Journal of Crohn's and Colitis, 2023, **17**, 1354–1363
https://doi.org/10.1093/ecco-jcc/jjad036
Advance access publication 1 March 2023
Review Article

Tofacitinib for Acute Severe Ulcerative Colitis: A Systematic Review

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Abstract

Background: Tofacitinib has emerged as a new potential treatment for acute severe ulcerative colitis [ASUC]. We conducted a systematic review to assess efficacy, safety and integration in ASUC algorithms.

Methods: Systematic searching was done in MEDLINE, EMBASE, Cochrane Library and Clinicaltrials.gov until August 17, 2022, including all studies reporting original observations on tofacitinib for ASUC, preferably defined according to Truelove and Witts criteria. The primary outcome was colectomy-free survival.

Results: Of 1072 publications identified, 21 studies were included of which three were ongoing clinical trials. The remaining comprised a pooled cohort originating from 15 case publications [*n* = 42], a GETAID cohort study [*n* = 55], a case-control study [*n* = 40 cases] and a paediatric cohort [*n* = 11]. Of these 148 reported cases, tofacitinib was used as second-line treatment after steroid failure in previous infliximab failures or third-line after sequential steroid and infliximab or cyclosporine failure, 69 [47%] were female, median age range was 17–34 years and disease duration was 0.7–10 years. Overall, 30-day colectomy-free survival was 85% [*n* = 123 of 145; *n* = 3 without colectomy had follow-up <30 days], 90-day 86% [*n* = 113 of 132; *n* = 16 follow-up <90 days] and 180-day 69% [*n* = 77 of 112; *n* = 36 follow-up <180 days]. Tofacitinib persistence at follow-up was 68–91%, clinical remission 35–69% and endoscopic remission 55%. Adverse events occurred in 22 patients, predominantly being infectious complications other than herpes zoster [*n* = 13], and resulted in tofacitinib discontinuation in seven patients.

Conclusion: Tofacitinib appears promising for treatment of ASUC with high short-term colectomy-free survival among refractory patients who are otherwise deemed to require colectomy. However, large high-quality studies are needed.

Key Words: Tofacitinib; JAK inhibitor; acute severe ulcerative colitis; ulcerative colitis; Truelove and Witt; Lichtiger score

1. Introduction

Acute severe ulcerative colitis [ASUC] is a potentially life-threatening, medical emergency that occurs in ~25% of patients.[1–3] It requires hospital admission and urgent treatment at a specialist facility.[1–3] The condition is defined by Truelove and Witts criteria comprising at least six bloody stools per day and with features of systemic toxicity.[4] The mainstay of initial treatment is intravenous [iv] corticosteroids with about two-thirds responding.[5,6] Rescue therapy for steroid-refractory ASUC is presently limited to infliximab [IFX] or cyclosporine.[3,6] Despite medical treatments, colectomy rates have remained high—~20% at first admission, 40% at second admission and 60% after 3 years.[1,5,6]

Tofacitinib is novel small-molecule agent approved as monotherapy for ulcerative colitis with inadequate response or intolerance to biologics. It targets Janus kinase [JAK] signalling, in particular JAK1 and JAK3 and, to some extent, JAK2 and tyrosine kinase [TYK] 2.[7] There has been increasing interest in use of tofacitinib as rescue therapy for ASUC in an effort to improve outcomes and provide additional medical treatment options.[8,9] Previous efforts to synthesize data have been hampered by very limited data at time of review.[10,11] There are several potential advantages including oral administration, high potency, rapid onset of action along with rapid clearance [i.e. quick in, quick out], less susceptibility to drug loss related to hypoalbuminaemia, no immunogenicity and treatment effects independent of prior responses to biologics.[7–10,12,13] On the other hand, effectiveness for this indication has not yet been established and there may be safety issues, for example infections due to excessive immunosuppression or thromboembolisms—a known potential side effect to tofacitinib that may be aggravated by the prothrombogenic state present during ASUC.[8,9,14] Here we provide a systematic review of currently available reports on tofacitinib for ASUC and summarize data on efficacy, safety and how treatment was integrated in current ASUC guidelines.

2. Methods

2.1. Inclusion and exclusion criteria

Studies were included if reporting on use of tofacitinib for treatment of hospitalized patients with ASUC preferably defined according to Truelove and Witts criteria for acute exacerbations of severe ulcerative colitis at time of admission.[4,6] All study types reporting original data were included without any restrictions except exclusion of non-English-language articles.

2.2. Search strategy

We systematically searched for publications reporting on tofacitinib for ASUC in MEDLINE, EMBASE, the Cochrane Library and Clinicaltrials.gov from inception to August 17, 2022. The search strategy is detailed in Supplementary Table 1. The reference lists of included studies and relevant reviews on the topic were also searched. The manufacturer [Pfizer] was also enquired but no new references were identified thereby. This systematic review was registered at the PROSPERO database [www.crd.york.ac.uk/prospero] [CRD42022359394] and complied with PRISMA guidelines.[15]

2.3. Outcomes

The primary outcome was colectomy-free survival after tofacitinib treatment of ASUC. Secondary outcomes were clinical remission, endoscopic remission and safety. As only observational studies were available, and because tofacitinib was used as last resort before colectomy, studies without a comparison group were allowed. For the same reasons, we neither required any predetermined fixed timepoints of outcome assessments, nor any predetermined formal definitions of clinical and endoscopic remission—these were reported in congruence with the original publications and preferably by standard clinical disease activity scores [e.g. full Mayo Score: maximum 12 points, remission ≤2 with no item >1; or partial Mayo Score: maximum 9 points, remission ≤1] and endoscopic disease activity scores [e.g. Mayo endoscopic subscore: maximum 3 points, remission ≤1]. Outcome data were presented for each individual publication. In addition, patient data from case reports and case series were collectively pooled and analysed as one common cohort.

