, Bennett D. Prevalence of inflammatory bowel disease in pediatric and adult populations: recent estimates from large national databases in the United States, 2007-2016. *Inflamm Bowel Dis*. 2020;26(4):619-625.
3. Benchimol EI, Bernstein CN, Bitton A, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol*. 2017;112(7):1120-1134.
4. Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. *JAMA Pediatr*. 2015;169(11):1053-1060.
5. Walters TD, Kim MO, Denson LA, et al; PRO-KIIDS Research Group. Increased effectiveness of early therapy with anti-tumor necrosis factor-α vs an immunomodulator in children with Crohn's disease. *Gastroenterology*. 2014;146(2):383-391.
6. Bouguen G, Levesque BG, Feagan BG, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13(6):1042-1050.e2.
7. Qiu Y, Chen BL, Mao R, et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNFα dose intensification in Crohn's disease. *J Gastroenterol*. 2017;52(5):535-554.
8. Turner D, Griffiths AM, Wilson D, et al. Designing clinical trials in paediatric inflammatory bowel diseases: a PIBDnet commentary. *Gut*. 2020;69(1):32-41.
9. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther*. 2017;45(10):1291-1302.
10. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology*. 2015;148(2):344-354.e5.
11. Hyams J, Crandall W, Kugathasan S, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132(3):863-873.
12. Ruemmele FM, Lachaux A, Cézard JP, et al; Groupe Francophone d'Hépatologie, Gastroentérologie et Nutrition Pédiatrique. Efficacy of infliximab in pediatric Crohn's disease: a randomized multicenter open-label trial comparing scheduled to on demand maintenance therapy. *Inflamm Bowel Dis*. 2009;15(3):388-394.
13. Hyams JS, Griffiths A, Markowitz J, et al. Safety and efficacy of adalimumab for moderate to severe Crohn's disease in children. *Gastroenterology*. 2012;143(2):365-374.e2.
14. Ruemmele FM, Veres G, Kolho KL, et al; European Crohn's and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. 2014;8(10):1179-1207.
15. Mack DR, Benchimol EI, Critch J, et al. Canadian Association of Gastroenterology clinical practice guideline for the medical management of pediatric luminal Crohn's disease. *J Can Assoc Gastroenterol*. 2019;2(3):e35-e63.
16. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring. *Gastroenterology*. 2019;157(4):985-996.e2.
17. Kierkus J, Dadalski M, Szymanska E, et al. The impact of infliximab induction therapy on mucosal healing and clinical remission in Polish pediatric patients with moderate-to-severe Crohn's disease. *Eur J Gastroenterol Hepatol*. 2012;24(5):495-500.
18. Nobile S, Gionchetti P, Rizzello F, Calabrese C, Campieri M. Mucosal healing in pediatric Crohn's disease after anti-TNF therapy: a long-term experience at a single center. *Eur J Gastroenterol Hepatol*. 2014;26(4):458-465.
19. Santha SL, Shankar PR, Pan A, Schoen B, Kugathasan S, Sauer CG. Mucosal healing in clinical practice: a single-center pediatric IBD experience. *Inflamm Bowel Dis*. 2017;23(8):1447-1453.
20. Kang B, Choi SY, Kim HS, Kim K, Lee YM, Choe YH. Mucosal healing in paediatric patients with moderate-to-severe luminal Crohn's disease under combined immunosuppression: escalation versus early treatment. *J Crohns Colitis*. 2016;10(11):1279-1286.
21. Lee YM, Kang B, Lee Y, Kim MJ, Choe YH. Infliximab "top-down" strategy is superior to "step-up" in maintaining long-term remission in the treatment of pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2015;60(6):737-743.
22. Church PC, Guan J, Walters TD, et al. Infliximab maintains durable response and facilitates catch-up growth in luminal pediatric Crohn's disease. *Inflamm Bowel Dis*. 2014;20(7):1177-1186.
23. Choi J, Kang B, Kim MJ, Sohn I, Lee HJ, Choe YH. Early infliximab yields superior long-term effects on linear growth in pediatric Crohn's disease patients. *Gut Liver*. 2018;12(3):255-262.
24. Faubion WA, Dubinsky M, Ruemmele FM, et al. Long-term efficacy and safety of adalimumab in pediatric patients with Crohn's disease. *Inflamm Bowel Dis*. 2017;23(3):453-460.
25. Thayu M, Leonard MB, Hyams JS, et al; Reach Study Group. Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. *Clin Gastroenterol Hepatol*. 2008;6(12):1378-1384.
26. Hyams JS, Lerer T, Griffiths A, et al; Pediatric Inflammatory Bowel Disease Collaborative Research Group. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm Bowel Dis*. 2009;15(6):816-822.
27. De Bie CI, Hummel TZ, Kindermann A, et al. The duration of effect of infliximab maintenance treatment in paediatric Crohn's disease is limited. *Aliment Pharmacol Ther*. 2011;33(2):243-250.
28. Crombé V, Salleron J, Savoye G, et al. Long-term outcome of treatment with infliximab in pediatric-onset Crohn's disease: a population-based study. *Inflamm Bowel Dis*. 2011;17(10):2144-2152.
29. Assa A, Hartman C, Weiss B, et al. Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease. *J Crohns Colitis*. 2013;7(5):369-376.
30. Vahabnezhad E, Rabizadeh S, Dubinsky MC. A 10-year, single tertiary care center experience on the durability of infliximab in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20(4):606-613.
31. Volonaki E, Mutalib M, Kiparissi F, Shah N, Lindley KJ, Elawad M. Adali-

