Tofacitinib in Acute Severe Ulcerative Colitis (TACOS): A Randomized Controlled Trial

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INTRODUCTION: **Intravenous corticosteroids are the mainstay of treatment of patients hospitalized with acute severe ulcerative colitis (ASUC). However, 30%–40% of the patients are refractory to corticosteroids. We investigated whether addition of tofacitinib to corticosteroids improved the treatment responsiveness in patients with ASUC.**

METHODS: **This single-center, double-blind, placebo-controlled trial randomized adult patients with ASUC (defined by the Truelove Witts severity criteria) to receive either tofacitinib (10 mg thrice daily) or a matching placebo for 7 days while continuing intravenous corticosteroids (hydrocortisone 100 mg every 6 hours). The primary end point was response to treatment (decline in the Lichtiger index by >3 points and an absolute score <10 for 2 consecutive days without the need for rescue therapy) by day 7. The key secondary outcome was the cumulative probability of requiring initiation of infliximab or undergoing colectomy within 90 days following randomization. All analyses were performed in the intention-to-treat population.**

RESULTS: **A total of 104 patients were randomly assigned to a treatment group (53 to tofacitinib and 51 to placebo). At day 7, response to treatment was achieved in 44/53 (83.01%) patients receiving tofacitinib vs 30/51 (58.82%) patients receiving placebo (odds ratio 3.42, 95% confidence interval 1.37–8.48, $P = 0.007$). The need for rescue therapy by day 7 was lower in the tofacitinib arm (odds ratio 0.27, 95% confidence interval 0.09–0.78, $P = 0.01$). The cumulative probability of need for rescue therapy at day 90 was 0.13 in patients who received tofacitinib vs 0.38 in patients receiving placebo (log-rank $P = 0.003$). Most of the treatment-related adverse effects were mild. One patient, receiving tofacitinib, developed dural venous sinus thrombosis.**

DISCUSSION: **In patients with ASUC, combination of tofacitinib and corticosteroids improved treatment responsiveness and decreased the need for rescue therapy.**

KEYWORDS: tofacitinib; ulcerative colitis; hydrocortisone; colectomy; acute severe ulcerative colitis

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D153

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INTRODUCTION

Acute severe ulcerative colitis (ASUC) is a potentially life-threatening and time-critical medical emergency. Nearly one-quarter of patients with ulcerative colitis (UC) experience an episode of ASUC and require hospitalization during their lifetime (1,2). The role of corticosteroids in the management of ASUC is established (2–4). However, approximately 30%–40% patients are refractory to corticosteroids and need rescue with either medical (infliximab/cyclosporine) or surgical (colectomy) therapies (5,6). Despite increasing availability and use of medical rescue therapy, colectomy rates still remain high (5,7,8). In addition, patients receiving medical rescue therapy for corticosteroid refractoriness have been reported to have shorter colectomy-free survival (9–11). The medical rescue therapies are also limited by their adverse effects, including risks of infections and malignancies, and high cost of therapy, placing

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additional burden on the health care systems, especially in low-income and middle-income countries. Therefore, a large therapeutic gap remains, and strategies are needed to improve the responsiveness to corticosteroids.

It has been postulated that apart from the genetic predisposition to corticosteroid nonresponsiveness, a higher expression of proinflammatory cytokines (such as interleukin [IL]–6, IL-8, etc) is associated with corticosteroid resistance in patients with UC. *In vitro* studies have also shown IL-2 to reduce the nuclear translocation of the glucocorticoid receptor through JAK1- and JAK3-mediated phosphorylation of STAT5, thereby contributing to corticosteroid resistance (12–14). Tofacitinib, through STAT inhibition, has the potential to block the signaling downstream of the IL-2 receptor and restore the corticosteroid sensitivity.

We hypothesized that addition of tofacitinib to corticosteroids in hospitalized patients with ASUC can have additive effects on the therapeutic efficacy and improve the treatment response rates. This double-blind randomized controlled trial (RCT) was therefore performed to determine whether addition of tofacitinib to corticosteroids was superior to corticosteroids alone in patients hospitalized with ASUC.

METHODS

Study design

This was a single-center, prospective, double-blind, RCT conducted at a tertiary care center in India. The study protocol was approved by Institutional Ethics Committee (DMCH/P/2021/626) and registered at International Standard Randomized Controlled Trial Number registry (ISRCTN42182437). Written informed consent was obtained from all the participants. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of the study.