2.4. Study selection

Two study investigators [C.S. and P.D.O.] independently screened all titles and abstracts for relevance based on inclusion and exclusion criteria. Full texts were retrieved, assessed for eligibility, and data extracted independently by these two investigators. Disagreements were resolved by consensus between all authors.

2.5. Data extraction

A customized data-extraction form was developed for case reports and case series reporting individual patient data and another for observational cohort studies. Authors were contacted for additional information in case of uncertainties or missing data.

2.6. Quality assessment and subgroup analysis

Quality assessment was carried out using The Joanna Briggs Institute [JBI] critical appraisal checklist for case-control studies, cohort studies and case reports, as appropriate [https://jbi.global/critical-appraisal-tools]. Risk of bias and heterogeneity was not assessed as only uncontrolled observations were available and a meta-analysis could not be carried out.

2.7. Statistical analysis

Outcomes were narratively described and summarized by descriptive statistics. A χ^2 test was used for comparisons of categorical outcomes. Outcomes retrieved from cases containing individual patient data were pooled and analysed collectively as one cohort including survival statistics and Kaplan–Meyer plots. In this analysis, two patients were colectomized due to multifocal dysplasia [after 5 and 6 months, respectively], but without treatment failure of tofacitinib and were therefore classified as such.[16,17] Statistical analyses were done in Graphpad Prism 5. Two-sided p-values <0.05 were considered statistically significant.

3. Results

3.1. Search results and study characteristics

The search strategy yielded 1040 non-duplicated publications of which 85 were potentially eligible on the basis of abstract review [Figure 1]. After retrieval, 64 of these publications were excluded predominantly because of not including ASUC patients [n = 31] or reviews without new references to original reportings on tofacitinib for ASUC [n = 25]. Of the remaining 21 studies, three were ongoing trials and 18 reported on tofacitinib for ASUC out of which one congress abstract had later been published as a full-text article.[18,19] In all, seven studies were case reports[20–26] and eight were case series reporting individual patient data from two to eight patients,[10,16,17,27–31] resulting in individual patient data from 42 patients, which were analysed as one cohort. In addition, there was three larger studies, a case-control study of 40 patients matched with 113 controls, a cohort study of 55 patients from the GETAID group, and a paediatric study of 11 patients.[19,32,33] In all, 148 ASUC patients treated with tofacitinib were eligible for inclusion. All studies except the case-control study consisted of uncontrolled observations.[32] All studies had adequate quality for inclusion according to The JBI Critical Appraisal Checklist [Supplementary Table 2].

3.2. Patient characteristics

The cohort of 42 individual cases comprised 17 [40%] females, with a median age of 34 years (interquartile range [IQR] 23–45), median disease duration 5.0 years [IQR 0.8–11.0], and seven [17%] had left-sided colitis, 14 [33%] pancolitis, and 21 [50%] unspecified left-sided or pancolitis [Supplementary Table 3].[10,16,17,20–31]

In the case-control study, 24 [60%] were female, with a median age of 34 years, median disease duration 10 years, and one [3%] had proctitis, eight [20%] left-sided colitis and 31 [78%] pancolitis [Table 1].[32] The GETAID cohort comprised 25 [46%] females, with a median age of 28 years [IQR 22–43], median disease duration 4 years [IQR 2–7], and 19 [35%] had left-sided colitis and 36 [65%] pancolitis [Table 1].[33] The paediatric cohort consisted of three [27%] females, with a median age of 17 years [range 12–18], median disease duration 0.7 years [range 0–1.5], and one [9%] had left-sided colitis and ten [91%] pancolitis [Table 1].[19]

3.3. Colectomy-free survival

The primary endpoint was colectomy-free survival following tofacitinib rescue therapy for ASUC. Pooled data from all 148 included patients revealed a global 30-day colectomy-free survival of 85% [123 of 145 patients; n = 3 without colectomy had follow-up <30 days], 90-day colectomy-free survival of 86% [113 of 132; n = 16 without colectomy had follow-up <90 days] and 180-day colectomy-free survival of 69% [77 of 112 patients; n = 36 without colectomy had follow-up <180 days].

