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REVIEW ARTICLE

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Review article: Updated management of acute severe ulcerative colitis: From steroids to novel medical strategies

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Abstract

Acute severe ulcerative colitis (ASUC) occurs in up to 25% of patients with ulcerative colitis (UC). Therapeutic approaches have evolved during the past years with the increasing bio exposure of admitted patients and the extension of the number of approved drugs for UC. In this review, we aimed to summarize the latest evidence in short-term and long-term medical strategies for ASUC. In addition to general principles such as venous thromboembolism prophylaxis, screening for triggering and worsening factors and close monitoring, first-line therapy for ASUC remains intravenous corticosteroids. In naive patients, the optimum maintenance strategy for steroid-responding patients does not necessarily include biologics. Second-line therapy includes infliximab or calcineurin inhibitors (CNIs) with similar short- and long-term colectomy rates. Despite its pathophysiological relevance, there is insufficient evidence to promote intensified induction with infliximab. Prior treatment exposure is a cornerstone for guiding therapeutic choice of short- and long-term therapies in the context of ASUC: in anti-TNF exposed patients, CNIs may be favored as a bridge therapy to vedolizumab or ustekinumab. Third-line salvage therapy could be a therapeutic option in selected patients referred to expert centers. Additionally, evidence is accumulating regarding the use of tofacitinib in ASUC.

KEYWORDS
ASUC, ciclosporin, infliximab, tofacitinib, ulcerative colitis

INTRODUCTION

For decades, intravenous corticosteroids have been the standard first-line medical treatment for acute severe ulcerative colitis (ASUC). However, despite its effectiveness, up to 30%–40% of patients do not respond to this treatment alone and require a second line of therapy.[1,2] Infliximab and ciclosporin are both effective second-line therapies, as shown in a randomized controlled trial (RCT).[3] With the increasing use of biologics in the IBD population, more patients with ASUC who have failed multiple biological treatments are being admitted to referral centers. As a result, new strategies are being developed that use newly approved treatments for moderate-to-severe UC with little or no evidence in ASUC. This review article first covers updated general principles of ASUC management that remain applicable in the biological era. It then explores innovative medical approaches for ASUC and examines evidence for new medical strategies in the management of ASUC.

SEARCH METHODOLOGY

Starting in September 2022, we performed a literature search using Medline and the Cochrane library. We searched for unpublished records on clinicaltrials.gov, conference abstracts and previous reviews. We used the keywords with various combinations "acute severe ulcerative colitis (UC)", "ASUC" and "severe UC", "infliximab", "ciclosporin", "tacrolimus", "calcineurin inhibitors", "vedolizumab", "tofacitinib" and "ustekinumab.

UPDATED AND GENERAL PRINCIPLES ON THE MANAGEMENT OF PATIENTS WITH ACUTE SEVERE ULCERATIVE COLITIS

Diagnosis of ASUC is still based on the Truelove and Witts criteria (Supplementary Table 1).[4] This score is linked to the risk of colectomy at days 3 and 5. The alternative Lichtiger score is mostly used in clinical trials and to assess response to treatment (Supplementary table 2).[5,6] The initial medical management of ASUC is summarized in Table 1 with methods and limitations of each key point detailed in Table 2.

Non-Steroidal Anti-Inflammatory Drugs should be looked for as a triggering and worsening factor[7] as well as enteric infections. In patients with IBD, *Clostridioides difficile* (C-diff) related colitis was associated with higher morbi-mortality than in patients without IBD.[8–10] Cytomegalovirus (CMV) is also associated with higher colectomy rates in acute colitis[11] especially in patients exposed to steroids or ciclosporin.[12] However, the advantage of giving an antiviral drug is debated and probably restricted to very selected cases. Viral inclusion bodies on biopsies evidencing a direct cytopathogenic effect and a high viral load on biopsies are factors in favor of initiating antiviral treatment.[13–15]

Standard biological evaluation should be performed as well as biological treatment eligibility, including testing for viral antibodies, latent tuberculosis (TB) screening, and cholesterol and magnesium-level monitoring.[16,17] However, it should not delay the start of necessary immunomodulatory treatment. Endoscopic evaluation of the rectal and colonic mucosa remains useful to assess severity and rule out alternative diagnoses. The most common score used with a predictive value to evaluate disease severity is the UC Endoscopic Index of Severity (UCEIS, Supplementary Table 3) that has good intra-investigator and moderate inter-investigator agreement.[18] Deep ulcers are associated with a higher risk of colectomy.[19]

