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Therapeutics for Inflammatory Bowel Diseases in Children and Adolescents: A Focus on Biologics and an Individualized Treatment Paradigm

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Abstract

Pharmacologic treatment of children and adolescents with inflammatory bowel diseases (IBD) [Crohn's disease and ulcerative colitis] requires consideration of disease and medication effects on growth and nutrition, the importance of durability of biologics, and concerns for long-term sequelae of disease and therapies. Achieving early remission in children with Crohn's disease correlates with improved outcomes and therefore allows a window of opportunity for maximizing growth. Thus, there is a great need to treat children and adolescents with the right drug at the right time while achieving adequate exposure. Improved understanding of disease phenotypes, disease natural history, and risk stratification will play a critical role in treatment selection for children, particularly as more therapeutic options become available. Here we summarize data supporting newer concepts of treating the individual child with IBD through targeted early biologic treatment, including utilization of therapeutic drug monitoring to optimize treatment effects and the use of early antitumor necrosis factor (TNF)- α therapies to mitigate long-term sequelae of the disease. Recent inception cohort studies provide important data regarding the risk stratification of children and adolescents with IBD, which support a move toward a personalized therapeutic approach to IBD in children and adolescents.

Keywords

Biologics; Crohn's disease; Inflammatory bowel diseases; Pediatrics; Therapeutics; Ulcerative colitis

1 Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the gastrointestinal tract, which include Crohn's disease (CD) and ulcerative colitis (UC). Clinical manifestations, evolution of the disease, and prognosis are variable. CD may manifest as

three different subtypes: inflammatory, penetrating, or stricturing disease. The latter two types may result in life-altering complications including fistulae, abscesses, bowel perforation, bowel obstruction, and intra-abdominal sepsis (Kugathasan et al. 2017). Inflammation in UC is confined to the large intestine; manifestations include hematochezia, anemia, and fatigue. Both are systemic diseases, however, with extraintestinal manifestations affecting approximately one third of patients. IBD is particularly challenging for children and adolescents due to long-term complications, including malnutrition, decreased bone health, and growth failure (Pappa et al. 2011; Gasparetto and Guariso 2014).

Average age of onset follows a bimodal distribution, which peaks in adolescence and middle age. About one quarter of IBD patients are diagnosed prior to 20 years of age (Rosen et al. 2015). The incidence of IBD in children less than 5 years of age has been shown to be rapidly increasing (Benchimol et al. 2017). The approach to treatment of children with IBD has changed in recent years, with increasing knowledge of the disease course, prognosis, and new revelations into optimizing treatment.

2 Treatment Goals in Pediatric IBD

Historically, the treatment target in pediatric IBD was control of symptoms via a step-up approach. Treatment was initiated with a course of glucocorticoids and 5-aminosalicylates. If 5-aminosalicylates failed to maintain symptom-free remission, symptoms were managed with additional glucocorticoids, and maintenance treatment was escalated to immunomodulators, biologics, or a combination. Surgical management was reserved for refractory patients.

It is increasingly appreciated that symptoms and clinical disease indices in children with CD correlate poorly with endoscopic disease activity, while endoscopic healing correlates with improved long-term outcomes for patients, including lower corticosteroid use and decreased hospitalizations (Carman et al. 2019; Kerur et al. 2017; Bossuyt et al. 2019; Colombel et al. 2011; Seow et al. 2010; Maser et al. 2006). Thus, the treatment target in pediatric IBD has evolved from isolated symptom control to an emphasis on endoscopic remission. Mucosal or endoscopic healing has been defined as lack of visible findings on colonoscopy (typically a Mayo score of 0 or 1 in trials), which differs from the absence of histologic findings on biopsies (Lega and Dubinsky 2018). An active area of study, histologic healing and bowel damage are also being considered treatment targets correlated with improved outcomes. Indeed, it has been demonstrated that endoscopically assessed mucosal healing does not eliminate the possibility of progression to bowel damage; in children with CD, residual transmural inflammation often persists despite mucosal healing on endoscopy (Weinstein-Nakar et al. 2018). In addition to endoscopic remission, growth and nutrition optimization, as well as bone health, are important clinical outcome measures, particularly in children and adolescents with CD.