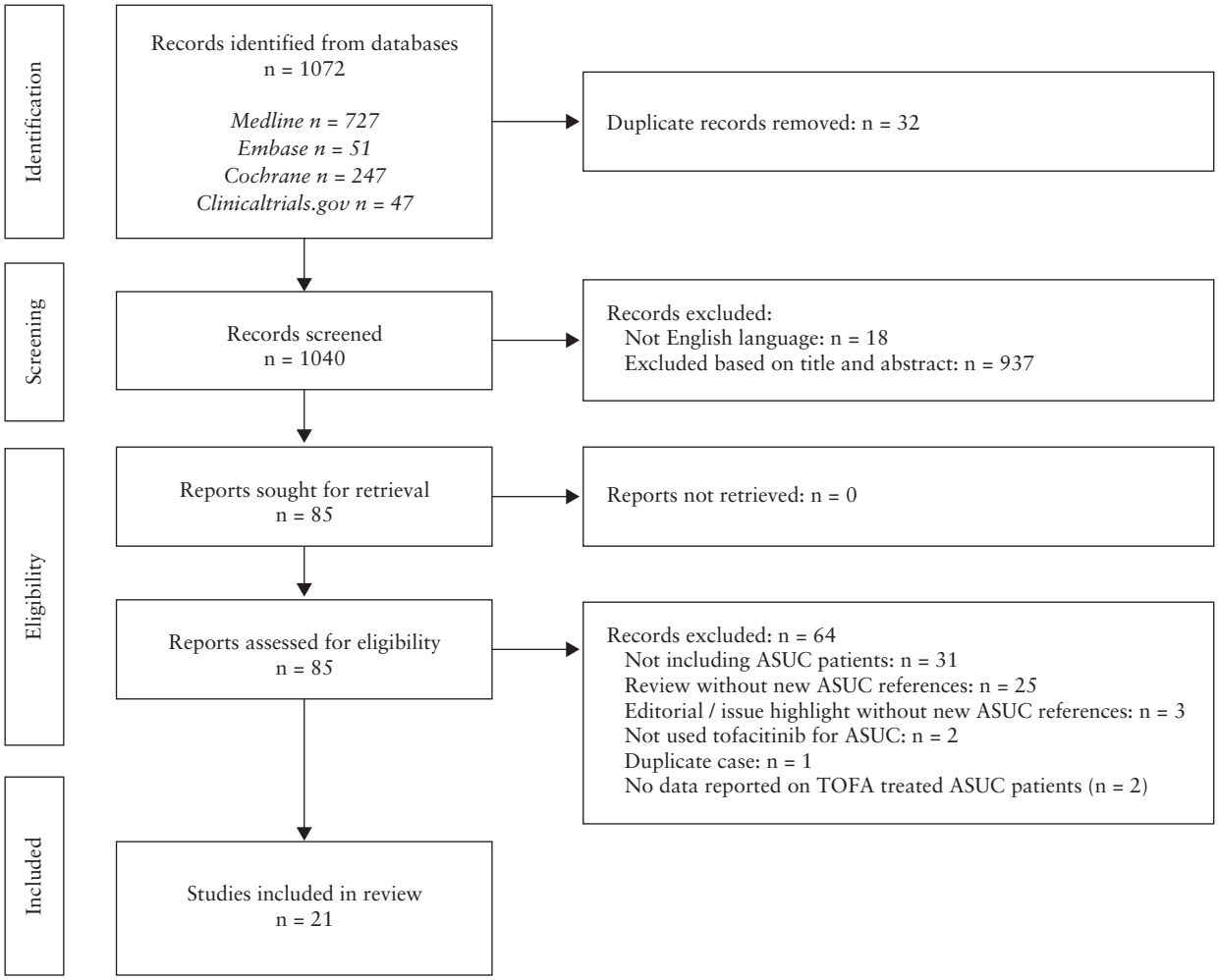

Figure 1. Study screening and selection flow diagram. Two congress abstracts were excluded as no details on tofacitinib-treated ASUC patients were provided [no response from the authors about further details despite repeat requests].[34,35]

The pooled cohort of 42 individual patient reportings had a median follow-up of 90 days [IQR 30–180] [Supplementary Table 3].[10,16,17,20–31] Nine patients [21%] were colectomized after a median of 14 days [IQR 7–30]. As shown in Supplementary Figure 1, all colectomies had been done 90 days after initiation of tofacitinib, and colectomy-free survival was 78% from 90 days onwards.

In the case-control study, 40 hospitalized patients treated with second-line tofacitinib after failure to iv steroids and with previous biologic treatment failures were compared with 113 controls matched according to gender and date [Table 1].[32] In all, 63% of the patients complied with Truelove and Witts criteria and the remaining 37% had laboratory or endoscopic features of severe disease. Four [10%] patients in the tofacitinib group vs 18 [16%, $p = 0.44$] in the control group had colectomy at day 30; six [15%] vs 23 [20%, $p = 0.64$] at day 90; and eight [20%] vs 26 [23%, $p = 0.83$] at day 180, respectively. Nevertheless, a multivariate model adjusting for variables associated with disease severity found that the 90-day risk of colectomy wassignificantly lower in the tofacitinib group (hazard ratio [HR] 0.28 [0.10–0.81], $p = 0.018$).

A combined retrospective and prospective uncontrolled cohort study from 14 GETAID centres included biologically experienced patients hospitalized because of a severe flare which in all cases was treated with tofacitinib a median of 3 days after admission [Table 1].[33] Data on patients complying with formal ASUC criteria were not provided (median Mayo score 10 [IQR 9.5–11], Mayo Endoscopic Score of 2 in 18 [33%] and of 3 in 37 [67%], median Lichtiger score 12 [IQR 9.5–13] of which 41 [75%] had a score ≥10,[36] median C-reactive protein 17 mg/L [IQR 7–66]). The primary endpoint of colectomy-free survival was 85% at day 30, 79% at day 90 and 74% at day 180.

The paediatric retrospective study of hospitalized patients with severe flare reported 90-day colectomy-free survival in eight [73%] of 11 patients, and in five [63%] of eight patients fulfilling formal paediatric ASUC criteria (Paediatric Ulcerative Colitis Activity Index [PUCAI] > 65) [Table 1].[19]

3.4. Secondary outcomes

3.4.1. Clinical and endoscopic efficacy

In all, 29 [69%] of 42 patients in the pooled cohort of individual patients had clinical remission by the end of follow-up and 16 [55%] of 29 had endoscopic remission [Supplementary Table 3].[10,16,17,20–31] Among those who avoided colectomy and continued to receive medical therapy at follow-up, 91% had clinical remission and 80% endoscopic remission.

