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Tofacitinib as rescue therapy in acute severe ulcerative colitis: a real-world prospective cohort study

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Abstract

Background Intravenous corticosteroids are the cornerstone of acute severe ulcerative colitis (ASUC) therapy, yet ~40% of patients are steroid-refractory and require rescue therapy with infliximab or cyclosporine, while up to 20% undergo colectomy within 3 months. Tofacitinib, a Janus kinase inhibitor with rapid onset, has been approved for ulcerative colitis. This study evaluated its role as rescue therapy in steroid-refractory ASUC.

Methods We conducted a prospective cohort study in hospitalized ASUC patients (Truelove and Witts' criteria). Those unresponsive to steroids at day 3 (Oxford criteria) received tofacitinib; non-responders were managed with alternative rescue therapy or colectomy. The primary endpoint was colectomy free survival at 14 weeks; secondary endpoints were clinical response, remission, steroid-free remission and safety at weeks 6, 10 and 14.

Results Among 335 ASUC patients, 181 (54.0%) responded to steroids, while 154 (45.98%) were non-responders; of the latter, 119 received tofacitinib, 23 infliximab, and 12 cyclosporine. Non-responders had greater prior therapy exposure and disease severity. Colectomy-free survival at week 14 was 96.1% for steroid responders, 79% for tofacitinib, 78.2% for infliximab and 75% for cyclosporine. At weeks 6, 10 and 14, response/remission rates were 84.0%/78.5%, 82.9%/74.0% and 81.2%/69.6% for steroid responders, 74.8%/59.7%, 72.3%/53.8% and 69.8%/45.4% for tofacitinib, 65.2%/56.5%, 65.2%/43.5% and 56.5%/30.4% for infliximab, and 75.0%/58.3%, 75.0%/50.0% and 58.3%/41.7% for cyclosporine. Infections, including herpes zoster, were more frequent in non-responders.

Conclusions Tofacitinib demonstrates promising efficacy and acceptable safety as rescue therapy in steroid-refractory ASUC. Larger multicenter trials are needed to validate its role in ASUC management.

Keywords Acute severe ulcerative colitis, ulcerative colitis, tofacitinib

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Conflict of Interest: None

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Introduction

Acute severe ulcerative colitis (ASUC) is an aggressive presentation of ulcerative colitis (UC) that affects up to 25% of patients during their disease course [1]. Standard first-line management includes hospitalization and intravenous corticosteroids; however, 30-40% of patients do not respond and require rescue therapy [2]. Infliximab and cyclosporine are commonly used in this context, but are limited by intravenous administration, a slower onset of action, and the need for drug monitoring or infusion support [3,4]. Infliximab is the most widely used rescue agent, with clinical response rates of ~60-70% and colectomy-free survival rates of 50-60% at 1 year [5]. Cyclosporine, an alternative option, has shown short-term response rates of 64-82%, but concerns

about nephrotoxicity and the need for close monitoring limit its use [6]. The emergence of biologic therapies has fundamentally shifted the prognosis for ASUC, drastically lowering the need for surgery. Current longitudinal rates reflect this progress, with colectomy occurring in just 3% of patients within the first year of diagnosis, and remaining as low as 10% after a decade [7]. A head-to-head trial (CYSIF trial) showed no significant difference between cyclosporine and infliximab for short-term colectomy rates, suggesting the need for further therapeutic options [8]. The limitations of current rescue therapies include high cost, delayed onset of action, immunogenicity, potentially higher costs due to limitations in the delivery infrastructure (for infliximab), and toxicity (for cyclosporine), all of which constrain their use in many clinical settings.

Tofacitinib is an oral small-molecule Janus kinase (JAK) inhibitor that acts rapidly by blocking JAK1/3-dependent cytokine signaling, including interleukin-2, thereby potentially restoring corticosteroid sensitivity. It has a rapid onset of action and a short half-life (~3 h), making it a promising candidate for inpatient use in ASUC [9]. Unlike biologics, it is administered orally, offering logistical advantages and eliminating concerns related to infusion reactions or immunogenicity, and it has been approved for moderate-to-severe UC. Emerging real-world evidence in a study by Kotwani *et al* (2020) demonstrated a response rate of 53% at day 7 in hospitalized ASUC patients, with acceptable safety [10]. Furthermore, in a case series of 6 corticosteroid-refractory ASUC patients, who failed dose-intensified infliximab and subsequently received JAK inhibitors, 4 of the 6 achieved a rapid clinical response within 72 hours, and at 90 days all responders were in corticosteroid-free clinical remission [11]. This suggests that tofacitinib may be effective as rescue therapy in ASUC, especially in steroid-refractory patients. A multicenter retrospective study by Berinstein *et al* (2021) reported a day 5 response rate of 68% and colectomy-free survival of 77% at 90 days with tofacitinib in ASUC patients [12]. However, prospective data in this context are limited, and the optimal positioning of tofacitinib in the ASUC treatment algorithm remains undefined. The TACOS trial, a recent randomized controlled study, demonstrated the potential of tofacitinib in combination with steroids in avoiding colectomy among steroid-refractory ASUC patients [13]. It demonstrated better short-term responsiveness and a lesser need for additional rescue therapy. In this context, we conducted a prospective observational study to evaluate the effectiveness and safety of tofacitinib in hospitalized patients with steroid refractory ASUC, thereby reflecting a real-world clinical population.