The new treatment paradigm for pediatric IBD focuses on a goal of “deep remission” for ongoing treatment. Disease response is based on clinical response or daily symptoms of disease, serum/fecal biomarkers, and endoscopic evaluation to assess for endoscopic and histologic healing. Patients with IBD are monitored regularly at outpatient clinical visits, at

least three to four times per year. These visits allow for assessment of clinical symptoms and biomarkers. There is currently no established guideline regarding the need for surveillance endoscopy and colonoscopy in pediatrics. However, more pediatric gastroenterologists are advocating for surveillance endoscopy and colonoscopy 6–12 months after treatment initiation, following the adult treat-to-target paradigm (Peyrin-Biroulet et al. 2015; Lega and Dubinsky 2018).

Complication-free survival in children with inflammatory CD is increased by early anti-TNF α therapy (Kugathasan et al. 2017). In children with newly diagnosed CD, early monotherapy with biologics, specifically anti-TNF α therapy, was demonstrated to be superior to early treatment with an immunomodulator and corticosteroids and facilitates catch-up growth (Walters et al. 2014; Church et al. 2014). Treatment with concomitant anti-TNF α and immunomodulator therapy has been shown to improve durability and reduce formation of antibodies to infliximab (Cheng et al. 2017; Chi et al. 2018). Proactive infliximab monitoring has also been shown to be a strategy to prevent antibody formation (Lega et al. 2019).

Despite these strategies, early anti-TNF α therapy has not been shown to prevent surgery or complications in stricturing CD and doesn't prevent colectomy in all children with severe, refractory UC (Kugathasan et al. 2017; Kerur et al. 2018; Hyams et al. 2017).

Variation in disease course and response to therapy underscore the growing appreciation for an individualized treatment paradigm for pediatric IBD and need for careful objective assessment of disease following treatment. In addition, it highlights the need for additional therapies for children with refractory inflammatory disease and fibrotic, stricturing disease.

3 Personalized Optimization of Biologics

The utilization of an individualized treatment paradigm is perhaps best illustrated through the use of biologics in pediatric IBD. Biologics used to treat IBD are monoclonal antibodies targeting components in the pathogenesis of IBD, although not all biologics have FDA approval for use in children or adolescents. Biologics used to treat IBD are summarized in Table 1. Anti-TNF α therapies are used as first-line treatment for severe disease or disease that is nonresponsive or poorly controlled by other medications. This class of medications offers various advantages improved efficacy in severe disease, ability to utilize therapeutic drug monitoring (TDM), and potential to mitigate long-term sequelae of poorly controlled IBD in children, such as decreased bone health and growth delay (Thayu et al. 2008; Church et al. 2014; Griffin et al. 2015).

3.1 Therapeutic Drug Concentrations and Achieving Adequate Exposure in Children

The pharmacokinetics of monoclonal antibodies is variable, and doses needed to achieve target serum concentrations are difficult to predict. TDM may be used to assess serum drug concentrations to guide dose adjustments. Several studies have established that consistent anti-TNF α serum drug concentrations are correlated with higher rates of clinical and endoscopic remission in children and adults (Ungar et al. 2016; van Hove et al. 2018; van de Casteele et al. 2018). The American Gastroenterology Association has established

guidelines for target serum concentrations for adult IBD patients during maintenance anti-TNF α treatment: infliximab serum concentration of 5 mg/dL and adalimumab serum concentration of 7.5 mg/dL (Feuerstein et al. 2017). One important challenge in the use of TDM is that target serum drug concentrations may vary with individual patient risk factors and severity of disease. For example, serum concentrations needed to close complex perianal fistulae are likely higher than those needed to maintain remission of luminal inflammatory disease (El-Matary et al. 2019). Patients with a higher inflammatory burden may require higher serum trough concentrations to achieve remission due to increased drug clearance (Fasanmade et al. 2011; Dotan et al. 2014).

