AU InforMed

Volume 21 Number 8 (Issue 334) *Friday, December 8, 2023*

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Crohn's and Colitis Awareness Week is December 1-7

Living with Inflammatory Bowel Disease takes guts! This year will be the 12th annual observation of Crohn's and Colitis Awareness week since it was created by U.S. Senate Resolution 199 in 2011.[1]

Key Inforbits

- What is Inflammatory Bowel Disease (IBD)?
- Pathophysiology & Etiology
- Ulcerative Colitis versus Crohn's Disease
- Preventative Treatment for IBD
- Current Treatments for IBD
- New therapies for IBD

What is Inflammatory Bowel Disease?

Inflammatory Bowel Disease (IBD) is an umbrella term that encompasses two diseases of the gastrointestinal tract, Ulcerative Colitis (UC) and Crohn's Disease (CD).

Epidemiology

image source: CDC.gov

Currently around 3.1 million people in the United States and 6.8 million people worldwide are affected with IBD.[2] Although anyone at any age can develop IBD it tends to follow a bimodal distribution with a new diagnosis occurring between the ages of 15-30 years old and then a second spike in incidence between the ages of 50-70 years old. Men and women are typically affected at similar rates, but CD tends to affect more females while UC affects slightly more males at older ages. While most patients do not consider IBD to be a disability and can live normal lives, IBD is associated with decreased quality of life, decreased productivity, and increased risk of hospitalization.[3] Inflammatory bowel disease is more prevalent in Western countries and as a result affects more Caucasian patients than other racial or ethnic groups. However, the incidence of IBD is slowly rising in Asian and Hispanic patients as well as other more recently industrialized portions of the world giving rise to new theories on IBD's etiology.

Etiology and Pathophysiology

Despite intense research and development in the management of IBD, the true etiology and pathology remain largely unknown. The environment of the gastrointestinal tract is usually

under homeostasis between the commensal microbiota, intestinal epithelial cells, and immune cells forming an integrated "supraorganism."[3] Leading consensus on the hypothetical pathogenesis of IBD is that each these major host compartments is affected by environmental factors, such as smoking, antibiotics, or enteropathogens, and genetic factors. This disrupts the the gastrointestinal environment resulting in chronic inflammation.

Ulcerative Colitis versus Crohn's Disease

Both CD and UC are similar in that they are inflammatory disorders of the intestines, but they have key distinctive factors that differentiate them from one another. Crohn's disease can affect any part of the intestine from the mouth to rectum.[3,4] It's classically characterized as non-continuous transmural inflammation that gives rise to a "cobblestone" appearance of the intestine with linear ulcerations. In contrast, inflammatory UC is continuous superficial mucosal inflammation confined to the colon and large intestine. However, in nearly 15% the discrimination between UC and CD at the time of diagnosis is nearly impossible and called indeterminate colitis. Most of those cases only become clear later in the disease progression.[3]

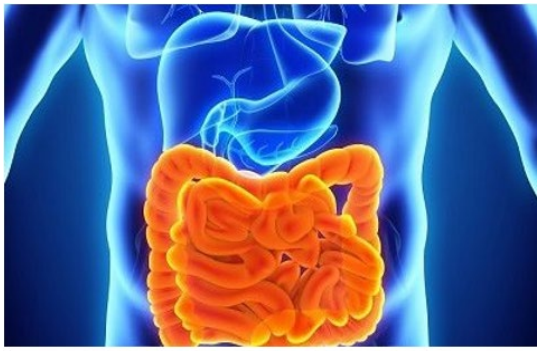

image source: CDC.gov

The major symptoms of UC are diarrhea, rectal bleeding, passage of mucus, bowel urgency, and crampy abdominal pain.[3,4] UC can present abruptly but symptoms are usually present for weeks to months prior. The severity of symptoms correlates positively to the severity of the disease. Longstanding UC is associated with a 2–6-time greater risk of colorectal carcinoma than the general population. Toxic megacolon, a right or transverse colon with dilation >6 cm, occurs rarely and can be brought on by electrolyte imbalances and narcotic use. Mortality associated with toxic megacolon is about 8% if untreated and can reach 15% if complicated by a perforation. Hemorrhage is another major, albeit rare, complication of UC.[4]

