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EDITORIAL

Navigating treatment resistance: Janus kinase inhibitors for ulcerative colitis

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Abstract

The management of refractory ulcerative colitis (UC) and acute severe UC (ASUC) is challenging due to the lack of standardized approaches in cases resistant to multiple treatments. In this editorial, I investigate the efficacy and safety of Janus kinase inhibitors, particularly upadacitinib and tofacitinib, in controlling severe and refractory disease. I highlight a notable case report by Xu *et al*, which explores the case of a patient with primary nonresponse to two classes of biologics and two fecal microbiota transplants who exhibited a remarkable response to upadacitinib. Furthermore, I discuss the use of tofacitinib in refractory UC and ASUC, either as monotherapy or in combination with biologics, which has shown promising response rates. Additionally, emerging evidence of upadacitinib efficacy in ASUC is presented. Overall, these cases emphasize the complex nature of managing refractory ASUC and the potential of small-molecule therapies to achieve remission. Further research is needed to refine treatment strategies for patients with treatment-resistant UC.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Janus kinase inhibitor; Upadacitinib; Tofacitinib; Infliximab

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Core Tip: This editorial explores the efficacy and safety of Janus kinase inhibitors, specifically upadacitinib and tofacitinib, in refractory ulcerative colitis (UC) and acute severe UC (ASUC). Highlighting a compelling case report, it underscores the potential of these small-molecule therapies, either alone or in combination with biologics, to achieve and maintain disease remission. Furthermore, it emphasizes the importance of considering overlapping infections in ASUC and the need for prompt recognition by colorectal surgeons. This editorial advocates for further research to refine treatment strategies for patients with treatment-resistant UC, shedding light on promising therapeutic approaches.

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INTRODUCTION

Managing ulcerative colitis (UC), especially cases of refractory acute severe UC (ASUC), poses significant challenges due to poor patient response or intolerance to conventional and biological treatments. There is no standardized approach for cases resistant to multiple treatments. However, recent research has shed light on the efficacy and safety of small-molecule Janus kinase inhibitors, such as upadacitinib[1] and tofacitinib[2], in controlling severe and refractory disease.

JANUS KINASE INHIBITORS FOR REFRACTORY ULCERATIVE COLITIS

A report by Xu *et al*[3] describes the case of a patient who showed primary nonresponse to two biologics and two fecal microbiota transplants (FMT) but exhibited a remarkable response to upadacitinib[3]. It should be noted that FMT for ASUC is considered an off-label indication. The available evidence supporting its use remains primarily anecdotal, and its application should be restricted to the treatment of *Clostridioides difficile* (*C. difficile*) infection, or to clinical trials, according to the American Gastroenterology Association[4,5].

Despite limited evidence, both upadacitinib and tofacitinib have shown promise in the management of refractory UC, either as monotherapy or in combination with biologics as rescue therapy. At our center, we have extensive experience in employing off-label combined therapy for ASUC. I am particularly inclined to share a specific case that I believe would enrich the ongoing discussion initiated by Xu *et al*[3], presenting an alternative approach.

JANUS KINASE INHIBITORS AS RESCUE THERAPY FOR ULCERATIVE COLITIS REFRACTORY TO INFLIXIMAB

A 57-year-old male patient with a decade-long history of UC presented with recurrent symptomatic episodes despite several treatments. Initially responsive to mesalazine 4 g daily and a course of prednisone, the patient relapsed after a few years. Subsequent treatment with azathioprine 150 mg daily and mesalazine 4 g daily controlled the disease for another few years. However, his symptoms recurred, requiring the use of oral enteric budesonide 9 mg daily. Despite these interventions, his symptoms worsened, leading to fecal incontinence and anemia.

Tests for *C. difficile* toxins A and B and immunohistochemistry for cytomegalovirus were negative. Colonoscopy revealed worsening of UC (Figure 1), prompting initiation of biologic therapy with infliximab induction at a dose of 5 mg/kg. Although the patient reported a mild reduction in the frequency of bloody stools upon initiation of infliximab, fecal incontinence persisted. Despite dose escalation to 500 mg every 4 wk, his symptoms persisted, indicating a partial response to infliximab. Another colonoscopy was performed, which demonstrated improvement of mucosal damage, but without resolution of UC (Figure 2).

