REVIEW

Current approaches to the management of new-onset ulcerative colitis

Renée Marchioni Beery[1]
Sunanda Kane[2]

[1]Division of Gastroenterology and Hepatology, University of Connecticut Health Center, Farmington, CT, USA;
[2]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Abstract: Ulcerative colitis (UC) is an idiopathic, inflammatory gastrointestinal disease of the colon. As a chronic condition, UC follows a relapsing and remitting course with medical maintenance during periods of quiescent disease and appropriate escalation of therapy during times of flare. Initial treatment strategies must not only take into account current clinical presentation (with specific regard for extent and severity of disease activity) but must also take into consideration treatment options for the long-term. The following review offers an approach to new-onset UC with a focus on early treatment strategies. An introduction to the disease entity is provided along with an approach to initial diagnosis. Stratification of patients based on clinical parameters, disease extent, and severity of illness is paramount to determining course of therapy. Frequent assessments are required to determine clinical response, and treatment intensification may be warranted if expected improvement goals are not appropriately reached. Mild-to-moderate UC can be managed with aminosalicylates, mesalamine, and topical corticosteroids with oral corticosteroids reserved for unresponsive cases. Moderate-to-severe UC generally requires oral or intravenous corticosteroids in the short-term with consideration of long-term management options such as biologic agents (as initial therapy or in transition from steroids) or thiopurines (as bridging therapy). Patients with severe or fulminant UC who are recalcitrant to medical therapy or who develop disease complications (such as toxic megacolon) should be considered for colectomy. Early surgical referral in severe or refractory UC is crucial, and colectomy may be a life-saving procedure. The authors provide a comprehensive evidence-based approach to current treatment options for new-onset UC with discussion of long-term therapeutic efficacy and safety, patient-centered perspectives including quality of life and medication compliance, and future directions in related inflammatory bowel disease care.

Keywords: ulcerative colitis, inflammatory bowel disease, new-onset treatment, acute management

Introduction

Ulcerative colitis (UC) is a chronic, idiopathic, inflammatory disease limited to the colon. Inflammation involves the rectum in a majority (95%) of patients and extends proximally in a continuous and circumferential fashion.[1] Disease may involve the entire colorectum (termed pancolitis) or only parts of it as manifested in cases of proctitis (limited to the rectum) or left-sided colitis (involving the sigmoid colon with or without descending colon). A few patients may develop limited terminal ileal involvement (backwash ileitis) that can be difficult to differentiate from Crohn's ileocolitis.

UC presents clinically as abdominal pain and bloody diarrhea commonly associated with symptoms of rectal urgency and tenesmus. Extraintestinal manifestations are common. The diagnosis is suspected based on clinical history after exclusion of

Correspondence: Renée Marchioni Beery
Division of Gastroenterology and Hepatology, 263 Farmington Avenue, Farmington, CT 06030-1845, USA
Tel +1 860 679 3158
Fax +1 860 679 3159
Email marchioni@uchc.edu

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infectious and noninfectious etiologies[2] and is supported by both characteristic endoscopic findings and histologic confirmation.[1] Endoscopic features include continuous mucosal ulceration from the rectum with erythema, friability, and loss of typical vascular pattern. Histologic features include crypt architectural distortion, cryptitis, and crypt abscesses. Mucosal inflammation is generally superficial, although patients with severe UC may develop transmural inflammation and deep colonic ulcerations that increase the risk of toxic megacolon. Severe symptoms are less commonly seen with left-sided colitis and proctitis.

As a chronic disease, UC is characterized by periods of relapse and remission with flares of disease activity occurring spontaneously or provoked by certain aggravating factors such as intercurrent illness, antibiotic use, or nonadherence with medical therapy. Achieving control over active disease and maintaining patients in steroid-free remission are the optimal goals of therapy. This review will provide an introduction to UC with focus on treatment strategies for the management of new-onset cases.

Epidemiology

Inflammatory bowel disease (IBD), encompassing both UC and Crohn's disease (CD), has been increasing in incidence and prevalence in various regions of the globe with the highest rates in North America and Europe.[3] A recent study using a large, regionally diverse population of commercially insured individuals in the US revealed a prevalence of 263 (95% confidence interval [CI] 260–266) per 100,000 for adult UC as of 2009. It is estimated that approximately 593,000 Americans have UC and that there has been a slight increase in the prevalence of IBD over time.[4] Regional variation in the US has been reported for adult UC, with a lower prevalence in the South and West as compared with the Northeast and Midwest.[4] In two large prospective cohorts of US women, the incidence of IBD was significantly lower among females living in southern versus northern latitudes, and residence beyond age 30 years was more strongly associated with risk.[5]

The onset of IBD has a bimodal distribution with a higher peak in the younger population aged 15–30 years; 50% of patients afflicted by IBD are diagnosed before age 35 years.[6,7] Most studies reveal a male:female ratio of about 1:1 across all ages.[8] Standardized disease-related mortality in UC is similar to that of the general population. Additionally, the cause of death in UC is overall comparable to that of the general population and is related to UC or its associated illnesses in approximately 17% of cases.[9]

The standardized incidence ratio of colorectal cancer in IBD patients is 1.7 (95% CI 1.2–2.2) and increases to 6.4 (95% CI 2.4–17.5) in patients with extensive colitis.[10] Despite recent therapeutic advances, morbidity remains high and can significantly impact a patient's quality of life (QOL).

Economic burden

The US economic burden of UC is increasing and has been estimated at approximately US$8.1–14.9 billion annually with total direct costs of about $3.4–8.6 billion.[11,12] US health care-associated treatment costs for UC totaled approximately $2.1 billion in 2008.[12] The estimated yearly per-patient direct medical cost of UC ranges from $6,217–11,477 with hospitalizations accounting for roughly 41%–55%; indirect costs comprise about one-third of the total US cost.[11] From 1998–2004, the overall hospitalization rate for UC was 10.8 per 100,000 with approximately 214,498 inpatient admissions for UC and an average hospital length of stay of 6.8 days.[13] Inpatient charges related to UC rose over time to an estimated annual total of $945 million nationally.[13] A significant increase in the number and incidence of US hospitalizations has been reported in the pediatric IBD population with 22,328 children carrying a hospital discharge diagnosis of UC and 7,127 children hospitalized for UC (incidence 15.2–26.0 cases per 100,000; $P<0.001$) from 2000–2009; this has also been linked to a significant increase in IBD-related complications (such as need for surgery, concurrent infection, and obstruction) and comorbid disease burden (at least three comorbidities).[14] Direct costs, hospitalizations, and surgeries appear to increase with severity of illness.[11]

Pathogenesis

The exact pathogenesis of UC is unknown; the underlying mechanisms appear complex and multifaceted. Mucosal inflammation is thought to result from an aberrant immune response to intestinal microbiota arising in genetically predisposed individuals with additional contributions of lifestyle and environmental factors among others.[15] Multiple genes[16] and cellular pathways have been implicated as well.[17]

Initial approach in consideration of new-onset UC

Diagnosis and management of new-onset UC, particularly in the setting of severe cases, requires a comprehensive and multidisciplinary approach. The primary focus is to stratify disease activity in order to determine course of medical therapy and

possible role for surgery. Assessment of disease extent should be pursued as a prognostic indication; pancolonic involvement is associated with higher rates of failed medical therapy, disease-related complications, and colectomy.[18,19]

Disease classification and assessment of activity

UC cases are organized into mild, moderate, and severe disease categories largely based on clinical symptoms and objective data (Table 1).[20] Such classification helps guide medical management and treatment options that can then be tailored based on patient response and progression. While there is no single standardized disease index for UC, the Truelove and Witts Index is often used in defining and quantifying cases of severe UC.[20]

The Mayo Clinic Index (or Disease Activity Index) is a scoring system for assessing disease activity in UC. This scoring can be used for initial evaluation and for monitoring of response to therapy. The Mayo Clinic Index score ranges from zero to twelve, taking into account stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment.[21,22] Scores from two to five indicate mild disease, while scores from six to twelve indicate moderate-to-severe disease. The endpoint definition of remission has been described as a Mayo Clinic Index score of two or less with no individual subscore greater than one. Each individual patient serves as a control in establishing the degree of abnormality in stool frequency. The daily bleeding score is based on the most severe bleeding episodes of the day. The physician's global assessment includes the patient's daily recall of abdominal discomfort and general sense of wellbeing in addition to other observations such as physical assessment and performance status.[22]

History and physical examination

Patients should be queried regarding current symptoms such as abdominal pain and distension, bowel habits (frequency, nocturnal movements, blood in stool), urgency or tenesmus, presence of extraintestinal manifestations, nausea, vomiting, fever, and weight loss. Potential inciting factors include cessation of cigarette smoking or use of concurrent medications such as nonsteroidal anti-inflammatories or oral contraceptives.[1] Recent hospitalization/stress, use of antibiotics or narcotics, travel, and dietary history should be considered and can be elicited during clinical history.

