

Fact Sheet

News from the IBD Help Center

BIOLOGICS

Medical treatment for Crohn's disease and ulcerative colitis has two main goals: achieving remission (control or resolution of inflammation leading to symptom resolution) and then maintaining remission.

Over the last several years, new treatments called biologics have been available for the treatment of inflammatory bowel disease (IBD) and other inflammatory diseases. These treatments are called biologics because, unlike chemical medications, they are made out of materials found in life.

Biologics are antibodies created in the laboratory that stop certain proteins in the body from causing inflammation. Biologic therapies offer a distinct advantage in IBD treatment because their mechanisms of action are more precisely targeted to the factors responsible for IBD. For example, unlike corticosteroids, which affect the whole body and may produce major side effects, biologic agents act more selectively. These therapies are targeted to particular proteins that have already been proven to be involved in IBD. While it is not possible to determine which biologic will work best for an individual patient, your physician will present you with various effective options and work with you until you reach remission.

Anti-Tumor Necrosis Factor Agents

Biologics known as anti-tumor necrosis factor (anti-TNF) agents bind and block a small protein called tumor necrosis factor alpha (TNF-alpha) that promotes inflammation in the intestine as well as other organs and tissues. All anti-TNF medications have been shown not only to reduce the symptoms of IBD, but also result in healing of the inflamed intestine. While anti-TNF medications are not effective for every individual, many patients benefit from this class of medication. It may take up to eight weeks after starting an anti-TNF to notice an improvement in symptoms, though many experience more immediate improvement. Examples of anti-TNF medications include:

- **Adalimumab (Humira®)** is a prescription medicine shown to induce and maintain clinical remission in patients with moderate to severe Crohn's disease (in adults and children) and ulcerative colitis (in adults and children). Adalimumab is given as a subcutaneous injection under the skin of the abdomen or thigh. Once instructed by a healthcare professional, the patient or family member can administer it at home. The injection process takes about 10 seconds. Typically, when starting adalimumab, patients will perform four injections for their first dose (four pens, 160mg), and then two weeks later they will perform two injections (two pens, 80mg). Thereafter, patients will perform one injection (one pen, 40mg) every two weeks.
- **Adalimumab-afzb (Abrilada™)** is biosimilar to adalimumab (Humira®). It is a prescription medicine shown to induce and maintain clinical remission in patients with moderate to severe Crohn's disease (in adults and children) and ulcerative colitis (in adults). Adalimumab-afzb is given as a subcutaneous injection under the skin of the abdomen or thigh. Once instructed by a health care professional, the patient or family member can administer it at home. The injection process takes about 10 seconds. Typically, when starting adalimumab-afzb patients will perform four injections for their first dose (four pens, 160mg), then two weeks later they will perform two injections (two pens, 80mg). Thereafter, patients will perform one injection (one pen, 40mg) every two weeks.