Patient population

Consecutive adult (aged 18 years or older) patients hospitalized due to ASUC were enrolled. ASUC was defined according to the Truelove Witts criteria (15). Patients with severe UC who did not meet the Truelove Witts criteria were excluded from the study along with those who had received intravenous corticosteroids or tofacitinib within 4 weeks before hospitalization. In addition, individuals with active infections (such as *Clostridioides difficile*, cytomegalovirus, etc), latent or active tuberculosis, Crohn's colitis, toxic megacolon, intestinal perforation, or massive hemorrhage requiring emergency colectomy, pregnant or lactating female individuals, those with a current diagnosis or history of thromboembolic disease, and patients with severe cardiorespiratory, renal, or hepatic comorbidities precluding participation in the trial were also excluded.

Randomization and allocation concealment

The eligible patients were randomized in a 1:1 ratio based on computer-generated random numbers to receive either tofacitinib or a matching placebo. Random numbers were generated by computerized random number schedule. The randomization list and numbered packing of the intervention were prepared by an independent person (site clinical research coordinator). Randomization was held centrally to ensure concealment of allocation. Both the investigators and the patients were blinded to the intervention.

Unblinding

On day 7, a planned unblinding was conducted after assessment of the clinical response. The unblinding procedure was conducted by the site's clinical research coordinator, ensuring that both the investigators and participants became aware of the intervention received. Subsequently, the trial continued as an open-label study until the 90th day after randomization.

In cases where a serious adverse event occurred, an emergency unblinding was considered necessary to determine the appropriate intervention to mitigate potential health risks. However, to maintain the integrity of the study, every possible measure was taken to prevent the disclosure of information regarding the emergency unblinding of a participant's treatment assignment to any additional study staff beyond the participant and the principal investigators/coinvestigators.

Definition of response

Response to therapy was defined using the Lichtiger index (16). The Lichtiger index is a clinical score incorporating the total number of stools, nocturnal frequency of stools, blood in stools, fecal incontinence, abdominal pain, abdominal tenderness, need for antidiarrheal agents, and general well-being. A decline in the Lichtiger index by >3 points by day 7 and an absolute score <10 for 2 consecutive days without the need for rescue therapy (infliximab or colectomy) was considered as response (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/D153)

Procedures

The standard-of-care treatment including intravenous hydrocortisone (100 mg every 6 hours), intravenous fluids, correction of dyselectrolytemia, and enteral feeding was continued in both the treatment arms. In addition, all patients received thromboprophylaxis with enoxaparin (40–60 mg subcutaneously every 24 hours) for the entire duration of hospitalization.

Tofacitinib (10 mg) or a matching placebo was administered thrice daily for 7 days. Intravenous hydrocortisone was stopped in all patients by day 7. After response assessment, the patients were categorized into responders and nonresponders, and unblinding was performed. For patients who responded to the intervention by day 7, per-oral prednisolone was started in a tapering dose schedule (40 mg/d, gradually tapered and stopped by week 12). The responders in the tofacitinib arm continued to receive tofacitinib, at a reduced dose of 10 mg twice daily, while responders in the placebo arm received standard-of-care treatment with oral 5-aminosalicylates (3.6–4.8 g/d) and azathioprine (1.5–2.0 mg/kg). The patients were followed up until 90 days after randomization. In case of increase in disease activity between days 7 and 90, the patients were considered for either infliximab or colectomy. The nonresponders at day 7 were advised rescue therapy with either infliximab or colectomy.

Routine evaluations

The demographic and disease characteristics were recorded during enrollment. The investigations, including hemogram, liver and renal function tests, erythrocyte sedimentation rate, C-reactive protein (CRP), fecal calprotectin, and a limited unprepared flexible sigmoidoscopy with biopsy for histopathology and cytomegalovirus immunohistochemistry, were performed in all patients within 24 hours of hospitalization. The investigations were repeated at the discretion of the treating physician.

All patients underwent daily clinical assessments (including total number of stools, nocturnal frequency of stools, blood in stools, fecal incontinence, abdominal pain, abdominal tenderness, need for antidiarrheal agents, and general well-being) till day 7 of the intervention. The follow-up clinical disease activity and safety assessments were performed at days 30, 60, and 90.

Safety evaluations

Monitoring for adverse event(s), including opportunistic infections and cardiovascular events, was performed daily till day 7, followed by assessments at days 30, 60, and 90. Any adverse event resulting in death, or threatening life, requiring prolongation of hospitalization, or resulting in persistent or significant disability/incapacity was considered as a serious adverse event.

Outcomes

The primary outcome was the proportion of patients who responded to treatment, defined by the Lichtiger index, by day 7. The secondary outcomes included cumulative probability of patients requiring initiation of infliximab or undergoing colectomy after discharge but within 90 days following randomization and duration of hospital stay.

Statistical analysis

The sample size was based on 60% response rates to intravenous corticosteroids in patients with ASUC (17,18). Assuming 25% higher remission rate in the tofacitinib arm compared with that in the placebo arm, with 80% power, and an alpha error of 5%, a total of 52 patients were computed to be needed in each arm.

