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Postoperative Outcomes in Tofacitinib-Treated Patients With Acute Severe Ulcerative Colitis Undergoing Colectomy

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BACKGROUND AND AIMS: **Up to 30% of patients with acute severe ulcerative colitis (ASUC) will require urgent colectomy despite initiation of intravenous corticosteroids and rescue therapies. Janus kinase inhibitors, such as tofacitinib, have emerged as an effective agent for ASUC; however, there are currently limited data evaluating the risk of postoperative complications among patients who received tofacitinib treatment for an episode of ASUC compared with infliximab.**

METHODS: **We conducted a multicenter, retrospective, case-control study of patients hospitalized with ASUC who underwent colectomy, comparing patients treated with tofacitinib prior to colectomy with infliximab-treated controls. The primary outcome was rate of serious postoperative complications within 30 days of colectomy. Outcomes were compared between the tofacitinib-treated cases and infliximab-treated controls using multivariable regression adjusted for open surgery and cumulative corticosteroid exposure.**

RESULTS: **Forty-one tofacitinib-treated patients were compared with 68 infliximab-treated patients with ASUC. Compared with tofacitinib-treated patients, infliximab-treated patients had higher overall rates of overall (44 [64.7%] vs 13 [31.7%]; $P = .002$) and serious (19 [27.9%] vs 3 [12%]; $P = .019$) postoperative complications. No significant different risk for developing serious postoperative complications (odds ratio, 0.28; 95% confidence interval, 0.06–0.96; $P = .061$) was observed in multivariable analysis; however, a significantly lower rate of overall postoperative complications (odds ratio, 0.38; 95% confidence interval, 0.16–0.87; $P = .023$) was observed in tofacitinib-treated patients compared with infliximab-treated patients.**

CONCLUSIONS: **We observed a significantly lower rate of overall postoperative complications in ASUC patients treated with tofacitinib compared with infliximab; however, no difference was observed in the**

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Abbreviations used in this paper: ASUC, acute severe ulcerative colitis; BID, twice daily; CI, confidence intervals; CRP, C-reactive protein; IQR, interquartile range; IV, intravenous; JAK, Janus kinase; OR, odds ratio; TID, 3 times daily; UC, ulcerative colitis; VTE, venous thromboembolic event.

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risk for serious postoperative complications. Larger prospective trials are needed to confirm these findings.

Keywords: Ulcerative Colitis; Tofacitinib; Acute Severe Ulcerative Colitis; Inflammatory Bowel Disease; Postoperative Complications.

Ulcerative colitis (UC) is a chronic, immune-mediated inflammatory condition that causes mucosal inflammation of the colon, leading to symptoms such as fecal urgency, diarrhea, rectal bleeding, and abdominal pain.[1] Recently, multiple effective treatments have been approved for UC, which have significantly lowered symptom severity and complications, including the need for surgery, hospitalization, and death. Despite these advances, 20%–25% of patients with UC will still experience significant flares and require hospitalization for an episode of acute severe ulcerative colitis (ASUC).[2,3]

The current standard of care for ASUC is rapid induction with intravenous (IV) corticosteroids; however, 30% of patients will not respond to corticosteroids alone.[4] Both cyclosporine and infliximab rescue therapies effectively reduce the risk of colectomy among corticosteroid-refractory patients with ASUC, yet up to 30% of these patients still fail to respond, necessitating urgent colectomy.[5–8] Recently, Janus kinase (JAK) inhibitor therapies such as tofacitinib and upadacitinib have emerged as a new treatment options for ASUC management.[9–15] Although JAK inhibitors have been shown to reduce the risk of colectomy, no head-to-head comparisons exist comparing JAK inhibitors to other advanced therapies. JAK inhibitors are well suited for ASUC, with rapid serum clearance of JAK inhibitors therapy due to its very short half-life (approximately 3.2 hours for tofacitinib) that theoretically minimizes intraoperative and postoperative complications as the drug is cleared prior to colectomy, even in urgent cases.[16–19] However, there is debate as to whether the downstream biologic effects of JAK inhibitors continue beyond 5 half-lives.[17]

Anecdotally, gastroenterologists and surgeons have expressed concern about JAK inhibitors leading to poor wound healing, as well as increasing both intraoperative and postoperative complications, despite limited data to support these claims. A retrospective, uncontrolled review of 53 outpatients who underwent total abdominal colectomy at the time of tofacitinib exposure at 4 centers found a low risk for early postoperative complications reporting 0 deaths, 20 (37.7%) complications (not graded by severity) with 6 (11%) experiencing infection-related complications and 7 (13.2%) venous thromboembolic events (VTEs).[20] This study did not adjust for other medication exposures, especially corticosteroids, which may have biased drug-outcome safety signals. Given this significant knowledge gap, we performed an adjusted, retrospective, case-control study to assess postoperative complications associated with tofacitinib use for patients with ASUC undergoing colectomy.

Materials and Methods

We conducted a multicenter, retrospective, adjusted case-control study of patients hospitalized with ASUC who underwent total abdominal colectomy or total proctocolectomy, comparing patients who were treated with tofacitinib prior to their colectomy with patients treated with infliximab, while adjusting for several established prognostic clinical factors.

Study Population

Patients over 10 years of age with an established diagnosis of ulcerative colitis who were hospitalized with an episode of ASUC between January 2015 and April 2023 from the following hospitals were included: Michigan Medicine (Ann Arbor, Michigan, USA), GETAID (Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif) (14 centers across France), and the Children's Hospital of Pennsylvania (Philadelphia, Pennsylvania, USA). Cases were defined as patients who underwent colectomy during index hospitalization or within 1 year of their index hospitalization for ASUC in which the patient was initiated on tofacitinib, at doses of either 10 mg twice a day (BID) or 10 mg three times a day (TID). Cases were excluded if the patient did not receive tofacitinib within the 4 weeks prior to colectomy. Additional details on individual center eligibility and tofacitinib treatment protocols are available in previously published reports.[10,12,14] Controls were defined as patients who underwent colectomy during index hospitalization or within 1 year of the index hospitalization for ASUC in which the patient received infliximab during their index hospitalization. Infliximab dosing was either 5 mg/kg or 10 mg/kg, administered as either a single infusion or with a repeat infusion 3 days apart per institutional protocols. Controls were excluded if they were initiated on tofacitinib at any point between their index admission and colectomy. Both cases and controls were excluded if their colectomy took place more than 1 year after their index hospitalization or if their colectomy was completed for an indication other than ASUC nonresponse or ASUC-related complication (ie, infectious colitis or neoplasia). Institutional Review Board approval or equivalent was obtained at each site.

