Seminars in Pediatric Surgery 26 (2017) 360–366

Contents lists available at ScienceDirect

Seminars in Pediatric Surgery

journal homepage: www.elsevier.com/locate/sempedsurg

Medical management of pediatric inflammatory bowel disease

Katherine R. Baldwin, MD, Jess L. Kaplan, MD*

Pediatric Gastroenterology and Nutrition, MassGeneral Hospital for Children, Harvard Medical School, Boston, MA

ARTICLE INFO

Keywords:
Crohn's disease
Ulcerative colitis
Pediatric
Inflammatory bowel disease
Management

ABSTRACT

Inflammatory bowel diseases (IBD) are chronic autoimmune conditions of the gut affecting both pediatric and adult patients. Medical therapy is often successful at inducing and maintaining remission and preventing disease complications. The mainstays of treatment are medications and other therapies that reduce inflammation and suppress the overactive immune system. Here we review current medical therapies for pediatric IBD, discuss future therapeutics, and present current treatment goals and approaches.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major conditions that constitute inflammatory bowel disease (IBD). IBDs are chronic and progressive disorders with a multifactorial etiology centered around an inappropriate immune response to intestinal microbes in genetically susceptible individuals, eventually leading to uncontrolled inflammation in the gastrointestinal (GI) tract.[1] Currently, neither condition has a medical cure. It is estimated that more than 1 million Americans have IBD and as many as 20% of those are children.[2] The goal of treatment in IBD is to reduce gut inflammation, which leads to both symptom improvement and a reduction in complications like fibrostenotic and penetrating CD, surgery, and malignancy. In children, additional complications like growth failure, pubertal delay, and poor social functioning are common and need to be considered.

Medical treatments for IBD have traditionally included anti-inflammatory and immune-suppressive medications. Over the last 2 decades, significant changes in management have occurred with the introduction of biologic medications with more precise targets in the immune system. As with any medical treatment, benefits and risks need to be considered and risk stratification may help determine who will benefit most from a particular therapy, and when, in order to help maximize efficacy and limit unnecessary risk.

Fortunately, the medical management of IBD is advancing relatively rapidly with new therapeutic options emerging regularly. Current treatments for children with IBD are similar to those in adults. However, support for these treatments in children is too often extrapolated from large clinical trials in adult patients leading to "off-label" use in children. Below we review the evidence supporting commonly used IBD therapeutics including anti-inflammatory and immunosuppressive agents, biologics, and primary dietary therapies. Emerging therapeutics in late phase clinical trials will also be reviewed. There will be a focus on pediatric evidence when available. Finally, current treatment goals and therapeutic strategies for children with UC and CD will be discussed.

Corticosteroids

The use of corticosteroids (CS) to treat IBD was pioneered in the first half of the last century by Truelove and Witts, who demonstrated clinical improvement in patients with UC, especially when CS were given at time of first flare or "attack."[3] While treatment options have significantly advanced since then, CS remain a mainstay of induction therapy in IBD. However, except in rare cases in which other safer alternative therapies are ineffective or contraindicated, CS are not used to maintain remission due to potentially serious side effects associated with long-term use including linear growth restriction, osteopenia, and insulin resistance amongst many others. CS can be given systemically (oral or intravenous) or topically and are most often used in patients with moderate to severe IBD. The most commonly used systemic CS are prednisone (PO) and IV formulations like methylpredisolone and hydrocortisone. Much of the evidence for CS use in children comes from studies in which their use is considered the standard of care and compared to newer therapeutic options. As many as 80–90% of patients with active IBD have an initial clinical response to systemic CS though response rates are lower in severe

* Corresponding author.
E-mail address: jlkaplan@partners.org (J.L. Kaplan).

http://dx.doi.org/10.1053/j.sempedsurg.2017.10.005
1055-8586/

presentations.[4] The limitations of CS are demonstrated by one cohort study of 86 pediatric patients with IBD, in which 89% of CD patients and 79% of UC patients had an initial clinical response, but at 1year follow-up, 27% of CD and 29% of UC patients required surgery and 31% of CD and 14% of UC patients were steroid-dependent.[5] As mentioned, there is no role for CS as maintenance agents in IBD and courses are typically 1–3 months in duration.