Baseline data were reported as number (%), mean ± SD, or median (interquartile range [IQR]) as appropriate and categorical variables summarized as frequencies with percentages. The binary end points, including the efficacy end point(s), were compared between the 2 arms using the Cochran–Mantel–Haenszel χ^2 test. The Student *t* test was used for continuous variables with normal distribution and Wilcoxon-Mann-Whitney *U* test for

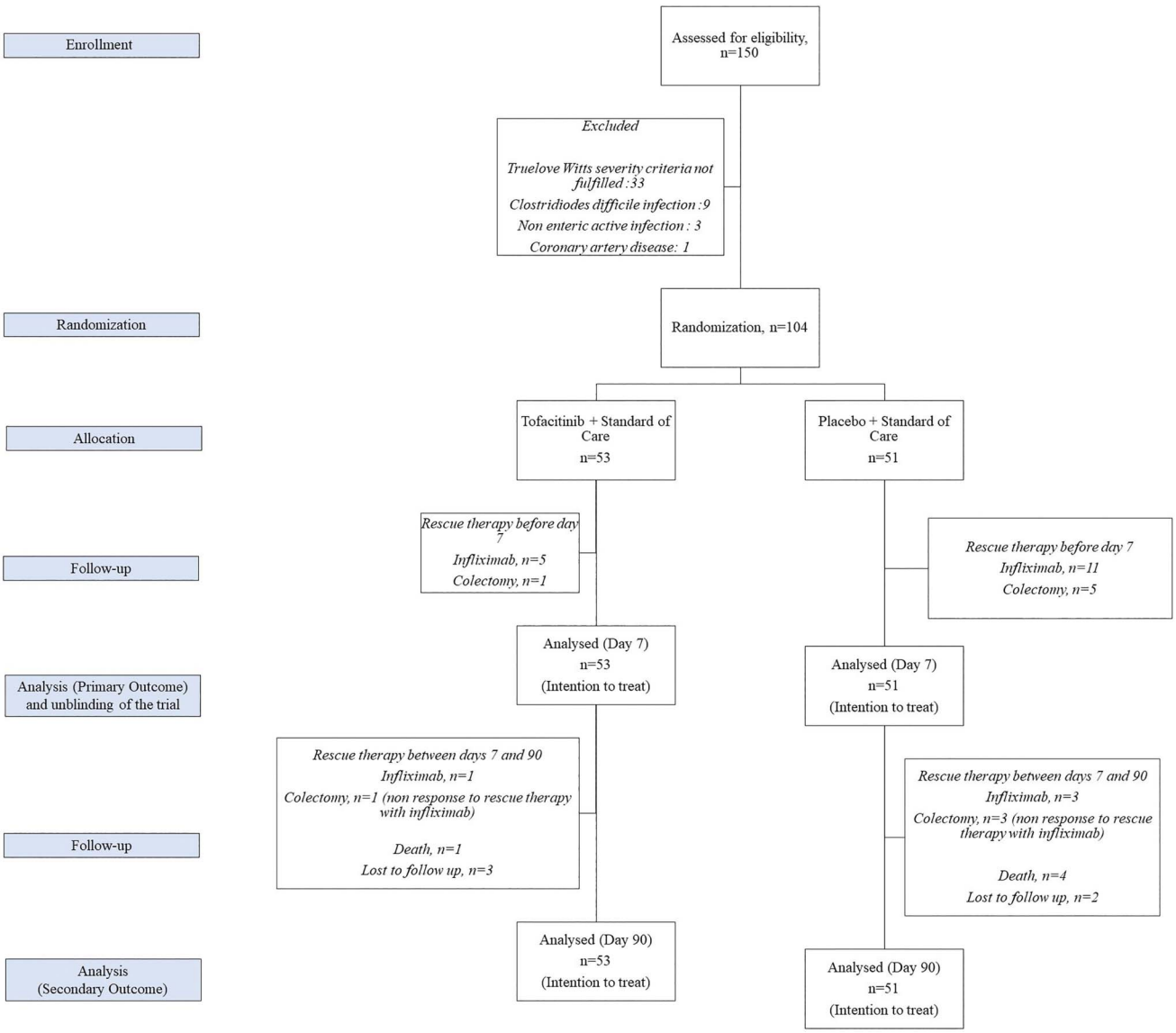

Figure 1. Trial profile.

continuous variables with skewed distribution. The Kaplan-Meier survival analysis was used to evaluate the cumulative probability of need for rescue therapy in the 2 intervention arms. A log-rank test was used to compare the Kaplan-Meier curves. The frequency and types of adverse events were summarized. The efficacy analyses were based on data from all patients who underwent randomization (intention to treat), and the safety analyses were based on data from the patients who underwent randomization and received at least 1 dose of the assigned treatment. All statistical calculations were performed using the SPSS version 21 (IBM SPSS Statistics for Windows, version 21.0; IBM, Armonk, NY, Released 2012).