Variables and Outcomes

Collected variables included patient demographics, disease characteristics, clinical details on ASUC hospital

course, operation details, and intraoperative and postoperative complications. The primary outcome was the rate of serious postoperative complications within 30 days of colectomy. A serious complication was defined as grade III or higher according to the Clavien-Demartines-Dindo classification scale.[21] The secondary outcome was the rate of overall postoperative complications (regardless of grade). Briefly, the Clavien-Demartines-Dindo classification scale classifies perioperative complications on a scale of I to V. Complications are classified as grade I if there was any deviation from the normal postoperative course without the need for pharmacological treatment (other than medications to reduce pain, nausea, or fever) or surgical, endoscopic, and radiological interventions. Grade II complications refer to a need for pharmacological treatment with drugs other than those allowed for grade I complications, such as antibiotics, blood transfusions, and total parenteral nutrition. Grade III complications refer to a patient requiring surgical, endoscopic, or radiographic intervention. Complications are classified as grade IV if a patient requires treatment in an intensive care setting due to failure of at least 1 organ system. Finally, complications are classified grade V when a patient has died as a result of a complication of their surgery.

What You Need to Know

Background

Up to 30% of acute severe ulcerative colitis (ASUC) patients need urgent colectomy despite intravenous corticosteroids and rescue therapies. Tofacitinib, a Janus kinase inhibitor, has shown promise as an effective agent for ASUC; however, data on the risk for postoperative complication remain limited.

Findings

Multivariable adjusted analysis showed no significant difference in the risk for serious postoperative complications between tofacitinib- and infliximab-treated patients with ASUC who underwent colectomy; however, our results suggest that there is a significantly lower risk for overall postoperative complications among tofacitinib-treated with ASUC who underwent colectomy compared with infliximab-treated patients.

Implications for patient care

Tofacitinib use appears safe in patients with ASUC who require colectomy, supporting its use in high-risk hospitalized patients with ASUC. Larger, prospective trials are needed to confirm these findings.

Statistical Analysis

Descriptive statistics were presented for continuous variables as median (interquartile range [IQR]) and as number and percentage for categorical variables. Distributions of demographics and operative outcomes were compared between the tofacitinib-treated cases and infliximab-treated controls using Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. Outcomes were compared between the tofacitinib-treated cases and infliximab-treated controls using univariable and adjusted multivariable regression analysis. We selected well-established clinical variables for regression adjustment a priori based on their previously demonstrated or theoretical associations with operative outcomes. These included age at the time of colectomy, inflammatory burden (C-reactive protein [CRP]), nutrition status (albumin), preoperative length of stay, open operative approach, American Society of Anesthesiologists physical status classification system, and cumulative corticosteroid exposure within the 90 days prior to colectomy (converted to prednisone equivalent dosing and measured in grams). We initially included all these variables in our analysis; however, to avoid overfitting and improve model performance, we finalized the model using a stepwise selection process to retain the most predictive and parsimonious set of variables while maintaining clinical relevance. Additional variables, including the year of colectomy and hospital center, were considered; however, there was significant collinearity between the treatment received and the year, and since one center did not contribute controls, we could not include these in our model. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to represent the association between the predictors and outcome of interest. A P value $<.05$ (2-tailed) was considered statistically significant. Two subgroup analyses were performed comparing primary and secondary outcomes in (1) patients who received tofacitinib 10 mg BID compared with patients who received tofacitinib 10 mg TID and (2) in patients who underwent colectomy during index admission compared with delayed colectomy following discharge from index admission. All analyses were performed using R version 4.3.3 (R Foundation for Statistical Computing).

Results

Forty-one tofacitinib-treated patients with ASUC (cases) were compared with 68 infliximab-treated patients with ASUC (controls). The baseline demographics and clinical characteristics are summarized in Table 1. Notably, tofacitinib-treated patients had higher rates of prior biologic exposure, specifically adalimumab (17 [41.5%] vs 18 [26.5%]), infliximab (32 [78.0%] vs 25 [36.8%]), and vedolizumab (21 [51.2%] vs 9 [13.2%]), compared with infliximab-treated patients. On the other hand, patients treated with infliximab had a higher median CRP (97.0 mg/L vs 36.0 mg/L) and lower median albumin (3.4 mg/dL vs 3.6 mg/dL). Among the tofacitinib-treated patients, 26

Table 1. Baseline Demographics and Clinical Characteristics

	Tofacitinib-Treated ASUC Patients (n = 41)	Infliximab-Treated ASUC Patients (n = 68)	*P* Value
Treatment center			<.001[a]
Children's Hospital of Philadelphia	6 (14.6)	1 (1.5)	
GETAID	13 (31.7)	0 (0)	
Michigan Medicine	22 (53.7)	67 (98.5)	
Age at admission, y	27.70 (20.43, 47.07)	36.35 (27.58, 47.83)	.047[a]
Sex			.903
Female	18 (43.9)	32 (47.1)	
Male	23 (56.1)	36 (52.9)	
Ulcerative colitis extent[b]			.697
Proctitis	0 (0)	0 (0)	
Left-sided colitis	9 (22.0)	11 (16.2)	
Pancolitis	32 (78.0)	54 (79.4)	
Previous medication exposures			
Adalimumab	17 (41.5)	18 (26.5)	.158
Infliximab	32 (78.0)	25 (36.8)	<.001[a]
Vedolizumab	21 (51.2)	9 (13.2)	<.001[a]
Ustekinumab	2 (4.9)	2 (2.9)	.99
Truelove & Witts' criteria met[c,d]	17 (41.5)	18 (26.5)	.158
Endoscopic Mayo score[d,e]			.458
Mayo 1	1 (2.4)	0 (0)	
Mayo 2	4 (9.8)	7 (10.3)	
Mayo 3	33 (80.5)	50 (73.5)	
ASA classification[f]			.597
ASA 1	0 (0)	1 (1.5)	
ASA 2	25 (61.0)	35 (51.5)	
ASA 3	16 (39.0)	31 (45.6)	
ASA 4	0 (0)	1 (1.5)	
Lab values at admission[d]			
C-reactive protein, mg/L	36.0 (16.0–74.0)	97.0 (36.8–147.5)	<.001[a]
Albumin, mg/dL	3.6 (3.0–4.1)	3.4 (3.1–3.8)	.36
Hemoglobin, mg/dL	11.5 (9.4–13.2)	11.6 (10.17–12.83)	.788
Inpatient medications[d]			
Tofacitinib 10 mg BID	26 (63.4)	—	
Tofacitinib 10 mg TID	15 (36.6)	—	
Tofacitinib duration, d[g]	23.0 (6.0, 185.0)	—	
Rescue infliximab	5 (12.2)	68 (100)	<.001[a]
Rescue cyclosporine	4 (9.8)	1 (1.5)	.126
Steroid use within 24 h of surgery	34 (82.9)	66 (97.1)	.025[a]
90-d cumulative steroid exposure, g[h]	0.73 (0.00–1.94)	0.91 (0.43–1.62)	.43
ASUC/preoperative length of stay, d[i]	10.00 (7.00–13.00)	8.00 (5.00–10.00)	.011[a]

Values are n (%) or median (interquartile range). *P* values were calculated using the Wilcoxon rank sum tests for continuous variables and the chi-square tests for categorical variables.