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Patients and methods

We conducted a prospective observational study at a tertiary care center, enrolling hospitalized patients diagnosed with ASUC between January 2022 and June 2024. All patients were followed up for a duration of 14 weeks. The study was approved by the institutional ethics committee (Approval No. SNMC/IEC/IIP/2022/063), and written informed consent was obtained from all participants after a thorough explanation of the risks, benefits, and the off-label use of tofacitinib in ASUC. Patients aged 18 years or older with ASUC, defined by the Truelove and Witts' criteria [1] (at least 6 bloody stools per day plus 1 or more of the following signs of systemic toxicity: a pulse rate over 90 beats/min, a temperature over 37.8°C, a hemoglobin level below 10.5 g/dL, or an erythrocyte sedimentation rate over 30 mm/h), were included. Steroid-refractory status was determined using the Oxford criteria on day 3 of intravenous corticosteroid therapy, identified by a stool frequency greater than 8 per day or 3 or more per day with a C-reactive protein (CRP) level above 45 mg/L [14]. Intravenous corticosteroids were discontinued beyond day 3 in patients who were classified as steroid non-responders according to the Oxford criteria. Rescue therapy (tofacitinib, infliximab, or cyclosporine) was initiated in steroid non-responders. Steroid responders were retained only as a descriptive reference group, whereas rescue-therapy outcomes were interpreted among steroid non-responders. Patients were excluded if they had Crohn's disease or IBD-unclassified, prior colectomy, colorectal malignancy, coronary artery disease, active infections including *Clostridioides difficile* ([*C. difficile*], excluded via stool toxin assay), or cytomegalovirus colitis (ruled out by biopsy/immunohistochemistry). Pregnancy and lactation were also exclusion criteria. Before the initiation of tofacitinib therapy, all patients underwent screening for infectious diseases, including tuberculosis (IGRA or Mantoux test), and serologies for hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and varicella-zoster virus. Baseline investigations included complete blood count, liver function tests, lipid profile and CRP. Flexible sigmoidoscopy was performed in all patients to assess disease severity and exclude cytomegalovirus colitis. Eligible patients received tofacitinib at a dose of 10 mg 3 times daily (TID) for 7 days, followed by 10 mg b.i.d. for 21 days, and subsequently maintained on 5 mg b.i.d. The initial t.i.d. dosing was chosen to achieve a rapid onset of action, guided by emerging real-world data from the TACOS trial [13] and Berinstein *et al* [12]. All patients received thromboprophylaxis with subcutaneous enoxaparin (40-60 mg q.d.) during hospitalization. Tofacitinib dosing was not adjusted based on body weight or renal function. The off-label nature of this regimen, potential risks, and alternative rescue options were discussed before written informed consent. Rescue-therapy allocation was not randomized. In patients with no response to tofacitinib, subsequent management with infliximab rescue therapy or colectomy was determined by the treating clinician, after consideration of the overall clinical status: endoscopic severity, prior biologic exposure, biochemical profile, local logistic factors and multidisciplinary surgical assessment where indicated. Therefore, the rescue-treatment groups should be interpreted as real-world treatment cohorts rather than

randomized or fully comparable groups. The primary endpoint was colectomy-free survival at 14 weeks; secondary endpoints were clinical response, remission, steroid-free remission and safety at weeks 6, 10 and 14. Remission outcomes in this study refer to clinical remission based on the partial Mayo score rather than endoscopic remission. We used the 9-point partial Mayo score, calculated as the sum (0-3 each) of stool frequency (relative to normal), rectal bleeding, and the physician's global assessment, excluding the endoscopic subscore, with higher values indicating greater disease activity. Clinical response was defined as a reduction in the partial Mayo score of ≥3 points and ≥30%, along with a reduction in rectal bleeding subscore by ≥1 point. Clinical remission was defined as a partial Mayo score <3 with no individual subscore exceeding 1. Steroid-free remission was defined as clinical remission achieved without systemic corticosteroids during the 2 weeks preceding assessment. Adverse events were closely monitored and categorized as mild (not requiring intervention, e.g., hair loss, upper respiratory tract infection), moderate (requiring outpatient care or temporary drug discontinuation), or severe (necessitating hospitalization, permanent cessation of therapy, or resulting in death). Particular attention was paid to herpes zoster, thromboembolic events, and hepatic or cardiovascular complications. No patients received prophylactic zoster vaccination.

Sample size estimation

The sample size was estimated for the primary endpoint of 14-week colectomy-free survival in patients receiving tofacitinib. Based on previously reported [12] colectomy-free survival of approximately 77% at 90 days with tofacitinib in hospitalized ASUC patients, assuming a 95% confidence level and an absolute precision of 8%, the required sample size was calculated using the single-proportion formula: $n = \frac{Z^2_{\alpha/2} \times p(1-p)}{d^2}$, where $Z_{\alpha/2} = 1.96$, $p = 0.77$ and $d = 0.08$.

Hence, $n = \frac{(1.96)^2 \times 0.77(1-0.77)}{(0.08)^2}$, $n = 106.3 \approx 107$

Thus, the calculated minimum sample size for the primary endpoint was 107 patients; however, as 119 eligible steroid-refractory ASUC patients received tofacitinib during the study period, all were included in the final analysis. Although the tofacitinib cohort met the estimated sample size for evaluation of the primary endpoint, the smaller infliximab and cyclosporine groups were not powered for definitive pairwise comparisons. Therefore, comparisons among rescue therapies were interpreted as exploratory.

