



## Novel Therapeutic Modalities in Pediatric Inflammatory Bowel Disease

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### Abstract

Management of inflammatory bowel disease in childhood poses great challenges. Apart from the disease complications, the drugs' adverse affects, especially corticosteroids, are significant. In the past decade major progress was made in elucidating the pathogenesis of IBD, which led to new treatment options aiming to achieve better control of the disease and decrease the various complications of current therapy. In this review we provide an overview of novel therapies for IBD, their efficacy, safety and their current use in children.

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Inflammatory bowel disease in childhood is often diagnosed at a vulnerable time of growth and development. Malnutrition secondary to reduced appetite, increased metabolism and decreased absorptive capacity increase the risk of complications in children and adolescents diagnosed with IBD. Current treatment options include 5-aminosalicylic acid, antibiotics, corticosteroids, nutritional therapy, as well as immunomodulators to induce and maintain remission. Apart from the disease complications, the adverse affects of drugs, especially corticosteroids, are significant. Although the etiology of IBD has not yet been clarified there has been remarkable progress in the understanding of this field in the past decade [1], which led to the development of novel therapies that specifically alter molecules involved in the inflammatory cascade. The aim of these therapies is to achieve better control of the disease and decrease the various complications of therapy currently used. The use of novel therapies for IBD in children lags after adults. In this review we provide an overview of these agents, their efficacy, safety and their current use in children with the hope that knowledge of the available medications in adults will advance their use in children.

### Inhibition of inflammatory cytokines

#### Inhibition of tumor necrosis factor

Infliximab is emerging as an important treatment in children and adults with IBD and was discussed in detail in a previous issue of this journal.

#### Anti-interleukin-12 p40 antibody

IL-12 plays a central role in Th1 development and is abundantly produced in the gut of patients with Crohn's disease [1]. Anti-IL-12 treatment was shown to effectively ameliorate intestinal inflammation in several animal models of Th1-mediated colitis [2]. Humanized immunoglobulin G1 monoclonal antibody against IL-12 p40 (ABT-874) was studied in a double-blind placebo-controlled randomized study in 79 patients with active Crohn's [3]. The patients were randomly assigned to receive seven weekly injections of 1 mg/kg, 3 mg/kg anti-IL-12, or placebo. The patients who received 3 mg/kg anti-IL-12 for 7 weeks showed a significantly greater clinical response than the patients treated with a placebo (75% vs. 25%). The rates of remission were also higher in the 3 mg/kg anti-IL-12 group (38%) than in the placebo group (0%) but the difference did not reach statistical significance. Anti-IL-12 therapy is therefore considered to be a safe and effective treatment for active Crohn's disease as no serious side effects requiring the discontinuation of the treatment were observed. Local reaction at the injection site was noted at a higher rate in the anti-IL-12-treated group. Anti-drug antibody was formed in some patients who received anti-IL-12 antibody. Currently, there are no data on anti-IL-12 treatment in children but it was shown that IL-12p40 levels by protein microarray analysis was significantly elevated in pediatric Crohn patients [4].

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*Current therapy for children with IBD, especially corticosteroids, may cause significant side effects, thus warranting alternative therapy*

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#### Anti-IL-6 receptor antibody

IL-6 is one of the major inflammatory cytokines. Both IL-6 ligand and its receptor expression are increased in patients with active Crohn's disease [5]. Humanized anti-IL-6 receptor

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IBD = inflammatory bowel disease

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IL = interleukin

monoclonal antibody was assessed in a randomized double-blind placebo-controlled trial [6], which showed that biweekly MRA led to significant clinical remission (80% vs. 31% in the placebo). Treatment was generally well tolerated with no significant side effects. There are no reports on treating children with MRA.