In the GETAID cohort, outcomes at week 6 revealed 33 [60%] of 55 patients having clinical response, 25 [46%]

Table 1. Cohort studies of tofacitinib for acute severe ulcerative colits

Reference	Study design	No. of patients	Patient characteristics -Female, *n.* [%] -Age -Disease duration -Disease extent	Previous treatments	ASUC hospitalization characteristics	TOFA regimen When and how used	TOFA dosing	Time to response	Follow-up	Follow-up therapy status	Efficacy at end of follow-up -Clinical -Endoscopic -Colectomy	Safety
Berinstein[32]	Case control	40 ASUC. 113 controls [matched [gender and date]	Female $n = 24$ [60%] Age 34 years Disease duration 10 years Proctitis $n = 1$ [3%], left-sided $n = 8$ [20%], pancolitis $n = 31$ [78%]	All cases [100%] had previously received biologic therapy vs 42% of controls. Cases had higher duration of prior steroid use [51 days] vs controls [9 days].	Biologically experienced patients hospitalized for ASUC defined as need for iv steroids and meeting Truelove and Witts criteria [63% of all cases and controls] OR having laboratory or endoscopic features of severe disease [37% of all cases and controls]. Treatment with TOFA as inpatient. A mixed cohort with variable disease activity and data on patients receiving TOFA for ASUC defined according to standard criteria were not explicitly detailed [Mayo Endoscopic score 1 in $n = 1$, 3%; score 2 in $n = 10$, 26%; score 3 in $n = 28$, 72%]. None of the cases had rescue IFX or cyclosporine vs 43 patients [38%] having rescue IFX and 2 [2%] cyclosporine in the control group. CRP 62.9 mg/L Albumin 34 g/L Haemoglobin 11.71 g/dL	Cases had failure to iv steroids followed by second-line rescue TOFA. Controls had failure to iv steroids followed by rescue cyclosporine [$n = 2$, 2%], standard IFX [$n = 43$, 38%], or accelerated IFX [$n = 12$, 12%].	TOFA 10 mg BID in 16 patients [40%]. TOFA 10 mg TID in 24 patients [60%] for 3 days followed by dose reduction to 10 mg BID. Dose selection based on patient and physician comfort and preference.	Length of hospital stay 9.35 days in the TOFA group and 7.01 in the control group.	Follow-up duration 0.83 years.	At day 90, $n = 30$ [75%] remained on TOFA, $n = 6$ [15%] had been colectomized, $n = 1$ [3%] discontinued TOFA due to insurance, $n = 1$ [3%] adverse event, $n = 1$ [3%] loss of response, and $n = 1$ [3%] was lost to follow-up. 17 patients [50%] in the TOFA group and 28 [31%, $p = 0.051$] in the control group were on steroids or required increase or re-initiation of steroids during 90 days.	-Clinical: Not reported. -Endoscopic: Not reported. -Colectomy: Multivariate model adjusted for disease severity variables showing 90-day risk of colectomy significantly lower in the tofacitinib group compared with controls: HR 0.28 [0.10–0.81], $p = 0.018$. This effect was driven by TOFA 10 mg TID (HR 0.11 [0.02–0.56], $p = 0.008$) but not TOFA 10 mg BID (HR 0.66 [0.21–2.09], $p = 0.5$).	No significant differences in rates between TOFA-treated or controls of infections ($n = 8$ [24%] vs $n = 11$ [12%], $p = 0.119$), cardiovascular events [$n = 0$ vs $n = 0$, p = NA], venous thromboembolic events ($n = 1$ [3%] vs $n = 1$ [1%], $p = 0.470$), or postoperative infections after colectomy ($n = 0$ [0%) vs $n = 9$ [39%], $p = 0.065$) were observed within 90 days. Of note, no patients had anticoagulation prophylaxis.

