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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Tofacitinib in Stricturing Colonic Crohn's Disease

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ABSTRACT

Tofacitinib has described efficacy in ulcerative colitis but not Crohn's disease (CD). However, patients with stricturing CD were excluded from initial randomized controlled trials. We report a case of stricturing colonic CD, which responded to tofacitinib therapy.

KEYWORDS: Janus kinase (JAK) inhibitors; stricturing Crohn's disease; Crohn's colitis; tofacitinib

INTRODUCTION

Tofacitinib is a Janus kinase (JAK) inhibitor with efficacy demonstrated in ulcerative colitis (UC) but not Crohn's disease (CD).[1,2] We describe a case of tofacitinib in a patient with stricturing Crohn's colitis.

CASE REPORT

A 59-year-old woman with a 2-year history of presumed UC commenced tofacitinib 10 mg 3 times daily (TID) as sequential salvage therapy, after presenting with acute severe colitis, which was refractory to steroid and rescue infliximab.

She was diagnosed with UC in 2020 after presenting with intermittent rectal bleeding and occasional bowel frequency. Her index colonoscopy demonstrated proctitis to 15 cm. Her UC management consisted of daily oral 5-animosalicylate therapy with 3.2 g oral mesalazine daily, along with intermittent budesonide and 5-animosalicylate enemas, used as required.

She reported onset of symptoms (non-bloody diarrhea) approximately 4 weeks before hospital presentation. Stool cultures isolated *Campylobacter jejuni*, and she commenced a course of oral ciprofloxacin. Despite this, she experienced progressively worsening symptoms, passing an average of 10 bloody bowel actions per day along with severe abdominal cramping. In this context, she switched to oral azithromycin 500 mg daily 4 days before hospitalization and additionally commenced 40 mg oral prednisolone 2 days before hospitalization.

On admission, she commenced on intravenous hydrocortisone 100 mg 4 times daily and underwent a flexible sigmoidoscopy. This demonstrated Mayo 3 colitis in a continuous pattern from the anus to the sigmoid colon, with normal colon seen past 40 cm of insertion. Biopsies were negative for cytomegalovirus infection. A repeat stool sample at this time was negative for *Campylobacter jejuni* and other infective pathologies. C-reactive protein (CRP) on admission was 53.1 mg/L (normal: $<$5 mg/L), and fecal calprotectin was 5,020 μg/g (normal: $<$50 μg/g).

She had an inadequate response to steroid by day 3 of her admission as per the Oxford criteria and, therefore, commenced infliximab therapy, receiving an initial 5 mg/kg dose followed by 2 further 10 mg/kg doses 4 and 7 days later. Repeat endoscopy with a colonoscopy showed severe segmental right- and left-sided colitis with deep ulceration, raising concern for Crohn's colitis.

She had a partial but incomplete response to the infliximab therapy (CRP remained elevated at 45.2 mg/L, Lichtiger score 13 [Lichtiger index is a score to reflect colitis activity, which incorporates scores for diarrhea, nocturnal diarrhea, blood in bowel movements, fecal incontinence, abdominal pain or cramping, general well-being, abdominal tenderness, and need for antidiarrheal