The major symptoms of CD are largely influenced by the site of disease. Ileocolitis often presents as right lower quadrant pain with diarrhea and often mimics appendicitis.[3,4] Jejunoileitis presents with diarrhea and malnutrition due to absorption deficiency. Colitis and perianal CD presents similarly to patients with UC but with less gross bleeding and greater risk of strictures causing bowel obstruction. Upper intestinal CD such as gastroduodenal disease presents with nausea, vomiting, and epigastric pain and can sometime be mistaken as a *Helicobacter pylori* infection. Complication associated with CD include fistula formation, strictures with bowel obstruction, and nutritional deficiencies associated with malabsorption. The risk of hemorrhage and carcinoma in CD is less than that in UC but can still occur.

Preventative treatment of IBD

Patients with IBD are at increased risk of malnutrition.[4] It may seem reasonable for patients to make drastic changes to their diet facing a new diagnosis, but that is generally not recommended. Elimination of specific trigger foods may be tried and be beneficial for symptom control, however exclusion diets are not recommended even for severe disease. Food restriction during severe flares may provide bowel rest but also increases the risk of malnourishment.

Patients who use over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) can exacerbate disease activity and should be avoided when possible.[4] NSAIDs cause mucosal permeability which can lead to increased exposure to luminal toxins and antigens which can cause damage to the mucosa of the small intestine such as ulcerations, erosions, and webs.

Cigarette smoking is considered to be protective for UC and a risk factor for CD that can cause flares and should be avoided.[3] Despite it being protective in UC all patients who smoke and use cigarettes should be encouraged to stop and offered nicotine replacement therapy, bupropion, or varenicline as appropriate to aid with smoking cessation.

Patients with UC should be screened for coexistent anxiety and depressive disorder due to the exacerbating effects they can have on UC.[5] If a patient is found to have anxiety or depression, it should be treated and managed.

Treatment approach to IBD

A treat-to-target approach is a commonly utilized strategy in clinical practice to help manage IBD patients, getting them into early remission and prolonging time between flares.[2,3,4] The immediate target is response to therapy according to clinical index scores that monitor symptomatic improvement. An intermediate target is clinical remission which includes normalization of C-reactive protein (CRP) and fecal calprotectin (FCP). The long-term treatment targets are endoscopic remission, improved quality of life, and absences of disability. Histological remission, by evaluation of pathology slides for inflammatory markers after endoscopy, is currently being evaluated as a new treatment target, but there is still uncertainty surrounding its clinical use and implementation.

Many treatment options are available for patients with IBD, and more are currently under investigation. However, there is no cure for IBD. Historically, IBD treatment would begin with the standard care for mild disease such as oral and rectal aminosalicylates regardless of severity.[6] Patients would then be escalated in a "step up" approach based on response and disease progression to more advanced therapies such as biologics or other small molecules. Today the standard of care has become selecting pharmacologic treatment based on severity at presentation. Patients classified as moderate-to-severe should be started on biologics empirically to induce early remission and maintain control.

It is estimated that 30-50% of patients may not respond to treatment and 50% lose response over time.[3] Unfortunately, most patients with IBD will undergo at least one surgery during their illness.[3] Surgical procedures may include resection of affected portions of the intestine or correction of complications. A colectomy may be indicated for UC patients when uncontrolled on maximal therapy or for complications such as toxic megacolon. Also, colectomy may be a preventative procedure against colorectal carcinoma in patients with longstanding disease. Proctocolectomy may be considered curative for ulcerative colitis, but patients are left with a permanent ileostomy that may lower their quality of life and has additional care considerations.

image source: CDC.gov

Surgery for Crohn's disease usually involves resection of affected intestine in segments where the free ends can be reconnected. Unfortunately, up to 50% of patients that undergo surgery will have recurrent CD within 5 years. Patients that undergo multiple surgical resections are at risk of short-bowel syndrome and malabsorption. For that reason, surgery is typically reserved for CD patients until necessitated by severe complications or they are truly medically refractory.

