Treatment Updates for Ulcerative Colitis and Crohn's Disease

Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders that cause chronic inflammation of the gastrointestinal (GI) tract. The two most common forms of IBD are Crohn's Disease (CD) and Ulcerative Colitis (UC). Both CD and UC are considered autoimmune conditions in which the immune system attacks healthy tissue in the gut causing inflammation. Ulcerative colitis involves inflammation and ulcers along the lining of the large intestine. Crohn's disease is characterized by inflammation of the lining as well as deeper layers of the small intestine. The inflammation of the intestine is not always continuous, leaving normal areas in between patches of inflamed intestine. Both diseases exhibit symptoms such as diarrhea, rectal bleeding, abdominal pain, fatigue, reduced appetite, and unintended weight loss.

The exact cause of UC and CD is unknown. Researchers believe IBD results from a combination of genetic, environmental, and lifestyle factors. More than 200 genes have been associated with IBD. Many of the major genes identified are involved in immune system function. The proteins from these genes help the immune system sense and respond appropriately to bacteria in the lining of the digestive tract. Variations in one or more of the inherited genes may lead to an abnormal immune response to certain environmental triggers. In a genetically susceptible individual, whatever the trigger is, it prompts the person's immune system to initiate an attack in the GI system inducing inflammation. Unfortunately, the immune system continues to attack the healthy tissues. The constant inflammation damages the digestive organs and causes symptoms of UC and CD.

According to the most recent data from the CDC, there are over 3 million adults in the United States or 1.3 percent of the adult population living with CD or UC. Ulcerative colitis is slightly more common than Crohn's disease in most age groups, except in children, among whom the trend is reversed. Researchers have determined that people who have a first degree relative such as a parent or sibling with the disease are more likely to suffer from IBD. It is also more common in non-Hispanic Caucasians but can affect people of any racial or ethnic group. On average, most patients are diagnosed before the age of 35, but the disease can occur at any age. Over the last decade, the number of people diagnosed with UC and CD has increased. As many as 56,000 new cases are diagnosed each year.

Medications are available that can control disease symptoms. While the medications do not actually cure the disease, many patients can go for long periods of time without symptoms. The use of medications can also lower the chances of developing complications later.

Medication therapy choice depends on disease location, disease severity, disease-associated complications, and disease prognosis. Treatment consists of two phases: induction and maintenance. The most commonly prescribed medications for CD and UC fall into the following categories:

- Aminosalicylates: These first line medications inhibit certain pathways that produce substances that cause inflammation, especially in the lining of the GI tract. Aminosalicylates work best in the colon and can be effective in treating mild-to-moderate flares of IBD. They are also useful as a maintenance treatment in preventing relapses, unless the disease is limited to the small intestine. Aminosalicylates are often given orally in the form of delayed release tablets to target the colon, or rectally as enemas or suppositories. Examples are sulfasalazine, mesalamine, olsalazine, and balsalazide. These generic products range in cost from $1,000 to $15,000 annually.

- Corticosteroids: These medications affect the body's ability to launch and maintain an inflammatory process. In addition, they work to keep the immune system in check. Corticosteroids are effective for short-term control of IBD activity. However, they are not recommended for long-term or maintenance use because of their potential side effects. Commonly used corticosteroids include budesonide, prednisolone, and prednisone and cost less than $2,000 per year.
- Immunomodulators: This class of medications controls or suppresses the body's immune response, therefore decreasing inflammatory activity. Immunomodulators generally are used in people for whom aminosalicylates and corticosteroids haven't been effective or have only been partially effective. Some immunomodulators are added to treatment regimens to make other medications, such as biologics, work better by preventing the formation of antibodies to biologic medications. They may also be useful in reducing or eliminating the need for corticosteroids. Immunomodulators include azathioprine, 6-mercaptopurine (6-MP), and cyclosporine and cost less than $2,500 per year.

- Biologic therapies: These protein-based complex medications are derived from living organisms and work to stop certain proteins in the body from causing inflammation. Biologics are usually administered via injection or intravenous infusion. There are different types of biologics for IBD.