Close physical examination with attention to vital signs, mentation, and clinical status is paramount to rule out sepsis or hypovolemia. Abdominal inspection (particularly for distension or hernias) should precede auscultation for bowel sounds and palpation for abdominal tenderness, organomegaly, rebound, or guarding. A rectal examination with investigation of the perianal region, stool, and rectal vault should always be performed. Examination of the skin, eyes, and joints can determine the presence of extraintestinal manifestations.

Differential considerations

Exclusion of alternate etiologies and concomitant infection are crucial steps in initial evaluation.[2] Differential diagnoses that can mimic UC include diverticulitis, appendicitis, bowel obstruction, infectious or medication-induced colitis, ischemic colitis, or vasculitis. Stool microbiologic testing

Table 1 Categorization of clinical parameters and disease severity in ulcerative colitis

Clinical parameters	Disease severity			
	Mild	**Moderate**	**Severe**	**Fulminant**
Stool variables				
Number per day	<4	≥4	>6	>10
Stool appearance	±blood	±blood	+blood	Continuous rectal bleeding
Clinical features				
Temperature (°C)	Normal	Normal or >37.5	>37.5	>37.5
Heart rate	Normal	Normal or tachycardic	Tachycardic	Tachycardic
Clinical signs	No signs of toxicity	Minimal signs of toxicity	Increasing signs of toxicity; abdominal pain	Toxic-appearing; abdominal pain/distension
Objective data				
Erythrocyte sedimentation rate (mm/hour)	≤30 (normal)	Normal or elevated	>30 (elevated)	>30 (elevated)
Hemoglobin	Normal	Normal or low	Anemia (<75% of normal value)	Anemia requiring transfusion
Radiographic imaging			Colonic air and bowel wall edema with thumbprinting	Colonic dilation

Note: Data from Truelove and Witts.[20]

with bacterial culture and ova and parasite assay should be undertaken with inclusion of specific stool assays for *Escherichia coli* 0157:H7 and *Clostridium difficile* toxin. *C. difficile* colitis in IBD is rising in incidence and prevalence[19,23] and carries an increased short-term and 5-year mortality in hospitalized UC patients; an increased rate of all-cause hospital readmissions has been observed, although colectomy rates appear to be unaffected.[24] Viral and amebic infections should also be considered. Cytomegalovirus infection can appear very similarly to active UC (both clinically and endoscopically) and occurs in up to 34% of patients with acute severe colitis and 36% of patients in the steroid-refractory subgroup.[25] A positive cytomegalovirus immunoglobulin G requires colonic biopsies with histologic examination (hematoxylin/eosin staining) searching for inclusion bodies as the most specific indicator for active viral replication.[25] Concern should exist for opportunistic infections in immunocompromised hosts (human immunodeficiency virus, post-transplant, steroid-dependent or immunosuppressed patients); expansion of differentials should be undertaken in predisposed individuals (tuberculosis in endemic populations, recent travelers).

Laboratory investigation

Initial laboratory evaluation should include a complete blood count with differential, comprehensive metabolic profile including liver function panel, erythrocyte sedimentation rate, and C-reactive protein.

Endoscopy

Colonoscopy with biopsy is the first-line investigation in diagnosing UC and assessing disease extent and severity. Visual inspection can identify alternate or concomitant pathology including pseudomembranous colitis associated with *C. difficile* infection or ischemic colitis. Deep ulcerations could indicate the presence of cytomegalovirus colitis, CD, or severe UC. The general safety of colonoscopy in patients with acute colitis has been documented[26] without an increased major complication rate based on disease activity.[27] However, a higher perforation risk during colonoscopy has been documented in hospitalized IBD patients versus controls without IBD (1% versus 0.6%, respectively; $P<0.0001$) with no significant difference between UC and CD patients.[28] Additionally, a higher perforation risk in IBD patients has been reported in association with increased endoscopic disease severity and steroid use.[29] Thus, caution is advised in cases of severe colonic ulceration or distension

to avoid precipitation of a perforation or toxic megacolon. The benefits of completing a full endoscopic examination to the terminal ileum must be weighed against the risks to the patient on an individual basis. Early flexible sigmoidoscopy with biopsy, perhaps coupled with abdominal imaging, may provide a safer alternative to full colonoscopy in selected cases. Endoscopy is generally contraindicated in the presence of toxic megacolon.

Imaging

Although imaging is not required for the diagnosis of UC, abdominal plain films should be considered in all patients presenting with colitis to exclude colonic dilation or free air. Abdominal radiography is usually normal in patients with mild-to-moderate disease but may identify proximal constipation, mucosal thickening ("thumbprinting") due to edema, or colonic dilation in severe cases. Computed tomography or magnetic resonance (MR) imaging of the abdomen/pelvis is indicated in patients demonstrating significant abdominal pain/distension, nausea, vomiting, fever, or leukocytosis.

In cases when conventional colonoscopy may not be completed or is not feasible due to the risk of complications such as perforation or toxic megacolon, a less invasive imaging modality may be considered. MR enterography is one such example and has advanced in recent years as a preferred imaging technique for providing a comprehensive view of intraluminal and extraluminal pathology without the use of ionizing radiation. In many North American sites, MR enterography has replaced gastrointestinal fluoroscopy and computed tomography enterography and has become a first-line imaging test for suspected or extant IBD.[30] Similarly, MR colonography has shown high accuracy for assessment of disease activity and severity in UC using objective MR imaging parameters including colonic contrast uptake, mural edema, enlarged lymph nodes, and the presence of engorged perienteric vasculature (comb sign).[31] As these MR findings correlate closely with endoscopy, this noninvasive study may be considered as an adjunct or alternative to colonoscopy in selected cases, particularly when colonoscopy is contraindicated or incomplete due to clinically severe illness.

Hospitalization and initial inpatient management

The risk of hospitalization in acute severe UC is 18%–25%.[32] Although the incidence rate of hospitalizations has declined,[8,34] the cumulative probability of first hospitalization

for UC has increased, particularly with consecutive years of disease, and has recently been reported as 29.4% at 5 years (95% CI 24.5%–34.1%), 38.7% at 10 years (95% CI 33.1%–43.8%), 49.2% at 20 years (95% CI 42.7%–55.2%), and 52.3% at 30 years (95% CI 45.1%–59.7%).[8] Early requirement both for hospitalization (hazard ratio 1.5; 95% CI 1.02–2.4) and for corticosteroids (hazard ratio 1.8; 95% CI 1.1–2.7) are independent predictors of hospitalization after illness of 90 days.[8] Extensive colitis is predictive of future hospitalizations.[8]

Indications for hospitalization include severe disease, toxic megacolon, failure of outpatient medical therapy, profound extraintestinal manifestations, or complications related to IBD (such as thromboembolism) or its pharmacotherapy. Supportive inpatient management includes intravenous (IV) fluid administration, electrolyte and hemoglobin monitoring with repletion as needed, and IV corticosteroids if indicated. Anti-peristaltic and narcotic agents should be avoided, as they can potentially contribute to ileus, exacerbate colitis severity, and precipitate toxic megacolon. Patients should undergo early colonoscopy (typically within initial 48 hours) as the preferred endoscopic test to evaluate the full extent of disease and to obtain mucosal biopsies. As aforementioned, colonoscopy should be pursued with caution in cases of severe colonic ulceration or dilation to avoid precipitation of a perforation or toxic megacolon.

Consideration of medical options for acute severe UC should be undertaken, and early surgical consultation should be requested. Careful frequent examinations and assessments are required to determine the response to pharmacotherapy and to assess the need for additional rescue measures including colectomy. Approximately 40%–50% of patients hospitalized for UC will fail corticosteroid therapy[32] so testing to facilitate forthcoming management should be pursued on admission. This includes testing for thiopurine methyltransferase enzyme activity for possible use of azathioprine (AZA) or 6-mercaptopurine; latent *Mycobacterium tuberculosis* (chest radiograph and purified protein derivative or QuantiFERON®-TB Gold [QIAGEN, Venlo, the Netherlands]) and hepatitis B (hepatitis B surface antigen, surface antibody, core antibody) for possible biologic agent; and serum cholesterol and magnesium levels for possible cyclosporine (CsA) or tacrolimus.

Careful monitoring for disease-related complications such as arterial or venous thromboembolism (VTE) is warranted. IBD is associated with a roughly 1.5- to 3.5-fold increased risk of thromboembolic events especially in the setting of active disease.[35,36] Thromboembolisms have been reported to arise in the arterial or venous system and in typical (deep extremity veins or pulmonary artery) or atypical (portal vein, retinal vein, central nervous system) locations. However, in a recent meta-analysis, the risk of VTE was particularly increased (by 96%) in IBD patients versus the general population (relative risk 1.96; 95% CI 1.67–2.30) while that of arterial thromboembolism was not (relative risk 1.15; 95% CI 0.91–1.45). The magnitude of the risk of VTE was higher in studies including IBD patients in general versus those looking at hospitalized IBD patients.[37] The incidence of VTE in UC is approximately 0.26% per year, and IBD activity is an independent risk factor for VTE development.[36] The relative risk of VTE is increased during periods of disease flare (hazard ratio 8.4) and appears more prominent during ambulatory versus hospitalized periods.[38] The prevalence of VTE appears to be greatest among IBD patients aged ≤40 years and is higher among hospitalized UC versus CD patients.[37,39] Mortality in IBD patients following VTE ranges from 8%–25%. Among hospitalized patients, the excess mortality associated with VTE is 2.1-fold higher for IBD patients than for non-IBD patients ($P<0.0001$).[39] The rate of VTE after UC-related surgery has been reported at 3.3%.[40] A number of published guidelines recommend administration of prophylactically dosed anticoagulants, such as unfractionated or low-molecular weight heparin, in hospitalized IBD patients.[1,35] The rates of major and minor bleeding have been shown to be similar between hospitalized IBD patients receiving and not receiving VTE prophylaxis.[41] The presence of rectal bleeding on admission is not a contraindication to prophylactic anticoagulation.

