

Crohn's Disease—Strategies to Improve Quality of Life

Dr. McNatty is an assistant professor of pharmacy practice at Midwestern University College of Pharmacy, Glendale, Arizona.

Crohn's disease is an inflammatory bowel disease that affects an estimated 50 of every 100,000 people in the United States.¹ It is characterized by transmural inflammation occurring in any part of the gastrointestinal (GI) tract.² The exact cause of Crohn's disease is unknown. Some evidence exists implicating genetics, diet, autoimmune response, and infectious microorganisms in the etiology of Crohn's disease.² Patients with Crohn's disease may experience short, infrequent exacerbations or continuous, unremitting disease.

Clinical Presentation and Classification of Disease Severity

Crohn's disease typically presents with symptoms of chronic or nocturnal diarrhea, abdominal pain, fever, malaise, rectal bleeding, and weight loss.³ For an accurate diagnosis, Crohn's disease must be differentiated from other GI disorders, namely ulcerative colitis. The Table shows a comparison of clinical presentation and manifestations of Crohn's disease and ulcerative colitis. In addition to the GI manifestations of Crohn's disease, extraintestinal complications often arise as well. Affected organs include the eyes (uveitis, iritis), skin (erythema nodosum, pyoderma gangrenosum), joints (arthritis), and liver (fatty liver, cholangiocarcinoma).⁴

Classification of disease severity in Crohn's disease is based on the ability to tolerate oral intake of food, presence of systemic symptoms, and response to treatment.¹ Mild-to-moderate disease is characterized by the ability to tolerate oral intake without dehydration, high fevers, abdominal tenderness, or obstruction. Moderate-to-severe disease applies to patients who have failed to respond to treatment for mild-to-moderate disease or patients with systemic manifestations, such as fevers, weight loss, nausea/vomiting, and anemia. Severe-to-fulminant disease applies to patients presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, or cachexia despite treatment.¹

Treatment

No curative therapy currently exists for Crohn's disease. Goals of therapy in Crohn's disease include treatment of acute inflammation, maintenance of remission, reducing extraintestinal complications, and improving quality of life.¹ Treatment should be individualized to achieve maximum symptomatic response while minimizing adverse effects. The established agents used to treat Crohn's disease include aminosalicylates, corticosteroids, immunosuppressive agents, and biologic agents. In addition, probiotics are being increasingly studied and used in some patients with Crohn's disease.

Aminosalicylates

Aminosalicylates are considered a firstline treatment to induce remission in mild-to-moderate Crohn's disease. They also can be used as maintenance therapy in many patients. The prototypical aminosalicylate is sulfasalazine, which is comprised of 5-aminosalicylic acid (5-ASA) and sulfapyridine. 5-ASA is the active component of the molecule responsible for improvement in Crohn's disease, whereas sulfapyridine is thought to be responsible for the significant adverse effects of sulfasalazine (nausea, vomiting, headaches, myalgias, arthralgias).⁵

More recently, aminosalicylates have been developed without the use of sulfapyridine. These include balsalazide (Colazal) and olsalazine (Dipentum), which use inactive carrier molecules instead of sulfapyridine, and mesalamine (Asacol, Pentasa, Rowasa, Canasa, Lialda), which contains only the 5-ASA portion of the molecule. Mesalamine is the most widely used agent due to its favorable adverse effect profile and variety of dosage forms. Topical mesalamine products such as Rowasa (enema) and Canasa (suppositories) are recommended for disease limited to the rectum and terminal colon. It is important to note that these dosage forms will not treat Crohn's disease located proximally to the terminal colon. Oral mesalamine products such as Asacol, Pentasa, and Lialda are delayed-release products designed to act specifically in the small and large intestine. These agents are recommended as first-line therapy to induce remission in mild-to-moderate disease and can be used in addition to corticosteroids in moderate-to-severe or fulminant disease. The evidence supporting the use of mesalamine for maintenance therapy is conflicting. Results from some trials show a benefit to using mesalamine, whereas other results indicate no significant difference over placebo.⁶

Corticosteroids

Corticosteroids are widely used to induce remission in moderate-to-severe and fulminant Crohn's disease. Approximately 50% of patients require steroids to treat active Crohn's disease.⁷ The most studied agents for this indication are prednisone and budesonide. Oral doses of 40 to 60 mg of prednisone or 9 to 18 mg of budesonide are often required to induce remission. Corticosteroids have a very limited role in maintenance therapy for Crohn's disease. These agents should be used at the lowest dose and for the shortest duration possible due to the risk of steroid dependence, which is a serious concern due to the frequency and severity of the adverse effects of corticosteroids.

Immunosuppressive Agents

An alternative to treating Crohn's disease patients with large doses of corticosteroids is to use immunosuppressive agents. Examples include azathioprine (Imuran) and 6-mercaptopurine (Purinethol). These medications are best used as "steroid-sparing" agents, as they often can help decrease the required doses of corticosteroids to induce remission of Crohn's disease.¹ Azathioprine and 6-mercaptopurine have been shown to be effective in treating active Crohn's disease as well as maintaining remission. Immunosuppressive agents are not without considerable risk of side effects, however. Azathioprine and 6-mercaptopurine can cause bone marrow suppression, hepatitis, pancreatitis, and in rare cases, lymphoma.⁸ An important point to communicate to patients is that azathioprine and 6-mercaptopurine can take up to 6 months to exert their effects.

