Chapter 26: Inflammatory Bowel Disease

INTRODUCTION

- There are two forms of idiopathic *inflammatory bowel disease* (IBD): ulcerative colitis (UC), a mucosal inflammatory condition confined to the rectum and colon, and Crohn disease (CD), a transmural inflammation of gastrointestinal (GI) mucosa that may occur in any part of the GI tract. The etiologies of both conditions are unknown, but they may have a common pathogenic mechanism.

ETIOLOGY AND PATHOPHYSIOLOGY

- Factors that cause IBD include infectious agents, genetics, the environment, and the immune system. This may involve abnormal regulation of the innate immune response or a reaction to various antigens. The microflora of the GI tract may provide an environmental trigger to activate inflammation in genetically susceptible individuals and is highly implicated in the development of IBD.
- Suspect infectious agents include viruses, protozoans, mycobacteria such as *Mycobacterium paratuberculosis* or *avium*, and other bacteria such as *Ruminococcus gnavus, Ruminococcus torques, Listeria monocytogenes, Chlamydia trachomatis*, and *Escherichia coli*.
- Th1 cytokine activity is excessive in CD, and increased expression of interferon-γ in the intestinal mucosa and production of IL-12 are features of the immune response in CD. In contrast, Th2 cytokine activity is excessive with UC (with excess production of IL-13). Tumor necrosis factor-α (TNF-α) is a pivotal proinflammatory cytokine that is increased in the mucosa and intestinal lumen of patients with CD and UC.
- Antineutrophil cytoplasmic antibodies are found in a high percentage of patients with UC and less frequently with CD.
- Smoking appears to be protective for UC but associated with increased frequency of CD. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) may trigger disease occurrence or lead to disease flares.
- UC and CD differ in two general respects: anatomical sites and depth of involvement within the bowel wall. There is, however, overlap between the two conditions, with a small fraction of patients showing features of both diseases (**Table 26-1**).

TABLE 26-1

Comparison of the Clinical and Pathologic Features of Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Clinical		
Malaise, fever	Common	Uncommon
Rectal bleeding	Common	Common
Abdominal tenderness	Common	May be present
Abdominal mass	Common	Absent
Abdominal pain	Common	Unusual
Abdominal wall and internal fistulas	Common	Absent
Distribution	Discontinuous	Continuous
Aphthous or linear ulcers	Common	Rare
Pathologic		
Rectal involvement	Rare	Common
Ileal involvement	Very common	Rare
Strictures	Common	Rare
Fistulas	Common	Rare
Transmural involvement	Common	Rare
Crypt abscesses	Rare	Very common
Granulomas	Common	Rare
Linear clefts	Common	Rare
Cobblestone appearance	Common	Absent

Ulcerative Colitis

- UC is confined to the colon and rectum and affects primarily the mucosa and the submucosa. The primary lesion occurs in the crypts of the mucosa (crypts of Lieberkühn) in the form of a crypt abscess.
- Local complications (involving the colon) occur in the majority of patients with UC. Relatively minor complications include hemorrhoids, anal fissures, and perirectal abscesses.

- A major complication is toxic megacolon, a severe condition that occurs in up to 7.9% of UC patients admitted to hospitals. Patients with toxic megacolon usually have a high fever, tachycardia, distended abdomen, elevated white blood cell count, and a dilated colon.
- The risk of colonic carcinoma is much greater in patients with UC than in the general population.
- Patients with UC may have hepatobiliary complications, including fatty liver, pericholangitis, chronic active hepatitis, cirrhosis, sclerosing cholangitis, cholangiocarcinoma, and gallstones.
- Arthritis commonly occurs in patients with IBD and is typically asymptomatic and migratory. Arthritis typically involves one or a few large joints, such as the knees, hips, ankles, wrists, and elbows.
- Ocular complications (iritis, episcleritis, and conjunctivitis) occur in some patients. Skin and mucosal lesions associated with IBD include erythema nodosum, pyoderma gangrenosum, aphthous ulceration, and Sweet syndrome.

Crohn Disease

- CD is a transmural inflammatory process. The terminal ileum is the most common site, but it may occur in any part of the GI tract. Most patients have some colonic involvement. Patients often have normal bowel separating segments of diseased bowel; that is, the disease is often discontinuous.
- Complications of CD may involve the intestinal tract or organs unrelated to it. Small bowel stricture with subsequent obstruction is a complication that may require surgery. Fistula formation is common and occurs much more frequently than with UC.
- Systemic complications of CD are common and similar to those found with UC. Arthritis, iritis, skin lesions, and liver disease often accompany CD.
- Nutritional deficiencies are common with CD (including deficiencies of folate, vitamin B_{12}, vitamins A to D, calcium, magnesium, iron, and zinc).