  Tumor necrosis factor-alpha (TNF-alpha) blockers were the first class of biologics approved to treat IBD in the United States. They work by blocking a small protein that causes inflammation in the intestine. Examples of TNF-alpha blockers include Remicade® (infliximab), Humira® (adalimumab), Simponi® (golimumab), and Cimzia® (certolizumab pegol). Remicade is available as an intravenous infusion while, Simponi, Cimzia, and Humira can be self-administered as a subcutaneous injection. Remicade and Humira both have numerous biosimilar products available, some of which provide significant discounts on treatment costs (see table below).

  In October, the FDA approved Zymfentra® (infliximab-dyyb), the first subcutaneous infliximab product. Zymfentra was approved for the treatment of adults with moderate-to-severe UC and CD, following treatment with an intravenously administered infliximab product. The intravenous version of Zymfentra is Inflectra® (also infliximab-dyyb) which was a biosimilar to Remicade approved in April 2016. Zymfentra is considered a biobetter because it was intentionally created to have a more appealing route of administration for infliximab. A biobetter is a biologic based on the innovator molecule but with improvements intended to improve efficacy, potency, safety or patient compliance. Zymfentra is unique because it is the only biobetter that improves upon a biosimilar (Inflectra) rather than an innovator product Remicade. The approval of the subcutaneous formulation could shift market share from the medical to the pharmacy benefit because it can be self-administered at home instead of being delivered as an infusion in a doctor's office or clinic. The manufacturer, Celltrion, will release the list price closer to when the product is available sometime during the first quarter of 2024.

  Integrin blockers like Entyvio® (vedolizumab) and Tysabri® (natalizumab) prevent white blood cells that cause inflammation from entering the GI tract. Entyvio is approved for treating moderate-to-severe UC and CD while Tysabri is approved for patients with moderate-to-severe Crohn's disease who do not respond to other types of therapy.

  In September, the FDA approved a subcutaneous formulation of vedolizumab, Entyvio® Pen, for maintenance therapy in adults with moderate-to-severe UC after induction therapy with intravenous Entyvio. Similar to infliximab, Entyvio® and Entyvio® Pen offer providers and patients another biologic choice that has an intravenous and subcutaneous treatment option.

The FDA approved Tyruko® (natalizumab-sztn), the first biosimilar for Tysabri in August. Like Tysabri, Tyruko is approved for treating adult patients with moderate-to-severe Crohn's disease who have had an inadequate response or do not tolerate conventional therapies or TNF-alpha inhibitors. Tyruko is expected to be available in the first half of 2024.

Interleukin inhibitors block interleukin (IL) proteins associated with inflammation in the GI tract. Examples include Stelara® (ustekinumab), Skyrizi® (risankizumab-rzaa), and Omvoh™ (mirikizumab-mrkz). Each medication has a slightly different interleukin target and FDA approved indication. However, all start with intravenous induction dosing and switch to subcutaneous dosing for maintenance therapy.

Stelara works by blocking interleukin-12 and interleukin-23 and is approved to treat moderate-to-severe UC and CD. On October 31, 2023, the FDA approved Wezlana® (ustekinumab-auub) by Amgen as the first biosimilar for Stelara. Wezluna has the same FDA approved indications as Stelara and was also granted interchangeability status. Wezlana's launch will be delayed until 2025 as a result of the patent lawsuit settlement with Johnson & Johnson, the manufacturer of Stelara. Although the settlement terms are confidential, Amgen said that it could sell the biosimilar no later than January 1, 2025. There are more ustekinumab products in the pipeline. As many as 8 Stelara biosimilars may launch in 2025.

Skyrizi is an interleukin-23 antagonist indicated for the treatment adults with moderate-to-severe active CD. In August 2023, AbbVie, the manufacturer announced they applied to the FDA for use in UC. A decision is expected in the second half of 2024.

On October 24, 2023, the FDA approved Omvoh for the treatment of adults with moderate-to-severe UC. Omvoh selectively targets the p19 subunit of IL-23 and inhibits the IL-23 pathway. More studies are needed to determine if the target specificity has significant clinical impact.