RESULTS

Patient characteristics

Between October 2021 and December 2022, of the 150 patients with UC who were hospitalized during the study period, 104 patients (median age 37.5 [IQR 27–47] years; 59 [56.73%] male individuals; and median disease duration of 2 [2–4.25] years) were included and randomized to receive either tofacitinib (n = 53) or placebo (n = 51) as an adjunct to intravenous corticosteroids (Figure 1). The disease characteristics and admission parameters were similar in the 2 arms with the exception of lower rates of previous exposure to corticosteroids among the patients who received placebo (Table 1).

Table 1. Baseline characteristics of the enrolled population

	Tofacitinib (n = 53)	Placebo (n = 51)
Age, yr, median (IQR)	37 (26–47)	38 (30–47)
Male, n (%)	29 (54.71)	30 (58.82)
Disease duration, yr, median (IQR)	3 (2–5)	2 (1–4)
Body mass index, kg/m^2, median (IQR)	21.64 (18.43–23.91)	21.27 (18.57–23.32)
Previous treatment exposures, n (%)		
5-ASA	52 (98.11)	51 (100)
Azathioprine	8 (15.09)	6 (11.76)
Corticosteroids	39 (73.58)	25 (49.01)
Anti-TNF agents	3 (5.66)	2 (3.92)
Oral corticosteroids on admission,[a] n (%)	26 (49.05)	23 (45.09)
Day 0 stool frequency, median (IQR)	9 (9–11)	10 (8–11)
Lichtiger score, median (IQR)	13 (11–15)	13 (11–16)
Number of criteria of systemic toxicity in the Truelove Witts criteria		
1	13 (24.53)	21 (41.17)
2	27 (50.94)	24 (47.06)
3 or more	13 (24.53)	6 (11.76)
UCEIS, median (IQR)	5 (5–6)	5 (5–6)
Disease extent[b]		
Proctitis	4 (7.54)	3 (5.88)
Left-sided colitis	35 (66.03)	36 (70.58)
Pancolitis	14 (26.41)	12 (23.52)
Hemoglobin, g/dL, median (IQR)	9.7 (7.9–11)	10.2 (9.25–11.65)
C-reactive protein, mg/L, median (IQR)	47.37 (14.25–75.48)	33.29 (12.34–93.02)
Fecal calprotectin, median (IQR)	2,000 (1,566–2,000)	2,000 (1,675–2,000)
Serum albumin, g/L, median (IQR)	3.16 (2.44–3.54)	3.13 (2.53–3.73)

5-ASA, 5-aminosalicylates; IQR, interquartile range; TNF, tumor necrosis factor.
[a]Median dose: 40 mg of prednisolone.
[b]At the time of diagnosis of ulcerative colitis.

Efficacy outcomes

The primary outcome, defined as response to treatment by day 7, was achieved in 44 of 53 (83.01%) patients receiving tofacitinib vs 30 of 51 (58.82%) patients receiving placebo (odds ratio [OR] 3.42, 95% confidence interval [CI] 1.37–8.48, $P = 0.007$) (Figure 2).

The need for rescue therapy by day 7 was seen in 6 of 53 (11.32%) patients in the tofacitinib arm when compared with 16 of 51 (31.37%) patients receiving placebo (OR 0.27, 95% CI 0.09–0.78, $P = 0.01$) (Figure 2). Five patients in the tofacitinib arm and 11 patients in the placebo arm received infliximab as rescue therapy, while 1 patient in the tofacitinib arm and 5 patients in the placebo arm underwent colectomy. In the open-label phase of the study (after unblinding at day 7 and until day 90), 1 patient in the tofacitinib arm and 3 in the placebo arm required initiation of infliximab. Furthermore, 1 patient in the tofacitinib arm and 3 patients in the placebo arm, who did not respond to the initial medical rescue therapy with infliximab, required colectomy between days 7 and 90. None of the patients received cyclosporine as rescue therapy.

The rates of both medical (infliximab) and surgical rescue therapy (colectomy) were lower in the patients receiving tofacitinib at days 7, 30, and 90 (Figure 3). The cumulative probability of need for rescue therapy at day 90 was 0.13 in patients who received tofacitinib vs 0.38 in patients receiving placebo (log-rank $P = 0.003$) (Figure 4).

The median CRP at day 7 was 5.17 (2.97–11.54) mg/L in the tofacitinib arm vs 6.18 (2.15–12.80) mg/L in the placebo arm. The total duration of hospital stay was shorter in the tofacitinib arm (9.69 ± 2.84 days) compared with that in the placebo arm (11.01 ± 5.99 days) though statistical significance could not be demonstrated ($P = 0.15$).