3.2 Utilization of TDM: Reactive vs. Proactive Monitoring

Recent research highlights how TDM may be used to optimize serum concentrations of biologic medication for individual patients. TDM may be used as a “reactive” measure for IBD patients undergoing biologic treatment who may present with concerns for disease flare. In this setting, TDM is used to assess whether the patient has a low drug trough concentration associated with the onset of symptoms. Minar et al. (2016) demonstrated the utility of reactive TDM through assessment of 72 children with CD who presented with signs and symptoms concerning for loss of response to therapy. Twenty-five of 72 (35%) had sub-therapeutic concentrations and required dose escalation. Subsequent to dose escalation, there was significant improvement in remission rates at 6 months. However, relying on reactive TDM may prevent the ability to proactively optimize pharmacokinetics of infliximab. In a pediatric cohort of 50 patients with IBD on infliximab therapy, only a minority had a target trough concentration of 3 μ g/mL at week 14. Most patients required more frequent infusions or higher dosing than standard therapy to achieve goal trough concentrations (Lega et al. 2019).

Proactive TDM requires obtaining TDM at set intervals during treatment, even in the absence of active symptoms. If concentrations are found to be suboptimal, they are then proactively optimized to ensure patients maintain a therapeutic drug concentration (Lega et al. 2019). Stronger consideration has been given to the use of proactive TDM as a strategy for personalized optimization of therapy. The Trough Concentration Adapted Infliximab Treatment (TAXIT) trial was a prospective randomized control trial in adults with IBD in which enrolled patients were dose optimized during infliximab induction dosing. Then patients were randomized to dosing based on concentration or dosing based on clinical status. The authors found no benefit to proactive TDM, but there is concern that this 1-year study may not have been long enough in duration to detect a difference in outcomes (van de Castele et al. 2015). In contrast, other studies of both infliximab and adalimumab have retrospectively found proactive TDM allowed for early identification of patients with low trough concentrations and better probability of patients remaining on drug in remission (Vaughn et al. 2014; Papamichael et al. 2019). A recent meta-analysis found limited existing evidence to support an association between any TDM strategy and superior clinical remission rates but does support a cost-saving benefit for reactive TDM and suggests a potential benefit for anti-TNF durability with proactive TDM. Authors concluded that further longer-term studies are needed, particularly to evaluate proactive TDM and to

generate data on other anti-TNF therapies, target drug concentrations during induction, and pediatric populations (Ricciuto et al. 2018).

An important question is whether proactive TDM will be equal or better than use of combination therapy (a biologic with immunomodulator, such as a thiopurine or methotrexate) as a strategy to increase drug concentration and prevent anti-drug antibody formation. In adults with treatment-naïve Crohn's disease, a combination of infliximab with a thiopurine has been demonstrated as superior to either use as monotherapy (Colombel et al. 2010). Combination therapy also optimizes pharmacokinetics and reduces antibodies in adult and pediatric studies (Colombel et al. 2018; Chi et al. 2018). Further studies are needed to compare long-term effectiveness, safety, and cost associated with biologic monotherapy with proactive TDM versus the use of concomitant biologics and immunomodulators.

3.3 PK Modeling and Dashboard Systems

Various clinical factors including anti-drug antibodies, elevated serum C-reactive protein, hypoalbuminemia, and male gender have been identified as risk factors for lower infliximab concentrations (Brandse et al. 2017; Buurman et al. 2015; Dotan et al. 2014). Pharmacokinetic (PK) modeling has emerged as a tool for drug concentration prediction and optimization. Using Bayesian statistics and modeling, dashboard systems may incorporate current clinical information to predict future drug concentrations and target appropriate dosing for an individual patient (Mould and Dubinsky 2015; Dubinsky et al. 2017). Such approaches are likely to provide a new avenue for individualizing biologic treatment optimization for pediatric IBD patients.