Treatment options and goals of therapy

Treatment for UC can become quite complex and requires an individualized and multidisciplinary approach. Collaboration among medical and surgical teams, nutritionists, psychiatrists, and social support services is important particularly in new-onset acute cases and those requiring complex decision making. Professional recommendations must then be synthesized and translated with a patient-centered, educational focus.

Patients with mild-to-moderate disease can usually be managed in the outpatient setting, while severe UC warrants inpatient care. In general, sequential therapy (Figure 1) based on disease severity and subsequent response is recommended

for both new-onset cases and periods of flare. The goal of treatment in the acute setting is to induce remission and avoid complications. Ideally, the agent selected to achieve remission is carried forward to maintain disease control.

Table 2 provides a summary of 5-aminosalicylic acid (aminosalicylates [5-ASAs]) formulations used in the treatment of UC with details including indication, delivery site, acute disease characteristics, typical dosing (for active disease and maintenance of remission), and common adverse reactions. Table 3 outlines the major categories of immunosuppressant medications used in treating UC (corticosteroids, thiopurines, biologics, and calcineurin inhibitors) with details including indication, typical dosing, efficacy, and common side effects.

Mild-to-moderate UC
5-ASAs, mesalamine, and topical corticosteroids

Induction of remission for mild-to-moderate distal colitis can be achieved with topical mesalamine, oral 5-ASAs, or topical steroids with topical mesalamine as a superior first-line agent.[1] Topical mesalamine has proven effective compared to placebo,[42] oral 5-ASAs,[43] and topical steroids.[44] The superiority of topical mesalamine to oral 5-ASAs in achieving clinical improvement for mild-to-moderate distal colitis has been shown in a meta-analysis of controlled trials.[45,46] Rectal administration is optimal for proctitis and left-sided colitis, while oral therapy is used for more extensive colonic disease.

Oral 5-ASA preparations have varying sites of delivery with the intent to deliver medication directly to sites of colonic inflammation with minimal systemic

side effects. Sulfasalazine, balsalazide, and olsalazine are released in the colon; delayed-release mesalamine and multimatrix (MMX) mesalamine are active in the terminal ileum and colon (release at pH ≥ 7); granulated mesalamine works in the terminal ileum and colon (release at pH ≥ 6); and controlled-release mesalamine takes effect in the duodenum, jejunum, ileum, and colon. A systematic review examining mesalamine formulations and prodrugs demonstrated no differences in absorption and systemic exposure to 5-ASA.[47] Effective doses of sulfasalazine range from 4–6 g/day in four divided doses, and balsalazide is dosed at 6.75 g/day in three divided doses. Olsalazine is dosed from 1.5–3 g/day in two divided doses; its benefit, however, has not been established in the setting of active UC perhaps due to the confounding potential side effect of diarrhea.[1] Effective doses of oral mesalamine range from 4–6 g/day in three divided doses. The MMX mesalamine formulation provides comparable results with a convenient dosing regimen of 2.4–4.8 g once daily.[48,49] Prolonged-release mesalazine dosed at 4 g once daily appears to be as well-tolerated and effective for inducing remission in mild-to-moderately active UC compared to a 2 g twice daily dosing regimen.[50] A multicenter, randomized, double-blind, active-control study conducted over 6 weeks compared delayed-release mesalamine 4.8 g/day with 2.4 g/day for moderately active UC; treatment success (overall improvement) using the Physician's Global Assessment (based on parameters of rectal bleeding, stool frequency, and sigmoidoscopy with no worsening in any individual clinical assessment) was seen in 70% of patients receiving 4.8 g/day versus 66% in those receiving 2.4 g/day. Higher doses of mesalamine
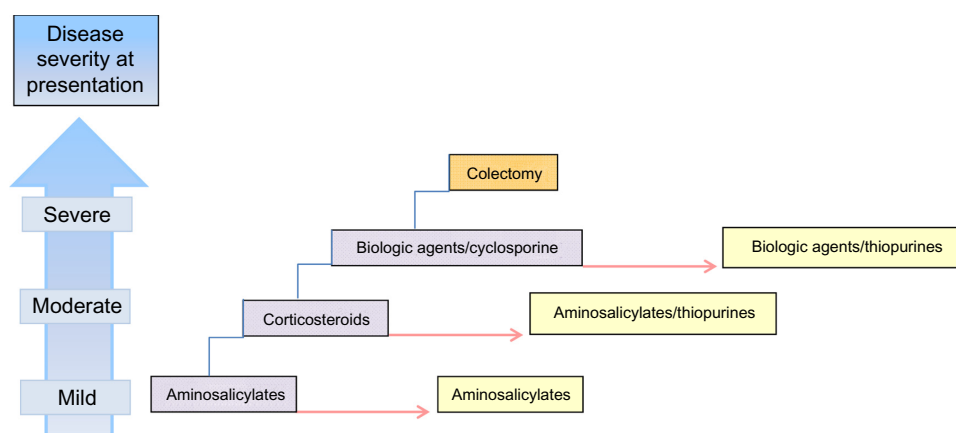

Figure 1 Sequential therapy in the treatment of ulcerative colitis based on disease severity at presentation (blue boxes, left). Initial treatment options based on disease category are shown (purple boxes). Therapy is escalated based on severity at presentation or failure to respond to prior step. Red arrow signifies time, and maintenance options are shown (yellow boxes). Colectomy (orange box) is considered in fulminant or recalcitrant disease.

Table 2 5-Aminosalicylate preparations in the treatment of ulcerative colitis

Generic drug name	Proprietary name	Formulation	Indication	Delivery sites	Acute disease characteristics	Typical dosing (active disease)	Typical dosing (maintenance)	Side effects
Sulfasalazine	Azulfidine®	5-ASA linked to sulfapyridine via azo bond	Active UC and remission maintenance	Colon	Distal Extensive Refractory	2–4 g orally daily	2–4 g orally daily	Common (dose-dependent reactions, 10%–40% of patients): sulfapyridine intolerance: nausea, vomiting, anorexia, dyspepsia, abdominal pain, malaise, rash Reversible oligospermia and infertility (males) *Hypersensitivity reaction to sulfapyridine (rarely to 5-ASAs): fever, exfoliative dermatitis, pancreatitis, hepatitis, pneumonitis, pericarditis, hemolytic anemia, worsening of colitis Severe, less common: interstitial nephritis, pancreatitis, hepatotoxicity, allergic reactions, hemolytic or megaloblastic anemia, bone marrow suppression, drug-induced connective tissue disease
Mesalamine (rectal)	Rowasa®	Enema suspension	Active distal UC and remission maintenance distal UC	Rectum and colon distal to splenic flexure	Distal Limited Refractory	4 g rectally daily	1–4 g rectally daily	Anal irritation, abdominal pain
	Canasa®	Suppository	Active proctitis and remission maintenance distal UC	Rectum	Distal Limited Refractory	1.0–1.5 g rectally daily	0.5–1.0 g rectally daily	
Mesalamine (oral)	Apriso®	Capsule containing delayed release enteric coated granules	Remission maintenance UC	Terminal ileum, colon	Distal Extensive Refractory		1.5 g orally daily	Common 5-ASA reactions (5% of patients, similar to placebo): gastrointestinal disturbances (abdominal pain, nausea, dyspepsia, flatulence), headache, malaise Less common 5-ASA reactions: rash, alopecia, worsening of colitis
	Asacol® HD	Eudragit-S-coated tablet (release at pH ≥7.0)	Active UC and remission maintenance	Terminal ileum, colon		1.6–4.8 g orally daily	0.8–4.8 g orally daily	
	Delzicol®	Capsule containing delayed release tablet (release at pH ≥7.0)	Active UC and remission maintenance	Terminal ileum, colon		2.4 g orally daily	1.6 g orally daily	
	Pentasa®	Ethylcellulose-coated microgranules (time- and pH-dependent release)	Active UC and remission maintenance	Duodenum, jejunum, ileum, colon		2–4 g orally daily	1.5–4.0 g orally daily	

(*Continued*)

Table 2 (*Continued*)