Overtime, mortality rates of ASUC have drastically decreased to about 0.84% after 3 months and 1.01% after 1 year.[20] However, when complications such as colonic perforation occur, the mortality rate is much higher. In addition to endoscopic assessment, early and repeated imaging should therefore be performed to look for complications such as colectasia.[7,21,22] Patients presenting with toxic megacolon described as a colonic dilatation larger than 6 cm, often associated with systemic symptoms, are at high risk of perforation and should be referred to a surgeon for emergent colectomy.[23]

Currently, there is no evidence supporting the systematic use of antibiotics in ASUC.[24] When suspected, venous thromboembolism (VTE) and pulmonary embolism must also be monitored as they are one of the leading causes of morbidity and mortality during IBD flare-ups.[25]

In a 2008 retrospective study of 7108 patients, the mortality rate of patients undergoing colectomy was 5.4% following urgent admission and 0.7% in elective admissions. The likelihood of post-colectomy morbidity and mortality increased with the number of days elapsed from admission.[26] In a retrospective study of 80 patients who underwent surgery after a median of 6 days of IV steroids, length of hospital stay prior to colectomy was the only independent factor linked to post-surgical complications (OR 1.12, *p*-value 0.044).[27] Therefore, these severity factors should be monitored daily to avoid delaying surgery (Table 3).

Overall, established general principles of the management of ASUC should continuously be reinforced and are still relevant even in the biological era. A holistic approach to the medical management of ASUC summarized in Tables 1 and 2 will allow the prevention of

TABLE 1 Proposed checklist of initial investigations and therapeutic actions to be conducted at admission for acute severe ulcerative colitis (ASUC).

Investigations at admission	Stool culture
	Stool test for *C. difficile* toxins
	Flexible sigmoidoscopy with biopsies and CMV immunohistochemistry testing
	Labs including kidney function, albumin, hemoglobin, CRP
	Pre-therapeutic evaluation with viral serologies and tuberculosis screening
	Abdominal CT-scan to assess extent of colitis and local complications
Therapeutic management on admission	Early IV steroids: At least 0.8 mg/kg for a maximum duration of 7 days (consider surgery if no response at 3 and 5 days).
	Low molecular weight heparin prophylaxis: Enoxaparin 40 mg daily
	Consider antibiotics if specific context including fever
	Consider exclusive enteral nutrition

TABLE 2 General principles of acute severe ulcerative colitis (ASUC) management.

Points to manage	Method	Limitations
Swift diagnosis to decrease colectomy rates	Truelove and Witts or Lichtiger score, lab tests (CRP, Hemoglobin, albumin)	Clinician extensive evaluation should also be performed
Identify triggering factors	Medical history (current or past digestive infections), treatment history (NSAIDS)	Systematic use of antibiotics does not decrease colectomy rates, selective information collection
Identify worsening factors including *C. difficile* and CMV	Stool culture and PCR for toxin	Treatment of infection only is most of the time insufficient
	Colonic biopsies and immunohistochemistry for CMV	Causality of CMV infection requires specific evaluation by trained pathologists.
Assess endoscopic severity	UCEIS	Inter-investigator agreement is moderate
	Deep ulcers	
Imaging for abscesses, colectasia, perforation	CT-scan	Consider ultrasound to avoid radiation
Manage thromboembolism risk	Low molecular weight heparin	Optimal duration requires further investigation
Mitigate surgery-associated morbi-mortality	Daily evaluation for surgery and early treatment response assessment	Acceptability of patients.
		Requirement of a tertiary IBD surgical center
Optimize nutritional status	Nutritional assessment including caloric input and iron levels	Exclusive enteral nutrition may be used to improve early outcomes but with limited acceptability
For all patients, early assessment of treatment eligibility through biology, viral and tuberculosis screening.		

TABLE 3 Severity factors of acute severe ulcerative colitis (ASUC).