mumab as a second-line biological therapy in children with refractory ulcerative colitis. *Eur J Gastroenterol Hepatol.* 2015;27(12):1425-1428.

32. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis [published online January 13, 2020]. *Clin Gastroenterol Hepatol.* doi:10.1016/j.cgh.2020.01.008.

33. Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. *Aliment Pharmacol Ther.* 2018;47(4):454-465.

34. Iwańczak BM, Kierkuś J, Ryżko J, et al. Induction and maintenance infliximab therapy in children with moderate to severe ulcerative colitis: retrospective, multicenter study. *Adv Clin Exp Med.* 2017;26(1):57-61.

35. Bolia R, Rajanayagam J, Hardikar W, Alex G. Impact of changing treatment strategies on outcomes in pediatric ulcerative colitis. *Inflamm Bowel Dis.* 2019;25(11):1838-1844.

36. Dan-Nielsen S, Wewer V, Paerregaard A, et al. Does infliximab prevent colectomy in acute and chronic active ulcerative colitis? *J Pediatr Gastroenterol Nutr.* 2014;58(6):768-772.

37. Turner D, Mack D, Leleiko N, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. *Gastroenterology.* 2010;138(7):2282-2291.

38. Larsen MD, Qvist N, Nielsen J, Kjeldsen J, Nielsen RG, Nørgård BM. Use of anti-TNFα agents and time to first-time surgery in paediatric patients with ulcerative colitis and Crohn's disease. *J Crohns Colitis.* 2016;10(6):650-656.

39. Aloi M, D'Arcangelo G, Capponi M, et al. Managing paediatric acute severe ulcerative colitis according to the 2011 ECCO-ESPGHAN guidelines: efficacy of infliximab as a rescue therapy. *Dig Liver Dis.* 2015;47(6):455-459.

40. Church PC, Ho S, Sharma A, et al. Intensified infliximab induction is associated with improved response and decreased colectomy in steroid-refractory paediatric ulcerative colitis. *J Crohns Colitis.* 2019;13(8):982-989.

41. Hyams J, Damaraju L, Blank M, et al; T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol.* 2012;10(4):391-399.e1.

42. Hyams JS, Lerer T, Griffiths A, et al; Pediatric Inflammatory Bowel Disease Collaborative Research Group. Outcome following infliximab therapy in children with ulcerative colitis. *Am J Gastroenterol.* 2010;105(6):1430-1436.

43. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of paediatric ulcerative colitis, part 2: acute severe colitis—an evidence-based consensus guideline from the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;67(2):292-310.

44. Hindryckx P, Novak G, Vande Casteele N, et al. Review article: dose optimisation of infliximab for acute severe ulcerative colitis. *Aliment Pharmacol Ther.* 2017;45(5):617-630.

45. Ordás I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther.* 2012;91(4):635-646.

46. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut.* 2011;60(6):780-787.

47. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology.* 2012;142(2):257-265.e1-e3.

48. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet.* 2017;389(10080):1710-1718.

