Journal of Crohn's and Colitis, 2025, **19(2)**, jjaf021
https://doi.org/10.1093/ecco-jcc/jjaf021
Advance access publication 31 January 2025
Review Article

Janus kinase inhibitors in the management of acute severe ulcerative colitis: a comprehensive review

Javier P. Gisbert*, and María Chaparro

Gastroenterology Unit, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain

*Corresponding author: Javier P. Gisbert, Gastroenterology Department, Hospital Universitario de La Princesa, Diego de León, 62. 28006 Madrid, Spain (javier.p.gisbert@gmail.com).

Abstract

Background: One-third of patients with acute severe ulcerative colitis (ASUC) are steroid-refractory. Cyclosporine and infliximab are currently the mainstays of salvage therapy. Janus kinase inhibitors (JAKi) could play a role in the treatment of ASUC.

Aim: To review the evidence on JAKi in the management of ASUC.

Methods: We performed a bibliographic search to identify studies focusing on the treatment of ASUC with JAKi.

Results: Potential advantages of JAKi for the management of ASUC include their oral administration, rapid onset of action, short half-life, lack of immunogenicity, and effectiveness in patients with prior biologic exposure. Thirty studies (including 373 patients) have evaluated the efficacy of tofacitinib in ASUC, with a response rate (avoidance of colectomy) ranging between 43% and 100%, with a weighted mean of 82%. Experience with upadacitinib is more limited (only 10 studies and 74 patients are available) but also encouraging: mean colectomy-free rate ranging between 67% and 100%, with a weighted mean of 79%. However, experience with filgotinib in ASUC is currently nonexistent. Regarding safety, the available data does not reveal any new safety concerns when JAKi are used in ASUC, although follow-up periods are still short.

Conclusion: JAKi seems to be a promising treatment option for ASUC, with both tofacitinib and upadacitinib achieving colectomy-free rates of approximately 80%. Further studies are essential to define whether JAKi can replace cyclosporine/infliximab as second-line therapy for the medical management of ASUC, or whether they can even be used as initial treatment in place of intravenous corticosteroids.

Key words: acute severe ulcerative colitis; anti-TNF; inflammatory bowel disease; JAK inhibitors; tofacitinib; ulcerative colitis; upadacitinib.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition affecting the colon and rectum, generally manifested by diarrhea and rectal bleeding. The disease usually has a mild or moderate course, but ~20% of patients will experience at least one severe acute flare-up during their lifetime, necessitating hospitalization.[1–5]

Acute severe UC (ASUC) represents a potentially life-threatening condition.[6] Before the 1950s, when urgent colectomy and systemic steroids were introduced, the mortality rate for ASUC patients was as high as 70%. In recent years, the combination of medical therapy and timely colectomy, when necessary, has reduced mortality rates to ≤1%.[7–10] However, despite significant therapeutic advancements, the incidence of ASUC seems to remain unchanged, and colectomy rates, although reduced over the past decade, remain high at ~30%.[7–10]

ASUC is typically diagnosed using Truelove and Witts' criteria, which include a bloody stool frequency ≥ 6 per day and at least one of the following: pulse rate > 90 bpm, temperature > 37.8 °C, hemoglobin < 10.5 g/dL, and erythrocyte sedimentation rate > 30 mm/h (currently, C-reactive protein is used in most cases).[11] Management of ASUC requires early collaboration with other medical specialties, involving a multidisciplinary team that includes, at a minimum, a gastroenterologist specialized in inflammatory bowel disease and an abdominal surgeon.[12,13] Intravenous (IV) corticosteroids are recommended as the initial standard treatment for ASUC, as this therapy induces clinical remission and decreases mortality.[6] However, "only" ~60%–70% of ASUC cases will respond adequately to IV corticosteroid therapy alone in the short term.[14]

Historically, the failure to achieve clinical remission with IV corticosteroids inevitably led to colectomy. The advent of medical rescue, or salvage, therapies in steroid-refractory cases has provided an alternative to surgical management for these refractory cases.[15] Cyclosporine and infliximab currently constitute the main options for salvage therapy. While their efficacy appears to be comparable, some uncertainties about this equivalence persist.[1,3–5,16] For patients who do not achieve clinical remission after treatment with cyclosporine or infliximab, switching to the alternative agent may be considered to avoid colectomy. This sequential therapy prevents colectomy in approximately half of the patients.[3] However, this rescue strategy is potentially risky because the immunosuppression induced by the first agent may be enhanced by the second.[3]

Recently, UC management has evolved significantly with the introduction of new therapeutic agents with distinct mechanisms of action. Vedolizumab, ustekinumab, and more recently, Janus kinase inhibitors (JAKi), have been added to the therapeutic arsenal for UC patients, and their use is being explored in the context of ASUC. In addition, the number of patients hospitalized with ASUC and refractory to anti-tumor necrosis factor (anti-TNF) or other biological agents is rising, highlighting the need for the development of alternative therapies such as JAKi.[5]

JAKi—including tofacitinib, upadacitinib, and filgotinib—are a new class of orally administered small-molecule drugs that modulate various cytokine signaling pathways and are approved for the treatment of moderate-to-severe UC.[17] Due to their rapid action onset and clearance, these drugs are an attractive therapeutic rescue option in inpatients with ASUC, mainly for those patients who fail to respond to biological agents before hospitalization or to infliximab during admission, although they could also represent a valid alternative in ASUC patients naïve to biologics. The use of JAKi could be even considered, theoretically, as a substitute for IV steroids (or in combination with them) in ASUC. Therefore, in this narrative review, we provide a comprehensive overview of the effectiveness and safety of JAKi in the management of ASUC.

2. Approach to the literature

A systematic bibliographic search was designed to identify studies assessing the role of JAKi in the management of ASUC (defined through clinical criteria, such as the Truelove and Witt criteria, and/or the necessity for hospitalization). An electronic search was performed in PubMed up to October 2024 using the following algorithm: ("acute severe ulcerative colitis" OR "acute severe colitis" OR "refractory ulcerative colitis" OR "steroid-refractory ulcerative colitis" OR "corticosteroid-refractory ulcerative colitis") AND (tofacitinib OR upadacitinib OR filgotinib OR "Janus kinase inhibitors" OR "JAK inhibitors"). In addition, the reference lists of the selected articles were reviewed to identify additional studies of potential interest. Only articles published in full-text format (as complete articles) were included. Articles published in any language were included. If a study was duplicated, the most recent one fulfilling the inclusion criteria was included. Up to October 2024, 83 articles were retrieved with this search strategy (including tofacitinib and/or upadacitinib, while no article evaluating the role of filgotinib in ASUC was detected).

3. General aspects of JAKi

Tofacitinib is an oral small-molecule that non-selectively inhibits the JAK-STAT pathway, which controls the signaling of various immune mediators. Tofacitinib is the first-in-class JAKi licensed for the treatment of moderate-to-severe UC.[17–21] The efficacy of tofacitinib for UC treatment has been demonstrated not only in randomized clinical trials (RCTs)[22] but also confirmed in real-world evidence studies in clinical practice.[23] Upadacitinib is a second-generation preferential JAK1 inhibitor, and the only JAKi licensed for both moderate-to-severe UC and CD.[17] Finally, filgotinib demonstrates approximately 30-fold greater inhibition of JAK1 compared to JAK2 and other members of the JAK family.[17] The effectiveness of filgotinib in UC was established in the pivotal phase IIb/III SELECTION studies.[24]

4. Potential advantages of JAKi for ASUC treatment

Tofacitinib is rapidly absorbed, reaching peak plasma concentration within 1 hour, and can produce rapid clinical improvements, as early as day 3 of oral therapy.[25,26] Regarding upadacitinib, significant improvement in UC symptoms (stool frequency and rectal bleeding) was observed with treatment as early as 24 hours.[27] However, the time to response to JAKi may vary from days to weeks or months.[25] As small molecules, they are less susceptible to drug loss associated with hypoalbuminemia and colonic protein loss (via a severely inflamed colon) compared to biological agents.[28,29] Furthermore, they do not require therapeutic drug monitoring. Finally, JAKi are a cheaper option compared to biologics. Consequently, these drugs offer an appealing therapeutic option for inpatient induction therapy and potential salvage therapy in ASUC.[30]

5. JAKi, instead of steroids, as first-line treatment in ASUC

Oral corticosteroids are still the first-line therapy for inducing remission in patients with moderately active UC.[1] JAKi, with their proven efficacy, oral administration, short half-life, rapid onset of action, and safety profile with a lower reported incidence of adverse events such as osteoporosis, diabetes, and hypertension, represent an alternative to corticosteroids as first-line agents for inducing remission in these patients.[31,32] Furthermore, JAKi could be an option for patients who cannot use corticosteroids due to contraindications.

A recent pilot study, the ORCHID trial, evaluated the effectiveness and safety of tofacitinib vs prednisolone in patients with moderately active UC (not in ASUC).[32] Patients were randomly assigned to receive either oral prednisolone (at initial doses of 40 mg daily) or tofacitinib (10 mg twice daily initially), including 78 patients in each group. The majority of the patients were anti-TNF-naïve. At week 8, the proportion of patients achieving composite remission in the tofacitinib (16%) and prednisolone groups (8.6%) were not significantly different, although a trend favoring tofacitinib was observed; the authors speculate that with a larger sample size, these trends may have resulted in better results in patients receiving tofacitinib.[32] One patient each in the tofacitinib and prednisolone groups discontinued treatment due to development of pulmonary tuberculosis and pustular acne, respectively. No serious adverse events or major adverse cardiovascular events were observed.

The time required to exert its effect is a key factor when choosing a therapy for inducing remission. In the aforementioned ORCHID trial, the time to noticeable symptomatic improvement (measured by a reduction of at least one point in stool frequency and rectal bleeding scores) was comparable between the 2 groups; the median time to observe symptomatic relief was 5 days for prednisolone and 6 days for tofacitinib.[32]

As previously discussed, IV corticosteroids play a well-established role in ASUC treatment. However, about 30%–40% of patients do not respond to corticosteroid treatment and require additional intervention with either medical therapies, such as infliximab or cyclosporine, or surgical options like colectomy.[1] In these cases, the use of JAKi could be potentially considered instead of IV steroids for ASUC treatment.