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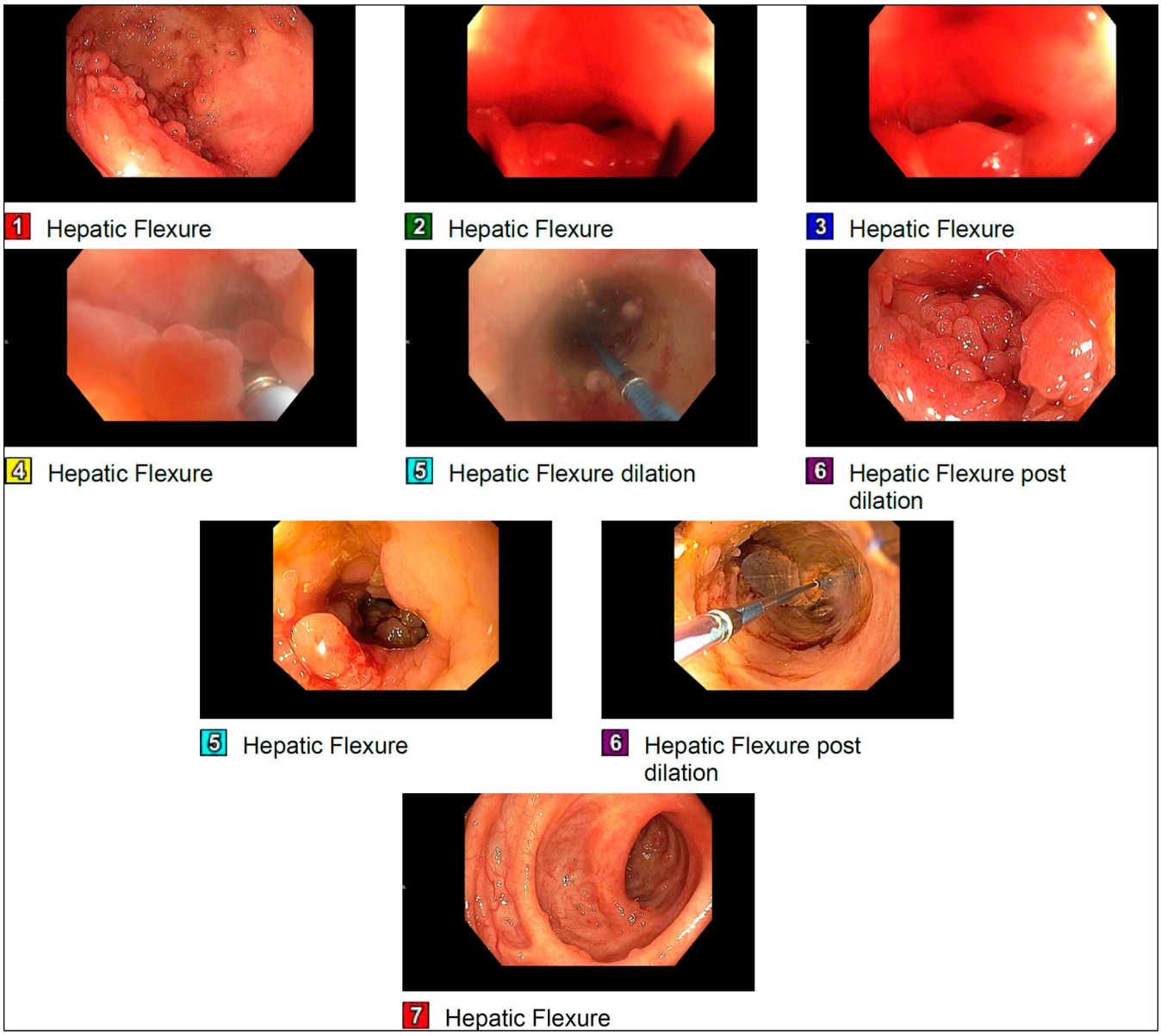

Figure 1. Endoscopic appearance of hepatic flexure stricture over time. (A) July 2022: Distal transverse colon stricture, seen after 3 months of tofacitinib. The remainder of the colonic mucosa appeared normal endoscopically. Biopsies of the stricture showed mildly active chronic colitis with focal fibrosis and were negative for dysplasia. (B) August 2022: Repeat colonoscopy with distal transverse colon stricture endoscopic balloon dilatation achieved to 12 mm, although the stricture remained impassable. (C) November 2022: 2 further strictures identified, 1 additional stricture in the transverse colon along with a hepatic flexure stricture. The hepatic flexure stricture was dilated to 15 mm. Biopsies of strictures and segmental colonic biopsies showed quiescent colitis only. (D) November 2023: All colonic strictures widely patent and no dilatation required.