Statistical analysis

Statistical analysis was performed using SPSS version 26 software (IBM Corp., NY, USA). Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as medians with interquartile ranges. Differences between groups were evaluated using the chi-square test for categorical variables and the independent *t*-test for continuous variables. Multivariable logistic regression and Cox proportional-hazards models were performed. Covariates entered into the adjusted models included age, sex, disease extent, baseline UCEIS, baseline CRP, serum albumin, prior anti-TNF exposure, and rescue-treatment group. Covariate selection was based on clinical relevance and baseline imbalance. Kaplan-Meier survival analysis was used to assess colectomy-free survival over 14 weeks. All key outcomes were reported with corresponding 95% confidence intervals (CI) and P-values. Cox proportional hazards regression models were used to evaluate time-to-event outcomes among steroid non-responders receiving rescue therapy. The outcomes assessed were time to clinical response, time to clinical remission, and time to colectomy during the 14-week follow-up period. Adjusted hazard ratios (HRs) with 95%CI and P-values were reported. For clinical response and clinical remission, an HR >1 indicated earlier achievement of the endpoint, whereas for colectomy, an HR <1 indicated a lower hazard of colectomy. For proportion-based outcomes, the standard error (SE) of each proportion was calculated as $\sqrt{[p(1-p)/N]}$, and the margin of error was calculated as 1.96 × SE; the corresponding 95%CI was reported as P±1.96 × SE. A complete-case analysis approach was used, and no imputation was performed for missing data. A CONSORT-style flow diagram (Fig. 1) was constructed to illustrate the number of patients screened, excluded, initiated on tofacitinib, and followed through to their outcomes over the 14-week period.

Results

A total of 335 patients with ASUC were enrolled, of whom 181 (54.02%) responded to steroid treatment by day

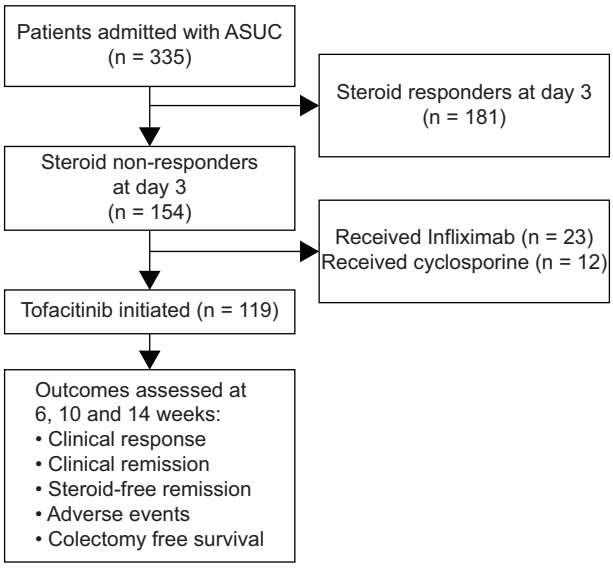

Figure 1 A CONSORT-style flow diagram showing the number of patients screened and initiated on tofacitinib, and followed through to their outcomes over the 14-week period
ASUC, acute severe ulcerative colitis

3, while 154 (45.98%) were steroid non-responders by day 3. Of the latter, 23 patients received infliximab and 12 patients cyclosporine as rescue therapy, while the remaining 119 were enrolled for tofacitinib as rescue therapy (Fig. 1). All steroid responders were biologic naïve. Among the steroid non-responder cohort (n=154), 126 patients (81%) were biologic naïve and 28 (18.2%) had prior exposure to anti-tumor necrosis factor (TNF) therapy (Table 1). None of the patients in the study had exposure to more than 1 biologic agent prior to hospitalization.

Baseline characteristics

Table 1 shows the baseline characteristics of 335 patients hospitalized with ASUC stratified by steroid response: 181 (54.0%) responders and 154 (46.0%) non-responders. Median age was significantly higher in responders than non-responders (44.0 [32.0-57.0] vs. 36.0 [27.0-47.0] years, P=0.01), while the sex distribution was similar (P=0.89). Non-responders had a greater number of prior flares and higher exposure to prior medical therapies (5-ASA, azathioprine, corticosteroids, anti-TNF; all P<0.001). Non-responders also had more extensive disease (pancolitis 70.8% vs. 45.9%), higher inflammatory markers (median CRP 67.5 vs. 45.2 mg/L; fecal calprotectin 1204.1 vs. 806.4 μg/g), lower hemoglobin, lower albumin, and more severe endoscopic disease (median UCEIS 6.0 vs. 5.0; P<0.001 for all).

Primary endpoint - colectomy free survival analysis

Kaplan–Meier curves for colectomy-free survival (Fig. 2) demonstrated a clear separation between steroid responders and rescue therapy groups over the 14-week period. Steroid responders maintained a flat, high survival curve (96.1% at week 14). Among rescue therapies, tofacitinib demonstrated the most favorable curve, particularly in the first 6-10 weeks, while infliximab and cyclosporine overlapped and were consistently lower than tofacitinib. Most colectomies occurred within the first 10 weeks, with minimal late divergence thereafter.

Secondary endpoints: clinical response, clinical remission and steroid free remission

Among steroid responders (n=181), the rates of clinical response remained consistently high, with 84.0% (95%CI 78.6-

Table 1 Baseline characteristics of patients with acute severe ulcerative colitis (ASUC) stratified by steroid response

