A Practical Clinical Approach to the Management of High-Risk Ulcerative Colitis

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Abstract: Patients with ulcerative colitis (UC) can experience periods of recurrent disease activity with a range of symptoms, including abdominal pain, rectal bleeding, urgency, and diarrhea. Although long-term remission will be achieved and maintained in most cases, the course of UC varies from patient to patient. Patients can be defined according to whether they are in remission or have mild, moderate, severe, or fulminant disease, and hospitalization can occur under different circumstances. In these cases, determining the next course of therapy is essential. The aim of this article is to present an approach to the treatment of high-risk UC in both the outpatient and inpatient settings. Also presented is a critical appraisal of alternative and emerging approaches to the management of patients with high-risk UC. Fundamental principles are key in the management of high-risk UC, including discussing the goals of treatment with the patient and family, assessing each patient's risk level and prognostic factors in addition to disease activity to inform therapeutic choices, understanding drug mechanisms and pharmacokinetics, and using objective measures to monitor disease response. In the treatment of all patients with high-risk UC, a balanced approach to deciding between medical and surgical options must be maintained.

Keywords
Ulcerative colitis, management, colectomy, cyclosporine, infliximab

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that is characterized by a superficial level of inflammation of the bowel. Patients with UC can experience recurrent disease activity with a range of symptoms, including abdominal pain, rectal bleeding, urgency, and diarrhea. Although long-term remission will be achieved and maintained in most patients, UC is heterogeneous, and its course varies from patient to patient.[1] Patients can be defined according to whether they are in remission or have mild, moderate, severe, or fulminant disease. Hospitalization can occur and may be related to relapsing disease, infection, severe or fulminant disease activity, or medically refractory disease. In these cases, it is vital to identify the patient's risk level early when determining the next course of therapy.[2] The aim of this article is to present an approach to the treatment of high-risk UC in

both the outpatient and inpatient settings, in addition to a critical appraisal of alternative and emerging approaches to the management of patients with high-risk UC.

Outlining the Patient With High-Risk Ulcerative Colitis

Identifying the patient with UC who is at high risk is a critical first step. High-risk UC may be defined by specific outcomes, including UC-related surgery, hospitalizations, emergency department visits, neoplasia, *Clostridioides difficile* infection (CDI), nonadherence, or loss of response to therapy. It is important to understand disease activity and prognosis by risk stratification to determine the choice of treatment.

Disease activity can be determined according to the new American College of Gastroenterology UC activity index.[3] UC activity can be classified as remission, mild, moderate, severe, or fulminant. Endoscopic evaluation uses well-established scoring systems such as the Mayo Endoscopic Subscore (MES), which ranges from 0 to 1 for normal findings or inactive disease to 3 for severely active disease.[4] Another, more recently proposed scoring system is the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), which is based on 3 main parameters: vascular pattern (scored 0-2), bleeding (scored 0-3), and erosions and ulcers (scored 0-3).[5] In a retrospective review by Xie and colleagues, 92 patients with acute severe colitis were assessed for the need for colectomy.[6] The UCEIS outperformed the MES as a predictor of the need for colectomy in patients with acute severe colitis. In predicting need for colectomy, the positive predictive value of a UCEIS score greater than or equal to 7 is higher than that of an MES equal to 3.[6] Use of a standardized endoscopic scoring system is highly recommended to obtain objective measures of disease activity that can be compared from one examination to the next.

A standard assessment of disease activity alone is insufficient to guide the selection of therapy; understanding disease severity also is essential.[3] Disease severity is determined on the basis of the inflammatory burden as assessed by inflammatory markers and endoscopic findings, disease course, and disease effect.[3] Poor prognostic factors refer to the likelihood of a need for colectomy, and include age younger than 40 years at diagnosis, extensive colitis, severe endoscopic disease (UCEIS ≥7, MES=3), hospitalization for colitis, corticosteroid requirement, elevated C-reactive protein (CRP) level or erythrocyte sedimentation rate, low serum albumin level, and CDI or cytomegalovirus (CMV) infection (Table 1).[3,7] Other indicators of high-risk UC include previous failure to achieve remission, progression of disease extent, and thromboembolic complications. Disease effect is also taken into account in identifying patients with high-risk UC. In a large cohort of patients with IBD, severe and active disease were risk factors for depression and anxiety.[8] In comparison with persons who do not have IBD, patients with IBD have health care costs that are 3 times higher, out-of-pocket costs that are 2 times higher, and more work-related lost wages.[9]

