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 Ulcerative Colitis (UC) and Crohn's Disease (CD). Both UC and CD are considered autoimmune conditions in which the immune system attacks healthy tissue in the gut causing inflammation. UC involves inflammation and ulcers along the lining of the large intestine. CD is characterised by inflammation of the lining as well as deeper layers of the small intestine. It can affect any segment of the GI tract, and the inflammation is not always continuous, leaving normal areas in between patches of inflamed intestine, which are known as skip lesions. Both UC and CD produce symptoms such as diarrhoea, constipation, rectal bleeding, abdominal cramping and 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.

IBD is estimated to affect over 3.4 million adults in Europe or 0.3% of the population. The prevalence of UC ranges from 2.4 to 294 cases per 100,000, while the prevalence of CD ranges from 1.5 to 213 cases per 100,000. Within Europe, there are geographical differences characterised by a north-south and an east-west gradient, with an incidence of UC in Northern and Southern Europe at 11.4 and 8.0 per 100,000, respectively, and an incidence of CD at 6.3 per 100,000 in Northern Europe in comparison to only 3.6 per 100,000 in Southern Europe. A notable increase in IBD rates has also been observed in Eastern Europe. UC 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 5 to 20% of people with IBD have a first degree relative such as a parent or sibling with the disease. On average, most patients are diagnosed between the ages of 15 and 35, but the disease can occur at any age. Medical management of UC and CD depends on disease location, disease severity, disease-associated complications, and disease prognosis. Treatment consists of two phases: induction and maintenance. While the medications available for UC and CD do not actually cure the disease, they can control disease symptoms and permit mucosal healing in mild disease, enabling many patients to go for long periods of time without symptoms. The use of more aggressive initial medications in moderate to severe disease can also lower the chances of developing complications. The most commonly prescribed medications for UC and CD 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 include sulfasalazine, mesalamine, olsalazine, and balsalazide.

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 and prednisolone.

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.

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 subcutaneous injection or intravenous infusion. There are different types of biologics for IBD.

- Tumour necrosis factor-alpha (TNF-α) inhibitors were the first class of biologics approved to treat IBD. They work by blocking tumour necrosis factor, a small protein that causes inflammation in the intestine. Examples of TNF-α inhibitors include Remicade® (infliximab), Humira® (adalimumab), and Simponi® (golimumab)). Remicade is available as an intravenous infusion, while Humira and Simponi can be self-administered as a subcutaneous injection. There are also numerous biosimilars to Remicade and Humira available in Europe. Integrin blockers: like Entyvio® (vedolizumab) prevent white blood cells that cause inflammation from entering the GI tract. Entyvio is a gut-selective immunosuppressant and is approved for treating adults with moderately to severely active CD or UC who have had an inadequate response with lost response to or were intolerant to either conventional therapy or a TNF-α inhibitor.

- Interleukin inhibitors: block interleukin (IL) proteins associated with inflammation in the GI tract. Examples include Stelara® (ustekinumab), Skyrizi® (risankizumab-rzaa), and Omvoh™ (mirikizumab-mrkz), with medication having a slightly different interleukin target and approved indication.

  Stelara works by blocking IL-12 and IL-23. It is approved to treat adult patients with moderately to severely active UC or CD who have had an inadequate response with lost response to or were intolerant to either conventional therapy or a biologic (specifically a TNF-α inhibitor for CD) or have medical contraindications to such therapies. On November 9, 2023, the EMA Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending marketing authorisation for Uzpruvo (ustekinumab). This recommendation marks the first biosimilar for Stelara in Europe.

Skyrizi is an IL-23 antagonist indicated for the treatment of adult patients with moderately-to-severely active CD who have had an inadequate response to, lost response to or were intolerant to conventional therapy or a biologic agent.

Omvoh is the most recently approved IL inhibitor. It is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with lost response to or were intolerant to either conventional therapy or a biologic treatment selectively targets the p19 subunit of IL-23 and inhibits the IL-23 pathway.

Janus kinase (JAK) inhibitors: These small molecule oral medications interact with cytokines, or signalling 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® (tofacitinib) and Rinvoq® (upadacitinib) are both considered JAK inhibitors. Xeljanz is indicated for the treatment of adult patients with moderately-to-severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Rinvoq is approved for the treatment of adult patients with moderately to severely active CD who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic agent. Due to class related safety concerns, recommendations have been published by the manufacturers in agreement with the EMA to minimise the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of these products.

Sphingosine-1-phosphate (S1P) receptor modulators: This is the newest class of oral small molecules to be approved by the EMA for the treatment of UC. This class of drugs works by targeting S1P receptors that are found on the surface membranes of immune cells. By binding to the receptors, they prevent the immune cells from being released in the bloo5d. In turn, this reduces the level of inflammation in people with UC. Studies are underway for their use in CD. In October 2021, Zeposia®(ozanimod) was approved by the EMA to treat adults with moderately-to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Etrasimod, another S1P modulator is currently under review by the EMA. Pfizer, the manufacturer of this product, expects a decision to be made regarding its approval in early 2024.

UC and CD are chronic, inflammatory diseases that usually require lifelong therapy. Fortunately, the treatment options have expanded significantly during the past decade, allowing for advanced 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. As the number of different drug classes available to treat IBD increases, more head-to-head trials in the future with direct comparative efficacy will be needed to facilitate optimal positioning of therapies.

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