CENTER FOR DIGESTIVE HEALTH & NUTRITION
725 CHERRINGTON PARKWAY • MOON TOWNSHIP, PA 15108

# Biologic Drugs and Inflammatory Bowel Disease

**What Is The Immune System?**

The human body consists of various systems, such as the cardiovascular, skeletal, nervous, and digestive systems. Another critical system is the immune system, which is composed of specialized white blood cells, mostly lymphocytes, that are distributed throughout the body, primarily in the bloodstream, lymphatic system, and bone marrow, as well as in the inner lining of the digestive tract.

Your immune system is like your body's personal army. Its main job is to protect you from germs, viruses, and harmful invaders. When your immune system detects something dangerous, it sends signals to special cells and proteins to attack and destroy the intruders. **To do its job, the immune system must clearly understand the difference between what is YOU and what is NOT YOU.** So, if you get a cut and germs enter your body, the immune system identifies the germs as invaders and quickly mobilizes an attack to destroy them. After the threat is neutralized, the immune system normally relaxes.

**What Is An Autoimmune Disease?**

For reasons that are unclear, the immune system sometimes becomes confused and can't tell the difference between YOU and NOT YOU. It mistakenly identifies a normal body part as an intruder and attacks itself. This is called an autoimmune disease. Common examples of an autoimmune disease include:

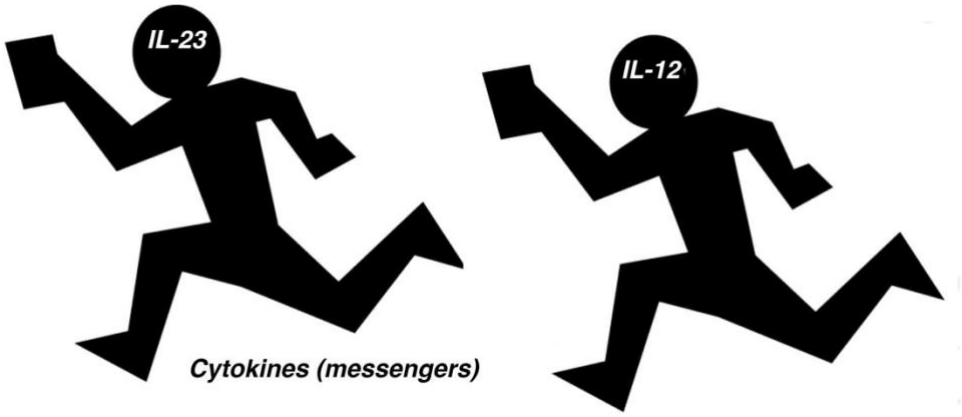
- Rheumatoid Arthritis (RA)
- Lupus (SLE)
- Multiple Sclerosis (MS)
- Type 1 Diabetes
- Celiac Disease
- Graves' Disease
- Inflammatory bowel disease
  - Crohn's Disease
  - Ulcerative Colitis

Each of these diseases involves the immune system mistakenly attacking healthy tissues, leading to inflammation and tissue damage.

**Immune Attack In Inflammatory Bowel Disease (IBD)**
Normally, the immune system protects you. However, in individuals with inflammatory bowel disease (Crohn's disease or ulcerative colitis), the immune system becomes confused and attacks the intestinal tract. Instead of calming down after the perceived danger has passed, it continues to fight, leading to chronic inflammation and damage.

**How Does This Occur?**
The workings of the human immune system are quite complex. Continuing the analogy, the soldiers (lymphocytes) of the immune system remain on standby in their barracks around the clock, awaiting an alarm to be raised.


When the alarm (TNF) sounds, special messengers known as cytokines (specifically IL-23 and IL-12) instruct these soldiers to prepare for battle, detailing where to go and what to target. In the case of IBD, the focus is on the digestive tract.




Cytokines transform lymphocytes into T-cells, which carry out the immune response. Th17 cells are a specialized subset of T-cells that typically fulfill a protective role, but in cases of IBD, they can provoke harmful autoimmune reactions.

