CASE STUDY SERIES IN IBD

Rescue Therapy for Acute Severe Ulcerative Colitis: A Case Report

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Patient Presentation

A 64-year-old man without a significant past medical history presented to a tertiary care center for a second opinion regarding management of his inflammatory bowel disease. Approximately 1.5 years prior to presentation, he developed cramping abdominal pain, frequent bowel movements up to 3 to 4 times per day with tenesmus, and intermittent hematochezia. Initial basic evaluation included a negative *Clostridioides difficile* polymerase chain reaction and a normal C-reactive protein (CRP) level (5.7 mg/L). His symptoms persisted for approximately 1 year with his bowel movements increasing in frequency up to 10 times per day, prompting a colonoscopy, which demonstrated active colitis in the descending and sigmoid colon. Biopsies demonstrated chronic active colitis in the descending and sigmoid colon as well as unremarkable colonic-type mucosa in the rectum. He was diagnosed with ulcerative colitis and treated with a methylprednisolone taper and metronidazole. His diarrhea and intermittent hematochezia persisted after 7 days of this therapy. He presented to his local emergency department (ED) and was prescribed an 8-week prednisone taper starting at 40 mg daily, mesalamine titrated to 4.8 g daily, and as-needed evening mesalamine enemas. His bowel movement frequency decreased while he was taking prednisone; however, when prednisone was tapered to 30 mg daily, the frequency of his bowel movements would increase again up to 10 times per day. He was hospitalized for ongoing symptoms, and he received intravenous (IV) methylprednisolone and was continued on mesalamine. Repeat colonoscopy demonstrated pancolitis. He received 1 dose of rescue infliximab of uncertain dosing at this outside institution. His bowel frequency decreased to 8 times per day, but he reported ongoing urgency and hematochezia. At this point, he had experienced a 30-pound weight loss over the course of several months. He was discharged on 40 mg of prednisone daily with the plan for a repeat dose of infliximab in 2 weeks.

The patient presented to our institution for a second opinion. Upon presentation to the clinic, he appeared chronically ill. He was afebrile with a blood pressure of 93/68 mm Hg and a heart rate of 108 beats per minute. His examination was remarkable for dry mucous membranes; a soft, nondistended, and nontender abdomen without organomegaly; and an unremarkable rectal examination revealing only a small skin tag. He reported 10 bowel movements per day. He denied use of any nonsteroidal anti-inflammatories, recent travel, or recent antibiotic use. He denied missing doses of his medications. Family history was notable for Crohn's disease in his brother. He was a former smoker but had quit several years prior. He had had a routine screening colonoscopy 2 months prior to the onset of his symptoms that was without evidence of colitis or neoplasm.

His laboratory tests were notable for a hemoglobin level of 9.1 g/dL, leukocyte count of 16.1 × 10^9/L, platelet count of 699 × 10^9/L, CRP level of 148.9 mg/L, and negative stool pathogen panel. Computed tomography enterography demonstrated left colonic predominant nonspecific active inflammatory changes without evidence of small bowel disease, stricturing, or penetrating disease. Outpatient flexible sigmoidoscopy demonstrated inflammation in a continuous and circumferential pattern from the rectum to the hepatic flexure with the appearance of pseudomembranes, graded with a Mayo score of 3 (severe with spontaneous bleeding and ulcerations).[1] Biopsies demonstrated moderate active chronic colitis without granulomas or dysplasia. Cytomegalovirus immunostaining was negative.

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Table. Criteria for Scoring Disease Activity

≥6 bloody stools per day PLUS any 1 of the following:	
Variable	**Value**
Temperature	Evening temperature >37.5° C or a temperature >37.8° C on at least 2 days out of 4
Pulse	>90 beats per minute
Anemia	Hemoglobin <10.5 g/dL
Erythrocyte sedimentation rate	>30 mm/hour

Adapted from Truelove and Witts' criteria for severe disease activity in ulcerative colitis.[2]

The patient was hospitalized for signs and symptoms consistent with severe ulcerative colitis for an expedited infliximab infusion (Table). Colorectal surgery was consulted for ulcerative colitis refractory to medical management at the time of hospital admission. His infliximab level drawn prior to this infusion came back at 25 mcg/mL. He also received IV methylprednisolone for 3 days, and his mesalamine was discontinued. His bowel movement frequency did not significantly decrease. Initially, the patient was extremely hesitant to proceed with surgery, as he felt that not enough had been done medically. After further discussion, he underwent a laparoscopic subtotal colectomy with diverting loop ileostomy on day 5 of his hospital stay, with a plan for laparoscopic proctectomy and creation of an ileal pouch–anal anastomosis in a staged fashion. Within 12 hours, he was feeling better and taking sips of fluids, and he was discharged within 48 hours. At 2-week follow-up, he was off corticosteroids and planning his return to work. His appetite had returned, and he was starting to gain weight.

