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# To study the effect of tofacitinib along with corticosteroids in patients with acute severe ulcerative colitis

**Submission date**
08/06/2023

**Recruitment status**
No longer recruiting

**Registration date**
14/06/2023

**Overall study status**
Completed

**Last Edited**
27/12/2023

**Condition category**
Digestive System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

## Plain English summary of protocol

Background and study aims
Ulcerative colitis (UC) is a long-term inflammatory condition of the large intestine that causes inflammation in the rectum and sometimes extends to other parts of the colon. It is a chronic condition that has periods of relapse and remission. While most patients have mild to moderate symptoms, around 15-25% will experience severe flare-ups, and 10-20% will have a severe form of the disease when diagnosed, requiring immediate hospitalization and intensive care.

The diagnosis of severe ulcerative colitis is based on specific criteria, including frequent bloody stools (at least six per day) and markers of systemic toxicity like a high pulse rate, fever, low hemoglobin levels, or high ESR (a blood test measuring inflammation).

Treatment usually starts with intravenous steroids, but 30-40% of patients do not respond well and need additional therapies like infliximab or cyclosporine. However, these second-line treatments come with risks of side effects, and if emergency surgery is needed, there is a 5% risk of death. Even with improvements in management, there is still a 20% risk of colectomy (removal of the colon) on the first admission, which increases to 40% after two admissions. Severe flare-ups of UC can also lead to a 1% mortality rate.

Tofacitinib, a type of medication that inhibits a specific cellular pathway involved in inflammation, is a new treatment option for UC. It has advantages over other drugs like monoclonal antibodies because it can be taken orally, has predictable effects on the body, acts quickly, is eliminated rapidly, has a lower risk of triggering immune reactions, and targets inflammation inside cells. Tofacitinib has a wider range of action compared to other medications that specifically target certain proteins or molecules involved in inflammation.

Researchers believe that some patients with UC have a higher expression of pro-inflammatory molecules and are less responsive to corticosteroid treatment. Tofacitinib, by inhibiting a specific pathway, has the potential to restore corticosteroid sensitivity.

This study aims to investigate if adding tofacitinib to corticosteroids is more effective than using corticosteroids alone in hospitalized patients with severe ulcerative colitis. The study will be conducted as a double-blind randomized controlled trial, where neither the patients nor the researchers know which treatment they are receiving in order to minimize bias.

Who can participate?
Adult patients (aged at least 18 years) hospitalized with ASUC, as defined by Truelove Witts criteria.

What does the study involve?
There will be two groups in the study:
1. Tofacitinib group: Some patients will receive tofacitinib along with the usual treatment for severe ulcerative colitis.
2. Placebo group: Other patients will receive a fake treatment (placebo) along with the usual treatment for severe ulcerative colitis.
Both groups will receive the standard care treatment, which includes intravenous hydrocortisone (a type of steroid medication) every 6 hours, intravenous fluids, correction of electrolyte imbalances, and enteral feeding (feeding through a tube). All patients will also receive medication to prevent blood clots called enoxaparin, given as a subcutaneous injection once a day throughout their hospital stay.

The patients in the tofacitinib group will take either tofacitinib (10 mg) or a fake pill (placebo) three times a day for 7 days.

By day 7, the intravenous hydrocortisone will be stopped for all patients. After assessing the response to treatment, patients will be divided into two groups: responders and non-responders. For patients who respond to the treatment by day 7, they will start taking prednisolone (a type of steroid) in pill form, with the dose gradually decreasing over 12 weeks. The responders in the tofacitinib group will continue taking tofacitinib, but at a lower dose of 10 mg twice a day. The responders in the placebo group will continue receiving the usual treatment with oral 5-aminosalicylates (a type of anti-inflammatory medication) along with azathioprine (another medication) if needed. The patients will be followed up for 90 days after being randomly assigned to their group. If the disease worsens between days 7 and 90, the patients may be given infliximab (a medication) or undergo surgery to remove the colon, depending on the decision of the treating doctor. The non-responders by day 7 will be offered rescue therapy with either infliximab, cyclosporine (another medication), or surgery.