An ongoing trial entitled "A Sequential Multiple Assignment Randomized Trial (SMART) Developing and Optimizing Patient-Tailored Adaptive Treatment Strategies (ATS) for ASUC" (NCT05867329) included hospitalized patients with UC and prior history of receiving at least one anti-TNF, and compared different therapeutic strategies, mainly IV methylprednisolone, upadacitinib (at initial doses higher than those approved in the prescribing information), and methylprednisolone plus upadacitinib.[33] The results of this study are eagerly awaited.

Corticosteroids are not suitable for maintenance therapy due to the risk of adverse events and a decline in effectiveness over time. Thus, remission induced by corticosteroids is typically sustained using immunomodulators, such as thiopurines. However, thiopurines have a slow onset of action, taking about 12–16 weeks to exhibit their steroid-sparing effect. Additionally, some patients may either fail to respond to thiopurines initially or experience a loss of response over time, necessitating additional courses of corticosteroids or a switch to biological therapies. On the contrary, the use of JAKi may be beneficial for induction because the same medication can be continued for maintaining remission. If a secondary loss of response occurs, increasing the dose (mainly in the case of tofacitinib and upadacitinib) can help restore effectiveness.[34]

Nevertheless, the advantages of JAKi over IV corticosteroids in the specific context of ASUC have not yet been demonstrated, as to date no randomized study has directly compared both strategies in patients with ASUC. Therefore, it is clear that further studies (ideally RCTs) are needed to evaluate and compare the efficacy and safety of JAKi vs corticosteroids in this ASUC.

6. JAKi in combination with steroids as first-line treatment in ASUC

It has been suggested that increased expression of proinflammatory cytokines (such as interleukin [IL]–6 and IL-8) is linked to corticosteroid resistance in UC patients. *In vitro* studies have demonstrated that IL-2 can reduce nuclear translocation of the glucocorticoid receptor via JAK1- and JAK3-mediated phosphorylation of STAT5, contributing to this resistance.[35] Tofacitinib, by inhibiting JAKs, may block IL-2 receptor downstream signaling, potentially restoring corticosteroid sensitivity. Thus, some authors have hypothesized that adding tofacitinib to corticosteroids in hospitalized patients with ASUC could enhance therapeutic efficacy and improve treatment response rates.[35]

A recent RCT, the TACOS trial, evaluated the effectiveness of tofacitinib (administered at an initial dose of 10 mg 3 times daily) in conjunction with IV steroids vs. the standard treatment with only IV steroids, in a double-blind, placebo-controlled study involving 104 (mostly biologic-naïve) patients with ASUC.[35] The primary endpoint was treatment response, defined as a decline in the Lichtiger index by more than 3 points and a total score below 10 for 2 consecutive days without the need for rescue therapy by day 7. Tofacitinib plus steroids were superior to isolated steroids for achieving clinical response by day 7 (83% vs 59%, $P = .007$), reducing the need for rescue (medical/surgical) therapy (11% vs 31%, $P = .01$). Patients who responded to tofacitinib plus steroids were transitioned to maintenance therapy with tofacitinib 10 mg twice daily, while those responding to steroids continued with oral 5-aminosalicylates and thiopurine therapy. In the medium term (90 days), patients on tofacitinib were less likely to require rescue therapy. Despite the off-label initial dosing of tofacitinib (10 mg 3 times daily), most treatment-related adverse events were mild, although one patient receiving tofacitinib developed a dural venous sinus thrombosis (however, a heightened inflammatory burden in ASUC and concomitant use of corticosteroids could also have contributed) and one patient died. Conversely, there were 4 deaths in the steroid group. These results indicate that in patients with ASUC, the combination of tofacitinib and corticosteroids improves treatment responsiveness and decreases the need for rescue therapy (compared to steroids alone). Nevertheless, this approach may risk over-treating those patients who would respond adequately to conventional therapy with steroids without requiring the addition of tofacitinib to their treatment.[36] As the authors recognize, the applicability of these findings may have limitations, as the study primarily involved patients who had not previously received biologic treatments and had relatively short disease durations, which may not fully represent the broader clinical characteristics of patients in real-world practice.[35]

On the other hand, in a recent multicenter study including 25 patients with ASUC treated with upadacitinib (in most of the cases at doses higher than those approved in the prescribing information) plus IV corticosteroids, 76% of the patients were able to avoid colectomy, with a low incidence of adverse events (8%) and readmission (20%).[37] Interestingly, patients who avoided colectomy during their initial hospitalization exhibited a favorable evolution, with only 2 (8%) additional colectomies within 90 days, and 83% of the patients achieved steroid-free clinical remission. These encouraging results suggest that patients receiving upadacitinib were not simply delaying an eventual colectomy.[37] Of note, there was no significant difference in the rate of colectomy between anti-TNF-naïve and anti-TNF-exposed patients.

7. JAKi, instead of infliximab or cyclosporine, as second-line treatment (after steroid failure) in ASUC

As previously discussed, cyclosporine and infliximab are effective as second-line therapies following IV steroid failure; however, a significant proportion of patients will undergo colectomy within a few months. Furthermore, cyclosporine has a number of limitations that relatively restrict its use, while many patients have prior exposure to anti-TNF agents, reducing the likelihood of infliximab efficacy.

JAKi, due to its short half-life and rapid clearance, would allow the immediate initiation of a second-line rescue therapy (with infliximab or cyclosporine) with complete washout from the system within 1–2 days after discontinuing JAKi treatment. Therefore, it would undoubtedly be interesting to evaluate the possible role of JAKi instead of cyclosporine or infliximab in second-line treatment after steroid failure in patients with ASUC.

Tofacitinib is currently approved for adults with moderately to severely active UC who have had an inadequate response or intolerance to one or more biological agents, but real-world evidence has also demonstrated efficacy in biologic-naïve patients. However, the experience of using tofacitinib, instead of infliximab or cyclosporine, as second-line treatment

(after steroid failure) in ASUC is almost null. Komeda et al. prescribed tofacitinib to 8 ASUC anti-TNF naïve patients, obtaining a colectomy-free rate of 75%.[38] Malakar et al. also tested the efficacy of tofacitinib in 8 ASUC anti-TNF naïve patients (only one patient was anti-TNF experienced) and reported a colectomy-free rate of 87%.[39] However, serious adverse events were noted in these 2 studies, including a case of herpes zoster and 2 deaths: one patient who developed sepsis after colectomy and another who died of bacterial pneumonia 1 month after starting tofacitinib. These preliminary findings indicate that while tofacitinib may be effective as a first-line rescue therapy for ASUC, it could be associated with significant risks. Therefore, further evaluation of its safety and efficacy in controlled clinical trials is warranted.[36]

TRIUMPH (NCT04925973) is a phase 4 prospective interventional trial aimed to determine the effectiveness and safety of tofacitinib in ASUC patients who experience treatment failure to steroids (either biologic-naïve or biologic-experienced). Although this is not a randomized study, it will surely provide valuable information for positioning tofacitinib as a second-line treatment after steroid failure.

Regarding the comparison between tofacitinib and cyclosporine in ASUC, TOCASU (NCT05112263) is an ongoing RCT where patients admitted with ASUC with failure to respond to IV steroids were randomized (in an open-label fashion) to receive either cyclosporine or tofacitinib (10 mg 3 times a day for 3 days, and then 10 mg twice daily to complete 8 weeks, followed by 5 mg twice daily for the rest of the study, up to 14 weeks). Considering the potential toxicity of cyclosporine, this study will also provide us with interesting information on the comparative safety of tofacitinib. Finally, regarding infliximab and tofacitinib in ASUC, to date, no study has been conducted (nor is currently underway) comparing these 2 treatments.

Interestingly, if tofacitinib is started first (instead of infliximab or cyclosporine), the effect may be judged within a short period of time (3–5 days), and infliximab or cyclosporine may be then safely administered without overlap. However, if the anti-TNF is administered in advance, it takes time to wash out once tofacitinib has been started as rescue therapy. Furthermore, in the long term, tofacitinib has a theoretical advantage over cyclosporine because it can be continued as a maintenance therapy after achieving remission. However, long-term data are limited, and some patients may experience a loss of response to JAKi over time.[23] This raises questions about the suitability of JAKi as a long-term therapy for all patients. In the GETAID-TALC study, the colectomy-free survival rate at 6 months of ASUC patients treated with tofacitinib (65% of them were receiving steroids at tofacitinib initiation) was 74%.[40] Among 3 other small series with long-term outcomes, response rates varied. In one study, 2 out of 5 initial responders to tofacitinib required IV steroids at 6 months.[41] In a second study, 2 out of 5 patients who initially avoided colectomy needed it by week 6.[42] In the third series, all patients who initially responded to tofacitinib remained colectomy-free for up to 12 months.[43]

8. Factors that may influence the choice between JAKi and traditional agents (infliximab and cyclosporine)

In the event that the efficacy and safety of JAKi were equivalent to those of traditional treatments for corticosteroid-refractory ASUC (such as cyclosporine and infliximab)—which has not yet been demonstrated in any RCT—, clinicians must also consider factors beyond clinical efficacy and safety to choose the optimal rescue therapy.[15] These factors are summarized below.

1) Predictors of treatment response: Ideally, accurate predictors of treatment response would guide the choice between 2 different drugs for a specific patient. Unfortunately, we currently lack sufficiently precise and reliable predictive markers.[44,45] What we do know is that at the time of admission, elevated C-reactive protein levels, low serum albumin, and severe endoscopic lesions are associated with an increased risk of colectomy in patients treated with infliximab.[46] Conversely, achieving a complete clinical response by weeks 10 to 14, along with endoscopic healing and infliximab serum levels exceeding 2.5 µg/mL at week 14, are associated with colectomy-free survival.[46]
2) Length of hospital stay: Some studies have shown that when comparing cyclosporine with infliximab, the use of the anti-TNF agent is associated with a shorter length of hospital stay.[47] In contrast to this, recent findings of the multicenter CONSTRUCT study demonstrated no significant difference in length of stay between the 2 treatments.[48] Unfortunately, we do not have direct comparative data on the duration of hospital stay for patients with ASUC treated with these traditional rescue therapies vs. those treated with JAKi. However, it is evident that the short time to response to JAKi previously discussed[25–27] could represent an advantage for these new drugs.
3) Endoscopic healing: Few data on the evolution of endoscopic findings are available in patients with ASUC. Endoscopic healing may have an impact on subsequent disease course as several studies have shown that patients with residual mild endoscopic inflammation experience more relapse and surgery than those who achieve mucosal healing.[49,50] Recently, endoscopic evolution has been described in a prospective cohort based on the CySIF original trial comparing infliximab and cyclosporine.[51] Once again, however, there is a lack of studies directly comparing endoscopic findings associated with JAKi treatment and those associated with cyclosporine or infliximab.
4) Tuberculosis screening requirement: Due to the significant immunosuppressive effect of infliximab and JAKi, several screening tests are necessary before starting therapy. Following national guidelines, these tests include serology for hepatitis B, varicella zoster, and HIV; a tuberculin skin test or interferon-gamma release assay is also required, since it is well known that both infliximab and JAKi increase the risk of latent tuberculosis reactivation.[52] Depending on the facilities available, results from these tuberculosis tests may take several days to obtain, potentially delaying the initiation of infliximab or JAKi in ASUC patients if screening has not been conducted beforehand. A benefit of cyclosporine therapy is that it does not require tuberculosis screening prior to use.
5) Ease of prescription: Ultimately, the decision will be influenced by the provider's and institution's experience.[53,54] Currently, many clinicians favor infliximab over cyclosporine due to its convenience (it only requires one initial

single infusion), its suitability for long-term maintenance therapy, and the lack of need for drug-level monitoring, which is necessary for calcineurin inhibitors.[55–60] In the case of JAKi, the oral route of administration is undoubtedly an advantage compared to the IV route, both during hospitalization and at discharge, as well as for long-term treatment.