Variable	Steroid responders (n=181)	Steroid non-responders (n=154)	P-value
Age, years	44.0 (32.0-57.0)	36.0 (27.0-47.0)	0.014
Sex – Male, n (%)	101 (55.8%)	88 (57.1%)	0.8916
Sex – Female, n (%)	80 (44.2%)	66 (42.9%)	0.872
Disease duration, years	3.2 (2.1-4.1)	3.0 (1.23-5.0)	0.4767
Number of prior flares	1.0 (1.0-3.0)	3.0 (2.0-5.0)	0.017
Biological naïve, n (%)	181 (100%)	126 (81%)	0.012
Previous treatment – 5-ASA, n (%)	79 (43.6%)	127 (82.5%)	0.001
Previous treatment – azathioprine, n (%)	30 (16.6%)	91 (59.1%)	0.001
Previous treatment – corticosteroids, n (%)	141 (77.9%)	85 (55.2%)	0.001
Previous treatment – anti-TNF, n (%)	0 (0.0%)	28 (18.2%)	0.001
UCEIS (0–8)	5.0 (4.0-5.0)	6.0 (5.0-6.0)	0.019
Mayo score (0–12)	7.0 (6.0-8.0)	8.0 (6.0-8.0)	0.0511
AST (IU/L)	29.5 (26.4-32.7)	28.8 (22.1-32.98)	0.1861
ALT (IU/L)	27.5 (24.1-31.0)	24.95 (20.4-31.15)	0.006
Extent – proctitis, n (%)	28 (15.5%)	9 (5.8%)	0.012
Extent – left-sided colitis, n (%)	70 (38.7%)	36 (23.4%)	0.025
Extent – pancolitis, n (%)	83 (45.9%)	109 (70.8%)	0.020
Hemoglobin, g/dL	9.6 (8.7-10.2)	8.25 (7.2-9.2)	0.061
C-reactive protein, mg/L	45.2 (34.5-56.8)	67.5 (43.78-73.9)	0.013
Fecal calprotectin, μg/g	806.4 (778.2-1104.8)	1204.1 (794.62-1297.6)	<0.001
Serum albumin, g/dL	3.96 (3.72-4.28)	3.3 (3.1-4.3)	<0.001

5-ASA, 5-Aminosalicylic acid; TNF, tumor necrosis factor; UCEIS, ulcerative colitis endoscopic index of severity; AST, aspartate aminotransferase; ALT, alanine aminotransferase

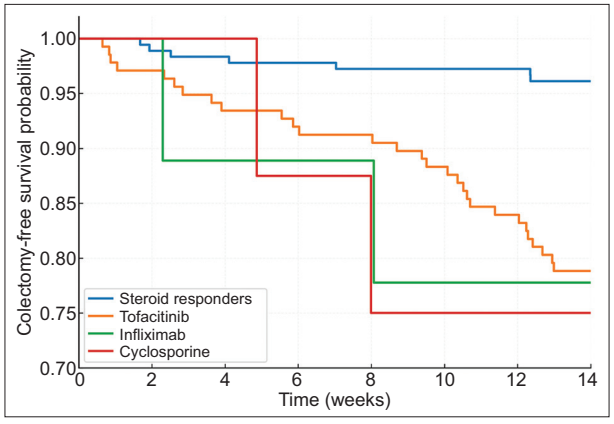

Figure 2 Kaplan–Meier curves for colectomy-free survival to 14 weeks

89.3; ±5.3%) at week 6, 82.9% (95%CI 77.4-88.4; ±5.5%) at week 10, and 81.2% (95%CI 75.5-86.9; ±5.7%) at week 14 (Table 2). In comparison, patients treated with tofacitinib (n=119) achieved a clinical response in 74.8% (95%CI 67.0-82.6; ±7.8%), 72.3% (95%CI 64.2-80.3; ±8.0%), and 69.8% (95%CI 61.5-78.0; ±8.3%) at weeks 6, 10, and 14, respectively. The infliximab group (n=23) demonstrated clinical response rates of 65.2% (95%CI 45.8-84.7; ±19.5%) at weeks 6 and 10, and 56.5% (95%CI 36.3-76.8; ±20.3%) at week 14, while cyclosporine (n=12) yielded responses of 75.0% (95%CI 50.5-99.5; ±24.5%), 75.0% (95%CI 50.5-99.5; ±24.5%), and 58.3% (95%CI 30.4-86.2; ±27.9%) over the same time points. Clinical remission rates followed a similar pattern: 78.5% (95%CI 72.5-84.4; ±6.0%), 74.0% (95%CI 67.6-80.4; ±6.4%), and 69.6% (95%CI 62.9-76.3; ±6.7%) at weeks 6, 10, and 14 in steroid responders, compared with 59.7% (95%CI 50.8-68.5; ±8.8%), 53.8% (95%CI 44.8-62.7; ±9.0%), and 45.4% (95%CI 36.4-54.3; ±8.9%) in the tofacitinib group, 56.5% (95%CI 36.3-76.8; ±20.3%), 43.5% (95%CI 23.2-63.7; ±20.3%), and 30.4% (95%CI 11.6-49.2; ±18.8%) in the infliximab group, and 58.3% (95%CI 30.4-86.2; ±27.9%), 50.0% (95%CI 21.7-78.3; ±28.3%), and 41.7% (95%CI 13.8-69.6; ±27.9%) in the cyclosporine group (Table 2).

Steroid-free remission was achieved in 48.7% (95%CI 39.8-57.7; ±9.0%), 41.2% (95%CI 32.3-50.0; ±8.8%), and 34.5% (95%CI 25.9-43.0; ±8.5%) of patients receiving tofacitinib, 43.5% (95%CI 23.2-63.7; ±20.3%), 30.4% (95%CI 11.6-49.2; ±18.8%), and 21.7% (95%CI 4.9-38.6; ±16.9%) with infliximab, and 50.0% (95%CI 21.7-78.3; ±28.3%), 41.7% (95%CI 13.8-69.6; ±27.9%), and 25.0% (95%CI 0.5-49.5; ±24.5%) with cyclosporine at weeks 6, 10, and 14, respectively (Table 2). Colectomy-free survival remained high across groups, with steroid responders showing rates of 97.8% (95%CI 95.6-99.9; ±2.1%), 97.2% (95%CI 94.8-99.6; ±2.4%), and 96.1% (95%CI 93.3-98.9; ±2.8%) at weeks 6, 10, and 14. In the tofacitinib group, colectomy-free survival declined from 91.6% (95%CI 86.6-96.6; ±5.0%) at week 6 to 79% (95%CI 71.7-86.3; ±7.3%) at week 14. Similarly, infliximab showed survival rates of 87% (95%CI 73.2-100.0; ±13.8%) at week 6 and 78.3% (95%CI 61.4-95.1; ±16.9%) at both weeks 10 and 14, while cyclosporine maintained rates of 83.3% (95%CI 62.2-100.0; ±21.1%), 75.0% (95%CI 50.5-99.5; ±24.5%), and 75.0% (95%CI 50.5-99.5; ±24.5%) at weeks 6, 10, and 14, respectively (Table 2). Week-14 risk differences with 95% confidence intervals between tofacitinib and the other rescue therapies are provided in Supplementary Table S1. As the infliximab and cyclosporine groups were small, the corresponding margins of error were wide, particularly for cyclosporine, and therefore apparent between-group differences should be interpreted cautiously.

