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Short Report

Upadacitinib Salvage Therapy for Infliximab-Experienced Patients with Acute Severe Ulcerative Colitis

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Abstract

Background and Aims: Acute severe ulcerative colitis [ASUC] is a medical emergency treated with intravenous steroids followed by infliximab or cyclosporin in the case of steroid failure with emergent colectomy required in refractory or severe cases. Case series have reported on the effectiveness of tofacitinib for refractory disease, but data regarding the effectiveness of upadacitinib in this setting have not been previously reported. We describe the use of upadacitinib therapy for steroid-refractory ASUC in patients with prior loss of response to infliximab.

Methods: Six patients who received upadacitinib for steroid-refractory ASUC were identified at two Australian tertiary inflammatory bowel disease centres. Patients were followed for up to 16 weeks after discharge with clinical, biochemical and intestinal ultrasound [IUS] outcomes.

Results: All six patients demonstrated clinical response to upadacitinib induction during their inpatient admission. Four patients achieved corticosteroid-free clinical remission by week 8, including complete resolution of rectal bleeding and transmural healing assessed by IUS, and sustained clinical remission at week 16. One patient proceeded to colectomy at week 15 due to refractory disease. No adverse events directly attributable to upadacitinib were identified.

Conclusions: Upadacitinib may have a role as a safe and effective salvage therapy for steroid-refractory ASUC in patients who have previously failed to respond to infliximab therapy. Prospective studies are required to determine the safety and efficacy of upadacitinib use in this setting before routine use can be recommended.

Key Words: Acute severe ulcerative colitis; upadacitinib

1. Background and Aims

Acute severe ulcerative colitis [ASUC] remains a significant cause of morbidity and mortality, affecting up to 25% of patients with 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 medical therapy. Upadacitinib, an oral selective Janus kinase [JAK] 1 inhibitor, is highly effective for induction and maintenance of remission in moderate to severe UC in a clinical trial setting.[4] A number of case series have described the effectiveness and safety of the pan-JAK inhibitor tofacitinb in patients with ASUC.[5,6] Upadacitinib has a very short half-life and induces rapid clinical remission with high efficacy and a favourable safety profile, underlining its potential role as an alternativee salvage therapy in steroid-refractory ASUC. Here, we describe the novel use of upadacitinib 45 mg once daily as oral rescue therapy for steroid-refractory ASUC in infliximab-experienced patients.

2. Methods

Six patients who initiated upadacitinib immediately following non-response to IV corticosteroid therapy for ASUC were identified from a prospectively maintained database across two tertiary Australian inflammatory bowel disease [IBD] centres [Table 1]. ASUC was defined according to modified Truelove and Witts criteria.[7] Corticosteroid non-response was determined using the day 3 Oxford criteria with more than four bowel motions a day or a C-reactive protein [CRP] of >15 mg/L.[8] All patients were previously exposed to infliximab, three ceased due to primary non-response, two due to secondary loss of response and one due to medication intolerance. No patient had received infliximab within 8 weeks of admission with ASUC.

Following an inadequate response to IV corticosteroids and after multidisciplinary discussion, all six patients were presented the option of cyclosporin therapy as a bridge to an alternative advanced drug therapy, proceeding to colectomy as per standard of care in the setting of inadequate response, or a trial of off-label salvage therapy with upadacitinib 45 mg once a day. The option to use upadacitinib as salvage

Table 1. Clinical, biochemical, and endoscopic characteristics within 24 h of admission.

Case	Baseline characteristics									
	Age [years]	Sex	Duration of disease [years]	Extent of disease	Prior therapies	FCP [µg/mL]	CRP [mg/L]	IUS [Limberg]	MES [UCEIS]	Partial Mayo score
1	22	F	3	E3	Infliximab, vedolizumab	936	47	3	2 [6]	9
2	25	F	2	E3	Infliximab, vedolizumab	6000	19	2	3 [6]	7
3	26	M	2	E3	Infliximab	3338	39	2	2 [5]	7
4	24	M	1	E3	Infliximab	2989	122	2	3 [5]	8
5	58	M	38	E3	Infliximab, vedolizumab	1355	5	3	2 [5]	7
6	41	M	5	E2	Infliximab, vedolizumab, golimumab	7000	28	3	3 [6]	8

MES: Mayo endoscopic score; FCP: faecal calprotectin; CRP: C-reactive protein; IUS: intestinal ultrasound; M: male; F: female, E3: pancolitis, E2: left-sided colitis; UCEIS: ulcerative colitis endoscopic index of severity.

therapy was presented based on its efficacy in clinical trials and in clinical practice, rapidity of onset, and once daily dosing regimen. All six patients commenced upadacitinib 45 mg daily salvage therapy and were transitioned from IV corticosteroid [after a median of 3 days from admission] to oral prednisolone 50 mg daily with weaning over 5 weeks. Prior advanced drug therapies and immunomodulators were ceased. Five of the patients were on maximally dosed oral 5-aminosalicylic acid with one patient having prior intolerance on admission, and this was continued after discharge. Concurrent venous thromboembolism prophylaxis with enoxaparin was prescribed whilst patients were in hospital, but was not continued after discharge.