CLINICAL PRESENTATION

Ulcerative Colitis

- There is a wide range of presenting symptoms in UC, from mild abdominal cramping with frequent small-volume bowel movements to profuse diarrhea (**Table 26-2**). Many patients have disease confined to the rectum (proctitis).
- Most patients with UC experience intermittent bouts of illness after varying intervals of no symptoms.
- Mild disease, which afflicts two-thirds of patients, has been defined as fewer than four stools daily, with or without blood, with no systemic disturbance and a normal erythrocyte sedimentation rate (ESR <30 mm/hr).
- Patients with moderate disease have more than four stools per day but with minimal systemic disturbance.
- With severe disease, the patient has more than six stools per day with blood, with systemic manifestations of fever, tachycardia, anemia, or ESR greater than 30 mm/hr (8.3 µm/sec). With fulminant disease there are more than 10 bowel movements per day with continuous bleeding, toxicity, abdominal tenderness, requirement for transfusion, and colonic dilation.

TABLE 26-2

Clinical Presentation of Ulcerative Colitis

Signs and symptoms • Abdominal cramping • Frequent bowel movements, often with blood in the stool • Weight loss • Fever and tachycardia in severe disease • Blurred vision, eye pain, and photophobia with ocular involvement • Arthritis • Raised, red, tender nodules that vary in size from 1 cm to several centimeters
Physical examination • Hemorrhoids, anal fissures, or perirectal abscesses may be present • Iritis, uveitis, episcleritis, and conjunctivitis with ocular involvement • Dermatologic findings with erythema nodosum, pyoderma gangrenosum, or aphthous ulceration
Laboratory tests • Decreased hematocrit/hemoglobin • Increased ESR, CRP, and fecal calprotectin • Leukocytosis and hypoalbuminemia with severe disease • (+) perinuclear antineutrophil cytoplasmic antibodies

Crohn Disease

- As with UC, the presentation of CD is highly variable (**Table 26-3**). A patient may present with diarrhea and abdominal pain or a perirectal or perianal lesion. Patients with mild-to-moderate CD are typically ambulatory and have no evidence of dehydration, systemic toxicity, less than 10% loss of body weight, or abdominal tenderness, mass, or obstruction.
- The course of CD is characterized by periods of remission and exacerbation. Some patients may be free of symptoms for years, whereas others experience chronic problems despite medical therapy.
- The Crohn Disease Activity Index (CDAI) is used to gauge response to therapy and determine remission. Disease activity may be assessed and correlated by evaluation of serum C-reactive protein concentrations.

TABLE 26-3

Clinical Presentation of Crohn Disease

Signs and symptoms • Malaise and fever • Abdominal pain • Frequent bowel movements • Hematochezia • Fistula • Weight loss and malnutrition • Arthritis
Physical examination • Abdominal mass and tenderness • Perianal fissure or fistula
Laboratory tests • Increased white blood cell count, ESR, CRP, and fecal calprotectin • (+) anti–*Saccharomyces cerevisiae* antibodies

TREATMENT

- Goals of Treatment: Resolution of acute inflammatory processes, resolution of attendant complications (eg, fistulas or abscesses), alleviation of systemic manifestations (eg, arthritis), maintenance of remission from acute inflammation, or surgical palliation or cure.
- Treatment often involves use of specific targets, such as mucosal healing and endoscopic remission, or resolution of symptoms such as abdominal pain and diarrhea, as the main indicators of treatment efficacy (referred to as “Treat to Target”).

Nonpharmacologic Treatment

- Protein–energy malnutrition and suboptimal weight are reported in up to 85% of patients with CD. The nutritional needs of the majority of patients can be adequately addressed with enteral supplementation.
- Elimination of specific foods that appear to exacerbate symptoms can be tried; however, exclusion diets are generally not endorsed, even in the setting of severe disease.
- Parenteral nutrition is generally reserved for patients with severe malnutrition or those who fail enteral therapy or have a contraindication to receiving enteral therapy, such as perforation, protracted vomiting, short bowel syndrome, or severe intestinal stenosis.
- While probiotics are considered to be generally safe in patients with IBD, the added cost and requirement to often take multiple doses per day, coupled with the lack of quality data to support their use, should weigh into the decision to use them in IBD.
- Colectomy may be necessary for UC patients with disease uncontrolled by maximum medical therapy or when there are disease complications such as colonic perforation, toxic megacolon, uncontrolled colonic hemorrhage, or colonic strictures.
- Surgery in patients with CD is usually reserved for patients with intractable hemorrhage, perforation, persistent or recurrent obstruction, abscess, dysplasia, cancer, or medically refractory disease. CD has a high recurrence rate after surgery.

