SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Effectiveness and Safety of Janus Kinase Inhibitors in Acute Severe Ulcerative Colitis: A Systematic Review and Meta-Analysis

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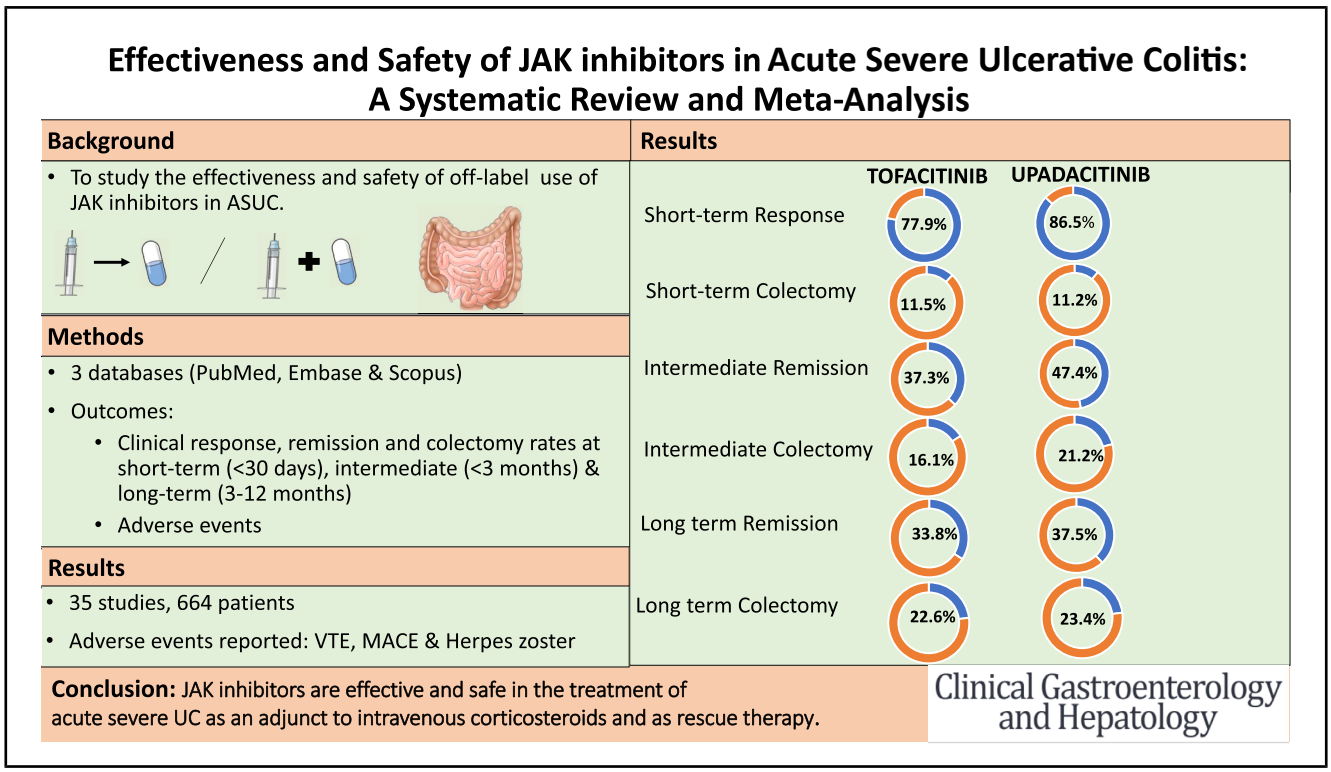

BACKGROUND & AIMS: **Janus kinase (JAK) inhibitors have been reported to be useful in acute severe ulcerative colitis (ASUC). We performed a systematic review and meta-analysis to assess their effectiveness and safety in ASUC.**

METHODS: **Electronic databases (PubMed, Embase, and Scopus) were searched on December 17, 2025, to identify reports about using JAK inhibitors in ASUC. We extracted data concerning clinical response, remission, colectomy, and adverse events with the use of JAK inhibitors in ASUC.**

[§]Authors share co-senior authorship.

Abbreviations used in this paper: ASUC, acute severe ulcerative colitis; CI, confidence interval; CRP, C-reactive protein; DOI, Difference of Means/Effects Index; IBD, inflammatory bowel disease; JAK, Janus kinase; LFK, Luis Furuya-Kanamori; LIMCs, low- and middle-income countries; MACE, major adverse cardiovascular events; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; UC, ulcerative colitis; VTE, venous thromboembolism.

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Pooled clinical response rates, remission rates and colectomy were calculated at short-term (<30 days), intermediate (<3 months) and long-term (3–12 months) therapy. The quality of studies was assessed using Joanna Briggs' tools.

RESULTS: **A total of 35 studies (664 patients) were included. In the short term (<1 month), the pooled clinical response and colectomy rate with tofacitinib was 77.9% (95% confidence interval [CI], 67.1%–86%) and 11.5% (95% CI, 7.1%–18.4%), whereas for upadacitinib, it was 86.5% (95% CI, 72.3%–94.1%) and 11.2% (95% CI, 7.2%–16.9%), respectively. In the intermediate term (<3 months), the pooled clinical response, remission, and colectomy rates with tofacitinib and upadacitinib were 57.2% (95% CI, 49.2%–64.8%), 37.3% (95% CI, 28.1%–47.5%), 16.1% (95% CI, 10.9%–23.1%), and 56.1% (95% CI, 39.3%–71.7%), 47.4% (95% CI, 37.6%–57.4%), 21.2% (95% CI, 15.8%–27.7%), respectively. In the long term (3–12 months), the pooled clinical response, remission, and colectomy rates with tofacitinib and upadacitinib were 41.4% (95% CI, 34.4%–48.8%), 33.8% (95% CI, 28.4%–39.5%), 22.6% (95% CI, 17.5%–28.6%), and 35.1% (95% CI, 21.1%–52.2%), 37.5% (95% CI, 19.1%–60.4%), 23.4% (95% CI, 17.1%–31.4%), respectively. The adverse events reported were venous thromboembolism (2.2%; 95% CI, 1.1%–4.7%), major adverse cardiovascular events (0.7%; 95% CI, 0.1–10.3%), and herpes zoster (3.4%; 95% CI, 1.9%–6.1%). There was no difference in the effectiveness of high-dose as compared with standard-dose tofacitinib.**

CONCLUSIONS: **JAK inhibitors are effective and safe in the treatment of ASUC as an adjunct to intravenous corticosteroids and as rescue therapy. Both tofacitinib and upadacitinib were associated with similar outcomes in ASUC. Randomized controlled trials evaluating the role of JAK inhibitors as co-therapy with corticosteroids and as a salvage therapy agent in corticosteroid non-responsive ASUC are required.**

Keywords: Colectomy; Small Molecules; Tofacitinib; Upadacitinib.

Acute severe ulcerative colitis (ASUC) is a medical emergency occurring in 20% of all cases of ulcerative colitis (UC), with a mortality rate reaching 1%.[1] Corticosteroids remain the first line of management with a response rate of 60%.[2,3] Infliximab, cyclosporine, and surgery have traditionally been used as salvage therapy.[4] The use of infliximab has been limited by its susceptibility to leak from an inflamed colon and early development of anti-drug antibodies, resulting in low trough levels.[5] In addition, even with the advent of biosimilars, the availability and cost remain a challenge in low- and middle-income countries (LMICs). Furthermore, the increasing use of biologics in patients with UC means that patients admitted with ASUC increasingly may have a history of prior or current infliximab exposure and/or failure, creating a need for approaches to management that do not depend upon use of infliximab as a rescue therapy. Similarly, the toxicity profile of cyclosporine and the practical aspects relating to administration have resulted in declining use of cyclosporine as rescue therapy.[6] Infliximab and cyclosporine have been found to have a similar efficacy in ASUC.[7] Despite the rescue drugs, up to 25% of patients with ASUC will require colectomy.[8]

There is an unmet need to explore new drugs to manage ASUC. Janus kinase (JAK) inhibitors are small molecules that have a fast onset of action, making them promising agents for the management of ASUC.[9] They act by inhibition of the JAK-signal transducer and activator of transcription (STAT) signaling pathway, which inhibits the proinflammatory cytokines.[10] These drugs, tofacitinib, upadacitinib, and filgotinib, have the advantages of oral administration, high potency, rapid clearance, effectiveness in hypoalbuminemia, and lack of immunogenicity.[11] JAK inhibitors have been approved for patients with moderate to severe UC who have intolerance or inadequate response to biologicals. However, their use in the setting of ASUC has been off-label so far. Furthermore, there are some concerns of risk of thromboembolism and cardiovascular events in the background of a prothrombotic state. Because patients with ASUC are excluded from licensing trials, the evidence on the efficacy and safety of JAK inhibitors will be pertinent in management algorithms.