Table 1. Continued

Reference	Study design	No. of patients	Patient characteristics -Female, *n*. [%] -Age -Disease duration -Disease extent	Previous treatments	ASUC hospitalization characteristics	TOFA regimen When and how used	TOFA dosing	Time to response	Follow-up	Follow-up therapy status	Efficacy at end of follow-up -Clinical -Endoscopic -Colectomy	Safety
Constant[19]	Retrospective uncontrolled cohort study	11	Female *n* = 3 [27%]. Age 17 years, range 12–18. Disease duration 0.7 years, range 0–1.5 Left-sided *n* = 1 [9%], pancolitis *n* = 10 [91%].	Ten patients had previously failed anti-TNF therapy with IFX [*n* = 8] or ADL [*n* = 2]. Three had non-response to VDZ.	Patients admitted to hospital for a severe flare of ulcerative colitis with failure to iv steroids [median 8 days, range 2–28] and initiation of TOFA during hospitalization. A mixed cohort with variable disease activity (PUCAI admission mean 54, SD 18; maximum 68 [12]) of which 8 fulfilled formal paediatric ASUC criteria [PUCAI > 65]. Data on patients receiving TOFA for ASUC defined according to PUCAI not explicitly detailed. Mayo endoscopic score mean 2.2 [SD 0.6]. Faecal calprotectin mean 1872 µg/g [SD 882] Haemoglobin mean 12.8 [SD 2.1], CRP 2.4 mg/dL [1.7], albumin 3.7 g/dL [0.7]	TOFA was initiated after median 11 days of admission. TOFA was used as either second-line rescue therapy [*n* = 4] or third-line rescue therapy [*n* = 7 of which *n* = 5 had second-line IFX, *n* = 1 ADL, and *n* = 1 tacrolimus].	Eight patients received 10 mg BID and three had 10 mg TID followed by tapering to 10 mg BID after 3–4 days.	Length of hospital stay median 22 days [range 5–36].	Follow-up median 182 days, range 17–461.	Duration of TOFA treatment was 171 days [range 11–450]. Patients discontinuing TOFA received the medication for a median of 71 days [range 11–171], whereas those remaining on TOFA as of last follow-up received the medication for a median of 226 days [range 174–450]. Two patients de-escalated from 10 mg BID, one to 10 mg daily [at 63 days] and the other to 5 mg BID [at 236 days]. Both remained colectomy-free.	-Clinical: PUCAI decrease in 9 patients not requiring colectomy mean 35, SD 15. -Endoscopic: Not reported.- Colectomy: Colectomy-free survival at 90 days was attained in eight [73%] of 11 patients. However, only two [18%] patients were in colectomy-free clinical remission. Among patients fulfilling criteria for ASUC, five [63%] of eight were colectomy-free at 90 days.	No side-effects observed.

Table 1. Continued

Reference	Study design	No. of patients	Patient characteristics -Female, *n.* [%] -Age -Disease duration -Disease extent	Previous treatments	ASUC hospitalization characteristics	TOFA regimen When and how used	TOFA dosing	Time to response	Follow-up	Follow-up therapy status	Efficacy at end of follow-up -Clinical -Endoscopic -Colectomy	Safety
Uzzan[33]	Retrospective [*n* = 31] and prospective [*n* = 24] uncontrolled cohort study	55	Female *n* = 25 [46%] Age 28 years, 18–34 Disease duration 4.4 [IQR 2.4–7.1] Left-sided *n* = 19 [35%] and pancolitis *n* = 36 [65%]	Previously received median 2.5 biologic agents: anti-TNF agents *n* = 54 [98%], VDZ *n* = 38 [69%], or UST *n* = 6[11%]. Cyclosporine *n* = 19 [35%].	Patients admitted to hospital for a flare of ulcerative colitis with initiation of TOFA during hospitalization and inadequate response, or loss of response, and/or intolerance to at least one anti-TNF agent, VDZ or UST. A mixed cohort with variable disease activity and data on patients receiving TOFA for ASUC defined according to standard criteria were not explicitly detailed. CRP median 17.2 mg/L [IQR 7.3–66.3] Albumin median 32 g/L [IQR 28–35] Haemoglobin median 11.4 g/dL [IQR 10–13]	TOFA was initiated after median 3 days of admission. Prior to TOFA initiation, *n* = 29 [53%] had iv steroids, *n* = 2 [4%] had IFX, and *n* = 8 [15%] had cyclosporine.	TOFA 10 mg BID in all patients. The dosage was maintained in all patients still receiving TOFA at week 6 [*n* = 43] and at week 14, *n* = 24 [77%] still had 10 mg BID and *n* = 7 [23%] received 5 mg BID.	Length of hospital stay median 14 days, IQR 8–27.	Follow-up duration median 6.5 months [IQR 3–12].	At end of follow-up, *n* = 28 [51%] still received TOFA. Survival without TOFA discontinuation was 82% at 1 month, 68% at 3 months, 45% at 6 months. Reasons for discontinuation were primary failure within 3 months [*n* = 17, 63%], secondary failure [*n* = 8, 30%], adverse events [*n* = 3, 11%].	-Clinical: at week 6, *n* = 33 [60%] had clinical response, *n* = 25 [46%] clinical remission, and *n* = 20 [38%] clinical steroid-free remission. At week 14, *n* = 23 [42%] had clinical response, *n* = 19 [35%] clinical remission, and *n* = 18 [33%] clinical steroid-free remission. -Endoscopy: Not reported. -Colectomy-free survival was 85% [76–95], 79% [69–91], and 74% [62–87] at 1, 3, and 6 months, respectively.	Two patients developed herpes zoster during TOFA therapy [one resulted in TOFA discontinuation], one patient stopped TOFA at day 3 because of unusual abdominal pain, nausea and vomiting, one patient discontinued TOFA due to recurrent viral pneumonia [history of chronic lung disease, bronchiectasis and prior recurrent infections], one patient experienced alopecia, and one had an episode of *C. difficile* infection. No thromboembolic or major adverse cardiovascular events occurred. Mortality: A 81-year-old male with history of chronic obstructive pulmonary disesae and diabetes mellitus died of infectious complications 17 days after colectomy. He was treated with TOFA for 7 days, which was stopped 19 days before colectomy. His death was considered not directly related to TOFA.

ADL: adalimumab. ASUC: acute severe ulcerative colitis. BID: twice a day. IFX: infliximab. IQR: interquartile range. PUCAI: Paediatric Ulcerative Colitis Activity Index. TID: three times a day. TOFA: tofacitinib. UST: ustekinumab. VDZ: vedolizumab.