ASA, American Society of Anesthesiologists; ASUC, acute severe ulcerative colitis; BID, twice daily; GETAID, Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif; TID, 3 times daily.

[a]Significant value.

[b]3 (4.4%) patients in the infliximab- treated patients had an unknown extent of disease.

[c]The proportion of patients meeting Truelove & Witts' criteria was calculated based on the traditional Truelove and Witts' criteria which required a patient to have ≥6 bowel movements per day with visible blood and 1 of the following: (1) temperature >37.8 °C, (2) pulse >90 beats/min, (3) hemoglobin <10.5 g/dL, (4) erythrocyte sedimentation rate ≥30 mm/h, or (5) C-reactive protein ≥30 mg/L.

[d]Pertains to index ASUC admission.

[e]3 (7.3%) tofacitinib-treated patients and 11 (16.2%) infliximab-treated patients did not complete an endoscopic evaluation during their index hospitalization.

[f]The ASA physical status classification system was determined by the anesthesiologist at the time of colectomy.

[g]Duration of tofacitinib includes both the duration administered during index hospitalization as well as following discharge.

[h]Cumulative steroid exposure is presented as prednisone equivalent dosing (in grams) and includes the dose received as oral prednisone or intravenous methylprednisolone or hydrocortisone in the 90 days prior to colectomy.

[i]ASUC/preoperative length of stay refers to either the length of stay for the index ASUC hospitalization (if the patient did not undergo colectomy during index hospitalization) or the length of time the patient was treated for ASUC prior to undergoing colectomy (if the patient underwent colectomy during their index hospitalization).

(63.4%) received tofacitinib 10 mg BID and 15 (36.6%) received tofacitinib 10 mg TID. All 21 (51.2%) patients who were initiated on tofacitinib in the hospital and were able to avoid colectomy during index admission were discharged on tofacitinib 10 mg BID, which they remained on for a median of 169 days (IQR, 64–234 days) from index admission. Among patients treated with tofacitinib, 5 (12.2%) patients received infliximab and 4 (9.8%) patients received cyclosporine rescue immediately prior to receiving tofacitinib during the same index admission. Among the patients who were treated with infliximab, 1 (1.5%) patient received rescue cyclosporine. The median cumulative 90 corticosteroid exposure was slightly higher among infliximab-treated patients compared with tofacitinib-treated patients (0.91 g vs 0.73 g); however, it should be noted that 66 (97.1%) of infliximab-treated patients compared with 34 (82.9%) of tofacitinib-patients received either oral or IV corticosteroids within 24 hours of colectomy. Of the 7 tofacitinib-treated patients not on corticosteroids within 24 hours of colectomy, 5 were from GETAID and 2 were from Children's Hospital of Pennsylvania. The reason that these patients in the treatment group were not on corticosteroids at the time of colectomy were as follows: 3 patients were considered steroid-refractory and therefore had corticosteroids discontinued prior to index colectomy, 2 patients were off corticosteroids by the time of delayed colectomy on their planned steroid taper, 1 patient refused corticosteroids, and 1 patient had a contraindication to corticosteroids. Among the infliximab-treated patients, both had their corticosteroids

Table 2. Intraoperative and Postoperative Outcomes

	Tofacitinib-Treated ASUC Patients (n = 41)	Infliximab-Treated ASUC Patients (n = 68)	*P* Value
Operative approach			.057
Open surgery	1 (2.4)	11 (16.2)	
Laparoscopic surgery	40 (97.6)	57 (83.8)	
Indication for colectomy			.99
Refractory to medical therapy	39 (95.1)	65 (95.6)	
Toxic megacolon/perforation	2 (4.9)	3 (4.4)	
Intraoperative complications	0 (0)	7 (10.3)	.085
Overall 30-d postoperative complications[b]	13 (31.7)	44 (64.7)	.002[a]
Intra-abdominal septic complication	1 (2.4)	15 (22.1)	.012[a]
Rectal stump leak	3 (7.3)	4 (5.9)	.99
Pelvic collection	0 (0)	7 (10.3)	.085
Surgical site infection	1 (2.4)	7 (10.3)	.253
Other infections	3 (7.3)	11 (16.2)	.297
Postoperative ileus	6 (14.6)	20 (29.4)	.128
VTE	2 (4.9)	4 (5.9)	.99
Stoma complication	3 (7.3)	1 (1.5)	.295
Other complications	3 (7.3)	13 (19.1)	.159
Serious 30-d postoperative complications[b]	3 (7.3)	19 (27.9)	.019[a]
Intra-abdominal septic complication	1 (2.4)	14 (20.6)	.017[a]
Rectal stump leak	0 (0)	3 (4.4)	.448
Pelvic collection	0 (0)	6 (8.8)	.128
Surgical site infection	0 (0)	1 (1.5)	.99
Other infections	1 (2.4)	2 (2.9)	.99
Postoperative ileus	0 (0)	0 (0)	.99
VTE	0 (0)	0 (0)	.99
Stoma complication	0 (0)	0 (0)	.99
Other complications	1 (2.4)	3 (4.4)	.996
Postoperative length of stay, d	5.00 (4.00–8.00)	6.00 (4.00–11.50)	.193
Hospital readmission	7 (17.1)	29 (42.6)	.014[a]
Delayed infection (within 31–90 d)	3 (7.3)	3 (4.4)	.833
Delayed VTE (within 31–90 d)	0 (0)	2 (2.9)	.71
Death	1 (2.4)	0 (0)	.797

Values are n (%) or median (interquartile range). *P* values were calculated using the Wilcoxon rank sum tests for continuous variables and the chi-square tests for categorical variables.

ASUC, acute severe ulcerative colitis; VTE, venous thromboembolic event.

[a]Significant value.

[b]Cumulative events were counted per person; therefore, individual events may not sum to the total if multiple events occurred in the same individual.

stopped shortly before index colectomy due to refractory disease and lack of corticosteroid-response.

Intraoperative and postoperative outcomes are presented in Table 2 for the entire cohort. Compared with tofacitinib-treated patients, infliximab-treated patients had higher rates of open surgery (11 [16.2%] vs 1 [2.4%]; $P = .057$), intraoperative complications (7.0% [10.3%] vs 0 [0%]; $P = .085$), overall postoperative complications (44 [64.7%] vs 13 [31.7%]; $P = .002$), serious postoperative complications (19 [27.9%] vs 3 [7.3%]; $P = .019$), and hospital readmissions (29 [42.6%] vs 7 [17.1%]; $P = .014$). Notably, overall rates of 30-day VTEs were similar between tofacitinib-treated and infliximab-treated patients (2 [4.9%] vs 4 [5.9%]; $P = .99$); however, higher rates of delayed VTEs (within 31–90 days) were observed in the infliximab-treated patients compared with tofacitinib-treated patients (2 [2.9%] vs 0 [0%]; $P = .71$). One (2.4%) patient died in the tofacitinib-treated group 14 days after surgery from septic shock secondary to infectious pneumonia, whereas no deaths occurred in the infliximab-treated group ($P = .797$).