On subgroup analysis, in the tofacitinib arm, of the 26 patients who were on oral corticosteroids at the time of hospitalization, 5 (19.23%) patients required rescue therapy. On the contrary, 13 (56.52%) of the 23 patients in the placebo arm, who were on oral corticosteroids at the time of hospitalization, required rescue therapy. Similarly, in patients with previous exposure to thiopurines, the use of rescue therapy was lower in the tofacitinib arm (1/8, 12.5%) compared with that in the placebo arm (6/6, 100%).

Safety outcomes

A total of 20 (19.23%) patients (13 [24.52%] in the tofacitinib arm and 7 [13.72%] in the placebo arm) experienced adverse effects

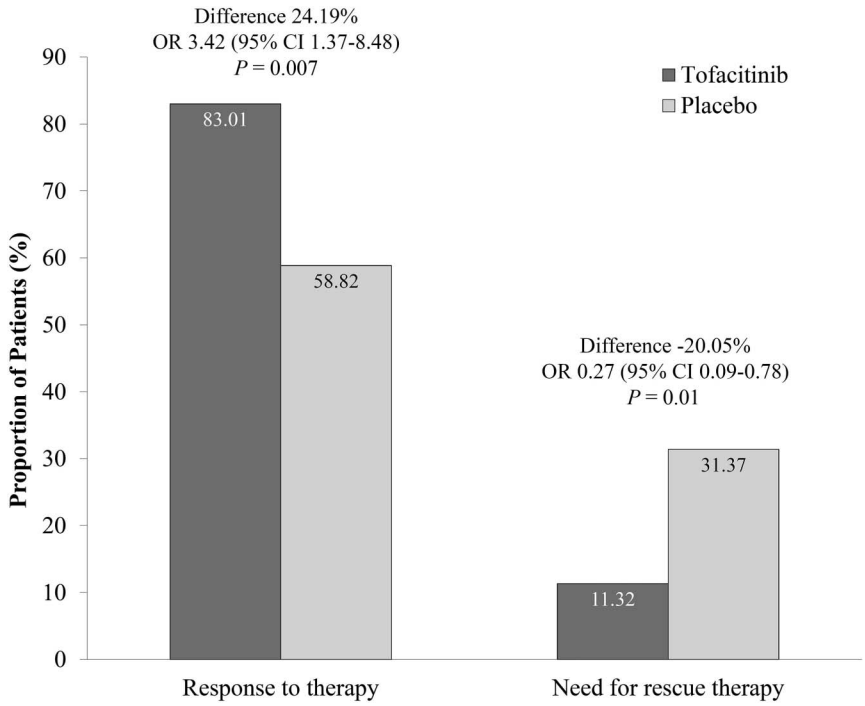

Figure 2. Efficacy outcomes at day 7. Rate of response to treatment by day 7 (primary outcome) and the percentage of patients requiring rescue treatment by day 7. CI, confidence interval; OR, odds ratio.

(Table 2). Most of the treatment-related adverse effects were mild. Hair loss (n = 5), acneiform skin eruptions (n = 3), and upper respiratory tract infection (n = 2) in the tofacitinib arm and acneiform skin eruptions (n = 2) and facial puffiness (n = 1) in the placebo arm were the commonest reported adverse effects. One patient, receiving tofacitinib, developed hemorrhagic venous infarct in the left temporal lobe and dural venous sinus thrombosis. Five patients died during the study period. One patient in the tofacitinib arm, a 47-year-old man, who did not respond to treatment and did not consent for medical/surgical rescue therapy died on day 14. Three patients (a 74-year-old man, a 56-year-old man, and a 42-year-old woman) in the placebo arm died in postcolectomy period due to sepsis and multiorgan failure. An 18-year-old woman in the placebo group who did not respond to rescue therapy with infliximab and did not consent for colectomy died at day 56. The patients who did not survive during the study period exhibited a lack of response to intravenous corticosteroids and had a higher prevalence of malnutrition, as indicated by a lower mean body mass index (BMI) (17.80 ± 3.63 kg/m^2) and lower mean serum albumin levels (1.86 ± 0.98 g/dL). In addition,