Triggers of severe and fulminant colitis can be unknown in many cases. However, CDI and CMV infection have been shown to exacerbate colitis. Other potential triggers of severe and fulminant colitis include polypharmacy,[10] cessation of smoking,[11] nonadherence to maintenance therapy,[12] pseudo-medical resistance (mesalamine intolerance),[13] and pregnancy.[14] Pregnant women with UC were at a higher risk for relapse than nonpregnant women with UC both during pregnancy (relative risk [RR], 2.19; 95% CI, 1.25-3.97) and in the postpartum period (RR, 6.22; 95% CI, 2.05-79.3).[14]

Table 1. Factors Associated With Increased Risk for Colectomy in Ulcerative Colitis

Age <40 years at diagnosis
Clostridioides difficile or cytomegalovirus infection
Colitis-related hospitalization
Corticosteroid requirement
Elevated C-reactive protein
Elevated erythrocyte sedimentation rate
Extensive colitis
Low serum albumin
Severe endoscopic disease (Mayo Endoscopic Subscore=3, Ulcerative Colitis Endoscopic Index of Severity ≥7)

Treatment of the Outpatient With High-Risk Ulcerative Colitis

First, risk factors for a poor prognosis should be identified (Table 1). Second, it is important to rule out concurrent CDI, CMV infection, and now severe acute respiratory syndrome coronavirus 2 infection.[15] A meta-analysis that included 6 studies with data from 1998 through 2009 found that CDI is a significant risk factor for colectomy in patients with IBD, mainly those with UC (odds ratio, 1.90; 95% CI, 1.23-2.93).[16] Third, the choice of therapy should be based on efficacy, safety, patient comorbidities, and patient choice. Patients may have preferences regarding the method of drug delivery (oral administration, injection, or infusion) depending on their lifestyle (Table 2). The medical therapy used to induce remission informs

Table 2. Treatment Options for the Outpatient With High-Risk Ulcerative Colitis

Treatment	Induction	Maintenance	Dosing Comments
Corticosteroids	✓	X	Prednisone 40 mg po every day
Thiopurines	X	✓	TPMT first (possibly NUDT15, too)
Anti-integrin (vedolizumab)	✓	✓	0, 2, and 6 weeks, then every 8 weeks IV (SC formulation coming)
Anti-p40 antibody (ustekinumab)	✓	✓	IV load, then SC every 8 weeks
Anti-TNF agent (adalimumab, golimumab, infliximab)	✓	✓	Variable depending on drug, best evidence for therapeutic drug monitoring
JAK inhibitor (tofacitinib)	✓	✓	Required to fail TNF inhibitor first

IV, intravenous; JAK, Janus kinase; NUDT15, nudix hydrolase 15; po, by mouth; SC, subcutaneous; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase.

the choice of therapy used to maintain remission. Not all therapies can or necessarily should be used for both. For example, corticosteroids can be used for the induction of response or remission, but not for maintenance. Thiopurines are recommended for maintenance in corticosteroid-responsive patients, but not for induction therapy. Biologics such as anti-integrins (vedolizumab [Entyvio, Takeda]), the anti-p40 antibody (ustekinumab [Stelara, Janssen]), anti–tumor necrosis factor (TNF) agents (adalimumab, golimumab [Simponi, Janssen], infliximab), and targeted synthetic small molecules such as Janus kinase (JAK) inhibitors (tofacitinib [Xeljanz, Pfizer]) can be used for both induction and maintenance (Table 2).[3,7,17]

Fourth, concomitant rectal therapy should be used to gain control of rectal urgency and improve response. An enema or suppository that acts directly on the affected area will decrease symptoms and improve patients' quality of life. Fifth, mucosal inflammation should be reassessed early. After the start of therapy, as early as 2 weeks but usually between 4 and 6 weeks after, reassessment should occur with measurement of the CRP or fecal calprotectin (FC) level to obtain an objective demonstration of improvement in the patient's condition. Ensuring that the patient understands the importance of this approach after starting a new therapy is essential to successful treatment, and will also improve adherence to therapy.