- **Adalimumab-atto (Amjevita™)** is biosimilar to adalimumab (Humira®). It is a prescription medicine shown to induce and maintain clinical remission in patients with moderate to severe Crohn's disease in (adults and children) and ulcerative colitis (in adults). Adalimumab-atto is given as a subcutaneous injection under the skin of the abdomen or thigh. Once instructed by a health care professional, the patient or family member can administer it at home. The injection process takes about 10 seconds. Typically, when starting adalimumab-atto patients will perform four injections for their first dose (four pens, 160mg), then two weeks later they will perform two injections (two pens, 80mg). Thereafter, patients will perform one injection (one pen, 40mg) every two weeks.
- **Adalimumab-adbm (Cyltezo™)** is a biosimilar to adalimumab (Humira®). It has been approved for the treatment of adult patients with moderately to severely active Crohn's disease or ulcerative colitis who have had an inadequate response to conventional therapy. Adalimumab-adbm is given as a subcutaneous injection under the skin of the abdomen or thigh. Once instructed by a health care professional, the patient or family member can administer it at home. The injection process takes about 10 seconds. Typically, when starting adalimumab-adbm, patients will perform four injections for their first dose (four pens, 160mg), then two weeks later they will perform two injections (two pens, 80mg). Thereafter, patients will perform one injection (one pen, 40mg) every two weeks.
- **Adalimumab-bwwd (HADLIMA)** is a biosimilar to adalimumab (Humira®). It has been approved for the treatment of adult patients with moderately to severely active Crohn's disease or ulcerative colitis who have had an inadequate response to conventional therapy. Adalimumab-bwwd is given as a subcutaneous injection under the skin of the abdomen or thigh. Once instructed by a health care professional, the patient or family member can administer it at home. The injection process takes about 10 seconds. Typically, when starting adalimumab-bwwd, patients will perform four injections for their first dose (four pens, 160mg), then two weeks later they will perform two injections (two pens, 80mg). Thereafter, patients will perform one injection (one pen, 40mg) every two weeks.
- **Adalimumab-fkjp (Hulio®)** is a biosimilar to adalimumab (Humira®). It has been approved for the treatment of adult patients with moderately to severely active Crohn's disease or ulcerative colitis who have had an inadequate response to conventional therapy. Adalimumab-fkjp is given as a subcutaneous injection under the skin of the abdomen or thigh. Once instructed by a health care professional, the patient or family member can administer it at home. The injection process takes about 10 seconds. Typically, when starting adalimumab-fkjp, patients will perform four injections for their first dose (four pens, 160mg), then two weeks later they will perform two injections (two pens, 80mg). Thereafter, patients will perform one injection (one pen, 40mg) every two weeks.
- **Adalimumab-adaz (Hymiroz™)** is a biosimilar to adalimumab (Humira®). It has been approved for the treatment of adult patients with moderately to severely active Crohn's disease or ulcerative colitis who have had an inadequate response to conventional therapy. Adalimumab-adaz is given as a subcutaneous injection under the skin of the abdomen or thigh. Once instructed by a health care professional, the patient or family member can administer it at home. The injection process takes about 10 seconds. Typically, when starting adalimumab-adaz, patients will perform four injections for their first dose (four pens, 160mg), then two weeks later they will perform two injections (two pens, 80mg). Thereafter, patients will perform one injection (one pen, 40mg) every two weeks.
- **Certolizumab pegol (Cimzia®)** is another self-injected anti-TNF used to reduce the signs and symptoms, as well as maintain clinical response, of moderate to severe Crohn's disease. Patients treated with certolizumab pegol usually receive an injection every two weeks for the first three injections. Once benefit has been established, it is usually given once every four weeks. Depending on the physician's orders, it is injected under the skin by either a health care professional (typically a nurse) or the patient.
- **Golimumab (Simponi®)** is indicated for the treatment of adult patients with moderate to severe ulcerative colitis who are unable to wean off of steroids or who have had an inadequate response to, or intolerance to, other ulcerative colitis medications. Golimumab is usually injected every four weeks after two starter doses. Once instructed by a health care professional, the patient or family member can administer it at home.
- **Infliximab (Remicade®)** has been approved for the treatment and maintenance of remission of moderate to severe Crohn's disease and ulcerative colitis (in adults and children). It is also approved for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease. It is given by an intravenous infusion lasting approximately two to four hours. The first three doses are given more closely together, at zero, two, and six weeks, and thereafter usually every eight weeks. An

unbranded biologic of Infliximab is also available in the market. This specific unbranded Infliximab is not a biosimilar (see information on biosimilars) because it is an exact copy of Remicade®