This systematic review and meta-analysis aim to estimate the effectiveness and safety of JAK inhibitors in ASUC. We also aimed to compare the use of different types and doses of JAK inhibitors in the setting of ASUC.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA).[12] The protocol was registered in PROSPERO (CRD42024576853)

Database and Search Strategy

A search was conducted in the databases, PubMed, EMBASE, and Scopus on December 17, 2025, from

inception. The keywords used in the search included 'Acute severe colitis' OR 'Hospitalized ulcerative colitis' OR 'acute severe ulcerative colitis' and 'JAKi' OR 'Janus Kinase inhibitor' OR 'JAK inhibitor' OR Tofacitinib OR Upadacitinib OR baricitinib OR filgotinib OR decernotinib OR peficitinib. The details of the search are shown in Supplementary Table 1. Relevant articles were selected for full-text screening. The bibliographies of included studies and reviews were searched for additional eligible studies. The screening was conducted by 2 authors (AJ, AC) and any discrepancy was resolved in discussion with a third reviewer (VS).

Study Selection, Inclusion and Exclusion Criteria

We included all studies (adult and pediatric) that reported the use of JAK inhibitors (tofacitinib, upadacitinib, and filgotinib) in the ASUC setting. The literature search was not restricted by the type of study. We included patients with ASUC who were started on JAK inhibitors as treatment at any time point since admission. We excluded non-English-language articles and manuscripts describing their use in mild-moderate UC, Crohn's disease, and indeterminate colitis. We excluded case reports and studies reporting fewer than 5 patients with ASUC. We excluded review articles, comments, and animal studies.

Data Extraction and Outcomes

The data extraction was done using a predesigned data sheet. Data regarding the age of patients, the type of JAK inhibitor, the dose used, the line of therapy (upfront along with steroids or as salvage therapy), concomitant drugs, outcomes of therapy (response or remission), the need for colectomy or additional salvage therapy, and adverse events were extracted. We categorized the outcomes of JAK inhibitors into short-term outcomes (<1 month), intermediate outcomes (<3 months), and long-term outcomes (3–12 months). These cutoffs were planned as per the recommendations suggested in a recent international Delphi consensus among experts for outcomes in ASUC.[13] The outcomes studied included clinical response, remission, and need for colectomy with tofacitinib and upadacitinib in the short, intermediate, and long term. Subgroup analysis was done based on dosages used and on the type of JAK inhibitor used. High-dose tofacitinib was defined as an off-label dose of more than 10 mg twice a day. The standard dose tofacitinib group was those who used 10 mg twice a day regimen. High-dose upadacitinib is denoted off-label more than 45 mg daily (commonly 30 mg twice a day) until response and shift to 45 mg once a day. Standard dose upadacitinib is denoted as 45 mg once a day.

Data Synthesis

The analyses were performed using R version 4.3.0.[14] The packages 'meta' and 'metafor' were used in addition to the base R package. We calculated the pooled rates of clinical response, clinical remission, and colectomy. We also calculated the pooled rates of adverse events. The pooled rates were estimated using an inverse variance approach using a random effects model after logit transformation. The heterogeneity was reported using I^2 and P values. We performed meta-regression analyses for outcomes of short-term clinical response and colectomy to explore potential sources of heterogeneity across the studies. Study-level covariates were assessed in univariable models using log odds ratios (ORs) for outcomes. A statistically significant regression coefficient was denoted by $P < .05$.

Risk of Bias Assessment

The risk of bias assessment for the study was done using Joanna Briggs's Critical Appraisal Tool for case-series.[15] Two reviewers (AJ and AC) independently assessed the risk of bias of the included studies on the use of JAK inhibitors in ASUC. If there was any difference in risk of bias assessment, a third reviewer (VS) settled the discrepancy by mutual discussion. Publication bias of the included studies was also assessed.

What You Need to Know

Background

Janus kinase (JAK) inhibitors are being used as off-label treatment in acute severe ulcerative colitis (ASUC). Because patients with ASUC are excluded from clinical trials, the efficacy of JAK inhibitors has been unclear.

Findings

In the short term (<1 month), intermediate term (<3 months), and long term (3–12 months), JAK inhibitors are effective and safe in the treatment of ASUC as rescue therapy. Tofacitinib and upadacitinib had similar outcomes in the ASUC setting.

Implications for patient care

JAK inhibitors should be considered as a rescue option in ASUC or as an adjunct to corticosteroids and could improve the management of ASUC.

Results

After searching the databases, we screened 1359 articles. After removing 518 duplicates, 779 studies were excluded for lack of relevance before the manual screen. Twenty-seven studies were excluded after full-text screening. Finally, 35 studies (664 patients) on the use of JAK inhibitors in ASUC were included. Details of the included studies are shown in Table 1.[16–50] The details of the excluded studies are shown in

Table 1. Details of the Included Studies in the Meta-Analysis

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
Berinstein JA, 2021[16] U.S.	40 adults	Tofacitinib (standard and high doses)	First line with concomitant steroids (experienced)	Mean age, 34.41 y Females, 24	Duration of IBD, 10.3 y	Prior biological use: 40 Infliximab: 34 Adalimumab: 16 Vedolizumab: 21 Ustekinumab: 1 Golimumab: 2	Intermediate: Rescue: 17 Readmission: 9 Colectomy: 6 (3 mo)
Berinstein JA, 2024[17] U.S.	25 adults	Upadacitinib (standard and high doses)	First line in combination with IV steroids (both bio-naive and experienced)	Age, 40.3 (14.6) y Females: 12	Duration of IBD, 9.8 ± 24.5 y Left-sided colitis: 6 Pancolitis: 19	Infliximab: 16 Adalimumab: 5 Golimumab: 1 Vedolizumab: 8 Ustekinumab: 4	Short: Colectomy: 4 (5.8 d) Intermediate: Remission: 15 Readmission: 3 Colectomy: 6 (54 d)
Chung CS, 2025[18] Taiwan	5 adults	Upadacitinib (standard dose)	Second/third line 4 patients: IV steroid failed; 1 patient: IV steroid and infliximab failed (both bio-naive and experienced)	Median age, 38.9 y Males: 5	Disease duration, 3.44 ± 3.30 y Pancolitis: 4 Left-sided colitis: 1	Three biologicals exposure: 2 Four biologicals exposure: 1 Two biologicals exposure: 1	Short: Response: 5 (2 wk) Intermediate: Response: 5 Remission: 4 Colectomy: 0 (12 wk) Readmission: 0
Constant BD, 2022[19] U.S.	11 children	Tofacitinib (standard and high doses)	Third line All patients failed IV steroids and anti-TNF (both bio-naive and experienced)	Median age, 17 y (range, 12–18 y) Females: 27%	Median disease duration, 0.7 y (range, 0–1.5 y) Pancolitis: 10	Infliximab: 8 Adalimumab: 2 Vedolizumab: 3	Short: Colectomy: 2 (20.5 d) Intermediate: Remission: 0 Readmission: 3 Colectomy: 3 (90 d) Long: Response: 6 Colectomy: 5 (6 mo)
Costaguta G, 2023[20] Canada	6 children	Tofacitinib (standard dose)	Third line after IV steroids and infliximab (biological experienced)	Mean age, 14.6 y Females: 2	Disease duration, 2–46 mo PUCAI scores from 65 to 85 on admission	Infliximab: 6 Adalimumab: 1 Vedolizumab: 2 Ustekinumab: 1 Azathioprine: 3	Short: Response: 6 Long: Response: 5 Remission: 4 (8.5 mo)