3.4 Prevention of Immunogenicity and Anti-drug Antibodies

The prevalence of circulating anti-drug antibodies (ADA) to anti-TNF α treatment is estimated to be between 8 and 60% of IBD patients and is associated with adverse drug reactions and loss of response (Nanda et al. 2013). Development of ADA has been associated with intermittent or inconsistent exposure to treatment and suboptimal serum drug concentrations (Lee et al. 2012). It has been suggestive that proactive TDM may improve the durability of infliximab monotherapy by maintaining higher infliximab concentrations entering into maintenance, ultimately either decreasing antibody formation or modulating the clinical impact of ADA (Lega et al. 2019). Further studies are needed to understand whether maintenance of adequate drug concentrations proactively will prevent clinically relevant complications of anti-drug antibodies.

4 Early Use of Anti-TNF Therapies in Children to Mitigate Long-Term Disease Consequences

4.1 Bone Health

Children with CD are at risk for decreased bone health. Associated risk factors include high levels of inflammation, low serum vitamin D, and albumin concentrations. Bone modeling, remodeling, and turnover are decreased in patients with pediatric IBD. At diagnosis, bone turnover markers are noted to be 30–50% of normal, and biopsies show low bone mineral

density (Dubner et al. 2009). Current guidelines recommend routine bone health screening with dual-energy X-ray absorptiometry as a baseline at diagnosis (Rufo et al. 2012).

Prospective studies have found improvement of trabecular bone mineral density and cortical structure improved by anti-TNF α treatment in children with CD (Dubner et al. 2009). Other studies have shown that bone turnover biomarkers serum insulin-like growth factor-1, bone-specific alkaline phosphatase, and n-terminal propeptide of type-1 collagen were found to increase after initiation of anti-TNF treatment in pediatric IBD (Thayu et al. 2008; DoBoer et al. 2018). These findings highlight the likely advantage of early initiation of anti-TNF α therapy in children with pediatric IBD with impaired bone health.

4.2 Growth

Borrelli et al. (2004) demonstrated improved weight and z-scores in a prospective trial of 18 children with CD after initiation of infliximab therapy. Population-based studies have shown that catch-up growth in pediatric IBD children occurs after initiation of anti-TNF α treatment (Cromb et al. 2011; Church et al. 2014). In a clinical trial of adalimumab in children with CD, this therapy significantly improved and normalized growth rate at weeks 26 and 52 in patients with baseline growth impairment (Walters et al. 2017). Therefore, early anti-TNF α treatment is an example of a personalized treatment intervention for children with CD and linear growth failure.

5 Risk Stratification of Disease Phenotypes and an Individualized Treatment Approach in Pediatric IBD

5.1 Risk Stratification in Crohn's Disease

Increasingly, studies of pediatric CD progression have highlighted the variable course of disease; patients at risk for severe disease or poor response to treatment may need more aggressive or targeted treatment. The RISK trial was a prospective inception cohort study of newly diagnosed children with CD, which aspired to create a risk stratification model. More than 1,800 patients, ages 6–17, were recruited at disease onset and prospectively followed for complications and response to therapies. Certain factors were positively correlated with development of severe CD including African-American race, older age and ASCA, and Cbir1 seropositivity. Notably, patients with a stricturing phenotype were not responsive to early anti-TNF α therapy (started in first 90 days) and had a terminal ileal signature with increased extracellular matrix genes, implying a different biologic process in these patients (Kugathasan et al. 2017). Plasma collagen type III alpha 1 chain has been identified as a biomarker of stricturing disease that may be useful for predicting the need for earlier surgery instead of early anti-TNF α therapy (Ballengee et al. 2018).

Perianal CD is a subset of CD defined as inflammation around or near the anus; manifestations include fissures, fistulae, skin tags, abscesses, and/or stenosis. Complex fistulae may involve the rectum and adjacent structures including the vagina and urinary bladder. The incidence of perianal CD is estimated to be about 13–62%. Anti-TNF α therapies have led to higher rates of clinical remission in perianal CD patients, and the American College of Gastroenterology recommends anti-TNF α treatment as a primary

treatment for induction and remission of complex fistulizing perianal disease (Lichtenstein et al. 2018). A prospective, multicenter cohort study of children with newly diagnosed CD assessed clinical response of perianal CD to infliximab therapy; a trough concentration of 12.7 µg/mL predicted fistula healing at week 24 (El-Matary et al. 2019). These data support that higher serum drug concentrations may be required for closure of perianal fistulae and demonstrate an opportunity for tailoring biologic dosing to achieve a specific treatment goal.

