CASE REPORT | INFLAMMATORY BOWEL DISEASE

Use of Ruxolitinib for the Simultaneous Treatment of Severe Refractory Ulcerative Colitis and Polycythemia Vera

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ABSTRACT

Tofacitinib is the only medicine in the class of Janus kinase (JAK) inhibitors that has been approved for use in moderate-to-severely active ulcerative colitis (UC). The potential of other JAK inhibitors to treat UC has not been fully explored. We present a case describing the successful use of the selective JAK inhibitor, ruxolitinib, to treat a patient with concomitant UC and polycythemia vera.

INTRODUCTION

The Janus associated kinase (JAK) inhibitors are a relatively new class of small molecule cytokine antagonists that have been approved for use in the treatment of various immune-mediated inflammatory diseases.[1] Tofacitinib, a pan-JAK inhibitor with preferential activity against JAK1 and JAK3, is currently the only medication in this class that has been approved for the treatment of moderate-to-severe ulcerative colitis (UC). OJAK inhibitors are currently being studied in clinical trials[2], however, efficacy and safety data in UC are limited. Ruxolitinib is a selective JAK1 and JAK2 inhibitor approved to treat polycythemia vera (PV), myelofibrosis, and acute graft-vs-host disease. We describe the use of ruxolitinib for the successful treatment of a patient with both severe refractory UC and PV.

CASE REPORT

A 61-year-old man presented to our clinic with a history of ulcerative pancolitis diagnosed at age 35 years. His medical history was also significant for *JAK2 V617F*-mutated PV diagnosed at age 49 years and managed with intermittent hydroxyurea during high-viscosity periods. At the time of UC diagnosis, he was treated with oral 5-aminosalicylic acid and, despite poor response, was maintained on this therapy for over 15 years. During this time, he had additionally been on a thiopurine which was discontinued because of an adverse effect of severe nausea and vomiting. When he first presented to our clinic, an index endoscopy demonstrated severe active pancolitis with a Mayo score of 3, and therefore, he was started on infliximab to induce remission with the addition of methotrexate to limit immunogenicity (Figures 1 and 2). He demonstrated some improvement with this regimen; however, he experienced frequent breakthrough symptoms requiring treatment with steroids. In addition, methotrexate was stopped after 6 months because of adverse effects of neutropenia. At 1 year, he underwent a follow-up endoscopy which redemonstrated Mayo 3 active colitis. Laboratory analyses revealed an undetectable infliximab level (<0.4 µg/mL) and an anti-infliximab antibody titer of 195 ng/mL. A fecal calprotectin during this period was as high as $>2,500$ µg/g. He was subsequently switched to vedolizumab at the usual loading dose and a maintenance dose of 300 mg intravenous infusion every 8 weeks.
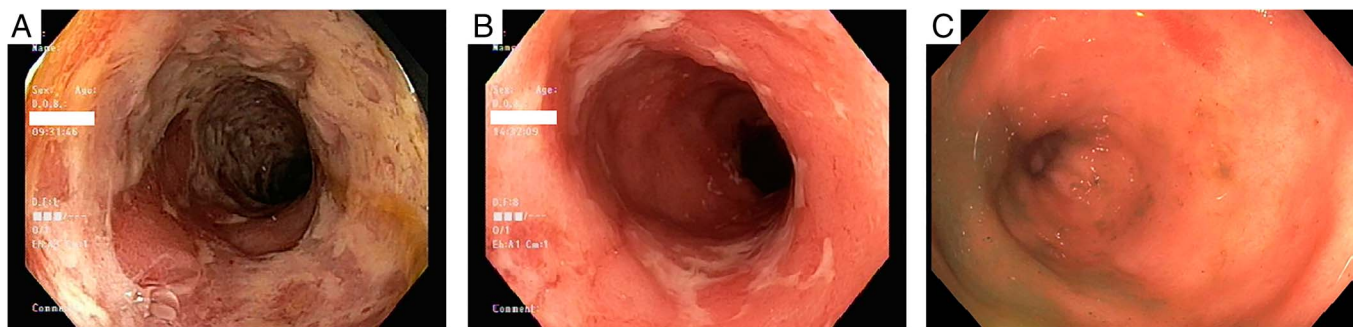
Figure 1. (A) Index endoscopy while on mesalamine monotherapy demonstrating severe active colitis. (B) Sigmoidoscopy after 6 months of vedolizumab infusion therapy (300 mg every 4 weeks) demonstrating persistent active colitis. (C) Sigmoidoscopy after 18 months of ruxolitinib therapy demonstrating endoscopic remission.

At the 6-month follow-up, he had persistent symptoms, and repeat endoscopy demonstrated persistent Mayo 3 colitis (Figure 1). His vedolizumab dose was subsequently increased to 300 mg every 4 weeks; however, at the 6-month follow-up, his symptoms remained unchanged, and repeat endoscopy demonstrated Mayo 3 colitis. Notably, before this, his PV was also poorly controlled, with complications of claudication and cardiovascular complications, including a myocardial infarction due to high-viscosity states. Hemoglobin around this time was 10.9 g/dL, white blood cell count of 12,000/μL, and platelets up to 1,223,000/μL. After discussion with the patient's hematologist, considering difficulties with medication adherence and titrating hydroxyurea, the decision was made to discontinue both vedolizumab and hydroxyurea and initiate ruxolitinib to treat PV with the potential additional benefit of treating UC. Ruxolitinib was started at the standard dose of 10 mg twice daily. After 6 months on this agent, he was noted to have marked symptom improvement in both frequency and consistency of bowel movements and a decrease in high-viscosity periods. His weight remained stable, and he experienced no adverse effects. At 1 year, the patient reported resolution of his diarrhea, and a fecal calprotectin around this time was 83 μg/g. The follow-up endoscopy at 18 months demonstrated quiescent disease (Figures 1 and 2).