Tofacitinib 5 mg twice daily was introduced as adjunctive therapy alongside infliximab, replacing azathioprine, with the aim of achieving disease remission, as suggested in the case series by Gilmore *et al*[6]. Over the subsequent 3 months, the patient's symptoms gradually improved, with a reduction in stool frequency and resolution of fecal incontinence and bleeding. Treatment with tofacitinib was then interrupted, and the patient was maintained on infliximab 5 mg/kg/dose infusions every 6 wk, adjusted to infliximab serum levels, and azathioprine 100 mg daily. He has remained in deep remission for the last 3 years, with a Mayo endoscopic score of 0 (Figure 3).

There are two crucial points I believe warrant discussion. First, the possibility of overlapping infections in ASUC (*i.e.*, *C. difficile* and cytomegalovirus) was ruled out before escalation of therapy[7-9]. Second, colorectal surgeons must be aware that the clinical condition of patients with refractory UC or ASUC can rapidly deteriorate, requiring urgent colectomy[10,11].

There is increasing evidence supporting the utilization of tofacitinib in cases of infliximab-refractory ASUC[12]. A previous randomized controlled trial reported a response rate as high as 83% in ASUC patients refractory to corticosteroids after 7 d of tofacitinib treatment[13]. Similarly, a retrospective study demonstrated a response rate of 87.5%[14].

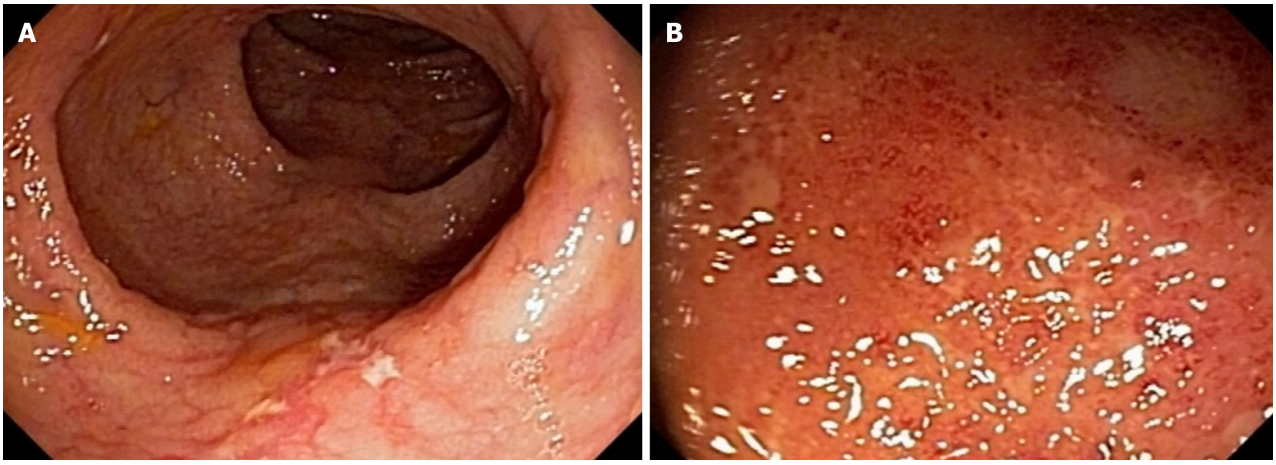

Figure 1 Colonoscopy. Pre-biologic. Ulcerative colitis with friability and ulcers, Mayo endoscopic score 2. A: Transition zone in the transverse colon; B: Sigmoid colon.