Factor	Effect
NSAIDs intake[7]	Frequent and early clinical relapse of quiescent diseases
Clostridioides difficile[8]	In hospitalized patients for IBD, the mortality rate is 4 times higher in the *Clostridoides difficile* group
CMV[11]	In steroid-refractory patients, 50% of colectomy in patients with CMV reactivation versus 15% in patients without CMV.
Toxic megacolon[22]	Small bowel distension is associated with steroids failure (odds ratio of 3.55 in patients who failed steroid therapy)
Venous thromboembolism[25,64]	Age and comorbidity excess mortality of 2.1 compared with non-IBD patients. Associated with longer length of hospital stay.
Time to colectomy[27]	Duration of in-hospitalization treatment associated with higher postoperative complications (OR 1.12, *p*-value 0.044)

complications, optimize the chance of success of anti-inflammatory medical therapies and ensure a continuous monitoring and a prompt referral to surgery to avoid morbi-mortality.

MEDICAL MANAGEMENT OF ACUTE SEVERE ULCERATIVE COLITIS

First line therapy

Current guidelines recommend the use of IV corticosteroids at a dose of 0.8–1 mg/kg of methylprednisolone equivalent for 5–7 days as a first line for ASUC.[10] In their historical trial, Truelove and Witts reported a remission rate of 41% and a mortality rate of 7% among IV-steroid-treated patients and of 16% and 24% in the placebo group.[4] In a 2007 meta-analysis, 67% of patients had a short-term response to steroids.[2] Of note, there is no benefit of adding aminosalicylate to steroids as demonstrated in an RCT of 149 patients.[28]

The Oxford criteria based on a retrospective study of 49 patients who had ASUC and were treated with IV steroids aimed to predict response rates and the risk of colectomy during the third to fifth day of steroid treatment. It includes the number of bowel movements and CRP levels with the persistence of more than 8 bowel movements or 3–8 stools and a CRP >45 mg/L at day 3 being associated with an 85%-risk of colectomy.[23] However, these criteria were developed in 1996 from a retrospective study with a small sample in a single tertiary hospital. Due to the overall improvement of standard-of-care, the Oxford criteria are no longer relevant, as evidenced by a study from 2017 which reported colectomy rates of 36%, compared to the historic rate of 85%.[29]

The Lichtiger score is a simple clinical score to assess disease activity at bedside.[30] It is derived from an RCT of 20 patients receiving placebo or ciclosporin. Scores below 10 were predictive of hospital discharge without surgery.[5] A new prognosis index has recently been developed in a cohort study of 117 patients and validated in 172 patients. This four-point model includes a CRP level ≥100 mg/L, albumin ≤25 g/L and UCEIS ≥4 or ≥7 on admission.[31] A score ≥3 predicted steroid failure in 84% of the patients (OR 11.9, 95%CI [confidence interval] 10.8–13.0).

These scores detailed in Table 4, while useful in predicting some outcomes of ASUC, do not substitute a comprehensive assessment to guide decisions on surgery or switch to second-line therapies.

Exclusive enteral nutrition could be considered in ASUC. In a recent RCT of 62 ASUC patients, combining semi-elemental nutrition with IV corticosteroids showed a statistically significant benefit on the primary endpoint of corticosteroid failure in the per protocol analysis (19% vs. 43%, $p = 0.04$). However, the enteral nutrition group showed clear advantages on key secondary endpoints such as length of hospital stay, day 7 albumin level, CRP levels, and fecal calprotectin levels.[32]

Maintenance treatment in steroid responders

The optimal long-term maintenance therapy for immunomodulator (IMM)-naïve patients having a first episode of ASUC and responding to steroids remains unclear. A multicenter retrospective study reviewed data from 141 thiopurine- and IMM-naïve patients hospitalized in 14 tertiary centers in Italy for their first admission for ASUC. All studied patients responded to IV steroids.[33] Aminosalicylates were prescribed for 82 patients (58.1%), 42 patients received IMMs and the remaining 17 patients received a combination therapy with infliximab and thiopurines. With a median follow-up of 48 months, 18 patients (12.8%) underwent colectomy. Overall survivals without relapse and without colectomy were 59.6% and 96.3% at 12 months and 23.1% and 88.9% at 60 months, respectively. There was no difference between the 3 maintenance regimens in patients receiving aminosalicylates, IMMs, or infliximab after propensity score matching. These findings suggest that aminosalicylates could still be used in monotherapy for treatment-naïve patients who respond to IV steroids in ASUC.