What are the possible benefits and risks of participating?
Possible benefits:
-Increased response rates to first line medical treatment with corticosteroids
-Shorter hospital stay
-Decreased use of second line medical therapy with biologics (infliximab)/cyclosporine or surgery
Possible risks:
-Increased risk of infections especially herpes zoster.
-Increased risk of cardiac adverse effects and/or clotting of blood in the blood vessels (thrombotic complications)
-Derangement of lipid profile
-Derangement of liver functions

Where is the study run from?
Dayanand Medical College and Hospital Ludhiana, India

When is the study starting and how long is it expected to run?
April 2021 to March 2023

Who is funding the study?
The investigational product and the matching placebo will be provided by Ipca Laboratories Ltd. Mumbai, India.
The cost of investigations in the study will be supported by the research and development center at Dayanand Medical College and Hospital, Ludhiana. The funder will not have a role in data collection, data analysis, data interpretation, or writing of the report.

Who is the main contact?
Ajit Sood, ajitsood10@gmail.com

# Contact information

### Type(s)
Principal investigator

### Contact name
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# Additional identifiers

### Protocol serial number
TACOS 2021

# Study information

### Scientific Title
A prospective placebo-controlled randomized clinical study of tofacitinib as an adjunct to corticosteroids in acute severe ulcerative colitis

### Acronym
TACOS

### Study objectives
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. The present double blind randomized controlled trial will determine if addition of tofacitinib to corticosteroids is superior to corticosteroids alone in patients hospitalized with ASUC.

## Ethics approval required
Ethics approval required

## Ethics approval(s)
Approved 28/07/2021, Institutional Ethics Committee of Dayanand Medical College and Hospital (Tagore Nagar Civil Lines, Ludhiana, 141001, India; +91-8146545367; info@dmch.edu), ref: DMCH /P/2021/626

## Primary study design
Interventional

## Study design
Single center interventional double blind randomized placebo controlled trial

## Study type(s)
Treatment, Safety, Efficacy

## Health condition(s) or problem(s) studied
Acute severe ulcerative colitis (ASUC)

## Interventions
• The eligible patients will be randomized in a 1:1 ratio based on a computer generated random numbers to receive either tofacitinib or a matching placebo.
• There will be two intervention arms
o Tofacitinib arm: Patients randomized to receive tofacitinib in addition to the standard treatment of acute severe UC
o Placebo arm: Patients randomized to receive tofacitinib in addition to the standard treatment of acute severe UC
• The standard of care treatment including intravenous hydrocortisone (100 mg q6h), intravenous fluids, correction of dyselectrolytemia, and enteral feeding will be provided to the patients in both the treatment arms. Additionally, all the patients will receive thromboprophylaxis with enoxaparin (40-60 mg subcutaneously q24h) for the entire duration of hospitalization.
• Tofacitinib (10 mg) or a matching placebo will be administered thrice daily for 7 days.
• Intravenous hydrocortisone will be stopped in all patients by day 7. After unblinding and response assessment, the patients will be categorized into responders and non responders. For patients who respond to the intervention by day 7, per-oral prednisolone will be started in a tapering dose schedule (40 mg/day, gradually tapered and stopped by week 12). The responders in the tofacitinib arm will continue to receive tofacitinib, at a reduced dose of 10 mg twice daily while standard of care treatment with oral 5-aminosalicylates (3.6-4.8 g/day) ± azathioprine (1.5-2.0 mg/kg) will be continued in responders in the placebo arm. The patients will be followed till 90 days after randomization. In case of increase in disease activity between days 7 and 90, the patients will be considered for either infliximab or colectomy, at the discretion of the treating physician. The non-responders at day 7 will be advised rescue therapy with either infliximab /cyclosporine or colectomy.
• The demographic and disease characteristics will be recorded at the time of enrolment. The investigations, including hemogram, liver and renal function tests, erythrocyte sedimentation