Cox regression analysis (Table 3)

In the adjusted Cox regression analysis restricted to steroid non-responders, tofacitinib was associated with earlier achievement of clinical response and clinical remission compared with the other rescue therapies. Compared with infliximab, tofacitinib was associated with a higher likelihood of achieving clinical response (adjusted HR 1.47, 95%CI 1.14-1.92, P=0.003) and clinical remission (adjusted HR 1.39, 95%CI 1.05-1.82, P=0.019). Similar findings were observed when tofacitinib was compared with cyclosporine for clinical response (adjusted HR 1.56, 95%CI 1.22-2.04, P<0.001) and clinical remission (adjusted HR 1.52, 95%CI 1.16-2.00, P=0.002). For the adverse endpoint of colectomy, tofacitinib was associated with a lower hazard of colectomy compared with infliximab (adjusted HR 0.69, 95%CI 0.50-0.95, P=0.024) and cyclosporine (adjusted HR 0.63, 95%CI 0.45-0.89, P=0.009). These findings were directionally consistent with the Kaplan–Meier curves (Fig. 2) for colectomy-free survival; however, because treatment allocation was influenced by physician preference, drug availability, affordability, and local logistics, these estimates should be interpreted as associations rather than evidence of treatment superiority.

Adverse events

Within 14 weeks of follow up, adverse events were observed in both steroid responders and non-responders (Table 4). Among mild events, hair loss was reported in 2.2% of responders compared to 11.7% of non-responders, with a median onset of 6 weeks in both groups. Upper respiratory tract infection occurred in 6.6% of responders and 10.4% of non-responders, typically at 3 weeks. Skin rash was seen in 3.3% of responders and 9.1% of non-responders, with a median onset of 5 weeks in both groups. Serious events included herpes zoster, which developed in 0.6% of responders versus 6.5% of non-responders (median onset 11 vs. 9 weeks), and deep-vein thrombosis, noted in 1.1% of responders and 2.6% of non-responders, with median onset at 10 and 12 weeks, respectively. Overall, adverse events were more frequent in the non-responder group. Among steroid non-responders receiving rescue therapy (Table 5), adverse events were most commonly observed in the tofacitinib arm. Hair loss occurred in 14 (11.7%) patients receiving tofacitinib, 1 (4.3%) receiving infliximab, and 3 (25.0%) receiving cyclosporine. Upper respiratory tract infection occurred in 10 (8.4%), 4 (17.4%),

Table 2 Primary and secondary outcomes

Outcome	Steroid responders (N=181)			Tofacitinib (N=119)			Infliximab (N=23)			Cyclosporine (N=12)		
	Week 6	Week 10	Week 14	Week 6	Week 10	Week 14	Week 6	Week 10	Week 14	Week 6	Week 10	Week 14
Clinical response	152/181 (84.0%, 78.6-89.3%); ±5.3%	150/181 (82.9%, 77.4-88.4%); ±5.5%	147/181 (81.2%, 75.5-86.9%); ±5.7%	89/119 (74.8%, 67.0-82.6%); ±7.8%	86/119 (72.3%, 64.2-80.3%); ±8.0%	83/119 (69.8%, 61.5-78.0%); ±8.3%	15/23 (65.2%, 45.8-84.7%); ±19.5%	15/23 (65.2%, 45.8-84.7%); ±19.5%	13/23 (56.5%, 36.3-76.8%); ±20.3%	9/12 (75.0%, 50.5-99.5%); ±24.5%	9/12 (75.0%, 50.5-99.5%); ±24.5%	7/12 (58.3%, 30.4-86.2%); ±27.9%
Clinical remission	142/181 (78.5%, 72.5-84.4%); ±6.0%	134/181 (74.0%, 67.6-80.4%); ±6.4%	126/181 (69.6%, 62.9-76.3%); ±6.7%	71/119 (59.7%, 50.8-68.5%); ±8.8%	64/119 (53.8%, 44.8-62.7%); ±9.0%	54/119 (45.4%, 36.4-54.3%); ±8.9%	13/23 (56.5%, 36.3-76.8%); ±20.3%	10/23 (43.5%, 23.2-63.7%); ±20.3%	7/23 (30.4%, 11.6-49.2%); ±18.8%	7/12 (58.3%, 30.4-86.2%); ±27.9%	6/12 (50.0%, 21.7-78.3%); ±28.3%	5/12 (41.7%, 13.8-69.6%); ±27.9%
Steroid-free remission	NA	NA	NA	58/119 (48.7%, 39.8-57.7%); ±9.0%	49/119 (41.2%, 32.3-50.0%); ±8.8%	41/119 (34.5%, 25.9-43.0%); ±8.5%	10/23 (43.5%, 23.2-63.7%); ±20.3%	7/23 (30.4%, 11.6-49.2%); ±18.8%	5/23 (21.7%, 4.9-38.6%); ±16.9%	6/12 (50.0%, 21.7-78.3%); ±28.3%	5/12 (41.7%, 13.8-69.6%); ±27.9%	3/12 (25.0%, 0.5-49.5%); ±24.5%
Colectomy-free survival	177/181 (97.8%, 95.6-99.9%); ±2.1%	176/181 (97.2%, 94.8-99.6%); ±2.4%	174/181 (96.1%, 93.3-98.9%); ±2.8%	109/119 (91.6%, 86.6-96.6%); ±5.0%	105/119 (88.2%, 82.4-94.0%); ±5.8%	94/119 (79.0%, 71.7-86.3%); ±7.3%	20/23 (87.0%, 73.2-100.0%); ±13.8%	18/23 (78.3%, 61.4-95.1%); ±16.9%	18/23 (78.3%, 61.4-95.1%); ±16.9%	10/12 (83.3%, 62.2-100.0%); ±21.1%	9/12 (75.0%, 50.5-99.5%); ±24.5%	9/12 (75.0%, 50.5-99.5%); ±24.5%