Table 1. Continued

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
Dalal RS, 2023[21] U.S.	9 adults	Upadacitinib (standard dose)	Second/third line 7 patients refractory to IV steroids; 3 failed infliximab (both bio-naive and experienced)	Median age, 33 y (IQR, 25–53 y) Females: 6	Median disease duration, 5 y (IQR, 2–11 y)	Infliximab exposure: 7 Vedolizumab exposure: 3	Short: Response: 8 Colectomy: 1 (9 d) Intermediate: Response: 6 Remission: 6 Colectomy: 1
Eqbal A, 2022[22] Australia	11 adults	Tofacitinib (high dose)	Third line All patients were IV steroid- and infliximab-refractory (biological experienced)	Mean age, 29.6 y Females: 2	Disease duration, newly diagnosed to 14 y	Infliximab exposure: 6 Vedolizumab exposure: 3	Short: Response: 9 Colectomy: 2 Intermediate: Response: 9 Colectomy: 2 Rescue: 1 Long: Rescue: 2
Etchegaray A, 2025[23] Australia	5 adults	Upadacitinib (standard dose)	Third line All patients were IV steroid- and infliximab-refractory (both bio-naive and experienced)	Mean age, 31.6 y	Median disease duration, 12.6 mo (IQR, 0.26–59.7 mo) Pancolitis: 2 Left-sided colitis: 3	Infliximab exposure: 1	Short: Response: 3 Colectomy: 2 (15 d) Intermediate: Remission: 3 (3 mo)
García MJ, 2024[24] Spain	13 adults	Tofacitinib (standard dose)	Third line All failed first-line steroids and second-line of infliximab or cyclosporine (biological experienced)	Median age, 34.9 y (IQR, 26.4–46.7 y)	Pancolitis: 51 Left-sided colitis: 24 Proctitis: 3	Prior immunomodulator exposure: 13	Intermediate: Response: 9 Remission: 7 Colectomy: 4 Long: Response: 3 Remission: 3
Gilmore R, 2022[25] Australia	5 adults	Tofacitinib (high dose)	Third line All patients were IV steroid- and infliximab-refractory (biological experienced)	Mean age, 22 y Males: 5	–	Infliximab exposure: 3 Vedolizumab exposure: 1	Short: Response: 4 Colectomy: 1 (3 d) Intermediate: Response: 3 Remission: 2 Rescue: 1 Colectomy: 1 (3 mo)

Table 1. Continued

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
Gilmore R, 2023[26] Australia	6 adults	Upadacitinib (standard dose)	Third line All patients were IV steroid- and infliximab-refractory (biological experienced)	Mean age, 32.6 y Females: 2	Disease duration, 1–38 y Pancolitis: 5 Left-sided colitis: 1	Infliximab exposure: 6 Vedolizumab exposure: 4 Golimumab exposure:1	Short: Response: 6 Intermediate: Response: 5 Remission: 4 Colectomy: 1 (15 wk)
Honap S, 2025[27] UK	44 adults	Tofacitinib (standard and high doses)	First/second line Adjunct to IV steroids or salvage to steroids (both bio-naive and experienced)	–	–	–	Short: Response: 24 (3–7 d) Intermediate: Response: 24 Remission: 21 Colectomy: 9 (98 d) Long: Response: 17 Remission: 15 Colectomy: 12 (182 d)
	42 adults	Upadacitinib (standard and high doses)					Short: Response: 35 (3–7 d) Intermediate: Response: 19 Remission: 15 Colectomy: 8 (98 d) Long: Response: 12 Remission: 12 Colectomy: 11 (182 d)
Khoo J, 2025[28] U.S.	6 children	Upadacitinib (standard dose)	Second line with or without steroids Refractory to anti-TNF (biological experienced)	Age, 12–16 y	Disease duration, 2–34 mo	–	Short: Response: 4 Colectomy: 2 (1 mo) Intermediate: Response: 2 Remission: 2 Colectomy: 2

Table 1. Continued

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
Komeda Y, 2023[29] Japan	8 adults	Tofacitinib (standard dose)	Second line after IV steroid failure (both bio-naive and experienced)	Median age, 47.1 y (range, 19–65 y) Males: 4	Median disease duration, 4 y (IQR, 0–20 y) Pancolitis: 8	Previous azathioprine: 1	Short: Response: 6 Colectomy: 1
Lee C, 2025[30] Australia	5 adults	Upadacitinib (standard dose)	Third line Steroid- and TNF-inhibitor-refractory ASUC (both bio-naive and experienced)	Age, 31.6 y Males: 2		Previous anti-TNF: 3	Short: Response: 5 Colectomy: 0
Malakar S, 2023[31] India	8 adults	Tofacitinib (standard dose)	Second line after failed IV steroids (biological experienced)	Mean age, 39 ± 15 y Females: 87.5%	Median disease duration, 24 mo (IQR, 12–120 mo) Pancolitis: 7 Left-sided colitis: 1	Prior thiopurine: 7 Infliximab exposure: 1 Vedolizumab exposure: 1	Short: Response: 7 Colectomy: 1 (10 d) Long: Response: 6 Rescue: 1 Colectomy: 1 (6 mo)
Manti M, 2025[32] UK	10 adults	Upadacitinib (standard dose)	Second line after steroids (both bio-naive and experienced)	Mean age, 39.7 ± 11.7 y Males: 75%	–	Infliximab exposure: 6 Mirikizumab exposure: 1 Vedolizumab exposure: 4 Adalimumab exposure: 2 Ustekinumab exposure: 2 Prior thioprine: 8	Short: Response: 10 Colectomy: 0 (4 wk) Intermediate: Remission: 3
Mingazov AF, 2023[33] Russia	12 adults	Tofacitinib	Third line after steroids and anti-TNF (both bio-naive and experienced)	Mean age, 35 y (IQR, 29–48 y) Females: 28	Duration of disease, 12 mo (IQR, 2–50 mo) Pancolitis: 65 Left-sided colitis: 6	Prior thiopurines: 23 Prior anti-TNF: 9 Prior anti-integrin: 2	Short: Response: 11 Colectomy: 1 (7 d)
Mundhra S, 2023[34] India	9 adults	Tofacitinib	Second line after failed IV steroids (both bio-naive and experienced)				Short: Response: 8

Table 1. Continued

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
Narula N, 2025[35] Canada	24 adults	Tofacitinib (standard dose)	Second line after IV steroids (biological experienced)	Mean age, 42.5 y (SD, 17.3 y) Females: 11	Disease duration, 3 y (IQR, 6 y) Pancolitis: 18 Extensive colitis: 4 Left-sided colitis: 2	Anti-TNF exposure: 8 Vedolizumab exposure: 2 Ustekinumab exposure: 2	Short: Response: 14 Remission: 5 Colectomy: 4 (7 d) Intermediate: Response: 9 Remission: 9 Colectomy: 6 Long: Response: 8 Remission: 7 Colectomy: 6 (52 wk)
Parra-Izquierdo V, 2024[36] Colombia	6: 1 child and 5 adults	Tofacitinib (both standard and high doses)	Second/third line after steroids and anti-TNF (both bio-naive and experienced)	Mean age, 33.2 y (SD, 8.5 y) Males: 5	Disease duration, 2.7 ± 2.2 y Pancolitis: 3 Left-sided colitis: 3	Prior 1 biological exposure: 2 Prior 2 biological exposure: 1	Short: Response: 6 Long: Response: 1 Remission: 3 Rescue: 2 Colectomy: 0
Patel PV, 2025[37] U.S.	5 adolescents	Upadacitinib (high dose)	First line along with IV steroids (biological experienced)	Age, 14–18 y Females: 2	Pancolitis: 2 Extensive colitis: 1 Left-sided colitis: 2	Infliximab exposure: 3 Adalimumab exposure: 1	Short: Response: 3 Rescue: 2 Colectomy: 0
Resal T, 2023[38] Multiple countries	106 adults	Tofacitinib (high dose)	Second/third line after steroids and anti-TNF (both bio-naive and experienced)	Mean age, 38 y (IQR, 29–48 y) Males: 45	Disease duration, 8 y (IQR, 5–12 y) Pancolitis: 69 Left-sided colitis: 34 Proctitis: 3	Infliximab exposure: 74 Adalimumab exposure: 37 Vedolizumab exposure: 64 Golimumab exposure: 1 Ustekinumab exposure: 9 Prior azathioprine: 5 Prior methotrexate: 2	Intermediate: Remission: 28 Colectomy: 8 (12 wk) Long: Remission: 36 Colectomy: 16 (52 wk)
Rose B, 2022[39] UK	5 children	Tofacitinib (standard dose)	First/second line with steroids or after steroids (both bio-naive and experienced)	Mean age, 11.2 y Females: 4	Pancolitis: 5	Prior at least 2 biologicals exposure: 4	Intermediate: Remission: 3 Readmission: 0 Colectomy: 0 (90 d) Long: Remission: 3 Colectomy: 1 (9.8 mo)