#### **Anti-interferon-gamma antibody (fontolizumab)**

IFN $\gamma$  is a key pro-inflammatory cytokine that enhances the development of a Th1 immune response in Crohn's disease. Fontolizumab is a humanized monoclonal antibody directed against IFN $\gamma$ . A phase 2 study of fontolizumab in 133 patients with moderate to severe active Crohn's demonstrated efficacy after two doses, the second 56 days after the initial dose [7]. This effect was most prominent in patients with elevated baseline concentrations of C-reactive protein. An additional study of fontolizumab in 45 patients with active Crohn's did not demonstrate efficacy at day 28 [8]. Both studies showed fontolizumab to be safe with no significant side effects. To date the use of fontolizumab in children has not been reported.

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### *Anti-TNF $\alpha$ treatment is the only biological treatment to date that is widely used in children*

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#### **Anti-IL-2 receptor (CD25) antibodies**

IL-2 is a major T cell growth factor that promotes cell survival and proliferation. The IL-2 receptor  $\alpha$ -chain (CD25) is a component of high affinity IL-2 receptor and it is expressed on activated T cells. Daclizumab is a humanized monoclonal antibody to CD25, which blocks the binding of IL-2 to the IL-2 receptor. The initial open-label pilot study of daclizumab suggested that it was beneficial for patients with active ulcerative colitis [9], but a further randomized double-blind placebo-controlled trial has not shown any benefit [10].

A chimeric monoclonal antibody against CD25B, basiliximab, blocks the binding of IL-2 to the IL-2 receptor. Two uncontrolled pilot studies suggested that basiliximab in combination with steroids may be effective for steroid-resistant ulcerative colitis [11,12], but further studies should be done to prove safety and efficacy. The use of basiliximab in children has not been reported.

#### **Adhesion molecules inhibition**

##### **Anti- $\alpha$ 4-integrin antibody (natalizumab)**

The integrins are a family of cell-surface glycoproteins involved in the adhesion, migration and activation of immune cells [13,14]. They are up-regulated in both Crohn's disease and ulcerative colitis [15]. The  $\alpha$ 4 integrins are expressed on lymphocytes,

usually exist in combination with a  $\beta$ -subunit and interact with adrenergins expressed on endothelium.  $\alpha$ 4 $\beta$ 1-integrin binds to vascular cellular adhesion molecule 1 and  $\alpha$ 4 $\beta$ 7-integrin binds to mucosal addressing cell adhesion molecule 1. The interaction between  $\alpha$ 4 $\beta$ 7-integrin and MAdCAM-1 is important in mediating lymphocytes homing to the gut mucosa [16].

Natalizumab, a humanized IgG4 anti- $\alpha$ 4-integrin monoclonal antibody, inhibits both  $\alpha$ 4 $\beta$ 7-integrin/MAdCAM-1 interaction and  $\alpha$ 4 $\beta$ 1/VCAM-1 binding. It was shown to effectively induce remission in a large placebo-controlled randomized trial including 248 patients with moderate to severe Crohn's disease [17]. Nevertheless, a larger (905 patients) phase 3 trial failed to show a benefit of natalizumab treatment in moderate to severe Crohn's [18]. However, in a subgroup analysis, natalizumab-treated patients with concurrent immunosuppressive therapies, prior anti-TNF $\alpha$  therapy or elevated CRP levels showed a significant response rate compared with placebo-treated patients. Along with the high efficacy it was reported that three patients treated with natalizumab developed JC virus-related progressive multifocal leukoencephalopathy [10,20,21]. These reported warranted reevaluation of this drug efficacy and safety. In children natalizumab was assessed only in adolescents with moderate to severe Crohn's with active disease and a safety and efficacy profile similar to that of adult natalizumab-treated Crohn disease patients [22]. This was an uncontrolled study of 38 adolescents aged 12 to 17 with PCDAI > 30. They received three intravenous infusions of natalizumab (3 mg/kg) at 0, 4 and 8 weeks. Natalizumab was well tolerated, with the greatest clinical response and remission rates at week 10 (55% and 29%, respectively). These results were comparable with studies of adult natalizumab-treated Crohn patients.