DISCUSSION

The JAK inhibitors are a promising class of drugs for the treatment of patients with moderate-to-severe UC. The mechanism of these drugs is through the inhibition of JAK, a family of kinases that when activated lead to a signal transduction cascade that ultimately results in the production of proinflammatory cytokines that have been implicated in autoimmune disease.[2] There are 4 known JAKs, namely, JAK1, JAK2, JAK3, and TYK2, all of which may serve as potential targets for drug therapy in inflammatory bowel disease. Tofacitinib, a pan-JAK inhibitor with preferential activity against JAK1 and JAK3, has had extensive use in the treatment of rheumatoid arthritis[3] and is the only JAK inhibitor that is currently approved for the treatment of UC.
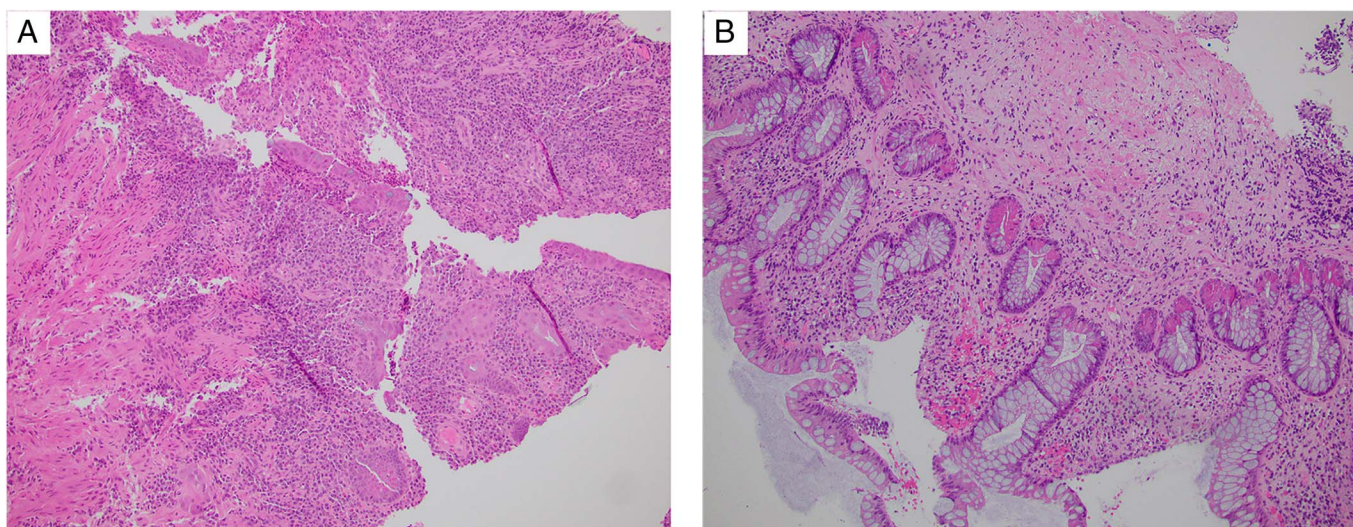

Figure 2. (A) Initial colonic biopsy demonstrating active chronic colitis with ulceration. (B) Sigmoid colon biopsy after 18 months of ruxolitinib therapy demonstrating chronic quiescent colitis.

Tofacitinib has demonstrated significant efficacy in inducing and maintaining clinical remission even in patients with refractory UC.[4,5]

There is ongoing interest in evaluating the safety and efficacy of selective JAK inhibitors in the induction and maintenance of UC, including recently completed phase 2b double-blind, randomized, placebo-controlled trials for the JAK1-specific filgotinib and upadicitinib[6,7] and ongoing clinical trials for the gut-specific pan-JAK inhibitor TD-1473[8]; however, the therapeutic potential of ruxolitinib in inflammatory bowel disease is less clear. Although ruxolitinib has long been used for the treatment of hematologic malignancies, such as myelofibrosis and PV,[9,10] where it has been proven safe and effective, it carries the undesirable side effect of myelosuppression due to the inhibition of hematopoietic cytokines.

In this case, our patient's unique combination of severe refractory UC and poorly controlled PV provided a unique opportunity to treat both conditions with ruxolitinib using a multidisciplinary approach. This case may provide insight into an alternative therapy in patients suffering from UC and reinforces the need for continued efforts to analyze the broad effectiveness and safety of selective JAK inhibitors.

DISCLOSURES

Author contributions: EC Swei wrote and edited the article, reviewed the literature, revised the article for intellectual content, and is the article guarantor. CM Fox wrote and approved the article and reviewed the literature. DW Bowles edited the article and revised the article for intellectual content. MN Rizeq provided the images. JC Onyiah edited the article, revised the article for intellectual content, and reviewed the literature.

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