Pharmacologic Therapy

- The major drug therapies used in IBD are **aminosalicylates; corticosteroids**; immunomodulators (**azathioprine**, **mercaptopurine**, and **methotrexate**); immunosuppressive agents (**cyclosporine** and **tacrolimus**); antimicrobials (**metronidazole** and **ciprofloxacin**); and agents to inhibit TNF-α (anti–TNF-α antibodies), leukocyte adhesion and migration (**natalizumab** and **vedolizumab**), interleukin function (**ustekinumab**), or Janus kinase function (**tofacitinib**).
- **Sulfasalazine** combines a sulfonamide (sulfapyridine) antibiotic and mesalamine (5-aminosalicylic acid) in the same molecule. Oral **mesalamine** derivatives are alternatives to sulfasalazine for treatment of mild-to-moderate UC with similar rates of efficacy. Mesalamine-based products are listed in **Table 26-4**.
- Oral corticosteroids in doses of 40–60 mg/day **prednisone** equivalent can be used for patients with moderate to extensive disease who are refractory to oral aminosalicylates or require more rapid control of symptoms.
- Immunomodulators such as azathioprine, mercaptopurine (a metabolite of azathioprine), methotrexate, or cyclosporine are used in the long-term treatment of IBD. These agents are generally reserved for patients who fail aminosalicylate therapy or are refractory to or dependent on corticosteroids.
- Cyclosporine has a short-term benefit in the treatment of acute, severe UC to avoid colectomy in patients failing corticosteroids but has little efficacy in CD.
- Methotrexate 15–25 mg intramuscularly or subcutaneously once weekly is useful for treatment and maintenance of CD and may be steroid sparing.
- Antimicrobial agents, particularly metronidazole and ciprofloxacin, are frequently used in attempts to control CD, particularly when it involves the perineal area or fistulas.
- **Infliximab** is an anti-TNFα antibody that is useful in moderate-to-severe active CD and UC as well as steroid-dependent or fistulizing disease, both as induction and maintenance therapy. **Adalimumab** is another anti-TNFα (fully humanized) antibody that is an option for patients with moderate-to-severe active CD or UC previously treated with infliximab who have lost response.
- Natalizumab and vedolizumab are leukocyte adhesion and migration inhibitors that are used for patients with CD who are unresponsive to other therapies.

TABLE 26-4

Agents for the Treatment of Inflammatory Bowel Disease

Drug	Brand Name	Initial Dose (g)	Usual Range
Sulfasalazine	Azulfidine	500 mg–1 g	4–6 g/day
	Azulfidine EN	500 mg–1 g	4–6 g/day
Mesalamine suppository	Rowasa	1 g	1 g daily to three times weekly
Mesalamine enema	Canasa	4 g	4 g daily to three times weekly
Mesalamine (oral)	Asacol HD	1.6 g/day	2.8–4.8 g/day
	Apriso	1.5 g/day	1.5 g/day once daily