In another retrospective study of 142 patients with ASUC responding to steroids, 59 patients (41.5%) were treated with aminosalicylates, 60 (42%) with immunomodulators, 18 (13%) with anti-TNF agents and 5 (3.5%) with vedolizumab.[34] The rates of relapse- and colectomy-free survival were at 58% and 96% at 1 year, and at 40% and 91% at 5 years. In the multivariate analysis, relapse-free survival was significantly higher in patients with fewer than 6 stools at day 3 (HR 0.56, 95% CI [0.34–0.91]), a partial Mayo score below 2 at day 5 (0.41, [021–0.80)], and who received anti-TNF maintenance therapy (0.37, [0.16–0.87]). This suggests that an early and significant clinical response to steroids is associated with favorable long-term course. As opposed to the former study, this study was not limited to IMM- and biologics-naive patients.

Overall, the best maintenance strategy in patients with ASUC responding to IV steroids is not established. Ongoing controlled trials may provide further evidence to choose the optimal strategy. In the meantime, maintenance treatment should be evaluated on a case-by-case basis taking into account prior treatment exposure and possibly the depth of response to IV steroids.

Second-line or salvage therapies

When the response to IV steroids based on clinical features and Oxford and Lichtiger scores is not achieved by day 3–5, second-line medical therapy should be considered. These include calcineurin inhibitors (CNIs) and infliximab, along with close monitoring of patients as colectomy should not be delayed if required.

Ciclosporin as a bridge to maintenance therapy

Before the advent of biologics, ciclosporin was mainly used in ASUC as a bridge therapy to azathioprine.[35] Regarding short-term use of ciclosporin, an RCT of 73 patients comparing ciclosporin doses

TABLE 4 Prognostic scores of corticosteroid failure in chronological order.

Composite criteria	Factors	Steroids failure
Oxford criteria[23]	>8 stools or 3 to 8 stools per day and CRP >45 mg/L on day 3	Colectomy rate 85% if one criterion is present
Lindgren et al[65]	Body temperature >37.4°C, number of bowel movements, persistence of bloody stools, elevated CRP on day 3. Score: Stool frequency/day +0.14 × CRP	72% of colectomy when score ≥8
Ho et al[66]	Mean stool number on first 3 days, albumin <30 g/L on admission, colonic dilatation >5.5 cm on Xray	85% of steroids failure when score ≥4
Gibson et al[67]	3 stools per day and CRP/albumin ratio on day 3	Relative risk of steroids failure of 3.9 (95% CI 2.1–7.2)
Adams et al[31]	Albumin <25 g/L, CRP ≥100 mg/L, UCEIS ≥4 or ≥ 7 on admission	84% of steroids failure when score ≥3

showed that while response rates at day 8 were similar between a 4 mg/kg/day dose (84.2%) and a 2 mg/kg/day regimen (85.7%), there was a trend toward higher blood pressure and nephrotoxicity for the 4 mg/kg group.[36] Current guidelines therefore recommend a 2 mg/kg/day regimen with drug-level monitoring.[37]

With the largest exposure to thiopurines and anti-TNF among UC patients and the development of new drugs, recent studies aimed to assess the efficacy of induction with ciclosporin in ASUC as a bridge to maintenance with vedolizumab or ustekinumab. In a retrospective observational study, tertiary centers in France collected data on 39 patients with steroid-refractory UC receiving ciclosporin or tacrolimus as induction therapy followed by vedolizumab as maintenance therapy. 85% of patients had been previously exposed to thiopurines and 92% to an anti-TNF agent.[38] After 12 months, the colectomy-free survival rate was 64% with more than half of the colectomies occurring within the first 14 weeks of treatment. Survival without vedolizumab discontinuation was estimated at 44% at 1 year.

In the largest retrospective study to date, 71 patients with steroid-refractory ASUC were treated with a CNI followed by vedolizumab. The primary endpoint of colectomy-free survival rate was 93% at 3 months, 67% at 1 year and 55% at 2 years. Half of the patients were in clinical remission at week 14, but vedolizumab was discontinued in 57% and 72% at 1 and 2 years.[39] The colectomy rate after a median of 25 months of follow-up was 42%. A recent prospective study also evaluated bridging ciclosporin with vedolizumab in 15 patients with steroid-refractory ASUC[40] (Table 5). More recently, given the increasing exposure to anti-TNF and vedolizumab, a small retrospective study of 10 patients evaluated the safety and efficacy of CNIs as a bridge to ustekinumab in ASUC.[41] At 6 months,

TABLE 5 Evidence from the main cohorts studying calcineurin inhibitors (CNIs) as a bridge therapy to vedolizumab or ustekinumab.