##### **Anti- $\alpha$ 4 $\beta$ 7-integrin**

A humanized anti- $\alpha$ 4 $\beta$ 7-integrin (MLN-02) blocks specifically the  $\alpha$ 4 $\beta$ 7-integrin/MAdCAM-1 interaction. In a randomized placebo-controlled trial in 185 patients with mild to moderately active Crohn's disease treated with placebo, MLN-02 led to remission significantly more than placebo [23]. Furthermore, MLN-02 was shown to be efficacious in ulcerative colitis as well. In both studies, apart from one patient with infusion reaction and angioedema, no significant adverse events were noted. MLN-02 appears to be an effective therapy especially for active ulcerative colitis, but further trials are warranted to confirm the efficacy of MLN-02 therapy for IBD. To date no studies in children have been reported.

#### **Immunomodulation**

##### **Mycophenolate mofetil**

Azathioprine and 6-mercaptopurine are well established as immunomodulator treatments in IBD. Another immunosuppressive

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MAdCAM-1 = mucosal addressing cell adhesion molecule 1

Ig = immunoglobulin

VCAM-1 = vascular cellular adhesion molecule 1

CRP = C-reactive protein

PCDAI = Pediatric Crohn Disease Activity Index

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MRA = anti-IL-6 receptor monoclonal antibody

IFN $\gamma$  = interferon-gamma

agent is mycophenolate mofetil, which inhibits purine synthesis. A retrospective study suggested a more rapid onset of action compared with azathioprine/6-mercaptopurine [24]. Nevertheless, patients treated with mycophenolate mofetil (25–35 mg/kg/day) had twice as many flares over 12 months as patients treated with azathioprine/6-mercaptopurine. Although the side effects of mycophenolate mofetil commonly include diarrhea and abdominal pain, it was well tolerated by 80% of the patients in this study.

### **Tacrolimus**

Tacrolimus (FK506), a calcineurin inhibitor, has a similar mode of action to that of cyclosporine, but it is 100 times more potent, has little effect on renal function, and has better intestinal absorption. Preliminary non-controlled studies have reported a beneficial effect of tacrolimus in both Crohn disease and ulcerative colitis [25] and showed long-term safety [26]. Bousvaros et al. [27] evaluated tacrolimus in 13 children with steroid-refractory fulminant colitis as an alternative to surgery. Nine children (69%) responded initially, but at one year follow-up 38% were receiving maintenance therapy and the rest had had a colectomy.

### **Granulocyte-macrophage colony-stimulating factor**

Defective functioning of intestinal innate immune defense is thought to play a role in the pathogenesis of Crohn's disease [28]. Breakdown of the intestinal defensive barrier, consisting of neutrophils and macrophages, may permit persistent exposure of lamina propria cells to luminal microbes and microbial products, resulting in a chronic inflammatory process mediated by T cells. Thus, treatment directed at augmenting the intestinal innate immune defense system rather than suppressing a secondary inflammatory response may be effective in Crohn's disease. GM-CSF, a myeloid growth factor, plays a pivotal role in the development and function of phagocytic cells. GM-CSF is used in glycogen storage disease type Ib, where neutropenia and IBD-like disease are dominant [29]. A randomized placebo-controlled trial assessing GM-CSF (sargramostim) in 124 patients with moderate-to-severe active Crohn's showed no significant difference in the rate of clinical response defined by a decrease of at least 70 points in the Crohn's Disease Activity Index score on day 57, but it did show significantly decreased disease severity and improved quality of life in patients with active Crohn's disease [30]. No trials in children have been reported.