Sixth, proactive optimization of therapies should occur by educating the patient and making sure that treatments and laboratory results are received in a timely manner. Identifying patients at risk for a higher rate of drug clearance is important to understand why certain therapies may be less likely to work. Increased drug clearance decreases exposure of the drug and decreases control of the disease. Although the data available are predominantly for anti-TNF agents, the risk factors for higher rates of drug clearance are similar to other monoclonal antibodies. Predictors of increased clearance of monoclonal antibodies include high levels of inflammatory markers, high body mass index, male sex, and, very importantly, a low albumin level.[18]

Part of proactive therapeutic optimization includes conducting a post-loading assessment of drug and the bowel to confirm drug levels and disease response. A post hoc analysis of data from ACT revealed that the infliximab level at week 8 is predictive of whether the response to therapy will continue at weeks 30 and 54. A higher infliximab level at week 8 is associated with a greater likelihood of clinical remission at weeks 30 and 54.[19] Therefore, early drug assessment in patients with high-risk disease can help determine the time to escalate the dose and monitor the patient more closely. Further, the ACT post hoc analysis indicated that early mucosal healing, defined by an MES of 0 or 1 at week 8, was associated with better long-term outcomes, including a lower risk for colectomy through 54 weeks of follow-up, a greater likelihood of corticosteroid-free symptomatic remission, and ongoing mucosal healing at weeks 30 and 54.[20] The fact that an MES of 0 or 1 was associated with these outcomes shows that a perfectly healed bowel is not necessary for preventing colectomy[20]; other research has since supported this observation.

As an alternative, measuring FC levels is a reliable way to predict endoscopic response to IBD therapy. In a study of 40 patients who had IBD treated with vedolizumab, an FC level below 250 μg/g at 8 weeks accurately predicted an endoscopic response and histologic remission at week 16.[21] In another study, performed in 38 patients who had Crohn's disease treated with ustekinumab, an FC

level below 250 μg/g at week 8 predicted an endoscopic response at week 16.[22] The FC level appears to respond to therapy rapidly, as early as by 2 weeks and certainly by 8 weeks, and a trend of the biomarker to below 250 μg/g is a good indication that the chosen therapy is effective. Overall, it is necessary for the outpatient with high-risk UC to be assessed within 6 to 8 weeks after starting a new therapy and to undergo continual proactive monitoring to ensure that a response is occurring, prevent hospitalization, and preserve an improved quality of life.

Treatment of the Inpatient With High-Risk Ulcerative Colitis

Indications for the hospital admission of the patient with high-risk UC and acute severe UC (ASUC) include severe disease activity that is impairing daily function, critical laboratory values, and nonresponse to outpatient medical management. Other indications include an adverse event related to the disease, such as deep vein thrombosis (DVT) or bowel perforation, and an adverse event related to therapy, such as infection. According to the American College of Gastroenterology UC guidelines, management of the hospitalized patient with UC begins by initiating DVT prophylaxis because patients with severe inflammation are at higher risk for venous thromboembolic complications.[3] DVT prophylaxis does not increase the risk for hemorrhage.[23] Stool should be tested to rule out CDI, and a flexible sigmoidoscopy with biopsies should be performed within 48 hours of admission to rule out CMV infection. An assessment for megacolon may be performed with radiologic imaging, but a physical examination of the patient can also indicate if the abdomen is distended, tender, and tympanic. Importantly, early involvement of the colorectal surgery team is essential to prepare proactively for the possibility of nonresponse to medical therapy or emergent events during the course of hospitalization.[3,7] Endoscopic assessment early in admission was associated with improved hospital outcomes in patients with UC in a cross-sectional study using data from the Nationwide Inpatient Sample database of 84,359 patients with UC-related hospitalizations. Early endoscopy was associated with decreased mortality, lower total hospital costs, and shorter length of stay, but risks of endoscopic procedures should be considered.[24]

Medical Options for the Inpatient With High-Risk Ulcerative Colitis

For management of the inpatient, 3 major options are supported by robust data: intravenous (IV) corticosteroids, infliximab, and cyclosporine (Table 3).

