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Case Report

Rescue Therapy with Upadacitinib for Infliximab-Refractory Acute Severe Ulcerative Colitis Patient: A Case Report and Mini Review of the Literature

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon, characterized by the presence of ulcers and potential extraintestinal symptoms. Approximately 20% of UC patients may progress to acute severe ulcerative colitis (ASUC), a serious condition marked by resistance to conventional treatment methods. Prompt and intensive treatment for ASUC is essential to prevent adverse outcomes. The primary therapeutic approach typically involves intravenous corticosteroids; however, when this is ineffective, biological agents such as infliximab or immunosuppressants like cyclosporine are necessary. Upadacitinib, a Janus kinase (JAK) inhibitor, is approved for the treatment of moderate to severe UC in adult patients. However, its safety and efficacy for ASUC have not yet been established. For ASUC patients previously treated with infliximab, treatment options are limited, underscoring the need for new approaches to improve patient outcomes. JAK inhibitors could play a crucial role in this regard. This case report discusses a 40-year-old male with UC unresponsive to therapy for two years, who was treated with upadacitinib. The patient demonstrated clinical and endoscopic improvement within one week of initiating upadacitinib, indicating the drug's potential effectiveness in this challenging clinical context.

Keywords: Acute severe ulcerative colitis, infliximab refractory, rescue therapy, upadacitinib

INTRODUCTION

Ulcerative colitis is a chronic inflammatory condition of unknown origin that begins in the rectum and extends through the colon, characterized by alternating periods of exacerbation and remission. Common symptoms include rectal bleeding, diarrhea, and abdominal discomfort. The condition typically manifests in individuals aged 15-30 and 50-70. Treatment selection depends on the severity of the disease. Acute severe ulcerative colitis (ASUC) is a serious complication affecting approximately 20% of individuals with the condition. Despite advancements in treatment that have reduced the mortality rate associated with ASUC, about 30% of affected individuals still require colectomy surgery.[1]

ASUC, as defined by the modified Truelove and Witts criteria, requires the rapid administration of corticosteroid therapy.[1] On day three, patients are reassessed, and if there has been no improvement, infliximab or cyclosporine is administered as rescue options. If medical treatment proves unsuccessful, a surgical evaluation for colectomy is recommended.[2] Tofacitinib, a JAK inhibitor, shows promise as a rescue therapy after failed infliximab or cyclosporine treatment.[2] Another JAK inhibitor, upadacitinib, is approved for moderate-to-severe ulcerative colitis; however, its effectiveness in ASUC remains to be established.

The range of available options is more limited for ASUC patients who have previously received infliximab treatment. Expanding therapeutic options may help improve patient outcomes. This report presents the case of a 40-year-old male patient with ASUC who did not respond to either infliximab or ustekinumab. This case report examines the efficacy and utility of upadacitinib in treating ASUC, with written informed consent obtained from the patient.

CASE REPORT

A 40-year-old man was diagnosed with severe UC after presenting with bloody diarrhea two years prior. He was initially treated with methylprednisolone, azathioprine, and mesalazine and was considered steroid-dependent. Colonoscopy revealed ulceration throughout the colon, loss of vascularity, spontaneous bleeding, and severe pancolitis (Mayo-3 pancolitis) (Figure 1A). Microscopic examination of colonoscopic biopsies showed cryptitis, crypt abscesses, and mixed inflammation primarily consisting of eosinophils and lymphoplasmocytes in the lamina propria. Infliximab at 5 mg/kg was initiated at 2-week intervals. After two infliximab treatments without clinical response, ustekinumab therapy was started. One month later, the patient was hospitalized again with severe bloody diarrhea and was diagnosed with ASUC according to the Truelove-Witts Score. Meth-

ylprednisolone at 1 mg/kg was administered. No CMV was detected in biopsy samples, and stool samples were negative for endopathogens, parasites, and *C. difficile*.

Upadacitinib at 45 mg/day orally was initiated as rescue therapy. By the fifth day of upadacitinib treatment, stool frequency had decreased. A follow-up colonoscopy on the seventh day of upadacitinib showed erythema, friability, and loss of vascularity in the sigmoid colon and rectum (Mayo 2) (Figure 1B). At a follow-up colonoscopy in the third month under upadacitinib, mild erythema was noted in the sigmoid colon (Mayo 1) (Figure 1C). Twelve months after starting upadacitinib, the colonoscopic appearance was completely normal (Mayo 0) (Figure 1D). The patient continues to maintain clinical, laboratory, endoscopic, and histological remission in the 13th month of upadacitinib treatment without steroids.