- **Infliximab-abda (Renflexis®)** is a biosimilar to infliximab (Remicade®). It has been approved for the treatment and maintenance of remission of moderate to severe Crohn's disease (in adults and children) and ulcerative colitis (in adults). It is also approved for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease. It is given by an intravenous infusion lasting approximately two to four hours. The first three doses are given more closely together, at zero, two, and six weeks, and thereafter usually every eight weeks.
- **Infliximab-axxq (Avsola™)** is a biosimilar to infliximab (Remicade®). It has been approved for the treatment and maintenance of remission of moderate to severe Crohn's disease (in adults and children) and ulcerative colitis (in adults). It is also approved for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease. It is given by an intravenous infusion lasting approximately two to four hours. The first three doses are given more closely together, at zero, two, and six weeks, and thereafter usually every eight weeks.
- **Infliximab-dyyb (Inflectra™)** is a biosimilar to infliximab (Remicade®). It has been approved for the treatment and maintenance of remission of moderate to severe Crohn's disease (in adults and children) and ulcerative colitis (in adults). It is also approved for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease. It is given by an intravenous infusion lasting approximately two to four hours. The first three doses are given more closely together, at zero, two, and six weeks, and thereafter usually every eight weeks.
- **Infliximab-qbtx (IXIFI™)** is a biosimilar to infliximab (Remicade®). It has been approved for the treatment and maintenance of remission of moderate to severe Crohn's disease (in adults and children) and ulcerative colitis (in adults). It is also approved for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease. It is given by an intravenous infusion lasting approximately two to four hours. The first three doses are given more closely together, at zero, two, and six weeks, and thereafter usually every eight weeks.

The interval of doses may need to be shortened based upon criteria that can be discussed with your health care provider.

NOTE: A medication is considered “biosimilar” if research data shows that the medication is “highly structurally and clinically similar” to an already FDA-approved biological product.

Integrin Receptor Antagonists

These biologics prevent the cells that cause inflammation from moving out of blood vessels and into tissues by blocking a protein on the surface of those cells. Examples of this type of medication include:

- **Natalizumab (Tysabri®)** has been approved for inducing and maintaining clinical response and remission in adult patients with moderate to severe Crohn's disease who have had an inadequate response to, or are unable to tolerate, other forms of therapy. It is infused into a vein at a certified infusion center and is usually given once every four weeks. It takes about one hour to receive the entire dose. Natalizumab works throughout the entire body. Natalizumab users carry an increased risk of a severe brain condition called progressive multifocal leukoencephalopathy (PML), resulting from infection with the John Cunningham (JC) virus. It is important to be tested for JC virus prior to starting natalizumab; patients who are negative for JC virus have a much lower risk of developing PML.
- **Vedolizumab (Entyvio™)** has been approved for inducing and maintaining clinical response and remission and achieving steroid-free remission in adult patients with moderate to severe Crohn's disease and ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to an anti-TNF or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Vedolizumab works through a mechanism similar to natalizumab but is gut-specific and has not been shown to enter the brain. In large clinical trials, it was not associated with the brain disorder progressive multifocal leukoencephalopathy (PML) that is rarely observed in those using natalizumab (Tysabri®). This drug is

infused intravenously over approximately 30 minutes at zero, two, and six weeks, then every eight weeks thereafter.

Interleukin-12 and -23 Antagonist

This biologic targets specific proteins (interleukin-23 and interleukin-12) that play a key role in the inflammation process. An example of this type of medication is:

- **Ustekinumab (Stelara®)** has been approved for the treatment of adults with moderately to severely active Crohn's disease and ulcerative colitis who have had an inadequate response to conventional therapy. The first dose is a one-time intravenous (IV) infusion based on body weight that is given under the supervision of a health care professional. The following doses are given as an injection under the skin every eight weeks by a health care provider or self-injected by the patient after proper training.
- **Risankizumab-rzaa (SKYRIZI®)** is a biologic treatment approved for adults with moderately to severely active Crohn's disease. The first doses are taken every four weeks as an IV infusion, and then can be taken as an injection under the skin every eight weeks by a health care professional or by the patient after proper training.