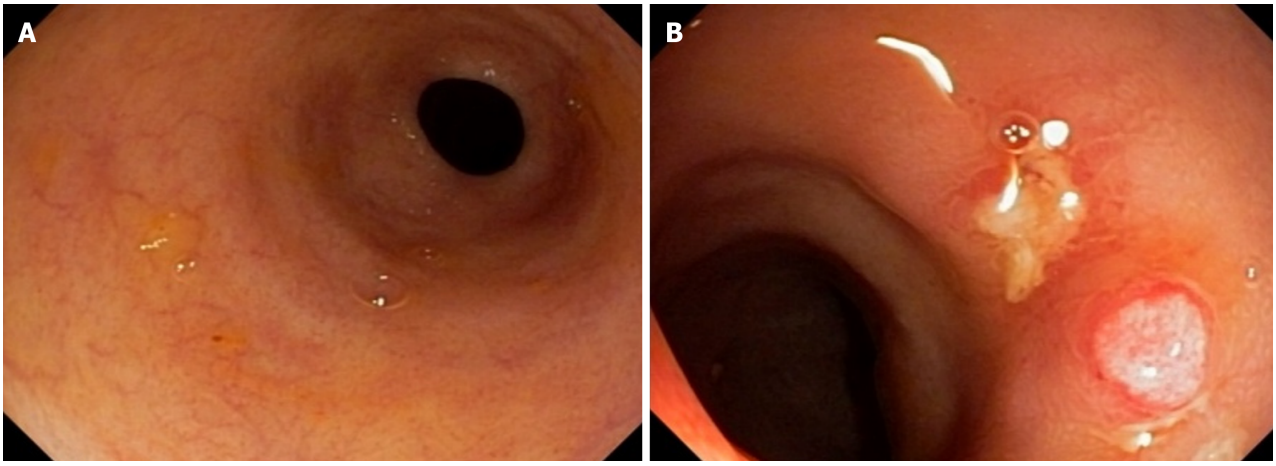

Figure 2 Colonoscopy. Pre-Tofacitinib. Improvement, but still presenting ulcerative colitis with patchy areas of friability and ulcers, Mayo endoscopic score 2. A: Transition zone in the transverse colon; B: Sigmoid colon.

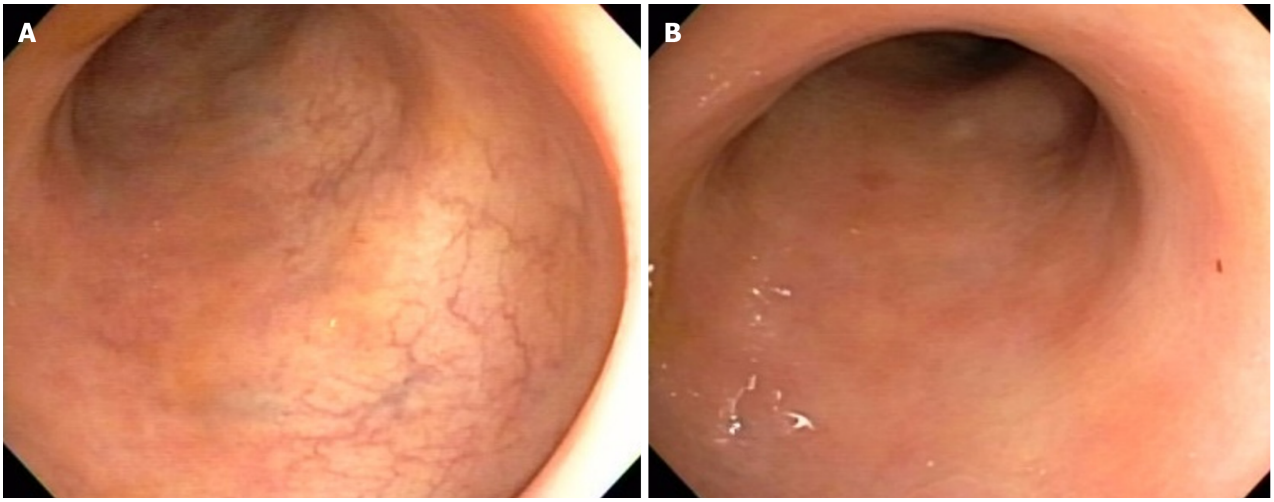

Figure 3 Colonoscopy. Maintenance therapy with infliximab, three years after tofacitinib was withdrawn. Scarred mucosa, Mayo endoscopic score 0. A: Transition zone in the transverse colon; B: Sigmoid colon.

Moreover, a noteworthy case series administered a higher dose of tofacitinib to eleven ASUC patients, achieving disease control in nine of them. Subsequently, these patients were transitioned to infliximab for maintenance therapy[15].

Tofacitinib has been investigated in combination with other biologics for the management of ASUC[16], including its use as replacement therapy for azathioprine alongside infliximab, demonstrating both efficacy and safety[6]. Of note, a systematic review revealed that the use of tofacitinib in ASUC led to a pooled 90-day and 6-month colectomy-free rate of 79.9%[17].