DISCUSSION

In this case, we administered upadacitinib as a rescue therapy to a 40-year-old man with worsening UC symptoms who had not responded to infliximab and ustekinumab. Although upadacitinib has proven effective in adult patients with moderate to severe UC, studies on its use as a rescue therapy are limited. One week after starting treatment, the patient showed both clinical and endoscopic improvement, and surgery was avoided.

ASUC occurs in 20% of UC patients and has an emergency colectomy rate of 30%. The diagnosis of ASUC is based on the Truelove-Witts criteria, requiring at least six bloody stools per day along with systemic toxicity (fever ≥37.8°C, hemoglobin <10.5 g/dL, erythrocyte sedimentation rate >30 mm/h, or pulse rate ≥90 bpm). The risk of surgery is assessed on days 3 and 5 after diagnosis.[1] Corticosteroids are the primary treatment, but 30-40% of patients require second-line therapies such as infliximab or cyclosporine.[3] Colectomy is reserved for patients who are refractory or ineligible for medical rescue therapy.[4]

The Oxford criteria are used to predict response rates and the risk of colectomy on days 3-5 of steroid treatment. They are defined by the persistence of more than eight bowel movements or 3-8 bowel movements with CRP >45 mg/L on day 3.[5] In patients meeting the Oxford criteria, the colectomy rate is 36%.[6]