Univariable analysis demonstrated a significantly lower risk for developing both serious postoperative complications (OR, 0.20; 95% CI, 0.05–0.65; $P = .016$) as well as overall postoperative complications regardless of grade (OR, 0.33; 95% CI, 0.14–0.72; $P = .006$) in the tofacitinib-treated group compared with the infliximab-treated group (Table 3). Multivariable regression adjusted for 90-day cumulative corticosteroid exposure and open surgery (after variable selection and retention of the best performing model) did not demonstrate a significantly different risk for developing serious postoperative complications (OR, 0.28; 95% CI, 0.06–0.96; $P = .061$); however, a significantly lower rate of overall postoperative complications (OR, 0.38; 95% CI, 0.16–0.87; $P = .023$) was observed in tofacitinib-treated patients compared with infliximab-treated patients.

Univariable and multivariable subgroup analysis looking at the dose of tofacitinib received during the index hospitalization demonstrated that tofacitinib 10 mg BID was associated with a significantly lower risk of both serious and overall postoperative complications compared with infliximab-treated patients, whereas tofacitinib 10 mg TID was not associated with a significantly different rate of serious or overall postoperative complications compared with infliximab-treated patients (Supplementary Table 1).

Further subgroup analysis looked at differences in demographics, clinical characteristics, and postoperative outcomes according to timing of colectomy. Among patients treated with tofacitinib, 20 (48.8%) underwent colectomy during their index admission, while 21 (51.2%) had a delayed colectomy following the index admission. In the infliximab-treated group, 58 (85.3%) underwent colectomy during the index admission, compared with 10 (14.7%) who had a delayed colectomy. The median time from index admission was 119 days (IQR, 71–221 days) for tofacitinib-treated patients compared with 32 days (IQR, 16.2–97.5 days) for infliximab-treated patients. Demographic, clinical course, and outcome variables are presented in (Supplementary Tables 2–5), with similar trends between colectomy subgroups and overall cohort. Among patients who underwent colectomy during index admission, univariable analysis demonstrated a significantly reduced risk for overall postoperative complications but not for serious postoperative complications. No significant difference in risk for serious postoperative complications was seen in adjusted multivariable analysis, although there was a significantly lower risk of postoperative complications of

Table 3. Risk of Postoperative Complications for Tofacitinib-Treated ASUC Patients Compared with Infliximab-Treated ASUC Patients

	Serious Postoperative Complications (Grade III or Higher)			Overall Postoperative Complications (Regardless of Grade)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Univariable analysis						
Treatment (unadjusted)						
Infliximab	—	—		—	—	
Tofacitinib	0.20	0.05–0.65	.016[a]	0.33	0.14–0.72	.006[a]
Multivariable analysis						
Treatment (adjusted)						
Infliximab	—	—		—	—	
Tofacitinib	0.28	0.06–0.96	.061	0.38	0.16–0.87	.023[a]
Cumulative corticosteroid exposure[b]	0.85	0.48–1.24	.5	1.10	0.87–1.43	.4
Open surgery	8.12	2.13–35.6	.003[a]	8.42	1.48–159	.048[a]

ASA, American Society of Anesthesiologists; ASUC, acute severe ulcerative colitis; CI, confidence interval; OR, odds ratio.
[a]Significant value.
[b]Cumulative steroid exposure is presented in prednisone equivalent dosing (in grams) and includes the dose received as oral prednisone or intravenous methylprednisolone or hydrocortisone in the 90 days prior to colectomy.

any grade (Supplementary Table 6). Univariable and multivariable regression is presented for patients undergoing delayed colectomy after index admission (Supplementary Table 7); however, the analysis lacks sufficient power to detect meaningful differences between the 2 subgroups due to the low number of events, limiting the interpretation and reliability of this subgroup analysis.

Discussion

Tofacitinib, a JAK inhibitor, has shown efficacy in managing ASUC, but concerns about postoperative complications have limited its adoption. This multicenter study suggests that tofacitinib use for ASUC prior to colectomy does not increase postoperative complications of any severity, including serious complications, compared with infliximab. Additionally, our findings indicate that there is no difference in the risk for postoperative complications at either the standard Food and Drug Administration–approved tofacitinib induction dose (10 mg BID) or the off-label, high-intensity tofacitinib induction dose (10 mg TID). In fact, our data demonstrate that there may be a possible protective effect of tofacitinib compared with infliximab, as tofacitinib was significantly associated with a lower risk for overall postoperative complications after adjusting for well-established prognostic variables. Although there was no significant difference in the risk of our primary outcome, serious postoperative complications, between tofacitinib-treated and infliximab-treated patients with ASUC, there was a noticeable trend toward a lower risk in the tofacitinib group, with both intraoperative and postoperative complications occurring less frequently compared with the infliximab group. Similarly, our findings demonstrate that tofacitinib 10 mg BID is associated with a significantly lower risk of both serious and overall postoperative complications compared with infliximab, whereas tofacitinib 10 mg TID did not show a significant difference in postoperative complication rates. Given that our prior case-control study demonstrated that tofacitinib 10 mg TID was significantly associated with a lower risk of colectomy compared with the standard Food and Drug Administration dose of 10 mg BID, these results highlight a critical trade-off between maximizing efficacy and minimizing postoperative complications that must be carefully weighed when selecting dosing strategies.[12] This observation may be related to (1) tofacitinib's short half-life and rapid drug clearance, allowing the drug to be theoretically cleared prior to colectomy, or (2) a direct reduction of the inflammatory burden prior to colectomy which may reduce surgical complexity and the cytokine-mediated systemic proinflammatory response, suspected to interfere with tissue healing and recovery after surgery.[22–24]

While some early retrospective studies suggest that infliximab administration before colectomy may increase the risk of postoperative complications, more recent studies, including PUCCINI (Prospective Cohort of Ulcerative Colitis and Crohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-Operative INfection I), did not show an association between infliximab use and postoperative or surgical site infections.[25–27] On the other hand, corticosteroid use and delays in colectomy (leading to propagation of inflammation in the absence of effective medical therapy) are well-established risk factors for postoperative complications independent of preprocedural infliximab administration.[22,26–29] Although corticosteroid use was relatively similar between the two treatment groups, we controlled for its effects by including cumulative corticosteroids exposure in our multivariable model.

It is important to note that we did not observe any increased risk of postoperative VTEs with tofacitinib, which is a major concern because tofacitinib exposure has been associated with an increased risk of VTEs independent of other prothrombotic factors common to patients with ASUC—namely decreased ambulation, active inflammation, corticosteroid use, and major colorectal surgery.[30–41] This observed absence of an increased VTE risk may alleviate some of the hypothetical postoperative safety concern attributed to JAK inhibitor therapy in this high-risk population.