JAK enzymes. JAK stands for Janus Kinase, a family of enzymes within T-cells. These enzymes act as messengers, helping to transmit signals from the exterior of the T-cell to the interior. Cytokines bind to receptors on the surface of immune cells and convey a message to the cell's nucleus to activate genes that trigger inflammation. After receiving this signal, TH17 becomes an aggressive fighting cell, prepared for combat and ready to destroy an invader, or, in the case of IBD, damage the intestinal lining.

*Th17 "Killer" T-cells*

The soldiers are transported through the bloodstream to the intestines. To enter the intestinal cells, they require a special KEY to unlock the door (Integrin proteins). Once inside the intestinal cell, they initiate inflammation, which damages the lining of the intestine. This leads to the typical chronic intestinal ulcers seen in Crohn's disease and ulcerative colitis, which are responsible for the classic symptoms of abdominal pain, diarrhea, and bleeding.

## Medicines for IBD: How They Calm Your Immune System

If you are living with moderate to severe Inflammatory Bowel Disease (IBD), your doctor may prescribe advanced medications like biologics or targeted oral therapies to manage your condition. These specialized treatments are designed to calm your immune system by targeting specific proteins and pathways that cause inflammation in your gut. Several types of these medications exist, each working in a unique way. Your doctor will consider the severity of your IBD, your treatment history, and your overall health to determine the best option for you.

### Anti-TNF Drugs

Anti-TNF drugs work by blocking a protein called Tumor Necrosis Factor (TNF), which promotes inflammation. Think of TNF as a persistent alarm ringing in your gut; these medications silence that alarm, helping to reduce damage. Although the name includes "tumor necrosis factor," these drugs are not related to cancer treatment. All anti-TNF medications have been shown not only to reduce the symptoms of IBD but also to promote healing of the inflamed intestine. While anti-TNF medications are not effective for everyone, many patients benefit from this type

of treatment. It may take up to eight weeks after starting an anti-TNF to notice an improvement in symptoms, although many experience more immediate relief.

Medications in this class include:

Infliximab (Remicade, Inflectra, Renflexis, IXIFI, Avsola, Zymfentra) is a highly effective intravenous (IV) infusion for both Crohn's disease and ulcerative colitis. It is known for its rapid action, which makes it a suitable option for managing fistulizing Crohn's disease. Four biosimilars are available.

Adalimumab (Humira, Amjevita, Cyltezo) treats both Crohn's disease and ulcerative colitis, offering effectiveness comparable to that of infliximab. It provides the convenience of at-home subcutaneous (under the skin) injections, though it may work slightly more slowly. There are 10 biosimilars available. Adalimumab is given as an injection under the skin of the abdomen or thigh and is also available in a citrate-free formulation, which causes less burning at the injection site.

Certolizumab pegol (Cimzia) is a subcutaneous injection used only for Crohn's disease. Its unique molecular structure may make it a safer choice during pregnancy. Certolizumab pegol is given as an injection under the skin of the abdomen or thigh.

Golimumab (Simponi) is a subcutaneous injection approved only for ulcerative colitis. It is given as an injection under the skin of the abdomen or thigh.

Common side effects of anti-TNF drugs include an increased risk of infections, such as tuberculosis and fungal infections, as well as infusion or injection site reactions. In rare instances, there is a possible risk of lymphoma, skin cancer, a lupus-like syndrome, or demyelinating disease.

**Anti-Interleukin (IL) Therapies**

This group of drugs targets interleukins, which are proteins that signal immune cells to promote inflammation. One key interleukin, IL-23, acts like gasoline for the fire of gut inflammation. It encourages certain immune cells to become active and prevents the growth of other cells that would normally calm the immune system, thus tipping the balance toward increased inflammation. By blocking interleukins like IL-23 and IL-12, these drugs cut off the fuel supply, preventing T-cells from receiving the signals they need to trigger inflammation. Some newer medications specifically target a part of IL-23 called the p19 subunit, enabling them to block IL-23 without affecting IL-12. This precise targeting may reduce the risk of significantly weakening the immune system. These therapies include:

IL-12 and IL-23

Ustekinumab (Stelara) treats both Crohn's disease and ulcerative colitis by blocking both IL-12 and IL-23. Treatment begins with an IV dose, followed by subcutaneous injections. It is a well-tolerated option often used when anti-TNF therapies have not been successful.

