evidence III, A), and may offer long-term benefits with decreased corticosteroid side effects. Budesonide MMX (Uceris 9 mg given once daily) has an extended release that targets the colon and is available for the treatment of mild to moderate UC (level of evidence I, A for induction and III, A for maintenance).

Immunomodulators

The immunomodulators used in IBD include azathioprine (Imuran, 2 to 2.5 mg/kg/day) and its active metabolite, 6-mercaptopurine (6-MP) (Purinethol, 1 to 1.5 mg/kg/day), as well as methotrexate and cyclosporine. Azathioprine and 6-MP are effective therapies for maintaining remission in both Crohn's disease and UC and are used primarily as steroid-sparing agents (level of evidence I, A). They have a slow onset of action (weeks to months). Side effects include nausea, abnormal liver enzymes, bone marrow suppression, opportunistic infections, and an increased risk of lymphoma and nonmelanoma skin cancer.

Methotrexate can be used for induction (25 mg subcutaneously once weekly) and maintenance of remission (15 to 25 mg subcutaneously once weekly) in active Crohn's disease (level of evidence IIa, B for induction and I, B for maintenance); the side effect profile is similar but also includes interstitial pneumonitis. Intravenous cyclosporine (2 mg/kg/day given over 24 hours) is used as a rescue medicine and, in severe UC refractory to intravenous steroids, as a *bridge* treatment to one of the above immunomodulators or biologic agents. Given the potential for both short-term and long-term side effects, as well as the need for close follow-up, patients needing these medications are best managed by gastroenterologists.

Biologic Agents

Biologics are a class of medications that target specific aspects of the immune system. The first such agent to be used in IBD was infliximab (Remicade), a chimeric monoclonal antibody to TNF-α, which has been shown to be effective in the treatment of both moderate to severe Crohn's disease, including fistulizing disease, and UC (level of evidence I, A). Because infliximab is a chimeric antibody, its toxicities include infusion reactions, delayed-type hypersensitivity reactions, and formation of autoantibodies (which can reduce its efficacy). Anti-TNF agents that are administered subcutaneously include adalimumab (Humira) and golimumab (Simponi), which are fully human monoclonal antibodies, and certolizumab pegol (Cimzia), which is a humanized anti-TNF antibody Fab fragment. Adalimumab and certulizumab are efficacious in patients with moderate to severe Crohn's disease, whereas adalimumab and golimumab are approved to treat moderate to severe UC.

Natalizumab (Tysabri), a humanized anti–α_4-integrin antibody, blocks inflammatory cell migration and adhesion, and has been approved for the treatment of moderate to severe Crohn's disease in patients who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies including inhibitors of TNF-α (level of evidence IIa, B for induction and IIa, A for maintenance). Vedolizumab (Entyvio), a humanized monoclonal antibody to α4β7 integrin, has been recently approved for the treatment and maintenance of both Crohn's and ulcerative colitis (level of evidence I, A).

Because of the potent effects these biologic agents have on the immune system, careful patient selection and monitoring for complications are necessary. Reactivation of latent tuberculosis and other serious infections have been reported with the anti-TNF agents. Other rare but serious complications include non-Hodgkin's lymphoma, exacerbation of congestive heart failure, abnormal complete blood count (CBC) and liver function test results, and demyelinating disease. Natalizumab has been linked to rare cases of progressive multifocal leukoencephalopathy caused by the human JC virus.

Future biologic agents with alternate mechanisms of action are being discovered and developed. Ustekinumab (Stellara), an IL-12/IL-23 inhibitor already approved for psoriasis, has shown promise and is in clinical trials for Crohn's disease. Tofacitinib, a JAK inhibitor, already approved for rheumatoid arthritis, is now being investigated for Crohn's disease.

Other Agents

Other agents for treatment of IBD include antibiotics, probiotics, antidiarrheals, bile salt resin binders, and nutritional support.

Antibiotics are used primarily in patients with Crohn's disease who have perianal or fistulizing disease. In colonic Crohn's disease, antibiotics can be used in combination with immunosuppressive drugs as an alternate strategy. The role of antibiotics in UC is unclear, and further studies are required. However, intravenous antibiotics are used in the initial treatment of severe, toxic, or fulminant colitis.

Probiotics are viable nonpathogenic organisms that, after ingestion, may prevent or treat intestinal diseases and have been explored in the treatment of IBD. Multiple studies have found them to be effective in treating pouchitis after ileal pouch–anal anastomosis. One probiotic mixture, termed VSL#3, includes four strains of *Lactobacillus* (*L. paracasei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp *bulgaricus*), three strains of *Bifidobacteria* (*B. longum*, *B. breve*, and *B. infantis*), and one strain of *Streptococcus* (*S. thermophiles*). It has been shown in randomized clinical trials to be a safe and effective adjunct modality for achieving clinical response and remission in patients with mild to moderately active UC. So far, none of the probiotics has been shown to be effective in induction or maintenance of remission in patients with Crohn's disease.

Antidiarrheal agents and bile salt resin binders can be used as adjuncts for management of diarrhea in patients with IBD, but antidiarrheal agents should be used cautiously during exacerbations of colitis because they can precipitate toxic megacolon. The main role of antidiarrheal medications involves controlling diarrhea in patients who have undergone previous resections. Patients with Crohn's disease who have had less than 100 cm of terminal ileum removed can develop a bile salt malabsorptive state, during which bile salts enter the colon and cause a secretory diarrhea. Bile salt resin binders such as cholestyramine are an effective treatment in these cases. When patients have undergone one or more extensive resections amounting to more than 100 cm of ileum, the bile salt pool is depleted and fat malabsorption develops. These patients may require a low-fat diet supplemented with medium-chain triglycerides and antidiarrheal agents, but bile salt resin binders should not be used.