This study has several notable strengths. First, this is the first study to compare ASUC patients undergoing colectomy who received tofacitinib with patients receiving infliximab. Second, the multicenter nature allowed us to collect data from diverse patient populations and practice patterns, increasing generalizability. However, it should be noted that most cases and controls were treated at the University of Michigan. Third, this study is the largest to evaluate postoperative outcomes in patients with ASUC. Previously, we have relied on systematic reviews of small, uncontrolled case series to guide management of our sickest patients hospitalized with ASUC who have numerous risk factors for a complicated postoperative course.

This study has several limitations that warrant consideration. One potential limitation is the possible disparity in baseline disease severity between patient groups. Notably, the tofacitinib-treated group presented with a lower average CRP at index admission compared with infliximab-treated patients, although this was not identified as a significant risk factor in our multivariable models. In addition, there is potential for selection bias, in which healthier patients were inadvertently preferentially selected to receive tofacitinib due to preconceived concerns about tofacitinib therapy safety. Nonetheless, adjusted analysis accounted for baseline differences in measurable confounding factors, allowing for the more precise isolation of the effects of tofacitinib on postoperative outcomes.[26–29,42,43] Another potential limitation is that the study may be underpowered to detect true differences in treatment effects, which could lead to a type II error; however, the lack of a significant

difference in serious postoperative complications between those treated with tofacitinib and those treated with infliximab is clinically meaningful.

In conclusion, this large multicenter adjusted case-control study found no difference in serious postoperative complications in tofacitinib-treated patients compared with infliximab-treated patients with ASUC. These findings can likely be extrapolated to upadacitinib, a selective JAK inhibitor, given its similar mechanism of action and the absence of any evidence suggesting increased safety concerns compared with tofacitinib, although further research will be needed to definitively answer that question. Ultimately, our findings support the safety of JAK inhibitor therapy as a treatment option, and reinforce the potential beneficial role, for patients hospitalized with ASUC who may ultimately require colectomy. Prospective randomized clinical trials are needed to validate our findings and establish clear treatment pathways for ASUC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.01.032.

References

1. Chang JT, Hays RD, Shekelle PG, et al. Patients' global ratings of their health care are not associated with the technical quality of their care. Ann Intern Med 2006;144:665–672.
2. Bartlett EE, Grayson M, Barker R, et al. The effects of physician communications skills on patient satisfaction; recall, and adherence. J Chronic Dis 1984;37:755–764.
3. Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. J Crohns Colitis 2010;4:431–437.
4. Mao EJ, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2017;45:3–13.
5. Koliani-Pace JL, Singh S, Luo M, et al. Changes in vedolizumab utilization across US academic centers and community practice are associated with improved effectiveness and disease outcomes. Inflamm Bowel Dis 2019;25:1854–1861.
6. Buie MJ, Quan J, Windsor JW, et al. Global hospitalization trends for Crohn's disease and ulcerative colitis in the 21st century: a systematic review with temporal analyses. Clin Gastroenterol Hepatol 2023;21:2211–2221.
7. Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 2007;5:103–110.
8. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330(26):1841–1845.
9. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805–1811.
10. Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial. Lancet Gastroenterol Hepatol 2016;1:15–24.
11. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012;380:1909–1915.
12. Berinstein JA, Sheehan JL, Dias M, et al. Tofacitinib for biologic-experienced hospitalized patients with acute severe ulcerative colitis: a retrospective case-control study. Clin Gastroenterol Hepatol 2021;19:2112–2120.e1.
13. Berinstein JA, Karl T, Patel A, et al. Effectiveness of upadacitinib for patients with acute severe ulcerative colitis: a multi-center experience. Am J Gastroenterol 2024;119:1421–1425.
14. Steenholdt C, Dige Ovesen P, Brynskov J, Benedict Seidelin J. Tofacitinib for acute severe ulcerative colitis: a systematic review. J Crohns Colitis 2023;17:1354–1363.
15. Singh A, Goyal MK, Midha V, et al. Tofacitinib in Acute Severe Ulcerative Colitis (TACOS): a randomized controlled trial. Am J Gastroenterol 2024;119:1365–1372.
16. 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;17:139–147.
17. Loftus EV, Colombel JF, Takeuchi K, et al. Upadacitinib therapy reduces ulcerative colitis symptoms as early as day 1 of induction treatment. Clin Gastroenterol Hepatol 2023;21:2347–2358.e6.
18. Dowty ME, Lin J, Ryder TF, et al. The pharmacokinetics, metabolism, and clearance mechanisms of tofacitinib, a Janus kinase inhibitor, in humans. Drug Metab Dispos Biol Fate Chem 2014;42:759–773.
19. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015;149:350–355.e2.
20. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. Inflamm Bowel Dis 2014;20:2247–2259.
21. Mohamed MEF, Trueman S, Othman AA, et al. Development of in vitro–in vivo correlation for upadacitinib extended-release tablet formulation. AAPS J 2019;21:108.
22. Lightner AL, Vaidya P, Holubar S, et al. Perioperative safety of tofacitinib in surgical ulcerative colitis patients. Colorectal Dis 2021;23:2085–2090.
23. Uzzan M, Bresteau C, Laharie D, et al. Tofacitinib as salvage therapy for 55 patients hospitalised with refractory severe ulcerative colitis: a GETAID cohort. Aliment Pharmacol Ther 2021;54:312–319.
24. Constant BD, Baldassano R, Kirsch J, et al. Tofacitinib salvage therapy for children hospitalized for corticosteroid- and biologic-refractory ulcerative colitis. J Pediatr Gastroenterol Nutr 2022;75:724–730.
25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213.
26. Kaplan GG, McCarthy EP, Ayanian JZ, et al. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. Gastroenterology 2008;134:680–687.