Discussion

Acute severe ulcerative colitis (ASUC) is a medical emergency and can be defined by Truelove and Witts' criteria (Table).[2] This patient had 2 signs of systemic toxicity (tachycardia and anemia) and had a significantly elevated CRP level. Disease extent in patients with ulcerative colitis should be characterized according to the Montreal classification (proctitis [E1], left-sided colitis [E2], or extensive colitis [E3]).[3] An unprepped flexible sigmoidoscopy should be performed within at least 72 hours of hospital admission and ideally within 24 hours of admission to examine disease activity and evaluate for concomitant infection.[4,5] Full colonoscopy should be avoided because of the risk of perforation. All patients should also undergo a stool pathogen panel to rule out *C difficile* infection and undergo some type of cross-sectional imaging to rule out dilation.[5]

The first-line treatment for ASUC is corticosteroids. Methylprednisolone at a maximum dose of 60 mg for 3 to 5 days should be initiated to induce remission. There is no additional benefit for doses above 60 mg or for extending treatment duration beyond 7 days.[6] Alternatively, hydrocortisone 100 mg 3 to 4 times per day can be used to induce remission. The mean response rate to corticosteroids is approximately 67%.[6] Response to corticosteroid treatment can be determined by evaluation of vital signs, physical examination to assess for toxic megacolon or perforation, and assessment of frequency of bowel movements, hematochezia, and pain.[5] The Oxford Index is used to predict nonresponders to therapy. Patients with greater than 8 bowel movements on day 3 of corticosteroid treatment, and patients with 3 to 8 bowel movements per day and a CRP level above 45 mg/L after treatment, have a greater than 85% likelihood of requiring colectomy.[7] This patient did not undergo a repeat CRP, but did continue to have 9 bowel movements per day.

All patients with ASUC should receive deep venous thrombosis (DVT) prophylaxis to prevent venous thromboembolism, as they are at a significantly increased risk for clotting.[5,8] DVT prophylaxis is safe even in patients who have active bleeding from their ulcerative colitis.[9] Empiric adjuvant antibiotic administration is not recommended in patients with ASUC unless there is concern for systemic infection.[5] Anticholinergic medications, nonsteroidal anti-inflammatory medications, and opioids should be avoided. Patients who are not responding to IV corticosteroids after 3 to 5 days of treatment should receive medical rescue therapy with either infliximab or cyclosporine. The standard induction regimen for infliximab is 5 mg/kg at weeks 0, 2, and 6.[10] Treatment efficacy is similar between both agents.[11-13] Cyclosporine therapy is limited by relatively common side effects, including nephrotoxicity, electrolyte derangements, and neurotoxicity, and has fallen out of favor given the availability of and comfort with using infliximab. Administering rescue infliximab in a patient with weight loss or

hypoalbuminemia should be avoided unless the patient will be in the hospital for monitoring or will be able to undergo close follow-up locally. Low serum albumin concentration is associated with rapid infliximab clearance, and serum albumin less than 2.5 g/dL is associated with failure of infliximab rescue therapy.[14,15] Although several trials have examined accelerated or high-dose infliximab induction to improve the efficacy of the drug, only the standard dosing is recommended currently.[5,16] Rescue therapy with golimumab (Simponi, Janssen), vedolizumab (Entyvio, Takeda), tofacitinib (Xeljanz, Pfizer), or adalimumab is not recommended at this time.[5]

Surgical consultation should be obtained at the time of hospital admission so that there is early discussion of the possibility of colectomy among patients who are not adequately responding to medical therapy within 3 to 5 days.

Patients with extensive colitis, those requiring systemic corticosteroids, those with an elevated CRP level, those with more severe endoscopic disease (Mayo endoscopic subscore of 3 or higher), and those with a previous hospitalization for ulcerative colitis are at higher risk for requiring a subsequent colectomy.[17] Surgical consultation should be obtained at the time of hospital admission so that there is early discussion of the possibility of colectomy among patients who are not adequately responding to medical therapy within 3 to 5 days.[5] Patients should not be discharged from the hospital if they are continuing to have greater than 8 bloody bowel movements per 24 hours. Surgery should not be delayed in patients who need it, as there is an increased risk of postoperative complications, including wound infections, small bowel obstruction, venous thromboembolism/pulmonary embolism, sepsis, and inadequate wound healing.[18,19] Although failure to respond to medical therapy is the most common reason for colectomy in ASUC, additional absolute indications for surgery are toxic megacolon, colonic perforation, and multiorgan dysfunction.[4] Surgery should not be delayed just because a patient has received medical rescue therapy with infliximab or cyclosporine, as there is no increased rate of postoperative complications associated with use of these medications.[20] The procedure of choice in a hospitalized patient is a subtotal colectomy with ileostomy.