Study	Treatments	Design, patients	Colectomy rate	Comments
Pellet et al.[38]	Ciclosporin 2 mg/kg intravenous or 4 mg/kg orally once daily. Switch to 4 mg/kg twice daily for IV treated patients when blood concentration target of 150–250 ng/mL was reached (95%). Tacrolimus orally delivered 0.05–0.1 mg/kg (blood concentration target 10–15 ng/mL until week 2, 5–10 ng/mL after week 2) (5%). Vedolizumab 300 mg at weeks 0, 2, 6 then every 8 weeks	Retrospective observational, 39 patients. Anti-TNFs: Previously exposed (92%) or contra-indication (8%)	11/39 (28%) at 11 months, 6/11 in the first 14 weeks	Colectomy-free survival rate: 68% at 1 year. Survival without vedolizumab discontinuation: 44% at 1 year
Ollech et al.[39]	Ciclosoporin 2–4 mg/kg continuous infusion (blood concentration target 300–400 ng/mL). Switch to oral formulation when stools decreased by 50% and no hematochezia (68%). Tacrolimus 0.1–0.2 mg/kg daily (blood concentration target 10–15 ng/mL) (32%). Vedolizumab 300 mg at weeks 0, 2, 6 then every 8 weeks in patients who responded to CNIs	Retrospective observational, 71 patients. Previous exposure to anti-TNFs: 85.4% for ciclosporin, 82.6% for tacrolimus	30/71 (42%) for a median of 25 months (IQR 16–36)	Colectomy-free survival rate: 93% at 3 months, 67% at 1 year and 55% after 2 years. Survival without vedolizumab discontinuation: 43% at 1 year, 28% at 2 years
Tarabar et al.[40]	Ciclosporin to vedolizumab in patients responding to ciclosporin	Prospective, uncontrolled, 17 patients admitted, 15 responded to ciclosporin	17.6% at 1 year (2/17 patients underwent colectomy before vedolizumab and 1 patient after)	Colectomy-free survival rate at 1 year: 14/17 (82%) in all admitted patients and 14/15 (93%) treated by vedolizumab. Endoscopic remission at 1 year: 71%. Clinical remission at 1 year: 79%
Veyrard et al.[41]	Ciclosporin 2 mg/kg daily (blood concentration target 150–250 ng/mL) (90%). Tacrolimus 0.05 mg/kg (10%). Both CNIs were switched to oral formulation after 7 days at target and withdrawn within 3 months. Ustekinumab 6 mg/kg followed by 90 mg subcutaneously every 8 weeks	Retrospective, 10 patients Previous exposure: - Anti-TNFs 9 patients (90%) - Vedolizumab 8 patients (80%)	No colectomy at 6 months	Clinical response and remission at 6 months: 90%. Dose optimization for 2 patients at 3 months

none of the patients had undergone colectomy, one patient (10%) failed to obtain remission and clinical response, and one patient still required steroids.

Together, multiple cohorts indicate a high short-term effectiveness of ciclosporin to treat ASUC, even in patients with multiple previous biological failures. While tolerance issues limit its use overtime, it remains an effective option as a bridge to maintenance therapy with favorable safety and slower mechanisms of action. Tacrolimus has also been considered in this clinical setting with data of key cohorts studying CNIs presented in Table 5.

Infliximab: What is the optimal regimen?

In the index trial published in 2005 evaluating infliximab in ASUC, 45 steroid refractory patients were randomized between infliximab at a single dose of 5 mg/kg and placebo.[42] Short-term colectomy rates were 29% (7/24) in the infliximab arm and 67% in the placebo arm ($p = 0.017$). However, whether patients could benefit from higher induction doses is unknown. Specifically, it has been shown that infliximab is lost in stools due to high inflammation and protein loss during severe flare-ups.[43] Patients who did not respond to infliximab at week 2 had significantly higher fecal concentrations of infliximab than responders (5.01 μg/mL vs. 0.54 μg/mL).

In the ASUC setting, standard induction of 5 mg/kg in 37 patients was compared with a 10 mg/kg dose in 35 patients in a 2019 retrospective study.[44] The 3-month colectomy rate was 5.4% in the standard induction group and 14.3% in the high-dose group (*p*-value 0.205), showing no superiority for the higher dose regimen.