Corticosteroids IV corticosteroids are used to induce response and remission but are not a maintenance option. In a meta-analysis of cohort studies and controlled clinical trials conducted between 1974 and 2006, 27% of patients who were administered IV corticosteroids for severe UC required colectomy, and the death rate was 1%. The predictors of medical failure with IV corticosteroids included more extensive disease, stool frequency after 3 days, systemic symptoms such as fever and tachycardia, a high CRP level, a low albumin level, and radiographic demonstration of a distended colon.[25] If no significant decrease in symptoms or improvement in objective markers such as the CRP level occurs after 3 to 5 days of IV corticosteroids, other treatment options,

Table 3. Medical Options for the Inpatient With High-Risk Ulcerative Colitis

Treatment	Induction	Dose	Duration of Induction Dosing	Maintenance	Maintenance Options
Corticosteroids (IV)	✓	Methylprednisolone 60 mg every day Hydrocortisone 100 mg TID/QID	3-7 days	X	• Thiopurines • Anti-TNF ± thiopurines or methotrexate • Vedolizumab • Ustekinumab • Tofacitinib (if failed anti-TNF agent)
Infliximab	✓	5 or 10 mg/kg IV	0, 2, and 6 weeks Possible accelerated dosing	✓	• Unknown if dose reduction possible after accelerated dosing for induction
Cyclosporine (IV)	✓	2-4 mg/kg IV continuously; target 250-400 ng/mL	7-14 days	X	• Thiopurines • Vedolizumab • Ustekinumab

IV, intravenous; QID, 4 times daily; TID, 3 times daily; TNF, tumor necrosis factor.

Table 4. Studies of Infliximab for Severe Ulcerative Colitis in the Hospital Setting

Study	N	Infliximab Dose	Outcome Measure	Response Rate		
				Infliximab	Placebo	Corticosteroid
Sands et al[30]	11	5, 10, and 20 mg/kg 1 infusion	Lichtiger score at 2 weeks	50%	0%	–
Armuzzi et al[26]	20	5 mg/kg 3 infusions	Sutherland score at 2 weeks	100%	–	100%
Ochsenkühn et al[29]	13	5 mg/kg 3 infusions	Lichtiger score at 3 and 13 weeks	83%	–	86%
Järnerot et al[27]	45	5 mg/kg 1 infusion	No colectomy at 90 days	71%	33%	–
Lees et al[28]	39	5 mg/kg 1 infusion	No colectomy at 90 days	67%	–	–

including infliximab, cyclosporine, and surgery, should be seriously considered.

Infliximab Infliximab is effective for severe UC in the hospital setting and may be continued as maintenance therapy (Table 3). Several studies have evaluated the efficacy of infliximab in this setting, although the types of infusions and outcome measures differed (Table 4).[26-30] Studies by Sands and colleagues,[30] Järnerot and colleagues,[27] and Lees and colleagues[28] evaluated a single infusion of infliximab, but with differing endpoints. The trial of Järnerot and colleagues demonstrated that a single 5-mg/kg infusion of infliximab prevented colectomy at 90 days significantly more effectively than placebo.[27] In a follow-up of the trial, although 50% of the patients did eventually undergo colectomy after 3 years, these patients had received only a single infusion of infliximab, and then went on to receive maintenance therapy, which included infliximab. The patients who received this single infusion were still significantly less likely to have undergone colectomy at 3-year follow-up (P=.012).[31] Known predictors of response to infliximab include interleukin-23 receptor gene variants and a negative antineutrophil cytoplasmic antibody status, whereas predictors of lack of response include a low infliximab level and a low serum albumin level at week 2. A low albumin level may indicate leakage of the monoclonal antibody into the stool and therefore a reduced exposure to drug. A large amount of infliximab in the stool of patients with colitis was correlated with a lack of response to therapy.[32,33] Escalation of the infliximab dose has been thought to be a solution to overcome rapid drug clearance, but small studies of accelerated dosing schedules have not demonstrated an overall benefit in preventing colectomy.[34,35] Furthermore, a meta-analysis suggested that higher dosing of infliximab was no better than standard dosing.[36] Therefore, although infliximab is effective in some hospitalized patients with ASUC, a patient who does not initially respond to infliximab should be moved to other options, including surgery.

