

Anti-TNFs in Pediatric Inflammatory Bowel Disease

Subjects: Gastroenterology & Hepatology

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Definition

Inflammatory bowel disease (IBD) is a chronic immune-mediated condition that affects the gastrointestinal tract. The incidence of the disease in children is increasing. However, most clinical trials in this disease have been carried out in adults, and the results have been extrapolated with minimal changes to determine treatment in children. Pediatric IBD (pIBD) is characterized by various factors, including a more severe phenotype than adult diseases. Since IBD is a chronic autoimmune disease, patients diagnosed during childhood live longer with the illness and consequently need treatment for longer. Biological drugs and, more specifically, anti-TNF drugs such as infliximab and adalimumab have proven efficient for treatment of IBD in adults and in children. However, the use of biological drugs differs between children and adults with IBD. For instance, the time between diagnosis and initiation of biological treatment is shorter in children than in adults. In addition, not all the biological drugs approved for adult IBD are approved for children.

1. Treatment of Pediatric IBD

The goal of the treatment of pediatric IBD is to induce and maintain clinical remission, achieve normal growth, provide optimal quality of life, promote psychological health, and reduce toxicity as much as possible. Additionally, the gold standard of optimal therapy is endoscopic mucosal healing, which makes it possible to modify the natural history of the disease and prevent complications of progressive bowel destruction. In observational adult studies, younger age at onset is repeatedly considered high-risk for poor prognosis, thus underlining the need for a highly effective treatment approach in children ^[1].

Treatment is selected based on the location, type of disease, severity of symptoms, and the goal of therapy (induction therapy or maintenance of remission). The pharmacological arsenal for pIBD treatment includes anti-inflammatory drugs such as aminosalicylates, corticosteroids, and immunomodulatory drugs (for example, thiopurines and methotrexate), which are used as maintenance therapy, and biologic drugs, which are used for induction and maintenance of remission. The doses and treatment guidelines for biologic drugs are very similar to those of adults, even though the metabolism and immune system of children may differ from those of adults ^{[2][3][4]}.

The introduction of monoclonal antibodies against tumor necrosis factor (anti-TNF) revolutionized the treatment of IBD. Infliximab and adalimumab are the two anti-TNF agents approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency for use in children, although adalimumab is not approved in perianal pCD ^[5]. Infliximab is administered as an intravenous infusion and adalimumab is administered subcutaneously for induction and maintenance therapy. Studies have shown that early use of anti-TNF drugs in children with CD is associated with increased rates of remission and mucosal healing, as well as with modest improvement in linear growth ^{[6][5][7][8]}.

Advances in the understanding of the etiology and pathogenesis of IBD in recent years have led to the development of new drugs based on inhibition of immune cells ^[9] or inhibition of cytokine signaling ^{[10][11][12]}. New categories of biologic drugs that have been shown to be effective and safe in adults are the new horizon for IBD treatment in children ^[5]. Some biological drugs that are currently approved in adults, such as vedolizumab or ustekinumab, are used off-label in children when treatment with infliximab or adalimumab fails ^[13].

Despite advances in medical treatment, surgery may still be warranted in refractory pIBD [1]. In pCD, the median time to first surgery is longer than in patients who debut in adulthood, although the need for surgery in pUC is earlier than in adults. Consequently, the risk of surgical resection before the age of 30 years is higher in children than in adults [14].

2. Clinical and Biochemical Biomarkers of Response to Anti-TNFs in pIBD

Anti-TNF α drugs have proven to be effective and safe for pIBD [15], although approximately one third of patients who initially respond to anti-TNF therapy lose that response over time [16][17]; and while various clinical and biochemical characteristics predict response to anti-TNF therapy, these are mainly based on studies in adult populations [18]. The characteristics include disease-related factors (such as disease phenotype, behavior, location, and severity), biochemical parameters (such as C-reactive protein, fecal calprotectin, and albumin levels) and drug-related characteristics (such as pharmacokinetic, pharmacodynamic, and immunogenic factors) [19][20][21][22][23]. The ECCO-ESPGHAN guideline update on management of CD in children recommends monitoring of fecal calprotectin or small bowel imaging as the best markers of treatment response [24].

The PANTS study is one of the few studies to evaluate the response to anti-TNFs in a population including children and adolescents over 6 years of age, although to date, no subanalysis of pediatric patients has been performed. Obesity, smoking, low albumin concentrations, higher baseline markers of disease activity, and development of immunogenicity were associated with low drug concentrations during induction, resulting in non-remission at week 54 after initiation of anti-TNF treatment [25].

The level of anti-TNF agent immediately before the following administration, known as the trough level, is increasingly used as a non-invasive biomarker. It is well known that serum levels of infliximab and adalimumab correlate with treatment response in patients with IBD [26][27] and pIBD [28][29][30][31]. Furthermore, these levels are associated with histological and endoscopic disease remission in both populations [32][33][34][35].

The therapeutic range of these drugs varies considerably, especially in pIBD. Most guidelines indicate that to achieve clinical remission of IBD, infliximab and adalimumab concentrations in the range of 3–7 and 5–12 $\mu\text{g/mL}$, respectively, are considered adequate [19][36][37][38][39]. The therapeutic ranges of both anti-TNF drugs may vary depending on the disease phenotype or on the treatment goals [25][35][40]. Further studies are needed to define optimal levels.

