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Short Report

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Sequential Use of High-Dose Tofacitinib After Infliximab Salvage Therapy in Acute Severe Ulcerative Colitis

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Abstract

Background and Aims. Preliminary data regarding the effectiveness of tofacitinib in acute severe ulcerative colitis [ASUC] have been presented in two previous case series. We aimed to describe the novel use of high-dose tofacitinib immediately following non-response to infliximab in the setting of steroid-refractory ASUC.

Methods. Five patients who received high-dose tofacitinib 10 mg three times a day immediately following non-response to infliximab for steroid-refractory ASUC were identified at an Australian tertiary inflammatory bowel disease centre.

Results. Four of the five patients demonstrated clinical response to high-dose tofacitinib induction during their inpatient admission, with one patient requiring colectomy owing to a lack of clinical response. At 90 days, all four initial responders remained colectomy-free, with two patients achieving combined clinical and endoscopic remission. No adverse events directly attributable to high-dose tofacitinib were identified.

Conclusions. High-dose tofacitinib may have a role as salvage therapy in the setting of steroid-refractory ASUC. Prospective studies are required to determine the safety and efficacy of high-dose tofacitinib to determine whether it can be routinely recommended as primary or sequential salvage therapy in the setting of steroid-refractory ASUC.

Key Words: Acute severe ulcerative colitis; tofacitinib; infliximab

1. Background and Aims

Acute severe ulcerative colitis [ASUC] remains a significant cause of morbidity and mortality, affecting up to 25% of patients with ulcerative colitis [UC].[1] Standard of care management for ASUC includes high-dose intravenous [IV] corticosteroids for a minimum of 3 days, followed by either cyclosporine or infliximab salvage therapy in steroid-refractory cases.[2,3] Colectomy is generally reserved for cases refractory to, or unsuitable for, salvage therapy. Tofacitinib, an oral small-molecule janus kinase [JAK] inhibitor, has been reported to improve clinical parameters within 3 days in UC.[4] Tofacitinib's rapid onset of action, combined with its proven efficacy and relatively short half-life, underline its potential role as an alternative salvage therapy in steroid-refractory ASUC. This is supported by two recent case series, each describing outcomes in four patients, reporting the clinical effectiveness of tofacitinib for steroid-refractory ASUC in biologic-experienced patients.[5,6] Patients across both series were treated with tofacitinib doses ranging between 20 and 30 mg daily, with rapid clinical response and 30-day colectomy-free survival reported in all but a single case. Here, we aimed to describe the novel use of high-dose tofacitinib 10 mg three times a day as rescue therapy following infliximab non-response in the setting of steroid-refractory ASUC.

2. Methods

Five patients who initiated tofacitinib immediately following non-response to infliximab therapy in the setting of steroid-refractory ASUC were identified from a prospectively maintained database at a tertiary Australian inflammatory bowel disease [IBD] centre [Table 1]. Three patients were admitted with ASUC within 7 days of completing infliximab induction reflective of primary non-response; the remaining two patients were naïve to biologics on admission. One patient had previously lost response to vedolizumab. On admission, all five patients met Truelove and Witts criteria for ASUC, with a median total Mayo score of 10 [range 10–11] and median Mayo endoscopy score of 3 [range 2–3]. All five patients failed to respond to at least 72 h of IV hydrocortisone 100 mg four times a day in keeping with steroid-refractory ASUC. Two patients, both of whom were biologic-naïve, failed to respond both clinically and biochemically to inpatient infliximab salvage [2 × 5–10 mg/kg doses over 3–5 days]. Varicella serology was performed in all patients, confirming prior exposure in four. The single patient without evidence of prior exposure was not subsequently vaccinated due to concurrent treatment with corticosteroids. Following multidisciplinary discussion, all five patients were presented the options of proceeding to colectomy as per standard of care or a trial of off-label salvage therapy with high-dose tofacitinib 10 mg three times a day. The decision to use high-dose tofacitinib 10 mg three times a day was based on the results of a phase 2 study which reported higher rates of week 8 clinical response using tofacitinib 15 mg twice a day [78%] compared with 10 mg twice a day [61%],[7] together with favourable outcomes reported in case series by Berinstein *et al.*[5]All five patients were transitioned from IV hydrocortisone to oral prednisolone 40 mg [weaned over 6 weeks] and discontinued immunomodulator therapy at the time of tofacitinib initiation. Concurrent venous thromboembolism and antimicrobial prophylaxis with enoxaparin and sulfamethoxazole/trimethoprim respectively were prescribed whilst patients were on high-dose tofacitinib.

