ACG CASE REPORTS JOURNAL

CASE REPORT | INFLAMMATORY BOWEL DISEASE

Efficacy and Safety of Upadacitinib in the Treatment of Chronic Pouchitis, Cuffitis, and Crohn's Disease of the Pouch

Nan Lan, MD, PhD[1], and Bo Shen, MD, FACG[2]

[1]*Division of Digestive and Liver Diseases, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, NY*
[2]*Center for Inflammatory Bowel Disease, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, NY*

ABSTRACT

Upadacitinib has shown efficacy in the treatment of moderate-to-severe ulcerative colitis and Crohn's disease (CD). The use of upadacitinib in the treatment of chronic antibiotics-refractory pouchitis (CARP), as well as CD of the pouch, has not been previously reported. We treated a series of 6 patients with CARP or CD of the pouch with a minimal 6 weeks of upadacitinib. The patients showed minimal or no significant improvement in clinical and endoscopic presentations. Our findings warrant further study to validate the efficacy and safety of upadacitinib in the treatment of CARP or CD of the pouch.

KEYWORDS: Crohn's disease; cuffitis; pouchitis; upadacitinib

INTRODUCTION

The management of chronic antibiotics-refractory pouchitis (CARP) and Crohn's disease (CD) of the pouch has been challenging. The inflammatory disorders of the pouch are common causes of poor quality of life and pouch failure.[1] Upadacitinib is a Janus kinase 1 (JAK) inhibitor that has shown efficacy in the treatment of moderate-to-severe ulcerative colitis (UC) and CD.[2,3] There have been reports in literature of using other JAK inhibitors such as tofacitinib in the treatment of CARP and CD of the pouch with a roughly 50% response rate.[4,5] The use of upadacitinib in the treatment of CARP, as well as CD of the pouch, had not been previously reported. We report a small case series of 6 patients with CARP or CD of the pouch who received minimal 6 weeks of upadacitinib in our Pouch Center.

CASE REPORTS

Patient 1, a 23-year-old man, had undergone colectomy and 2-stage ileal pouch-anal anastomosis (IPAA) in 2020 for medically refractory UC. He developed urgency, frequency, and intermittent incomplete evacuation with endoscopically confirmed pouchitis soon after pouch surgery. He has been on antibiotics, mesalamine, or budesonide, or adalimumab individually, with no significant improvement. The patient underwent pouchoscopy, which showed severe pouchitis, cuffitis, and afferent limb syndrome. He was treated upadacitinib for 6.5 weeks without a response in symptoms. Repeat pouchoscopy in 6 weeks after the therapy showed no improvement in severe pouchitis and cuffitis. He was switched to vedolizumab and 40 sessions of hyperbaric oxygen therapy.

Patient 2, a 59-year-old man, had undergone 3-stage IPAA in 2009 for medically refractory UC. His postoperative course was complicated by pouch inlet stricture, presacral sinus, and pouch fistula since 2015. He developed diarrhea, nocturnal symptoms, and incontinence. He was treated with ciprofloxacin and tinidazole with some response. Because of the concern for the CD of the pouch, he was also given adalimumab, ustekinumab, vedolizumab, and tofacitinib monotherapy. The inlet stricture was treated with multiple sessions of endoscopic stricturotomy, and the pouch-to-pouch fistula was treated with fistulotomy. He was also recommended for hyperbaric oxygen therapy with no significant clinical response. He was eventually started on upadacitinib for a total of 16 weeks, but he also failed to respond when assessed on pouchoscopy after 14 weeks. He is now being considered for risankizumab.

ACG Case Rep J 2024;11:e01245. doi:10.14309/crj.0000000000001245. Published online: January 25, 2024

Correspondence: Bo Shen, MD, FACG (bs3270@cumc.columbia.edu).