Table 1. Continued

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
Schreiber-Stainthorp W, 2024[40] U.S.	14 adults	Upadacitinib (standard dose)	First line with IV steroids (both bio-naive and experienced)	Median age, 30 y (IQR, 25.5–36 y) Males: 7	Median disease duration, 72 mo (IQR, 14–180 mo) Pancolitis: 10 Left-sided colitis: 2 Proctitis: 2	Prior at least 2 biologicals exposure: 1 Prior at least 1 biological exposure: 1	Short: Response: 13 Colectomy: 1 Intermediate: Response: 9 Readmission: 2 Colectomy: 4 (90 d)
Sierra Ausin M, 2025[41] Spain	9 adults	Tofacitinib (high dose)	Third line after IV steroids and anti-TNF (both bio-naive and experienced)	Age, 64.57 y (IQR, 21–92 y)	-	Prior at least 1 biological exposure: 3	Short: Response: 6 Colectomy: 3 Long: Response: 4 Rescue: 1 Colectomy: 4 (12 mo)
Singh A, 2024[42] India	53 adults	Tofacitinib (high dose)	First line with IV steroids (both bio-naive and experienced)	Median age, 37 y (IQR, 26–47 y) Males: 29	Median disease duration, 3 y (IQR, 2–5 y) Pancolitis: 14 Left-sided colitis: 35 Proctitis: 4	Anti-TNF exposure: 3 Prior azathioprine exposure: 8	Short: Response: 44 Rescue: 6 Colectomy: 1 Intermediate: Colectomy: 2 (90 d)
Singh A, 2025[43] India	9 adults	Tofacitinib (dose: NA)	Second line after IV steroids (both bio-naive and experienced)	–	–	–	Short: Colectomy: 0
St-Pierre J, 2024[44] U.S.	10 adults	Upadacitinib (standard dose)	Second/third line After IV steroids failure (both bio-naive and experienced)	Age, 21–78 y Females: 4	–	Prior at least 2 biologicals exposure: 8	Short: Response: 5 Rescue: 2 Colectomy: 3 Intermediate: Colectomy: 5 Long: Remission: 2 Colectomy: 5 (6 mo)
Unal Gulsen N, 2025[45] Turkey	31 adults	Upadacitinib (dose: NA)	Third line All patients failed IV		Mean disease duration,		Short: Response: 16

Table 1. Continued

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
			steroids and infliximab (both bio-naive and experienced)	Mean age, 36 ± 13 y Females: 16	6.9 ± 5.4 y Pancolitis: 26	Anti-TNF exposure: 12 Prior at least 3 biologicals exposure: 10	Colectomy: 2 (4 wk) Intermediate: Response: 12 Colectomy: 6 (8 wk) Long: Response: 10 Colectomy: 6 (16 wk)
Uzzan M, 2021[46] France	55 adults	Tofacitinib (standard dose)	Third line All patients failed IV steroids and infliximab (both bio-naive and experienced)	Median age, 23.6 (IQR, 18.0–33.6 y) Females: 25	Median disease duration, 4.4 y (IQR, 2.4–7.1 y) Pancolitis: 36 Left-sided colitis: 19	Prior anti-TNF use: 54 Infliximab exposure: 49 Vedolizumab exposure: 38 Ustekinumab exposure: 6	Intermediate: Response: 33 Remission: 20 Colectomy: 12 (3 mo) Long: Response: 23 Remission: 18 Colectomy: 15 (6 mo)
Xiao Y, 2022[47] Canada	8 adults	Tofacitinib (both standard and high dose)	Second/third line All patients failed IV steroids and 3 patients failed anti-TNF (both bio-naive and experienced)	Age, 32.5 y (IQR, 27.5–38.8 y) Males: 5	Disease duration, 4.0 y (IQR, 2–5.5 y) Pancolitis: 6 Left-sided colitis: 2	Anti-TNF use: 6 Anti-IL-12/23 use: 2 Anti-integrin use: 5	Short: Response: 5 Colectomy: 2 (30 d) Intermediate: Remission: 5 Colectomy: 3 (90 d) Long: Remission: 3 Rescue: 1 Colectomy: 3 (6 mo)
Yerushalmy-Feler A, 2025[48] Multicenter (Europe, North America)	22 children	Upadacitinib (standard dose)	Second/third line After IV steroids and anti-TNF use (biological experienced)	Age, 15.7 y Females: 9		Prior infliximab: 22 Prior adalimumab: 4 Prior vedolizumab: 10 Prior ustekinumab: 8	Short: Colectomy: 3 Intermediate: Remission: 11 Colectomy: 5 Long: Remission: 14 Colectomy: 6
Zdychyncova K, 2025[49] Czech	13 adults	Upadacitinib (mixed doses)	Second/third line After non-response to IV steroids and infliximab (both bio-naive and experienced)				Short: Response: 12 Colectomy: 1 Long: Response: 8 Colectomy: 1

Table 1. Continued

Study name with place of study	No. patients, adults/children	Drug used with dose (standard/high/both)	Line of therapy during ASUC hospitalization (biological naive/ experienced/mixed)	Demographics	Disease characteristics	Previous therapy prior admission	Outcomes: Short (<1 mo) Intermediate (<3 mo) Long (3–12 mo) (duration)
Zhang J, 2024[50] China	14 adults	Upadacitinib (high dose)	Second/third line after steroids and infliximab (both bio-naive and experienced)	Mean age, 41.7 y	Pancolitis: 12 Left-sided colitis: 2	Infliximab exposure: 14 Adalimumab exposure: 2 Vedolizumab exposure: 3 Prior azathioprine: 1	Short: Response: 14 Colectomy: 0 Intermediate: Remission: 4 Colectomy: 1 (8 wk) Long: Colectomy: 2 (16 wk)

IBD, inflammatory bowel disease; IL, interleukin; IQR, interquartile range; IV, intravenous; NA, not available; PUCAI, Pediatric Ulcerative Colitis Activity Index; SD, standard deviation; TNF, tumor necrosis factor; UK, United Kingdom; U.S., United States.

Supplementary Table 2. Nineteen studies report the use of tofacitinib, and 15 studies report the use of upadacitinib in ASUC. One study reported the use of both tofacitinib and upadacitinib. No study reported the use of filgotinib. There were 28 studies in adults, 6 studies with children, and 1 study with both. There were only 2 prospective studies among the included studies.[35,42] The definitions used for various outcomes are shown in Supplementary Table 3. The PRISMA diagram is shown in Figure 1.

Short-Term Outcomes (<1 Month)

A total of 13 studies reported short-term clinical response (<1 month) of tofacitinib in ASUC. The pooled short-term clinical response of tofacitinib was 77.9% (95% confidence interval [CI], 67.1%–86%; $I^2 = 26.5\%$). A total of 14 studies reported the short-term clinical response (<1 month) of upadacitinib in ASUC. The pooled short-term clinical response of upadacitinib in ASUC was 86.5% (95% CI, 72.3%–94.1%; $I^2 = 23.4\%$) (Figure 2).

Twelve studies reported the short-term colectomy rate (<1 month) of tofacitinib in ASUC. The pooled short-term risk of colectomy with treatment of tofacitinib in ASUC was 11.5% (95% CI, 7.1%–18.4%; $I^2 = 0\%$). Thirteen studies reported the short-term colectomy rate (<1 month) of upadacitinib. The pooled short-term risk of colectomy with treatment of upadacitinib in ASUC was 11.2% (95% CI, 7.2%–16.9%; $I^2 = 0\%$) (Figure 2).