Table 1: Treatment options for Crohn's Disease:

Class:: **- Generic (Brand)**	**Action:**[7]	**Effect:**[8]	**Role in Therapy:**[9, 10]
Glucocorticoids: - Prednisone - Budesonide - Prednisolone - Triamcinolone - Methylprednisolone	Suppression of leukocyte migration and reversing capillary permeability; Reducing volume and activity of lymphatic system	Decreased inflammation. Suppressed immune system	Induction and active symptom control of moderate to severe disease Not intended for long term use No role in maintenance therapy
Aminosalicylates: - Sulfasalazine	Prodrug activated by gut bacteria to active anti-inflammatory mesalamine	Modulates local chemical mediators of the inflammatory response; free radical scavenging; inhibition of tumor necrosis factor	Marginally effective in low-risk mild colonic disease Newer mesalamine derivatives have not shown efficacy.
Thiopurines: - Azathioprine - Mercaptopurine	False purine metabolite that is incorporated into replicating DNA	Disrupts synthesis of DNA in rapidly proliferating immune cells	Adjunct to biologics in moderate to severe disease Effective steroid sparing agents Effective for maintenance of remission
Dihydrofolate reductase inhibitor: - Methotrexate	Folate antimetabolite that binds to and inhibits dihydrofolate reductase	Inhibition of purine synthesis interfering with DNA synthesis, repair, and cellular replication in proliferating cells. May have immune modulator and anti-inflammatory activity in Crohn's Disease	Adjunct to biologics in moderate to severe disease Effective for maintenance of remission of steroid dependent disease
Anti-TNF-α - Infliximab (Remicade) - Adalimumab (Humira) - Certolizumab(Cimzia)	Monoclonal antibodies against the proinflammatory cytokine TNF-α	Blocks TNF-α receptor binding and the subsequent cytokine-driven inflammatory processes	First line for induction or maintenance of remission of moderate to severe disease
Anti-Integrin - Vedolizumab (Entyvio) - Natalizumab (Tysabri)	Humanized anti-alpha-4-beta-7 integrin monoclonal antibody.	Blocks leukocyte migration to sites of inflammation	First Line (Vedolizumab) or second/third line for induction and maintenance of remission in moderate to severe disease
IL12/IL23 inhibitor - Ustekinumab (Stelara)	Humanized monoclonal IgG against the p40 subunit of proinflammatory cytokines IL-12 and IL-23	Blocks activation of $CD4^+$ T-cells and natural killer cells	First line for induction or maintenance of remission of moderate to severe disease
IL23p19 Inhibitor - Risankizumab (Skyrizzi)	Humanized monoclonal antibody against the p19 subunit of proinflammatory cytokine IL-23	Decreases differentiation, expansion, and survival of T cell subsets and innate immune cell subsets	Moderate to severe disease Approved after most recent guidelines.
JAK Inhibitor - Upadacitinib (Rinvoq)	Small molecule inhibitor of Janus kinase enzymes	Prevents cytokine or growth factor-mediated gene expression and intracellular activity of immune cells	Moderate to severe disease Approved after most recent guidelines. Studied in second line after anti-TNF-α biologic

CD = cluster of differentiation IL = interleukin

DNA = deoxyribonucleic acid	TNF = tumor necrosis factor
IgG = Immunoglobulin G	

Table 2: Treatment options for Ulcerative Colitis:

Class:: **- Generic (Brand)**	**Action:**[7]	**Effect:**[8]	**Role in Therapy:**[6,11]
Corticosteroids: - Prednisone - Budesonide - Prednisolone - Triamcinolone - Methylprednisolone	Suppression of leukocyte migration and reversing capillary permeability; Reducing volume and activity of lymphatic system	Decreased inflammation. Suppressed immune system	Induction and active symptom control of moderate to severe disease Not intended for long term use No role in maintenance therapy
Aminosalicylates: - Sulfasalazine - Mesalamine - Balsalazide - Osalazine	Prodrugs (Sulfasalazine, Balsalzide, or Osalazine) activated by gut bacteria to active anti-inflammatory mesalamine	Modulates local chemical mediators of the inflammatory response; free radical scavenging; inhibition of TNF	First line for induction and maintenance of remission in mild disease
Thiopurines: - Azathioprine - Mercaptopurine	False purine metabolite that is incorporated into replicating DNA	Disrupts synthesis of DNA in rapidly proliferating immune cells	Adjunct to biologics in moderate to severe disease Effective steroid sparing agents Effective for maintenance of remission
Calcineurin Inhibitor - Cyclosporine - Tacrolimus	Small molecule that binds intracellular immunophilin forming a complex to inhibit calcineurin	Suppresses production of IL-2 inhibiting T-lymphocyte activation	Acute severe disease in patients unresponsive to intravenous corticosteroids
Anti-TNF-α - Infliximab (Remicade) - Adalimumab (Humira) - Golimumab (Simponi)	Monoclonal antibodies against the proinflammatory cytokine TNF-α	Blocks TNF-α receptor binding and the subsequent cytokine-driven inflammatory processes	First line for induction or maintenance of remission of moderate to severe disease
Anti-Integrin - Vedolizumab (Entyvio)	Humanized anti-α -4-beta-7 integrin monoclonal antibody.	Blocks leukocyte migration to sites of inflammation	First line for induction or maintenance of remission of moderate to severe disease
S1P Receptor Modulator - Ozanimod (Zeposia)	Small molecule antagonist of S1P receptors 1 and 5	Blocks the movement of lymphocytes from the lymph nodes to the intestine	Alternative for induction and maintenance if inadequate response to first line agent in moderate to severe disease
IL12/IL23 inhibitor - Ustekinumab (Stelara)	Humanized monoclonal IgG against the p40 subunit of proinflammatory cytokines IL-12 and IL-23	Blocks activation of $CD4^+$ T-cells and natural killer cells	First line for induction or maintenance of remission of moderate to severe disease
IL23p19 Inhibitor - Mirikizumab (Omvoh)	Humanized monoclonal antibody against the p19 subunit of proinflammatory cytokine IL-23	Decreases differentiation, expansion, and survival of T-cell subsets and innate immune cell subsets	Moderate to severe disease Approved after most recent guidelines.
JAK Inhibitor - Upadacitinib (Rinvoq) - Tofacitinib (Xeljanz)	Small molecule inhibitor of Janus kinase enzymes	Prevents cytokine- or growth factor-mediated gene expression and intracellular activity of immune cells	Second line in moderate to severe disease after anti-TNF-α therapy

CD = cluster of differentiation	IL = interleukin
DNA = deoxyribonucleic acid	S1P = sphingosine 1-phosphate
IgG = Immunoglobulin G	TNF = tumor necrosis factor

Vaccines and IBD:

Because most of the treatment options for IBD suppress the immune system, vaccinations are an important aspect of patient management. Patients with IBD are 15% more likely to be up to date on influenza and pneumococcal vaccinations and 13% more likely to be up to date on tetanus boosters compared to the general population.[12] However, due to patients with IBD being managed by multiple providers vaccines are often overlooked and less than 40% of IBD patients are vaccinated against hepatitis A and B or shingles.[13] Pharmacists are in a unique position to help ensure all IBD patients are up to date on the recommended vaccines prior to or during treatment.