3. Results

High-dose tofacitinib 10 mg three times a day was initiated in five patients over a median of 4 days after admission [range 3–8 days]. Four patients demonstrated clinical response during their inpatient admission, with one patient requiring colectomy owing to lack of clinical response 3 days after tofacitinib initiation. Clinical responders also demonstrated improvement in laboratory markers. In the setting of clinical response, high-dose tofacitinib was continued for a maximum of 14 days, following which the dose was reduced to 10 mg twice a day for a further 8 weeks, with 5 mg twice a day continued as maintenance therapy thereafter if response was maintained. At 90 days, all four initial responders remained colectomy-free, with two achieving combined steroid-free clinical and endoscopic remission. The median total Mayo score was 3 [range 0–6] and the median Mayo endoscopic score was 2 [range 0–3]. Patients were followed up for a median of 7 months [range 4–18] following initiation of high-dose tofacitinib. One patient was commenced on combination ustekinumab–tofacitinib therapy in the setting of persisting endoscopic disease after 90 days of tofacitinib monotherapy. No major adverse events were associated with the use of high-dose tofacitinib, nor were any encountered during subsequent follow-up.

4. Discussion and Conclusion

This series is the first to highlight the potential role of high-dose tofacitinib as rescue therapy following non-response to infliximab in the setting of steroid-refractory ASUC. While four of five patients avoided colectomy over the duration of clinical follow-up, only two of five patients achieved combined steroid-free clinical and endoscopic remission at 90 days. These findings are similar to those reported by Berinstein *et al.*, wherein three of four patients achieved short-term colectomy-free clinical emission. One patient in their series demonstrated rapid clinical improvement following initiation of high-dose tofacitinib but experienced clinical deterioration warranting colectomy following dose reduction of tofacitinib to 5 mg twice a day on day 5. A point of difference is that Berinstein *et al.*[5] used three times daily tofacitinib for 3 days, whilst in our cohort, up to 14 days of this dosage in combination with prednisolone was utilized. This extended duration of high-dose tofacitinib may be safe and clinically effective. Across both Berinstein and our series, seven of nine patients have demonstrated short-term clinical response and colectomy-free survival following high-dose tofacitinib therapy. While these preliminary findings are encouraging, it should be emphasized that colectomy remains standard of care in cases of ASUC refractory to infliximab salvage. We acknowledge that sequential therapy, following non-response to initial infliximab or cyclosporin, remains controversial with existing evidence insufficient to support recommendations for or against its use.[8] Our preliminary data suggest that tofacitinib may have a role as second-line salvage therapy following infliximab non-response in a select group of patients managed within specialized referral centres. Prospective studies are required to determine the safety and efficacy of high-dose tofacitinib to determine whether it can be routinely recommended as primary or sequential salvage therapy in the setting of steroid-refractory ASUC.

Table 1. Baseline patient, treatment, clinical, biochemical and endoscopic characteristics prior to tofacitinib salvage therapy, followed by treatment response at 90 days

Case	Baseline characteristics							Follow up at 90 days			
	Age [years]	Sex	Prior biologic	FCP [µg/mL]	CRP [mg/L]	MES	Total Mayo score	FCP [µg/mL]	CRP [mg/L]	MES	Total Mayo score
1	33	M	No	1690	61	3	11	52	0.2	1	1
2	22	M	No	872	25	3	11	Colectomy			
3	18	M	IFX	1670	7	2	11	179	24	3	6
4	19	M	IFX	NA	25	3	10	NA	1	0	0
5	18	M	IFX, VDZ	550	8	3	10	1630	5	2	5

MES: Mayo endoscopic score; FCP: faecal calprotectin; CRP: C-reactive protein; IFX: infliximab; VDZ: vedolizumab; M: male; F: female.

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Conflict of Interest

M.C.C. has served as a speaker for DiaSorin, has received research funding from Janssen, and has received educational support from Ferring, Shire, Janssen, AbbVie, Takeda and Orphan. P.D.C. has served as a speaker, a consultant and an advisory board member for Ferring, Shire, Janssen, AbbVie, Takeda and Baxter.

Author Contributions

R.G., M.C., P.D.C.: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision. P.H., A.S.: acquisition of data; analysis and interpretation of data; drafting of the manuscript and critical revision of the manuscript for important intellectual content.

Data Availability Statement

The data underlying this article are available in the article.

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