rate (ESR), C-reactive protein (CRP), fecal calprotectin, and a limited unprepared flexible sigmoidoscopy with biopsy for histopathology and cytomegalovirus immunohistochemistry, will be performed in all patients within 24 hours of hospitalization. The investigations can be repeated at the discretion of the treating physician.
• All the patients will undergo 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 will be done at days 30, 60 and 90.
• Monitoring for adverse event(s), including opportunistic infections (particularly herpes zoster) and cardiovascular events, will be done daily till day 7, followed by assessments at days 30, 60 and 90. Any adverse event related to the use of tofacitinib resulting in death, or threatening life, requiring prolongation of hospitalization, or resulting in persistent or significant disability /incapacity will be considered as serious adverse event.
• The following investigations will be carried out at baseline in all the enrolled subjects.
1. Hemogram.
i. Hemoglobin
ii. Total leucocyte count
iii. Platelet count
2. C-Reactive Protein (quantitative)
3. Fecal Calprotectin
4. Liver Function Tests.
i. AST (Aspartate aminotransferase).
ii. ALT (Alanine aminotransferase).
iii. ALP (Alkaline phosphatase).
iv. Bilirubin.
v. Total protein.
vi. Albumin.
5. Renal Function Tests
i. Blood Urea.
ii. Serum Creatinine.
6. Fasting Blood Sugar.
7. Lipid profile
i. Cholesterol (Total, HDL, LDL, VLDL)
ii. Triglycerides
8. Sigmoidoscopy and biopsy for cytomegalovirus infection (unprepared)
9. Stool for Clostridioides difficile infection (glutamate dehydrogenase and toxins A and B)

## Intervention Type
Drug

## Phase
Not Applicable

## Drug/device/biological/vaccine name(s)
Tofacitinib

## Primary outcome(s)
The proportion of subjects responding to treatment by day 7. Response to therapy will be defined using Lichtiger index.
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 Lichtiger index by >3 points the day 7, and an absolute score <10 for 2 consecutive days without the need for rescue therapy (infliximab/cyclosporine or colectomy) was considered as response.

### Key secondary outcome(s)
Measured using patient records at the end of the study:
1. The proportion of patients requiring medical (infliximab/cyclosporine) or surgical (colectomy) rescue therapy by day 7.
2. The duration of hospital stay
3. The proportion of patients requiring initiation of infliximab/cyclosporine or undergoing colectomy after discharge but within 90 days following randomization.

### Completion date
31/03/2023

## Eligibility

### Key inclusion criteria
1. Adult (aged > 18 years)
2. Subjects hospitalized with ASUC, as defined by Truelove Witts criteria, i.e. 6 or more blood stained stools daily, with 1 or more of the 4 additional criteria: hemoglobin <105g/L, ESR >30 mm /h, fever >37.8, and tachycardia >90/min.
3. Subjects who are willing and able to comply with treatment plan, laboratory tests, daily bowel movement diary call, and other study procedures.
4. Subjects who are willing to provide a written informed consent.

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
18 Years

### Upper age limit
75 Years

### Sex
All

### Total final enrolment
104

### Key exclusion criteria
1. Patients hospitalized with severe UC but did not fulfil the Truelove Witts criteria
2. Prior exposure to intravenous corticosteroids or tofacitinib within 4 weeks before

hospitalization
3. Active enteric or extra-intestinal infection (including Clostridioides difficile, tuberculosis, etc.)
4. Crohn’s colitis
5. Toxic megacolon, intestinal perforation, or massive haemorrhage requiring emergency colectomy
6. Pregnancy/lactation
7. Current or prior history of thromboembolic disease
8. Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses
9. Subjects who have been vaccinated with live or attenuated vaccine within 6 weeks of baseline or scheduled to receive these vaccines during study period or within 6 weeks after last dose of study medication
10. Subjects with malignancies or a history of malignancies, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin.
11. Subjects with current or recent history of severe, progressive, or uncontrolled renal, hepatic, haematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological disease.

### Date of first enrolment
01/10/2021

### Date of final enrolment
31/12/2022

## Locations

### Countries of recruitment
India

### Study participating centre
**Dayanand Medical College and Hospital**
Tagore Nagar Civil Lines
Ludhiana
India
141001

## Sponsor information

### Organisation
Dayanand Medical College & Hospital

### ROR
https://ror.org/005fgpm31

## Funder(s)

### Funder type
Other

### Funder Name
Investigator initiated and funded

### Funder Name
Dayanand Medical College and Hospital, Ludhiana

# Results and Publications

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are /will be available upon request from Ajit Sood (ajitsood10@gmail.com).

### IPD sharing plan summary
Available on request

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 22/12/2023 | 27/12/2023 | Yes | No |
| Participant information sheet | | | 14/06/2023 | No | Yes |
| Protocol file | version 1.0 | 01/07/2021 | 14/06/2023 | No | No |