



Infliximab to treat severe ulcerative colitis

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Abstract

A 48-year-old female with severe ulcerative colitis refractory to conventional therapy was referred to our facility for management. The patient showed extensive ulcerative colitis since the age of 20 years and had failed therapy with 5-aminosalicylic acid agents and azathioprine. The disease remained active despite treatment with steroids and cyclosporine. The clinical and endoscopic parameters were consistent with severe disease. Infectious precipitants were ruled out. Given the severity of the disease and in order to avoid a colectomy, we started the patient on infliximab therapy. A dramatic clinical and endoscopic response was observed and she remained in remission at the end of a 1-year follow-up period. We discuss findings in the literature regarding the use of infliximab therapy in patients with ulcerative colitis who have failed steroids and cyclosporine.

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Key words: Cyclosporine; Infliximab; Treatment failure; Ulcerative colitis; Inflammatory bowel diseases

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INTRODUCTION

Infliximab is a monoclonal antibody against tumor necrosis factor alpha (TNF- α) used in the treatment of Crohn's disease and ulcerative colitis. It has demonstrated efficacy in patients with moderate to severe ulcerative colitis, as well as in those with severe disease who have failed intravenous (IV) steroids^[1]. According to historical data, patients with severe disease who fail IV steroids have a risk of colectomy of up to 60%. Currently, there are three therapeutic options: cyclosporine, infliximab and colectomy^[2]. Such patients are often treated empirically with cyclosporine or infliximab. If the patient fails to respond to either, colectomy is typically performed. Using infliximab to treat patients who have failed steroids and cyclosporine is controversial, since the risk of opportunistic infection is considered to be high. We report a case in which infliximab was safely introduced and successfully used in a patient with severe ulcerative colitis who would otherwise have undergone colectomy.

CASE REPORT

A 48-year-old female with ulcerative colitis presented to our facility for the management of refractory disease. She had extensive ulcerative colitis since the age of 20 years and had a number of flares requiring IV and oral (PO) steroids, having failed 5-aminosalicylic acid agents. In the prior 6 mo, the patient had been treated with azathioprine at 2 mg/kg per day and both IV and subsequent PO cyclosporine (8 mg/kg per day). She was referred for further management as she was passing in excess of six stools per day, as well as presenting bloody diarrhea and abdominal pain. She had severe anemia, with repeated need for blood transfusions. Sigmoidoscopy confirmed active ulcerative colitis (Figures 1 and 2). This clinical spectrum was despite current therapy with cyclosporine and azathioprine.

At the time of presentation, her blood pressure was 160/100 mmHg, with a pulse rate of 150 bpm, and an intense generalized abdominal pain. She had a white blood cell count of 161 000/mm³, hematocrit of 13%, hemoglobin of 5.0 g/dL, erythrocyte sedimentation rate of 130 mm in the first hour, C-reactive protein of > 5 mg/dL, iron of 10 mg/dL, albumin of 2 g/dL, and alpha 1-acid glycoprotein of 230 mg/dL. A colonoscopy revealed severe ulcerative colitis extending from the rectum (Figure 1). Biopsies confirmed chronic active colitis.

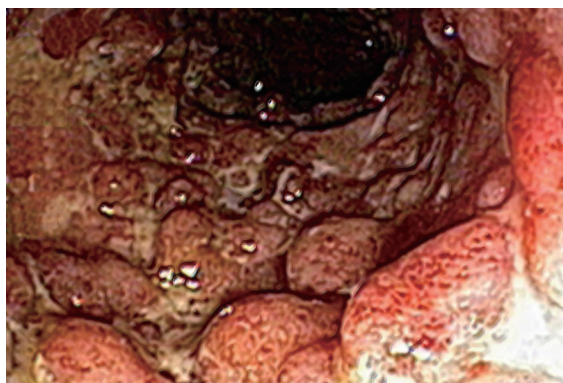


Figure 1 Rectal view during treatment with azathioprine.