Cyclosporine Cyclosporine or tacrolimus may be used as induction therapy, and rarely as short-term maintenance, but both are more often used as a bridge to thiopurines, vedolizumab, or more recently ustekinumab (Table 3). Cyclosporine and tacrolimus are calcineurin inhibitors, which are non–protein-based, lipid-bound therapies. Cyclosporine is an older therapy, delivered as a continuous IV infusion at a dose of 2 to 4 mg/kg in the hospital setting, with an optimal drug level between 250 and 400 ng/mL to induce a response. IV or oral corticosteroids are continued concomitantly with *Pneumocystis jirovecii* pneumonia prophylaxis, usually trimethoprim-sulfamethoxazole (1 tablet 3 times weekly). IV cyclosporine is converted to oral therapy on discharge. Several studies have demonstrated a strong benefit of cyclosporine in ASUC either with or without corticosteroids, with a significant response occurring within 7 to 14 days.[37-40] However, there are contraindications to cyclosporine. Because cyclosporine is a lipid-bound therapy, the likelihood of seizures may increase in patients with very low cholesterol levels, so lower doses should be used in the setting of low serum lipid levels. Given the renal clearance of drug, diminished renal function is a relative contraindication to cyclosporine use. In addition, a relative contraindication is the previous failure of optimized thiopurines or failure of vedolizumab because these are the 2 primary treatments used after cyclosporine success.

In deciding between cyclosporine or infliximab to induce remission in a patient failing to respond to IV

corticosteroids, the GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives) experience from centers in France and Belgium reported that no significant difference was found between patients with severe UC who were randomized to cyclosporine and those randomized to infliximab within the first 100 days of therapy initiation and after 7-year follow-up.[41,42] Importantly, no differences were noted in effectiveness, adverse events, or baseline albumin levels. However, it is our strong contention that non–protein-based therapies are preferable when the serum protein levels are low. Another consideration in the choice between cyclosporine and infliximab is sequencing. This pertains to the half-life of each drug. If cyclosporine is ineffective for induction, its short half-life allows the drug to be washed out in several days, and infliximab can then be started. This is preferable to stacking immunosuppression if infliximab is used first and found to be ineffective, with the patient then cycled to cyclosporine.[43] Two studies have demonstrated that cyclosporine can be used safely after infliximab, and one of them also demonstrated that infliximab can be used after cyclosporine.[44,45] Neither study reported any substantial adverse events. Often, patients were salvaged when the second therapy was initiated. We have previously published a case report suggesting the utility of knowing the serum infliximab concentration before cyclosporine is started; infliximab was undetectable in our patient, prompting the use of cyclosporine, which was successful.[43]

Other Medical Therapies for the Inpatient With Acute Severe or Fulminant Ulcerative Colitis

Calcineurin Inhibitor Therapy as a Bridge to Vedolizumab Maintenance Therapy We have demonstrated that in patients with acute severe or fulminant UC who receive cyclosporine or tacrolimus induction therapy, vedolizumab is a safe and efficacious option for maintenance therapy (Table 5). In a retrospective study of 11 patients, 55% of the patients on vedolizumab maintenance therapy after cyclosporine induction therapy were in clinical remission at week 14, and 45% of them at week 52.[46] Our larger, longer-term, retrospective study demonstrated that 50% of patients on vedolizumab maintenance therapy after cyclosporine induction were in clinical remission at week 14, and 43% at week 52; 76% remained in remission on vedolizumab at 2-year follow-up.[47] A retrospective study from GETAID reported a similar success rate, with 38% of patients in clinical remission at week 14.[48] In a retrospective study of 13 patients who were transitioned from IV to oral cyclosporine in combination with vedolizumab, the corticosteroid-free remission rate at 14 weeks was 54% and at week 52 was 63%.[49] No study reported significant adverse events. An open-label prospective study that included long-term follow-up of patients with ASUC who were bridged from cyclosporine to vedolizumab demonstrated a 93% clinical remission rate at week 14 and a 79% clinical remission rate at week 52, with corresponding endoscopic improvement.[50] Given our understanding of vedolizumab as a safe, organ-selective therapy and these published findings, it is reasonable to consider this approach in patients with high-risk UC. We recently shared our experience with a cyclosporine bridge to ustekinumab in 2 patients.[51]