Generic drug name	Proprietary name	Formulation	Indication	Delivery sites	Acute disease characteristics	Typical dosing (active disease)	Typical dosing (maintenance)	Side effects
	Lialda®	Eudragit-S-coated tablets (release at pH ≥7.0); lipophilic and hydrophilic matrices	Active UC and remission maintenance	Terminal ileum, colon		2.4–4.8 g orally daily	2.4 g orally daily	Severe, less common 5-ASA reactions: interstitial nephritis, agranulocytosis, pneumonitis, hepatitis, pancreatitis, pericarditis
Balsalazide	Generic	5-ASA linked to inert unabsorbed carrier via azo bond	Active UC	Colon	Distal Extensive Refractory	2.00–6.75 g orally daily	2.00–6.75 g orally daily	
	Giazo®	5-ASA linked to inert unabsorbed carrier via azo bond	Remission maintenance UC	Colon	Distal Extensive Refractory		6.6 g orally daily (for male patients)	Anemia, diarrhea, pharyngolaryngeal pain, urinary tract infection, arthralgia, insomnia, musculoskeletal pain
Olsalazine	Dipentum®	5-ASA dimer linked via azo bond	Remission maintenance UC	Colon	Distal Extensive Refractory	2–3 g orally daily	1 g orally daily	Ileal secretory diarrhea

Notes: Treatments for mild-to-moderate UC. Choice of 5-ASA formulation(s) depends on disease indication and location, patient preference, and compliance, cost, and drug availability.[47] Remission rate for rectal 5-ASAs is approximately 62% (versus 30% placebo; *P*<0.01).[42] Similar efficacy and safety profiles are seen among oral formulations that are generally effective in 40%–80% of patients with time to effect of approximately 2–4 weeks.[1,47,68] Dose ranges reflect those used in clinical practice and are more broad than doses specifically studied in clinical trials. Combination therapy with oral and rectal 5-ASA is more effective than oral formulation alone for extensive mild-to-moderate UC.[42,57,58]
Abbreviations: 5-ASA, 5-aminosalicylate; UC, ulcerative colitis.

appeared to be effective and well-tolerated. At 6 weeks, patients receiving 4.8 g/day achieved significantly higher clinical remission rates versus those receiving 2.4 g/day (43% versus 35%, respectively; *P*=0.04). Both dosing regimens had similar reported tolerability and side effects.[51]

Historically, early registration trials used four times daily or three times daily 5-ASA dosing to mirror the regimen used for sulfasalazine. However, post-marketing data suggests that less frequent dosing of agents for induction and maintenance is possible,[48,52–55] and newer agents are indicated for once daily dosing.[48,56]

Oral 5-ASAs are effective in approximately 40%–80% of patients and demonstrate effect in about 2–4 weeks,[1] although longer treatment induction courses may be required. Patients who fail to respond to the first 8 weeks of mesalamine therapy may achieve clinical and endoscopic remission with an 8-week, high-dose MMX mesalamine extension before being considered for step-up therapy with steroids or immunosuppressants.[49] Oral mesalamine (2.4 and 4 g/day) combined with mesalamine enema achieves a more rapid response and more effective clinical improvement versus either agent alone.[57,58]

Topical agents as an alternative or supplement to oral 5-ASAs include mesalamine suppositories or enemas and hydrocortisone foam or enemas. In general, suppositories reach the upper rectum (10 cm above the anal verge), while enemas can extend as far as the splenic flexure and distal transverse colon. Foams can be effective for disease involving the rectum and distal sigmoid (15–20 cm above the anal verge) but do not reach as far as enemas.[1,46] Mesalamine suppositories or enemas may be effective in inducing remission for patients unresponsive to oral 5-ASAs or topical steroids particularly for patients with proctitis and distal symptoms.[59] Mesalamine suppositories can be dosed at 500 mg twice daily or 1 g once daily; doses of 1 g administered nightly are considered optimal.[1,60] The high efficacy and low side effect profile of rectal 5-ASA suppositories makes this formulation the treatment of choice for ulcerative proctitis.[46] Mesalamine enemas in doses of 1–4 g/day can cover more proximal disease to the splenic flexure and can induce and maintain remission in distal colitis.[61,62] Mesalazine foam (not available in the US) and enemas are equally effective for the treatment of active proctitis, proctosigmoiditis, and left-sided colitis;[63] the foam modality is often better tolerated with better rectal retention.[1]

Topical corticosteroids are effective in the treatment of acute distal colitis and are available in the US as a

hydrocortisone enema (100 mg) or 10% hydrocortisone foam. Patients intolerant of or unresponsive to rectal mesalamine after 2 weeks can be switched to hydrocortisone formulations. Other effective rectal corticosteroids include beclomethasone and budesonide. Beclomethasone dipropionate and mesalamine foam and enema have similar efficacy and tolerability in mild active distal colitis.[64] Budesonide is a second-generation corticosteroid with low systemic bioavailability (10%–15%) due to first-pass hepatic metabolism and has resultant modest effects on the hypothalamic–pituitary–adrenal axis. As a compounded enema, budesonide is safe and effective for treating active distal UC and proctitis with a lowest effective dose of 2 mg/100 mL.[65] As an oral formulation, budesonide is absorbed in the gastrointestinal tract more proximal to the colon; MMX technology allows extension of release into the colon. Oral budesonide MMX at a dose of 9 mg/day has recently proven more effective than placebo in inducing endoscopic and clinical remission in mild-to-moderate UC.[66,67]

Topical therapy generally provides a more rapid response with less frequent dosing and less systemic side effects versus oral therapy. Agents are determined by both patient preference and proximal disease extent.[1] Although they can help significantly with distal disease, topical therapies may pose difficulty or discomfort for patients secondary to the sense of tenesmus. Administration can be inconvenient, especially while outside of the home or in social situations. Patients can also experience anal leakage that could be uncomfortable and embarrassing; foam modalities may be easier to tolerate in this regard.

Sulfasalazine is a prodrug composed of sulfapyridine bonded to active mesalamine, and up to one-third of treated patients experience side effects thought to be attributed to the sulfur moiety.[68] Common reactions include headache, indigestion, nausea, vomiting, and abdominal pain. More severe but less frequent effects include pancreatitis, hepatotoxicity, allergic reactions, bone marrow suppression, drug-induced connective tissue disease, hemolytic or megaloblastic anemia, and interstitial nephritis.[1] Reversible sperm abnormalities (count/morphology/motility) can be seen related to the sulfapyridine component but are not seen with mesalamine products. 5-ASA products containing only the active ingredient were engineered with the intent to reduce the aforementioned side effects. Approximately 80% of patients intolerant to sulfasalazine are able to handle olsalazine, balsalazide, and mesalamine; some allergic reactions formerly attributed to the sulfur component of

sulfasalazine have been documented with the newer 5-ASA preparations.[69]

Moderate-to-severe UC
Oral and IV corticosteroids

Patients who are refractory to rectally administered 5-ASAs and/or corticosteroids or oral 5-ASAs at maximal doses may require systemic corticosteroids.[46] A typical dosing regimen is oral prednisone 40–60 mg/day (or equivalent) for 1–2 weeks until clinical response is established followed by steroid taper by 5–10 mg/week depending on disease severity and rapidity of response at onset of therapy. Once at a 20 mg dose, tapering of a patient's dose customarily proceeds at 2.5 mg/week. A double-blind, non-placebo-controlled outpatient trial of 58 patients with active mild UC examining optimal oral prednisone dosing at 20, 40, and 60 mg daily found that 40 or 60 mg daily dosing achieved greater symptomatic improvement with two times the remission rate versus 20 mg daily over 2 weeks. Additionally, patients in the 40 mg arm experienced fewer side effects than those in the 60 mg arm. Thus, oral prednisone starting at 40 mg daily has been considered optimal.[70] Oral and rectal 5-ASA agents should generally be continued through the corticosteroid course with the intent of maintaining remission at completion of the taper.[1,46]

Severe UC or failure of response to oral steroids requires consideration for hospitalization and IV steroid therapy with a recommended dosing regimen of methylprednisolone (40 mg to 1 mg/kg) as a single IV bolus. Administering IV methylprednisolone at doses >60 mg/day is not supported by current literature.[71] Randomized controlled trials of IV corticosteroids for severe UC are lacking. Sixty percent of patients hospitalized for severe UC will achieve clinical remission within 5–7 days of treatment initiation.[32] A systematic review of response to corticosteroids in severe UC incorporating 32 cohort and controlled studies from 1974–2006 (1,991 patients) revealed an average colectomy rate of about 27% and death rate of 1%.[71] Stool frequency, disease extent, temperature, heart rate, C-reactive protein, albumin, and radiologic assessments were consistently reported variables involved in treatment failures.[71]

Steroids carry a significant side effect profile and can distort metabolic activity in a multitude of organ systems. Such adverse effects include diabetes, cushingoid features, glaucoma, cataracts, and psychiatric instability.[1] The risk for opportunistic infections is increased about threefold in IBD patients exposed to steroids with a higher relative risk in patients aged over 50 years; when steroids are combined with other immunosuppressants, this risk elevates