27. Rubin DT, Salese L, Cohen M, et al. Presence of risk factors associated with colectomy among patients with ulcerative colitis: a post hoc analysis of data from the tofacitinib OCTAVE ulcerative colitis clinical program. Ther Adv Gastroenterol 2023; 16:17562848231189122.
28. Schineis C, Lehmann KS, Lauscher JC, et al. Colectomy with ileostomy for severe ulcerative colitis-postoperative complications and risk factors. Int J Colorectal Dis 2020;35:387–394.
29. Bartels SAL, Gardenbroek TJ, Bos L, et al. Prolonged preoperative hospital stay is a risk factor for complications after emergency colectomy for severe colitis. Colorectal Dis 2013; 15:1392–1398.
30. Bain CR, Myles PS, Martin C, et al. Postoperative systemic inflammation after major abdominal surgery: patient-centred outcomes. Anaesthesia 2023;78:1365–1375.
31. Cohen BL, Fleshner P, Kane SV, et al. Prospective cohort study to investigate the safety of preoperative tumor necrosis factor inhibitor exposure in patients with inflammatory bowel disease undergoing intra-abdominal surgery. Gastroenterology 2022; 163:204–221.
32. Yang Z, Wu Q, Wu K, et al. Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis. Aliment Pharmacol Ther 2010; 31:486–492.
33. Bregnbak D, Mortensen C, Bendtsen F. Infliximab and complications after colectomy in patients with ulcerative colitis. J Crohns Colitis 2012;6:281–286.
34. Ferrante M, D'Hoore A, Vermeire S, et al. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. Inflamm Bowel Dis 2009;15:1062–1070.
35. Subramanian V, Saxena S, Kang JY, et al. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. Am J Gastroenterol 2008;103:2373–2381.
36. Nguyen GC, Elnahas A, Jackson TD. The impact of preoperative steroid use on short-term outcomes following surgery for inflammatory bowel disease. J Crohns Colitis 2014;8: 1661–1667.
37. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010;375(9715):657–663.
38. Sandborn WJ, Panés J, Sands BE, et al. Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme. Aliment Pharmacol Ther 2019;50:1068–1076.
39. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med 2022;386:316–326.
40. Fleming F, Gaertner W, Ternent CA, et al. The American Society of Colon and Rectal Surgeons clinical practice guideline for the prevention of venous thromboembolic disease in colorectal surgery. Dis Colon Rectum 2018;61:14–20.
41. McKechnie T, Wang J, Springer JE, et al. Extended thromboprophylaxis following colorectal surgery in patients with inflammatory bowel disease: a comprehensive systematic clinical review. Colorectal Dis 2020;22:663–678.
42. Lo BD, Stem M, Zhang GQ, et al. The reduced risk of septic shock/sepsis with laparoscopic surgery among ulcerative colitis patients with preoperative chronic steroid use. Surgery 2021; 170:1047–1053.
43. Telem DA, Vine AJ, Swain G, et al. Laparoscopic subtotal colectomy for medically refractory ulcerative colitis: the time has come. Surg Endosc 2010;24:1616–1620.

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Conflicts of interest

These authors disclose the following: Jakob Benedict Seidelin has served as a national coordinator of studies for AbbVie, Amgen, Arena Pharmaceuticals, Eli Lilly, and Boehringer Ingelheim. Peter D.R. Higgins has received consulting fees from AbbVie, Amgen, and Genentech. Casper Steenholdt has received lecture fees from MSD and Janssen-Cilag; and a research grant from Takeda. Lindsey Albenberg has received lecture fees from Nestlé Health Sciences and Abbott Nutrition. David Laharie has received counseling, boards, transports, or fees from AbbVie, Amgen, Biogaran, Biogen, Celltrion, Ferring, Galapagos, Janssen, Lilly, Medac, MSD, Pfizer, Prometheus, Takeda, and Theradiag. Alexandre Nuzzo has received consulting fees from AbbVie, Janssen, Celltrion, and Amgen; research grants from MSD-Avenir, Fondation de l'Avenir, and SNFGE. The remaining authors disclose no conflicts.

Supplementary Table 1. Risk of Postoperative Complications of Tofacitinib According to Tofacitinib Dose

	Serious Postoperative Complications (Grade III or Higher)			Overall Postoperative Complications (Regardless of Grade)		
	OR[a]	95% CI	*P* Value	OR[a]	95% CI	*P* Value
Univariable analysis						
Treatment (unadjusted)						
Infliximab	—	—		—	—	
Tofacitinib 10 mg BID	0.10	0.01–0.54	0.031[b]	0.23	0.08–0.58	0.003[b]
Tofacitinib 10 mg TID	0.40	0.06–1.62	0.3	0.58	0.19–1.85	0.4
Multivariable analysis						
Treatment (adjusted)						
Infliximab	—	—		—	—	
Tofacitinib 10 mg BID	0.12	0.01–0.67	0.048[b]	0.27	0.09–0.70	0.009[b]
Tofacitinib 10 mg TID	0.74	0.10–3.38	0.7	0.69	0.21–2.27	0.5
Cumulative corticosteroid exposure[b]	0.79	0.42–1.18	0.4	1.06	0.83–1.38	0.7
Open surgery	8.57	2.18–39.5	0.003[b]	8.75	1.51–167	0.046[b]

BID, twice daily; CI, confidence interval; OR, odds ratio; TID, 3 times daily.

[a]Cumulative steroid exposure is presented in prednisone equivalent dosing (in grams) and includes the dose received as oral prednisone or intravenous methylprednisolone or hydrocortisone in the 90 days prior to colectomy.

[b]Significant value.

Supplemental Table 2. Baseline Demographics and Clinical Characteristics for Patients who Underwent Colectomy Within Index Admission

	Tofacitinib-Treated ASUC Patients (n = 20)	Infliximab-Treated ASUC Patients (n = 58)	*P* Value
Treatment center			<.001[a]
Children's Hospital of Philadelphia	2 (10.0)	1 (1.7)	
GETAID	7 (35.0)	0 (0)	
Michigan Medicine	11 (55.0)	57 (98.3)	
Age at admission, y	50.4 (49.7–50.8)	48.0 (45.8–50.1)	<.001[a]
Sex			.704
Female	8 (40.0)	28 (48.3)	
Male	12 (60.0)	30 (51.7)	
Ulcerative colitis extent[b]			.99
Proctitis	0 (0%)	0 (0)	
Left-sided colitis	4 (20.0)	10 (17.2)	
Pancolitis	16 (80.0)	45 (77.6)	
Previous medication exposures			
Adalimumab	7 (35.0)	16 (27.6)	.732
Infliximab	14 (70.0)	19 (32.8)	.008[a]
Vedolizumab	4 (20.0)	6 (10.3)	.468
Ustekinumab	0 (0)	2 (3.4)	.983
Truelove and Witts' criteria met[c,d]	18 (90.0)	55 (94.8)	.99
Endoscopic Mayo score[d,e]			.212
Mayo 1	1 (5.0)	0 (0)	
Mayo 2	2 (10.0)	4 (6.9)	
Mayo 3	14 (70.0)	44 (75.9)	
ASA classification[f]			.868
ASA 1	0 (0)	1 (1.7)	
ASA 2	11 (55.0)	30 (51.7)	
ASA 3	9 (45.0)	26 (44.8)	
ASA 4	0 (0)	1 (1.7)	
Lab values at admission[d]			
C-reactive protein, mg/L	52.5 (29.4–103.0)	100.5 (44.8–152.8)	.02[a]
Albumin, mg/dL	3.60 (2.85–4.30)	3.40 (3.00–3.80)	.532
Hemoglobin, mg/dL	11.8 (10.1–13.2)	11.55 (10.1–12.6)	.394
Inpatient medications[d]			
Tofacitinib 10 mg BID	14 (70.0)	—	
Tofacitinib 10 mg TID	6 (30.0)	—	
Tofacitinib duration, d[g]	5.5 (4.0–8.0)	—	
Rescue infliximab	4 (20.0)	58 (100)	<.001[a]
Rescue cyclosporine	3 (15.0)	1 (1.7)	.083
Steroid use within 24 h of surgery	15 (75.0)	56 (96.6)	.014[a]
90-d cumulative steroid exposure, g[h]	0.94 (0.13–1.77)	0.87 (0.42–1.4)	.814
ASUC/preoperative length of stay, d[i]	10.0 (7.2–14.5)	8.0 (6.0–10.0)	.063

Values are n (%) or median (interquartile range). *P* values were calculated using the Wilcoxon rank sum tests for continuous variables and the chi-square tests for categorical variables.