## **Other treatment modalities**

### **Probiotics and prebiotics**

One of the prevailing theories on the etiology of IBD is that the adaptive immune system is hyper-responsive to the commensal intestinal microflora in genetically susceptible individuals [31]. This hypothesis is supported by several observations: most inflammation occurs in areas with the highest density of intestinal bacteria, broad-spectrum antibiotics improve chronic intestinal inflammation, surgical diversion may prevent recurrence, and a consistent feature of animal models of IBD is the failure to

develop the disease in a germ-free environment. In IBD patients, there are enhanced and persistent cell-mediated and humoral responses to commensal bacteria [32]. The susceptibility gene associated with Crohn's disease, the NOD2 polymorphism, is associated with the defective clearance of invasive bacteria by macrophages [33]. The recognition of the association between IBD and intestinal microflora has led to clinical studies investigating the therapeutic potential of altering the luminal bacteria using probiotics or prebiotics.

Probiotics are living microorganisms or components of microbial cells which affect the host beneficially. This benefit may be direct or indirect, including enhanced barrier function, modulation of the mucosal immune system, and alteration of the intestinal microflora and the production of antimicrobial agents. Prebiotics are non-digestible dietary carbohydrates that stimulate the growth of endogenous enteric protective bacteria. Synbiotics are combinations of probiotics and prebiotics and may become an emerging therapeutic modality.

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*Various biological therapies, such as inflammatory cytokine inhibitors, adhesion molecule inhibitors and novel immunomodulators are being developed and are studied in adults but their use in children is scarce*

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Administering probiotics to IL-10-deficient mice with bowel inflammation decreased the levels of pro-inflammatory cytokines TNF $\alpha$  and IL-12 and reduced intestinal inflammation. Despite promising results with animal models, the efficacy of probiotic use in humans with IBD is unclear. The one disorder associated with IBD for which probiotics has been shown to be efficacious is pouchitis. A probiotic mixture of eight bacterial species was shown to be effective in the treatment and prevention of pouchitis after ileo-anal pouch creation [34]. Studies using a probiotics mixture in patients with ulcerative colitis showed induction of remission in over 75% of the patients [35]. However, the efficacy of probiotics in ulcerative colitis is still controversial.

Clinical trials have also been conducted in Crohn's disease, comparing mesalazine with probiotics. The latter contributed to the decrease in the recurrence rate. In children, the most widely used probiotic is Lactobacillus GG. The addition of LGG to prednisone decreased disease activity in a small study in children, but in a larger study in children there was no difference in remission rate observed over 2 years [36].

Studies using prebiotics have been performed mostly in animal models. Lactulose and inulin have been shown to at-

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GM-CSF = granulocyte-macrophage colony-stimulating factor

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LGG = Lactobacillus GG

tenuate inflammation in IL-10 knockout mice [37]. Treatment with fructo-oligosaccharide in an open-label study in 10 patients with Crohn disease resulted in clinical improvement and enhanced lamina propria dendritic cell IL-10 production and toll-like receptor expression [38].

Synbiotics, which is the combination of probiotics and prebiotics, is a novel idea to maximize the favorable intestinal environment. The probiotic *Bifidobacterium longum* in combination with inulin-oligofructose was administered to 16 patients with ulcerative colitis for a period of one month in a double-blind randomized controlled trial. There was an improvement in sigmoidoscopy score and inflammatory markers [39].

The alteration of the composition of the gut microflora is promising as a therapeutic strategy for IBD. Larger, controlled trials including species-specific studies must be performed.

### Growth hormone

Growth hormone therapy in IBD was assessed in 18 adult patients with IBD and showed significant reduction of Crohn activity index when compared with the control group [40]. The side effects were mild and self-limited. The use of growth hormone in children may not only affect the disease severity but also affects growth retardation, a common manifestation of Crohn's disease in children. Thus, further studies are needed in children and adults alike.

### Conclusions

There have been major advances in the treatment of IBD in the past decade in both adults and children. Our aim as pediatricians and gastroenterologists is to improve treatment efficacy, decrease adverse effects and improve quality of life without affecting normal growth. All the novel drugs discussed in this review were studied initially in adults for efficacy and safety, with the hope of future use in children. Knowledge of these treatment modalities in adults will bring forward their use in children.

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