Patient information Sheet
Tofacitinib as an add on therapy to corticosteroids in Acute Severe Ulcerative Colitis

Background

Ulcerative colitis (UC) is a chronic relapsing and remitting immune-mediated inflammatory condition of the large intestine that is frequently associated with inflammation of the rectum but often extends proximally to involve additional areas of the colon.

Approximately 15–25% of patients with UC experience at least one episode of severe flare of their disease and 10–20% will present with acute severe ulcerative colitis (ASUC) at diagnosis. ASUC requires prompt hospitalization and intensive care. The diagnosis of ASUC is based on the Truelove and Witts criteria described in 1955, which combines frequency of bloody stools (⩾6 per day) with at least one marker of systemic toxicity: pulse rate >90 per minute, temperature >37.8°C, hemoglobin <10.5 g/dl and/or an ESR >30 mm/h.

Intravenous steroids are the mainstay of therapy, but 30–40% of patients fail to respond to steroids and require progression to second-line therapy [infliximab (IFX) or cyclosporine (CsA)]. These second-line therapies are associated with a significant risk for adverse events, and colectomy carries a 5% postoperative mortality risk when done emergently in the hospital setting. Despite improvements in management, ASUC is associated with a 20% risk for colectomy on first admission and this risk rises to 40% after two admissions. Moreover, there remains a 1% mortality associated with severe flares of UC. Therefore, a large therapeutic gap remains and strategies are needed to improve the responsiveness to corticosteroids.

Tofacitinib, a JAK-STAT (Janus kinase-signal transducers and activators of transcription) inhibitor and an anti-inflammatory drug, is a new addition to the treatment modalities for UC. It has been postulated tofacitinib, via STAT inhibition, has the potential to restore the corticosteroid sensitivity.

We hypothesize 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.

Aims of the study

- To compare the efficacy of tofacitinib used as an adjunct to corticosteroids versus corticosteroids alone in inducing treatment response among subjects with acute severe ulcerative colitis.
- To compare the rates of rescue (second line) medical therapy and colectomy (surgery) in the two intervention groups at day 90 of randomization.

Who can participate?

- Adult (aged > 18 years)
- Patients hospitalized with ASUC, as defined by Truelove Witts criteria
- Patients who are willing and able to comply with treatment plan, laboratory tests, daily bowel movement diary call, and other study procedures.
- Patients who are willing to provide a written informed consent.

What does the study involve?

- 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
    - Tofacitinib arm: Patients randomized to receive tofacitinib in addition to the standard treatment of acute severe UC

- 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)

What are the possible benefits 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

What is the dosage schedule of tofacitinib?

Induction: 10 mg thrice daily for 7 days (in patients with ASUC) followed by twice daily for at least 8 weeks; based on therapeutic response, may continue 10 mg twice daily for a maximum of 16 weeks or transition to maintenance dose. Discontinue therapy if inadequate response achieved after 16 weeks using 10 mg twice daily.

Maintenance: 5 mg twice daily; if patient experiences loss of response on 5 mg twice daily, then use 10 mg twice daily after assessing the benefits and risks and use for the shortest duration; use lowest effective dose to maintain response.

What are the dose modifications in patients with deranged liver and kidney functions?

Patients with severe liver or kidney disease will not be enrolled in the study. However the dosing protocols in such patients are summarised below:

Renal Impairment

- Mild impairment: No dosage adjustment necessary.
- Moderate to severe impairment:
- Reduce dose to 5 mg twice daily (if taking 10 mg twice daily) or 5 mg once daily (if taking 5 mg twice daily).
- End-stage renal disease requiring hemodialysis. Administer after dialysis session on dialysis days; if dose given prior to dialysis, supplemental dose is not recommended after dialysis session.
- Reduce dose to 5 mg twice daily (if taking 10 mg twice daily) or 5 mg once daily (if taking 5 mg twice daily).

Hepatic Impairment

- Mild impairment: No dosage adjustment necessary.
- Moderate impairment:
- Reduce dose to 5 mg twice daily (if taking 10 mg twice daily) or 5 mg once daily (if taking 5 mg twice daily).
- Severe impairment: Use is not recommended (has not been studied in patients with severe hepatic impairment or in patients with hepatitis B or hepatitis C viruses).

What is the side effect profile of tofacitinib?

- Nasopharyngitis (3% to 14%)
- Hypertension (2%)
- Headache (3% to 9%)
- Skin rash (6%), acne vulgaris (≥2%)
- Increased serum cholesterol (5% to 9%)
- Diarrhea (3% to 5%), gastroenteritis (4%), nausea (4%)
- Urinary tract infection (2%)
- Anemia (4%)
- Herpes zoster infection (5%; including disseminated cutaneous, meningoencephalitis, ophthalmologic)
- Increased creatine phosphokinase (3% to 7%)
- Increased serum creatinine (<2%)
- Upper respiratory tract infection (4% to 7%)
- Fever (≥2%)
- Peripheral edema
- Fatigue, insomnia, paresthesia
- Erythema, pruritus
- Dehydration
- Abdominal pain, diverticulitis of the gastrointestinal tract, dyspepsia, gastritis, vomiting
- Malignant lymphoma, skin carcinoma (nonmelanoma)
- Increased liver enzymes, liver steatosis
- Bacterial infection, fungal infection, opportunistic infection, serious infection, viral infection
- Arthralgia, joint swelling, musculoskeletal pain, tendinopathy
- Cough, dyspnea, interstitial pulmonary disease, paranasal sinus congestion

What are the concerns related to adverse effects with tofacitinib?