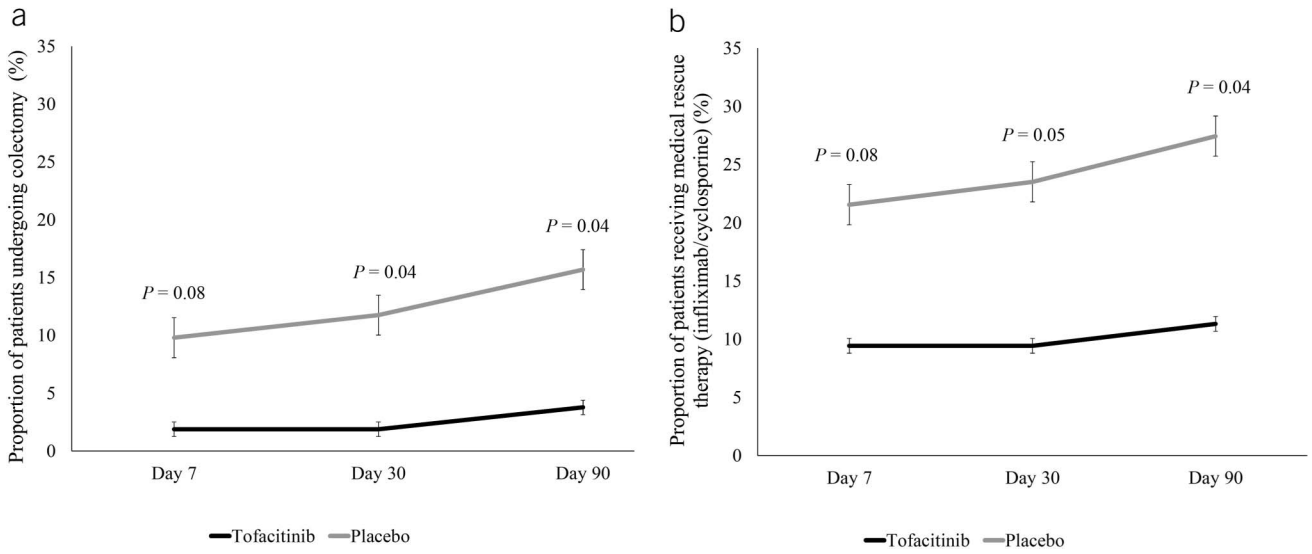

Figure 3. (**a**) Percentage of patients undergoing colectomy within 90 days of randomization. (**b**) Percentage of patients requiring medical rescue therapy (infliximab) by day 90 according to trial arm allocation.

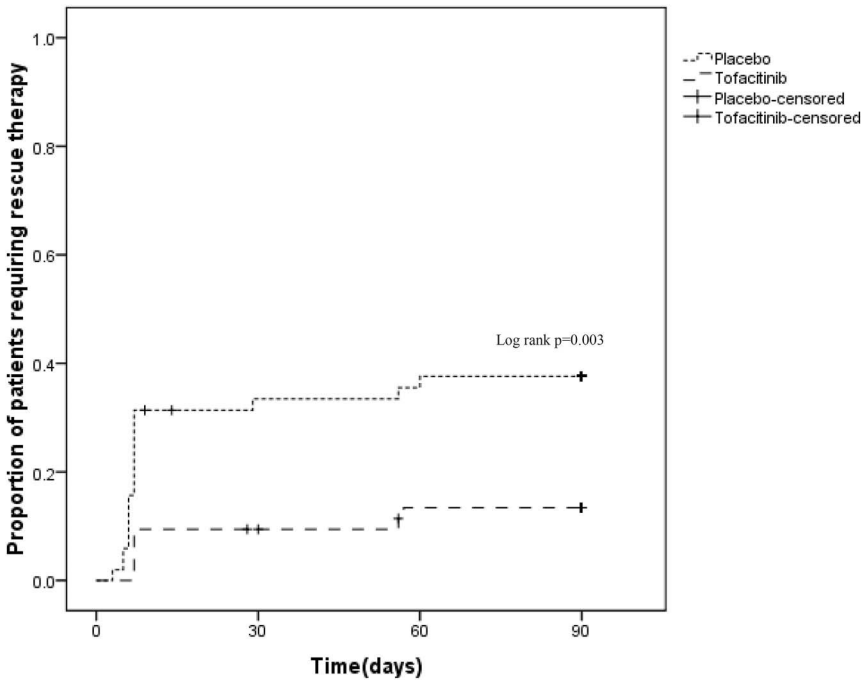

Figure 4. Cumulative probability of need for medical/surgical rescue therapy by day 90 according to trial arm allocation.

these patients had higher Ulcerative Colitis Endoscopic Index of Severity score at the index sigmoidoscopy (6.33 ± 1.14) and an elevated median CRP (53.1 [22.86–14.53] mg/L) during hospitalization. The patients who did survive had higher mean BMI (22.19 ± 4.06 kg/m^2), higher mean serum albumin levels (3.21 ± 0.91 g/dL), lower mean Ulcerative Colitis Endoscopic Index of Severity score (5.26 ± 1.03), and a lower median CRP of 36.29 (11.91–93.35).