Intermediate Outcomes (<3 Months)

Six studies reported clinical response to tofacitinib at <3 months in ASUC. The pooled clinical response of tofacitinib at <3 months in ASUC was 57.2% (95% CI, 49.2%–64.8%; $I^2 = 29.4\%$). A total of 7 studies reported clinical response of upadacitinib at <3 months in ASUC. The pooled clinical response of upadacitinib at <3 months in ASUC were 56.1% (95% CI, 39.3%–71.7%; $I^2 = 10.3\%$). (Supplementary Figure 1)

Nine studies reported clinical remission of tofacitinib at <3 months with pooled clinical remission at <3 months of 37.3% (95% CI, 28.1%–47.5%; $I^2 = 32.1\%$). A total of 10 studies reported clinical remission of upadacitinib at <3 months with pooled clinical remission at <3 months of 47.4% (95% CI, 37.6%–57.4%; $I^2 = 22\%$) (Figure 3).

Twelve studies reported the risk of colectomy with tofacitinib at <3 months and the pooled risk of colectomy at <3 months was 16.1% (95% CI, 10.9%–23.1%; $I^2 = 40.8\%$). Eleven studies reported the risk of colectomy with upadacitinib at <3 months with a pooled risk of colectomy of 21.2% (95% CI, 15.8%–27.7%; $I^2 = 0\%$) (Figure 3).

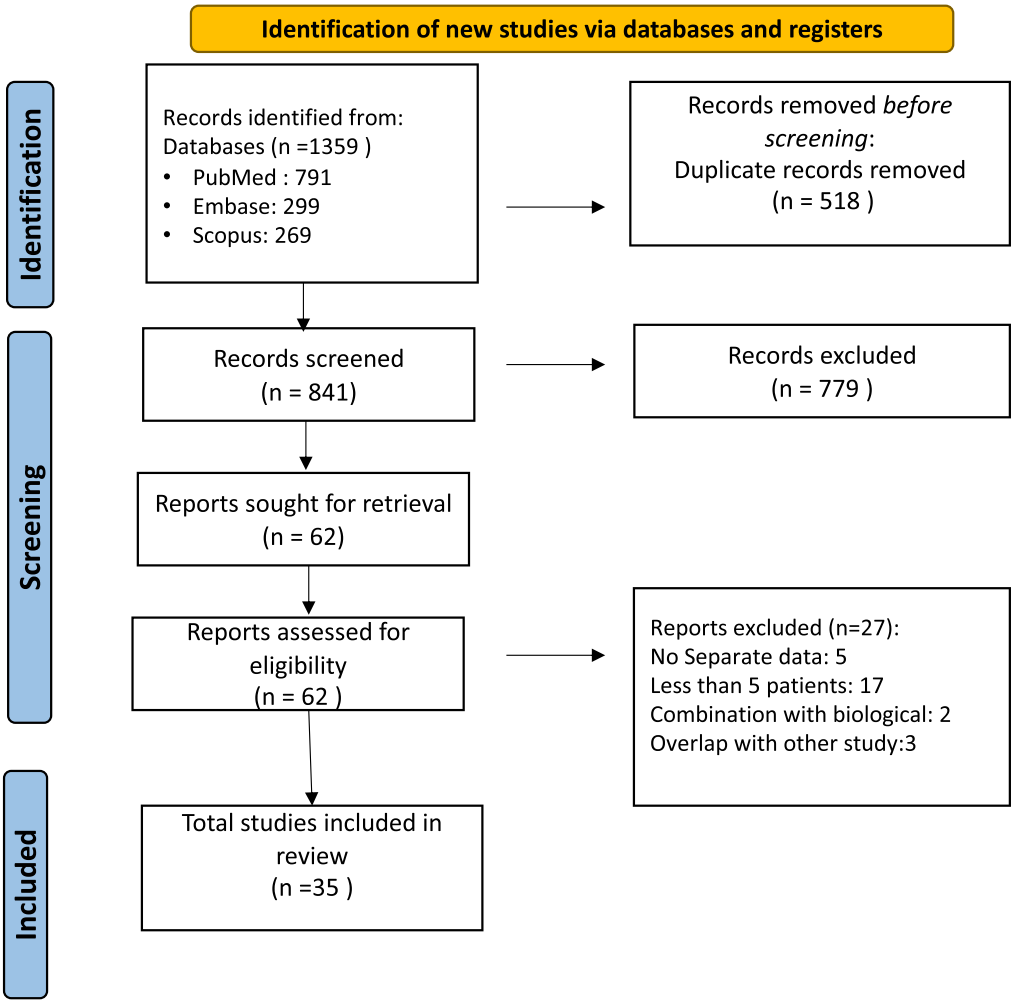

Figure 1. PRISMA diagram of the study.

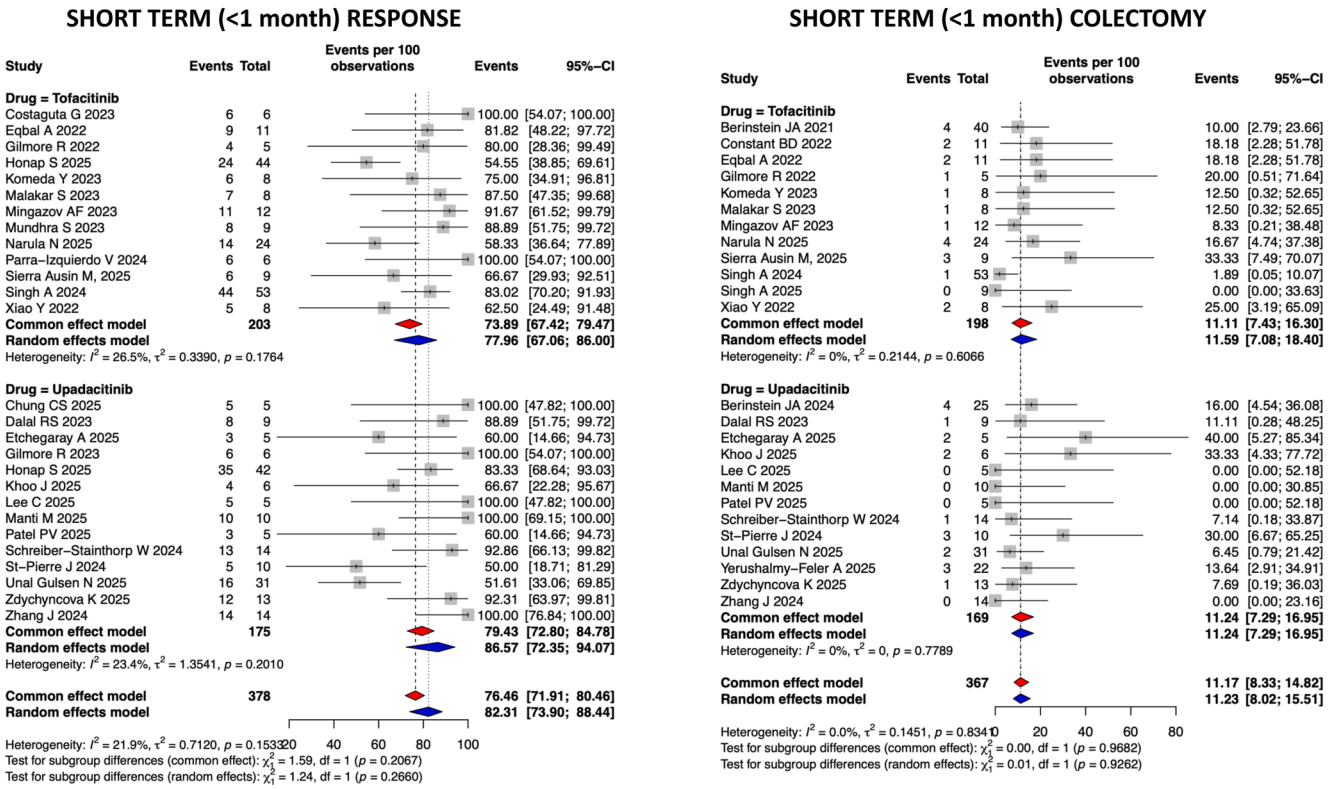

Figure 2. Short-term (<1 month) response (*left panel*) and short-term (<1 month) colectomy (*right panel*) with the use of JAK inhibitors in ASUC.