ASA, American Society of Anesthesiologists; ASUC, acute severe ulcerative colitis; BID, twice daily; GETAID, Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif; TID, 3 times daily.

[a]Significant value.

[b]3 (5.2%) patients in the infliximab- treated patients had an unknown extent of disease.

[c]The proportion of patients meeting Truelove and Witts' criteria was calculated based on the traditional Truelove and Witts' criteria, which required a patient to have ≥6 bowel movements per day with visible blood and 1 of the following: (1) temperature >37.5 °C, 2) pulse >90 beats/min, (3) hemoglobin <10.5 g/dL, (4) erythrocyte sedimentation rate ≥30 mm/h, or (5) C-reactive protein (CRP) ≥30 mg/L.

[d]Pertains to index ASUC admission.

[e]3 (15.0%) tofacitinib-treated patients and 10 (17.2%) infliximab-treated patients did not complete an endoscopic evaluation during their index hospitalization.

[f]The ASA physical status classification system was determined by the anesthesiologist at the time of colectomy.

[g]Duration of tofacitinib includes both the duration administered during index hospitalization as well as following discharge.

[h]Cumulative steroid exposure is presented in prednisone equivalent dosing (in grams) and included the dose received as oral prednisone or IV methylprednisolone or hydrocortisone in the 90 days prior to colectomy.

[i]ASUC/preoperative length of stay refers to either the length of stay for the index ASUC hospitalization (if the patient did not undergo colectomy during index hospitalization) or the length of time the patient was treated for ASUC prior to undergoing colectomy (if the patient underwent colectomy during their index hospitalization).

Supplemental Table 3. Baseline Demographics and Clinical Characteristics for Patients who Underwent Delayed Colectomy After Index Admission

	Tofacitinib-Treated ASUC Patients (n = 21)	Infliximab-Treated ASUC Patients (n = 10)	*P* Value
Treatment center			.03[a]
Children's Hospital of Philadelphia	4 (19.0)	0 (0)	
GETAID	6 (28.6)	0 (0)	
Michigan Medicine	11 (52.4)	10 (100)	
Age at admission, y	50.0 (49.1–50.8)	48.0 (46.9–49.6)	.015[a]
Sex			.99
Female	10 (47.6)	4 (40.0)	
Male	11 (52.4)	6 (60.0)	
Ulcerative colitis extent[b]			.672
Proctitis	0 (0%)	0 (0)	
Left-sided colitis	5 (23.8)	1 (10.0)	
Pancolitis	16 (76.2)	9 (90.0)	
Previous medication exposures			
Adalimumab	10 (47.6)	2 (20.0)	.28
Infliximab	18 (85.7)	6 (60.0)	.254
Vedolizumab	17 (81.0)	3 (30.0)	.018[a]
Ustekinumab	2 (9.5)	0 (0)	.82
Truelove and Witts' criteria met[b,c]	19 (90.5)	9 (90.0)	.99
Endoscopic Mayo score[c,d,e]			
Mayo 1	0 (0)	0 (0)	
Mayo 2	2 (9.5)	3 (30.0)	
Mayo 3	19 (90.5)	6 (60.0)	
ASA classification[e,f]			
ASA 1	0 (0)	0 (0)	
ASA 2	14 (66.7)	5 (50.0)	
ASA 3	7 (33.3)	5 (50.0)	
ASA 4	0 (0)	0 (0)	
Lab values at admission[c]			
C-reactive protein, mg/L	30.0 (10.0–51.0)	30.5 (21.2–116.5)	.263
Albumin, mg/dL	3.6 (3.3–4.1)	3.6 (3.4–4.1)	.99
Hemoglobin, mg/dL	11.0 (9.2–12.7)	12.8 (11.7–13.5)	.091[a]
Inpatient medications[c]			
Tofacitinib 10 mg BID	12 (57.1)	—	
Tofacitinib 10 mg TID	9 (42.9)	—	
Tofacitinib duration, d[g]	169.0 (64.0–234.0)	—	
Rescue infliximab	1 (4.8)	10 (100)	<.001[a]
Rescue cyclosporine	1 (4.8)	0 (0)	.99
Steroid use within 24 h of surgery	19 (90.5)	10 (100)	.82
90-day cumulative steroid exposure, g[h]	0.72 (0.00–3.1)	1.92 (0.7–2.3)	.278
ASUC/preoperative length of stay, d	10.0 (7.0–13.0)	8.0 (5.0–10.0)	.011[a]
Days from index admission to colectomy	119.0 (71.0–221.0)	32.0 (16.2–97.5)	.011[a]

Values are n (%) or median (interquartile range).
P values were calculated using the Wilcoxon rank sum tests for continuous variables and the chi-square tests for categorical variables.
ASA, American Society of Anesthesiologists; ASUC, acute severe ulcerative colitis; BID, twice daily; GETAID, Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif; TID, 3 times daily.
[a]Significant value.
[b]The proportion of patients meeting Truelove and Witts' criteria was calculated based on the traditional Truelove and Witts' criteria, which required a patient to have ≥6 bowel movements per day with visible blood and 1 of the following: (1) temperature >37.5 °C, (2) Pulse >90 beats/min, (3) hemoglobin <10.5 g/dL, (4) erythrocyte sedimentation rate ≥30 mm/h, or 5) C-reactive protein ≥30 mg/L.
[c]Pertains to index ASUC admission.
[d]1 (10.0%) infliximab-treated patient did not complete an endoscopic evaluation during their index hospitalization.
[e]Statistical analysis could not be performed on these categorical variables due to low numbers in 1 of the groups.
[f]The ASA physical status classification system was determined by the anesthesiologist at the time of colectomy.
[g]Duration of tofacitinib includes both the duration administered during index hospitalization as well as following discharge.
[h]Cumulative steroid exposure is presented in prednisone equivalent dosing (in grams) and included the dose received as oral prednisone or intravenous.