Table 2. Adverse events reported during tofacitinib therapy for acute severe ulcerative colitis across all studies

Adverse events	No. [%] [n = 148 patients]	No. who discontinued tofacitinib because of adverse events*
Alopecia	1 [0.7]	0
Cholesterol increases necessitating statins	1 [0.7]	0
Death	1 [0.7]	1
Fatigue, body ache, abdominal pain, nausea, vomiting	2 [1.4]	2
Infections any	13 [8.8]	2
Herpes zoster	2 [1.4]	1
Rash	1 [0.7]	1
Venous thromboembolic events	1 [0.7]	0

*Reason for discontinuation not detailed in one patient.[32].

clinical remission and 20 [38%] clinical steroid-free remission [Table 1].[33] At week 14, 23 [42%] patients had clinical response, 19 [35%] clinical remission and 18 [33%] clinical steroid-free remission. Endoscopic outcomes were not assessed here.[33] Neither clinical nor endoscopic outcomes were reported in the case-control study or paediatric study.[19,32]

3.4.2. Safety

Reported side effects during tofacitinib treatment for ASUC across all included studies including a total of 148 patients are summarized in Table 2. One patient with recent COVID-19 infection and receiving tofacitinib 10 mg BID died 1 month after discharge due to sudden-onset breathlessness and hypoxaemia suggestive of pulmonary thromboembolism but this was not documented.[10] There were no cardiovascular events, cancer or postsurgical infections. The case-control study found no significant difference in side effects between tofacitinib-treated patients and controls.[32]

3.5. Characteristics of tofacitinib treatment of ASUC

3.5.1. Timing with respect to ASUC algorithm

The timing of tofacitinib in the ASUC algorithm is shown in Figure 2. The majority received second-line tofacitinib rescue therapy after initial failure to iv steroids [n = 69], and with previous failure to one or more biologics, notably IFX [n = 66, 96%]. Eighteen patients had tofacitinib as third-line rescue therapy after failure to iv steroids and IFX—12 of whom were biologically naïve [67%, $p < 0.0001$]. A few patients had third- or fourth-line tofacitinib rescue after variations of failure to steroids, IFX and cyclosporine [Figure 2]. There was no difference in colectomy rates between patients treated with second- or third-line tofacitinib (n = 17 [25%] vs n = 3 [17%], p = 0.75).

The timing of tofacitinib was not specified in the GETAID study but this cohort comprised biologically experienced patients [median 2.5 biologics per patient, 98% anti-TNF, 69% vedolizumab, 11% ustekinumab] and flares were initially treated with iv steroids [53%], cyclosporine [15%] or IFX [4%].[33] Thus, the remaining 28% had tofacitinib as first-line therapy.

3.5.2. Regimens and time to response

In the pooled cohort, induction dosage of tofacitinib was 10 mg BID [n = 26, 62%] or 10 mg TID [n = 16, 38%] [Supplementary Table 3].[10,16,17,20–31] Colectomy rates were similar between these groups (n = 5 [19%] vs n = 4 [25%], p = 0.71]. Tofacitinib maintenance dosing was 5 mg BID [n = 13], 10 mg BID [n = 8] or not specified [n = 11].

In the case-control study, 16 [40%] patients had tofacitinib induction of 10 mg BID and 24 [60%] had 10 mg TID for 3 days followed by 10 mg BID [Table 1].[32] Multivariate analysis showed tofacitinib was significantly protective against colectomy at 90 days at an induction dose of 10 mg TID (HR 0.11 [0.02–0.56], p = 0.008) but not 10 mg BID (HR 0.66 [0.21–2.09], p = 0.50). All patients in the GETAID cohort received 10 mg BID for induction; this was maintained at week 6 in all patients, and at week 14, 77% still had 10 mg BID and 23% had 5 mg BID [Table 1].[33] The paediatric cohort used 10 mg BID for induction in eight patients and three patients had 10 mg TID for 3–4 days followed by tapering to 10 mg BID; maintenance dosing was 10 mg BID except two patients tapered to 5 mg BID [Table 1].

The timespan from tofacitinib initiation to hospital discharge ranged from a few days to 3 weeks [Table 1 and Supplementary Table 3]. At end of follow-up, tofacitinib was maintained in most patients in the pooled cohort (n = 29 [91%]) [Supplementary Table 3]. Likewise, the majority maintained tofacitinib at 3 months in the case-control cohort [75%], GETAID cohort [68%] and paediatric cohort [75%] [Table 1]. Concomitant steroid usage was reported in the case-control study, being 50% at 90 days.

4. Discussion

The current treatment algorithm for ASUC has been used for almost two decades and comprises first-line therapy with iv steroids, second-line IFX or cyclosporine, and then colectomy in case of medical treatment failure.[6] There is an unmet need for more, and better, medical treatment options as colectomy rates remain high, many patients have already failed numerous biology therapies including IFX at the time of ASUC presentation rendering this option obsolete, and widespread use of cyclosporine limited by side effects. In this study we systematically reviewed all reports on tofacitinib as a potential new treatment option for ASUC, which comprised a total of 148 patients. Our analysis shows a global 30- and 90-day colectomy-free survival of ~85% and 180-day colectomy-free survival of 69%. Of note, a substantial proportion [32%] of those not undergoing colectomy had been followed-up for less than 180 days, thus rendering the 180-day colectomy-free survival estimate uncertain. Collectively, these data suggest that tofacitinib is effective for ASUC and may have a place in the treatment of this condition. In fact, efficacy of first-line ASUC therapy with iv steroids has a colectomy rate of 29%, and despite typically being used compassionately as a last resort in patients facing colectomy as the only other alternative treatment option, tofacitinib showed quite similar outcomes.[5] It is very important to stress, however, that all available