Values are presented as n/N (%, 95% confidence interval); margin of error. The ± value represents the margin of error, calculated as 1.96 × standard error of the proportion. Steroid responders represent a distinct clinical subgroup and are shown only as a descriptive reference group; rescue-therapy comparisons apply only to steroid non-responders and should be interpreted as exploratory

Table 3 Adjusted Cox regression analysis of time-to-event outcomes among steroid non-responders treated with tofacitinib compared with infliximab or cyclosporine

Outcome	Comparison	Adjusted HR	95%CI	P-value
Time to clinical response	Tofacitinib vs. infliximab	1.47	1.14-1.92	0.003
	Tofacitinib vs. cyclosporine	1.56	1.22-2.04	<0.001
Time to clinical remission	Tofacitinib vs. infliximab	1.39	1.05-1.82	0.019
	Tofacitinib vs. cyclosporine	1.52	1.16-2.00	0.002
Time to colectomy	Tofacitinib vs. infliximab	0.69	0.50-0.95	0.024
	Tofacitinib vs. cyclosporine	0.63	0.45-0.89	0.009

Hazard ratios (HRs) with 95% confidence intervals (CIs) and P-values are shown for time to clinical response, clinical remission, and colectomy risk within 14 weeks of follow up.
Hazard ratios were derived from adjusted Cox proportional hazards models. For clinical response and clinical remission, an HR >1 indicates earlier achievement of the endpoint with tofacitinib. For colectomy, an HR <1 indicates a lower hazard of colectomy with tofacitinib. Adjusted models included age, sex, disease extent, baseline UCEIS, baseline CRP, serum albumin, prior anti-TNF exposure, and rescue-treatment group

Table 4 Adverse events within 14 weeks among steroid responders versus non-responders

Category	Event	Steroid responders n/N (%)	Median onset (weeks) – SR	Steroid non-responders n/N (%)	Tofacitinib arm (n=119)	Infliximab arm (n=23)	Cyclosporine arm (n=12)	Median onset (weeks) – SNR
Mild	Hair loss	4/181 (2.2%)	6	18/154 (11.7%)	14 (11.7%)	1 (4.3%)	3 (25.0%)	6
	Upper-respiratory tract infection	12/181 (6.6%)	3	16/154 (10.4%)	10 (8.4%)	4 (17.4%)	2 (16.7%)	3
	Skin rash	6/181 (3.3%)	5	14/154 (9.1%)	9 (7.6%)	2 (8.7%)	3 (25%)	5
Serious	Herpes zoster	1/181 (0.6%)	11	10/154 (6.5%)	8 (6.7%)	1 (4.3%)	1 (8.3%)	9
	Deep-vein thrombosis	2/181 (1.1%)	10	4/154 (2.6%)	3 (2.5%)	1 (4.3%)	0 (0%)	12

SR, Steroid responders; SNR, steroid non-responders

and 2 (16.7%) patients, respectively. Herpes zoster developed in 8 (6.7%) patients receiving tofacitinib, 1 (4.3%) receiving infliximab, and 1 (8.3%) receiving cyclosporine, while deep vein thrombosis occurred in 3 (2.5%) patients receiving tofacitinib and 1 (4.3%) receiving infliximab. There was no treatment discontinuation due to adverse events.

Discussion

In this study, we present our experience with the use of tofacitinib as a rescue therapy in patients hospitalized with ASUC. While infliximab and other biologics are effective rescue options, their feasibility in resource-constrained environments is often limited by delivery infrastructure rather than efficacy alone. Biologics typically require an infusion facility, trained staff, reliable venous access, prolonged chair time, and consistent supply chains with cold-chain storage and transport. In addition, administration may be delayed by the need for insurance or governmental authorization processes, and intermittent product availability. In contrast, tofacitinib is an orally administered small-molecule therapy with no infusion or cold-chain requirements, allowing rapid initiation in hospitalized patients and easier continuation after discharge. In some regions, procurement pathways, formulary decisions, hospital tendering, or the availability of lower-cost generic versions may also make oral small molecules more accessible than biologics, despite limited overall resources. However, cost, affordability, procurement delays, and infusion or cold-chain logistics were not formally evaluated and thus, the logistical advantages of tofacitinib should be viewed as center-specific observations rather than proven resource-limited setting benefits.

