

Fact Sheet

News from the IBD Help Center

IMMUNOMODULATORS

Medical treatment for Crohn's disease and ulcerative colitis has two main goals: achieving remission (control or resolution of inflammation leading to symptom resolution with healing of the inflamed tissue) and then maintaining remission. To accomplish these goals, treatment is aimed at controlling the ongoing inflammation in the intestine—the cause of inflammatory bowel disease (IBD) symptoms.

As the name implies, immunomodulators modify the activity of the immune system, in turn, decreasing the inflammatory response. Immunomodulators are most often used in organ transplantation to prevent rejection of the new organ as well as in autoimmune diseases such as rheumatoid arthritis. Since the late 1960s, they have also been used to treat people with IBD, where the normal regulation of the immune system is affected.

Immunomodulators, by themselves or with another agent, may be appropriate in the following treatment situations:

- Nonresponse or intolerance to aminosalicylates, antibiotics, or corticosteroids
- Steroid-dependent disease or frequent need for steroids
- Perianal (around the anus) disease that does not respond to antibiotics
- Fistulas (abnormal channels between two loops of intestine, or between the intestine and another structure—such as the skin)
- To bolster or optimize the effect of a biologic drug and prevent the development of resistance to biologic drugs
- To prevent recurrence after surgery

Because it can take up to three to six months to see an improvement in symptoms with immunomodulators, steroids may be started at the same time to produce a faster response. Lower doses of the steroid may be utilized in some cases, producing fewer side effects. However, the main benefit of these drugs is to decrease the long-term need for steroids and prevent recurring flares. For that reason, immunomodulators are sometimes referred to as “steroid-sparing” drugs. They also may be used in combination with other agents such as the biologics to help prevent antibody formation, which can result in loss of response to biologics.

Oral Medications

The first two immunomodulators to be used widely in IBD were azathioprine (Imuran[®], Azasan[®]) and 6-mercaptopurine (6-MP, Purinethol[®]), drugs that are chemically quite similar. They are used to maintain remission in Crohn's disease and ulcerative colitis. Both agents have a slow onset of action (three to six months for full effect). Accordingly, they are usually given along with another faster-acting drug (such as a corticosteroid or in combination with a biologic).

Other examples of immunomodulators to treat IBD are methotrexate, cyclosporine A (Sandimmune[®], Neoral[®]) and tacrolimus (Prograf[®]). Cyclosporine A has a more rapid onset of action (one to two weeks) than azathioprine and 6-MP. Both cyclosporine A and tacrolimus have been more effective in treating people with severe ulcerative colitis, and are generally given until one of the slower-acting immunomodulators begins to work or until the patient undergoes curative surgery. Tacrolimus can be used in Crohn's disease when corticosteroids are not effective or when fistulas develop. The

immunomodulators require monitoring with periodic assessments of blood counts, chemistries, and levels, depending on which one is prescribed.

Alternate Methods of Delivery

Tacrolimus may be applied topically for Crohn's disease that affects the mouth or perineal area. Topical tacrolimus is also used to treat pyoderma gangrenosum, an ulcerating skin disorder often associated with IBD. Methotrexate (MTX[®], Rheumatrex[®], Mexate[®]) may work more rapidly than azathioprine or 6-MP, and is most effective when given by weekly injections. It may be an option for people with Crohn's disease who have not responded to other treatments and cannot tolerate other immunosuppressants. The effectiveness of methotrexate in ulcerative colitis is uncertain based on recent clinical trials.

Side Effects

- **Azathioprine and 6-MP:** Infrequent reported side effects may include headache, nausea, vomiting, diarrhea, and malaise (general feeling of illness). Changing from azathioprine to 6-MP or vice versa may reduce some of these reactions. Canker sores in the mouth, rash, fever, joint pain, and liver inflammation are unlikely to be affected by changing from azathioprine to 6-MP or vice versa. Less common side effects include pancreatitis (inflammation of the pancreas) and bone marrow suppression, which may increase the risk of infection or serious bleeding. A return to normal blood cell production may take several weeks after discontinuing the medication. A four-fold (four out of 10,000 people with IBD on these drugs) increased risk in non-Hodgkin's lymphoma (cancer of the lymph nodes) has also been recognized; however, it remains a rare adverse event in patients taking 6-MP or azathioprine.
- **Cyclosporine and tacrolimus:** Infrequently reported side effects include decreased kidney function, hepatitis, increased risk of infections, diabetes, increased cholesterol levels, sleep problems, headache, mild tremor, seizure, high blood pressure, swollen gums, tingling of the fingers and feet, increased facial hair, and a small increased risk of lymphoma.
- **Methotrexate:** Infrequently reported side effects include flu-like symptoms (nausea, vomiting, headache, fatigue, and diarrhea), severe mouth sores and low white blood cell count. Less common but more serious side effects include scarring of the liver and lung inflammation. Scarring of the liver can be made worse by diabetes, being overweight, and alcohol consumption. Some of the side effects with methotrexate can be prevented by adding folic acid, a vitamin.

Special Considerations

- Immunomodulators reduce the activity of the immune system. In so doing, they also decrease the body's ability to combat infection and certain cancers like skin cancer or lymphoma. Be sure to report any incidence of fever, chills, or sore throat to your doctor.
- Blood tests should be performed frequently with all immunomodulators to check for effects on the bone marrow, liver, and kidneys. Blood pressure and kidney function need to be closely monitored with cyclosporine A and tacrolimus.
- Women who are pregnant or wish to become pregnant should talk to their doctors before taking methotrexate. Methotrexate use should be avoided (by pregnant women and by both men and women for several months before conception) because it may lead to pregnancy loss or possible birth defects.
- Patients receiving immunomodulators should be regularly vaccinated for transmissible infections such as flu (yearly) and pneumonia, both vaccines are safe to administer to persons receiving immunosuppression. However, live forms of the flu vaccine should be avoided in patients taking immunomodulators. The shingles vaccine may also be recommended. There is an inactivated shingles vaccine series, given as two injections spaced two to six months apart, currently available for persons over the age of 50. Other live vaccines and travel immunizations (yellow fever) should not be given unless this is specifically discussed with the prescribing physician or a travel medicine expert.

- Be educated—learn as much as possible about these treatments from your doctor and pharmacist. Other information can be obtained from reliable internet sources, such as the Crohn's & Colitis Foundation (www.crohnscolitisfoundation.org) and treatment manufacturer websites.

Combination Therapy

In some circumstances, a health care provider may recommend adding an additional therapy that will work in combination with the initial therapy to increase its effectiveness. For example, combination therapy could include the addition of a biologic to an immunomodulator. As with all therapy, there are risks and benefits of combination therapy. Combining therapies may increase the effectiveness of IBD treatment, but there may also be an increased risk of additional side effects and toxicity. Your healthcare provider will identify the treatment regimen that is most effective for your individual health care needs.

Drug Interactions

People taking several different medicines, whether prescription or over-the-counter, should always be on the lookout for interactions between drugs. Drug interactions may decrease a medication's effectiveness, intensify the action of a drug, or cause unexpected side effects. Before taking any medication, read the label carefully and speak with your doctor. Be sure to include over-the-counter medications and complementary or alternative therapies (supplements, herbals, vitamins, etc.) when discussing your medications.

Take Medications as Prescribed

The best way to control IBD is by taking medications as recommended by your doctor. Even during times of remission, it is important to continue taking your medications as prescribed to prevent asymptomatic inflammation and future flares. If you are experiencing unpleasant side effects or you continue to have IBD symptoms, do not stop taking your medications until speaking with your doctor. Do not on your own alter the amount of medication or how frequently you take it.

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