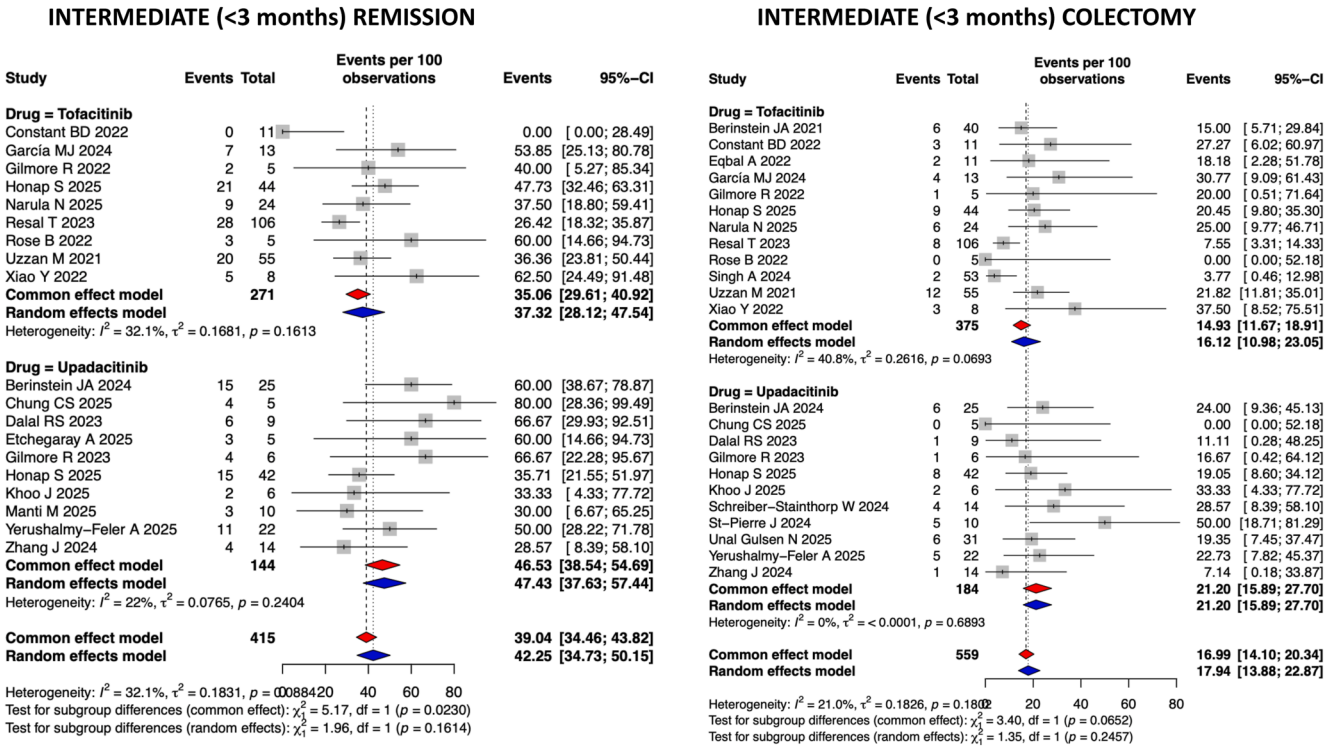

Figure 3. Intermediate (<3 months) remission (*left panel*) and intermediate (<3 months) colectomy (*right panel*) with the use of JAK inhibitors in ASUC.

Long-Term Outcomes (3–12 Months)

Nine studies reported long-term response to tofacitinib at 3 to 12 months in ASUC. The pooled long-term response of tofacitinib at 3 to 12 months was 41.4% (95% CI, 34.4%–48.8%; I^2 = 26.8%). Only 3 studies reported long-term clinical response of upadacitinib at 3 to 12 months, with a pooled long-term clinical response at 3 to 12 months of 35.1% (95% CI, 21.1%–52.2%; I^2 = 55.6%). (Supplementary Figure 2)

Ten studies reported long-term remission of tofacitinib at 3 to 12 months. The pooled long-term remission with use of tofacitinib at 3 to 12 months was 33.8% (95% CI, 28.4%–39.5%; I^2 = 0%). Only 3 studies reported long-term remission of upadacitinib at 3 to 12 months in ASUC, with a pooled long-term remission of 37.5% (95% CI, 19.1%–60.4%; I^2 = 76.3%) (Figure 4).

Twelve studies reported the long-term risk of colectomy with tofacitinib at 3 to 12 months following admission with ASUC. The pooled risk of colectomy with tofacitinib at 3 to 12 months was 22.6% (95% CI, 17.5%–28.6%; I^2 = 2.4%). Six studies reported the long-term risk of colectomy with upadacitinib at 3 to 12 months, with a pooled risk of colectomy with upadacitinib at 3 to 12 months of 23.4% (95% CI, 17.1%–31.4%; I^2 = 19.7%) (Figure 4).

Subgroup Analysis

Subgroup analysis was done as per the dosing of tofacitinib in ASUC for short-term outcomes (<1 month). The high dose of tofacitinib was used in 4 studies of ASUC, whereas the standard dose of tofacitinib was used in 4 studies. The pooled short-term clinical response (<1 month) of high-dose tofacitinib in ASUC was 80.7% (95% CI, 70.5%–88.1%; I^2 = 0%), whereas the pooled short-term clinical response (<1 month) of standard-dose tofacitinib in ASUC was 77.1% (95% CI, 50.5%–91.7%; I^2 = 0%) (Supplementary Figure 3). The pooled analysis of high-dose vs low-dose upadacitinib could not be done due to only 1 study reporting high-dose upadacitinib in ASUC.

Among children, only 3 studies reported the short-term response rates of JAK inhibitors in ASUC. The pooled short-term (<1 month) response of JAK inhibitors in ASUC was 76.4% (95% CI, 51.4%–90.8%; I^2 = 0%). Three studies reported the intermediate- and long-term remission rates of JAK inhibitors in ASUC, respectively. The pooled intermediate (<3 months) remission of JAK inhibitors in ASUC was 30.3% (95% CI, 9.4%–64.6%; I^2 = 0%). The pooled long-term (3–12 months) remission of JAK inhibitors in ASUC was 63.6% (95% CI, 46.2%–78.1%; I^2 = 0%) (Supplementary Figure 4).

Among children, 4 studies reported the short-term colectomy rate of JAK inhibitors in ASUC. The pooled short-term (<1 month) colectomy of JAK inhibitors in ASUC was 15.9% (95% CI, 7.7%–29.7%; I^2 = 0%). Three studies reported the intermediate and long-term colectomy rates of JAK inhibitors in ASUC, respectively. The pooled intermediate (<3 months) colectomy of JAK inhibitors in ASUC was 22.7% (95% CI, 12.6%–37.3%;