Table 2. Safety outcomes

	Tofacitinib (n = 53)	Placebo (n = 51)
Adverse effects, n (%)	13 (24.52)	7 (13.72)
Serious adverse effects, n (%)		
Dural venous sinus thrombosis	1 (1.88)	0
Death	1 (1.88)	4 (7.84)
Most frequent adverse effects, n (%)		
Hair loss	5 (9.43)	0
Acneiform skin eruptions	3 (5.66)	2 (3.92)
Upper respiratory tract infection	2 (3.77)	0
Arthralgia	1 (1.88)	0
Facial puffiness	0	1 (1.96)
Adverse effects of special interest, n (%)		
Herpes zoster	0	0
Dyslipidemia requiring initiation of lipid-lowering drugs	0	0
Adverse effects leading to discontinuation of therapy	0	0

DISCUSSION

This is the first RCT to evaluate the efficacy of tofacitinib, used upfront, as an adjunct to corticosteroids, in improving the treatment response in patients with ASUC. We found that tofacitinib, as add-on therapy to corticosteroids, significantly improved the treatment responsiveness in patients with ASUC at day 7 (OR 3.42, 95% CI 1.37–8.48). Fewer patients receiving tofacitinib required rescue medical or surgical therapy within 7 days of hospitalization (OR 0.27, 95% CI 0.09–0.78). The benefit of adding tofacitinib to corticosteroids also extended beyond 7 days and the cumulative probability of need for rescue therapy (either medical or surgical) at 90 days was significantly lower in patients receiving tofacitinib (log-rank $P = 0.003$). In addition, tofacitinib was associated with lower disease-related mortality rates.

The choice of optimal maintenance therapy in patients who respond to corticosteroids is unclear. While azathioprine is the most commonly used drug in this clinical setting, the long-term disease course is poorly defined. In a multicenter retrospective study, the probabilities of relapse-free survival and colectomy-free survival were 58%, 48%, and 40% and 96%, 95%, and 91% at 1, 2, and 5 years, respectively (19). Multivariate analysis revealed maintenance therapy with biologics to be associated with lower rates of relapse (19). The use of biologics as maintenance therapy is limited in developing countries that struggle to strike a balance between the health care costs and potential adverse effects including infections and malignancies (20–22). The continuation of treatment with tofacitinib beyond 7 days, in reduced doses, provides an effective therapeutic option for maintenance of remission in these patients, though long-term outcomes are yet to be evaluated. In this study, maintenance therapy with tofacitinib was associated with lower rates of use of medical or surgical rescue therapy at day 90 compared with maintenance treatment with azathioprine. One of the reasons could be continuation of the

same drug (tofacitinib) as used for inducing remission/response. In addition, azathioprine has a slow onset of action and requires at least 12–16 weeks before achieving its maximal therapeutic efficacy (23).

The need for rescue therapy in patients with prior exposure to thiopurines or those who were on oral corticosteroids at the time of hospitalization was lower in the tofacitinib arm, suggesting a subgroup of patients who might benefit from consideration of early escalation of therapy. This exploratory signal, however, needs further evaluation.

Tofacitinib has been reported to be associated with increased risk of major adverse cardiovascular events in patients with rheumatoid arthritis. However, these findings have not been replicated in patients with UC. The risk of thrombotic events with tofacitinib in UC has been reported to be comparable with anti-TNF agents (24). Recently, the post hoc analysis of the data from UC clinical program demonstrated increased incidence of adverse events, including major adverse cardiovascular events, with increasing age (older than 65 years). However, the number of patients in the age category older than 65 years was small (25). A recent systematic review, including 148 patients with ASUC, reported venous thromboembolism and death in only 1 patient each (26). Similar rates of serious adverse effects were reported in this study. One patient developed hemorrhagic venous infarct and dural venous sinus thrombosis. This thrombotic event could be attributed to tofacitinib. However, a heightened inflammatory burden in ASUC and concomitant use of corticosteroids could also have contributed to the development of venous sinus thrombosis. Despite an increased immune suppression in the combination treatment arm, the risk of infectious complications or adverse effects was comparable with that in the placebo arm.

Five (4.8%) patients died during the trial period. The mortality in this study was higher than previously reported mortality rates (27). Previously, nonresponse to intravenous corticosteroids, low hospital colectomy volume, advanced age, and comorbid illnesses have been associated with increased mortality rates in patients with ASUC (27–29). In this study, all the deaths were reported in corticosteroid nonresponders. However only 2/5 (40%) patients were aged older than 50 years. A substantial portion of the patients presented with a severe disease phenotype. Roughly half of the patients were already receiving oral corticosteroids on hospitalization. Moreover, most (67.31%) of the individuals within the study cohort exhibited 2 or more criteria indicative of systemic toxicity according to the Truelove Witts criteria. In addition, the increased prevalence of malnutrition, characterized by both low BMI and lower serum albumin levels, played a significant role in driving up the mortality rates. Furthermore, when considering the postoperative period, the higher mortality rates can be largely attributed to the urgency of the surgical procedures and the poor nutritional status of these patients.