Table 3 Immunosuppressant medications in the treatment of ulcerative colitis

Major category/drug	Indication	Typical dosing	Efficacy	Common side effects	Other
CORTICOSTEROIDS				General: cushingoid features, flushing, hypernatremia/fluid retention, hypokalemia, metabolic alkalosis, hypertension, diabetes, osteopenia/osteoporosis/ avascular necrosis, mood changes/ psychosis, sleep disturbances/ insomnia, acne, hirsutism, cataracts, glaucoma, myopathy, ecchymosis/petechial bleeding, striae rubrae, adrenal insufficiency without tapering	
Topical (rectal) glucocorticoids	Mild-to-moderately active distal UC and proctitis. Loss of response to or intolerance of rectal 5-ASA			Topical (rectal): anal leakage, tenesmus, or discomfort with administration	
Hydrocortisone suppository		30 mg (one suppository) per rectum twice daily			
Hydrocortisone enema		100 mg (one 60 mL unit) per rectum twice daily			
Hydrocortisone aerosol foam (10%)		90 mg (one applicator) per rectum twice daily			
Budesonide (multimatrix) compounded enema		2 mg/100 mL per rectum daily			
Oral corticosteroids					
Prednisone or prednisolone (or equivalent)	Mild-to-moderately active UC or disease refractory to rectal 5-ASAs and/or corticosteroids or oral 5-ASAs at maximal dosage	40–60 mg orally daily	Induction of response by 14 days with remission in approximately 54%–66% of patients by 4–5 weeks[129]	Corticosteroid effects as above	Maintain typical initial dose for 1–2 weeks until clinical response; then taper dose by 5–10 mg/week. Once at 20 mg dose, taper by 2.5 mg/week
Budesonide (multimatrix)	Mild-to-moderately active UC	9 mg orally daily	Combined clinical and endoscopic remission rate of 17.9% at 8 weeks versus placebo (7.4%; P=0.0143)[66]	Corticosteroid effects are minimal. Common side effects: colitis, headache, fever, back pain, insomnia, nausea, abdominal pain	Second-generation corticosteroid with low (10%–15%) bioavailability due to first-pass hepatic metabolism

	Indication	Dosing	Efficacy/pharmacokinetics	Side effects	Monitoring/comments
Intravenous corticosteroids	Severe UC or failure of response to oral corticosteroids	Methylprednisolone 40 mg to 1 mg/kg daily (single bolus) or equivalent	60% of patients hospitalized for severe UC achieve clinical remission in 5–7 days[32]	Corticosteroid effects as above	
THIOPURINES					
AZA/6-MP	Maintenance therapy; for persistent moderate or steroid-dependent UC. Not indicated for monotherapy in new-onset or acutely relapsed cases	AZA: 1.5–2.5 mg/kg orally daily. 6-MP: 1.0–1.5 mg/kg orally daily. Initiate drug at low dose (0.5–1.5 mg/kg for AZA and 0.25–0.5 mg/kg for 6-MP) with gradual increase to maximum dose+. Serum level of drug active metabolite (6-thioguanine) achieves therapeutic level at 235–450 pg/mL	Mean efficacy for AZA/6-MP is 75% for maintenance of remission in UC[73]. Active drug metabolites with half-life 3–5 days; steady state achieved in 2–4 weeks. Maximal clinical effect seen in 8–10 weeks[73]	Fever, nausea, allergic reactions, rash, diarrhea, arthralgia, pancreatitis, hepatotoxicity, myelosuppression, immunosuppression, infection, malignancy such as hepatosplenic T-cell lymphoma and non-Hodgkin lymphoma	Thiopurine-S-methyltransferase enzyme activity or genotype testing suggested prior to administration[75]. Monitor complete blood count with differential and liver enzymes every week for 1 month, then twice monthly for 1 month, then every 1–3 months thereafter to monitor for toxicity. High risk of relapse with drug discontinuation
BIOLOGICS **TNF-α inhibitors**				Antibody formation (see below), autoantibody formation, drug-induced lupus, infection (particularly tuberculosis, fungal, viral, and parasitic infections), reactivation of hepatitis B or herpes zoster, psoriasis, opportunistic infections, malignancies (skin cancers, solid tumors, lymphomas such as non-Hodgkin lymphoma and hepatosplenic T-cell lymphoma)	Contraindications: active, uncontrolled infection, active malignancy, untreated latent tuberculosis, moderate-to-severe congestive heart failure, demyelinating conditions and other neurologic disorders such as optic neuritis, systemic lupus erythematosus, lupus-like syndrome, uveitis, thyroiditis, interstitial lung cancer. Live vaccinations contraindicated once patient is initiated on anti-TNF-α therapy

(*Continued*)

Table 3 (*Continued*)

Major category/drug	Indication	Typical dosing	Efficacy	Common side effects	Other
IFX (human–murine chimeric monoclonal immunoglobulin G$_1$ antibody against TNF-α)	Moderate-to-severe UC (outpatient);[22] medication rescue therapy in severe UC (inpatient)[76,77]	Induction dosing: 5 mg/kg intravenously at 0, 2, and 6 weeks Maintenance: 5–10 mg/kg every 8 weeks	ACT 1: clinical response at 8 weeks in 69% of patients receiving 5 mg/kg IFX versus 37% in placebo ($P<0.001$). Clinical response at 8 weeks in 61% of patients receiving IFX 10 mg/kg versus 37% in placebo ($P<0.001$). ACT 2: clinical response at 8 weeks in 64% of patients receiving 5 mg/kg IFX versus 29% in placebo ($P<0.001$). Clinical response at 8 weeks in 69% of patients receiving 10 mg/kg IFX versus 29% in placebo ($P<0.001$). ACT 1-2: patients receiving IFX more likely to have clinical response at 30 weeks ($P\leq0.002$ for all comparisons). ACT 1: patients receiving 5 or 10 mg IFX more likely to have sustained clinical response at 54 weeks (45% and 44%, respectively) versus placebo (20%; $P<0.001$ for both comparisons).[22] At 2 weeks, treatment success seen in 50% of patients with acute severe steroid-refractory UC treated with IFX versus 0% in placebo.[76]	Anti-TNF-α effects as above Formation of human anti-chimeric antibodies, delayed-type hypersensitivity reactions, acute transfusion reactions (chest pain, shortness of breath, palpitations, flushing, headache, fever, urticarial rash, hypotension)	
Adalimumab (fully humanized monoclonal immunoglobulin G$_1$ antibody against TNF-α)	Moderate-to-severe UC (outpatient); current data does not support use for hospitalized patients with UC	Induction dosing: 160 mg injected subcutaneously at 0 weeks, 80 mg at 2 weeks Maintenance: 40 mg injected subcutaneously every 2 weeks	Overall rate of clinical remission 16.5% in patients receiving adalimumab versus placebo (9.3%; $P=0.019$) and sustained at 52 weeks (17.3% versus 8.5%, respectively; $P=0.004$)[79]	Anti-TNF-α effects as above Formation of human anti-human antibodies, local injection site reaction	
Golimumab (fully humanized monoclonal immunoglobulin G$_1$ antibody against TNF-α)	Moderate-to-severe UC (outpatient); current data does not support use for hospitalized patients with UC	Induction dosing: 200 mg injected subcutaneously at 0 weeks, 100 mg at 2 weeks Maintenance: 100 mg injected subcutaneously every 4 weeks	Clinical remission and endoscopic healing at 30 and 54 weeks were 27.8% and 42.4% in patients receiving golimumab compared to placebo (15.6% and 26.6%; $P=0.04$ and $P=0.02$, respectively) Clinical response was maintained through 54 weeks in 49.7% of patients receiving golimumab versus placebo (31.2%; $P<0.001$)[81,82]	Anti-TNF-α effects as above Formation of human anti-human antibodies, local injection site reaction	

					Contraindications
CALCINEURIN INHIBITORS					
Cyclosporine	Severe/fulminant UC refractory to systemic corticosteroids (inpatient)	Continuous IV infusion: 2–4 mg/kg/day (target whole blood level 200–250 mg/mL)[86]	Clinical response rate 76.9% in steroid-resistant UC Effect within 3–7 days[86]	Nephrotoxicity, opportunistic infections, seizures (contraindicated in patients with low cholesterol <100 mg/dL), hypomagnesemia, hyperkalemia, paresthesia, hypertension, hypertrichosis, nausea, vomiting, headache, gingival hyperplasia	Contraindications: infection, hypocholesterolemia (<100 mg/dL), significant renal impairment
Tacrolimus	Severe/fulminant UC refractory to systemic corticosteroids (inpatient)	0.1 mg/kg/day orally targeted to trough level 10–15 ng/mL[90]	Clinical remission seen in 72% of patients[94]	Tremor, paresthesia, hyperglycemia, hyperkalemia, hypertension, opportunistic infections	

Notes: [+]Dose based on estimated lean body weight and for patients with wild-type thiopurine-S-methyltransferase enzyme activity or genotype. Patients with intermediate enzyme activity or heterozygote genotype should have a 50% dose reduction. In general, those with low enzyme activity or homozygote or compound heterozygote genotype should not receive AZA/6-MP.
Abbreviations: 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; ACT 1 and 2, Active Ulcerative Colitis Trials1 and 2, respectively; AZA, azathioprine; IFX, infliximab; IV, intravenous; TNF-α, tumor necrosis factor-α; UC, ulcerative colitis.