Supplemental Table 4. Intraoperative and Postoperative Outcomes for Patients who Underwent Colectomy Within Index Admission

	Tofacitinib-Treated ASUC Patients (n = 20)	Infliximab-Treated ASUC Patients (n = 58)	*P* Value
Operative approach			.109
Open surgery	0 (0)	10 (17.2)	
Laparoscopic surgery	20 (100)	48 (82.8)	
Indication for colectomy			
Refractory to medical therapy	20 (100)	55 (94.8)	.717
Toxic megacolon/perforation	0 (0)	8 (13.8)	.185
Intraoperative complications	0 (0)	6 (10.3)	.312
Overall 30-d postoperative complications[a]	7 (35.0)	40 (69.0)	.016[b]
Intra-abdominal septic complication	1 (5.0)	13 (22.4)	.158
Rectal stump leak	3 (15.0)	3 (5.2)	.349
Pelvic collection	0 (0)	6 (10.3)	.312
Surgical site infection	0 (0)	7 (12.1)	.24
Other infections	1 (5.0)	11 (19.0)	.257
Postoperative ileus	5 (25.0)	18 (31.0)	.821
Venous thromboembolic event	1 (5.0)	4 (6.9)	.99
Stoma complication	2 (10.0)	1 (1.7)	.324
Other complications	0 (0)	12 (20.7)	.064
Serious 30-d postoperative complications[a]	1 (5.0)	17 (29.3)	.055
Intra-abdominal septic complication	1 (5.0)	12 (20.7)	.202
Rectal stump leak	0 (0)	2 (3.4)	.983
Pelvic collection	0 (0)	5 (8.6)	.408
Surgical site infection	0 (0)	1 (1.7)	.99
Other infections	0 (0)	2 (3.4)	.983
Postoperative ileus	0 (0)	0 (0)	.99
Venous thromboembolic event	0 (0)	0 (0)	.99
Stoma complication	0 (0)	0 (0)	.99
Other complications	0 (0)	2 (3.4)	.983
Postoperative length of stay, d	5.0 (4.0–7.0)	7.0 (4.0–12.5)	.203
Hospital readmission	5 (25.0)	25 (43.1)	.243
Delayed infection (within 31-90 d)	1 (5.0)	3 (5.2)	.99
Delayed VTE (within 31-90 d)	0 (0)	2 (3.4)	.983
Death	0 (0)	0 (0)	.99

Values are n (%) or median (interquartile range). *P* values were calculated using the Wilcoxon rank sum tests for continuous variables and the chi-square tests for categorical variables.

ASUC, acute severe ulcerative colitis; VTE, venous thromboembolic event.

[a]Cumulative events were counted per person; therefore, individual events may not sum to the total if multiple events occurred in the same individual.

[b]Significant value.

Supplemental Table 5. Intraoperative and Postoperative Clinical Course for Patients who Underwent Delayed Colectomy After Index Admission

	Tofacitinib-Treated ASUC Patients (n = 21)	Infliximab-Treated ASUC Patients (n = 10)	*P* Value
Operative approach			.99
Open surgery	1 (4.8)	1 (10.0)	
Laparoscopic surgery	20 (95.2)	9 (90.0)	
Indication for colectomy			
Refractory to medical therapy	19 (90.5)	10 (100)	.82
Toxic megacolon/perforation	1 (4.8)	0 (0)	.99
Intraoperative complications	0 (0)	1 (10.0)	.7
Overall 30-d postoperative complications[a]	6 (28.6)	4 (40.0)	.822
Intra-abdominal septic complication	0 (0)	2 (20.0)	.181
Rectal stump leak	0 (0)	1 (10.0)	.7
Pelvic collection	0 (0)	1 (10.0)	.7
Surgical site infection	1 (4.8)	0 (0)	.99
Other infections	2 (9.5)	0 (0)	.82
Postoperative ileus	1 (4.8)	2 (20.0)	.489
Venous thromboembolic event	1 (4.8)	0 (0)	.99
Stoma complication	1 (4.8)	0 (0)	.99
Other complications	3 (14.3)	1 (10.0)	.99
Serious 30-d postoperative complications[a]	2 (9.5)	2 (20.0)	.81
Intra-abdominal septic complication	0 (0)	2 (20.0)	.181
Rectal stump leak	0 (0)	1 (10.0)	.7
Pelvic collection	0 (0)	1 (10.0)	.7
Surgical site infection	0 (0)	0 (0)	.99
Other infections	1 (4.8)	0 (0)	.99
Postoperative ileus	0 (0)	0 (0)	.99
Venous thromboembolic event	0 (0)	0 (0)	.99
Stoma complication	0 (0)	0 (0)	.99
Other complications	1 (4.8)	1 (10.0)	.99
Postoperative length of stay, d	5.0 (4.0–8.0)	4.5 (3.2–7.5)	.739
Hospital readmission	2 (9.5)	4 (40.0)	.146
Delayed infection (within 31-90 d)	2 (9.5)	0 (0)	.82
Delayed VTE (within 31-90 d)	0 (0)	0 (0)	.99
Death	1 (4.8)	0 (0)	.99

Values are n (%) or median (interquartile range). *P* values were calculated using the Wilcoxon rank sum tests for continuous variables and the chi-square tests for categorical variables.

ASUC, acute severe ulcerative colitis; VTE, venous thromboembolic event.

[a]Cumulative events were counted per person; therefore, individual events may not sum to the total if multiple events occurred in the same individual.

Supplementary Table 6. Risk of Postoperative Complications of Tofacitinib Among Patients Undergoing Colectomy During Index Admission

	Serious Postoperative Complications (Grade III or Higher)			Overall Postoperative Complications (Regardless of Grade)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Univariable analysis						
Treatment (unadjusted)						
Infliximab	—	—		—	—	
Tofacitinib	0.13	0.01–0.69	.053	0.34	0.12–0.96	.043[a]
Multivariable analysis						
Treatment (adjusted)						
Infliximab	—	—		—	—	
Tofacitinib	0.16	0.01–0.95	.10	0.41	0.14–1.19	.10
Cumulative corticosteroid exposure[b]	0.70	0.29–1.31	.3	1.01	0.63–1.70	>.9
Open surgery	4.40	1.05–20.4	.046	4.52	0.74–87.8	.2

CI, confidence interval; OR, odds ratio.
[a]Significant value.
[b]Cumulative steroid exposure is presented in prednisone equivalent dosing (in grams) and includes the dose received as oral prednisone or intravenous methylprednisolone or hydrocortisone in the 90 days prior to colectomy.

Supplementary Table 7. Risk of Postoperative Complications of Tofacitinib Among Patients Undergoing Delayed Colectomy After Index Admission

	Serious Postoperative Complications (Grade III or Higher)			Overall Postoperative Complications (Regardless of Grade)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Univariable analysis						
Treatment (unadjusted)						
Infliximab	—	—		—	—	
Tofacitinib	0.42	0.04–4.01	.4	0.75	0.16–3.75	.7
Multivariable analysis						
Treatment (adjusted)						
Infliximab	—	—		—	—	
Tofacitinib	0.42	0.02–11.6	.6	0.91	0.16–5.90	>.9
Cumulative corticosteroid exposure[a]	1.07	0.50–1.68	.8	1.30	0.96–1.94	.12
Open surgery[b]	∞	0.00	>.9	∞	0.00	>.9

CI, confidence interval; OR, odds ratio.
[a]Cumulative steroid exposure is presented in prednisone equivalent dosing (in grams) and includes the dose received as oral prednisone or intravenous methylprednisolone or hydrocortisone in the 90 days prior to colectomy.
[b]ORs could not be reliably estimated for open surgery due to low event counts, resulting in model instability. Reported *P* values and CIs are not meaningful in this context.