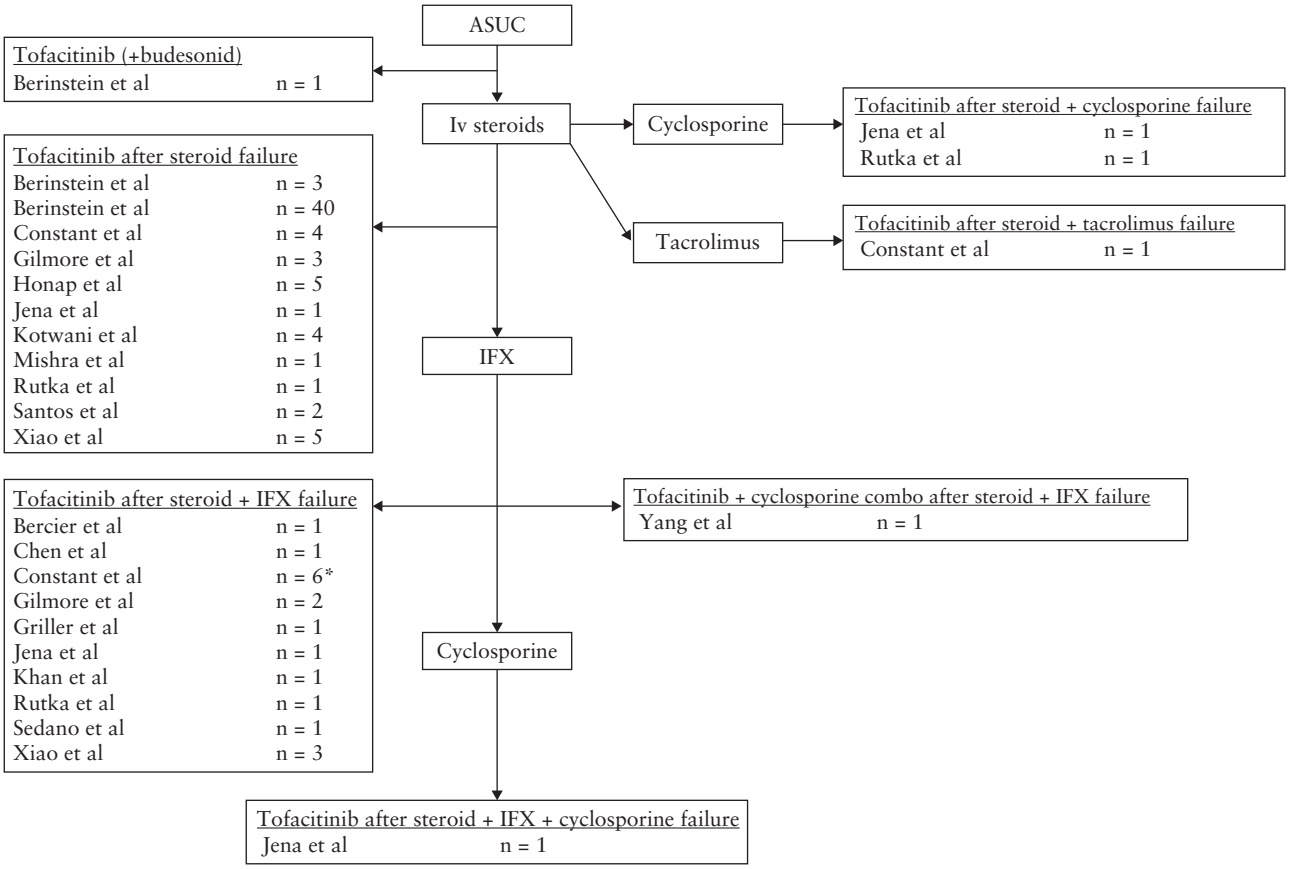

Figure 2. Timing of rescue tofacitinib therapy for treatment of ASUC. *One patient had second-line adalimumab. Data were not available for the GETAID cohort of 55 patients; see details in text.[33]

studies were low in the hierarchy of evidence [case reports, case series, cohort studies, uncontrolled] and with few observations, thus introducing a high risk of bias and necessitating great caution when interpreting the results, calling for observations in larger cohorts, and preferably, prospectively controlled trials.

Our review also shows that tofacitinib thus far predominantly has been used as a last resort before colectomy and either as a second-line agent after steroid failure in biologically experienced patients with previous IFX failure or as a third-line agent after sequential steroid and IFX/cyclosporine failure. The induction dose utilized was 10 mg BID or, alternatively, 10 mg TID for 3 days typically followed by dose reduction to 10 mg BID. Notably, the case-control study found only 10 mg TID to be significantly protective of colectomy.[32] Maintenance dosings were 5–10 mg BID but sparsely reported along with tapering regimens and steroid persistence. Tofacitinib persistence at follow-up was generally high [68–91%] and with clinical remission reported in 35–69% and endoscopic remission in about half of patients. However, it was not possible to make a global estimate on clinical and endoscopic outcomes because these had only been sparsely reported.