IL-23 Selective

Guselkumab (Tremfya) is a biologic treatment approved for patients with moderate to severely active Crohn's disease and ulcerative colitis. The first three doses are given by an intravenous infusion, and then can be taken as an injection under the skin.

Risankizumab-rzaa (Skyrizi) is a biologic treatment that also selectively targets IL-23. It is also approved for patients with moderately to severely active Crohn's disease and ulcerative colitis. The first three doses are given by an intravenous infusion, and then can be taken as an injection under the skin.

Mirikizumab-mrkz (Omvoh) is a newer biologic treatment approved for patients with moderately to severely active ulcerative colitis. It is "gut-selective" by selectively targeting IL-23 without affecting IL-12. The first three doses are administered via intravenous infusion, and subsequent doses can be taken as an injection under the skin.

Side effects are often mild and can include upper respiratory infections, headaches, and pain at the injection site.

**Anti-Integrin Therapies**

Integrin inhibitors work by preventing inflammatory immune cells from entering your digestive tract. You can think of integrins as keys that T-cells use to unlock doors into your gut lining. These drugs block those keys, preventing the cells from getting into the intestinal tissues to cause inflammation.

Vedolizumab (Entyvio) is a treatment for both Crohn's disease and ulcerative colitis that specifically targets an integrin in the gut called α4β7. This gut-selective action provides an excellent safety profile with fewer systemic side effects. It is administered as an IV infusion, with a subcutaneous option available in certain regions, though its onset of action may be slower. Side effects are generally rare and can include headache, joint pain, or unusual infections.

**Oral Small Molecule Drugs**
Unlike biologics, which are large proteins, these medications are smaller molecules taken as pills to control inflammation through different mechanisms.

JAK Inhibitors: Drugs like Tofacitinib (Xeljanz) and Upadacitinib (Rinvoq) work by blocking signals inside immune cells. They inhibit enzymes called Janus kinases (JAKs), which act like a phone line to transmit inflammatory messages within a cell. If JAKs can't deliver the message, the cell doesn't turn on inflammatory genes. By disconnecting this line, the drugs decrease inflammation quickly.

Tofacitinib (Xeljanz) is an oral tablet for ulcerative colitis only, known for providing rapid symptom relief.

Upadacitinib (Rinvoq) is an oral tablet approved for both Crohn's and ulcerative colitis.

Because they impact the broader immune system, JAK inhibitors have risks such as infections (including herpes zoster or shingles), blood clots, increased cholesterol, and potential cardiovascular events. They are usually reserved for patients without significant heart disease who have not responded to biologics.

S1P Receptor Modulators: Ozanimod (Zeposia) and Etrasimod (Velcipity)is an oral capsule used for moderate ulcerative colitis. It works by trapping specific immune cells (T-cells) in the lymph nodes, preventing them from traveling to the gut and causing inflammation. Imagine the lymph nodes as parking lots where these cells get stuck. This newer medication provides gut-targeted immune suppression and is generally well tolerated. Because it can cause a slow heart rate when starting the medication, monitoring is required. Other potential side effects include an increased risk of infections and elevated liver enzymes.

**Risks and Special Considerations**
Generally, the less a medication suppresses the immune system as a whole, the lower the risk of side effects. The new drugs tend to be more gut-selective without compromising overall immunity. While the benefits usually far exceed the risks of biologic medications for individuals with IBD, it is important to keep the following in mind when using biologics:

Side effects and intolerance. Because biologics are administered through intravenous infusions or subcutaneous injections, they may cause redness, itching, bruising, pain, or swelling at the injection site. Additional side effects can include headache, fever, chills, hives, and other rashes. Severe allergic reactions may occur rarely.

Infections. Because biologics affect the immune system to help control IBD, this class of medication can influence your ability to fight off infections, which can increase the risk of developing less common infections. While most patients using biologics never experience a medication-related infection, it is important to discuss this with your IBD specialist. To help prevent infections, patients should stay up-to-date on appropriate vaccinations, including yearly influenza vaccinations, COVID-19, the pneumonia vaccine, and hepatitis vaccines.