In a retrospective cohort of 66 cases with ASUC, initial infliximab dosing, either 5 or 10 mg/kg, was guided by an algorithm using a CRP to albumin ratio and subsequent perfusion intervals were based on CRP levels at day 3 and 6. After 90 days of follow-up, the colectomy rate was 30.3% in patients who received accelerated optimized induction and 24.2% in those who received single-dose rescue therapy ($p = 0.58$).[45]

A retrospective study and meta-analysis with 213 patients, of which 132 received standard induction of 5 mg/kg infliximab at weeks 0, 2, and 6 and 81 received the same dose at shorter intervals (3 doses within 4 weeks) evaluated colectomy rates.[46] Colectomy rates were similar in both groups and no significant differences were found in short- or long-term outcomes.

A 2019 systematic review of 2158 cases assessed several treatment regimens.[47] Overall colectomy-free survival was 79.7% and 69.8% at 3 and 12 months. In patients receiving 5 mg/kg infliximab, multiple dose-induction at weeks 0, 2 and 6 was superior to a single-dose regimen at 3 months (OR for colectomy-free survival 4.24, p-val <0.001) and there was a trend without statistical significance toward similar results at 12 months. However, an accelerated 3-dose regimen delivered in 4 weeks was not found to be statistically superior to a 6-week regimen (OR 0.93, p-val 0.87 at 3 months; OR 0.96, p-val 0.89 at 12 months). Likewise, dose-intensified induction of 10 mg/kg delivered during 6 weeks or in an accelerated 4-week regimen did not improve colectomy-free survival at 1, 3 and 2 months compared with the standard induction regimen. Most of the data were derived from small uncontrolled retrospective studies and patients exposed to higher concentrations of infliximab often presented with a more severe disease, which may have confounded the results.

Although current state of knowledge based mostly on retrospective and heterogeneous data does not suggest a benefit of intensified infliximab induction regimen in ASUC,[6] there is a pathophysiological relevance to suggest that higher induction doses may benefit selected patients, that is, those with low albumin reflecting important loss of infliximab in feces and a major inflammatory burden. Controlled trials are ongoing (NCT02770040 and NCT03937609) to obtain further data on the matter.

Infliximab or ciclosporin: Considerations for the choice of treatment

As seen previously, infliximab and ciclosporin have both proved effective for the management of ASUC. The selection of second-line therapies can be influenced by clinicians' habits, patients' features, safety, or efficacy concerns. While CNIs can induce a swift response, infliximab is usually favored due to fewer monitoring and better safety profile.

In the CYSIF (Study Comparing Cyclosporine With Infliximab in Steroid-refractory Severe Attacks of Ulcerative Colitis) RCT, 115 patients with steroid-refractory ASUC were randomized to either infliximab at weeks 0, 2 and 6 or IV ciclosporin followed by oral treatment for 98 days.[3] Treatment failure occurred in 35 patients treated with ciclosporin (60%) and 31 (54%) treated with infliximab ($p = 0.52$).

Another RCT of 270 patients, the CONSTRUCT trial, bore similar results.[48] There were no significant differences in the infliximab and the ciclosporin groups in terms of survival, colectomy rates, median time to colectomy, and serious adverse events.

Although RCTs did not show any significant difference, a meta-analysis of non-randomized studies suggested that infliximab was associated with better treatment response (OR 2.96, CI95[2.12–4.14]) and a lower 12-month colectomy rate (OR 0.42, CI95[0.22–1.28]).[1]

In the long-term follow-up of the 115 patients from the CYSIF trial (median duration of 5.4 years), colectomy-free survival rates were 70.9% and 61.5% at 1 and 5 years, respectively, in patients treated with ciclosporin and 69.1% at 1 year and 65.1% at 5 years in those receiving infliximab ($p = 0.97$).[49] Importantly, 45.7% of patients initially treated with ciclosporin received infliximab after 1 year and 57.1% at 5 years.

To summarize, both treatments yielded close results in terms of clinical response and early colectomy rates. Long-term efficacy and safety results remain similar for both treatments; however, ciclosporin-treated patients had a higher relapse rate than those treated with infliximab. Conversely, in case of previous failure to anti-TNF and especially to infliximab, ciclosporin is an alternative to surgery and a bridge to another biological maintenance therapy.

Third-line strategies and sequential therapy

The main concern in sequential therapy is whether the benefits outweigh the risks or the opposite. If second-line therapy fails, referral to expert IBD centers should be considered. In a small retrospective study, 9 patients received ciclosporin after infliximab and 10 patients received the opposite sequence.[50] Four patients achieved remission within the ciclosporin to infliximab group (40%) and 3 within the alternate group (33%, $p = 0.45$).

