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Short Report

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Tofacitinib for Rescue Therapy in Acute Severe Ulcerative Colitis: A Real-world Experience

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Abstract

Background: Acute severe ulcerative colitis is a high stakes event with significant numbers still requiring emergent colectomy, representing a need to establish alternative medical management options. We report a case series of tofacitinib as rescue therapy in biologic-experienced patients with acute severe ulcerative colitis.

Methods: Four patients were identified over a 1-year period at our institution who initiated tofacitinib for acute severe ulcerative colitis. All four had previously failed at least two biologics, including infliximab, and were failing high-dose oral prednisone therapy before admission. All patients had Mayo disease activity index of at least 10 at admission. After no significant improvement despite receiving a minimum of 3 days of intravenous methylprednisolone and based on elevated Ho and Travis indices at Day 3, patients were offered rescue tofacitinib for induction of remission, or colectomy. Standard induction of tofacitinib was used [10 mg twice daily], and one patient was escalated to 15 mg twice daily after inadequate response.

Results: All patients experienced improvement in objective symptoms and laboratory markers, and were discharged without colectomy on tofacitinib as maintenance therapy and prednisone taper; 30-day and 90-day colectomy rates on tofacitinib maintenance therapy were zero and 90-day readmission rate was also zero. Two of four patients achieved steroid-free remission on maintenance tofacitinib monotherapy based on clinical symptoms and follow-up endoscopy. No major adverse reaction was reported during induction or maintenance therapy.

Conclusions: Tofacitinib may be an acceptable rescue agent in biologic-experienced patients with acute severe ulcerative colitis. Tofacitinib may also be safely continued as maintenance therapy once remission has been achieved.

Key Words: Tofacitinib; acute severe ulcerative colitis; rescue; remission

1. Introduction

Acute severe ulcerative colitis [ASUC] requiring hospitalisation is common and a high-stakes event for patients with ulcerative colitis [UC]. Approximately 15% to 25% of UC patients will require hospitalisation during their disease course.[1] About 37 000 hospitalisations for UC occur annually in the USA, with an estimated cost of more than $450 million.[2] First-line management of ASUC includes initiation of intravenous [IV] corticosteroids; though more than 30% may not respond to IV corticosteroids alone,[3] necessitating second-line rescue therapy with infliximab or cyclosporine. Among those receiving rescue therapy, as many as half may ultimately undergo colectomy within 3 months, representing a need to establish alternative medical management options.[4] Recent reports suggest that tofacitinib, a rapidly acting oral janus kinase inhibitor, may have clinical effect within days of induction therapy.[5] A case series of four patients suggested efficacy of short-term high-dose induction therapy with tofacitinib in ASUC.[6] We now report our experience of using standard induction of tofacitinib as rescue therapy in four

Table 1. Clinical features and outcomes with tofacitinib rescue therapy.

	Patient 1	Patient 2[a]	Patient 3	Patient 4
Gender	Female	Female	Female	Male
Age at diagnosis	25	46	32	23
Disease duration [years]	5	5	2	12
Extent of disease	Left-sided	Pancolitis	Left-sided	Pancolitis
Biologics used previously	Infliximab, adalimumab, vedolizumab	Infliximab, vedolizumab	Infliximab, vedolizumab	Infliximab, vedolizumab
Biologic use history	Developed anaphylaxis to infliximab and adalimumab. Started vedolizumab 5 months before admission. Dose escalated to Q4 weeks 3 months before admission along with initiation of prednisone, without improvement	Unable to tolerate infliximab and vedolizumab due to dermatological reactions despite >8 months' therapy with each agent. Started prednisone 1 month before admission, without improvement	Secondary loss of response to infliximab. Subsequently, maintained on 6-MP and vedolizumab for 2 years. Vedolizumab increased to Q4 week dosing and started prednisone 3 months before admission for severe flare	Vedolizumab primary non-responder. Started infliximab 3 months before admission due to severe symptoms, but primary non-response and concern for eosinophilic pneumonia as side effect of anti-TNF therapy
Medications on admission	Vedolizumab, mesalamine, prednisone, hydrocortisone enema	Prednisone	Vedolizumab, prednisone	Infliximab, prednisone
Last biologic use before admission [days]	30	200	6	<60
Albumin [g/dL] on admission	3.5	2.7	2.5	1.8
CRP [mg/L] on admission	13.3	146.4	1.7	165.5
Number of bowel movements/day on admission	>10	>10	9	15
Percentage of bloody bowel movements on admission	100%	100%	100%	30%
Mayo score on staging endoscopy on admission	3	3	3	3
Travis index on Day 3 after IV steroids	Negative	Positive	Positive	Positive
Ho score on Day 3 after IV steroids	2	5	3	3
Time to rescue therapy with tofacitinib [days]	6	6	3	6
Time from initiation of tofacitinib to discharge [days]	4	21 [11 days to discharge after dose escalated to 15 mg BID]	2	6
CRP [mg/L] on discharge	-	22.9	-	6.3
Number/day of bowel movements on discharge	5	5	3	5
30-day readmission	No	No	No	No
90 days free of colectomy	Yes	Yes	Yes	Yes
Disease activity on follow-up endoscopy	Mayo 2	Mayo 0	Mayo 0	Mayo 3
Steroid-free remission	No	Yes	Yes	No
Current therapy	Tofacitinib, ustekinumab[b]	Tofacitinib	Tofacitinib	Surgery referral for repeated 'indefinite for dysplasia' on random colon biopsies
Follow-up [months]	14	11	6	5

6MP, 6-mercaptopurine; TNF, tumour necrosis factor; CRP, C-reactive protein; IV, intravenous.