AVOID LIVE VACCINES WHEN ON AN IMMUNOSUPPRESSIVE DRUG. In healthy individuals, these vaccines typically don't cause illness and can be very effective. However, if your immune system is suppressed, even a weakened virus can multiply and cause disease. That's why live vaccines are generally not recommended for individuals on biologic drugs or other strong immune-suppressing therapies. If you notice any signs of infection while taking these medications, such as fever, a new cough, or flu symptoms, inform your doctor immediately.

***Live Vaccines to Avoid***

- *MMR (Measles, Mumps, Rubella)*
- *Varicella (Chickenpox)*
- *Oral Polio Vaccine*
- *Rotavirus*
- *Yellow Fever*
- *Oral Typhoid*
- *Intranasal Flu Vaccine (FluMist®)*
- *Zostavax® (the older shingles vaccine)*

Cancer Risk. Hearing this scares patients the most. Anti-TNF medications have been linked to a threefold increase in the incidence of lymphoma, a rare blood cancer. This sounds frightening. However, it's important to put this in perspective. The lifetime risk of lymphoma in the general U.S. population is very low, approximately 2 in 10,000. *So, anti-TNF therapy raises your risk of lymphoma to about 6 in 10,0000, which is still a very low risk.* (In my 25 years of experience prescribing Remicade, I have never seen a single case of lymphoma related to this medication.)

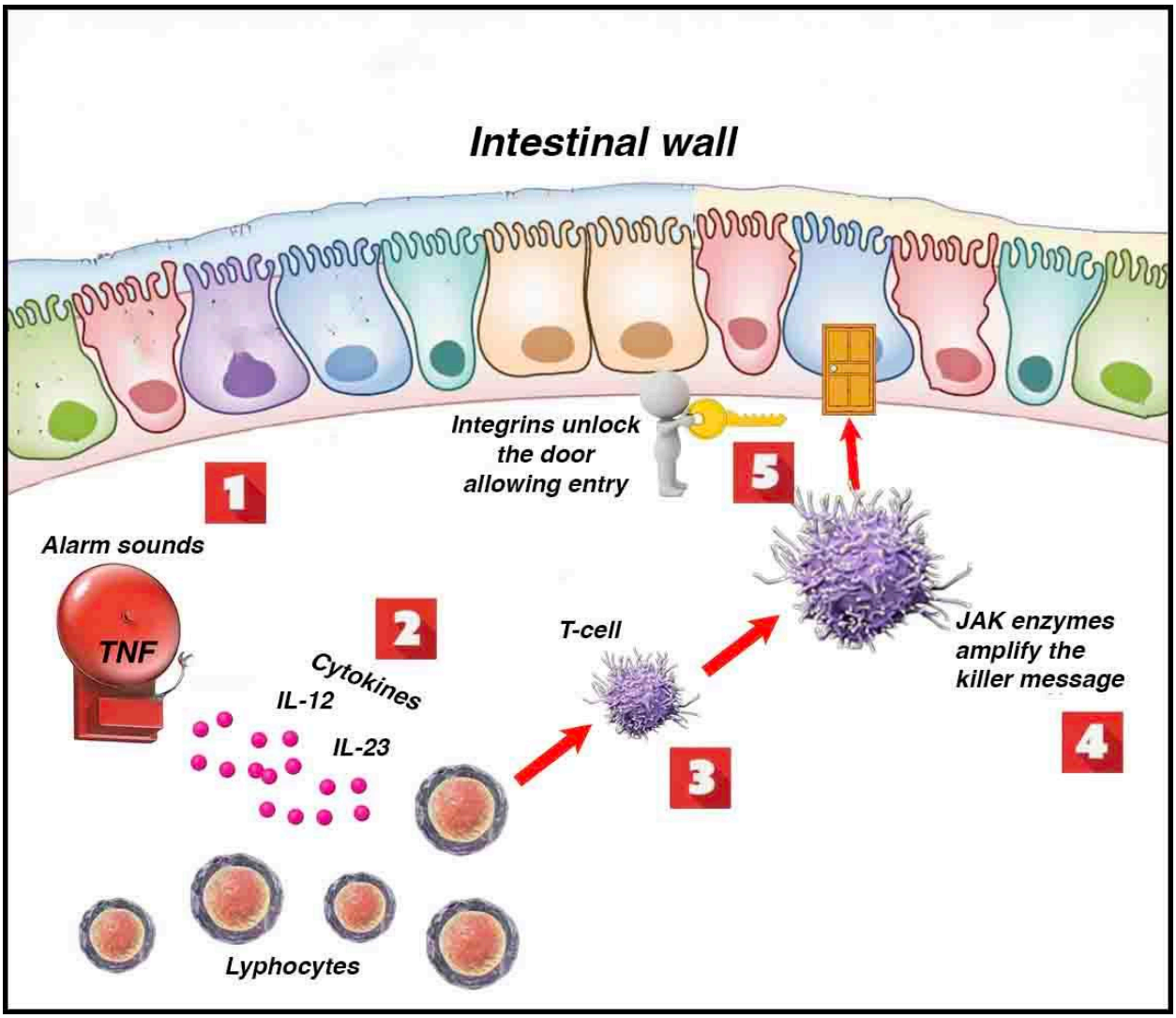
Arthritis: While anti-TNF medications are often effective treatments for inflammatory arthritis (joint pain), they may, in some cases, lead to new joint discomfort. If you experience any new joint pain while taking anti-TNF medications, please notify your doctor.