substantially.[72] Other steroid side effects include impaired wound healing, hyperlipidemia, metabolic bone disease, hypernatremia/fluid retention, hypokalemia, metabolic alkalosis, steroid myopathy, and accelerated atherosclerosis. Adrenal insufficiency can develop and requires consideration when tapering.[1] Glucocorticoid effects of budesonide MMX are minimal and appear to be similar to placebo; most commonly reported effects include colitis, headache, and pyrexia. Drug-related adverse events are low, and serious side effects leading to treatment abortion are infrequent.[66]

Thiopurines

AZA and 6-mercaptopurine have limited utility in the acute setting. The active drug metabolites have a half-life of approximately 3–5 days. A steady state can be achieved after about 2–4 weeks, but maximal clinical effect can take up to 8–10 weeks.[73] A prospective, investigator-blinded, randomized controlled trial comparing AZA and 5-ASA for induction of remission in steroid-dependent UC patients found that AZA is significantly more effective than 5-ASA in achieving clinical and endoscopic remission with discontinuation of steroids at 6 months.[74] Although not indicated to induce remission in the acute setting, thiopurines can be used as an adjunct to infliximab (IFX) therapy or as a maintenance medication after treatment with tacrolimus or CsA. Thiopurines offer a steroid-sparing maintenance therapy and can be considered for patients with persistent moderate disease who are unresponsive to/cannot be weaned from steroids and who do not meet the need for IV alternatives.[1] Thiopurines are not well-studied in the setting of limited distal disease. Thiopurine methyltransferase enzyme activity should be assessed prior to inception of the therapy to determine recommended starting dose and potential for early severe side effects.[75] Adverse effects of thiopurines include fever, rash, nausea, diarrhea, arthralgia, thrombocytopenia, leukopenia, infection, pancreatitis, hepatitis, non-Hodgkin lymphoma, and hepatosplenic T-cell lymphoma among others.

Biologic agents: tumor necrosis factor-α (TNF-α) inhibitor therapy
IFX

IFX is a chimeric human–murine monoclonal immunoglobulin G_1 antibody against TNF-α. It is indicated for moderate-to-severely active UC in the outpatient setting.[22] IFX has also been shown in two placebo-controlled trials to be effective in hospitalized patients with severe active UC unresponsive to conventional therapy.[76,77] Induction dosing for IFX is 5 mg/kg

IV at 0, 2, and 6 weeks followed by maintenance dosing at 5–10 mg/kg every 8 weeks. Two randomized double-blind, placebo-controlled trials (Active UC Trials 1 and 2 [ACT 1 and ACT 2, respectively]) evaluating the efficacy of IFX versus placebo for induction and maintenance therapy in moderate-to-severe UC with failed medical therapy have demonstrated sustained clinical response and remission at 8 and 30 weeks in both trials and at 54 weeks in ACT 1; patients receiving IFX were significantly more likely to have endoscopic mucosal healing at these landmarks.[22] At baseline, 61.0% and 51.1% were receiving steroids in ACT 1 and 2, respectively, with a median daily dose of 20 mg/day; a higher proportion of patients in the IFX versus placebo group achieved clinical remission and discontinued steroids at 30 weeks (ACT 1 and 2) and at 54 weeks (ACT 1). Adverse events were similar in placebo compared to IFX groups.

IFX is contraindicated for use in patients with active uncontrolled infection, moderate-to-severe congestive heart failure, untreated latent tuberculosis, preexisting demyelinating conditions, optic neuritis, and active malignancies. Acute transfusion reactions (characterized by chest pain, shortness of breath, palpitations, flushing, headache, fever, and sometimes urticarial rash or hypotension) and delayed-type sensitivity reactions may occur with administration. Other adverse events include the development of opportunistic infections, non-Hodgkin lymphoma, hepatosplenic T-cell lymphoma, and skin cancers among others.[1]

Adalimumab (ADA)

ADA is a fully humanized monoclonal antibody against TNF-α. Current data does not support use of ADA for hospitalized patients with UC, and the comparative efficacy between IFX and ADA has not been reported. A randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy of ADA for induction and maintenance of moderate-to-severe UC unresponsive to conventional medical therapy. Clinical remission was seen after 8 weeks of therapy.[78] Clinical response at 8 weeks was seen in 50% of patients receiving 160 mg at week 0 and 80 mg at week 2 versus 35% in the placebo group (P<0.001). Standard induction dosing is 160 mg subcutaneously at week 0 and 80 mg subcutaneously at week 2 followed by 40 mg subcutaneously every 2 weeks, starting at week 4.[79] Recent data supports that adding ADA to standard UC therapy significantly reduces risks of all-cause, UC-related, and UC- or drug-related hospitalizations (40%, 50%, and 47%, respectively; P<0.05) as observed over the first 8 weeks of therapy in patients with moderate-to-severe UC versus placebo; furthermore,

decreased incidence rates for all-cause (0.18 versus 0.26; P=0.03), UC-related (0.12 versus 0.22; P=0.02), and UC- or drug-related (0.024 versus 0.24; P=0.005) hospitalizations were observed during 1 year of ADA therapy versus placebo. Rates of colectomy did not differ between the two groups.[80] Adverse events of ADA are similar to those of IFX.

Golimumab

Golimumab is a fully humanized monoclonal antibody against TNF-α used to induce clinical response, remission, and mucosal healing in moderate-to-severe UC unresponsive to conventional medical therapy.[81] A Phase III double-blind trial of patients with moderate-to-severe UC responsive to golimumab induction (Program of UC Research Studies Utilizing an Investigational Treatment) demonstrated that golimumab injected at 50 or 100 mg subcutaneously once monthly maintained clinical response through 54 weeks in 47% of patients dosed with 50 mg golimumab, 49.7% of patients dosed with 100 mg golimumab, and 31.2% of patients dosed with placebo (P=0.10 and P<0.0001, respectively). Patients receiving 100 mg golimumab attained higher rates of clinical remission and mucosal healing compared to 50 mg golimumab (23.3% and 41.7%, respectively) and to placebo (27.8% and 42.4% versus 15.6% and 26.6%; P=0.004 and P=0.002, respectively). Patients receiving a 100 mg dose had both clinical remission and endoscopic healing at 30 and 54 weeks.[82] The safety profile is similar to that reported for other anti-TNF agents. Golimumab recently received Food and Drug Administration approval for UC in the US and is indicated for moderate-to-severe UC for outpatients.

Severe UC

Acute severe colitis afflicts approximately 25% of patients with UC,[83] and the mainstay of therapy is IV corticosteroids. Patients who are fulminant or refractory to systemic glucocorticoids require salvage medical therapy with CsA or IFX (see section above), or colectomy. Severity of disease at admission is related to outcome. Timely consideration of surgery is crucial in this subset of patients experiencing a potentially life-threatening situation that carries a high risk of colectomy. Approximately 30%–40% of patients are refractory to steroids and require emergent colectomy as a life-saving surgery.[19]

Clinical prediction of steroid responsiveness

Clinical predictions have been established in an attempt to determine which patients will respond to IV corticosteroid

therapy through several investigations. In one study of 51 inpatients undergoing intensive therapy for severe UC, predictive factors of colectomy on same hospital admission included stool frequency of more than eight per day or three to eight stools with C-reactive protein levels (>45 mg/L) assessed on day 3 of hospitalization with 85% success. Incomplete responders having more than scant bloody stools per day after 1 week of treatment had a 60% chance of continuous symptoms and a 40% chance of colectomy in the months following hospitalization.[84] The Ho Index is an updated clinical prediction scoring system formulated through a retrospective analysis of 167 consecutive patients at one medical center with the purpose of identifying severe UC patients who may be unresponsive to IV steroid therapy at an early stage. Patients are assessed on day 3 of IV corticosteroid administration with points assigned for stool frequency, albumin, and colonic dilation; a total score of more than three has an 80% positive predictive value for colectomy. Additionally, the Ho Index appears to predict response to CsA and colectomy avoidance after failure of corticosteroid treatment over 5 days.[85] The Ho Index has not been prospectively validated. Although clinical prediction scoring is not a substitute for clinical judgment, it may aid in organizing realistic plans and anticipating need for potential surgery.

