Abstract

Protocol Title: 12 and 18 Month Outcomes and Long-Term Survival of Tofacitinib in Ulcerative Colitis

Protocol Number (date and version): A3921416, 08 February 2022, Version 1

Rationale and background: Tofacitinib is an oral Janus kinase inhibitor that was approved for the treatment of moderate-to-severe ulcerative colitis (UC) in 2018. Clinical trials demonstrated the efficacy of induction and maintenance tofacitinib in this population. A small number of real-world cohort studies have investigated clinical outcomes of tofacitinib therapy, and none to-date have assessed long-term outcomes beyond 52 weeks. We therefore aim to perform a retrospective cohort study to assess long-term clinical outcomes of tofacitinib therapy in UC.

Research question and objectives:

Primary objective:

1. Assess proportions of clinical remission (Simple clinical colitis activity index (SCCAI) or Mayo score ≤2 or provider global assessment (PGA)) and corticosteroid-free clinical remission at week 52 and 78 after tofacitinib induction in a real-world cohort of patients with UC.

Secondary objectives:

1. Use univariable and multivariable logistic regression to identify baseline predictors of corticosteroid-free clinical remission at weeks 52 and 78.
2. Use multivariable cox regression to identify baseline predictors of drug survival (ie, time to tofacitinib discontinuation or colectomy due to refractory disease activity).
3. Assess proportions of endoscopic response (ie, decrease in Mayo endoscopic subscore by 1 point), endoscopic remission (Mayo endoscopic subscore <1) >8 weeks post-tofacitinib induction.
4. Assess proportions of biochemical response (improvement in CRP or calprotectin by >25% or normalization) and remission (normalization of CRP or calprotectin) at weeks 8, 26, 52, and 78.
5. Describe proportions of dose de-escalation (10 to 5 mg) or dose re-escalation (5 to 10 mg).
6. Assess proportions of clinical remission and corticosteroid-free remission 8-16 weeks after does de-escalation and dose re-escalation.
7. Describe proportions of colectomy, IBD-related hospitalization, and corticosteroid use within 52 weeks of tofacitinib induction.
8. Assess proportions of patient-reported improvement in extraintestinal manifestations at 52 weeks after tofacitinib induction.
9. Assess proportions of potential complications (eg, infection, thromboembolism, shingles, new malignancy) during available follow-up.
10. Describe reasons for treatment discontinuation.

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Study design: This is a retrospective cohort study of adults with UC who initiate tofacitinib therapy after 01 October 2018 (month of FDA approval) in the Mass General Brigham (MGB) health system. Patients will be followed from the time of tofacitinib initiation to tofacitinib discontinuation, total colectomy, or the last available gastroenterology encounter. Independent variables will be recorded as the most recent values available within 3 months prior to tofacitinib initiation.

Population: Patients of age 18 years or older with UC who initiate tofacitinib therapy after 01 October 2018 (month of FDA approval) in the Mass General Brigham (MGB) health system in Boston, MA. Patients with prior total proctocolectomy, diagnosis of Crohn's disease or indeterminate colitis, and those on dual biologic therapy (eg, tofacitinib and ustekinumab) will be excluded.

Variables: age, sex, race/ethnicity, disease duration (years), BMI, disease extent/severity and histologic activity (based on last colonoscopy), last Mayo or Simple Clinical Colitis Activity Index, daily bowel movement frequency, C-reactive protein, serum albumin, erythrocyte sedimentation rate, fecal calprotectin, concomitant and prior medications (corticosteroids, 5-ASA, azathioprine, 6-mercaptopurine, methotrexate, biologic therapies), , substance use (current or former smoking, current cannabis, current opioids), history of malignancy, extraintestinal manifestation, and UC-related hospitalization within the prior 12 months.

Outcomes: Clinical remission and corticosteroid-free clinical remission at 52 and 78 weeks, drug survival (ie, treatment persistence during all available follow-up), endoscopic response and remission, biochemical response and remission, de-escalation, colectomy, hospitalization, corticosteroid use, improvement in extraintestinal manifestation, adverse effects/complications, tofacitinib discontinuation.

Data sources: Epic, the electronic medical record of Mass General Brigham (MGB) and the MGB Research Patient Data Registry (RPDR).

Study size: The estimated sample size is 100 patients per the MGB RPDR. Among these, approximately 85 patients have 12 or more months of potential follow-up.

Data analysis: Univariate and multivariable logistic regression models will be built utilizing independent variables as predictors of corticosteroid-free remission at week 52 and week 78 (two separate models). Variables on univariable analysis associated with the outcome at $p<0.10$ will be included in the final multivariable model.

Univariable and multivariable Cox proportional hazards modeling will be used to identify predictors of tofacitinib drug survival. Variables on univariable analysis associated with drug survival at $p<0.10$ will be included in the final multivariable model.

Milestones

Milestone	Planned date
Start of data collection	01 March 2022
End of data collection	30 April 2022
Registration in the EU PAS register	28 February 2022
Final study report	30 March 2023