Budesonide is a newer CS with a comparably favorable side effect profile due to drug deactivation via first pass metabolism in the liver, reducing systemic activity and potential toxicity.[6] In the US, there are currently two budesonide formulations available for IBD, Uceris® (budesonide, Salix Pharmaceuticals, Bridgewater, NJ), an extended release multimatrix formulation with colonic release used for UC, and Entocort EC® (budesonide, Perrigo, Allegan, MI), which has a pH-dependent release in the ileum and right colon and is used for CD. Small studies comparing ileal-release budesonide with prednisone in children with mild to moderate CD have shown budesonide to be safer, though slightly less effective.[6,7] A large North American Pediatric IBD registry recently reported budesonide use in 13% of newly diagnosed CD patients. Of patients that received budesonide <30 days after diagnosis, 57% did not require step-up to conventional CS, potentially sparing this group from systemic toxicity.[8] However, despite the favorable side effect profile, budesonide, like any CS, should not be used to maintain remission in IBD and courses are generally limited to 3–4 months in clinical practice.

5-Aminosalicylates (5-ASA)

5-ASA medications (sulfasalazine, mesalamine, olsalazine, and balsalazide) have a long history of use in IBD. Although their exact mechanism of action remains unknown, 5-ASA are thought to exert their immunomodulatory and anti-inflammatory effects topically rather than systemically; they also do not appreciably suppress the host immune system, leading to a favorable side effect profile. 5-ASA are effective at inducing and maintaining remission in mild to moderate UC, for which they remain a mainstay of therapy. The efficacy of 5-ASA in CD is less clear though they are used frequently in children with CD.[9] Mesalamine is the most frequently used 5-ASA as it is generally better tolerated than sulfasalazine and is available in multiple formulations with different mechanisms and sites of release in the GI tract (Table 1). Mesalamine is also available in topical formulations, both as a suppository and enema, for patients with proctitis or left-sided colitis, although topical formulations are sometimes not acceptable to children. Mesalamine is typically dosed at 60–80 mg/kg/day divided, up to 4.8 g/day, for induction. In children, higher doses of up to 100 mg/kg/day have been used as well.[10] Lower doses of 40 mg/kg/day or 1.2–2.4 g/day are often used to maintain remission.

5-ASA induces remission in 40–50% of adults with active UC and is more effective than placebo in preventing relapse.[11] A combination of oral and topical 5-ASA appears superior to oral 5-ASA alone at inducing remission in adults with mild to moderate UC.[12] Although efficacy data in children is limited, one recent pediatric study found that 47% of newly diagnosed UC patients treated with 5-ASA alone were in CS-free remission without escalation of therapy 1 year after diagnosis.[13] In real-world practice, many children with UC who are treated with 5-ASA never require an escalation to immunosuppressive therapies. 5-ASA are effective and relatively safe and thus remain a mainstay of treatment in children with mild to moderate UC.

Thiopurines

Thiopurine medications include azathioprine (AZA) and its metabolite, 6-mercaptopurine (6-MP). They are immunosuppressive agents that have proven effective in maintaining remission in CD and UC but are generally not effective in inducing remission due, in part, to a delay in onset of action as long as 12 weeks.[14]

Table 1
5-Aminosalicylate (5-ASA) medications including trade names, formulations, release sites, and notes for general usage.

Trade name (U.S. only)	Manufacturer	Formulation	Release sites	Notes
Pentasa	Shire US Wayne, PA	Mesalamine, controlled release via ethyl cellulose membrane	Proximal small intestine to colon	Capsule can be opened and sprinkled in water or acidic food
Asacol	Allergan Irvine, CA	Mesalamine, delayed release, pH-dependent	Distal ileum and colon	
Lialda	Shire US Wayne, PA	Mesalamine, pH-dependent multimatrix system	Colon	Daily medication
Apriso	Salix Pharmaceuticals Bridgewater, NJ	Mesalamine, delayed release, pH-dependent, extended release matrix core	Colon	Daily medication
Delzicol	Allergan Irvine, CA	Mesalamine, capsule containing delayed release enteric-coated tablet	Colon	Capsules can be opened and 4 smaller tablets inside swallowed
Dipentum	Meda Pharmaceuticals Somerset, NJ	Olsalazine capsule (azo-bonded prodrug, activated by bacteria	Colon	
Colazal	Salix Pharmaceuticals Bridgewater, NJ	Balsalazide (azo-bonded prodrug, activated by bacteria)	Colon	Capsules can be opened and sprinkled in applesauce
Azulfidine	Pharmacia & Upjohn Kalamazoo, MI	Sulfasalazine	Colon	• Allergy (20%) • Folic acid must be taken • Can be compounded to liquid formulation