- Janus kinase (JAK) inhibitors: These small molecule oral medications interact with cytokines, or signaling proteins, that help control inflammation in the body. In contrast to the biologics, which can block a single cytokine protein, JAK inhibitors have the potential to affect multiple cytokine-dependent immune pathways. This may result in an improved therapeutic response in some IBD patients. JAK inhibitors work quickly and can induce and maintain remission. Xeljanz®/Xeljanz XR® (tofacitinib) and Rinvoq® (upadacitinib) are both considered JAK inhibitors. Xeljanz is indicated for the treatment of adult patients with moderate-to-severe active UC and CD while Rinvoq is approved for moderate-to-severe UC. Due to safety concerns, the use of all JAK inhibitors is limited to certain patients who have not responded or cannot tolerate one or more TNF inhibitors. In 2021, the FDA issued a Drug Safety Communication linking JAK inhibitors with an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death. Prior to this, the labels of all JAK inhibitors already included boxed warnings regarding the risk of serious infections, malignancies, and thrombosis. This labeling effectively makes JAK inhibitors a second line class of drugs.

- Sphingosine 1-Phosphate Modulators (S1Ps) –This is the newest class of oral small molecules to be approved by the FDA for the treatment of UC. Studies are underway for their use in CD. They work by targeting S1P1 receptors that are found on the surface membranes of immune cells. By binding to the receptor, they prevent the immune cells from being released in the blood. In turn, this reduces the level of inflammation in people with ulcerative colitis. In May 2021, Zeposia® (ozanimod) was approved by the FDA to treat moderate-to-severe UC in adults. On October 12, 2023, the FDA

approved Velsipity® (etrasimod) to treat adults with moderate to severe active UC. Similar to Zeposia, Velsipity can reduce heart rate, elevate certain liver enzymes, and increase fluid build-up in the eyes. Therefore assessments prior to initiating Zeposia and Velsipity are required, including an electrocardiogram (ECG), liver function tests, and an ophthalmic exam.

Ulcerative colitis and Crohn's disease are chronic, inflammatory diseases that usually require lifelong therapy. Fortunately, the treatment options have expanded significantly during the past decade and have made treatment advances enhancing therapy options. The mainstay of treatment involves using immunosuppression and immunomodulation to induce remission and improve quality of life. Some newly diagnosed IBD patients may not respond to initial therapies, while other patients may lose response to therapy over time. Multiple intravenous and subcutaneous biologic agents are available as well as newer oral small molecule medications that may work for patients without preexisting risk factors. The number of cost-effective treatment options for moderate-to-severe disease has expanded significantly in the last six months. Humira biosimilars have proven effectiveness and some products offer aggressive pricing. This trend should continue into 2025 as multiple biosimilars for Stelara are expected to be available. Newer more expensive agents like Omvah or Velsipity will likely face some barriers to adoption unless more data becomes available demonstrating clear meaningful clinical benefits over existing proven treatment options and the new, lower cost biosimilar choices. Nonetheless, with the increasing number of different drug classes available to treat inflammatory bowel disease, more head-to-head trials in the future with direct comparative efficacy will be needed to facilitate optimal positioning of therapies.

Annualized Current Drug Costs for IBD

Medication	Annual Price*
TNF-alpha blockers	
Humira (adalimumab)	$89,994
Adalimumab biosimilars (High WAC) Examples include Amjevita, Abrilada, Cyltezo, Hulio, Idacio)	$85,494 (average 5% discount to Humira)
Adalimumab biosimilars (Low WAC) Examples include Hadlima, Hyrimoz, Yusimry)	$17,099 (average >80% discount to Humira)
Simponi (golimumab)	$87,718
Cimzia (certolizumab pegol)	$70,207
Remicade (infliximab)	$49,340
Inflectra (infliximab)	$39,982
Renflexis (infliximab)	$31,831
Avsola (infliximab)	$21,125
Zymfentra (infliximab-dyyb)	TBA
Integrin blockers	
Tysabri	$106,722
Tyruko	TBA
Entyvio	$53,144
Entyvio Pen	$76,528
Interleukin inhibitors	
Stelara (SC) - maintenance	$172,361
Stelara (IV) - induction	$5,784

Medication	Annual Price*
Wezlana	TBA closer to 2025
Skyrizi (SC) - maintenance	$128,000
Skyrizi (IV) - induction	$28,000
Omvoh (SC) - maintenance	$134,689
Omvoh (IV) - induction	$29,000
JAK Inhibitors	
Xeljanz/XR	$67,084
Rinvoq	$74,520
S1Ps Modulators	
Zeposia	$102,038
Velsipity	$75,000
*Annual price includes medication cost only; it does not include ancillary costs for administration	

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