In another retrospective study of 86 patients sequentially treated with infliximab and ciclosporin, 49 (57%) did not respond to the second line of salvage treatment and underwent colectomy. Seven infections and one death occurred in the ciclosporin to infliximab group, while two infections occurred in the other group.[51]

These conflicting data lead to initial guidelines not recommending a second line of salvage therapy as it delays colectomy.[52,53] Additionally, a systematic review in 2016 reported data from 314 patients included in 10 studies.[54] After sequential treatment, the overall short-term response rate was 62.4% (66.8% for ciclosporin, 59.5% for infliximab and 50.8% for tacrolimus), the remission rate was 38.9%, colectomy rates were 28.3% at 3 months and 42.3% at 1 year with no significant difference between the sequences of salvage therapies. Adverse events occurred in 23% of patients, including 6.7% of serious infections and a mortality rate of 1%.

Therefore, a third-line medical therapy in ASUC patients should be a limited option for highly selected patients and restricted to expert IBD centers. However, colectomy remains the standard-of-care for third-line management as still recommended by European Crohn's and Colitis Organisation (ECCO) guidelines.[6,37]

Tofacitinib as an emerging therapy for acute severe ulcerative colitis

Tofacitinib is an orally delivered, quick acting panJAK inhibitor recently approved in UC.[55] A recent warning was reported regarding the risk of thromboembolic events and cancer associated with tofacitinib.[56] However, these data stemmed from patients with cardiovascular risk factors and rheumatoid arthritis aged over 50 years. Similar data were not found in a population of patients with IBD and reassuring data from administrative databases were subsequently published.[57]

Tofacitinib was considered as a promising option in ASUC notably because of its rapid onset of action. A proof-of-concept use of tofacitinib in ASUC was first reported in 4 patients.[58]

In a larger case-control study of biologic-exposed patients with ASUC and treated with tofacitinib, the hazard ratio for colectomy at 3 months was 0.28 in 40 patients receiving tofacitinib compared with 113 matched historical controls with biological-experienced ASUC and initially treated with IV steroids ($p = 0.018$). However, high doses of treatment were required as a thrice daily regimen of 10 mg was superior to the historical control cohort but not a traditional twice daily dose of 10 mg.[59]

In the largest study to date, data on 55 patients with ASUC and those treated with tofacitinib were subsequently reported.[60] Of the 55 patients, 49 had failed infliximab and 19 had been exposed to ciclosporin. Colectomy-free survival was 78.9% at 3 months and 73.6% at 6 months. Three patients had to withdraw tofacitinib due to adverse events including two herpes zoster infections, but no deaths, no VTE and no cardiovascular events were reported.

Upon validation with prospective trials, tofacitinib could be a new therapeutic option in ASUC as summarized in Table 6. Short-term adverse events seemed limited, but safety concerns should restrict its use in selected patients (i.e., young patients without cardiovascular risk factors). Two ongoing prospective open-label studies (TRIUMPH and TOCASU) could provide further evidence.

Although no current evidence exists for other JAK inhibitors, recently approved filgotinib and upadacitinib may be promising options in ASUC due to their quick onset of action.

THE FUTURE OF ACUTE SEVERE ULCERATIVE COLITIS: THE PERSPECTIVE

With the increasing availability of drugs for treating UC with a wide variety of mechanisms of action, it is necessary to accumulate specific and stronger data for their use in ASUC. These drugs can be employed either as monotherapy or in combination therapy with other treatments. As patients with ASUC have a particularly high risk of complications, designing trials with placebo-only arms are not acceptable. However, it may be time to challenge the hegemonic position of steroids as the first-line treatment. Quick-acting agents, such as anti-JAK drugs, have been approved for UC and have demonstrated a rapid onset of action.[61] Moreover, a recent RCT was conducted that compared steroids and tofacitinib for UC flares and showed similar efficacy.[62] Another potential approach is to combine steroids with advanced therapies as the first line of treatment. Berinstein et al. proposed an aggressive strategy to start with IV steroids combined with tofacitinib 10 mg thrice daily from hospital admission, with promising retrospective data.[59] This approach of combining treatments, including steroids, was recently used in an RCT in patients with ASUC. Raine et al. recently presented their findings at ECCO 2023. In this meriting RCT, 113 patients were randomized to a placebo with IV steroids arm or anakinra (anti-IL1) with IV steroids arm. The study showed that adding anakinra did not improve the outcomes (i.e. need for a second-line treatment and/or colectomy) of ASUC at day 10 compared to steroids only.[63] This RCT has paved the way for subsequent RCTs in this specific clinical situation.