6) Cost: Total costs of infliximab therapy are significantly higher than costs associated with cyclosporine use.[47] However, since 2013, lower-cost infliximab biosimilars are available, which may result in large cost savings. Thus, currently, the price of JAKi is higher than that of the infliximab biosimilar. In addition, healthcare expenses related to ASUC remain high, driven predominantly by the length of stay during initial hospitalization and the need for colectomy. Therefore, if the rapid efficacy of JAKi is confirmed, their prescription may be advantageous from a healthcare cost perspective.
7) Patient's preference: Finally, in clinical practice, treatment choice should be guided by physician experience and, obviously, by patient's preference. Patients are, in general, more positive about treatment with infliximab than cyclosporine, mainly due to the cumbersome IV regimen required for cyclosporine.[61] Finally, from the patient's perspective, the ease of oral administration of JAKi may represent an advantage over the IV administration of cyclosporine and infliximab, although the role of the route of administration in patients with ASUC is probably minor.

9. JAKi together with infliximab or cyclosporine as second-line treatment (after steroid failure) in ASUC

The effectiveness and, more importantly, the safety of JAKi in combination with biologics or calcineurin inhibitors are unknown. Recent studies have shown that combining tofacitinib with biological therapies can effectively achieve corticosteroid-free remission in medically-refractory (not ASUC) patients with UC.[62] In this respect, Gilmore et al. described the use of tofacitinib (10 mg/8 h) in combination with infliximab for the management of a patient with ASUC, who avoided colectomy.[63] Regarding calcineurin inhibitors, Yang et al. reported the first combination therapy approach for cyclosporine and tofacitinib (10 mg/12 h) in a patient with steroid-refractory ASUC who previously showed no response to infliximab; this patient was colectomy-free at one year.[64] Future studies should explore to what extent combination therapy with JAKi plus cyclosporine and, especially, infliximab augments response, the duration of therapy required to provide such benefit, and above all, the identification of patients who are most likely to benefit from these combination therapies.

10. JAKi as third-line treatment (after steroid and cyclosporine/infliximab failure) in ASUC

To the best of our knowledge, there is no RCT (neither completed nor ongoing) evaluating the efficacy/safety of JAKi in ASUC patients who have failed cyclosporine or infliximab. The previously mentioned TRIUMPH study (NCT04925973) could include patients with previous failure to anti-TNF/anti-integrin/anti-interleukin therapies but not during the same admission. The REASUC observational study evaluated colectomy-free survival and safety of third-line treatment in patients with ASUC refractory to IV steroids who failed either infliximab or cyclosporine; third-line treatment with tofacitinib (at an induction dosage of 10 mg/12 h) was administered to 13 patients, achieving a relatively high colectomy-free rate (69%) in this very refractory cohort.[65]

11. Systematic reviews and meta-analyses on the efficacy of JAKi in ASUC

In 2021, Jena et al. published the first systematic review on tofacitinib in ASUC, including only 6 studies and 21 patients, and showed an efficacy of 75% (3/4 patients) as first-line therapy, 86% (12/14) as second-line therapy (steroid failure), and 67% (2/3) as third-line therapy, with 71% long-term colectomy avoidance.[66]

In a more recent meta-analysis performed by Mpakogiannis et al. and published in 2023, 134 patients who received tofacitinib for ASUC were included across 14 studies, including 2 observational studies, 7 case series, and 5 case reports.[67] The overall pooled colectomy-free rate was 76% (80% at 90 days and 72% at 6 months).

In another meta-analysis performed by Steenholdt et al., also published in 2023, 148 patients from 21 studies were included.[68] Tofacitinib was used as second-line treatment after steroid failure in patients with previous infliximab failure or as third-line after sequential steroid and infliximab or cyclosporine failure. The authors reported colectomy-free survival rates of 85% at 30 days, 86% at 90 days, and 69% at 180 days.

Finally, a network meta-analysis assessing the effectiveness of rescue therapies for steroid-refractory ASUC has been recently published.[69] A total of 6 RCTs and 15 cohort studies involving 2000 patients were analyzed. The rescue therapies included tofacitinib (20 mg/day), infliximab, tacrolimus, cyclosporine, ustekinumab, and adalimumab. Tofacitinib, infliximab, and tacrolimus were significantly effective in reducing colectomy rates compared to placebo. The ranking of rescue therapies was determined by their effect sizes regarding colectomy rate, and tofacitinib was the most effective treatment. Cyclosporine showed a tendency to prevent colectomies, although its effects were not as pronounced. Conversely, ustekinumab and adalimumab did not exert a significant impact on colectomy rates.[69]

Regarding other JAKi different from tofacitinib, Damianos et al. performed the first and only systematic review on the role of upadacitinib in ASUC, including 11 studies (not only full-text articles but also abstracts presented at different congresses), with a pooled total of 55 patients, and the overall colectomy-free rate at 90 days was 84%.[70]

12. An updated review of the literature on the efficacy of JAKi in ASUC

Table 1 summarizes the studies that have evaluated the efficacy of tofacitinib for the treatment of ASUC.[29,35,38–43,63–66,71–88] Thirty studies were included, totaling 373 patients, mostly adults. Of note, this updated review has allowed us to identify a considerably larger number of patients than that included in the previously mentioned meta-analyses. Most of the studies were observational and retrospective, while only 3 were prospective, and only one was an RCT.[35] Most of the studies

Table 1. Studies evaluating the efficacy and safety of tofacitinib for the treatment of acute severe ulcerative colitis.

Author	Study design	Number of patients	Previous (failed) treatments (different from steroids)	Follow-up (median or range, months)	Response rate (avoiding colectomy)[a] (%)	Serious adverse events or leading to discontinuation (%)	Mortality rate (%)	Initial tofacitinib dose and notes
Berinstein[71]	OR	4	Anti-TNF (IFX +/- ADA) in 2 patients	2-18	75	0	0	10 mg/8 h (in ¾ patients)
Berinstein[29]	OR	40	Prior failed therapies: One: 13 (32%) Two: 21 (52%) Three: 5 (12%) Four: 1 (2.5%) IFX: 34 (85%) ADA: 16 (40%) Golimumab: 2 (5%) Vedolizumab: 21 (52%) Ustekinumab: 1 (2.5%)	3	85	No differences compared with controls	0	10 mg/12 h or 10 mg/8 h
Constant[72]	OR	11 (children)	Anti-TNF: 10 (91%) Vedolizumab (27%) 1 was biologic naïve at time of presentation 1 failed to respond to IFX rescue therapy on the same admission	3	54	0	0	10 mg/12 h or 10 mg/8 h
Costaguta[73]	OR	6 (children)	Anti-TNF: 6 (100%) All patients had previously received IFX, and either ustekinumab, vedolizumab, or immunomodulators	8.5	100	0	0	10 mg/12 h
Dolinger[74]	OR	1 (children)	Anti-TNF: 1 (100%)	-	100	-	0	10 mg/12 h
Eqbal[43]	OR	11	IFX: 11 (100%); of these, 5 patients had IFX rescue therapy on the same admission Vedolizumab: 3 (27%)	12	82	9.1 (1 transient hepatitis)	0	10 mg/8 h for 14 days, then 10 mg/12 h
Festa[75]	OR	1	IFX, ADA	6	100	0	0	10 mg/12 h
Fortuny[76]	OR	1	IFX	4	100	0	0	10 mg/12 h
García[65]	OR	13	IFX or CYA	5	69	7.7 (1 cardiovascular event)	0	10 mg/12 h
Gilmore[63]	OR	1	IFX	3	100	0	0	10 mg/8 h (combined with IFX)
Gilmore[77]	OP	5	IFX	3	80	0	0	10 mg/8 h
Girard[78]	OR	1 (children)	IFX, vedolizumab	6	100	0	0	10 mg/12 h
Griller[79]	OR	1	IFX (on the same admission), vedolizumab	8	100	0	0	10 mg/12 h
Honap[42]	OR	7	Anti-TNF (1 patient received tofacitinib after the failure of rescue IFX on the same admission)	0.5-12	43	0	0	10 mg/12 h
Jena[66]	OR	4	Two patients had also failed IFX as second-line therapy and 1 had failed CYA	0.5-1	75	(see mortality section)	0 (1 death in a patient with COVID-19 and probable pulmonary thromboembolism)	10 mg/12 h (in ¾ patients)