Although the use of tofacitinib as monotherapy in this setting has been extensively researched, some reports have also described the efficacy of upadacitinib in ASUC. For instance, a case report documented a positive response to upadacitinib in a patient for whom treatment with infliximab, adalimumab, and tofacitinib had previously failed[18]. A case series evaluating upadacitinib in ASUC resistant to steroids has demonstrated comparable efficacy to previous case series with tofacitinib, with 5 out of 6 patients showing improvement[19]. As upadacitinib has recently been approved for use in UC, promising results have been described in several recent case series of ASUC. One study reported steroid-free remission in 6 out of 9 patients[20], while another showed a response rate of 83% among 25 patients[21].

CONCLUSION

In conclusion, both cases underscore the complexity of managing refractory ASUC and highlight the potential synergistic effect of employing small molecule therapies either in combination or sequentially with biologics to achieve and sustain disease remission. Further studies are warranted to elucidate the optimal treatment strategies for patients who have completely or partially failed multiple available therapies.

FOOTNOTES

Author contributions: Soldera J contributed to writing and reviewing the final draft of the manuscript.

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REFERENCES

1 **Danese S**, Vermeire S, Zhou W, Pangan AL, Siffledeen J, Greenbloom S, Hébuterne X, D'Haens G, Nakase H, Panés J, Higgins PDR, Juillerat P, Lindsay JO, Loftus EV Jr, Sandborn WJ, Reinisch W, Chen MH, Sanchez Gonzalez Y, Huang B, Xie W, Liu J, Weinreich MA, Panaccione R. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. *Lancet* 2022; **399**: 2113-2128 [PMID: 35644166 DOI: 10.1016/S0140-6736(22)00581-5]

2 **Sandborn WJ**, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G, Lawendy N, Yu D, Woodworth D, Mukherjee A, Zhang H, Healey P, Panés J; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2017; **376**: 1723-1736 [PMID: 28467869 DOI: 10.1056/NEJMoa1606910]

3 **Xu X**, Jiang JW, Lu BY, Li XX. Upadacitinib for refractory ulcerative colitis with primary nonresponse to infliximab and vedolizumab: A case report. *World J Clin Cases* 2024; **12**: 1685-1690 [PMID: 38576732 DOI: 10.12998/wjcc.v12.i9.1685]

4 **Costello SP**, Day A, Yao CK, Bryant RV. Faecal microbiota transplantation (FMT) with dietary therapy for acute severe ulcerative colitis. *BMJ Case Rep* 2020; **13** [PMID: 32843418 DOI: 10.1136/bcr-2019-233135]

5 **Peery AF**, Kelly CR, Kao D, Vaughn BP, Lebwohl B, Singh S, Imdad A, Altayar O; AGA Clinical Guidelines Committee. Electronic address: clinicalpractice@gastro.org. AGA Clinical Practice Guideline on Fecal Microbiota-Based Therapies for Select Gastrointestinal Diseases. *Gastroenterology* 2024; **166**: 409-434 [PMID: 38395525 DOI: 10.1053/j.gastro.2024.01.008]

6 **Gilmore R**, Hilley P, Srinivasan A, Choy MC, Grace JA, de Cruz P. Tofacitinib Is Safe and Effective When Used in Combination With Infliximab for the Management of Refractory Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2021; **19**: 1302-1303 [PMID: 33248087 DOI: 10.1016/j.cgh.2020.07.046]

7 **Furlan RG**, Soldera J, Balbinot RS, Terres AZ, Balbinot SS, Balbinot RA. Ulcerative Proctosigmoiditis Exacerbated by Recurrent Clostridium colitis: Case Report. *J Gastroenterol Hepatol Endosc* 2017; **2**: 1025

8 **Kanika A**, Soldera J. Pulmonary cytomegalovirus infection: A case report and systematic review. *World J Meta-Anal* 2023; **11**: 151-166 [DOI: 10.13105/wjma.v11.i5.151]

9 **da Cruz ER**, Forno AD, Pacheco SA, Bigarella LG, Ballotin VR, Salgado K, Freisbelen D, Michelin L, Soldera J. Intestinal Paracoccidioidomycosis: Case report and systematic review. *Braz J Infect Dis* 2021; **25**: 101605 [PMID: 34461048 DOI: 10.1016/j.bjid.2021.101605]

10 **Mowlah RK**, Soldera J. Risk and management of post-operative infectious complications in inflammatory bowel disease: A systematic review. *World J Gastrointest Surg* 2023; **15**: 2579-2595 [PMID: 38111772 DOI: 10.4240/wjgs.v15.i11.2579]