Biologic Agents

The newer biologic agents are starting to accrue evidence supporting their use in both active Crohn's disease and in the maintenance of remission. Agents that have been approved for Crohn's disease include infliximab (Remicade), adalimumab (Humira), natalizumab (Tysabri), and certolizumab (Cimzia). Infliximab is an anti-tumor necrosis factor (TNF)- α chimeric monoclonal antibody.⁹ It is recommended for use in moderate-to-severe Crohn's disease. Infliximab is especially beneficial for those patients who develop fistulas.¹ Contraindications to infliximab therapy include class III or IV congestive heart failure, active or latent tuberculosis, multiple sclerosis, and active infection. The dosing schedule is a 5-mg/kg infusion on weeks 0, 2, and 6, then a 5-mg/kg infusion every 8 weeks for maintenance.¹⁰ Because infliximab is a chimeric antibody, the potential exists for patients to develop antibodies against infliximab, rendering it ineffective over time.⁹ If this occurs, adalimumab can be used. Adalimumab is a fully humanized monoclonal antibody against TNF- α . It is given as a subcutaneous injection every 2 weeks for maintenance therapy.¹⁰ Certolizumab is another available antibody against TNF- α and was approved by the FDA in April 2008. Like adalimumab, it is given as a subcutaneous injection. It is given every 4 weeks for maintenance therapy. Natalizumab was approved by the FDA in January 2008 and is available only for patients enrolled in a special restricted distribution program. It is given intravenously every 4 weeks. The primary barrier to more widespread use of the biologic agents for the treatment of Crohn's disease is the high cost of these medications.

Probiotics

Due to the variable efficacy, adverse effects, and high cost of the more established agents, clinicians and investigators have been increasingly turning to probiotics as a potential therapeutic option for patients with Crohn's disease. Probiotics are living microorganisms that can alter a patient's intestinal flora and may provide benefit in numerous GI diseases, including Crohn's disease. Probiotics have been studied in Crohn's disease and have shown promising results in small studies. A recent review of the available literature concluded that, thus far, there is not enough evidence to draw any conclusions regarding the efficacy of probiotics in the treatment of Crohn's disease.¹² More research is needed, including randomized, controlled trials to determine the utility of probiotics for Crohn's disease. The appropriate organism(s), dose, and duration of therapy have yet to be established for this indication.

Role of the Pharmacist

Many of the symptoms of Crohn's disease are subjective, making it important for patients to have a good patient-provider relationship. Pharmacists should educate patients about their disease. It is very important for patients to help providers identify and address the systemic complications of Crohn's disease, such as vitamin deficiency and growth deficiency in children. If these complications are present, patients will need appropriate treatment, including vitamin supplementation. Identifying and eliminating barriers to medication adherence and stressing the importance of smoking cessation are 2 additional ways pharmacists can help patients with Crohn's disease. Patients who are taking corticosteroids for an extended period of time to induce remission should be counseled about the potential risks of long-term steroid use, including osteoporosis and hyperglycemia. Most importantly, patients need to know that Crohn's disease has no cure and that the primary goal of therapy is to improve quality of life by minimizing GI and extraintestinal complications of the disease.

References

- Hanauer SB, Sandborn W. Practice parameters committee of the American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2001;96(3):635-643.
- Shanahan F. Crohn's disease. *Lancet*. 2002;359(9300):62-69.
- Podolsky DK. Inflammatory bowel disease. *N Engl J Med*. 2002;347(6):417-29.
- Kethu SR. Extraintestinal manifestations of inflammatory bowel diseases. *J Clin Gastroenterol*. 2006;40(6):467-475.
- Harrell LE, Hanauer SB. Mesalamine derivatives in the treatment of Crohn's disease. *Gastroenterol Clin N Am*. 2004;33(2):303-317.
- Bebb JR, Scott BB. Systematic review: how effective are the usual treatments for Crohn's disease? *Aliment Pharmacol Ther*. 2004;20(2):151-159.
- Sch?lmerich J. Review article: systemic and topical steroids in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2004; 20(suppl 4):66-74.
- Derijks LJJ, Gilissen LPL, Hooymans PM, Hommes DW. Review article: thiopurines in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006;24:715-29.
- Panes J, Gomollon F, Taxonera C, Hinojosa J, Clofent J, Nos P. Crohn's disease: a review of current treatment with a focus on biologics. *Drugs*. 2007;67(17):2511-2537.
- Micromedex Healthcare Series [intranet database]. Version 5.1. Greenwood Village, CO: Thomson Healthcare.
- Rioux KP, Fedorak RN. Probiotics in the treatment of inflammatory bowel disease. *J Clin Gastroenterol*. 2006;40(3):260-263.
- Butterworth AD, Thomas AG, Akobeng AK. Probiotics for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2008;16(3):CD006634.