49. Hyams JS, Davis S, Mack DR, et al. Factors associated with early outcomes following standardised therapy in children with ulcerative colitis (PROTECT): a multicentre inception cohort study. *Lancet Gastroenterol Hepatol.* 2017;2(12):855-868.

50. Hyams JS, Davis Thomas S, Gotman N, et al. Clinical and biological predictors of response to standardised paediatric colitis therapy (PROTECT): a multicentre inception cohort study. *Lancet.* 2019;393(10182):1708-1720.

51. Vermeire S, Dreesen E, Papamichael K, Dubinsky MC. How, when, and for whom should we perform therapeutic drug monitoring? *Clin Gastroenterol Hepatol.* 2020;18(6):1291-1299.

52. Barnes EL, Allegretti JR. Are anti-tumor necrosis factor trough levels predictive of mucosal healing in patients with inflammatory bowel disease?: a systematic review and meta-analysis. *J Clin Gastroenterol.* 2016;50(9):733-741.

53. Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable

sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut.* 2014;63(11):1721-1727.

54. Bodini G, Giannini EG, Savarino V, et al. Infliximab trough levels and persistent vs transient antibodies measured early after induction predict long-term clinical remission in patients with inflammatory bowel disease. *Dig Liver Dis.* 2018;50(5):452-456.

55. Carman N, Mack DR, Benchimol EI. Therapeutic drug monitoring in pediatric inflammatory bowel disease. *Curr Gastroenterol Rep.* 2018;20(5):18.

56. Choi SY, Kang B, Lee JH, Choe YH. Clinical use of measuring trough levels and antibodies against infliximab in patients with pediatric inflammatory bowel disease. *Gut Liver.* 2017;11(1):55-61.

57. Sharma S, Eckert D, Hyams JS, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. *Inflamm Bowel Dis.* 2015;21(4):783-792.

58. Ricciuto A, Dhaliwal J, Walters TD, Griffiths AM, Church PC. Clinical outcomes with therapeutic drug monitoring in inflammatory bowel disease: a systematic review with meta-analysis. *J Crohns Colitis.* 2018;12(11):1302-1315.

59. Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S; American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. *Gastroenterology.* 2017;153(3):827-834.

60. Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of paediatric ulcerative colitis, part 1: ambulatory care—an evidence-based guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.* 2018;67(2):257-291.

61. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology.* 2015;149(2):350-355.e2.

62. Singh N, Rosenthal CJ, Melmed GY, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2014;20(10):1708-1713.

63. Adedokun OJ, Xu Z, Padgett L, et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. *Inflamm Bowel Dis.* 2013;19(13):2753-2762.

64. Stein R, Lee D, Leonard MB, et al. Serum infliximab, antidrug antibodies, and tumor necrosis factor predict sustained response in pediatric Crohn's disease. *Inflamm Bowel Dis.* 2016;22(6):1370-1377.

65. Clarkston K, Tsai YT, Jackson K, Rosen MJ, Denson LA, Minar P. Development of infliximab target concentrations during induction in pediatric Crohn disease patients. *J Pediatr Gastroenterol Nutr.* 2019;69(1):68-74.

66. Dubinsky MC, Rosh J, Faubion WA Jr, et al. Efficacy and safety of escalation of adalimumab therapy to weekly dosing in pediatric patients with Crohn's disease. *Inflamm Bowel Dis.* 2016;22(4):886-893.

67. Ruemmele FM, Rosh J, Faubion WA, et al. Efficacy of adalimumab for treatment of perianal fistula in children with moderately to severely active Crohn's disease: results from IMAgINE 1 and IMAgINE 2. *J Crohns Colitis.* 2018;12(10):1249-1254.

68. El-Matary W, Walters TD, Huynh HQ, et al. Higher postinduction infliximab serum trough levels are associated with healing of fistulizing perianal Crohn's disease in children. *Inflamm Bowel Dis.* 2019;25(1):150-155.

69. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther.* 2017;45(7):933-940.

70. Crandall W, Hyams J, Kugathasan S, et al. Infliximab therapy in children with concurrent perianal Crohn disease: observations from REACH. *J Pediatr Gastroenterol Nutr.* 2009;49(2):183-190.

71. Juncadella A, Papamichael K, Vaughn BP, Cheifetz AS. Maintenance adalimumab concentrations are associated with biochemical, endoscopic, and histologic remission in inflammatory bowel disease. *Dig Dis Sci.* 2018;63(11):3067-3073.

72. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology.* 2015;148(7):1320-1329.e3.

73. D'Haens G, Vermeire S, Lambrecht G, et al; GETAID. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology.* 2018;154(5):1343-1351.e1.

74. Colombel JF, Sandborn WJ, Reinisch W, et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010;362(15):1383-1395.

75. Colombel JF, Adedokun OJ, Gasink C, et al. Combination therapy with inflix-imab and azathioprine improves infliximab pharmacokinetic features and efficacy: a post hoc analysis. *Clin Gastroenterol Hepatol*. 2019;17(8):1525-1532.e1.

76. Hyams JS, Dubinsky M, Rosh J, et al. The effects of concomitant immu-nomodulators on the pharmacokinetics, efficacy and safety of adalimumab in paediatric patients with Crohn's disease: a post hoc analysis. *Aliment Pharmacol Ther*. 2019;49(2):155-164.

77. Matar M, Shamir R, Turner D, et al. Combination therapy of adalimumab with an immunomodulator is not more effective than adalimumab monotherapy in children with Crohn's disease: a post hoc analysis of the PAILOT random-ized controlled trial [published online December 3, 2019]. *Inflamm Bowel Dis*. doi:10.1093/ibd/izz294.

78. Lega S, Phan BL, Rosenthal CJ, et al. Proactively optimized infliximab monotherapy is as effective as combination therapy in IBD. *Inflamm Bowel Dis*. 2019;25(1):134-141.

79. de Ridder L, Turner D, Wilson DC, et al; Porto IBD Working Group of ESP-GHAN. Malignancy and mortality in pediatric patients with inflammatory bowel disease: a multinational study from the Porto Pediatric IBD group. *Inflamm Bowel Dis*. 2014;20(2):291-300.

80. Day AS, Gulati AS, Patel N, Boyle B, Park KT, Saeed SA. The role of combi-nation therapy in pediatric inflammatory bowel disease: a clinical report from the North American Society for Pediatric Gastroenterology, Hepatology and Nutri-tion. *J Pediatr Gastroenterol Nutr*. 2018;66(2):361-368.

81. Gordon J, Ramaswami A, Beuttler M, et al. EBV status and thiopurine use in pediatric IBD. *J Pediatr Gastroenterol Nutr*. 2016;62(5):711-714.

82. Hyams JS, Dubinsky MC, Baldassano RN, et al. Infliximab is not asso-ciated with increased risk of malignancy or hemophagocytic lymphohistiocy-tosis in pediatric patients with inflammatory bowel disease. *Gastroenterology*. 2017;152(8):1901-1914.e3.

83. Shah ED, Coburn ES, Nayyar A, Lee KJ, Koliani-Pace JL, Siegel CA. System-atic review: hepatosplenic T-cell lymphoma on biologic therapy for inflammatory bowel disease, including data from the Food and Drug Administration Adverse Event Reporting System. *Aliment Pharmacol Ther*. 2020;51(5):527-533.

84. Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2015;13(3):514-521.e4.

85. Raychaudhuri SP, Nguyen CT, Raychaudhuri SK, Gershwin ME. Incidence and nature of infectious disease in patients treated with anti-TNF agents. *Autoim-mun Rev*. 2009;9(2):67-81.

86. Dulai PS, Thompson KD, Blunt HB, Dubinsky MC, Siegel CA. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pedi-atric inflammatory bowel disease: a systematic review. *Clin Gastroenterol Hepatol*. 2014;12(9):1443-1451.

87. Singh S, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative risk of serious infections with biologic and/or immunosuppressive therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18(1):69-81.e3.

88. Ardura MI, Toussi SS, Siegel JD, Lu Y, Bousvaros A, Crandall W. NASP-GHAN clinical report: surveillance, diagnosis, and prevention of infectious diseases in pediatric patients with inflammatory bowel disease receiving tumor necrosis factor-α inhibitors. *J Pediatr Gastroenterol Nutr*. 2016;63(1):130-155.

89. Kelsen JR, Baldassano RN. The role of monogenic disease in children with very early onset inflammatory bowel disease. *Curr Opin Pediatr*. 2017;29(5):566-571.