In the present study, only 23 patients received infliximab, highlighting the limited availability and utilization of infliximab in our cohort. Notably, the estimated incidence of colectomy at week 14 in our study was 21.2%, which appears similar to reported colectomy rates in ASUC. For instance, in the landmark randomized controlled trial by Laharie *et al*, comparing cyclosporine and infliximab in steroid-refractory ASUC, colectomy rates at 90 days were reported as 21% and 17%, respectively [8]. Emerging literature has begun to explore tofacitinib as a therapeutic option in ASUC, although data remain limited. Kotwani *et al* described a small cohort of 4 patients with ASUC, all of whom had prior failure of at least 2 biologics, including infliximab. Remarkably, no colectomies were observed within 90 days [10]. In contrast, Honap *et al* reported on 7 anti-TNF-experienced ASUC

patients treated with tofacitinib, of whom 3 (42.8%) required colectomy within 3 months [15]. These findings underscore the variability in response and the need for larger studies to delineate predictors of response to tofacitinib. Our study, using strict ASUC criteria, showed better short-term response and colectomy-free survival compared with prior heterogeneous cohorts, supporting its potential role while underscoring the need for further controlled trials to define long-term safety and dosing [17].

In the adjusted time-to-event analyses, the direction of effect was consistent with the Kaplan-Meier curves for colectomy-free survival. In the Cox regression comparisons, with tofacitinib as the active comparator, tofacitinib was associated with a lower adjusted hazard of colectomy compared with infliximab and cyclosporine. Similarly, tofacitinib was associated with earlier achievement of clinical response and clinical remission. However, these findings should be interpreted cautiously, as treatment allocation was not randomized and the infliximab and cyclosporine groups were small. Therefore, the adjusted Cox regression results should be regarded as exploratory and hypothesis-generating rather than confirmatory evidence of superiority. Because rescue therapies were not assigned under comparable clinical circumstances, patients receiving different rescue therapies may have differed at treatment initiation in ways not fully captured by adjusted analyses. Therefore, between-group comparisons should be interpreted cautiously.

Our findings are also consistent with a multicenter observational study by Uzzan *et al*, which included both retrospective and prospective data across 14 centers, and evaluated tofacitinib as salvage therapy in severe refractory UC. Clinical response, clinical remission and steroid-free remission rates were 60%, 45.5% and 37.5% at week 6, and 41.8%, 34.5% and 32.7% at week 14, respectively. Importantly, no deaths were reported, and safety outcomes were acceptable, with 3 patients discontinuing therapy because of adverse events and 2 cases of herpes zoster infection noted. No thrombotic events were observed in that study [16]. The TACOS trial by Singh *et al* [13] further added to the evidence base, being a randomized controlled trial that evaluated tofacitinib in combination with corticosteroids in 104 patients with ASUC. At day 7, clinical response was significantly better in the tofacitinib group compared to placebo (83.0% vs. 58.8%, P=0.007), and the cumulative probability of requiring additional rescue therapy by day 90 was significantly lower in the tofacitinib arm (P=0.003). Notably, this study assessed tofacitinib as an adjunct to corticosteroids, rather than as monotherapy, in the treatment of ASUC. Safety is a critical concern in severely ill patients who are hospitalized for ASUC [13]. In our study, no discontinuation occurred in patients due to adverse effects of tofacitinib, while they experienced relatively fewer side-effects, the majority of which were mild adverse effects. Herpes zoster and deep-vein thrombosis were numerically more frequent than in the comparator rescue-therapy groups. However, these findings require cautious interpretation because of the short 14-week follow-up, small comparator cohorts, and lack of statistical power for comparative safety assessment. As highlighted in the editorial by Honap *et al* [17], tofacitinib represents an attractive rescue option in ASUC. Our findings reflect the practice pattern at our center, where rescue-therapy selection during the index hospitalization was influenced by local logistics, immediate drug availability, affordability and physician preference. In this setting, oral tofacitinib represented a practical therapeutic option because of its ease of administration and rapid onset of action.

The recent literature has further expanded the evidence base for JAK inhibition in ASUC. Steenholdt *et al* [18], in a systematic review, concluded that tofacitinib appears promising for ASUC, particularly among refractory patients who may otherwise require colectomy, while emphasizing the need for larger high-quality studies. Brennan *et al* [19] subsequently reported, in a systematic review and meta-analysis of 6 studies, a pooled 90-day colectomy rate of 15.1% (95%CI 8.5-25.3) with tofacitinib. The pooled clinical response rate was 45.4% (95%CI 32.6-58.9) at weeks 12-14 and 30.0% (95%CI 17.4-46.5) at week 52, while clinical remission was 38.1% (95%CI 28.7-48.5) at weeks 12-14 and 27.1% (95%CI 15.2-43.5) at week 52; steroid-free clinical remission was 28.6% (95%CI 22.2-36.1) at weeks 12-14 and 33.1% (95%CI 25.6-41.6) at week 52. For safety in that meta-analysis, reported adverse-event rates included cardiovascular events in 2.6%, venous thromboembolism in 1.8%, *C. difficile* infection in 3.1%, herpes zoster in 2.2%, and pneumonia in 1.6% of tofacitinib-treated ASUC patients. Komeda *et al* [20] described a case series of steroid-resistant ASUC patients treated successfully with tofacitinib, supporting its potential role as an early rescue strategy in selected patients. More recently, the prospective TRIUMPH study [21] reported day-7 clinical response in 58.3% of hospitalized steroid-refractory ASUC patients treated with tofacitinib, with a mean time to response of 2.4 days, further supporting its rapid onset of action. In addition, Honap *et al* [22] compared tofacitinib and upadacitinib in 111 hospitalized ASUC patients (60 tofacitinib, 51 upadacitinib) across 23 international centers. Upadacitinib was associated with a higher early response between days 3 and 7 (84% vs. 54%; P=0.02), but clinical response/remission was comparable at day 98 (45%/36% with tofacitinib vs. 55%/48% with upadacitinib) and day 182 (29%/29% vs. 39%/34%). Colectomy-free survival was also similar at day 98 and day 182 (79% and 75% with tofacitinib vs. 80% and 78% with upadacitinib; P=0.99), and the frequency of adverse events was reported to be comparable between treatment groups. Our findings are consistent with this evolving evidence base, although the observational design, unequal group sizes and center-specific treatment pathways require cautious interpretation.