CsA

CsA, a calcineurin inhibitor, is a rapidly-acting immunosuppressant effective in treating severe refractory UC. IV CsA appeared to be safe and effective for treating moderately severe steroid-refractory UC in a small prospective open-label study.[33] Doses of 3.7±0.5 mg/kg IV were given until response was achieved followed by oral dosing for 3.5±2.6 months. Clinical response was seen in almost 77% of patients within 5.7±2.8 days. Relapse rate was 60% at approximate 28-month follow-up; five of six treatment failures underwent proctocolectomy. The probability of surgical avoidance was 52% at 78 months, and the sole factor associated with this was concomitant AZA therapy (P=0.007).[86] A retrospective analysis of 24 patients who received IV CsA (4 mg/kg/day for an average of 6.63 days) for severe steroid-refractory UC followed by oral CsA dosed for 3 months showed that colectomy was avoided in approximately 79% during the early stages of treatment. Three patients required surgery over time (average 38 months; range 12–62 months), but 67% remained colectomy-free overall. One patient required colectomy in the acute setting due to convulsions with IV CsA administration.[87]

CsA is given as a continuous IV infusion of 2 mg/kg over 24 hours (target whole-blood level 200–250 mg/mL). A typical response is achieved within 1 week, and lack of response warrants colectomy. Patients showing a response to IV CsA should be transitioned to oral CsA beginning with doubled dose of the IV formulation (goal whole-blood trough level 200–250 mg/mL). Oral CsA should be bridged with AZA or 6-mercaptopurine for 2–3 months prior to consideration of CsA taper. Steroid-dependent chronic active UC patients placed on oral CsA (5 mg/kg/day titrated to reach whole-blood therapeutic range 60–240 mg/mL) with steroid tapering over 3 months showed an 89% initial response rate and about 56% remission rate in a very small retrospective study.[88] Larger studies are needed to validate this concept of oral CsA as a steroid-sparing maintenance medication in chronic UC. Up to one-third of patients with severe UC are unresponsive to CsA and must be considered for alternative therapy.[86,89]

Contraindications to use of CsA include infection, hypocholesterolemia (seizure risk), and significant renal impairment. Reported major toxicities of CsA dosed at 2–4 mg/kg for severe steroid-refractory UC include nephrotoxicity (24%), infection (20%), seizure (4%), and death (1%–2%).[32] Other adverse effects include paresthesia (51%), hypertension (39%), hypertrichosis (27%), hypomagnesemia (20%), hyperkalemia (13%), nausea, vomiting, headache, tremors, and gingival hyperplasia.[87]

Tacrolimus

Tacrolimus is a calcineurin inhibitor that can be considered in cases of severe steroid-refractory UC. A 2-week double-blind, placebo-controlled study of oral tacrolimus therapy performed in hospitalized patients with steroid-refractory moderate-to-severe UC revealed that treated patients whose tacrolimus drug trough level was targeted at 10–15 ng/mL were more likely than placebo to achieve clinical response, although they were unable to achieve complete remission.[90] Some open-label series have also been published showing efficacy and relative safety of tacrolimus as a rapid-acting option in treating severe UC.[91–93] A recent retrospective three-center study of 130 patients with moderate-to-severely active steroid-refractory UC analyzed patients within 3 months of initiation of tacrolimus. In most cases, an oral dose was given at 0.1 mg/kg/day; in a minority of patients, an IV dose was given at 0.01 mg/kg/day with a fast transition to oral formulation. Daily tacrolimus doses were adjusted at the discretion of the treating physician based on clinical requirements. Steroids were tapered

individually and, in some cases of prior refractoriness, were not even started; extant thiopurines were continued. Most patients (59%) in the series had pancolitis. At 12 weeks, the median Lichtiger score decreased from 13 at baseline to three. Clinical remission was achieved in 72%, and 18 patients required colectomy within the 3-month period after tacrolimus treatment. Overall adverse effects due to tacrolimus were seen in 53% of patients, leading to medication discontinuation in two cases (due to drug intolerance and increased serum creatinine). The most common reported side effects in this study were tremor/ paresthesia (38%) and hyperglycemia (10%). Concomitant thiopurine use significantly increased remission (P=0.002) and favored colectomy sparing in the short-term.[94] Side effects of tacrolimus include acute kidney injury, tremor, paresthesia, hypertension, hyperkalemia, and opportunistic infections.[92] Overall, insufficient available data limit the ability to guide optimal initial and maintenance dosing and follow-up care.

Medical rescue therapy considerations and failure of response

Risks and benefits of medical rescue therapies should be weighed with consideration for maintenance therapy options; for example, a potential benefit of IFX is that it can be continued in patients who respond to initial therapy. Concomitant thiopurine administration should be considered in patients receiving CsA or IFX who are appropriate candidates, although this further compounds immunosuppression.

Patients failing to show a response to rescue therapy within 5–7 days should undergo colectomy. Switching from one to another rescue therapy can achieve remission in 30%–40% of cases. However, in the setting of intense immunosuppression, serious adverse events including infections (16%–20% of patients) as well as death have been reported.[32,95]

Surgery

Approximately 27% of patients with acute severe UC undergo colectomy,[32] and extensive colitis is a risk factor for surgery. The cumulative probability of colectomy in relation to time of diagnosis has been reported as 13.1% at 5 years (95% CI 9.4%–16.6%), 18.9% at 10 years (95% CI 14.4%–23.3%), and 25.4% at 20 years (95% CI 19.8%–30.8%). The short-term colectomy rate in cases of severe hospitalized UC has been constant around 27% for multiple years.[10,32] In one study, patients requiring hospitalization for medical management of UC were five times more likely to require

colectomy after adjustments for other factors; need for IFX therapy was a second independent predictor of colectomy.[96] Patients >65 years of age have an increased rate of early colectomy (within 3 months of diagnosis).[10]

The importance of early surgical involvement cannot be overemphasized. Emergent surgical indications include severe disease or fulminant colitis unresponsive to medical therapy, perforation, toxic megacolon, and refractory hemorrhage. Perforation in patients with UC can occur without typical signs of peritonitis and in the absence of colonic dilation. Identifying patients who require early surgery is important because delayed surgical intervention can lead to poor short-term outcomes[97] and measureable longer-term mortality.[9] In a retrospective review of patients undergoing surgery for fulminant UC, those who developed postoperative complications underwent colectomy significantly later (3.6 versus 7.4 days; P=0.01) than those without such complications. Specifically, patients who underwent >72 hours of preoperative medical therapy had a significantly higher risk of developing a major postoperative complication. Major complications occurred in 27% of patients, and those most frequently reported included infection (superficial and organ-space surgical site infections) and small bowel obstruction. Sustaining postoperative complications, however, did not appear to influence eventual pursuit of ileal pouch–anal anastomosis (IPAA; 68% versus 77%; P=0.5).[98]

Emergent colectomy bears a 30-day mortality rate of about 5% while that of elective surgery is less.[9,97] The goal of emergency surgery is to treat fulminant colitis, restore patient health, and subsequently allow for systemic recovery with nutrition optimization in preparation for a future procedure. Emergent UC surgery typically requires a three-stage IPAA approach beginning with total or subtotal abdominal colectomy and diverting end ileostomy that leaves behind a rectal or rectosigmoid stump as a Hartmann's pouch. This procedure eliminates most of the diseased colon in a relatively straightforward fashion, avoiding pelvic dissection and intestinal anastomosis.[99] Disease in the remaining rectum after emergent surgery is generally inconsequential; a majority of patients can discontinue previous colitis medications.[100] After sufficient recovery, patients can then undergo a future restorative surgery (described below) or a completion proctectomy with end ileostomy.

Restorative proctocolectomy with IPAA is currently the standard of care for patients undergoing elective surgery for UC. The procedure is most often completed as a two-stage process and can be performed with an open, robotic, or laparoscopic approach. The first stage is a total procto-

colectomy with creation of IPAA and temporary diverting loop ileostomy. The ileostomy serves to avert fecal material, allowing for healing of the pouch-anal anastomosis. The second surgical stage, undertaken after a few months, involves reversing the loop ileostomy and restoring intestinal continuity. The two-stage approach may reduce the risks of abdominal leakage and sepsis.[99] Modifications of this two-stage system include excluding diversion at initial surgery (one-stage procedure) and performing a subtotal colectomy in a separate procedure prior to creating a diverting IPAA (three-stage procedure). The three-stage system has been used for patients with severely active disease, those on high-dose or long-term steroid therapy, or in cases without a clear diagnosis (namely UC versus CD). This procedure carries an overall morbidity rate of 19%–27% and a mortality rate of 0.2%–0.4%. Additionally, postoperative QOL approaches that of the general population.[100] In a single-institution retrospective study comparing two-stage and three-stage IPAA procedures, the decision to perform a three-stage procedure was affected by emergent indication ($P<0.001$) and hemodynamic instability ($P=0.04$) but was not influenced by such factors as use of steroids or anti-TNF agents. Interestingly, two-stage IPAA procedures did not change the risk of anastomotic leakage when accounting for all operations (odds ratio 1.09; $P=0.94$). An increased risk of perioperative complications in patients undergoing two-stage versus three-stage procedures appeared to be affected by surgeon experience in IBD ($P=0.02$) versus creation of an IPAA at initial operation ($P=0.55$).[101]

Although curative in UC, surgery is associated with potential risks and complications. These include infection, hemorrhage, small bowel obstruction, intra-abdominal or pelvic abscess/sepsis, anastomotic strictures, fistulas, functional pouch issues including leakage and incontinence, pouchitis, cuffitis, reduced female fertility, male impotence and/or reverse ejaculation, sexual dysfunction, and surgical revision or pouch excision.