- Bone marrow suppression: Lymphocytopenia (after an initial lymphocytosis), neutropenia (<2,000 cells/mm^3), and anemia have been observed with tofacitinib therapy. Lymphocyte counts <500 cells/mm^3 were associated with increased incidence of treated and serious infections; avoid tofacitinib initiation in patients with lymphocytes <500 cells/mm^3 at baseline. Avoid use in patients with ANC <1,000 cells/mm^3 at baseline; interrupt therapy if ANC is persistently between 500 to 1,000 cells/mm^3 or if ANC <500 cells/mm^3 during treatment. Consider resuming tofacitinib when ANC ≥1,000 cells/mm^3. Avoid tofacitinib initiation in patients with hemoglobin<9 g/dL; interrupt therapy if hemoglobin decreases >2 g/dL or if hemoglobin<8 g/dL. Monitor lymphocyte counts at baseline and every 3 months thereafter; ANC, platelet counts, and hemoglobin should be assessed at baseline, after 4 to 8 weeks of therapy, and every 3 months thereafter.

- GI perforations: Use with caution in patients at increased risk for GI perforation (eg, history of diverticulitis); perforations have been reported in clinical trials. Promptly evaluate new-onset abdominal symptoms in patients taking tofacitinib.

- Hepatotoxicity: Increased incidence of liver enzyme elevation was observed in patients taking tofacitinib compared to placebo. Routine LFT monitoring is recommended; interrupt therapy if drug-induced liver injury is suspected.

- Hypersensitivity: Hypersensitivity reactions, including angioedema and urticaria, have occurred; discontinue therapy and evaluate cause for serious reactions.

- Infections: Patients receiving tofacitinib are at increased risk for serious infections, which may result in hospitalization and/or fatality. The most common serious infections reported included pneumonia, cellulitis, urinary tract infections, diverticulitis, appendicitis, and herpes zoster infections, although other serious infections may occur. Reactivation of viral infections (eg, herpes zoster, hepatitis B) have been observed; the incidence of chronic viral hepatitis reactivation is unknown. The risk for herpes zoster is increased with tofacitinib; patients within Asian countries appear to have a higher incidence of herpes zoster cases (Winthrop 2014). Use with caution in patients that have been exposed to tuberculosis (TB), with a history of serious or opportunistic infection, taking concomitant immunosuppressants, with comorbid conditions that predispose them to infections (eg, diabetes), or in patients who live in or travel to/from areas of endemic mycoses (ie, blastomycosis, coccidioidomycosis, histoplasmosis). Do not initiate tofacitinib in patients with active infections, including localized infections. The risk of serious infections and opportunistic herpes zoster infections may be increased with use of higher doses. Risk of infection may be higher with increasing degrees of lymphopenia; monitor lymphocyte counts.

- Interstitial lung disease: Interstitial lung disease (ILD) has been reported; patients developing ILD were receiving concomitant therapy associated with ILD (eg, methotrexate). Use with caution in patients with risk/history of ILD (Xeljanz Canadian product monograph).

- Lipid abnormalities: Dose-dependent increases in lipid parameters (eg, total cholesterol, low-density lipoprotein, and high-density lipoprotein cholesterol) were observed in patients receiving tofacitinib; maximum lipid increases were typically seen within 6 weeks of initiation. Assess lipids 4 to 8 weeks after tofacitinib initiation and manage lipid abnormalities accordingly.

- Malignancy: Malignancies, including lymphomas and solid cancers, have been reported in patients receiving tofacitinib. The most common types of malignancy observed were lung, breast, gastric, colorectal, renal cell, prostate, lymphoma, pancreatic, and malignant melanoma. The risk of malignancies, including nonmelanoma skin cancers (NMSCs), may be increased with higher doses. Consider risks

versus benefits prior to use in patients with a known malignancy (other than successfully treated NMSCs) or when continuing tofacitinib in patients who develop a new malignancy. NMSCs have been reported; patients at increased risk for skin cancer should have periodic skin examinations.

- Tuberculosis: TB (pulmonary or extrapulmonary) has been reported in patients receiving tofacitinib. Active TB has developed in patients with initial negative tuberculin skin tests during treatment with tofacitinib. Use with caution in patients who have resided in regions where TB is endemic. Consider antituberculosis therapy if an adequate course of treatment cannot be confirmed in patients with a history of latent or active TB or for patients with risk factors despite negative skin test.

- Immunizations: Immunization status should be current before initiating therapy. Live vaccines should not be given concomitantly with tofacitinib; recommended interval between receipt of live vaccines and initiation of immunosuppressive agents, such as tofacitinib, should follow current vaccination clinical guidelines. Dissemination of the vaccine strain of varicella zoster virus has been reported in a varicella virus-naive patient 16 days following vaccination with Zostavax (live attenuated zoster) and 2 days after the initiation of tofacitinib.

Can tofacitinib be used in pregnancy and breastfeeding?

- Outcome data following tofacitinib exposure in pregnancy are limited
- It is not known if tofacitinib is present in breast milk.

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?

- The study start date : 01.04.2021
- Recruitment Start Date: 01.10.2021
- Recruitment stop Date: 31.12.2022
- Last Follow Up Date: 31.03.2023
- Total duration of the study : 24 months

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?

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