Randomized controlled trials remain the gold standard for evaluating therapeutic efficacy, given their rigorous design and ability to minimize bias. Observational studies, however, provide complementary insights regarding treatment effectiveness in routine clinical practice. This becomes especially pertinent in resource-constrained environments, where biologics or advanced therapies may not be readily accessible. Our findings, in alignment

with an expanding body of real-world data, suggest that tofacitinib may represent a practical and potentially effective rescue option in selected steroid-refractory ASUC patients, particularly in settings where biologic access is limited. However, comparative efficacy against infliximab or cyclosporine cannot be definitively established from the present observational cohort. The infliximab and cyclosporine cohorts had small sample sizes, resulting in wide 95% confidence intervals and large margins of error across clinical response, clinical remission, steroid-free remission, and colectomy-free survival outcomes. These estimates therefore indicate substantial imprecision and should be interpreted descriptively rather than as evidence of definitive differences between rescue therapies.

We acknowledge several limitations. This was a single-center study, which may limit generalizability to other populations and institutions with different rescue-therapy pathways. Follow-up was limited to 14 weeks, precluding assessment of long-term durability of remission, corticosteroid dependence, delayed colectomy, long-term colectomy-free survival, and delayed adverse events associated with JAK inhibition. Endoscopic remission, mucosal healing, serial CRP, fecal calprotectin, patient-reported outcomes, and quality-of-life measures were not systematically evaluated during follow-up. Formal post-discharge adherence assessment was also not performed. The tofacitinib protocol did not include dose adjustment according to renal function or body weight. In addition, treatment allocation after steroid failure and subsequent management after tofacitinib non-response were non-randomized and reflected real-world clinician judgment, which may have introduced selection bias. Although the tofacitinib cohort met the estimated sample size for the primary endpoint, the infliximab and cyclosporine groups were small, with wide margins of error; therefore, between-group comparisons should be interpreted as exploratory rather than definitive. Despite these limitations, our findings contribute to the growing body of evidence supporting the potential role of tofacitinib as an effective and relatively safe salvage therapy for ASUC, particularly in resource-limited settings where access to biologics is restricted by infrastructural constraints, cold-chain logistics and administrative delays. Larger, prospective, controlled studies are needed to validate these findings and to further elucidate the safety profile and long-term outcomes of tofacitinib in this critically ill patient population.

In conclusion, tofacitinib appears to be a useful short-term rescue option in selected hospitalized patients with steroid-refractory ASUC. In this prospective real-world cohort, tofacitinib was associated with encouraging clinical response, remission, and colectomy-free survival over 14 weeks, supporting its potential role as a practical rescue therapy in this setting. These findings should be interpreted in the context of non-randomized treatment allocation, small comparator groups, and limited follow-up. Further adequately powered multicenter controlled studies are warranted to confirm its comparative efficacy, optimal dosing strategy, long-term durability, and safety.

Summary Box

What is already known:

- Approximately 30-40% of patients hospitalized with acute severe ulcerative colitis (ASUC) are refractory to intravenous steroids and need rescue therapy; infliximab or cyclosporine are standard, but limited by cost, logistics, toxicity and immunogenicity
- Short-term colectomy rates remain substantial despite current rescue options, with many surgeries occurring within months of admission
- Tofacitinib, an oral Janus kinase inhibitor with rapid onset, has been approved for ulcerative colitis and has emerging real-world and trial data suggesting a benefit in ASUC, but prospective evidence has been limited

What the new findings are:

- In a prospective cohort of steroid-refractory ASUC patients, tofacitinib used as rescue therapy achieved 14-week colectomy-free survival of ~79%, comparable to infliximab (78.2%) and cyclosporine (75%)
- Tofacitinib showed encouraging clinical response/remission through weeks 6-14 (e.g., week-14 response 69.8%, remission 45.4%)
- Adjusted Cox models indicated a faster time to response/remission and lower 14-week colectomy risk with tofacitinib versus infliximab or cyclosporine
- Safety was acceptable over 14 weeks; infections (including herpes zoster) occurred more often in non-responders overall, but no tofacitinib-related discontinuations were reported

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Supplementary material

Supplementary Table 1 Week-14 risk differences between tofacitinib and comparator rescue therapies among steroid-refractory ASUC patients

Week-14 outcome	Tofacitinib vs infliximab risk difference, % (95% CI)	Tofacitinib vs cyclosporine risk difference, % (95% CI)
Clinical response	+13.2% (-8.7 to +35.1)	+11.4% (-17.7 to +40.5)
Clinical remission	+14.9% (-5.9 to +35.8)	+3.7% (-25.6 to +33.0)
Steroid-free remission	+12.7% (-6.2 to +31.6)	+9.5% (-16.5 to +35.4)
Colectomy-free survival	+0.7% (-17.6 to +19.1)	+4.0% (-21.6 to +29.6)

Confidence intervals were calculated for differences between independent proportions. Because treatment allocation was non-randomized and the infliximab and cyclosporine cohorts were small, these estimates should be interpreted as descriptive and exploratory rather than definitive evidence of comparative efficacy

ASUC, acute severe ulcerative colitis; CI, confidence interval