Upadacitinib for Refractory Ulcerative Colitis with Primary Non-Response to Infliximab and Vedolizumab: A Case Report

Xia-xi Li et al. Upadacitinib for RUC with Primary Non-Response.

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Abstract
BACKGROUND
Many patients with ulcerative colitis (UC) do not respond well or at all, or cannot tolerate conventional or biological therapies. The treatment of refractory ulcerative colitis has not reached a consensus yet. Studies have demonstrated that the selective JAK1 inhibitor upadacitinib, a small molecule drug, is effective and safe for ulcerative colitis. However, no relative studies have revealed that upadacitinib is effective in treating refractory ulcerative colitis with primary non-response to infliximab and vedolizumab.

CASE SUMMARY
We report the case of a 44-year-old male patient with a chief complaint of bloody diarrhea with mucus and pus and dizziness. The patient had recurrent disease after receiving mesalazine, prednisone, azathioprine, infliximab and vedolizumab over four years. Combined with endoscopic findings and pathological biopsy, he was finally diagnosed as refractory ulcerative colitis. In particular, the patient showed primary non-response to infliximab and vedolizumab. Based on his past history and recurrent disease, we decided to administer upadacitinib to the patient. During hospitalization,
he then received upadacitinib under our guidance. Eight weeks after initiating upadacitinib treatment, we found that the symptoms and endoscopic findings improved significantly. In addition, no notable adverse reactions have been observed so far.

CONCLUSION
Our case report suggests upadacitinib may represent a valuable strategy in treating refractory ulcerative colitis with primary non-response.

Key Words: Upadacitinib; Refractory ulcerative colitis; Primary non-response; Infliximab; Vedolizumab; Case report


Core Tip: Ulcerative colitis (UC) is a major type of inflammatory bowel disease. Many patients do not respond well to current therapies. We report the case of the patient who was diagnosed as refractory ulcerative colitis with primary non-response to infliximab and vedolizumab. The patient experienced recurrent symptoms after receiving mesalazine, prednisone, azathioprine, infliximab and vedolizumab over four years. After optimizing upadacitinib, the patient achieved UC remission. Our report suggests the small molecule upadacitinib may be a new perspective that deserved to be reported and studied.

INTRODUCTION
Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) with multiple contributing factors. Its etiology and pathogenesis are still incompletely understood.
The main clinical manifestations are diarrhea, mucus, pus and blood in the stool and abdominal pain. The disease course is often relapsing and remitting.

For UC treatment, 5-aminosalicylic acid preparations (5-ASA), glucocorticoids and immunosuppressants are the traditional drugs. Various biological agents, such as infliximab, have also shown good efficacy in treating IBD in recent years. However, many UC patients do not respond well or at all, or cannot tolerate conventional or biological therapies. Therefore, more treatment options are needed for refractory UC patients.

We report a case of refractory UC that was successfully treated with upadacitinib, a small molecule drug that inhibits Janus kinase (JAK) signaling. The patient had failed to respond to both infliximab and vedolizumab, two biologic agents commonly used for IBD. We also review the relevant literature on the use of JAK inhibitors for IBD and discuss their advantages of oral administration and low immunogenicity.

**CASE PRESENTATION**

*Chief complaints*

The patient was a 44-year-old Caucasian male with a body mass index of 26.5 (Height 178 cm, weight 84 kg). He presented to the hospital on December 15, 2022 with a chief complaint of hematochezia and dizziness.

*History of present illness*

The patient had frequent episodes of bloody diarrhea with mucus and pus for more than 10 days.

*History of past illness*

He had a history of chronic intermittent hematochezia for 5 years, with a frequency of more than 10 episodes per day and a small volume.

The patient underwent colonoscopy at another hospital and was diagnosed with ulcerative colitis (left-sided, active phase) (Figure 1). Despite receiving mesalazine and
other symptomatic treatments, the patient experienced recurrent flares. In November 2019, the patient received induction therapy with mesalazine 4g and prednisone 64mg, which resulted in significant relief of symptoms, reduced ESR to 37mm/h, and normalized stool frequency and quality (no mucus, pus or blood). A follow-up colonoscopy in February 2021 showed complete mucosal healing (Figure 2).

Mesalazine was maintained at 4g/d after the initial treatment. In January 2022, the patient had recurrent symptoms of abdominal pain and bloody stool, ranging from 2 to 5 times a day, and an elevated ESR of 93mm/h. The symptoms were alleviated by oral methylprednisolone (64mg), azathioprine (100mg) and metronidazole. However, the symptoms recurred with bloody stool increasing to 2 to 10 times a day. The patient was then treated with infliximab (400mg) and azathioprine (100mg) in July 2022.

The patient had recurrent symptoms after the second infliximab infusion, such as passing mucus, pus or blood in over 10 stools per day. The dose of infliximab was increased to 500mg at the fourth infusion. However, there was no improvement in the colonoscopic findings, which showed chronic relapsing UC involving the entire colon (UCEIS 6).

The patient exhibited primary non-response to infliximab and continued to experience the symptoms.

Personal and family history

The patient denied any family history of malignant tumours.

Physical examination

There were no obvious abnormalities except tenderness in the left lower abdomen.

Laboratory examinations

EB-DNA quantization 1.28E+3copies/mL. Hemoglobin 123g/L, ESR 33mm/h. ALB 38.4g/L, hepatorenal function was normal. Fecal erythrocyte 4+, OB+. Fecal culture and C. difficile culture were negative. CRP, ANCA, ANA, CMV antibody, T-
SPOT, thyroid function, tumor markers, eight items of infectious diseases (HBsAg, Anti-HCV, Ag-HIV/Ab-HIV, Ab-Syphilis), coagulation function, D-dimer, tuberculosis T-SPOT all within normal ranges.