Table 1. Continued

Author	Study design	Number of patients	Previous (failed) treatments (different from steroids)	Follow-up (median or range, months)	Response rate (avoiding colectomy)[a] (%)	Serious adverse events or leading to discontinuation (%)	Mortality rate (%)	Initial tofacitinib dose and notes
Komeda[80]	OR	1	Anti-TNF naïve CYA	12	100	0	0	10 mg/12 h
Komeda[38]	OR	8	Anti-TNF naïve	-	75	0	0	10 mg/12h
Kotwani[81]	OR	4	At least 2 biologics before hospitalization, including both an anti-TNF (IFX and/or ADA) and vedolizumab	5-14	100	0	0	10 mg/12 h (1 patient was escalated to 15 mg/12 h)
Malakar[39]	OR	8	Anti-TNF naïve (only 1 patient was anti-TNF and vedolizumab experienced)	24	87	12	0	10 mg/12 h
Naganuma[82]	OP	9	IFX, tacrolimus, apheresis or CYA during the same admission	1	56	11 (1 CMV reactivation)	0	10 mg/12 h (assumed from the information in the article)
Parra-Izquierdo[83]	OR	1 (child)	Anti-TNF: 1 (100%)	12	100	0	0	50 mg/12h
Parra-Izquierdo[84]	OR	6 (1 children)	Anti-TNF: 3 (50%) Vedolizumab: 1 (16%)	>6 in 3 patients	100	0	0	10 mg/12 h in 5 patients 10 mg/8 h in 1 patient
Resal[85]	OR	106	IFX: 74 (70%) ADA: 37 (35%) Golimumab: 1 (0.9%) Vedolizumab: 64 (60%) Ustekinumab: 9 (8.5%)	12	82	-	0	10 mg/12 h
Rutka[86]	OR	3	At least 2 biologics before hospitalization IFX: 3 (100%) ADA: 2 (67%) Vedolizumab: 2 (67%) CYA: 1 (33%)	3	100	0	0	10 mg/12 h
Santos[87]	OR	2	At least 2 biologics before hospitalization, including both an anti-TNF (IFX and/or ADA) and vedolizumab	11-14	100	0	0	10 mg/12 h
Sedano[88]	OR	1	IFX and tofacitinib 10 mg/12h	2.5	100	0	0	30 mg/24 h
Singh[35]	RCT	53	Anti-TNF: 3 (5.7%)	3	98.1	1.9 (1 case of dural venous thrombosis)	1.9 (1 death in a patient who did not respond to treatment and did not consent for medical/surgical rescue)	10 mg/8 h (combined with steroids)
Uzzan[40]	OR & OP	55	49 (89%) IFX and 19 (34%) CYA. 53% received iv steroids prior to tofacitinib, and 14% and 3.6% received CYA and IFX, respectively, on the same admission	6.5	74	5.4 (herpes zoster, abdominal pain/nausea/vomiting, viral pneumonia)	0 (1 death not directly related with tofacitinib)	10 mg/12 h This was a mixed group in terms of disease severity, rather than a pure, ASUC cohort

Table 1. Continued

Author	Study design	Number of patients	Previous (failed) treatments (different from steroids)	Follow-up (median or range, months)	Response rate (avoiding colectomy)[a] (%)	Serious adverse events or leading to discontinuation (%)	Mortality rate (%)	Initial tofacitinib dose and notes
Xiao[41]	OR	8	IFX 3 (43%) received IFX during the admission	6	63 (100% in those receiving tofacitinib after the failure of rescue IFX on the same admission)	0	0	10 mg/12 h or 10 mg/8 h
Yang[64]	OR	1	IFX	12	100	0	0	10 mg/12 h (combined with CYA)

Mean response rate (defined as avoiding colectomy) was 82% (weighted mean; 95% CI from 78% to 86%). When studies prescribing tofacitinib together with other agents (such as steroids, cyclosporine, or infliximab) were excluded, the mean response (avoidance of colectomy) rate was 79% (95% confidence interval, 74-84%).
Abbreviations: ADA: adalimumab; CYA: cyclosporine; IFX: infliximab; OR: observational retrospective; OP: observational prospective; RCT: randomized controlled trial.
[a]Most of the studies reported colectomy rates only during the hospitalization or in the short term (shortly after discharge); however, when several times of follow-up were available, the longest follow-up was considered.

included fewer than 10 patients (only 7 studies included ≥ 10 patients). Virtually all patients had received IV steroid treatment prior to initiating tofacitinib (in one study, tofacitinib was co-administered with steroids[35]). Most of the patients were anti-TNF exposed, and many had also failed to respond to other biological agents before admission; however, these studies rarely included ASUC patients refractory to steroids and infliximab, and receiving tofacitinib within the same admission (ie, in the same ASUC episode). Only few studies included patients with previous failure to cyclosporine (within the same admission). Study follow-up times markedly varied between 1 and 24 months. Most of the studies prescribed only tofacitinib, while some of them combined tofacitinib with other treatments, such as steroids,[35] cyclosporine,[64] or infliximab.[63] Response rate (avoidance of colectomy, in most of the studies reported during the hospitalization or shortly after discharge) ranged between 43% and 100%, with a weighted mean of 82% (95% confidence interval [CI], 78%–86%). When studies prescribing tofacitinib together with other agents (such as steroids, cyclosporine, or infliximab) were excluded, the mean response (avoidance of colectomy) rate was 79% (95% CI, 74%–84%). Finally, when only studies with a follow-up time ≥ 6 months were included, the colectomy-free rate was 81% (95% CI, 75%–86%).

The results of the more extensive studies with tofacitinib are briefly summarized below. The largest study was performed by Resal et al. and included 106 ASUC patients previously exposed to anti-TNF and/or vedolizumab or ustekinumab; the dose of tofacitinib was 10 mg/12 h and the follow-up time was 12 months, this study reported a colectomy-free rate of 82%.[85] The second largest study, performed by Uzzan et al., included 55 patients and reported 79% and 74% colectomy-free survival rates at 3 and 6 months, respectively.[40] The third largest study, the previously discussed TACOS RCT, included 53 patients (mostly biologic-naïve) with ASUC treated with tofacitinib (administered at an initial dose of 10 mg 3 times daily) in conjunction with IV steroids.[35] Finally, Berinstein et al. included 40 biologic-experienced patients with ASUC in a case-control study, showing that tofacitinib (at doses of 10 mg every 12 hours or 8 hours) reduced the risk of colectomy at 90 days (85%) compared to matched controls.[29]

Table 2 summarizes the studies that have evaluated the efficacy of upadacitinib for the treatment of ASUC.[37,89–97] Ten studies, totaling 74 patients (all adults), were included. All studies were observational and retrospective. Almost all the studies (except for two) included fewer than 10 patients. Virtually all patients received IV steroid treatment prior to initiating upadacitinib (except for one study, where upadacitinib was co-administered with steroids[37]). Most of the patients were anti-TNF exposed, and many had also failed to respond to other biological agents (such as vedolizumab or ustekinumab) prior to admission; however, as it was the case with tofacitinib, these studies rarely included ASUC patients refractory to steroids and infliximab, and receiving upadacitinib within the same admission (ie, in the same ASUC episode). No study included patients with previous failure to cyclosporine (within the same admission). A few patients had previously failed to tofacitinib.[37,89,90] The most common upadacitinib induction regimen was 45 mg daily. Study follow-up times varied between 2 and 6 months. Most of the studies prescribed only upadacitinib, while one of them combined upadacitinib with steroids,[37] and another one with apheresis.[94] Mean response rate (defined as avoiding colectomy, reported during the hospitalization or shortly after discharge) ranged between 67% and 100%, with a weighted mean of 79% (95% CI from 70% to 90%). When studies prescribing upadacitinib together with other agents (such as steroids or apheresis) were excluded, the mean response (avoidance of colectomy) rate was 81% (95% CI, 69%–93%).

The results of the more extensive studies with upadacitinib are briefly summarized below. The largest study, performed by Berinstein et al., included 25 patients treated with upadacitinib together with corticosteroids and has been previously described in this review.[37] In the second largest study, Zhang et

Table 2. Studies evaluating the efficacy and safety of upadacitinib for the treatment of acute severe ulcerative colitis.

Author	Study design	Number of patients	Previous (failed) treatments (different from steroids)	Follow-up (median or range, months)	Response rate (avoiding colectomy)[a] (%)	Serious adverse events or leading to discontinuation (%)	Mortality rate (%)	Initial upadacitinib dose and notes
Ali[89]	OR	1	IFX & adalimumab Loss of response to tofacitinib	6	100	0	0	45 mg/day
Berinstein[37]	OR	25	Anti-TNF naïve: 9 (36%) Anti-TNF exposed: 16 (64%) Vedolizumab: 8 (32%) Ustekinumab: 4 (16%) Tofacitinib: 2 (8%)	3	76	4 (1 case of venous thromboembolism)	0	45 mg/day or 30 mg/12h (combined with steroids)
Clinton[90]	OR	12	Anti-TNF: 12 (100%) Vedolizumab: 3 (25%) Ustekinumab: 1 (8%) Tofacitinib: 1 (8%)	3	67	0	0	45 mg/day
Dalal[91]	OR	9	Anti-TNF: 7 (78%) (3 IFX on the same admission)	4	86	11 (1 case of pulmonary embolism, attributed to heparin induced thrombocytopenia, not leading to upadacitinib discontinuation)	0	45 mg/day
Gilmore[92]	OR	6	Before hospitalization: Anti-TNF: 6 (100%) (3 primary non-response, 2 secondary loss of response, and 1 intolerance) Golimumab: 1 (17%) Vedolizumab: 4 (67%)	4	83	0	0	45 mg/day
Hilley[93]	OR	1	IFX, vedolizumab and ustekinumab failure previous to hospitalization	4	100	0	0	45 mg/day (reduced to 30 mg/day after 3 days) Patient had end stage renal disease
Tanida[94]	OR	1	Naïve to biological therapy	2.5	100	0	0	45 mg/day (combined with apheresis)
Xu[95]	OR	1	IFX and vedolizumab failure previous to hospitalization	2	100	0	0	45 mg/day
Zhang[96]	OR	14	Non-response to previous corticosteroids: 11 (79%) Anti-TNF: 14 (100%) Vedolizumab: 3 (21%) Ustekinumab: 1 (8%)	4	86	0	0	45 mg/day
Zinger[97]	OR	4	Anti-TNF: 4 (100%) (4 IFX on the same admission)	4	75	0	0	45 mg/day

The mean response rate (defined as avoiding colectomy) was 78% (weighted mean; 95% CI from 67% to 90%). When studies prescribing upadacitinib together with other agents (such as steroids or apheresis) were excluded, the mean response (avoidance of colectomy) rate was 79% (95% confidence interval, 64%–94%).
Abbreviations: IFX: infliximab; OR: observational retrospective.
[a]Most of the studies reported colectomy rates only during the hospitalization or in the short term (shortly after discharge); however, when several times of follow-up were available, the longest follow-up was considered.

al. included 14 patients and all of them initially exhibited a clinical response to 45 mg upadacitinib.[96] The clinical remission rate was 29% after 8 weeks. Eight-week and 16-week colectomy rates were 7.1% and 14.3%, respectively. Finally, Clinton et al. prescribed upadacitinib to 12 ASUC patients previously exposed to anti-TNF (all patients), vedolizumab

(3 patients), ustekinumab (one patient), and even tofacitinib (one patient).[90] Overall, 8 patients (67%) avoided surgery. One patient required re-induction with upadacitinib within 90 days. Most of the patients who did not undergo surgery were in clinical remission within 90 days.