This RCT has various strengths. Tofacitinib, thus far, has been used as a rescue therapy, that is, after corticosteroid or infliximab or cyclosporine failure, or as a last resort before colectomy (26,30–32). This is the first RCT using tofacitinib as a first-line therapy in ASUC, albeit in combination with corticosteroids. The double-blind placebo-controlled nature of the RCT limits the possibilities of bias or confounding factors creeping in. The study is limited by being a single-center study, though it is adequately powered to demonstrate the efficacy of tofacitinib in improving treatment responsiveness. The optimal dose of tofacitinib in ASUC is unclear. The dose of tofacitinib used in this study (10 mg thrice daily for 7 days) is similar to the dose used in rescue therapy with tofacitinib (26). Whether a lower dose of tofacitinib (10 mg twice daily for 7 days), when used in conjunction with intravenous corticosteroids, would have been equally effective is arguable, and needs evaluation. A generic formulation of tofacitinib was used in this study. Although a formal cost analysis was not performed, lower rates of use of rescue therapy in the tofacitinib arm point toward a potential cost benefit, especially in regions where low-cost generic formulations of tofacitinib are available. However, certain countries have regulations restricting the use of Janus kinase inhibitors as a first-line therapy, and cost/affordability may be different in countries with no availability of generic form of the drug. This, nevertheless, warrants further investigation. Furthermore, it is important to acknowledge that the applicability of our results may have certain constraints. The study primarily consisted of patients who had not previously received biologic treatments and had relatively short durations of the disease. This might not perfectly mirror the clinical realities in all situations.

To conclude, tofacitinib as an add-on therapy to corticosteroids improved treatment responsiveness in patients with ASUC. The beneficial effect of the combination therapy of tofacitinib and corticosteroids was sustained beyond 7 days, as evidenced by the lower rates of medical or surgical rescue therapy at 90 days. Further studies assessing the efficacy of tofacitinib, either as monotherapy or in combination with other therapies, are needed to determine the position of tofacitinib in the therapeutic algorithms of ASUC. An exploratory signal of increased corticosteroid responsiveness with tofacitinib, in patients with previous exposure to thiopurines or ongoing oral corticosteroids during hospitalization, warrants further evaluation.

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CONFLICTS OF INTEREST

Guarantor of the article: Ajit Sood, DM.

Specific author contributions: A. Singh: conception, design, data collection, analysis and interpretation, literature review, writer, and critical review. Approved the final draft submitted. M.K.G.: data collection, analysis and interpretation, literature review, writer, and critical review. Approved the final draft submitted. V. Midha: conception, design, data collection, analysis and interpretation, literature review, writer, and critical review. Approved the final draft submitted. R.M.: literature review, critical review. Approved the final draft submitted. Y.K.G.: literature review, critical review. Approved the final draft submitted. K.K.: literature review, writer, and critical review. Approved the final draft submitted. D.S.: data collection, analysis and interpretation, and critical review. Approved the final draft submitted. N.B.: analysis and interpretation, critical review. Approved the final draft submitted. R.K.: data collection, critical review. Approved the final draft submitted. S.K.: literature review, critical review. Approved the final draft submitted. O.G.: literature review, critical review. Approved the final draft submitted. V. Mehta: literature review, critical review. Approved the final draft submitted. A. Sood: conception, design, supervision, analysis and interpretation, literature review, writer, and critical review. Approved the final draft submitted.

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did not have a role in data collection, data analysis, data interpretation, or writing of the report.

Potential competing interests: A. Sood declares receiving speaker honorarium from Pfizer India and Takeda India and being on advisory board for Janssen Asia Pacific. A. Sood and A. Singh are supported by an IOIBD grant for an unrelated project. All other authors declare no conflicts of interest.

Trial registration number: ISRCTN42182437.

Study Highlights

WHAT IS KNOWN

- ✓ Nearly one-third of patients with acute severe ulcerative colitis (ASUC) are refractory to corticosteroids and require rescue therapy.
- ✓ Tofacitinib, through inhibition of JAK-STAT pathway, is postulated to decrease the corticosteroid refractoriness and may improve the corticosteroid responsiveness.
- ✓ The role of tofacitinib in combination with corticosteroids in ASUC has not been explored.

WHAT IS NEW HERE

- ✓ Tofacitinib, as add-on therapy to corticosteroids, significantly improved the treatment responsiveness in patients with ASUC at day 7.
- ✓ Fewer patients receiving tofacitinib required rescue medical or surgical therapy within 7 days of hospitalization.
- ✓ The benefit of adding tofacitinib to corticosteroids also extended beyond 7 days, and the cumulative probability of need for rescue therapy (either medical or surgical) at 90 days was significantly lower in patients receiving tofacitinib.

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