CONCLUSION

Acute severe ulcerative colitis represents the most severe expression of UC and remains a life-threatening condition still associated with a 1% mortality rate. Medical therapy with IV steroids and second-line therapy with infliximab or ciclosporin in case of treatment failure

TABLE 6 Tofacitinib use in retrospective cohorts of patients with acute severe ulcerative colitis (ASUC).

Study	Treatment regimen	Design, patients	Colectomy rate	Comments
Berinstein et al., 2019[58]	Tofacitinib 10 mg 3 time daily for 9 doses. IV methylprednisolone 60 mg daily: 3/4 patients	Retrospective observational, 4 patients. Previous exposure: Anti-TNFs: 2 patients. Chronic steroids: 2 patients	2/4 (50%): one early for treatment failure and one at 6 months for dysplasia despite clinical remission	Clinical remission was obtained in 2 patients with a combination of tofacitinib and IV steroids and 1 patient with budesonide
Honap et al., 2020[68]	Tofacitinib after IV hydrocortisone. No specific regimen was detailed.	Retrospective, observational, 7 patients including 5 with ASUC. All patients were refractory to anti-TNFs	3/7 (42.9%) at week 16 and 4/7 (57.1%) at week 26	Endoscopic improvement 4/7 (57.1%) at week 16 but one patient underwent colectomy later. Tofacitinib maintained at week 26: 3/7 (42.9%). Clinical, endoscopic, and histological remissions maintained at week 52 for one patient
Xiao et al., 2022[69]	Tofacitinib after IV steroids and infliximab if infliximab naïve. No specific regimen was detailed.	Retrospective observational, 8 patients	3/8 (37.5%): 2 within 30 days, 1 within 90 days	Clinical response during hospitalization: 5/8 (62.5%). Clinical remission achieved at 30 and 90 days for all 5 early responders
Berinstein et al., 2021[59]	Standard induction doses of 10 mg twice daily or high-intensity regimen of 10 mg three times daily for 9 doses followed by twice daily. Dose selection based on patient and physician.	Retrospective, case-controlled study, 40 patients matched with 113 controls. Prior long-term failure of infliximab (85%), adalimumab (40%) vedolizumab (52.5%)	Hazard ratio 0.28 at 90 days ($p = 0.018$)	Tofacitinib three times daily seemed protective (HR 0.11, $p = 0.008$) but not twice daily (HR 0.66, $p = 0.5$)
Uzzan et al., 2021[60]	Treatment for current flare: Tofacitinib after steroids (52.7%), infliximab (3.6%), IV ciclosporin (14.5%). No specific regimen was detailed at onset. At week 6, all patients treated by a 10 mg twice daily regimen.	Retrospective and prospective, 55 patients. Previous exposure to a median of 2.5 lines of treatment: Anti-TNFs (98.1%) Ciclosporin (34.5%) Vedolizumab (69.1%)	15/55 (27.3%) at a median of 6.5 months	Colectomy-free survival: 85.2%, 78.9%, 73.6 at 1, 3 and 6 months Withdrawal linked to herpes zoster but not to cardiovascular events.

should induce a quick response with acceptable safety to avoid salvage colectomy. To date, there is no sufficient evidence to recommend the systematic use of higher induction doses of infliximab. In patients previously exposed to biologics, new therapeutic strategies with promising short-term efficacy and safety results based on retrospective series could be considered awaiting further validation by controlled trials.

AUTHOR CONTRIBUTIONS

Louis Calméjane: Literature review and writing the manuscript. Mathieu Uzzan: Study design, literature review, reviewing and editing the manuscript. Julien Kirchgesner and David Laharie: Reviewing and editing the manuscript. Louis Calméjane acted as the submission's guarantor. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

MU declares counseling, boards and/or fees from AbbVie, Celltrion, Fresenus, Galapagos, Janssen, Takeda. DL declares counseling, boards, transport and/or fees from Abbvie, Amgen, Biogaran, Biogen, Celltrion, Ferring, Galapagos, Janssen, Lilly, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag. JK declares counseling, boards and/or fees from Celltrion, Pfizer, Janssen, Lilly. LC declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

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