

IMMUNOMODULATORS

Medical treatment for Crohn's disease and ulcerative colitis has two main goals: *achieving* remission (the absence of symptoms) and, once that is accomplished, *maintaining* remission (prevention of flare-ups). To accomplish these goals, treatment is aimed at controlling the ongoing inflammation in the intestine—the cause of IBD symptoms.

As their name implies, immunomodulators weaken or modulate the activity of the immune system. That, in turn, decreases the inflammatory response. Immunomodulators are most often used in organ transplantation to prevent rejection of the new organ, and in autoimmune diseases such as rheumatoid arthritis. Since the late 1960s, they have also been used to treat people with IBD, which appears to be caused by an overactive immune system. These drugs are appropriate for those who:

- do not respond to aminosalicylates, antibiotics, or corticosteroids
- have steroid-dependent disease or frequently require steroids
- have experienced side effects with corticosteroid treatment
- have perineal disease that does not respond to antibiotics
- have fistulas (abnormal channels between two loops of intestine, or between the intestine and another structure—such as the skin)
- need to maintain remission

An immunomodulator may be combined with a corticosteroid to speed up response during active flares of disease. Lower doses of the steroid are required in this case, producing fewer side effects. Corticosteroids also may be withdrawn more rapidly when combined with immunomodulators. For that reason, immunomodulators are sometimes referred to as “steroid-sparing” drugs.

ORAL MEDICATIONS

The first two immunomodulators to be used widely in IBD are 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 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 corticosteroids).

Other immunomodulators to treat IBD are cyclosporine A (Sandimmune[®], Neoral[®]) and tacrolimus (Prograf[®]), both used for organ transplantation as well. Cyclosporine A has a more rapid onset of action (one to two weeks) than azathioprine and 6-MP. It is useful in people with active Crohn's disease, but only when given intravenously and at high doses. 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.

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[®]) works more rapidly than azathioprine or 6-MP, and is given by weekly injections. It is an effective 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 as yet unproven.



SIDE EFFECTS

- **AZATHIOPRINE AND 6MP:** Infrequently reported side effects may include headache, nausea, vomiting, diarrhea, and malaise (general feeling of illness). Sometimes 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.
- **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, high blood pressure, swollen gums, tingling of the fingers and feet, increased facial hair, and increased risk of lymphoma (a cancer of the lymphatic system).
- **METHOTREXATE:** Infrequently reported side effects include flu-like symptoms (nausea, vomiting, headache, fatigue, and diarrhea) 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.

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. Be sure to tell your doctor about all the drugs you're taking (even over-the-counter medications or complementary therapies) and any medical condition you may have.

SPECIAL CONSIDERATIONS

- Immunomodulators reduce the activity of the immune system. In so doing, they also decrease the body's ability to combat infection. 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 immunomodulators. 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.

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