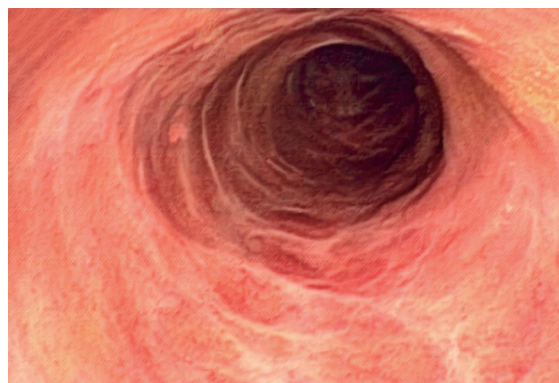


Figure 3 Colonoscopy: Rectal view after 18 mo of treatment with infliximab.



Figure 2 Colonoscopy: Sigmoid view during treatment with azathioprine.



Figure 4 Colonoscopy: Sigmoid view after 18 mo of treatment with infliximab.

Table 1 Laboratory test results by treatment regimen

	Azathioprine	Cyclosporine	Infliximab (after 18 mo of treatment)
Hemoglobin, g/dL	5.0	8.0	13.0
Hematocrit (%)	13	19	40
Erythrocyte sedimentation rate, mm in the first hour	130	230	7
Albumin, g/dL	2	2.5	3.5
Iron, mg/dL	10	15	55
α -1 glycoprotein, mg/dL	230	245	< 100
C-reactive protein, mg/dL	> 5	> 5	< 5

After 18 mo of infliximab treatment, the patient was in remission, with one stool per day and no abdominal pain. A repeat colonoscopy demonstrated marked endoscopic improvement (Figures 3 and 4). There was a dramatic improvement in the overall nutritional status of the patient and in the serum levels of all parameters, as shown in Tables 1 and 2. She remained in remission on maintenance infliximab and azathioprine at the last assessment.

DISCUSSION

Refractory ulcerative colitis is currently defined as an inadequate response to conventional treatment. In cases of ulcerative colitis, the symptoms used to determine whether an individual is refractory to treatment include

Table 2 Mayo scale score for ulcerative colitis by treatment regimen

	Azathioprine	Cyclosporine	Infliximab
Frequency of evacuations	3	3	0
Rectal bleeding	3	3	0
Endoscopic findings	3	3	0
Overall medical evaluation	3	3	0

fever, diarrhea three or more times per day, bleeding, and fecal urgency^[3]. Immunomodulators, such as azathioprine, have been used as adjuvant therapy in patients with ulcerative colitis who are classified as non-responders to oral steroids, the recommended initial dose being 2 mg/kg per day, which can be gradually increased if a satisfactory response is not achieved^[4].

Cyclosporine has been used in refractory patients, as well as in patients classified as non-responders, who typically present extensive or severe colitis. For such patients, treatment with cyclosporine appears to control the disease in approximately 90% of cases^[5-8]. In the present case, the patient did not exhibit a sustained response to cyclosporine, and there was recurrence within 1 mo, at which point infliximab was initiated.

Infliximab, a chimeric monoclonal antibody to TNF- α , was originally believed to bind biologically active TNF- α freely present in the lamina propria and expressed on inflammatory cells. However, it soon became clear that this binding phenomenon had to be

followed by complement binding and activation, leading to apoptosis of the activated inflammatory TNF- α -bearing cells, as well as inducing apoptosis of T cells^[9-11].

In two large-scale studies, designated Active Ulcerative Colitis Trial 1 and Active Ulcerative Colitis Trial 2, patients with ulcerative colitis were treated with infliximab, together with corticosteroids or the 6-mercaptopurin/azathioprine combination, and were monitored/evaluated using the Mayo scale^[12,13]. The authors found that the rate of remission was higher in patients treated with infliximab than in those receiving placebo.

Currently, the use of infliximab in patients with ulcerative colitis is recommended for those with corticosteroid dependence, refractory pouchitis and pouchitis in the maintenance phase, although there is still controversy regarding the appropriate duration of treatment^[14,15]. Treating patients with infliximab after failing steroids and cyclosporine is controversial, as one study reported a serious adverse event rate of 15%, due to opportunistic infections^[16-18]. In the case described here, we opted to maintain the infliximab, taking into account the quality of life that could be sustained without surgical intervention. The patient remained under treatment with infliximab every 8 wk for 2 years, at a dose of 5 mg/kg without adverse events and recurrence of the symptoms.

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