To help us interpret these figures, and given that tofacitinib and upadacitinib have almost always been used in patients refractory not only to steroids but also to other drugs (eg, biologics), it may be useful to consider the efficacy of rescue therapy with cyclosporine and infliximab in previous studies performed in patients with ASUC. The CYSIF study reported colectomy rates of 17% for cyclosporine treatment and 21% for infliximab treatment at 98 days.[98] The CONSTRUCT trial found colectomy rates of 21% for infliximab and 25% for cyclosporine during hospitalization, increasing to 29% vs 30% at 3 months, and 35% vs 45% at 12 months, with overall rates of 41% vs 48%.[48] Finally, studies evaluating sequential therapy with cyclosporine and infliximab (in either order) reported a relatively high mean colectomy rate (47%).[3] Therefore, it appears that treatment with tofacitinib or upadacitinib is associated with favorable outcomes (mean colectomy-free survival of ~80%, see Tables 1 and 2). These figures are at least similar, and probably superior, to those described for other therapeutic options such as cyclosporine and infliximab.

13. Upadacitinib vs tofacitinib for ASUC: is there any difference?

In theory, upadacitinib could have better efficacy than tofacitinib due to its selectivity for JAK1. Several studies have shown greater clinical efficacy, and similar safety for upadacitinib compared to tofacitinib in patients with active UC (not ASUC), suggesting a favorable benefit-risk profile for upadacitinib.[99–104] Furthermore, in the absence of head-to-head studies, network meta-analyses have ranked upadacitinib highest for induction of remission[105,106] and for maintenance treatment[107] in moderate-to-severe UC.

However, the experience analyzing the benefit of upadacitinib over tofacitinib (or vice versa) specifically in patients with ASUC is practically nonexistent, as very few patients have received upadacitinib after failure to tofacitinib in this clinical scenario.[37,89,90] A case report has documented colectomy-free survival up to 6 months in a patient with ASUC treated with upadacitinib who had prior exposure to azathioprine, infliximab, adalimumab, and tofacitinib (the patient had a history of loss of response to tofacitinib).[89] In a small series, one of the 2 patients who had received tofacitinib before admission and were treated with upadacitinib, avoided colectomy.[37]

The mean efficacy (in terms of avoidance of colectomy) from ASUC studies included in Tables 1 (tofacitinib) and 2 (upadacitinib) was very similar (82% and 79%, respectively). Furthermore, when studies prescribing JAKi together with other agents (such as steroids, cyclosporine, infliximab, apheresis, among others) were excluded, the mean response rates were very similar (79% for tofacitinib and 81% for upadacitinib). Although these comparisons are obviously indirect and come from different studies (and therefore should considered with caution), in both cases they included very refractory ASUC patients (anti-TNF exposed, and also generally exposed to other biological agents), suggesting that the efficacy of tofacitinib and upadacitinib in ASUC is quite similar.

14. JAKi dose for ASUC treatment

The optimal dosing regimen for tofacitinib in ASUC remains to be determined. The most common induction dose used in the studies included in Table 1 was 10 mg/12 h (ie, the standard dose), although some studies used higher doses (mainly 10 mg/8 h). In fact, the only RCT comparing tofacitinib vs placebo prescribed a dose of tofacitinib of 10 mg/8 h.

The relevance of using higher doses of tofacitinib in patients with moderate-to-severe UC was informed by a phase 2 study, which found that a dosing regimen of 15 mg/12 h resulted in a higher clinical response rate at week 8 (78%) compared to a 10 mg/12 h regimen (61%).[108] These results suggest that a higher dose (exceeding the standard 10 mg twice daily) may be especially necessary for efficacy in ASUC patients. In fact, in a case-control study, 10 mg of tofacitinib 3 times daily significantly reduced the risk of colectomy, whereas 10 mg twice daily did not exert the same protective effect.[29]

However, when we conducted a sub-analysis of the studies from Table 1, including only those that prescribed the standard dose of 10 mg every 12 hours (and excluding studies prescribing tofacitinib together with other agents), the mean colectomy-free rate was 79%, a figure that was exactly the same as the one calculated when all studies, regardless of dose, were included. Furthermore, the same colectomy-free rate (79%) was obtained when only those studies prescribing (at least in some patients) doses higher than 10 mg/12 h were considered, although the number of patients in this last sub-analysis was very low (only 90). A previous systematic review also failed to show significant differences in 90-day colectomy rates between tofacitinib 30 and 20 mg daily doses (14% vs 23%).[67]Therefore, the advantage of increasing the tofacitinib dose in ASUC remains to be confirmed.

Regarding upadacitinib, the phase 3 clinical program (U-ACHIEVE and U-ACCOMPLISH) established a upadacitinib dosing protocol of 45 mg once daily in moderate-to-severe UC.[109] The dosing used for ASUC has varied, ranging from 45 mg once daily (in most cases) to 30 mg twice daily. In the largest study to date, no difference in colectomy rate was observed between patients receiving 45 mg once daily (ie, the standard dose) and 30 mg twice daily.[37]

15. Safety of JAKi in ASUC treatment

A recent warning was reported regarding the risk of thromboembolic events and cancer associated with tofacitinib.[110] However, it is important to keep in mind that these data were derived from patients with cardiovascular risk factors and rheumatoid arthritis aged over 50 years. In this respect, similar findings have not been observed in patients with UC.[111,112] Furthermore, the risk of thrombotic events with tofacitinib in UC appears to be comparable to that associated with anti-TNF agents.[113] Finally, potential concerns with tofacitinib, particularly those regarding increased cardiovascular and thrombosis risk, were not supported by findings of a systematic review and meta-analysis evaluating the real-world effectiveness of tofacitinib for moderate-to-severely active UC.[23]

A previous meta-analysis including 148 patients with ASUC treated with tofacitinib showed adverse events in 22 patients (15%), predominantly infectious complications other than herpes zoster, which resulted in tofacitinib discontinuation in 7 patients.[68] In another meta-analysis including 134

patients who received tofacitinib for ASUC, the most frequent adverse events were infectious.[67] Nevertheless, it has been advised to restrict JAKi use—in UC in general and in ASUC in particular—to younger otherwise healthy patients without cardiovascular or any other known risk factors, as a precautionary measure.[68,114]

In the 30 studies (and 167 patients with safety information) included in Table 1, serious adverse events (or adverse events leading to discontinuation) associated with tofacitinib ranged from 0% to 12% (with a weighted mean of 4.1%, 95% CI from 0.8 to 7.5%), including one transient hepatitis, one cardiovascular event, one pulmonary thromboembolism, one cytomegalovirus reactivation, one dural venous thrombosis, one herpes zoster, one abdominal pain/nausea/vomiting, and one viral pneumonia. Regarding mortality, 3 studies reported one death each: one death not directly related with tofacitinib (an 81-year-old man with chronic obstructive pulmonary disease and concomitant diabetes mellitus, who underwent a delayed colectomy),[40] one death in a patient with COVID-19 (and probable pulmonary thromboembolism),[66] and one death in a patient who did not respond to treatment (and did not consent for medical/surgical rescue).[35] No new adverse events different from those already documented in clinical trials were reported.

In the 9 studies (and 60 patients with safety information) included in Table 2, serious adverse events (or adverse events leading to discontinuation) associated with upadacitinib ranged from 0% to 11% (with a weighted mean of 2%, 95% CI from 0.05 to 11%), including one case of venous thromboembolism and one case of pulmonary embolism attributed to heparin-induced thrombocytopenia, which did not lead to upadacitinib discontinuation. Regarding mortality, no deaths were reported. As it was the case with tofacitinib, no new adverse events different from those already documented in clinical trials were reported.

In summary, the available data did not reveal any significant or new safety concerns when JAKi were used in the context of ASUC. However, definitive conclusions cannot be drawn due to the limited, uncontrolled observations and short follow-up periods. Therefore, newer treatment strategies including the use of JAKi should only be implemented in expert centers following multidisciplinary discussions involving gastroenterologists and colorectal surgeons. Furthermore, all JAKi should be used with caution in patients with cardiovascular risk factors or cancer, and it is recommended that patients be up-to-date with vaccinations, including zoster vaccines, as appropriate.[109]

16. Does JAKi treatment increase the risk of postoperative complications after colectomy for UC?

The rapid plasma clearance of JAKi would theoretically minimize postoperative complications.[115] However, one of the main concerns with these drugs is the potential increased risk of venous thromboembolism in patients with already heightened risk due to inflammatory burden.[30,116] In the study by Lightner et al., the risk of postoperative venous thromboembolism events within 4 weeks of colectomy for medically refractory UC was increased by preoperative tofacitinib exposure[117]; however, this study did not include a control group (not treated with tofacitinib), so it cannot be entirely ruled out that this increased risk is simply due to the severity of the patient with UC and the associated surgery. Additionally, in the study by Russell et al, tofacitinib exposure before surgery for medically refractory UC was associated with 3 times increased odds of venous thromboembolism compared with patients without tofacitinib exposure[118]; however, the retrospective nature and the small sample size of this study constitute a limitation.

In contrast, more recent studies have been unable to demonstrate a higher risk of postoperative complications (including thrombotic complications) in tofacitinib-exposed patients undergoing IBD-related surgery compared to unexposed patients or to patients exposed to anti-TNF or other biological agents.[119–122] In summary, being practical, it may be concluded that an urgent surgery—typically a colectomy for ASUC—should not be delayed to wait for JAKi washout.[123] In this respect, it is crucial to emphasize that decisions regarding the response to rescue therapy in ASUC must be made promptly, as prolonged medical therapy (any one) before colectomy is associated with increased postoperative complications. The primary objective should always be to reduce patient mortality rather than focusing solely on saving the colon.

17. Limitations of studies assessing the role of JAKi in ASUC

The conclusions from the studies assessing the efficacy of JAKi for the treatment of ASUC should be taken with caution as these studies have relevant methodological limitations summarized below.