90. Kelsen JR, Grossman AB, Pauly-Hubbard H, Gupta K, Baldassano RN, Mam-ula P. Infliximab therapy in pediatric patients 7 years of age and younger. *J Pediatr Gastroenterol Nutr*. 2014;59(6):758-762.

91. Kelsen JR, Conrad MA, Dawany N, et al. The unique disease course of children with very early onset-inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26(6):909-918.

92. Bramuzzo M, Arrigo S, Romano C, et al; SIGENP IBD Working Group. Efficacy and safety of infliximab in very early onset inflammatory bowel disease: a national comparative retrospective study. *United European Gastroenterol J*. 2019;7(6):759-766.

93. deBruyn JC, Jacobson K, El-Matary W, et al. Long-term outcomes of inflix-imab use for pediatric Crohn disease: a Canadian multicenter clinical practice experience. *J Pediatr Gastroenterol Nutr*. 2018;66(2):268-273.

94. Kelsen JR, Sullivan KE, Rabizadeh S, et al. NASPGHAN position paper on the evaluation and management for patients with very early-onset inflammatory bowel disease (VEO-IBD) [published online December 30, 2019]. *J Pediatr Gas-troenterol Nutr*. doi:10.1097/MPG.0000000000002567.

95. Joung J, Robertson JS, Griffiths E, Knezevic I; WHO Informal Consultation

Group. WHO informal consultation on regulatory evaluation of therapeutic bio-logical medicinal products held at WHO headquarters, Geneva, 19-20 April 2007. *Biologicals*. 2008;36(4):269-276.

96. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, par-allel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis*. 2013;72(10):1605-1612.

97. Strik AS, van de Vrie W, Bloemsaat-Minekus JPJ, et al; SECURE study group. Serum concentrations after switching from originator infliximab to the biosimilar CT-P13 in patients with quiescent inflammatory bowel disease (SECURE): an open-label, multicentre, phase 4 non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2018;3(6):404-412.

98. Crohn's and Colitis Foundation. Biosimilars position statement. https://www.crohnscolitisfoundation.org/sites/default/files/2019-06/biosimilars-state-ment-needs.pdf. Accessed July 15, 2020.

99. Dotan I, Allez M, Danese S, Keir M, Tole S, McBride J. The role of integrins in the pathogenesis of inflammatory bowel disease: approved and investigational anti-integrin therapies. *Med Res Rev*. 2020;40(1):245-262.

100. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedoli-zumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.

101. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711-721.

102. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology*. 2014;147(3):618-627.e3.

103. Engel T, Ungar B, Yung DE, Ben-Horin S, Eliakim R, Kopylov U. Vedol-izumab in IBD—lessons from real-world experience; a systematic review and pooled analysis. *J Crohns Colitis*. 2018;12(2):245-257.

104. Schreiber S, Dignass A, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *J Gastroenterol*. 2018;53(9):1048-1064.

105. Vermeire S, Loftus EV Jr, Colombel JF, et al. Long-term efficacy of vedoli-zumab for Crohn's disease. *J Crohns Colitis*. 2017;11(4):412-424.

106. Loftus EV Jr, Colombel JF, Feagan BG, et al. Long-term efficacy of vedoli-zumab for ulcerative colitis. *J Crohns Colitis*. 2017;11(4):400-411.

107. Noman M, Ferrante M, Bisschops R, et al. Vedolizumab induces long-term mucosal healing in patients with Crohn's disease and ulcerative colitis. *J Crohns Colitis*. 2017;11(9):1085-1089.

108. Sands BE, Sandborn WJ, Van Assche G, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease in patients naïve to or who have failed tumor necrosis factor antagonist therapy. *Inflamm Bowel Dis*. 2017;23(1):97-106.

109. Feagan BG, Rubin DT, Danese S, et al. Efficacy of vedolizumab induc-tion and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. *Clin Gastroenterol Hepatol*. 2017;15(2):229-239.e5.

110. Biancheri P, Di Sabatino A, Rovedatti L, et al. Effect of tumor necrosis fac-tor-α blockade on mucosal addressin cell-adhesion molecule-1 in Crohn's disease. *Inflamm Bowel Dis*. 2013;19(2):259-264.

111. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381(13):1215-1226.

112. Conrad MA, Stein RE, Maxwell EC, et al. Vedolizumab therapy in severe pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22(10):2425-2431.