Baseline demographics including clinical, biochemical (faecal calprotectin [FCP] and CRP), endoscopic and intestinal ultrasound [IUS] data were collected for all patients. Patients were followed for up to 16 weeks from initiation of upadacitinib.

Primary outcomes were inpatient clinical response to upadacitinib salvage therapy by day 7 and need for colectomy by week 16. Clinical response to inpatient salvage therapy was defined using modified Oxford criteria for ASUC [bowel opening <4/day, CRP < 15] by day 7 of admission.

Secondary outcomes included clinical remission at week 8 [±1 week], biochemical remission, IUS response and remission [transmural healing], and rate of adverse events. Clinical remission was defined using PRO-2 and partial Mayo scores [as per STRIDE-II guidelines].[9] Biochemical remission was defined as FCP < 150 µg/mL and CRP < 5 mg/L. IUS remission was defined as a normalization of bowel wall thickness [BWT] to <3 mm in the most affected segment with a modified Limberg score of 0. Serious adverse events were defined as those requiring admission to hospital.

3. Results

Six patients were identified and included as summarized in Table 1. Median patient age was 25 years [range 22–58] and four patients were male [67%]. The two female patients were counselled regarding the risks of upadacitinib in pregnancy. Two patients had prior admissions with ASUC, and five had extensive disease endoscopically at baseline. All were exposed to prior advanced drug therapies for UC [prior exposure = 1, 33%; prior exposure >1, 67%]. On admission, all patients met modified Truelove and Witts' criteria for ASUC, with a median PRO-2 score of 5 [range 4–6], median total Mayo score of 10 [range 9–12], median Mayo endoscopic subscore of 3 [range 2–3] and median Ulcerative Colitis Endoscopic index of severity [UCEIS] of 6 [range 5–6]. Baseline median FCP was 1355 µg/mL and CRP was 17 mg/L. IUS showed a median BWT of 6.1 mm [range 4.4–7.0] in the most affected segment and a median modified Limberg score of 3 [range 2–3].

Five patients demonstrated clinical response as per modified Oxford criteria by day 5 of admission, with the sixth patient responding by day 7. Patients were discharged after a median length of stay of 5 days. By week 16, one patient proceeded to uncomplicated colectomy [at 15 weeks] due to ongoing clinical, biochemical and endoscopic disease activity, while five remain colectomy free.

At week 8, four patients [67%] were in clinical remission and had successfully tapered off corticosteroids [with an additional fifth patient successfully ceasing corticosteroids but not meeting criteria for remission]. The median PRO-2 score was 1 [range 0–4], median partial Mayo score was 1 [range 0–7], and median total Mayo score was 2 [range 0–8]. Three patients underwent follow-up endoscopy within the follow-up period with a median Mayo endoscopic subscore of 1 [range 0–3] and median UCEIS of 2 [range 0–7]. Three patients [50%] achieved biochemical remission, with four patients achieving resolution of rectal bleeding, and two achieving complete normalization of bowel frequency. Four patients achieved IUS remission [transmural healing], including a median BWT of 2 mm and median modified Limberg score of 0 [Figure 1]. At the discretion of the treating clinician, four patients [67%] received an extended 16-week induction of 45 mg daily, with the remaining two patients decreasing to a 30-mg maintenance dose at week 8.

Adverse events included colectomy for refractory disease [$n = 1$], and acne [$n = 2$] not requiring treatment. No significant adverse events or adverse events of special interest including severe infection, major adverse cardiovascular events, venous thromboembolism or malignancy were identified over the 16-week follow-up.

4. Discussion and Conclusion

This series is the first to highlight the potential role of upadacitinib as rescue therapy for infliximab-experienced patients with steroid-refractory ASUC. Five of six patients avoided colectomy over the duration of clinical follow-up, with four achieving steroid-free clinical remission by week 8 without significant adverse events. With the rising prevalence