Antibiotics

Antibiotics have not proven to be of therapeutic benefit in the management of acute UC. If a documented or suspected coexisting infection exists, antibiotics should be tailored to the inciting organism. A double-blind, placebo-controlled trial of oral tobramycin as an adjunct to steroid therapy improved short-term outcomes in acute relapsing UC[102] but showed no maintenance benefit.[103] One study showed that a 6-month course of oral ciprofloxacin in addition to conventional treatment with mesalamine and prednisone

decreased the rate of treatment failure,[104] but this result was not sustained in other trials. In a prospective randomized controlled trial, oral ciprofloxacin as an adjunct to corticosteroids did not influence remission in patients with mild or moderately active UC.[105] Similarly, IV ciprofloxacin did not augment corticosteroid therapy in the treatment of acute, severe UC.[106] In a prospective double-blind trial, the addition of oral vancomycin (versus placebo) to conventional medical therapy for exacerbated colitis showed no significant overall difference in outcomes.[107] In cases of severe UC, routine use of IV tobramycin and metronidazole[108] or IV metronidazole[109] in addition to corticosteroids is not supported. However, intensive IV regimens, generally including broad-spectrum antibiotics, have been advocated for patients with evidence of severe toxicity or worsening symptoms despite optimal medical therapy. Such regimens have provided the benefits of inducing clinical remission or determining need for emergent surgery.[1,110–112]

New and future therapies for UC
Vedolizumab

Vedolizumab is a humanized monoclonal antibody targeting $\alpha4\beta7$ integrin, a surface glycoprotein variably expressed on circulating B- and T-lymphocytes that interacts with intestinal mucosal addressin cell adhesion molecule.[113] The drug selectively inhibits lymphocyte trafficking in the gut. Natalizumab, a monoclonal antibody with similar mechanism of action used to treat CD and multiple sclerosis, blocks both $\alpha4\beta7$ and $\alpha4\beta1$ integrins; it works upon multiple organs including the brain and gut and carries the potential rare but serious and irreversible side effect of progressive multifocal leukoencephalopathy.[114] Vedolizumab does not cross the blood–brain barrier and has not been shown to interfere with trafficking in the central nervous system. Two integrated randomized, double-blind, placebo-controlled trials demonstrated vedolizumab as a new and effective treatment for induction and maintenance of remission in active UC compared to placebo with 6-week response rates of 47.1% in the vedolizumab group and 25.5% in the placebo group (95% CI 11.6–31.7; $P<0.001$).[115] Induction dosing is 300 mg IV at 0, 2, and 6 weeks. No significant difference in safety profiles was detected between the two groups particularly regarding serious infections. No cases of progressive multifocal leukoencephalopathy were reported. Few clinically important infusion reactions were seen, and there were no documented cases of anaphylaxis or serum sickness. Infection rates did not appear significantly different between

groups. Further studies are needed to obtain long-term efficacy and safety data.

Tofacitinib

Tofacitinib is an oral agent that selectively inhibits the family of Janus tyrosine kinases 1–3. Janus tyrosine kinases are expressed in lymphoid cells and mediate signal transduction of multiple cytokines (such as interleukins 2, 4, 7, 9, 15, and 21) important for T-cell function such as lymphocyte activation and proliferation; blockade of the common signaling molecule shared by numerous cytokines should suppress B- and T-cells while maintaining regulatory T-cell function and leading to a state of immunosuppression or immunomodulation.[115] A double-blind, placebo-controlled Phase II study evaluated the efficacy of tofacitinib in patients with moderate-to-severe UC. Clinical response as the primary outcome was achieved at 8 weeks and occurred with the highest rate in patients taking tofacitinib 15 mg orally twice daily versus placebo (78% versus 42%; 95% CI 66–89; $P<0.001$). Clinical remission rates were highest in the groups receiving tofacitinib 10 mg twice daily (95% CI 31–66; $P<0.001$) and 15 mg twice daily (95% CI 27–55; $P<0.001$) versus placebo. The most common side effects related to infection included nasopharyngitis and influenza. There was a dose-dependent increase in low-density and high-density lipoprotein cholesterol levels that reversed after drug cessation. Absolute neutrophil count was $<1,500$ cells/mm^3 in three patients while taking the therapy, but overall levels did not drop $<1,000$ cells/mm^3.[116] The efficacy of tofacitinib as a maintenance therapy is unknown at this time, and further studies are needed to obtain long-term safety data.

Patient-centered issues: QOL and medication compliance

As a chronic disease, UC can significantly impact a patient's functional status and QOL. A significant reduction in both general life satisfaction and in health-related QOL scores have been documented in IBD particularly for patients exhibiting active disease compared to the general population and to IBD patients with quiescent disease.[117] A large sample of 945 randomly selected IBD patients from the Crohn's and Colitis Foundation of America Partners Internet cohort completed a validated Patient Assessment of Chronic Illness Care (PACIC) instrument in order to assess perceptions of various facets of care within the Chronic Care Model. Scoring ranged from one to five, with five being the highest perception of care. The average PACIC score overall was 2.4 (standard deviation 0.93). Recent gastroenterology appointment, hospitalization, surgery, and current pouch/ostomy were associated with higher PACIC scores ($P<0.05$). Positive correlation was seen with PACIC and QOL but not with adherence to medication or disease activity. Additionally, patients who had more subspecialist interactions had elevated perceptions of care, underscoring the importance of direct patient–physician connections.[118]

Medication compliance and patient education are important issues in IBD-related care. Nonadherence can be substantial, impacting disease activity and associated complications and contributing to both inpatient and outpatient health care costs.[119,120] Factors associated with nonadherence or intermittent medication compliance include younger age, female sex, multiple daily pill burden, involvement of noncommercial payer or preferred provider organization insurance, nonuse of biologics/immunosuppressants/rectal 5-ASAs, and absence of specialist care.[121]

Nonadherence to 5-ASAs is particularly high with reported index medication compliance of 57.2% in one study.[119] Greater risk of disease relapse has been seen in both nonadherent patients and in adherent patients whose mesalazine formulations were switched.[122] Patients on single daily dose MMX mesalamine appear to have the lowest discontinuation risk and highest adherence rate.[121] Over 75% of IBD patients are compliant with anti-TNF therapy. Factors predicting nonadherence for IFX or ADA include female sex, smoking, anxiety, moodiness, and treatment-related constraints.[123] It has been reported that IBD patients may misperceive the risks and benefits of anti-TNF therapy, namely IFX; as per questionnaire results, a majority of IBD patients would be unwilling to accept treatment-related side effects if the remission rate at 1 year was <75%. Such perceptions appear to be independent of age and duration of disease.[124] In one study, highest adherence rates were seen with immunomodulators.[125]

Medication compliance should be assessed during each patient evaluation, especially in the setting of quiescent disease. Stress and mental health-related disorders like anxiety and depression reflect health-related QOL in IBD patients and may affect compliance so should be addressed in conjunction with medical and/or surgical therapy.[126] Development of a patient-administered tool to assist practitioners in evaluating noncompliance would be beneficial in the clinical setting.[125] Web-based health care designs may improve patients' knowledge and QOL in the setting of chronic disease and may encourage adherence through a model of continued care.[127]

Practitioners should have a heightened sensitivity for the aforementioned patient-centered issues. Individualized

therapeutic approaches are required and must take into account extent and severity of inflammatory disease with additional considerations for such factors as medication administration (route, pill burden), financial costs, age, lifestyle, occupation, and fertility/pregnancy status among others. Careful provision of informed consent relating to IBD therapy includes discussion of available therapeutic options, risks associated with lack of or suboptimal treatment and/or noncompliance, and pharmacotherapeutic alternatives such as colectomy. The ability of patients to comprehend and procure information about their chronic disease state is paramount. Shared decision making is an optimal model in such medical treatment encounters and should thus be advocated.[128]

Conclusion

UC is a chronic inflammatory colonic disease with a relapsing and remitting course. Once the diagnosis is established, new-onset cases should be stratified into mild, moderate, or severe disease categories to guide initial therapy. In general, mild-to-moderate UC can be managed in the outpatient setting with 5-ASAs, mesalamine, and topical corticosteroids (combined topical and rectal therapy ideal) and with oral corticosteroids in unresponsive cases. Oral or IV corticosteroids in the short-term are used for moderate UC with consideration of long-term options such as biologic agents or immunomodulators. Patients with moderate UC, those recalcitrant to IV corticosteroids, or those with disease complications should be considered for a biologic agent or CsA; colectomy is also a rescue option for moderate-to-severe cases. Early surgical involvement is crucial, and colectomy may be life-saving in refractory or fulminant cases. Frequent assessments are needed to determine clinical response with intensification of therapy as needed to achieve disease control. Short-term treatment choices may be influenced by long-term management goals. Several new drugs have shown efficacy and safety for UC. Medication compliance and health-related QOL are important patient-centered issues. Future directions include continued drug development with longer-term safety and efficacy profiling and patient initiatives to encourage continued quality IBD care.

Disclosure

Dr Sunanda Kane is a consultant for AbbVie and Shire. Renée Marchioni Beery reports no conflicts of interest in this work.

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