113. Schneider AM, Weghuber D, Hetzer B, et al. Vedolizumab use after failure of TNF-α antagonists in children and adolescents with inflammatory bowel disease. *BMC Gastroenterol*. 2018;18(1):140.

114. Singh N, Rabizadeh S, Jossen J, et al. Multi-center experience of vedoli-zumab effectiveness in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2016;22(9):2121-2126.

115. Jossen J, Kiernan BD, Pittman N, Dubinsky MC. Anti–tumor necrosis factor-alpha exposure impacts vedolizumab mucosal healing rates in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*. 2020;70(3):304-309.

116. Ledder O, Assa A, Levine A, et al. Vedolizumab in paediatric inflammatory bowel disease: a retrospective multi-centre experience from the Paediatric IBD Porto Group of ESPGHAN. *J Crohns Colitis*. 2017;11(10):1230-1237.

117. Hamel B, Wu M, Hamel EO, Bass DM, Park KT. Outcome of tacrolimus and vedolizumab after corticosteroid and anti-TNF failure in paediatric severe colitis. *BMJ Open Gastroenterol*. 2018;5(1):e000195.

118. Rosario M, French JL, Dirks NL, et al. Exposure-efficacy relationships for vedolizumab induction therapy in patients with ulcerative colitis or Crohn's disease. *J Crohns Colitis.* 2017;11(8):921-929.

119. Osterman MT, Rosario M, Lasch K, et al. Vedolizumab exposure levels and clinical outcomes in ulcerative colitis: determining the potential for dose optimisation. *Aliment Pharmacol Ther.* 2019;49(4):408-418.

120. Sandborn WJ, Colombel JF, Panaccione R, et al. Deep remission with vedolizumab in patients with moderately to severely active ulcerative colitis: a GEMINI 1 post hoc analysis. *J Crohns Colitis.* 2019;13(2):172-181.

121. Dreesen E, Verstockt B, Bian S, et al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2018;16(12):1937-1946.e8.

122. Ungaro RC, Yarur A, Jossen J, et al. Higher trough vedolizumab concentrations during maintenance therapy are associated with corticosteroid-free remission in inflammatory bowel disease. *J Crohns Colitis.* 2019;13(8):963-969.

123. Pouillon L, Rousseau H, Busby-Venner H, et al. Vedolizumab trough levels and histological healing during maintenance therapy in ulcerative colitis. *J Crohns Colitis.* 2019;13(8):970-975.

124. Van den Berghe N, Verstockt B, Tops S, Ferrante M, Vermeire S, Gils A. Immunogenicity is not the driving force of treatment failure in vedolizumab-treated inflammatory bowel disease patients. *J Gastroenterol Hepatol.* 2019;34(7):1175-1181.

125. Pouillon L, Vermeire S, Bossuyt P. Vedolizumab trough level monitoring in inflammatory bowel disease: a state-of-the-art overview. *BMC Med.* 2019;17(1):89.

126. ClinicalTrials.gov. Predicting response to vedolizumab in pediatric inflammatory bowel diseases. https://clinicaltrials.gov/ct2/show/NCT02862132. Identifier: NCT02862132. Accessed July 13, 2020.

127. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther.* 2017;46(1):3-15.

128. Card T, Ungaro R, Bhayat F, Blake A, Hantsbarger G, Travis S. Vedolizumab use is not associated with increased malignancy incidence: GEMINI LTS study results and post-marketing data. *Aliment Pharmacol Ther.* 2020;51(1):149-157.

129. Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. *J Crohns Colitis.* 2017;11(2):185-190.

130. Lightner AL, McKenna NP, Tse CS, Raffals LE, Loftus EV Jr, Mathis KL. Postoperative outcomes in vedolizumab-treated Crohn's disease patients undergoing major abdominal operations. *Aliment Pharmacol Ther.* 2018;47(5):573-580.

131. Zimmerman LA, Zalieckas JM, Shamberger RC, Bousvaros A. Postoperative complications of pediatric patients with inflammatory bowel disease treated with vedolizumab. *J Pediatr Surg.* 2018;53(7):1330-1333.

132. Lightner AL, Tse CS, Potter DD Jr, Moir C. Postoperative outcomes in vedolizumab-treated pediatric patients undergoing abdominal operations for inflammatory bowel disease. *J Pediatr Surg.* 2018;53(9):1706-1709.