1) The first and obvious limitation is that most of the studies have enrolled a small number of subjects treated with JAKi. In fact, the majority of data originate from case series and case reports.
2) Most of the studies are observational and retrospective, and only one study is an RCT (which compared tofacitinib combined with steroids vs. the standard treatment only with steroids).[35] In particular, no study has directly compared, through a randomized design, a JAKi vs other alternatives (such as steroids, infliximab, or cyclosporine). Therefore, guidance on managing ASUC with JAKi comes, at present, only from real-world data.[36]
3) There are different definitions of ASUC among studies. Some of them utilized clinical judgment to decide on hospitalization and the need for IV steroids as the criteria for enrollment. In others, however, various indices were employed to define ASUC (mainly Truelove and Witts criteria, the Lichtiger score, and the Mayo score). Unfortunately, there is no consensus on defining disease severity in ASUC trials. Even the Truelove and Witts criteria, commonly used since 1955, lack prospective validation and therefore may not be suitable to accurately identify eligible trial subjects in 2024.[4] On the other hand, the Mayo score is frequently employed in RCTs focused on chronic active moderate-to-severe UC, where it serves as the basis for regulatory-approved and validated endpoints. However, these last trials typically exclude patients with ASUC. Consequently, symptom and endoscopy-based indices used to evaluate disease activity have not been validated specifically for the ASUC population.[4]

4) There is variability in disease extension (extensive colitis, left-sided colitis, or even proctitis) in included patients; in fact, patients with proctitis are excluded in some ASUC trials, included in others, and are not mentioned in most of them.[4]
5) There is discordance regarding the inclusion of patients with multiple prior drug exposures. Furthermore, there is heterogeneity among studies regarding the positioning of JAKi for ASUC treatment as first-line (instead of steroids), second-line (instead of infliximab or cyclosporine), or third-line (after failure to infliximab or cyclosporine).
6) There is no consensus on inpatient steroid dosing or tapering regimens upon discharge after a successful treatment of ASUC.[4]
7) There is marked heterogeneity in the regimen protocols of the included studies, with variations in dosing and duration of JAKi therapy.
8) Endpoint/evaluation of efficacy is highly variable among ASUC studies. It must be acknowledged that there is currently no formal consensus on primary endpoints for ASUC trials, nor is there agreement on definitions for treatment response and treatment failure.[4] Thus, clinical response or remission served as the primary efficacy endpoint in some studies, albeit with considerable variability in their definitions. Trials primarily considered improvements in the Truelove and Witts/Lichtiger/Mayo scores to define the primary endpoint.[4] However, endoscopic assessment, considered the gold standard for objectively evaluating UC disease activity in outpatient clinical trials, was only exceptionally utilized in ASUC studies.[4] To address some of these limitations, in the present review we considered "colectomy-free rate" as the primary outcome since it serves as a universal objective marker of efficacy (see Tables 1 and 2).
9) Finally, the follow-up time after treatment with JAKi was generally short, while information on the evolution of the patients in the medium and long term was very limited. Consequently, the long-term effectiveness of JAKi in ASUC patients remains unclear.

18. Conclusions

ASUC is a medical emergency that affects ~20%–30% of patients with UC during their lifetime and carries a mortality risk of 1%. Corticosteroids remain the primary initial treatment; however, ~30% of patients do not respond and require rescue therapy. Cyclosporine and infliximab are currently the mainstays of salvage therapy and are generally considered comparable. JAKi have recently been incorporated into the treatment options for patients with UC, and their potential use is being investigated in the context of ASUC. Meanwhile, the increasing number of hospitalized ASUC patients who have failed to respond to previous anti-TNF therapies or other biological agents underscores the necessity for developing alternative treatments like JAKi.

In the present article, we have comprehensively reviewed the role of JAKi in the treatment of ASUC. Although the experience is still limited, to date, 30 studies (including 373 patients) have assessed the efficacy and safety of tofacitinib in ASUC, while the experience with upadacitinib is significantly more limited (with only 10 studies and 74 patients available). Moreover, experience with filgotinib in ASUC is currently nonexistent.

Both tofacitinib and upadacitinib appear to be quite effective in treating ASUC, with colectomy-free rates of approximately 80%. Future treatment strategies might evolve to incorporate JAKi either as an alternative or as a complement to IV steroids. In addition, for patients with prior exposure to biologics, these new therapeutic agents have shown promising efficacy in place of infliximab. Furthermore, among patients with ASUC who fail to respond to cyclosporine or infliximab, JAKi can theoretically be considered as a last salvage therapy to avoid colectomy.

Regarding safety, the available data did not reveal any significant or new safety concerns when JAKi were used in the context of ASUC. However, definitive conclusions cannot be drawn due to the limited, uncontrolled observations, and short follow-up periods.

The potential advantages of JAKi for the management of ASUC include their oral administration, rapid onset of action, short half-life with quick clearance, reduced susceptibility to drug loss associated with hypoalbuminemia, ease of transition from induction to maintenance therapy, lack of immunogenicity, and effectiveness in patients with prior biologic exposure.

In summary, JAKi seem to be a promising treatment option for ASUC. However, additional studies are needed to further evaluate their efficacy, safety, and the optimal timing, dosage, and treatment duration for managing ASUC cases. In addition, it is imperative to directly—through randomized trials—compare the efficacy and safety of JAKi with that of steroids (as first-line) and with that of cyclosporine and infliximab (as rescue regimens). Thus, RCTs will be essential to define whether JAKi can replace cyclosporine/infliximab as second-line therapy for the medical management of ASUC, or whether they can even be used as initial treatment in place of IV corticosteroids.

Author Contributions

J.P.G. wrote the first draft of the manuscript and critically reviewed the final version. M.C. complemented draft sections and critically reviewed the final version.

Funding

None declared.

Conflicts of Interest

J.P.G. has served as a speaker, a consultant, and advisory member for or has received research funding from MSD, Abbvie, Hospira, Pfizer, Kern Pharma, Biogen, Takeda, Janssen, Roche, Sandoz, Celgene, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Vifor Pharma. M.C. has served as a speaker, or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, and Lilly.

Data Availability

No new data are generated.

References

1. Gisbert JP, Chaparro M. Acute severe ulcerative colitis: state of the art treatment. *Best Pract Res Clin Gastroenterol.* 2018;**32-33**:59–69.
2. Levy LC, Coburn ES, Choi S, Holubar SD. The management of the hospitalized ulcerative colitis patient: the medical-surgical conundrum. *Curr Opin Gastroenterol.* 2020;**36**:265–276.
3. Gisbert JP, Garcia MJ, Chaparro M. Rescue therapies for steroid-refractory acute severe ulcerative colitis: a review. *J Crohns Colitis.* 2023;**17**:972–994.
4. Honap S, Jairath V, Sands BE, Dulai PS, Danese S, Peyrin-Biroulet L. Acute severe ulcerative colitis trials: the past, the present and the future. *Gut.* 2024;**73**:1763–1773.
5. Riviere P, Li Wai Suen C, Chaparro M, De Cruz P, Spinelli A, Laharie D. Acute severe ulcerative colitis management: unanswered questions and latest insights. *Lancet Gastroenterol Hepatol.* 2024;**9**:251–262.
6. Spinelli A, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: surgical treatment. *J Crohns Colitis.* 2022;**16**:179–189.
7. Lynch RW, Lowe D, Protheroe A, Driscoll R, Rhodes JM, Arnott ID. Outcomes of rescue therapy in acute severe ulcerative colitis: data from the United Kingdom inflammatory bowel disease audit. *Aliment Pharmacol Ther.* 2013;**38**:935–945.
8. Verdon C, Bessissow T, Lakatos PL. Management of acute severe colitis in the era of biologicals and small molecules. *J Clin Med.* 2019;**8**:2169.
9. Dong C, Metzger M, Holsbo E, Perduca V, Carbonnel F. Systematic review with meta-analysis: mortality in acute severe ulcerative colitis. *Aliment Pharmacol Ther.* 2020;**51**:8–33.
10. Mak WY, Zhao M, Ng SC, Burisch J. The epidemiology of inflammatory bowel disease: East meets west. *J Gastroenterol Hepatol.* 2020;**35**:380–389.
11. Holvoet T, Lobaton T, Hindryckx P. Optimal management of acute severe ulcerative colitis (ASUC): challenges and solutions. *Clin Exp Gastroenterol.* 2021;**14**:71–81.
12. Lauricella S, Brucchi F, Cavalcoli F, et al. Current management of acute severe ulcerative colitis: new insights on the surgical approaches. *J Pers Med.* 2024;**14**:580.
13. Kuriakose Kuzhiyanjal AJ, Limdi JK. Management of acute severe ulcerative colitis-an update for generalist and specialist clinicians. *Br Med Bull.* 2024;**151**:3–15.
14. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol.* 2007;**5**:103–110.
15. Seah D, De Cruz P. Review article: the practical management of acute severe ulcerative colitis. *Aliment Pharmacol Ther.* 2016;**43**:482–513.
16. Gergely M, Prado E, Deepak P. Management of refractory inflammatory bowel disease. *Curr Opin Gastroenterol.* 2022;**38**:347–357.
17. Honap S, Agorogianni A, Colwill MJ, et al. JAK inhibitors for inflammatory bowel disease: recent advances. *Frontline Gastroenterol.* 2024;**15**:59–69.
18. Panes J, Gisbert JP. Efficacy of tofacitinib treatment in ulcerative colitis. *Gastroenterol Hepatol.* 2019;**42**:403–412.
19. Chaparro M, Garre A, Mesonero F, et al. Tofacitinib in ulcerative colitis: real-world evidence from the ENEIDA registry. *J Crohns Colitis.* 2021;**15**:35–42.
20. Macaluso FS, Maida M, Ventimiglia M, Orlando A. Effectiveness and safety of tofacitinib for the treatment of ulcerative colitis: a single-arm meta-analysis of observational studies. *Dig Liver Dis.* 2022;**54**:183–191.
21. Banerjee R, Sharma V, Patel R, et al. Tofacitinib use in ulcerative colitis: an expert consensus for day-to-day clinical practice. *Indian J Gastroenterol.* 2024;**43**:22–35.
22. Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. *Clin Gastroenterol Hepatol.* 2020;**18**:2179–2191.e6.
23. Taxonera C, Olivares D, Alba C. Real-world effectiveness and safety of tofacitinib in patients with ulcerative colitis: systematic review with meta-analysis. *Inflamm Bowel Dis.* 2022;**28**:32–40.
24. Feagan BG, Danese S, Loftus EV Jr., et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. *Lancet.* 2021;**397**:2372–2384.
25. Sandborn WJ, Su C, Sands BE, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2017;**376**:1723–1736.
26. 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.
27. Loftus EV Jr., 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.
28. Battat R, Hemperly A, Truong S, et al. Baseline clearance of infliximab is associated with requirement for colectomy in patients with acute severe ulcerative colitis. *Clin Gastroenterol Hepatol.* 2021;**19**:511–518.e6.
29. 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.
30. AbdelMeguid AMA, Whitehead E, Sebastian S. Modern practical management of acute severe colitis. *Indian J Gastroenterol.* 2024;**43**:78–92.
31. Danese S, D'Amico F, Bonovas S, Peyrin-Biroulet L. Positioning tofacitinib in the treatment algorithm of moderate to severe ulcerative colitis. *Inflamm Bowel Dis.* 2018;**24**:2106–2112.
32. Singh A, Midha V, Kaur K, et al. Tofacitinib versus oral prednisolone for induction of remission in moderately active ulcerative colitis [ORCHID]: a prospective, open-label, randomized, pilot study. *J Crohns Colitis.* 2024;**18**:300–307.
33. Berinstein. A sequential multiple assignment randomized trial (SMART) developing and optimizing patient-tailored adaptive treatment strategies (ATS) for acute severe ulcerative colitis. Clinicaltrials.Gov; November 2023. Accessed July 1, 2024. https://clinicaltrials.gov/study/NCT05867329
34. Chaparro M, Acosta D, Rodriguez C, et al.; To-ReWard Study Group. Real-world evidence of tofacinitib in ulcerative colitis: short-term and long-term effectiveness and safety. *Am J Gastroenterol.* 2023;**118**:1237–1247.
35. 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.
36. Suen CFDLW, Choy MC, De Cruz P. What to do when traditional rescue therapies fail in acute severe ulcerative colitis. *Intest Res.* 2024;**22**:397–413.
37. Berinstein JA, Karl T, Patel A, et al. Effectiveness of upadacitinib for patients with acute severe ulcerative colitis: a multicenter experience. *Am J Gastroenterol.* In press;**119**:1421–1425.
38. Komeda Y, Kono M, Kashida H, et al. Successful initial tofacitinib treatment for acute severe ulcerative colitis with steroid resistance: a case series. *Ann Gastroenterol.* 2023;**36**:97–102.
39. Malakar S, Kothalkar S, Shamsul Hoda U, Ghoshal UC. Tofacitinib in steroid-refractory acute severe ulcerative colitis: a retrospective analysis. *Cureus.* 2023;**15**:e45416.
40. Uzzan M, Bresteau C, Laharie D, et al.; GETAID-TALC Study Group. Tofacitinib as salvage therapy for 55 patients hospitalised with refractory severe ulcerative colitis: a GETAID cohort. *Aliment Pharmacol Ther.* 2021;**54**:312–319.
41. Xiao Y, Benoit N, Sedano R, et al. Effectiveness of tofacitinib for hospitalized patients with acute severe ulcerative colitis: case series. *Dig Dis Sci.* 2022;**67**:5213–5219.