Risks and Special Considerations

While the benefits often far outweigh the risks of biologic medications in patients suffering from IBD, patients should consider the following when using biologics:

- **Side Effects & Intolerance.** Because biologics are given by intravenous infusions or subcutaneous injections, they may produce redness, itching, bruising, pain, or swelling at the injection site. Other side effects may include: headache, fever, chills, hives and other rashes. Occasional severe allergic reactions may occur.
- **Infections.** Because biologics affect the immune system to help control IBD, biologics can impact your ability to fight infections. Further, anti-TNF medications increase the risk of developing less common, or atypical, infections. While the majority of patients using biologics never experience an infection related to the medication, it is important to discuss this issue with your IBD specialist. Because of this risk, it is important to determine if a patient has any chronic asymptomatic infections that may become reactivated when using these medications, including tuberculosis (TB) and chronic Hepatitis B virus. Further, to help prevent infections, patients should be up to date on appropriate vaccinations, including yearly influenza vaccinations, pneumonia vaccine, and hepatitis vaccines. If you develop any signs of infection while taking these medications, such as fever, new cough, or the flu, inform your doctor immediately.
- **Cancer Risk.** Anti-TNF medications have been associated with a small, but measurable, increase in the incidence of lymphoma, an uncommon cancer. While the overall risk of lymphoma is very low, the risk is highest in patients using anti-TNF medications in combination with another immunosuppressant, such as azathioprine (Imuran®).
- **Liver Problems.** Biologic therapies have been rarely associated with changes in liver function. If you develop jaundice (yellowing of skin and eyes) while using biologics, inform your doctor immediately. Your liver enzymes and bilirubin may be evaluated by your doctor.
- **Arthritis.** While anti-TNF medications often are effective treatments for inflammatory arthritis (joint pain), in some situations they may cause new joint pain. Notify your doctor if you are experiencing new joint discomfort while using anti-TNF medications.
- **Lupus-Like Reaction.** Rarely, an anti-TNF medication can cause a lupus-like reaction (LLR) which may present with symptoms such as a rash, joint pain, muscle ache, and/or fever. The LLR usually resolves with stopping the anti-TNF but may require a course of corticosteroids.
- **Skin reactions.** Rashes and anti-TNF-induced psoriasis have been reported.

- **Other Considerations.** Tell your doctor if you have any other health problems such as heart failure, hepatitis or multiple sclerosis before taking these treatments. Your doctor will determine if the benefits of biologics outweigh the risks in your individual situation.

On rare occasions, nervous system disorders also have been reported. 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 using anti-TNF medications.

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 an immunomodulator to a biologic. As with all therapy, there are risks and benefits of combination therapy. Combining therapies can increase the effectiveness of IBD treatment, but there may also be an increased risk of additional side effects and toxicity. Your health care provider will identify the treatment option 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 flare-ups and the medication losing its effectiveness. 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.

Disclaimer: *The Crohn's & Colitis Foundation provides information for educational purposes only, which is current as of the print date. We encourage you to review this educational material with your health care professional as this information should not replace the recommendations and advice of your doctor. The Foundation does not provide medical or other health care opinions or services. The inclusion of another organization's resources or referral to another organization does not represent an endorsement of a particular individual, group, company, or product.*

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Fact Sheet

News from the IBD Help Center

Targeted Synthetic Small Molecules

Targeted synthetic small molecules are medications that help reduce inflammation by specifically targeting parts of the immune system that play a role in inflammation in the intestine and other organs. There are currently three FDA approved targeted synthetic small molecules to treat ulcerative colitis.

JAK Inhibitors

JAK (Janus kinase) inhibitors are small molecules that are broken down in the gastrointestinal tract and directly absorbed into the bloodstream through the intestines. Due to their small size, they can be carried to nearly anywhere in the body through the bloodstream to work directly on the immune system. These small substances block multiple inflammatory pathways to help control IBD.

Tofacitinib (Xeljanz[®]) and upadacitinib (Rinvoq[®]) are JAK inhibitors that are FDA-approved to treat adult patients with moderate-to-severe ulcerative colitis. They are taken orally in pill form.