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 aches, and/or fever. Talk to your doctor if you experience these symptoms.

Skin reactions: Rashes and psoriasis induced by anti-TNF (a skin condition) have been reported.

Robert Fusco MD
June 2025

**Center For Digestive Health & Nutrition**
725 Cherrington Parkway • Moon Township, PA 15108
412.262.1000 • www.gihealth.com • IG: @thedigestivetract




## How the immune system attacks the intestines in IBD

1. An alarm is raised (TNF). Nobody really knows why
2. This releases cytokine messengers (IL12 and IL23) to activate the lymphocytes and other white blood cells held in reserve.
3. The cytokines quickly transform resting lymphocytes into active duty fighters (T-cells) who are given orders to attack the intestines.
4. JAK enzymes communicate with Th17 killer T-cells to enhance their ability to kill.
5. The intestinal wall is secure, but Integrins are the keys that unlock the door, allowing killer T-cells to enter the intestinal cells and damage them, leading to the ulcers associated with Crohn's disease and ulcerative colitis.

# HOW BIOLOGICS WORK

*(Refer to diagram on page 8)*

## 1 Anti-TNF Drugs

**Think of TNF as a persistent alarm ringing in your gut; these medications silence that alarm, helping to reduce damage.**

**Infliximab** (Remicade, Inflectra...)
**Adalimumab** (Humira...)
**Certolizumab** pegol (Cimzia)
**Golimumab** (Simponi)

## 2 Anti-Interleukin (IL) Therapies

## 3 IL-12 and IL-23

**By blocking interleukins like IL-23 and IL-12, this drugs cut off the fuel supply, preventing T-cells from receiving the signals they need to trigger inflammation.**

***Ustekinumab (Stelara)***

### IL-23 Selective

***Specifically block IL-23 without affecting IL-12. This precise targeting may reduce the risk of significantly weakening the immune system***

***Guselkumab (Tremfya)***
***Risankizumab-rzaa (Skyrizi)***
***Mirikizumab-mrkz (Omvoh)***

## 4 JAK inhibitors

***They inhibit enzymes called Janus kinases (JAKs), which act like a phone line to transmit inflammatory messages within a cell. If JAKs can't deliver the message, the cell doesn't turn on inflammatory genes.***

***Tofacitinib (Xeljanz)***
***Upadacitinib (Rinvoq)***

## 5 Anti-Integrin Therapies

***You can think of integrins as keys that T-cells use to unlock doors into your gut lining. These drugs block those keys, preventing the cells from getting into the intestinal tissues to cause inflammation***

***Vedolizumab (Entyvio)***

## S1P Receptor Modulators:

***It works by trapping specific immune cells (T-cells) in the lymph nodes, preventing them from traveling to the gut and causing inflammation. Imagine the lymph nodes as parking lots where these cells get stuck.***

***Ozanimod (Zeposia)***
***Etrasimod (Velcipity)***