There are natural concerns when considering introducing a new medical treatment option for ASUC, for example related to effectiveness including risk of unnecessarily prolonging the time to surgery and thus potentially increasing the risk of complications. Safety is also very important as patients are already heavily immunosuppressed and with a priori increased infection and thromboembolic risk, which may by aggregated by tofacitinib.[6,37] Tofacitinib is approved only as monotherapy in ulcerative colitis but was nevertheless used in combination with steroids and an anti-tumour necrosis factor [anti-TNF] agent or cyclosporine without a clear washout period. Across all included studies, comprising 148 patients, 22 adverse events had been recorded of which seven led to discontinuation of tofacitinib, and the vast majority were related to infectious complications other than herpes zoster.[10,16,17,19–33] A single death possibly linked to tofacitinib is noteworthy. A recent systematic review observed marginal safety issues for off-label combinations of tofacitinib and biologics including anti-TNF agents, but with limited exposed inflammatory bowel disease patients.[38] The only controlled study included here found similar adverse event rates between tofacitinib-treated patients and controls.[32] Taken together, the available data did not indicate significant or new safety signals when tofacitinib was used for ASUC but do not allow conclusions as observations are limited, uncontrolled and with short follow-up, and because tofacitinib was employed primarily in highly selected individuals. If used for ASUC, we advise giving tofacitinib only to younger otherwise healthy patients without cardiovascular or any other known risk factors, as a precautionary measure.[39]

Our systematic review identified three registered trials of tofacitinib for ASUC. A prospective, uncontrolled, observational study plans to recruit 26 ASUC patients with failure to either anti-TNF, anti-integrin, anti-interleukin therapies, immunomodulators or iv steroids to treatment with tofacitinib 10 mg BID and evaluate clinical response by day 7 [clinicaltrials.gov: NCT04925973]. Furthermore, as shown

in Supplementary Figure 2, two randomized controlled studies have recently been initiated exploring: [a] first-line tofacitinib [10 mg TID for 3 days followed by 10 mg BID for 2 days] and iv steroid combination therapy vs steroid monotherapy, aiming to include 96 patients and primarily evaluating treatment failure at day 6 defined as failure to achieve a Lichtiger score reduction by ≥3 points and overall score 10 or requirement for colectomy [WHO International Clinical Trial Registry Platform: CTRI/2022/11/047186]; and [b] second-line tofacitinib [10 mg TID for 3 days followed by 10 mg BID for 8 weeks followed by 5 mg BID] vs cyclosporine [2 mg/kg continuous infusion for 5–7 days followed by oral cyclosporine 4 mg/kg/day in two divided doses for 12 weeks], aiming to include 96 patients and with a dual primary end-point of treatment failure defined as absence of clinical response at day 7 or by relapse between day 7 and 14 weeks, absence of steroid-free clinical remission at week 14, colectomy or serious adverse effects resulting in treatment discontinuation [clinicaltrials.gov: NCT05112263]. As employed in these trials and described above, it appears that tofacitinib preferably should be started at a high dose of 10 mg TID, although current dosing data may have been prone to confounding by indication. As shown in Supplementary Figure 2, there are currently no registered trials assessing first-line tofacitinib monotherapy vs steroids, second-line tofacitinib monotherapy vs IFX, or second-line tofacitinib and IFX/cyclosporine combo therapy vs IFX/cyclosporine monotherapy.[8,32,33]

Our systematic review is hampered by limited and low-quality uncontrolled data from few patients arising from case studies and cohort studies, and the findings thus are subject to a high risk of bias for example due to publication bias. Furthermore, there was no standardized reporting of efficacy [clinical and endoscopic] and safety outcomes, short follow-up, selected study populations not necessarily representative of all ASUC patients, and not all patients fulfilling formal ASUC criteria.[19,32,33] In an effort to statistically handle case reports and small case series, individual patient data were extracted and analysed as one cohort, although we recognize that this may introduce bias, for example because of differences between centres. Also, case reports are at risk of publication bias. To accommodate some of these limitations, colectomy was used as the primary measure as it is a universal objective marker of efficacy, although thresholds may indeed vary to some extent by institutions. Global colectomy-free survival was reported according to data provided in the original publications and available only at 30, 90 and 180 days. Despite these substantial limitations, this review is the first to extensively summarize all available data on tofacitinib for ASUC.

In conclusion, tofacitinib appears promising for treatment of ASUC with notable 30- and 90-day colectomy-free survival of 85% and thus seemingly comparable to iv corticosteroids even among refractory patients who are deemed to require colectomy. Our findings should, however, be interpreted with great caution because of limited observations and low quality of currently available studies with a high risk of bias and confounding. Thus, there is a need for high-quality studies to evaluate efficacy and safety, and define optimal timing and dosing strategies—several of which are underway. Until then, treatment with tofacitinib for ASUC is still experimental and should be done with caution on a case-to-case basis with careful consideration of risks vs benefits.

Funding

None.

Conflict of Interest

C.S. speaker and advisory board for MSD and Janssen-Cilag. J.B. has been a consultant and/or advisory board member and received fees and/or research grants from Abbvie, Pfizer, MSD, Takeda, Janssen, Bristol Myers Squibb and Gilead. J.S. has received research grants from Takeda, Janssen, the Danish Research Council and the Capital Region Denmark, and is national coordinator of studies from AbbVie, Arena Pharmaceuticals, Ely Lilly and Boehringer Ingelheim. P.D.O.: none.

Acknowledgements

None.

Author Contributions

Study concept and design: C.S. + J.S. Acquisition of data: C.S. + P.D.O. Analysis of data: All authors. Drafting of the manuscript: C.S. Critical revision for important intellectual content: All authors. Final approval of manuscript: All authors.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

Supplementary Data

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

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