42. Honap S, Pavlidis P, Ray S, et al. Tofacitinib in acute severe ulcerative colitis-a real-world tertiary center experience. *Inflamm Bowel Dis*. 2020;**26**:e147–e149.
43. Eqbal A, Hilley P, Choy M, Srinivasan A, de Cruz P. Outcomes out to 12 months after sequential use of high-dose tofacitinib following infliximab in acute severe ulcerative colitis. *Intern Med J*. 2023;**53**:1497–1500.
44. Cuccia G, Privitera G, Di Vincenzo F, et al. Predictors of efficacy of janus kinase inhibitors in patients affected by ulcerative colitis. *J Clin Med*. 2024;**13**:766.
45. Li Wai Suen CFD, Seah D, Choy MC, De Cruz P. Factors associated with response to rescue therapy in acute severe ulcerative colitis. *Inflamm Bowel Dis*. 2024;**30**:1389–1405.
46. Harbord M, Eliakim R, Bettenworth D, et al.; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis*. 2017;**11**:769–784.
47. Lowenberg M, Duijvis NW, Ponsioen C, van den Brink GR, Fockens P, D'Haens GR. Length of hospital stay and associated hospital costs with infliximab versus cyclosporine in severe ulcerative colitis. *Eur J Gastroenterol Hepatol*. 2014;**26**:1240–1246.
48. 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.
49. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology*. 2011;**141**:1194–1201.
50. Ardizzone S, Cassinotti A, Duca P, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol*. 2011;**9**:483–489.e3.
51. Laharie D, Bourreille A, Branche J, et al. Evolution of endoscopic lesions in steroid-refractory acute severe ulcerative colitis responding to infliximab or cyclosporine. *Clin Gastroenterol Hepatol*. 2021;**19**:1180–1188.e4.
52. Kucharzik T, Ellul P, Greuter T, et al. ECCO guidelines on the prevention, diagnosis, and management of infections in inflammatory bowel disease. *J Crohns Colitis*. 2021;**15**:879–913.
53. Ananthakrishnan AN. Infliximab or ciclosporin for acute severe ulcerative colitis? *Lancet Gastroenterol Hepatol*. 2016;**1**:2–3.
54. Macaluso FS, Orlando A, Papi C, et al.; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Use of biologics and small molecule drugs for the management of moderate to severe ulcerative colitis: IG-IBD clinical guidelines based on the GRADE methodology. *Dig Liver Dis*. 2022;**54**:440–451.
55. Rolny P, Vatn M. Cyclosporine in patients with severe steroid refractory ulcerative colitis in the era of infliximab. Review article. *Scand J Gastroenterol*. 2013;**48**:131–135.
56. Durai D, Hawthorne AB. Review article: how and when to use ciclosporin in ulcerative colitis. *Aliment Pharmacol Ther*. 2005;**22**:907–916.
57. Shah SC, Naymagon S, Cohen BL, Sands BE, Dubinsky MC. There is significant practice pattern variability in the management of the hospitalized ulcerative colitis patient at a tertiary care and IBD referral center. *J Clin Gastroenterol*. 2018;**52**:333–338.
58. Spiegel BM, Ho W, Esrailian E, et al. Controversies in ulcerative colitis: a survey comparing decision making of experts versus community gastroenterologists. *Clin Gastroenterol Hepatol*. 2009;**7**:168–74, 174.e1.
59. Rodriguez-Lago I, Ferreiro-Iglesias R, Nos P, Gisbert JP; en representación del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). Management of acute severe ulcerative colitis in Spain: a nationwide clinical practice survey. *Gastroenterol Hepatol*. 2019;**42**:90–101.
60. Festa S, Scribano ML, Pugliese D, et al. Long-term outcomes of acute severe ulcerative colitis in the rescue therapy era: a multicentre cohort study. *United European Gastroenterol J*. 2021;**9**:507–516.
61. Rapport F, Clement C, Seagrove AC, Alrubaiy L, Hutchings HA, Williams JG. Patient views about the impact of ulcerative colitis and its management with drug treatment and surgery: a nested qualitative study within the CONSTRUCT trial. *BMC Gastroenterol*. 2019;**19**:166.
62. Ahmed W, Galati J, Kumar A, et al. Dual biologic or small molecule therapy for treatment of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2022;**20**:e361–e379.
63. Gilmore R, Hilley P, Srinivasan A, Choy MC, Grace JA, de Cruz P. Tofacitinib is safe and effective when used in combination with infliximab for the management of refractory ulcerative colitis. *Clin Gastroenterol Hepatol*. 2021;**19**:1302–1303.
64. Yang Q, Chen L, Feng L, et al. Success of cyclosporin and tofacitinib combination therapy in a patient with severe steroid-refractory ulcerative colitis. *Inflamm Bowel Dis*. 2021;**27**:e157–e158.
65. Garcia MJ, Riestra S, Amiot A, et al. Effectiveness and safety of a third-line rescue treatment for acute severe ulcerative colitis refractory to infliximab or ciclosporin (REASUC study). *Aliment Pharmacol Ther*. 2024;**59**:1248–1259.
66. Jena A, Mishra S, Sachan A, Singh H, Singh AK, Sharma V. Tofacitinib in acute severe ulcerative colitis: case series and a systematic review. *Inflamm Bowel Dis*. 2021;**27**:e101–e103.
67. Mpakogiannis K, Fousekis FS, Christodoulou DK, Katsanos KH, Narula N. The current role of Tofacitinib in acute severe ulcerative colitis in adult patients: a systematic review. *Dig Liver Dis*. 2023;**55**:1311–1317.
68. 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.
69. Huang CW, Yen HH, Chen YY. Rescue therapies for steroid-refractory acute severe ulcerative colitis: a systemic review and network meta-analysis. *J Crohns Colitis*. 2024;**18**:2063–2075.
70. Damianos JA, Osikoya O, Brennan G. Upadacitinib for acute severe ulcerative colitis: a systematic review. *Inflamm Bowel Dis*. 2024:izae191. https://doi.org/10.1093/ibd/izae19
71. Berinstein JA, Steiner CA, Regal RE, et al. Efficacy of induction therapy with high-intensity tofacitinib in 4 patients with acute severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2019;**17**:988–990.e1.
72. Constant BD, Baldassano R, Kirsch J, Mitchel EB, Stein R, Albenberg L. Tofacitinib salvage therapy for children hospitalized for corticosteroid- and biologic-refractory ulcerative colitis. *J Pediatr Gastroenterol Nutr*. 2022;**75**:724–730.
73. Costaguta GA, Girard C, Groleau V, Grzywacz K, Dirks MH, Deslandres C. The role of tofacitinib in the treatment of acute severe colitis in children. *J. Can. Assoc. Gastroenterol.*. 2024;**7**:196–203.
74. Dolinger MT, Spencer EA, Lai J, Dunkin D, Dubinsky MC. Dual biologic and small molecule therapy for the treatment of refractory pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;**27**:1210–1214.
75. Festa S, De Biasio F, Aratari A, Papi C. Intentional treatment with tofacitinib in a patient with severe refractory ulcerative colitis and concomitant Sars-CoV-2 infection. *Dig Liver Dis*. 2022;**54**:1598–1599.
76. Fortuny M, Cañete F, Calm A, Calafat M, Domènech E. Tofacitinib for the treatment of acute severe ulcerative colitis refractory to infliximab. *Gastroenterol Hepatol*. 2022;**45**:11–12.
77. Gilmore R, Hilley P, Srinivasan A, Choy M, De Cruz P. Sequential use of high-dose tofacitinib after infliximab salvage therapy in acute severe ulcerative colitis. *J Crohns Colitis*. 2022;**16**:166–168.
78. Girard C, Dirks M, Deslandres C. Tofacitinib to treat severe acute refractory colitis in a teenager: case report and review of the literature. *JPGN Rep*. 2022;**3**:e241.
79. Griller N, Cohen L. Rapid onset of tofacitinib induction therapy for the treatment of ulcerative colitis. *Clin Gastroenterol Hepatol*. 2019;**17**:1213.