In retrospect, was there anything that could have been done differently in this patient to potentially avoid this outcome? At the time of his diagnosis and first exposure to corticosteroids, he had not significantly improved in a week's time and required an ED visit. The initial corticosteroid course was too short, and he was not given a follow-up plan for the corticosteroids. In the ED, he was started on corticosteroids as well as mesalamine, and when hospitalized the first time was continued on the mesalamine. There is no role for its use in ASUC. He was discharged from that first hospitalization too soon, as he was still exhibiting signs and symptoms of ASUC; in addition, no surgical consult was obtained. In ulcerative colitis, a large weight loss, like that experienced by this patient, is a warning sign of severe disease, and a CRP level of greater than 100 mcg/mL in the absence of infection reflects severe inflammation. A random infliximab level of 25 mcg/mL also suggested that more rescue infliximab was not going to be of value, and surgery should have been recommended on hospital day 2 rather than day 5. Gastroenterologists often feel that surgery is a failure and a last resort, but then do not see how well the patient looks and feels after that colectomy, and how continued medical therapy, especially in an older patient, is not optimal care.

Conclusion

ASUC is a medical emergency requiring hospitalization. Patients should be tested for *C difficile* infection on hospital admission and should undergo an unprepped flexible sigmoidoscopy within 72 hours. IV corticosteroids are the first-line treatment for ASUC, and their use should be limited to a maximum of 5 days. Patients who are not responding to corticosteroids may be considered for rescue medical therapy with either infliximab or cyclosporine. Low serum albumin concentration is associated with a worse prognosis and even treatment failure, so these patients should be monitored closely after receiving rescue therapy. Surgical consultation should be obtained at the time of hospital admission. Surgery should not be viewed as a failure in patients who are not responding to optimal medical therapy, and should not be delayed in those who need it.

Disclosures

Dr Rolak has no relevant conflicts of interest to disclose. Dr Kane serves as a consultant to Boehringer Ingelheim, Bristol

Myers Squibb, InveniAI, Gilead, Janssen, Predicta Med, Seres Therapeutics, TechLab, and Takeda. In addition, she serves as the editor for the IBD section of UpToDate.

References

1. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629.
2. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *BMJ*. 1955;2(4947):1041-1048.
3. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol*. 2005;19(suppl A):5A-36A.
4. Dulai PS, Jairath V. Acute severe ulcerative colitis: latest evidence and therapeutic implications. *Ther Adv Chronic Dis*. 2018;9(2):65-72.
5. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
6. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol*. 2007;5(1):103-110.
7. Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut*. 1996;38(6):905-910.
8. Scoville EA, Konijeti GG, Nguyen DD, Sauk J, Yajnik V, Ananthakrishnan AN. Venous thromboembolism in patients with inflammatory bowel diseases: a case-control study of risk factors. *Inflamm Bowel Dis*. 2014;20(4):631-636.
9. Ra G, Thanabalan R, Ratneswaran S, Nguyen GC. Predictors and safety of venous thromboembolism prophylaxis among hospitalized inflammatory bowel disease patients. *J Crohns Colitis*. 2013;7(10):e479-e485.
10. Chen JH, Andrews JM, Kariyawasam V, et al; IBD Sydney Organisation and the Australian Inflammatory Bowel Diseases Consensus Working Group. Review article: acute severe ulcerative colitis—evidence-based consensus statements. *Aliment Pharmacol Ther*. 2016;44(2):127-144.
11. Narula N, Marshall JK, Colombel JF, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. *Am J Gastroenterol*. 2016;111(4):477-491.
12. Laharie D, Bourreille A, Branche J, et al; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet*. 2012;380(9857):1909-1915.
13. Williams JG, Alam MF, Alrubaiy L, et al. Comparison of infliximab and ciclosporin in steroid resistant ulcerative colitis: pragmatic randomised trial and economic evaluation (CONSTRUCT). *Health Technol Assess*. 2016;20(44):1-320.
14. Whaley KG, Rosen MJ. Contemporary medical management of acute severe ulcerative colitis. *Inflamm Bowel Dis*. 2019;25(1):56-66.
15. Syal G, Robbins L, Kashani A, et al. Hypoalbuminemia and bandemia predict failure of infliximab rescue therapy in acute severe ulcerative colitis. *Dig Dis Sci*. 2021;66(1):199-205.
16. Chao CY, Al Khoury A, Aruljothy A, et al. High-dose infliximab rescue therapy for hospitalized acute severe ulcerative colitis does not improve colectomy-free survival. *Dig Dis Sci*. 2019;64(2):518-523.
17. Fumery M, Singh S, Dulai PS, Gower-Rousseau C, Peyrin-Biroulet L, Sandborn WJ. Natural history of adult ulcerative colitis in population-based cohorts: a systematic review. *Clin Gastroenterol Hepatol*. 2018;16(3):343-356.e3.
18. Leeds IL, Truta B, Parian AM, et al. Early surgical intervention for acute ulcerative colitis is associated with improved postoperative outcomes. *J Gastrointest Surg*. 2017;21(10):1675-1682.
19. Randall J, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg*. 2010;97(3):404-409.
20. Nelson R, Liao C, Fichera A, Rubin DT, Pekow J. Rescue therapy with cyclosporine or infliximab is not associated with an increased risk for postoperative complications in patients hospitalized for severe steroid-refractory ulcerative colitis. *Inflamm Bowel Dis*. 2014;20(1):14-20.