Anti-TNF drugs are antibodies against TNF that can induce the immune response and generate anti-drug antibodies (ADAs). ADAs bind to the anti-TNF drug, thus reducing free functional drug levels, neutralizing the therapeutic effect, and resulting in a loss of response [41]. ADA levels inversely correlate with drug levels and treatment response in adults [21][42], as well as in children [43][44][45][46].

For this reason, therapeutic drug monitoring (TDM) has been proposed as a means of optimizing biological therapies in both adults [47][48][49][50] and children [29][51][52][53] with IBD. This approach appears to be more advantageous in pediatric patients, since fluctuations in pharmacokinetic variables tend to be more pronounced in children than in adults, possibly owing to physiological differences, such as volume of distribution, and immaturity of enzyme systems and of clearance mechanisms [29]. In fact, Jongsma MME et al. reported that, over one year of treatment with infliximab, patients under 10 years of age require a more intensive treatment regimen than older patients and that these patients are more likely to develop antibodies to infliximab [54].

Data on the optimal timing of TDM are conflicting, since some professionals use reactive monitoring, i.e., measuring drug levels in the case of loss of response, whereas others use proactive monitoring, i.e., measuring them at preset time points [55]. Proactive monitoring has been shown to achieve clinical improvement and endoscopic remission in IBD patients treated with anti-TNFs [56][57][58], as well as in

children [59][60]. However, this issue is quite controversial and, in fact, the recommendations from the ECCO for adults are indecisive [24].

The current recommendation in pIBD is to measure drug levels and ADA titers after the induction period, even though studies in this population are insufficient and data are conflicting [5][31][61]. The use of TDM in pIBD is increasing in clinical practice, and efficacy similar to that of adults has been demonstrated in children, with loss of response to anti-TNF therapy [28].

Considering the high cost and potentially severe side effects of anti-TNF biologics, the identification of underlying factors involved in the individual responses is sorely needed. The usefulness of TDM is therefore limited, as monitoring helps physicians to modify the existing treatment by adjusting the dose of the biological drug and/or the frequency of administration. However, to choose the best biological drug and the best starting dose, other types of biomarkers are needed. Moreover, these new biomarkers should be inexpensive and easy to implement in clinical routine, which is not always simple.

3. Genomic Biomarkers of Response to Anti-TNFs in pIBD

Pharmacogenomics may play an important role in predicting response, mainly before initiation of anti-TNF treatment in pIBD. Genetic variants and gene expression could be useful markers for predicting response to biological drugs in children with IBD. Since pediatric patients will have to live longer with the disease and will therefore need treatment for longer, identification of pharmacogenomic biomarkers with the aim of personalizing treatment is especially important in this population.

4. Other Biomarkers of Response to Anti-TNFs in pIBD

Regulatory T cells (Tregs) play an essential role in the pathogenesis of IBD, in which Treg counts are decreased [62]. Anti-TNF therapy is known to increase the number and function of Tregs in IBD [63]. The study of these cells may help to predict response to anti-TNF agents, because upregulation is not as efficient in non-responders as in responders [64][65].

Few studies have assessed Tregs in children, although preliminary results suggest an effect similar to that observed in adults. Ricardelli et al. showed that FOXP3+ T-cell counts were lower in the mucosal samples of children with active CD than in healthy controls. However, this difference disappeared after the initiation of infliximab [66].

Furthermore, intestinal microbiota may also modulate the immune system and play an acute role in IBD [67]. It has been suggested that defects in Treg function might induce changes in the gut microbiome, leading to loss of tolerance to commensal bacteria [68]. In children, Conte et al. observed higher numbers of mucosa-associated aerobic and facultative anaerobic bacteria in IBD patients than in healthy controls [69]. The authors also observed a decrease in counts of *Bacteroides vulgatus*. A subsequent study differentiating between CD and UC in children showed a decrease in counts of *Faecalibacterium prausnitzii* and an increase in those of *Escherichia coli* in children with CD [70]. However, no differences were found in the composition of microbiota in children with UC, in contrast with findings in adults [70].

Concerning anti-TNF therapy and the gut microbiome in children with IBD, a higher number of multiple short-chain, fatty-acid-producing bacteria has been associated with a sustained response to infliximab in pediatric CD [71]. In addition, infliximab increased the diversity of the gut microbiome, and its composition resembled that of healthy children. These results were recently confirmed in a larger cohort of pediatric CD patients, where bile salt hydrolase-producing bacteria are also enriched after treatment with infliximab [72].

The aforementioned data suggest that Treg count and functionality, as well as the gut microbiome, could act as relevant biomarkers of response to anti-TNFs. However, this observation is restricted to infliximab. More studies are necessary to validate these biomarkers and to find new ones associated with the different biological drugs used in pIBD.

The list of factors thought to affect the efficacy of anti-TNFs is growing. It was recently reported that vitamin D deficiency was associated with a higher risk of early discontinuation of anti-TNF therapy (14.5% vs. 0%) in children with IBD [73].

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