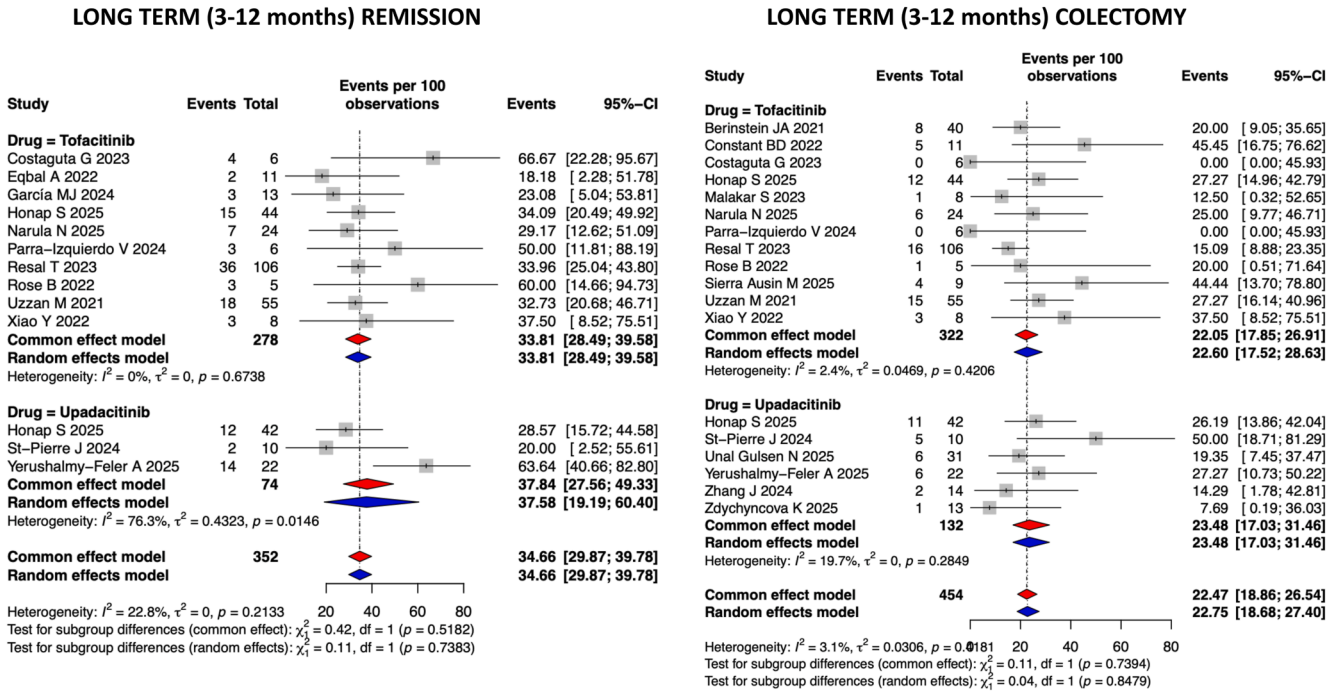

Figure 4. Long-term (3–12 months) remission (*left panel*) and long-term (3–12 months) colectomy (*right panel*) with the use of JAK inhibitors in ASUC.

I^2 = 0%). The pooled long-term (3–12 months) colectomy of JAK inhibitors in ASUC was 31.5% (95% CI, 18.8%–47.7%; I^2 = 0%) (Supplementary Figure 5).

Meta-Regression

In random-effects meta-regression of included studies, age (P = .57), proportion of female patients (P = .19), intravenous corticosteroid use (P = .53), C-reactive protein (CRP) level (P = .068), baseline albumin (P = .68), and prior anti-tumor necrosis factor (TNF) exposure (P = .08) were not associated with efficacy of JAK inhibitors in ASUC (Supplementary Table 4).

Adverse Effects

The pooled proportion of venous thromboembolism (VTE) as an adverse event of JAK inhibitors in ASUC was 2.2% (95% CI, 1.1%–4.7%; I^2 = 0%). Major adverse cardiovascular events (MACE) were seen in 2 patients with a pooled proportion of 0.7% (95% CI, 0.1%–10.3%; I^2 = 0%) with the use of JAK inhibitors. The pooled proportion of risk of infection with the use of JAK inhibitors was 8.8% (95% CI, 5.1%–15.1%; I^2 = 51.3%). The pooled proportion of risk of herpes zoster with the use of JAK inhibitors in ASUC was 3.4% (95% CI, 1.9%–6.1%; I^2 = 0%). The pooled proportion of risk of acne with the use of JAK inhibitors in ASUC was 12.9% (95% CI, 6.9%–22.7%; I^2 = 31%). The pooled proportion of lipid abnormalities with the use of JAK inhibitors was 6.3% (95% CI, 3.4%–11.4%; I^2 = 0%) (Figure 5).

There was one report of pulmonary embolism with upadacitinib (47 days after start of therapy); however, this did not lead to drug discontinuation, as the cause of embolism was attributed to heparin-induced thrombocytopenia. One patient had postoperative intra-abdominal venous thrombosis with upadacitinib. One patient on tofacitinib had dural sinus thrombosis. There was 1 death reported in an 81-year-old male who had tofacitinib for 1 week with comorbidities, who succumbed 17 days after colectomy. The mortality was not attributed to tofacitinib use, as it was stopped 19 days before surgery. There was 1 death reported where a 47-year-old on tofacitinib did not respond to treatment and did not consent to colectomy. One patient, a 34-year-old female, died of pneumonia after 1 month of follow-up with an initial response to tofacitinib. Another 76-year-old female patient died of pneumonia 1 month after starting therapy with a JAK inhibitor. One patient on tofacitinib became pregnant after 18 weeks of therapy and was switched to vedolizumab. She had a spontaneous abortion at week 21. The detailed adverse events profile of the included studies is in Supplementary Table 5.

Risk of Bias Assessment

The risk of bias of included studies for the effectiveness of JAK inhibitors in patients with ASUC is summarized in Supplementary Table 6. As the Joanna Briggs guidance suggests against using a score cutoff for quality assessment, we also did not score the studies. The majority of the studies described demographics as well as clinical information of the included patients. The majority of the studies did not include consecutive

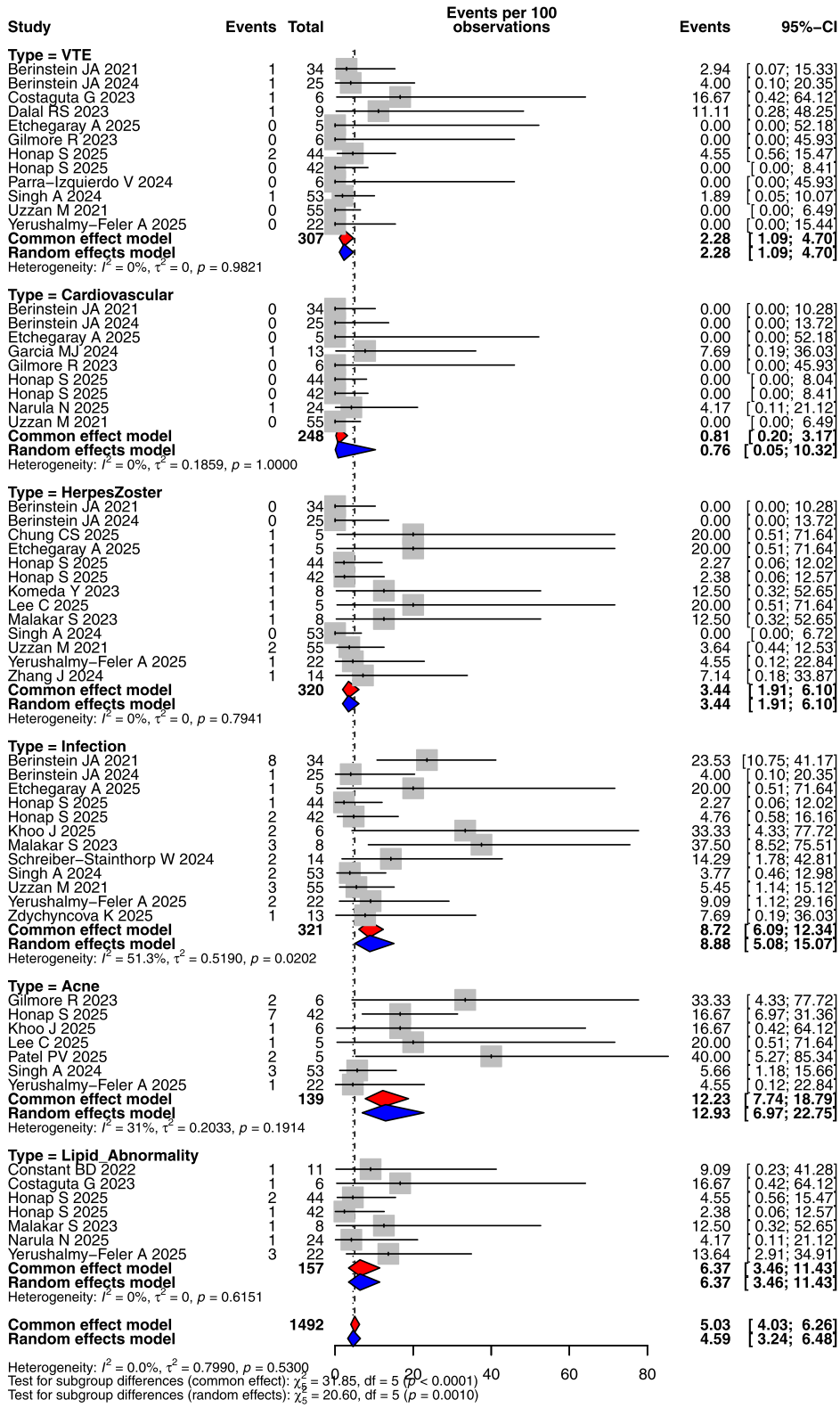

Figure 5. Forest plot showing pooled proportion of adverse events with the use of JAK inhibitors in ASUC.

patients with ASUC, as they were retrospective in nature. For a meta-analysis of proportion data, funnel plot and Egger's tests are not deemed to be appropriate tests.[51] Therefore, we performed a Trim and Fill plot, which suggested a publication bias (Supplementary Figure 6). The Difference of Means/Effects Index (DOI) plot also suggested an asymmetry with an Luis Furuya-Kanamori (LFK) index of 5.54, hinting at publication bias or small study effect[52] (Supplementary Figure 7).