	Lialda	1.2–2.4 g/day	1.2–4.8 g/day once daily
	Pentasa	2 g/day	2–4 g/day
	Delzicol	1.2 g/day	2.4–4.8 g/day
Olsalazine	Dipentum	1.5 g/day	1.5–3 g/day
Balsalazide	Colazal	2.25 g/day	2.25–6.75 g/day
Azathioprine	Imuran, Azasan	50–100 mg	1–2.5 mg/kg/day
Cyclosporine	Gengraf	2–4 mg/kg/day IV	2–4 mg/kg/day IV
	Neoral, Sandimmune	2–8 mg/kg/day oral	
Mercaptopurine	Purinethol	50–100 mg	1–2.5 mg/kg/day
Methotrexate	No branded IM injection	15–25 mg IM weekly	15–25 mg IM weekly
Adalimumab Adalimumab-atto Adalimumab-abdm	Humira Amjevita Cyltezo	160 mg SC day 1	80 mg SC 2 (day 15), and then 40 mg every 2 weeks
Certolizumab	Cimzia	400 mg SC	400 mg SC weeks 2 and 4, and then 400 mg SC monthly
Infliximab Infliximab-dyyb Infliximab-abda Infliximab-qbtx	Remicade Inflectra Renflexis IXIFI	5 mg/kg IV	5 mg/kg weeks 2 and 6, 5–10 mg/kg every 8 weeks
Natalizumab	Tysabri	300 mg IV	300 mg IV every 4 weeks
Budesonide	Entocort EC capsule, Uceris tablet	9 mg orally once daily	6–9 mg daily
	Uceris rectal foam	2 mg twice daily	2 mg daily
Vedolizumab	Entyvio	300 mg IV	300 mg IV weeks 2 and 6 and then every 8 weeks
Golimumab	Simponi	200 mg SC	100 mg SC weeks 2 and 4
Ustekinumab	Stelara	Weight-based initial IV dose <55 kg (260 mg), 55–85 kg (390 mg), >85 kg (520 mg)	90 mg SC every 8 weeks
Tofacitinib	Xeljanz	10 mg twice daily for 8 weeks; may continue for maximum of 16 weeks	5 mg twice daily

IM, intramuscular; SC, subcutaneous.

Ulcerative Colitis

Mild-to-Moderate Disease

- Most patients with mild-to-moderate active UC can be managed on an outpatient basis with oral and/or topical aminosalicylates (**Fig. 26-1**). For patients with extensive disease, oral once-daily mesalamine is generally preferred in doses of 2–3 g/day. Doses greater than 3 g/day can be used in patients who are unresponsive to standard doses and generally should be combined with a rectal mesalamine formulation at a dose of 1 g/day.
- Oral mesalamine derivatives (see **Table 26-4**) are reasonable alternatives to sulfasalazine for treatment of UC because they are better tolerated. Topical mesalamine in an enema or suppository formulation is more effective than oral mesalamine or topical steroids for distal disease.
- **Budesonide** 9 mg/day is preferred for patients who are unresponsive to optimized doses of mesalamine.

FIGURE 26-1

Treatment approaches for ulcerative colitis.

AZA, azathioprine; MMX, Multi-Matrix System; MP, mercaptopurine; TNF, tumor necrosis factor.

image

Moderate-to-Severe Disease

- Oral mesalamine products may be effective for moderately severe UC, but budesonide is an alternative before using more systemic corticosteroids and is preferred for moderate disease.
- Steroids have a place in the treatment of moderate-to-severe UC or in patients who are unresponsive to maximal doses of oral and topical mesalamine. Oral corticosteroids in doses of 40–60 mg prednisone equivalent daily are recommended for adults.
- TNF-α inhibitors are an option for patients with moderate-to-severe disease who are unresponsive to aminosalicylates, corticosteroids, or other immunosuppressive agents. In general infliximab, adalimumab, and golimumab and their respective biosimilars have similar rates of efficacy when used as monotherapy in UC.

Severe or Intractable Disease

- Patients with uncontrolled severe UC or incapacitating symptoms require hospitalization for effective management. Most medications are given parenterally. Patients should be tested for *Clostridoidies difficile* infection and receive venous thromboembolism (VTE) prophylaxis.
- IV **hydrocortisone** 300 mg daily in three divided doses or **methylprednisolone** 60 mg once daily for 3–5 days is considered a first-line agent. A trial of corticosteroids is warranted in most patients before proceeding to colectomy, unless the condition is grave or rapidly deteriorating.
- Patients who are unresponsive to parenteral corticosteroids after 3–7 days can receive cyclosporine or infliximab. A continuous IV infusion of cyclosporine 2–4 mg/kg/day is the typical dose range used and may delay the need for colectomy.

Maintenance of Remission

- Once remission from active disease has been achieved, the goal of therapy is to maintain the remission.
- The major agents used for maintenance of remission are sulfasalazine and the newer mesalamine derivatives, infliximab, adalimumab and its biosimilars, golimumab, and azathioprine or mercaptopurine.
- Oral agents, including sulfasalazine, mesalamine, and **balsalazide**, are all effective options for maintenance therapy. The optimal dose to

prevent relapse is 2–2.4 g/day of mesalamine equivalent, with rates of relapse over 6–12 months reported as 40%.

- Steroids do not have a role in the maintenance of remission with UC because they are ineffective. Steroids should be withdrawn gradually over 2–4 weeks after remission is induced.