[a]Tofacitinib dose escalated to 15 mg BID after 10 days due to insufficient improvement

[b]Patient moved to another state and transferred care to another institution

biologic-experienced patients with ASUC, who were at high risk of colectomy.

2. Case Report

All hospital admissions at our institution over a 1-year period between July 2018 and July 2019 were screened for inpatient administration of tofacitinib. Twelve patients received inpatient tofacitinib during this period; two with rheumatoid arthritis and six with inflammatory bowel disease, who were taking tofacitinib before admission, were excluded. Four patients were identified who had new initiation of tofacitinib during inpatient admission for UC flare. All four had previously failed at least two biologics [due to drug intolerance or loss of response—see Table 1], including infliximab, and were failing high-dose oral prednisone therapy before admission. All patients received laboratory evaluation with stool-based testing for *Clostridiodes difficile*, and endoscopic assessment with biopsies for cytomegalovirus staining and to stage disease severity. After no significant improvement despite receiving a minimum of 3 days of intravenous [IV] methylprednisolone and based on elevated Ho[7] and Travis[8] indices at Day 3, patients were offered rescue tofacitinib for induction of remission, or colectomy. After shared decision making, all patients received standard induction with oral tofacitinib 10 mg twice daily.

All patients had a Mayo disease activity index of at least 10 at the time of admission, including Mayo stage 3 for endoscopic disease severity. Clinical features are summarised in Table 1. Time to rescue therapy with tofacitinib after IV corticosteroid failure ranged from 3 to 6 days after admission. Time from tofacitinib initiation to discharge ranged from 2 to 21 days. All patients experienced improvement in objective symptoms and laboratory markers, and were discharged without colectomy on tofacitinib as maintenance therapy. Tofacitinib was continued at 10 mg twice daily [BID] [and 15 mg BID for patient 2] at discharge, with plans for outpatient tapering pending repeat endoscopic evaluation within 8–12 weeks. Patients were also discharged on prednisone taper [decrease 5–10 mg per week] per treating clinician's recommendations; 30-day and 90-day colectomy rates on tofacitinib maintenance therapy were zero and 90-day readmission rate was also zero. Two patients achieved steroid-free remission on maintenance tofacitinib monotherapy. One patient has been referred for surgical management given repeated 'indefinite for dysplasia' on random colon biopsies and persistent symptomatic disease [Mayo 3 on follow-up sigmoidoscopy]. One patient has transferred care to another institution where alternaivte clinical management is being considered for ongoing clinically and endoscopically active disease. No major adverse reaction was reported during induction or maintenance therapy. Specifically, no new thromboembolic events were noted. Notably, one patient had history of venous thromboembolism [VTE] and did not experience recurrent VTE since initiating tofacitinib [maintained on chronic anticoagulation]. Last biologic use beforetofacitinib induction ranged from 6–200 days, and no infectious complications were observed.

3. Discussion

We report outcomes from a real-world application of tofacitinib as rescue therapy in ASUC. One previous case series[6] described efficacy of high-dose [10 mg three times daily for 3 days] tofacitinib induction therapy in ASUC, though this study was limited by inclusion of biologic-naïve patients and an inadequate trial of IV steroids. Our conventional approach to ASUC management in patients failing IV steroids for at least 3 days, who are biologic-experienced (specifically, anti-tumour necrosis factor [TNF] agents), suggests that standard induction therapy with 10 mg BID may be an efficacious regimen without increased risk of adverse effects. In addition, we safely and successfully escalated the dose to 15 mg BID in one patient after inadequate response to standard induction, who went on to achieve clinical and endoscopic remission. Tofacitinib may also be safely continued as maintenance therapy once remission has been achieved. Two of four patients in our series achieved clinical and endoscopic healing on follow-up with maintenance tofacitinib. Recent evidence suggests that tofacitinib has a rapid onset of action and thus may have a role in patients who have failed first-line therapy for ASUC. Given rapid clearance of the drug, it may be less likely to lead to adverse surgical outcomes should emergent colectomy be necessary for ASUC. Our study is limited by its design as a retrospective case series, but it lends support to a more systematic evaluation of tofacitinib as rescue agent in ASUC. Further high-quality, controlled trials are needed to assess the role of tofacitinib as rescue therapy in ASUC.

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Conflict of Interest

PK and SL have no disclosures. JT has received research support from AbbVie and Celgene.

Author Contributions

PK: study design, concept, data acquisition, data interpretation, initial draft, critical revision, final approval. JT: data interpretation, critical revision, final approval. SL: study design, concept, data interpretation, critical revision, final approval.

References

1. Pola S, Patel D, Ramamoorthy S, *et al.* Strategies for the care of adults hospitalized for active ulcerative colitis. *Clin Gastroenterol Hepatol* 2012;**10**:1315–25.e4.
2. Peery AF, Crockett SD, Murphy CC, *et al.* Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: Update 2018. *Gastroenterology* 2019;**156**:254–72.e11.
3. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007;**5**:103–10.
4. Laharie D, Bourreille A, Branche J, *et al.*; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. *Lancet* 2012;**380**:1909–15.
5. Hanauer S, Panaccione R, Danese S, *et al.* Tofacitinib induction therapy reduces symptoms within 3 days for patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2019;**17**:139–47.
6. Berinstein JA, Steiner CA, Regal RE, *et al.* Efficacy of induction therapy with high-intensity tofacitinib in 4 patients with acute severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2019;**17**:988–90.e1.
7. Ho GT, Mowat C, Goddard CJ, *et al.* Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther* 2004;**19**:1079–87.
8. Travis SP, Farrant JM, Ricketts C, *et al.* Predicting outcome in severe ulcerative colitis. *Gut* 1996;**38**:905–10.