BIOLOGIC THERAPY

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.

The newest class of drugs to be used in IBD, these include Adalimumab (Humira®), Certolizumab pegol (Cimzia®), Infliximab (Remicade®), and Natalizumab (Tysabri®). Biologics are genetically engineered medications made from living organisms and their products, such as proteins, genes engineered medications are made from living organisms and their products, such as proteins, genes, and antibodies. Biologics interfere with the body's inflammatory response in IBD by targeting specific molecular players in the process such as *cytokines*— specialized proteins that play a role in increasing or decreasing inflammation. Promising targets include tumor necrosis factor (TNF)-alpha, interleukins, adhesion molecules, colony-stimulating factors, and others. Learning how these factors work has enabled researchers to design special treatment approaches that interrupt inflammation at various stages.

Biologic therapies offer a distinct advantage in IBD treatment. Their mechanism of action is targeted. Unlike corticosteroids, which tend to suppress the entire immune system and thereby produce major side effects, biologic agents act *selectively*. Therapies are targeted to particular enzymes and proteins that have already been proven defective, deficient, or excessive in people with IBD and in animal models of colitis.

INTRAVENOUS (IV) MEDICATIONS

Infliximab (Remicade®) is the first FDA-approved biologic therapy for Crohn's disease, and was recently approved for ulcerative colitis. The medication is a chimeric monoclonal antibody. In other words, it's a hybrid consisting of 75 percent human, 25 percent mouse protein sequence. It works by binding to and preventing the activity of a specific protein in the body called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is a cytokine, a specialized protein that promotes inflammation in the intestine and other organs and tissues.

It is given as a drip via intravenous infusion. Infusions take about two hours to complete and usually are given every eight weeks.

Infliximab has been approved for the treatment and maintenance of remission of moderately to severely active Crohn's disease and ulcerative colitis that is unresponsive to conventional therapy. It also has been approved for the treatment and maintenance of fistulizing Crohn's disease. (Fistulas are abnormal channels between two loops of intestine, or between the intestine and another structure, such as the skin.) Treatment with infliximab is often an effective method for tapering patients off steroids.

Natalizumab (Tysabri®) has been approved for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies, including inhibitors of TNF-alpha.

Natalizumab (Tysabri®) is an antibody thought to inhibit certain types of white blood cells that are involved in the inflammatory process. It is infused into a vein at a certified infusion center and usually given once every 4 weeks. It takes about 1 hour to receive the entire dose.

SUBCUTANEOUS INJECTIONS

Adalimumab (Humira®) is a synthetic (man-made) protein, similar to human protein that blocks tumor necrosis factor alpha (TNF- α), a protein in your body that can cause inflammation. Adalimumab works by attaching to TNF- α and blocking its effects and thereby reducing the inflammation and relieving symptoms associated with Crohn's disease.

Adalimumab is taken by injection every other week. It can be administered at home by the patient or family member once instructed by a healthcare professional.

Adalimumab has been approved for adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy, and in those patients who did not benefit from treatment, or who were intolerant to previous treatment with infliximab.

Certolizumab pegol (Cimzia ®) is the most recent biologic approved by the FDA for the treatment of Crohn's disease. Certolizumab pegol is used to reduce the signs and symptoms of moderately to severely active Crohn's disease in adult patients who have not been helped enough by usual treatments.

Certolizumab pegol is the first and only PEGylated anti-TNF- alpha. The antibody portion of the drug is combined with a special chemical called polyethelyene glycol (PEG), which delays its excretion from the body.

Patients treated with Cimzia ® receive an injection every two weeks for the first three injections. Once benefit has been established, Cimzia® is usually given once every four weeks.

IN THE PIPELINE

Additional biologic therapies under investigation for IBD include another antibody to TNF, CDP-870. Thalidomide and IL-11 are also being studied as biologic treatments. Drugs targeting a number of other cytokines and the inflammatory response, such as alpha 4 integrin, interleukin-6, interleukin-12, interferon gamma, and GM-CSF are being evaluated in clinical trials. Another experimental therapy for Crohn's disease is a mixture of colon-extracted proteins derived from the individual patient. Self-derived proteins represent an individualized approach to treatment.

SIDE EFFECTS

Because biologics are given either by intravenous infusions or subcutaneous injections, it may produce redness, itching, bruising, pain, or swelling on the injection site. Other side effects may include: headache, fever, chills, difficulty breathing, low blood pressure, and hives. Additionally, patients may experience stomach pain, back pain, rash, nausea, and upper respiratory infection (cough and sore throat).

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 conditions you may have.

SPECIAL CONSIDERATIONS

- There have been some reports of serious infections associated with infliximab, adalimumab, and certolizumab use, including tuberculosis (TB) and sepsis, a life-threatening blood infection. You should always have a TB test before you use infliximab, adalimumab or certolizumab because the drugs can

increase the risk of re-activating TB for those who have been exposed. It's not that you will "catch" TB when taking infliximab, adalimumab,or certolizumab but if you have latent (inactive) TB, the drug can reactivate the infection.

Cases of new infection with TB have also been reported. If you have prior exposure to TB, your doctor should begin TB treatment before you start infliximab, adalimumab or certolizumab. The same precaution should be taken before beginning treatment with corticosteroids.

- Biologics may reduce the body's ability to fight other infections as well. If you are prone to infections or develop any signs of infection while taking these medications, such as fever, fatigue, cough, or the flu, inform your doctor immediately.
- It may be inadvisable for people with heart failure to take any of these medications, so tell your doctor if you have any heart condition before starting this medication. Inform your doctor at once if you develop new or worsening symptoms of heart failure—namely shortness of breath or swelling of the ankles or feet.
- On rare occasions, blood disorders have been noted with infliximab, adalimumab, and certolizumab. Inform your doctor if you develop possible signs such as persistent fever, bruising, bleeding, or paleness while taking infliximab, adalimumab, and certolizumab. Nervous system disorders also have been reported occasionally. Let your doctor know if you have or have had a disease that affects the nervous system, or if you experience any numbness, weakness, tingling, or visual disturbances while taking infliximab, adalimumab, and certolizumab.
- Although reports of lymphoma (a cancer of the lymphatic system) in patients taking infliximab, adalimumab, certolizumab and other TNF-blockers are rare, they do occur more often than in the general population.
- Progressive multifocal leukoencephalopathy (PML), a rare brain infection, has been reported with natalizumab use. Natalizumab may also cause liver damage and allergic reactions.
- Your physician will monitor you closely while you are on biologic therapy. It is not advisable to stop and then try to restart infliximab. To achieve and maintain remission, it is advisable to stay on the medication.