drugs.[3] Higher scores (maximum 21) reflect severe disease activity.]). After discussion with the patient about medical and surgical options, she commenced tofacitinib 10 mg TID. Given a history of atrial fibrillation and use of high-dose tofacitinib, she also commenced apixaban 5 mg twice daily (BID). She improved after 7 days of tofacitinib (Lichtiger 1 from 13, CRP 6.2 from 45.2) and was discharged, completing 14 days of tofacitinib 10 mg TID before deescalation to 10 mg BID. Oral trimethoprim-sulphamethoxazole prophylaxis was continued on discharge. She also returned a positive Quantiferon-Gold result during her admission, which was felt to be consistent with latent tuberculosis in the context of a negative chest X-ray. She commenced isoniazid and pyridoxine before discharge and completed a total of 6 months therapy.

Although asymptomatic, colonoscopy after 3 months of tofacitinib demonstrated a nontraversable stricture, presumed to be located at the distal transverse colon based on endoscopist experience (Figure 1). This had not previously been seen on endoscopy and remained impassable despite repeat colonoscopy with stricture dilatation to 12 mm (Figure 1). At colonoscopy 3 months later, 2 further strictures were identified: an additional

transverse colon stricture and a hepatic flexure stricture. The latter was dilated to 15 mm (Figure 1). She remained in clinical and biochemical remission (calprotectin 85 μg/g, CRP 0.4) and, therefore, continued tofacitinib 10 mg BID. At subsequent colonoscopy, all 3 strictures were widely patent (Figure 1). Her dose of tofacitinib was reduced to 5 mg BID. Given the stricturing phenotype and review of previous endoscopies demonstrating deep ulceration and patchy, discontinuous, segmental colonic inflammation, her diagnosis was revised to CD.

DISCUSSION

Randomized controlled data have not shown conclusive benefit of tofacitinib, a pan-JAK inhibitor, for CD.[2] The trial may have been limited by a short induction period of 8 weeks and the inclusion of relatively less potent induction dosing schedules. Nevertheless, patients on 10 mg demonstrated improvement in CRP and numerically higher clinical response and remission rates compared to placebo, suggesting a possible role for tofacitinib in some cases of CD.[2] Indeed, JAK-inhibition has elsewhere been shown to have efficacy in CD, with the JAK-1 selective inhibitor upadacitinib achieving superior rates of clinical remission at week 12 and 52 compared to placebo.[4] Furthermore, although stricturing CD phenotype patients were excluded from the initial tofacitinib trial, more recent data suggest a role for tofacitinib in suppressing intestinal fibroblast activation in vitro.[5]

Tofacitinib may also be beneficial in refractory situations such as our case, given the advantage of reduced immunogenicity. In one study of patients with biologic-exposed CD (including 5 patients with stricturing CD), 70% achieved clinical response (defined as ≥3-point decrease in Harvey Bradshaw Index) after a mean 29.4 weeks with no adverse safety signals identified.[6] Clinical response (defined as >50% reduction in symptoms at week 8 and/or 16) was achieved in half of patients with CD or IBD-unspecified from the tofacitinib real-world outcomes in patients with ulceratIve colitis and crohn's disease (TROPIC) consortium.[7] Cases of successful treatment of Crohn's-like disease of the pouch have also been described.[8] Our patient with refractory Crohn's colitis achieved clinical, endoscopic, and histologic response with an extended period of high dosing and colonic stricture remodeling with combined endoscopic therapy. No adverse events occurred. Although upadacitinib is now available for CD, tofacitinib may be considered a viable option off-label in select cases of medically refractory CD.

DISCLOSURES

Author contributions: PD Cruz conceptualized the study; S. Chin recruited the patient, reviewed the literature, collected and analyzed the data, and wrote the first draft of the original manuscript; PD Cruz and M. Choy edited the original manuscript and provided important intellectual content. All authors critically appraised and approved the final manuscript before submission. PD Cruz is the article guarantor.

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Informed consent was obtained for this case report.

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