11 **Dall'Oglio VM**, Balbinot RS, Muscope ALF, Castel MD, Souza TR, Macedo RS, Oliveira TB, Balbinot RA, Balbinot SS, Brambilla E, Soldera J. Epidemiological profile of inflammatory bowel disease in Caxias do Sul, Brazil: a cross-sectional study. *Sao Paulo Med J* 2020; **138**: 530-536 [PMID: 33206912 DOI: 10.1590/1516-3180.2020.0179.R2.10092020]

12 **Fortuny Bauzá M**, Cañete Pizarro F, Calm Salvans A, Calafat Sard M, Domènech Morral E. Tofacitinib for the treatment of acute severe ulcerative colitis refractory to infliximab. *Gastroenterol Hepatol* 2022; **45** Suppl 1: 11-12 [PMID: 34118322 DOI: 10.1016/j.gastrohep.2021.05.005]

13 **Singh A**, Goyal MK, Midha V, Mahajan R, Kaur K, Gupta YK, Singh D, Bansal N, Kaur R, Kalra S, Goyal O, Mehta V, Sood A. Tofacitinib in Acute Severe Ulcerative Colitis (TACOS): A Randomized Controlled Trial. *Am J Gastroenterol* 2024 [PMID: 38131615 DOI: 10.14309/ajg.0000000000002635]

14 **Malakar S**, Kothalkar S, Shamsul Hoda U, Ghoshal UC. Tofacitinib in Steroid-Refractory Acute Severe Ulcerative Colitis: A Retrospective Analysis. *Cureus* 2023; **15**: e45416 [PMID: 37854768 DOI: 10.7759/cureus.45416]

15 **Eqbal A**, Hilley P, Choy M, Srinivasan A, de Cruz P. Outcomes out to 12 months after sequential use of high-dose tofacitinib following infliximab in acute severe ulcerative colitis. *Intern Med J* 2023; **53**: 1497-1500 [PMID: 37599224 DOI: 10.1111/imj.16192]

16 **Hilley P**, Gilmore R, Srinivasan A, Choy M, De Cruz P. Combined Targeted Treatment Using Biologic-Tofacitinib Co-Therapy in Chronic Active Ulcerative Colitis. *Inflamm Bowel Dis* 2021; **27**: e105-e106 [PMID: 33999191 DOI: 10.1093/ibd/izab095]

17 **Mpakogiannis K**, Fousekis FS, Christodoulou DK, Katsanos KH, Narula N. The current role of Tofacitinib in acute severe ulcerative colitis in adult patients: A systematic review. *Dig Liver Dis* 2023; **55**: 1311-1317 [PMID: 37316363 DOI: 10.1016/j.dld.2023.05.021]

18 **Ali NM**, Shehab MA. Upadacitinib as a Rescue Therapy in Acute Severe Ulcerative Colitis: A Case Report and Review of the Literature. *Am J Case Rep* 2023; **24**: e940966 [PMID: 37926993 DOI: 10.12659/AJCR.940966]

19 **Gilmore R**, Tan WL, Fernandes R, An YK, Begun J. Upadacitinib Salvage Therapy for Infliximab-Experienced Patients with Acute Severe Ulcerative Colitis. *J Crohns Colitis* 2023; **17**: 2033-2036 [PMID: 37422724 DOI: 10.1093/ecco-jcc/jjad115]

20 **Dalal RS**, Winter RW, Gupta S, Sasson GF, Hamilton MJ, Allegretti JR. Clinical Outcomes at 8-16 Weeks After Upadacitinib Initiation for Acute Severe Ulcerative Colitis: A Case Series in the United States. *Inflamm Bowel Dis* 2024 [PMID: 38408096 DOI: 10.1093/ibd/izae038]

21 **Berinstein JA**, Karl T, Patel A, Dolinger M, Barrett TA, Ahmed W, Click B, Steiner CA, Dulaney D, Levine J, Hassan SA, Perry C, Flomenhoft D, Ungaro RC, Berinstein EM, Sheehan J, Cohen-Mekelburg S, Regal RE, Stidham RW, Bishu S, Colombel JF, Higgins PDR. Effectiveness of Upadacitinib for Patients With Acute Severe Ulcerative Colitis: A Multicenter Experience. *Am J Gastroenterol* 2024 [PMID: 38275248 DOI: 10.14309/ajg.0000000000002674]

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