Crohn Disease

Active Crohn Disease

- Mesalamine derivatives have not demonstrated significant efficacy in CD. They are often tried as an initial therapy for mild-to-moderate CD given their favorable adverse effect profile.
- Mesalamine derivatives that release mesalamine in the small bowel (eg, Pentasa) may be more effective than sulfasalazine for ileal involvement.
- Systemic corticosteroids are frequently used for treating moderate-to-severe active CD; however, controlled-release budesonide (Entocort) 9 mg daily is a preferred first-line option for patients with mild-to-moderate ileal or right-sided (ascending colonic) disease.
- Oral corticosteroids, such as prednisone 40–60 mg/day, are generally considered first-line therapy and are frequently used for moderate-to-severe CD unresponsive to aminosalicylates.
- Metronidazole 10–20 mg/kg/day orally in divided doses may be useful in some patients with CD, particularly for patients with colonic or ileocolonic involvement, those with perineal disease, or those who are unresponsive to sulfasalazine.
- Azathioprine, mercaptopurine, and methotrexate are not recommended to induce remission in moderate-to-severe CD; however, they are effective in maintaining steroid-induced remission and are generally limited to use for patients not achieving adequate response to standard medical therapy or in the setting of steroid dependency.
- Clinical response to azathioprine and mercaptopurine may be related to whole-blood concentrations of the metabolite 6-thioguanine (TGN). Concentrations of TGN greater than 230–450 pmol/8 × 10^8 erythrocytes have beneficial effects, but monitoring is not routinely performed or may not be available at some sites.
- Patients deficient in thiopurine S-methyltransferase (TPMT) are at greater risk of bone marrow suppression from azathioprine and mercaptopurine. Determination of TPMT or TPMT genotype is recommended to guide dosage.
- Methotrexate given weekly intramuscularly or subcutaneously in doses of 15–25 mg is effective in reducing steroid dependency and maintaining remission, and may be considered as an alternative to azathioprine or mercaptopurine.
- The TNF-α inhibitors are the most effective and thus the preferred agents in managing moderate to severe CD. All agents in this class, with the exception of golimumab, which is not approved for use in CD in the United States, have similar rates of efficacy. The use of TNF-α inhibitors in combination with thiopurines has quickly become the preferred approach to treatment of moderate-to-severe CD.
- The integrin antagonists are options for patients who do not respond to steroids or TNF-α inhibitors, and vedolizumab is also considered a first-line alternative to TNF-α inhibitors for moderate-to-severe disease.

Maintenance of Remission

- Prevention of recurrence of disease is more difficult with CD than with UC. There is minimal evidence that sulfasalazine and oral mesalamine derivatives are effective for maintenance of CD remission following medically induced remission, and therefore these agents are not preferred (**Fig. 26-2**).
- Systemic steroids have no role in the maintenance of remission or prevention of recurrence of CD; these agents do not appear to alter the long-term course of the disease. Budesonide can be considered for maintenance therapy for up to 4 months.
- All of the TNF-α inhibitors currently approved for use in CD are viable options for maintenance of remission. Combination therapy with a

thiopurine should be highly considered to further improve efficacy and to extend the duration of TNF-α inhibitor efficacy by reducing immunogenicity.

- There is weak evidence to suggest that methotrexate is effective in maintaining remission in CD.

FIGURE 26-2

Treatment approaches for Crohn disease.

image

Select Complications

Toxic Megacolon

- The treatment required for toxic megacolon includes general supportive measures to maintain vital functions, consideration for early surgical intervention, and antimicrobials.
- Aggressive fluid and electrolyte management are required for dehydration. When the patient has lost significant amounts of blood (through the rectum), blood transfusion may be necessary.
- Steroids in high doses (eg, hydrocortisone 100 mg every 8 hours) should be administered IV to reduce acute inflammation.
- Broad-spectrum antimicrobials that include coverage for gram-negative bacilli and intestinal anaerobes should be used as preemptive therapy if perforation occurs.

Extraintestinal Manifestations

- For arthritis, **aspirin** or another NSAID may be beneficial, as are corticosteroids. However, NSAID use may exacerbate the underlying IBD and predispose patients to GI bleeding.
- Anemia secondary to blood loss from the GI tract can be treated with oral **ferrous sulfate**. **Vitamin B_{12}** or **folic acid** may also be required.
- If the patient is deemed high risk for osteoporosis or exhibits a reduced serum vitamin D concentration, **vitamin D** and **calcium** should be administered. If osteoporosis is present, then calcium, vitamin D, and a **bisphosphonate** or possibly **teriparatide** are recommended.