5.2 Risk Stratification in UC

The Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) trial was a natural history study of 428 children with newly diagnosed UC designed to identify characteristics of disease associated with outcomes following standard-of-care therapy for pediatric UC. Clinical presentations ranged from 48% of children with mild-moderate disease treated only with mesalamine, 33% with moderate to severe disease treated initially with oral corticosteroids, and 21% with severe disease treated with intravenous corticosteroids. At 12 weeks, corticosteroid-free remission was achieved in 48% of patients in the mesalamine group, 33% in the oral corticosteroid group, and 21% in the intravenous corticosteroid group. Treatment escalation during the first 12 weeks (to anti-TNFα therapy, immunomodulators, colectomy) was required by 9 (7%) patients in the mesalamine group, 21 (15%) in the oral corticosteroid group, and 52 (36%) in the intravenous corticosteroid group. Eight patients, all of whom were initially treated with intravenous corticosteroids, underwent colectomy. Importantly, the need for biological therapy during the first 12 weeks was confined to those requiring IV steroids as first-line therapy. Moreover, the strongest predictor of corticosteroid-free remission by week 12 without the need for escalation to biologics was clinical response at 4 weeks, regardless of corticosteroid status. Thus, the study highlighted the importance of initial disease severity as a predictor of disease course. Additional risk factors for more severe disease in this population also included lower serum albumin, decreased eosinophils on rectal biopsies, and surface villiform changes on rectal biopsy (Hyams et al. 2017). Higher levels of serum perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) were associated with more extensive disease (Spencer et al. 2018).

6 Conclusion

Recent studies in adults and pediatrics have demonstrated that targeting deep remission improves outcomes for pediatric IBD patients. Individualizing dosing of biologics has translated to improved outcomes for patients, considering clinical risk factors. Additionally, cohort studies in pediatric IBD have highlighted baseline phenotyping of patients to predict the severity of their course. These studies have led to a shift in the treatment paradigm for pediatric IBD, with increasing data demonstrating a need to focus therapeutic choices on individual patients and treatment goals rather than use of a broad, step-up approach for all patients. However, numerous questions remain, including ideal strategies for monitoring patients during induction and in remission. While studies have mainly been focused on anti-TNFα therapies, newer biologics are now approved for use in adults with IBD, with more promising candidates under development. Additional studies are needed to clarify dosing and safety of these drugs in children and adolescents and to understand how various new

biologics can be targeted for use in the safest and most efficacious way, alone or in combination with other medications.

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Table 1

Summary of biologics used to treat inflammatory bowel disease

Generic name	Trade Name	Target	Mechanism of action	Pediatrics FDA-approved?	IBD indication in adults
Infliximab	Remicade®	Chimeric monoclonal antibody against TNF α	Decreases TNF α -related inflammatory cascade	Yes, for CD and UC	CD, UC
Adalimumab	Humira®	Recombinant monoclonal antibody against anti-TNF α	Decreases TNF α -related inflammatory cascade	Yes (for CD only)	CD, UC
Certolizumab pegol	Cimzia®	Humanized antigen-binding fragment (Fab') of a monoclonal antibody that has been conjugated to polyethylene glycol	Decreases TNF α -related inflammatory cascade	No	CD
Golimumab	Simponi®	Binds to both soluble and transmembrane forms of TNF α	Decreases TNF α -related inflammatory cascade	No	UC
Vedolizumab	Entyvio®	Humanized monoclonal antibody to α 4 β 7 integrin	Blocks α 4 β 7 integrin interaction with cell adhesion molecules inhibiting leukocyte migration across endothelium	No	CD, UC
Ustekinumab	Stelara®	Antibody to p40 subunit of IF-12 and IF-23	Decreases IF-12- and IF-23-related pro-inflammatory cascade	No	CD

CD Crohn's disease, *UC* ulcerative colitis