Emerging Consideration of Tofacitinib for Acute Severe Ulcerative Colitis The small-molecule JAK inhibitor tofacitinib is another non–protein-based therapy that may be useful to induce a response or remission in an inpatient with ASUC. In a case series, 4 patients with ASUC and a high likelihood of failing IV corticosteroids received off-label tofacitinib as induction therapy at a dose of 10 mg 3 times daily.[52] Although their symptoms rapidly decreased and their CRP levels improved, 2 patients subsequently went to colectomy, and the other 2 did not continue with tofacitinib as maintenance therapy.

Table 5. Calcineurin Inhibitor Therapy as a Bridge to Vedolizumab Maintenance Therapy in Ulcerative Colitis

Study	Design	N	Week 14 Clinical Remission Rate	Week 52 Clinical Remission Rate
Resál et al[49]	Retrospective	13	54%	63%
Christensen et al[46]	Retrospective	11	55%	45%
Ollech et al[47]	Retrospective	71	50%	43% (76% at 2 years)
Pellet et al[48]	Retrospective	39	38%	–
Tarabar et al[50]	Prospective	17	93%	79%

However, these initial findings may be encouraging for future clinical trials of inpatient induction therapy with high-dose tofacitinib.

We have reported tandem therapy with cyclosporine and tofacitinib in a 24-year-old man with severe UC.[53] The patient had a history of primary sclerosing cholangitis and autoimmune hepatitis, and pancolitis was diagnosed at age 20 years. The patient was in remission and maintained on mesalamine. As an inpatient, he failed vedolizumab and infliximab and so began IV cyclosporine followed by oral cyclosporine. While he was in remission and was an outpatient, the oral cyclosporine was stopped for 2 days, and he then started tofacitinib at 10 mg twice daily. He remained in remission on tofacitinib at 2 years of follow-up.

Although tofacitinib therapy may allow a patient to avoid corticosteroids and may be beneficial in a patient with a low albumin level or as salvage after failure of other biologic therapies, the clinician must be sure to screen for venous thromboembolism risk, vaccinate with attenuated herpes zoster vaccine, and check laboratory values (lymphocytes, neutrophils, hemoglobin, lipids, liver enzymes) at initiation, at 4 to 8 weeks, and every 3 to 6 months thereafter.

Planning for Surgery in Acute Severe Ulcerative Colitis

Although both patients and gastroenterologists wish to avoid colectomy, it is important to acknowledge that colectomy is a safe and effective option for patients with UC that is not responding to medical therapy. Patients admitted with ASUC should be aware that surgery is an option and consult with the surgery team at the time of admission. Early involvement of the colorectal surgery team is important for a patient with high-risk UC so that the option is well-known and the patient can be monitored by both surgeons and gastroenterologists. Collaboration with the surgical team regarding the timing of a staged approach and appropriate medical management is recommended.[54] In discussion with the patient, it is essential to indicate that the surgery is curative of colitis by definition but is not curative of IBD; it is becoming increasingly understood that the underlying immune response may be associated with a subsequent IBD-like presentation in another anatomic region after colectomy and ileal pouch construction.

Patients for whom urgent colectomy is appropriate include those with toxic megacolon, bowel perforation, or severe hemorrhage. Examination upon admission is essential in these cases because delayed surgery is associated with an increase in postoperative complications.[54,55]

Performing colectomy effectively is much preferred to waiting until it is urgent or until all other options have been tried. In a large, retrospective, matched-cohort study, the mortality rate after elective surgery in patients with advanced UC who were older than 50 years was significantly lower than the mortality rate after further medical therapy (hazard ratio, 0.60; 95% CI, 0.45-0.79).[56]

Conclusion

We have presented a practical clinical approach to the management of patients with high-risk UC. It is essential to identify patients according to their risks and to be proactive in their management, with a consideration for factors such as unfavorable pharmacokinetics and the early involvement of colorectal surgery.

Disclosures

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