133. Yung DE, Horesh N, Lightner AL, et al. Systematic review and meta-analysis: vedolizumab and postoperative complications in inflammatory bowel disease. *Inflamm Bowel Dis.* 2018;24(11):2327-2338.

134. Law CCY, Narula A, Lightner AL, McKenna NP, Colombel JF, Narula N. Systematic review and meta-analysis: preoperative vedolizumab treatment and postoperative complications in patients with inflammatory bowel disease. *J Crohns Colitis.* 2018;12(5):538-545.

135. Sandborn WJ, Gasink C, Gao LL, et al; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med.* 2012;367(16):1519-1528.

136. Feagan BG, Sandborn WJ, Gasink C, et al; UNITI–IM-UNITI Study Group. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2016;375(20):1946-1960.

137. Sandborn WJ, Feagan BG, Fedorak RN, et al; Ustekinumab Crohn's Disease Study Group. A randomized trial of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology.* 2008;135(4):1130-1141.

138. Rutgeerts P, Gasink C, Chan D, et al. Efficacy of ustekinumab for inducing endoscopic healing in patients with Crohn's disease. *Gastroenterology.* 2018;155(4):1045-1058.

139. Glass J, Alsamman Y, Chittajallu P, Ahmed T, Fudman D. 26 Ustekinumab dose escalation effective in real-world use for luminal and perianal Crohn's disease. *Inflamm Bowel Dis.* 2020;26(suppl 1):S76.

140. Sands BE, Kramer BC, Gasink C, et al. Tu1724 Association of ustekinumab serum concentrations and perianal fistula resolution in the Crohn's disease UNITI program. *Gastroenterology.* 2019;156(6):S1099-S1100.

141. Sands BE, Sandborn W, Panaccione J, et al. Safety and efficacy of ustekinumab induction therapy in patients with moderate to severe ulcerative colitis: results from the phase 3 UNIFI study. *United European Gastroenterol J.* 2018;6(suppl 1).

142. Sandborn WJ, Sands BE, Panaccione R, et al. OP37 Efficacy and safety of ustekinumab as maintenance therapy in ulcerative colitis: week 44 results from UNIFI. *J Crohns Colitis.* 2019;13(suppl 1):S025-S026.

143. Dayan JR, Dolinger M, Benkov K, et al. Real world experience with ustekinumab in children and young adults at a tertiary care pediatric inflammatory bowel disease center. *J Pediatr Gastroenterol Nutr.* 2019;69(1):61-67.

144. Chavannes M, Martinez-Vinson C, Hart L, et al. Management of paediatric patients with medically refractory Crohn's disease using ustekinumab: a multi-centred cohort study. *J Crohns Colitis.* 2019;13(5):578-584.

145. Fusillo SJ, Chang V, Stein RE, et al. 329–Ustekinumab responders versus non-responders in refractory pediatric inflammatory bowel disease. *Gastroenterology.* 2018;154(6 suppl 1):S82.

146. ClinicalTrials.gov. A pharmacokinetic study of ustekinumab in pediatric subjects with moderately to severely active Crohn's disease (Stelara). https://clinicaltrials.gov/ct2/show/NCT02968108. Identifier: NCT02968108. Accessed July 13, 2020.

147. Adedokun OJ, Xu Z, Gasink C, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. *Gastroenterology.* 2018;154(6):1660-1671.

148. Battat R, Kopylov U, Bessissow T, et al. Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease. *Clin Gastroenterol Hepatol.* 2017;15(9):1427-1434.e2.

149. Gottlieb AB, Kalb RE, Langley RG, et al. Safety observations in 12095 patients with psoriasis enrolled in an international registry (PSOLAR): experience with infliximab and other systemic and biologic therapies. *J Drugs Dermatol.* 2014;13(12):1441-1448.

150. ClinicalTrials.gov. A study of mirikizumab (LY3074828) in children and teenagers with ulcerative colitis (UC) (SHINE 1). https://clinicaltrials.gov/ct2/show/NCT04004611. Identifier: NCT04004611. Accessed July 13, 2020.

151. Ruemmele FM, Hyams JS, Otley A, et al. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. *Gut.* 2015;64(3):438-446.

152. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics.* 2011;128(5):e1242-e1249.