Table 3: Vaccine recommendations for IBD patients based on therapy:[2, 13]

	Aminosalicylates	**Thiopurines**	**Anti-TNF-α**	**JAK-inhibitor**
Influenza	Annually	Annually	Annually	Annually
COVID-19	Recommended to be up to date	Recommended to be up to date	Recommended to be up to date	Recommended to be up to date
Pneumococcal Vaccine	Recommended	Recommended	Recommended	Recommended
Hepatitis A/B	Recommended	Recommended	Recommended	Recommended
Recombinant Zoster	≥ 50 years old	Recommended any age >19 years	Recommended any age >19 years	Recommended any age >19 years
Tdap	Tdap once with booster every 10 years	Tdap once with booster every 10 years	Tdap once with booster every 10 years	Tdap once with booster every 10 years
Meningococcal	Recommended	Recommended	Recommended	Recommended
Any Live Vaccine	Contraindicated. Hold immuno-suppressive therapy ≥4 weeks after last live vaccine	Contraindicated. Hold immuno-suppressive therapy ≥4 weeks after last live vaccine	Contraindicated. Hold immuno-suppressive therapy ≥4 weeks after last live vaccine	Contraindicated. Hold immuno-suppressive therapy ≥4 weeks after last live vaccine

Anti-TNF-α = anti-Tumor Necrosis Factor-α
JAK = Janus Kinase
Tdap = Tetanus, diphtheria, and pertussis
Td = Tetanus and diphtheria

New Approvals for IBD:

FDA approves first oral treatment for moderate to severe Crohn's Disease

On July 5, 2023, the FDA announced that it had approved upadacitinib (Rinvoq), a Janus kinase inhibitor, as the first oral option indicated for the treatment of moderate to severe CD.[14] Upadacitinib had previously been approved for the treatment of moderate to severe UC. The approval comes after the results of three phase 3 trials, two induction studies and one maintenance study.

The U-EXEED induction study included 419 patients with moderate to severe CD who had all had an inadequate response or intolerance to anti-TNF-α therapy.[15] The co-primary endpoint for the trial was clinical remission and endoscopic response at 12 weeks of treatment

with 45 mg upadacitinib once daily by mouth versus placebo. At 12 weeks of treatment more patients treated with upadacitinib achieved clinical remission (38.9%) and endoscopic response (34.6%) compared to placebo (21.1% and 3.5% with respect to the outcomes).

The U-EXCEL induction trial included 526 patients with moderate to severe CD but the majority of them (55%) had no previous exposure to biologic therapy but inadequate response to immunomodulatory treatments.[15] The co-primary endpoint and interventions were the same as the U-EXEED trial, being clinical remission and endoscopic response at 12 weeks of treatment on 45 mg upadacitinib once daily by mouth versus placebo. At 12 weeks of treatment more patients treated with upadacitinib achieved clinical remission (49.5%) and endoscopic response (45.5%) compared to placebo (29.1% and 13.1% with respect to the outcomes).

For the U-ENDURE maintenance trial 502 patients that achieved clinical response in both the U-EXCEL and U-EXCEED were re-randomized to receive either 15 mg upadacitinib, 30 mg upadacitinib, or placebo.[15] The co-primary outcomes were clinical remission and endoscopic response at 52 weeks of treatment. Clinical remission was achieved in more patients in the 30 mg group (47.6%) compared to the 15 mg group (37.3%) and the placebo group (15.1%). A similar trend was seen for endoscopic response being achieved most in the 30 mg group (33.7%) compared to the 15 mg group (27.6%) and the placebo group (7.3%).