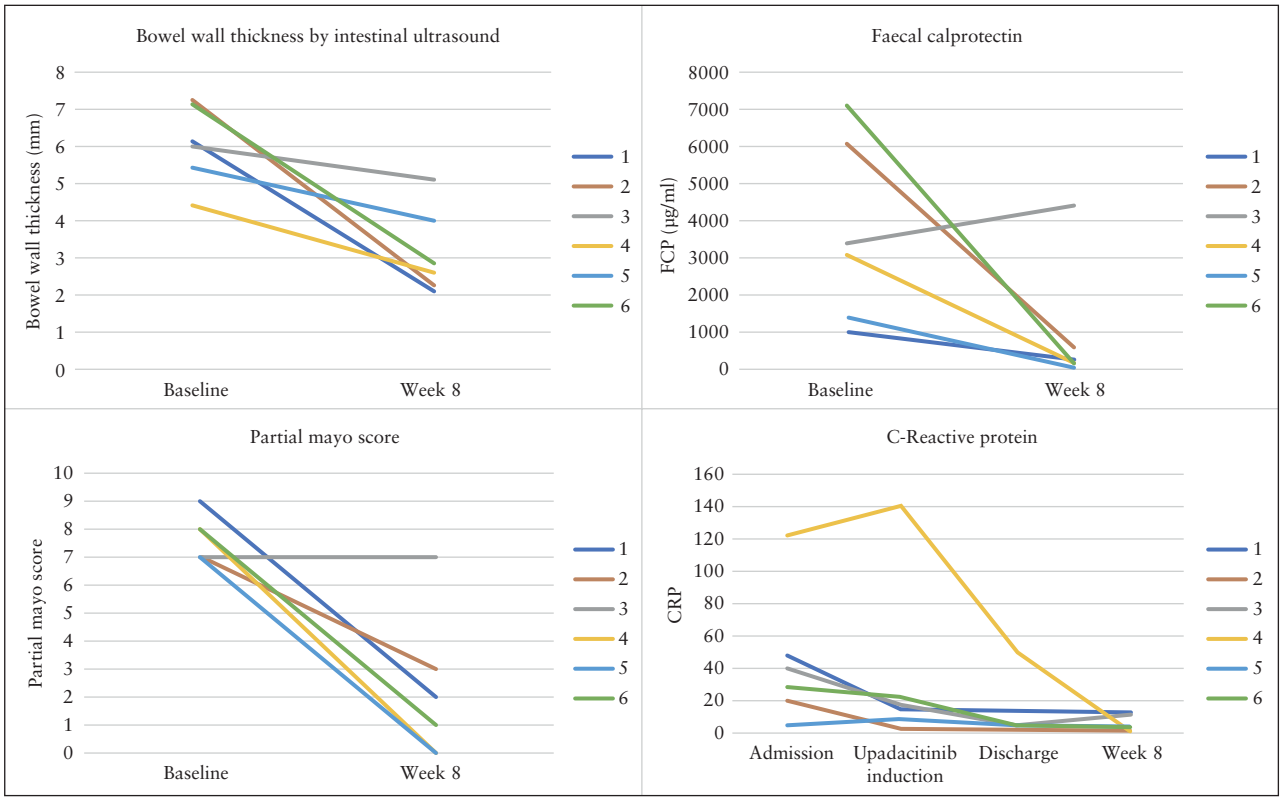

Figure 1. Faecal calprotectin, bowel wall thickness by intestinal ultrasound, partial Mayo score and CRP at baseline and after 8 weeks of upadacitinib 45 mg daily. FCP: faecal calprotectin; CRP: C-reactive protein.

of UC, the incidence of ASUC in infliximab-experienced patients is increasing. Options for medical salvage therapy in infliximab-experienced ASUC are more limited given this aggressive disease phenotype, and expanding therapeutic options could help improve outcomes. While these preliminary findings are encouraging, the optimal standard of care for salvage therapy in steroid-refractory patients with prior infliximab failure is still evolving. In a recent review of available literature, Gisbert *et al.*[10] suggested cyclosporin as standard of care in this setting, potentially as a bridge to an alternative biological therapy such as vedolizumab or ustekinumab. While this option was discussed with our patients, the success in several case series with JAK inhibition, alongside the daily dosing schedule and oral route of administration of upadacitinib, was favoured. Colectomy in the setting of non-response to medical therapy has an important role, but given the expanding arsenal of advanced drug therapies it is often reserved for the most refractory patients. We acknowledge that the off-label use of upadacitinib in the setting of ASUC was outside the criteria of the registration trials, and was used in these cases only in an appropriate clinical context and with informed patient consent. The collaborative decision to use upadacitib over tofacitinib in this context was based on available clinical data and patient preference. We felt available data suggested a favourable safety profile with upadacitinib, with a faster onset of clinical response in moderate to severe UC seen in registry trials.

Our preliminary data suggest that upadacitinib may have a role as salvage therapy for ASUC in a select group of patients managed within specialized referral centres. Prospective studies are required to assess the safety and efficacy of upadacitinib and to determine whether it can be added to our armamentarium as primary or sequential salvage therapy for steroid-refractory ASUC.

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Conflict of Interest

YA has served as a speaker, a consultant, and an advisory board member for Abbvie. JB has served as a speaker, a consultant, and an advisory board member for Abbvie

Author Contributions

RG, LT, RF—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. YA, JB—study concept; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; study supervision.

Data Availability

The data underlying this article are available in the article and in its online Supplementary Material.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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