EVALUATION OF THERAPEUTIC OUTCOMES

- See **Table 26-5** for drug monitoring guidelines.
- Patients receiving sulfasalazine should receive oral **folic acid** supplementation because sulfasalazine inhibits folic acid absorption.
- The success of therapeutic regimens to treat IBDs can be measured by patient-reported complaints, signs and symptoms, direct physician examination (including endoscopy), history and physical examination, select laboratory tests, and quality of life measures.
- Adverse effects of corticosteroids include hyperglycemia, hypertension, osteoporosis, acne, fluid retention, electrolyte disturbances, myopathies, muscle wasting, increased appetite, psychosis, infection, and adrenocortical suppression. To minimize corticosteroid effects, clinicians may use alternate-day steroid therapy; however, some patients do not do well clinically on the days when no steroid is given.
- To create more objective measures, disease-rating scales or indices have been created. CDAI is a commonly used scale, particularly for evaluation of patients during clinical trials. The scale incorporates eight elements: (1) number of stools in the past 7 days, (2) sum of abdominal pain ratings from the past 7 days, (3) rating of general well-being in the past 7 days, (4) use of antidiarrheals, (5) body weight, (6) hematocrit, (7) finding of abdominal mass, and (8) a sum of symptoms present in the past week.

- Standardized assessment tools have also been constructed for UC. Elements in these scales include: (1) stool frequency; (2) presence of blood in the stool; (3) mucosal appearance (from endoscopy); and (4) physician's global assessment based on physical examination, endoscopy, and laboratory data.

TABLE 26-5

Drug Monitoring Guidelines

Drug(s)	Adverse Drug Reaction	Monitoring Parameters	Comments
Sulfasalazine	Nausea, vomiting, headache Rash, anemia, pneumonitis Hepatotoxicity, nephritis Thrombocytopenia, lymphoma	Folate, complete blood count Liver function tests, Scr, BUN	Increase the dose slowly, over 1–2 weeks
Mesalamine	Nausea, vomiting, headache	GI disturbances	
Corticosteroids	Hyperglycemia, dyslipidemia Osteoporosis, hypertension, acne Edema, infection, myopathy, psychosis	Blood pressure, fasting lipid panel Glucose, vitamin D, bone density	Avoid long-term use if possible or consider budesonide
Azathioprine/Mercaptopurine	Bone marrow suppression, pancreatitis, Lymphoma Liver dysfunction, rash, arthralgia	Complete blood count Scr, BUN, liverfunction tests, genotype/phenotype	Check TPMT activity May monitor TGN
Methotrexate	Bone marrow suppression, pancreatitis Pneumonitis, pulmonary fibrosis, hepatitis	Complete blood count, Scr, BUN Liver function tests	Check baseline pregnancy test Chest x-ray
Infliximab Adalimumab Certolizumab Golimumab	Infusion-related reactions (infliximab), infection Heart failure, optic neuritis, demyelination, injection site reaction, signs of infection	Blood pressure/heart rate (infliximab) Neurologic exam, mental status Trough concentrations (infliximab) Antidrug antibodies (all agents)	Need negative PPD and viral serologies
Natalizumab Vedolizumab	Infusion-related reactions	Brain MRI, mental status, progressive multifocal leukoencephalopathy	Vedolizumab not associated with PML
Ustekinumab	Infections, skin cancers	Signs/symptoms of infection, annual skin exam	Rare instances of reversible posterior leukoencephalopathy syndrome (RPLS) Avoid live vaccines
Tofacitinib	Infection, thrombosis, lymphoma, elevated cholesterol, CK, LFTs, lymphopenia, neutropenia, anemia	Symptoms of infection or thrombosis	Avoid live vaccines Screen for baseline TB Do not initiate in patients with lymphocytes <500/mm^3, ANC

			<1000/mm^3, or hemoglobin <9 g/dL Monitor lipids and LFTs every 4–8 weeks Gastrointestinal perforation has been reported with use of the XR formulation Drug interactions with CYP3A4 and 2C19 inhibitors

ANC, absolute neutrophil count; BUN, blood urea nitrogen; CK, creatine kinase; GI, gastrointestinal; LFTs, liver function tests; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; PPD, purified protein derivative; SCr, serum creatinine; TGN, thioguanine; TPMT, thiopurine methyltransferase; XR, extended-release.

See Chapter 51, Inflammatory Bowel Disease, authored by Brian A. Hemstreet, for a more detailed discussion of this topic.