Table 1. Clinical presentation and response to treatment with upadacitinib

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (yr)	23	59	71	59	24	19
Gender	Male	Male	Male	Male	Male	Male
Smoking	No	No	No	Former	No	No
Precolectomy diagnosis	UC	UC	UC	UC	UC	UC
Extraintestinal manifestations	No	No	Arthritis	No	Arthritis	Autoimmune hepatitis; primary sclerosing cholangitis
Year of pouch constructed	2020	2009	1996	2001	2015	2021
Type of the pouch	J	J	J	J	J	J
Pouch diagnosis (CARP/CD of the pouch/cuffitis)	CARP; cuffitis	CD of the pouch	CD of the pouch	CARP	CARP	CARP
Year of diagnosis of CARP/CD of the pouch/cuffitis	2020	2015	2022	2021	2015	2021
Any use of steroids for pouch before upadacitinib	Budesonide	Budesonide	No	Budesonide	Prednisone	Budesonide
Use of anti-TNF for pouch before upadacitinib	Adalimumab	Adalimumab	Adalimumab	Infliximab; adalimumab	Adalimumab	No
Use of ustekinumab for pouch before upadacitinib	No	Yes	Yes	Yes	No	Yes
Use of vedolizumab for pouch before upadacitinib	Yes	Yes	No	Yes	Yes	No
Use of other small-molecule agents before upadacitinib	No	Tofacitinib	Tofacitinib	Tofacitinib	No	No
PDAI symptom subscores at the time of upadacitinib	4	4	3	4	4	4
PDAI endoscopy scores at the time of upadacitinib (prepouch ileum/ body/cuff)	6/6/6	4/0/2	0/0/0 Enterovesicle fistula	0/1/0	0/1/2	0/1/6
PDAI symptom subscores after upadacitinib	4	3	3	5	4	4
Duration from start of upadacitinib to endoscopic evaluation (wk)	6.5	14.7	8.7	17.6	8.1	11.7
PDAI endoscopy scores at after upadacitinib (prepouch ileum/ body/cuff)	6/6/6	4/0/1	0/0/0 No enterovesicular symptoms	0/1/0	1/0/1	0/1/6
Improvement of extraintestinal manifestations	NA	NA	NA	NA	Resolution of symptoms of juvenile rheumatoid arthritis	No improvement in liver function tests

Table 1. (*continued*)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Duration of upadacitinib (wk)	6.5	16.5	12.4	19.4	8.1	16.0
Adverse events possibly related to upadacitinib	None	None	None	None	None	None
Concurrent medications to upadacitinib	Budesonide	None (short-term piperacillin and tazobactam)	Ciprofloxacin; tinidazole	Ciprofloxacin; rifaximin	Ciprofloxacin; tinidazole	Budesonide; azathioprine for autoimmune hepatitis
Pouch failure (permanent diversion with or without pouch excision)	No	No	Pending	No	No	No

CARP, chronic antibiotic-refractory pouchitis; CD, Crohn's disease; PDAI, Pouchitis Disease Activity Index; TNF, tumor necrosis factor; UC, ulcerative colitis.

Patient 3, a 71-year-old man, had undergone IPAA in 1996 for medically refractory UC. He presented with frequent diarrhea with nocturnal seepage and dyschezia. Pouchoscopy showed pouch prolapse, mild anastomotic stricture, and suspected perianal fistula since 2021. Anorectal manometry showed paradoxical contractions with a sawtooth pattern. The patient underwent biofeedback therapy with partial response. He was initially diagnosed with chronic pouchitis and was treated with ciprofloxacin, tinidazole, and tofacitinib without response. He was later diagnosed with CD of the pouch based on the development of an enterovesicular fistula. He was given 12 weeks of upadacitinib with mild improvement in pouch and urinary symptoms. Mild improvement of inflammation was observed on pouchoscopy at week 8.

Patient 4, a 59-year-old man, had undergone IPAA in 2001 for medically refractory UC. He was found to have a complex fistula confirmed on MRI and severe pouchitis on pouchoscopy with concerns for CD of the pouch. He has been treated with rifaximin, ciprofloxacin, tinidazole, pramocaine foam, budesonide, in conjunction with adalimumab, vedolizumab, infliximab, ustekinumab, and tofacitinib sequentially. He continued to develop multiple courses of perianal abscesses requiring antibiotics. He had a pouch revision in 2020 with no improvement in symptoms. His course was soon complicated by pouch inlet stricture treated with endoscopic stricturoplasty; presacral sinus was treated with endoscopic sinusotomy; active pouchitis, and cuffitis were treated with ciprofloxacin, tinidazole, budesonide, adalimumab, and then tofacitinib. He was then treated with upadacitinib for 19 weeks with no significant improvement in symptoms. Repeat pouchoscopy at week 17 showed persistent multiple ulcerated inlet strictures.

Patient 5, a 24-year-old man, had undergone 2-stage IPAA in 2011. The initial pouch was complicated by an anastomotic leak and fistula, requiring a redo pouch in 2015. His redo pouch was complicated by recurrent sinus as well as CARP soon. The recurrent sinus was treated successfully with endoscopic sinusotomy. CARP was treated with ciprofloxacin, tinidazole, and vedolizumab with minimal improvement in symptoms. On the other hand, the patient also has juvenile rheumatoid arthritis treated with etanercept and methotrexate. He had a repeat pouchoscopy, showing active pouchitis with clinical symptoms of diarrhea and arthralgia. He was started on upadacitinib. After 6 weeks, he reported significant improvement in arthritis symptoms but no change in abdominal cramping, bloating, pelvic pain, and stool frequency. A repeat pouchoscopy at week 8 showed modest improvement in endoscopic inflammation.