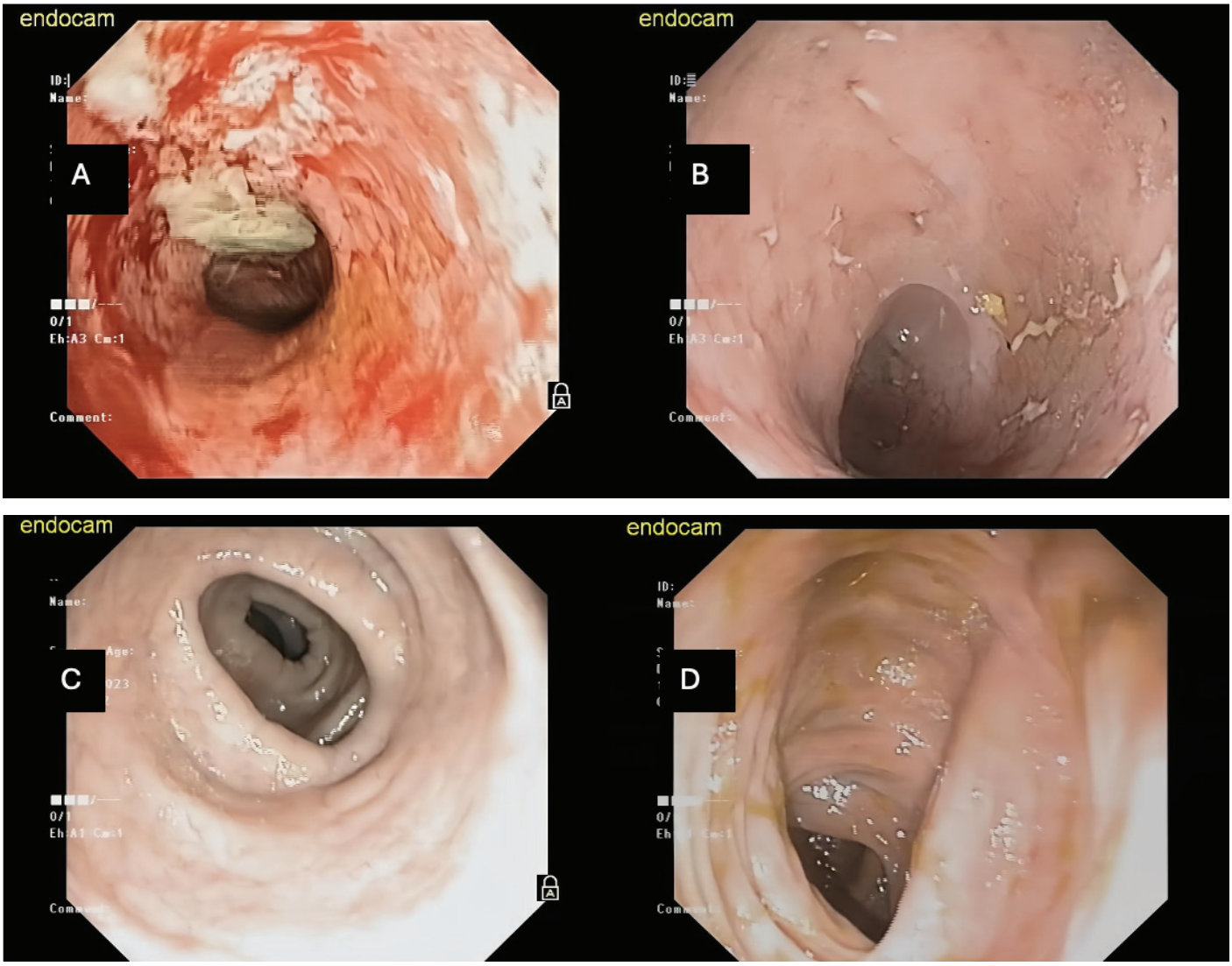

Figure 1. (A) Before starting upadacitinib, with severe ulcerations, loss of vascularity, spontaneous bleeding (Mayo 3). (B) 7th day of treatment initiation of upadacitinib, with erythema, friability, loss of vascularity (Mayo 2). (C) 12th weeks of upadacitinib, with mild erythema (Mayo 1). (D) After 12th months of upadacitinib, colonoscopic appearance was completely normal (Mayo 0).

The Phase 2b U-ACHIEVE induction study (UC1) provided crucial evidence for the efficacy of upadacitinib in treating adults with moderate-to-severe UC who have had an inadequate response, loss of response, or intolerance to steroids, immunosuppressive agents, and/or biologics. Studies have shown that symptomatic relief of UC symptoms is evident 1-3 days after starting upadacitinib treatment.[4] Similarly, our patient experienced symptomatic improvement 5 days after beginning treatment with upadacitinib.[3]

A systematic review involving 148 adult patients evaluated the use of tofacitinib as a rescue therapy for adults with ASUC who did not respond to steroids, infliximab, or cyclosporine and were potential candidates for colectomy. The review found that tofacitinib was associated with high short-term colectomy-free survival rates, offering a promising alternative for patients facing colectomy due to inadequate responses to other treatments.[7] Another review of 134 patients treated with tofacitinib reported a colectomy-free rate of 79.9% at 90 days and 71.6% at 6 months.[8,9] These results suggest that upadacitinib, another JAK inhibitor, may also be effective as a rescue therapy in ASUC.

Upadacitinib was trialed as a rescue therapy in six infliximab-experienced patients with ASUC, with only one patient undergoing total colectomy after 16 weeks.[3] In another study, the experience of using upadacitinib in four ASUC patients previously treated with infliximab was documented. A clinical response was achieved in three of the four patients, and one patient underwent total colectomy. The mean response time was 4-8 days.[10]

One series examines the potential role of upadacitinib as rescue therapy for infliximab-experienced patients with steroid-refractory ASUC. Five of six patients avoided colectomy during the clinical follow-up period, and four achieved steroid-free clinical remission at week eight without significant adverse events.[3]

A systematic review investigated the effectiveness of upadacitinib in treating ASUC, compiling data from eleven studies with a total of 55 patients. The findings demonstrated that upadacitinib led to rapid and sustained improvement for most patients, with a colectomy rate of only 16.3% at 90 days. Among those who avoided colectomy, 80% achieved steroid-free remission during the follow-up period, suggesting that upadacitinib could be a viable option for managing ASUC, offering favorable outcomes and minimal need for surgical intervention.[11] Additionally, a recent multicenter study evaluated 25 ASUC patients treated with upadacitinib. Of these, six patients (24%) required colectomy. Among the 18 patients who did not undergo surgical intervention, 15 achieved steroid-free clinical remission, underscoring the potential of upadacitinib to effectively manage severe cases of ulcerative colitis and reduce reliance on corticosteroids.[12]

Upadacitinib shows potential as an alternative rescue therapy for patients with ASUC, particularly those refractory to infliximab, and may contribute to reducing colectomy rates. Further randomized controlled trials are necessary to confirm its efficacy and safety.

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