FDA approves new anti-IL23p19 biologic for the treatment of moderate to severe UC:

On October 26th, 2023 the FDA granted marketing approval for mirikizumab-mrkz (Omvoh), a new IL23p19 inhibitor, based on the efficacy and safety results from the LUCENT program which included two phase three clinical trials UC-1 and UC-2.[16] Both trials were randomized, double-blinded, placebo-controlled trials that included patients with moderate to severe UC who had inadequate response, loss of response, or were unable to tolerate other first line agents. UC-1 included 1,279 patients and evaluated the effect of mirikizumab on clinical remission at 12 weeks as the primary endpoint and key secondary endpoints of clinical response, endoscopic improvement, and histologic-endoscopic mucosal improvement also at 12 weeks. More patients who took mirikizumab achieved clinical remission (24%) compared to those on placebo (15%).

The UC-2 maintenance phase study re-randomized 581 patients from UC-1 that had a clinical response to either receive mirikizumab (300 mg IV) or placebo.[16] The primary endpoint of UC-2 was clinical remission at 40 weeks or 52 weeks of total treatment at that point. By the 40-week endpoint more patients taking mirikizumab achieved clinical remission (51%) compared to placebo (27%). Also, more mirikizumab increased steroid-free remission (50%) compared to placebo (27%) with most of those patients (99%) being steroid free for at least 12 weeks at that point.

Mirikizumab (Omvoh) joins risankizumab (Skyrizzi) as another anti-IL23p19 biologic for the treatment of IBD.[17] Mirikizumab is only approved for the treatment of ulcerative colitis while risankizumab is currently only approved for the treatment of Crohn's disease.[16,17] Both agents are currently in phase 3 trials for new indication approvals in the other respective patient groups of IBD.[18,19]

Etrasimod for treating moderate to severe ulcerative colitis:

Etrasimod (Velsipity) was approved by the FDA on October 13, 2023. Etrasimod is an oral, once-daily sphingosine 1-phosphate (S1P) receptor modulator for treating adults with moderate to severe active ulcerative colitis.[5] The approval from the FDA was based on safety and efficacy data from the ELEVATE UC Phase 3 trials. The ELEVATE trials included two independent randomized multicenter, double-blind, placebo-controlled trials that studied adults with active moderate-to-severe ulcerative colitis with inadequate response or loss of response to prior therapy. In the induction phase of the trial including over 780 patients, etrasimod 2 mg daily resulted in higher rates of clinical remission than placebo after 12 weeks (25% to 27% versus 7% to 15%). In the maintenance phase of this trial, etrasimod resulted in higher rates of sustained clinical remission after 52 weeks (32% versus 7%).

Table 4: Summary of new approved treatments for IBD:

Medication:	Drug Class:	Indication:	Importance:	Manufacturer	Approval Date:	Other indications:
Mirikizumab (Omvoh)	Humanized monoclonal antibody	Moderate-to-severe UC	First IL-23p19 inhibitor approved in UC	Eli Lilly and Company	October 26, 2023	Novel molecular entity
Etrasimod (Velsipity)	Small Molecule S1P receptor modulator	Moderate-to-severe UC	Novel mechanism of action in the treatment of UC	Pfizer	October 13, 2023	Novel molecular entity
Upadacitinib (Rinvoq)	Small molecule JAK inhibitor	Moderate-to-severe CD	First oral treatment option in moderate-to-severe CD	AbbVie	July 5, 2023	- Atopic dermatitis - Rheumatoid arthritis - Psoriatic arthritis - Ulcerative colitis - Ankylosing spondylitis - Non-radiographic axial spondylarthritis

CD = Crohn's disease S1P = sphingosine 1-phosphate
IL = interleukin UC = ulcerative colitis
JAK = Janus kinase

The last "dose" …

"Life takes us on unexpected paths. Although we may not anticipate the twists and turns we face, they become very much a part of our personal journey. As a woman living with Crohn's disease for the past 20 years, I've faced a lot of uncertainty. I've undergone major surgeries and numerous extended hospitalizations that have challenged me physically and mentally. Conquering these many physical battles has made me stronger and more resilient. And for that, I am grateful."

- Rocio Castrillon, [IBD Patient and Advocate, Grateful for Life With IBD]

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