Patient 6, a 19-year-old man with a complex history of UC, primary sclerosing cholangitis, and autoimmune hepatitis, underwent a 3-stage IPAA surgery in 2021. He developed persistent pouchitis, enteritis, and cuffitis with symptoms of stool frequency, incomplete evacuation, excessive straining, and rectal burning in the same year. He was treated with ciprofloxacin, metronidazole, mesalamine, budesonide, and

ustekinumab. He has also been treated with azathioprine for the autoimmune hepatitis. Because of the uncontrolled symptoms, he was started on upadacitinib, azathioprine, and budesonide. He reported he had not noticed a difference after being on upadacitinib for 16 weeks (Table 1).

DISCUSSION

In summary, we present 6 predominantly male patients with postoperative biologics-exposed CARP or CD of the pouch who, after 6 weeks or more of upadacitinib, showed minimal or no significant improvement in clinical and endoscopic presentations. Interestingly, upadacitinib seemed to have had a positive impact on extraintestinal manifestations. Age, duration of pouchitis, and concurrent use of other medications, such as budesonide, did not show any significant difference in outcome.

Acute pouchitis usually responds favorably to short-term courses of antibiotic agents.[6,7] The treatment for CARP and CD of the pouch is more complicated. CARP has recently been listed 1 of 5 difficult-to-treat inflammatory bowel disease conditions by an expert panel from the International Organization of IBD.[8] It has been reported that the use of anti–tumor necrosis factor, ustekinumab, and vedolizumab may be effective in the treatment of CARP.[9–11] In patients with inadequate response to biologics, tofacitinib has been trialed in multiple case series with inconsistent response rate.[4,12]

The patients in our current series have also failed most conventional antibiotics, biologics, and tofacitinib. Because of the practice pattern of our subspecialty Pouch Center, patients often had concurrent structural and/or functional disorders of the pouch, which may be contributing factors for poor response to medical therapy. Our findings warrant further study to validate the efficacy and safety of upadacitinib in the treatment of CARP or CD of the pouch in a larger population.

DISCLOSURES

Author contributions: N. Lan and B. Shen: conception or design of the work. N. Lan and B. Shen: acquisition, analysis, or interpretation of data for the work and drafting the work or reviewing it critically for important intellectual content. B. Shen: final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy are appropriately investigated.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received September 1, 2023; Accepted November 22, 2023

REFERENCES

1. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. *Ann Surg*. 2003;238(2):229–34.
2. Panaccione R, Collins EB, Melmed GY, et al. Efficacy and safety of advanced therapies for moderately to severely active ulcerative colitis at induction and maintenance: An indirect treatment comparison using Bayesian network meta-analysis. *Crohns Colitis 360*. 2023;5(2):otad009.
3. Friedberg S, Choi D, Hunold T, et al. Upadacitinib is effective and safe in both ulcerative colitis and Crohn's disease: Prospective real-world experience. *Clin Gastroenterol Hepatol*. 2023;21(7):1913–23.e2.
4. Akiyama S, Cohen NA, Kayal M, Dubinsky MC, Colombel JF, Rubin DT. Treatment of chronic inflammatory pouch conditions with tofacitinib: A case series from 2 tertiary IBD centers in the United States. *Inflamm Bowel Dis*. 2023;29(9):1504–7.
5. Tome J, Raffals LE, Pardi DS. Management of acute and chronic pouchitis. *Dis Colon Rectum*. 2022;65(S1):S69–76.
6. Dalal RL, Shen B, Schwartz DA. Management of pouchitis and other common complications of the pouch. *Inflamm Bowel Dis*. 2018;24(5):989–96.
7. Chis RS, Silverberg MS. Measurement of disease activity of pouchitis. *Dis Colon Rectum*. 2022;65(S1):S50–6.
8. Parigi TL, D'Amico F, Abreu MT, et al. Difficult-to-treat inflammatory bowel disease: Results from an international consensus meeting. *Lancet Gastroenterol Hepatol*. 2023;8(9):853–9.
9. Ollech JE, Rubin DT, Glick L, et al. Ustekinumab is effective for the treatment of chronic antibiotic-refractory pouchitis. *Dig Dis Sci*. 2019;64(12):3596–601.
10. Verstockt B, Claeys C, De Hertogh G, et al. Outcome of biological therapies in chronic antibiotic-refractory pouchitis: A retrospective single-centre experience. *United European Gastroenterol J*. 2019;7(9):1215–25.
11. Travis S, Silverberg MS, Danese S, et al; EARNEST Study Group. Vedolizumab for the treatment of chronic pouchitis. *N Engl J Med*. 2023;388(13):1191–200.
12. Uzzan M, Nachury M, Amiot A, Peyrin-Biroulet L, Kirchgesner J, Bouhnik Y; GETAID TOFA-POUCH study group. Effectiveness and safety of tofacitinib in patients with chronic pouchitis multirefractory to biologics. *Dig Liver Dis*. 2023;55(8):1158–60.