80. Komeda Y, Sakurai T, Sakai K, et al. Refractory case of ulcerative colitis with idiopathic thrombocytopenic purpura successfully treated by Janus kinase inhibitor tofacitinib: A case report. *World J Clin Cases*. 2020;**8**:6389–6395.
81. Kotwani P, Terdiman J, Lewin S. Tofacitinib for rescue therapy in acute severe ulcerative colitis: a real-world experience. *J Crohns Colitis*. 2020;**14**:1026–1028.
82. Naganuma M, Kobayashi T, Kunisaki R, et al.; Japanese UC Study Group. Real-world efficacy and safety of advanced therapies in hospitalized patients with ulcerative colitis. *J Gastroenterol*. 2023;**58**:1198–1210.
83. Parra-Izquierdo V, Frias-Ordonez JS, Cuadros C, et al. Tofacitinib in the treatment of moderate to severe ulcerative colitis in Colombian pediatric patients: Real world experience. *Gastroenterol Hepatol*. 2024;**47**:574–581.
84. Parra-Izquierdo V, Frias-Ordonez JS, Juliao-Banos F, Cuadros C, Romero Sanchez C, Florez-Sarmiento C. Colombian experience with the use of tofacitinib in severe acute ulcerative colitis: a case series study. *Gastroenterol Hepatol*. 2024;**47**:582–590.
85. Resal T, Bacsur P, Keresztes C, et al.; TFB Study Group . Real-life efficacy of tofacitinib in various situations in ulcerative colitis: a retrospective worldwide multicenter collaborative study. *Inflamm Bowel Dis*. 2024;**30**:768–779.
86. Rutka M, Pigniczki D, Molnar T. Tofacitinib therapy, the lender of last resort. *J Crohns Colitis*. 2021;**15**:694.
87. Santos S, Gamelas V, Saraiva R, Simoes G, Saiote J, Ramos JT. An option for acute severe ulcerative colitis? *GE Port J Gastroenterol*. 2022;**29**:132–134.
88. Sedano R, Jairath V. High-dose rescue tofacitinib prevented inpatient colectomy in acute severe ulcerative colitis refractory to anti-TNF. *Inflamm Bowel Dis*. 2021;**27**:e59–e60.
89. Ali NM, Shehab MA. Upadacitinib as a rescue therapy in acute severe ulcerative colitis: a case report and review of the literature. *Am J Case Rep*. 2023;**24**:e940966.
90. Clinton J, Motwani KK, Schwartz S, et al. Upadacitinib as rescue therapy for the treatment of acute severe colitis in an acute care setting. *Dig Dis Sci*. 2024;**69**:1105–1109.
91. Dalal RS, Winter RW, Gupta S, Sasson GF, Hamilton MJ, Allegretti JR. Clinical outcomes at 8-16 weeks after upadacitinib initiation for acute severe ulcerative colitis: a case series in the United States. *Inflamm Bowel Dis*. 2024;**30**:1042–1043.
92. Gilmore R, Tan WL, Fernandes R, An YK, Begun J. Upadacitinib salvage therapy for infliximab-experienced patients with acute severe ulcerative colitis. *J Crohns Colitis*. 2023;**17**:2033–2036.
93. Hilley P, Con D, Choy MC, Srinivasan A, De Cruz P. Upadacitinib in end stage renal disease: a case of acute severe ulcerative colitis. *JGH Open*. 2023;**7**:1012–1015.
94. Tanida S, Kubo R, Yoshii S, et al. Upadacitinib plus intensive granulocyte and monocyte adsorptive apheresis for ulcerative colitis achieved ulcer healing for pyoderma gangrenosum. *J Clin Med Res*. 2023;**15**:446–455.
95. Xu X, Jiang JW, Lu BY, Li XX. Upadacitinib for refractory ulcerative colitis with primary nonresponse to infliximab and vedolizumab: a case report. *World J Clin Cases*. 2024;**12**:1685–1690.
96. Zhang J, Li R, Chen L, et al. Effectiveness and safety of upadacitinib in acute severe ulcerative colitis patients from single Chinese IBD Center: a monocentric study. *Clin Exp Med*. 2024;**24**:233.
97. Zinger CH, Ringel Y, Eitan M, et al. Upadacitinib for acute severe ulcerative colitis. *Inflamm Bowel Dis*. 2023;**29**:1667–1669.
98. Laharie D, Bourreille A, Branche J, et al.; Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. 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.
99. Boneschansker L, Ananthakrishnan AN; Massachusetts General Hospital Crohn's And Colitis Center Collaborators. Comparative effectiveness of upadacitinib and tofacitinib in inducing remission in ulcerative colitis: real-world data. *Clin Gastroenterol Hepatol*. 2023;**21**:2427–2429.e1.
100. Levine J, McKibbin J, Ham R, et al. Use of upadacitinib in 16 tofacitinib-refractory ulcerative colitis patients: a single-center case 2Series. *Inflamm Bowel Dis*. 2023;**30**:2232–2235.
101. Reinisch W, Melmed GY, Nakase H, et al. Comparative efficacy and safety of upadacitinib vs. vedolizumab, ustekinumab, and tofacitinib after induction and maintenance for ulcerative colitis: three matching-adjusted indirect comparisons. *Adv Ther*. 2024;**41**:3832–3849.
102. Kochhar GS, Khataniar H, Jairath V, Farraye FA, Desai A. Comparative effectiveness of upadacitinib and tofacitinib in ulcerative colitis: a us propensity-matched cohort study. *Am J Gastroenterol*. 2024;**119**:2471–2479.
103. Dalal RS, Kallumkal G, Cabral HJ, Barnes EL, Allegretti JR. One-year comparative effectiveness of upadacitinib vs tofacitinib for ulcerative colitis: a multicenter cohort study. *Am J Gastroenterol*. 2024;**119**:1628–1631.
104. Odah T, Karime C, Desai A, et al. Response to upadacitinib in patients with inflammatory bowel disease previously treated with tofacitinib. *Dig Dis Sci*. 2024;**69**:3911–3919.
105. Burr NE, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. *Gut*. 2021;**71**:1976–1987.
106. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2022;**7**:161–170.
107. Rokkas T, Gisbert JP, Ekmektzoglou K, Dassopoulos T, Niv Y, O'Morain C. Comparative maintenance performance of all biologic agents and small molecules in ulcerative colitis: a network meta-analysis. *Eur J Gastroenterol Hepatol*. 2024;**36**:520–533.
108. Sandborn WJ, Ghosh S, Panes J, et al.; Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med*. 2012;**367**:616–624.
109. Weiss A, Barnes EL, Bewtra M. A Practical guide to the use of upadacitinib in ulcerative colitis and Crohn's disease. *Am J Gastroenterol*. 2024;**119**:1211–1217.
110. Ytterberg SR, Bhatt DL, Mikuls TR, et al.; ORAL Surveillance Investigators. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med*. 2022;**386**:316–326.
111. Olivera PA, Dignass A, Dubinsky MC, et al. Preventing and managing cardiovascular events in patients with inflammatory bowel diseases treated with small-molecule drugs, an international Delphi consensus. *Dig Liver Dis*. 2024;**56**:1270–1280.
112. Panes J, D'Haens GR, Sands BE, et al. Analysis of tofacitinib safety in ulcerative colitis from the completed global clinical developmental program up to 9.2 years of drug exposure. *United European Gastroenterol J*. 2024;**12**:793–801.
113. Kochar BD, Cheng D, Cai T, Ananthakrishnan AN. Comparative risk of thrombotic and cardiovascular events with tofacitinib and anti-TNF agents in patients with inflammatory bowel diseases. *Dig Dis Sci*. 2022;**67**:5206–5212.
114. Calmejane L, Laharie D, Kirchgesner J, Uzzan M. Review article: updated management of acute severe ulcerative colitis: from steroids to novel medical strategies. *United European Gastroenterol J*. 2023;**11**:722–732.
115. 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*. 2014;**42**:759–773.
116. D'Amico F, Peyrin-Biroulet L, Danese S. Tofacitinib for acute severe colitis: when the going gets tough, the tough get going. *J Crohns Colitis*. 2020;**14**:883–885.
117. Lightner AL, Vaidya P, Holubar S, et al. Perioperative safety of tofacitinib in surgical ulcerative colitis patients. *Colorectal Dis*. 2021;**23**:2085–2090.
118. Russell TA, Banerjee S, Lipman JM, et al. Tofacitinib is associated with increased risk of postoperative venous thromboembolism in patients with ulcerative colitis. *Dis Colon Rectum*. 2024;**67**:693–699.

119. Deepak P, Alayo QA, Khatiwada A, et al. Safety of tofacitinib in a real-world cohort of patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2021;**19**:1592–1601.e3.
120. Hyman NH, Cheifetz AS. PUCCINI: safety of anti-TNF in the perioperative setting. *Gastroenterology*. 2022;**163**:44–46.
121. Gomaa I, Aboelmaaty S, Bhatt H, et al. Tofacitinib exposure does not increase postoperative complications among patients with ulcerative colitis undergoing total colectomy: a retrospective case-control study. *Dis Colon Rectum*. 2024;**67**:1443–1449. In press.
122. Dragoni G, Innocenti T, Amiot A, et al.; "TOFA-poSTOP" Study Group. Rates of adverse events in patients with ulcerative colitis undergoing colectomy during treatment with tofacitinib vs biologics: a multicenter observational study. *Am J Gastroenterol*. 2024;**119**:1525–1535.
123. Fudman D, McConnell RA, Ha C, Singh S. Modern advanced therapies for inflammatory bowel diseases: practical considerations and positioning. *Clin Gastroenterol Hepatol*. 2024:S1542-3565(24)00728-6. https://doi.org/10.1016/j.cgh.2024.06.050