Common Side Effects:

- *Tofacitinib*: Upper respiratory tract infections (common cold, sinus infections), runny nose (nasopharyngitis), elevated cholesterol, headache, and anemia
- *Upadacitinib*: Headache, fatigue, acne, nausea, urinary tract infection, and elevated cholesterol

Risks/Safety:

- Taking tofacitinib or upadacitinib may include risk of serious infections, blood clots, certain types of cancer, and may increase risk of death or major cardiovascular events. Notably, these more serious events were seen in rheumatoid arthritis patients treated with tofacitinib who were older than 50 years and had at least one cardiovascular risk factor; **these serious events have not been observed in clinical trials for ulcerative colitis**. There have been rare reports of tears (perforations) in stomach or intestines, serious allergic reactions, and changes in certain lab test results.

S1P Receptor Modulator

Ozanimod (Zeposia[®]), a sphingosine 1-phosphate (S1P) receptor modulator, is an oral small molecule drug FDA-approved for the treatment of moderate-to-severe ulcerative colitis in adults. S1P receptor modulators work by preventing the migration of immune cells from the lymph nodes to the intestines where they cause inflammation in ulcerative colitis.

Side Effects/Safety

Common side effects:

- *Ozanimod*: Upper respiratory tract infections (common cold, sinus infections), elevated liver enzymes, headache, low blood pressure (when you stand up), and alterations in pulmonary function testing.

Risks/Safety:

- Taking ozanimod may include risk of serious infections, progressive multifocal leukoencephalopathy (PML), abnormal heart rhythms, including heart block, and fluid build-up in the retina that can cause vision problems. Before you start ozanimod, your physician may request an electrocardiogram (EKG) and/or consultation with a cardiologist. In addition, some patients may require an eye exam with an ophthalmologist.

Special Considerations

- Targeted synthetic small molecule medications reduce the activity of the immune system. In so doing, they also decrease the body's ability to fight infections. Be sure to report any signs of infection, including fever, chills, night sweats, sore throat, and other similar symptoms, to your doctor.
- While on one of these medications, it is important to be vaccinated against infections that are preventable. You must, however, avoid live vaccines while you are on one of these agents. There may be an increased risk of zoster (shingles) associated with targeted small molecule medications; all individuals should consider receiving a 2-dose inactivated shingles vaccine series, which is not a live vaccine.
- Prior to starting these medications, your healthcare team will request blood work. Blood work that will be collected may include blood counts to look for anemia or a low white blood cell count, chronic infections, such as tuberculosis (TB) and hepatitis B, liver and kidney function tests, and cholesterol levels.
- There is insufficient data with these medications to establish a risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Women who are pregnant or wish to become pregnant should talk to their doctors before starting targeted small molecule medications. Contraception is recommended during treatment and up to 4 weeks post discontinuation of these medications.
- Become an active participant in your care! Learn as much as possible about these treatments from your doctor and/or pharmacist. Other information can be obtained from reliable sources, such as the Crohn's & Colitis Foundation (www.crohnscolitisfoundation.org) and treatment manufacturer websites.

Combination Therapy

For patients with IBD, these targeted synthetic small molecule medications are used as individual therapy and have not been studied in combination with certain immunosuppressant medications. Combination therapy with another immunomodulators or biologics is not routinely recommended. Steroids should be tapered shortly after starting your medication.

Drug Interactions

Taking several different medicines, whether prescription or over-the-counter, together may cause interactions. Drug interactions may change how well a medication works, or cause unexpected side effects, some more harmful than others. Before taking any medication, be sure to read the label carefully and take it exactly as prescribed. Also, ask your doctor

and pharmacist if there are any interactions to note with your existing medications. Be sure to include over-the-counter medications and complementary therapies (supplements, herbals, vitamins, etc.) when discussing your medications. If you are taking ozanimod, it is recommended that you avoid foods that are rich in tyramine (do not consume >150 g). These include aged cheese, fermented foods, including wines, beers, sauerkraut, fish sauce and soy sauce.

Take Medications as Prescribed

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

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