**Imaging examinations**

CT showed the mucosa of the rectum and sigmoid intestinal wall were uniformly thickened and significantly strengthened, indicating UC-related alterations. Pelvic magnetic resonance imaging revealed thickening of the colorectal wall.

**FINAL DIAGNOSIS**

The final diagnosis was ulcerative colitis (chronic recurrent type, total colon type, active, moderate, Mayo score 6).

**TREATMENT**

The patient declined glucocorticoid therapy after admission and received vedolizumab and azathioprine 100mg/day, along with two daily enemas of Brinider suspension, starting from December 20, 2022. However, the symptoms persisted, with 5 to 10 stools per day, mostly with pus and blood. The ESR was 42 mm/h five days later. The patient then underwent oral mesalazine, mesalazine enema, fecal microbiota transplantation, and the second dose of vedolizumab.

Despite receiving fecal microbiota transplantation (FMT) on February 17, 18, and 19, 2023, and the third dose of vedolizumab on February 18, the patient did not experience any symptom relief. The patient received the fourth dose of vedolizumab on April 1 and the fifth dose on May 10, with no improvement in clinical outcomes.

The patient experienced recurrent symptoms of mucus, pus and bloody stool 2 to 5 times per day on May 12, suggesting primary non-response to vedolizumab. He received upadacitinib 45mg/d on May 14.

**OUTCOME AND FOLLOW-UP**
On June 9, the patient reported significant improvement in hematochezia symptoms and no other discomfort. A follow-up colonoscopy after 8 wk (Figure 4) showed that UC was in remission and Mayo endoscopic score was 0. He is currently on upadacitinib 30mg/d. We plan to review in six months and reduce to 15mg/d as appropriate.

**DISCUSSION**

Ulcerative colitis is a major type of inflammatory bowel disease that was first described in 1895 [1]. The main clinical feature of UC is bloody diarrhea. Many patients also experience left-sided abdominal pain, especially if the inflammation is limited to the left colon. Patients with pancolitis, or inflammation of the entire colon, often have diffuse abdominal pain and tenesmus [2]. Endoscopic examination reveals continuous inflammation of the colonic mucosa, starting from the rectum and extending proximally to the ileocecal valve [1].

Currently, the available treatments for UC comprise conventional drugs (such as 5-ASA, glucocorticoids and immunosuppressants), biologics (such as infliximab, vedolizumab and ustekinumab), JAK inhibitors and SI1 receptor modulators. 5-ASA is the standard first-line therapy for mild to moderate active UC [3]. Glucocorticoids are indicated for patients with moderate-to-severe disease or those who are refractory to standard therapies.

However, many patients with UC do not respond adequately or lose response to conventional or biological therapies, or experience adverse effects from these treatments [4]. Previous studies have shown even after switching to new biological agents, only one-third of patients achieve or maintain clinical remission at 1 year [5]. Patients who depend on glucocorticoids, or who are unresponsive or intolerant to at least one of 5-ASA, corticosteroids or immunosuppressants, are considered to have refractory UC [6].

This patient had recurrent disease despite multiple courses of mesalazine, prednisone, azathioprine, and vedolizumab over four years, and showed primary non-response to infliximab and vedolizumab. These features meet the criteria for refractory UC. The evidence for the efficacy of optimizing vedolizumab or combining it with
azathioprine is inconsistent across different studies [7, 8]. However, the patient’s symptoms did not improve significantly after optimizing vedolizumab treatment.

Upadacitinib is a selective small molecule JAK1 inhibitors. In clinical trials, upadacitinib is highly effective in remission in moderate to severe UC [9].

We reviewed relevant literature and found few studies on upadacitinib treatment for intractable UC. A multicenter retrospective cohort study reported most patients achieved steroid-free clinical remission (SFCR) and clinical response within 8 to 16 wk of starting upadacitinib, and most of them had previously received anti-TNFs and vedolizumab [9]. Phase II and phase III trial results demonstrated the selective JAK1 inhibitor for UC was effective and safe.

The patients in this study had previously failed to respond adequately or lost response to, or had experienced adverse effects from, at least one conventional or biologic therapy [4].

The previous two studies did not specify the type of non-response (primary or secondary) of the patients they included. In contrast, our patient had primary non-response to vedulizumab and infliximab, as well as inadequate response to other drugs. His condition was more complex and severe than patients in the previous two studies. Considering his lack of response to multiple therapies and the efficacy of upadacitinib in phase II and III trials, we decided to administer upadacitinib to him after obtaining his informed consent.

We administered upadacitinib at a dose of 45mg/d to our patient. Colonoscopy revealed that the patient had achieved UC remission eight weeks later. He continued to receive a maintenance dose of 30mg/d upadacitinib monotherapy and remained in remission, demonstrating the efficacy of upadacitinib in this challenging case.

CONCLUSION
In summary, our patient experienced recurrence of symptoms after receiving mesalazine and prednisone, and showed primary non-response to infliximab and vedolizumab. This case demonstrates upadacitinib is effective in treating refractory
UC in a patient who failed to respond to infliximab and vedolizumab, with significant improvement in symptoms and endoscopic findings, and no notable adverse reactions observed so far. This provides an alternative option for refractory UC patients with primary non-response. Moreover, small molecule drugs may have advantages such as reducing immunogenicity and enhancing patient adherence. However, this is a single case report. The efficacy of upadacitinib in refractory UC patients with primary non-response needs to be verified by further clinical studies.
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