Discussion

The rapidity of action, combined with a short half-life, has made JAK inhibitors an attractive proposition

either as a co-therapy with corticosteroids or as a salvage therapy option in the setting of ASUC. The present study showed a good short-term response (tofacitinib 77.9% and upadacitinib 86.5%) at <1 month with a pooled colectomy rate of 11.5% with tofacitinib and 11.2% with upadacitinib. There was not much difference in outcomes at 1 month with the high dose as compared with the standard dose of tofacitinib in ASUC. In the intermediate term (<3 months), the pooled clinical response, remission, and colectomy rates with tofacitinib and upadacitinib were 57.2%, 37.3%, 16.1% and 56.1%, 47.4%, 21.2%, respectively. In the long term (3–12 months), the pooled clinical response, remission, and colectomy rates with tofacitinib and upadacitinib were 41.4%, 33.8%, 22.6% and 35.1%, 37.5%, 23.4%, respectively. The adverse events reported were VTE and infections, but were seen in a minority of patients. Herpes zoster infection was reported as an adverse event of JAK inhibitors in 3.4% only, who had a good recovery with antivirals. Although upadacitinib may be more potent than tofacitinib for the induction of clinical remission in moderate to severe UC, in our analysis, tofacitinib and upadacitinib had similar outcomes in the setting of ASUC.[53]

An earlier network meta-analysis of rescue therapies (6 randomized controlled trials and 15 cohort studies, including 2004 patients) in ASUC, included 1 study (13 patients) on tofacitinib, revealed a reduction in short-term colectomy rates with tofacitinib, accelerated infliximab, infliximab, and tacrolimus.[54] The pooled OR for short-term colectomy of tofacitinib was 9% (95% CI, 2%–52%). It was similar to the findings of the present study (11.5%). They, however, could not do the dose-based analysis due to limited studies on tofacitinib at that time. Later, in a systematic review (134 patients) on tofacitinib in ASUC, no difference in 90-day colectomy rate between 30 mg/d dose and 20 mg/d dose of tofacitinib was identified.[55] In a previous systematic review on upadacitinib, the pooled colectomy rate at 90 days was 16.3%, which was similar to our findings (21.2%).[56]

There were 3 studies where JAK inhibitors were used as upfront first-line therapy along with intravenous steroids in patients with ASUC.[17,40,42] The rest of the studies used JAK inhibitors either as rescue therapy or did not give separate data for the timing of the use of JAK inhibitors following admission. In view of the limited studies on JAK inhibitors as first-line treatment in ASUC, the comparative analysis of first-line vs rescue could not be done. Similarly, all studies on the use of JAK inhibitors in ASUC were either on biological experienced patients or a mixed subset of bio-naive and biological experienced patients. This will be pertinent to study the effect of JAK inhibitors in bio-naive vs biological experienced patients with ASUC.

Upadacitinib is effective in cases of tofacitinib failure in UC in a case series.[57] Upadacitinib was effective in induction in cases of medically refractory UC after tofacitinib failure, but there was no additional benefit on maintenance.[58] A large retrospective study of 131 patients with UC showed the effectiveness of a second JAK inhibitor when there was an inadequate response to the first JAK inhibitor.[59] However, in the setting of ASUC, whether upadacitinib is superior to tofacitinib is unclear. Our finding that tofacitinib and upadacitinib were similar in effectiveness in outcome in ASUC was also shown in a study from Australia, which reported no significant difference in colectomy rates in index admission and at 12 months follow-up.[60] These findings are similar to a multicenter study done in 111 patients from the United Kingdom.[27] They showed similar effectiveness and safety profiles between upadacitinib and tofacitinib.

There are concerns of adverse events with the use of JAK inhibitors. The real-world safety observations on the use of JAK inhibitors in patients with ASUC should be interpreted in the context of high-risk clinical settings: a population that is typically sicker, treatment-refractory, and exposed to multiple therapies than those enrolled in clinical trials. Adverse events like infections, embolism, and thrombosis have been associated with tofacitinib.[61] The use of upadacitinib has been associated with adverse events like hepatic dysfunction, neutropenia, acne, and herpes zoster in systematic review of randomized controlled trials of upadacitinib.[62] There was 1 report of pulmonary embolism and another report of postoperative abdominal thrombosis with the use of upadacitinib in ASUC.[17,21] However, both cases had additional risk factors for the thrombosis event. Herpes zoster is one of the concerns when prescribing JAK inhibitors, especially in patients with ASUC.[63,64] A recent study showed a lower risk of overall postoperative complications in patients who underwent colectomy on tofacitinib as compared with infliximab.[65]

Among children, tofacitinib is increasingly used as therapy in refractory inflammatory bowel disease (IBD).[66,67] A study has also reported the efficacy of upadacitinib in refractory IBD in children.[68] Six studies reported the efficacy of JAK inhibitors in ASUC in children in our systematic review. The drug was tolerated well, with only 1 patient developing peripherally inserted central catheter thrombosis with upadacitinib. A recent study on the use of upadacitinib in ASUC reported steroid-free clinical remission in 64% by the end of 26 weeks.[48] Prospective multicenter studies of JAK inhibitors are warranted for real-world evidence in ASUC in children.

This systematic review is the largest so far describing the effectiveness and adverse events of JAK inhibitors in the setting of ASUC. Both tofacitinib and upadacitinib were included to give an overall estimate of effectiveness. The outcomes (response, remission, and colectomy) were analyzed based on short term (<1 month), intermediate (<3 months), and long term (3–12 months). The dosing regimens (high vs standard dose) of JAK inhibitors were also compared.

This systematic review has certain limitations. There is heterogeneity in the treatment protocols for the use of

JAK inhibitors in the management of ASUC. The use of steroids as a first line either along with JAK inhibitors or as a tapering dose as part of rescue therapy with JAK inhibitors, can be a confounding factor. The ongoing placebo-controlled randomized trial called the ACESO study (ISRCTN;17100156) may provide data on the role of co-therapy with steroids. An important limitation is the heterogeneity in methodological rigor across the included studies, from small case reports with <5 patients to retrospective cohorts and only 2 prospective trials. This variability reflects the current evidence base for JAK inhibitor use in this setting, where off-label prescribing has largely preceded the availability of robust prospective data. Inclusion of lower-level evidence was necessary to capture the full scope of real-world clinical experience and emerging safety and efficacy signals. We could not compare the outcomes based on biological exposure, as limited studies were reporting exclusively on bio-naive patients. There was heterogeneity in the definitions of outcomes like partial Mayo score, Physician Global Assessment, and Pediatric UC Activity Index, with different assessment windows. The outcomes ranged from clinical improvement to a stringent endpoint of steroid-free clinical remission. These differences may lead to variability in reported efficacy and limit direct comparability across the studies. Finally, the data on long-term outcomes were limited, particularly for upadacitinib.

Conclusion

To conclude, JAK inhibitors (tofacitinib and upadacitinib) are promising and effective options in the management of patients with ASUC with good rates of clinical response and remission and low colectomy rates at short- (<1 month), intermediate- (<3 months), and long-term (3–12 months) follow-up. There are minor concerns of VTE and infections, including herpes zoster, with the use of JAK inhibitors 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.2026.02.006.

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