Abstract

Protocol Title: Comparative Effectiveness of Tofacitinib vs Ustekinumab and Vedolizumab among Ulcerative Colitis Patients with Prior Anti-TNF Failure

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Rationale and background: With limited head-to-head clinical trial data of advanced therapies in moderate-to-severe ulcerative colitis (UC), the optimal relative positioning of tofacitinib, ustekinumab, and vedolizumab is unclear. Recent meta-analytic data has identified infliximab as the preferred first-line therapy for induction of remission in UC, followed by tofacitinib and ustekinumab after anti-tumor necrosis factor (TNF) failure, and vedolizumab thereafter.

However, conclusions regarding the performance of tofacitinib relative to ustekinumab and vedolizumab were not made. As tofacitinib, ustekinumab, and vedolizumab therapy are commonly considered after failure of the anti-TNF class for UC, additional comparative data that reflect real-world outcomes are needed.

Research question and objectives:

Primary objectives:

1. Compare proportions of corticosteroid-free clinical remission ((Simple Clinical Colitis Activity Index) SCCAI $\leq$2, if not available Mayo $\leq$2, if not available by physician global assessment [PGA] AND no use of oral or intravenous corticosteroids within 30 days of assessment) at 8-12 weeks after tofacitinib, ustekinumab, or vedolizumab initiation among patients with prior anti-TNF exposure.
2. Compare proportions of corticosteroid-free clinical remission at 12 months after tofacitinib, ustekinumab, or vedolizumab initiation among patients with prior anti-TNF exposure.
3. Compare drug survival (time to treatment discontinuation or colectomy) of tofacitinib versus ustekinumab and vedolizumab.

Secondary objectives:

1. Compare proportions of endoscopic response (ie, decrease in Mayo endoscopic subscore by 1 point) and endoscopic remission (Mayo endoscopic subscore <1) >8 weeks post-treatment initiation.
2. Assess proportions of biochemical response (improvement in C-reactive protein (CRP) or calprotectin by >25% or normalization) and remission (normalization of CRP or calprotectin) at first available assessment 8 weeks or later after drug initiation.
3. Compare proportions of colectomy, inflammatory bowel disease (IBD)-related hospitalization, and corticosteroid use within 52 weeks of treatment initiation.
4. Compare proportions of patient-reported improvement in articular extraintestinal manifestations within 52 weeks after treatment initiation.
5. Report proportions of potential complications (eg, infection, thromboembolism, shingles, new malignancy) during all available follow-up.
6. Describe reasons for treatment discontinuation.

Study design: This is a retrospective cohort study of patients aged ≥18 years with UC who initiate tofacitinib, ustekinumab, or vedolizumab therapy after 01 May 2018 (month of tofacitinib FDA approval) in the Mass General Brigham (MGB) health system. Only patients with prior anti-TNF alpha exposure will be included. Because the cohort of vedolizumab-treated patients is expected to be more than 4 times the size of the cohort of tofacitinib-treated patients, 2:1 frequency matching by age (+/- 3 years) and sex will be used to define the vedolizumab cohort using data automatically extracted from the RPDR. The ustekinumab cohort is anticipated to be similar in size to the tofacitinib cohort, therefore, all eligible ustekinumab-treated patients will be included. Researchers will then perform manual chart review to collect other baseline independent variables, relevant confounders, and outcome data. Outcomes will be assessed at clinic visits 8-12 weeks and 12 months after drug initiation. Drug survival will also be assessed by following patients from the time of drug initiation to discontinuation due to loss of response (including colectomy due to loss of response). Patients will be censored at total colectomy due to dysplasia/cancer or the last available gastroenterology encounter through 01 April 2022. Independent variables to be abstracted are baseline characteristics present at the time of drug initiation (or most recent available values within 3 months of initiation).

Population: Patients of age 18 years or older with UC who initiate tofacitinib ustekinumab or vedolizumab for UC therapy after 01 May 2018 (month of FDA approval) in the MGB health system. Only patients with prior anti-TNF exposure (infliximab, adalimumab, golimumab, or certolizumab) will be included. Patients with prior total proctocolectomy, diagnosis of Crohn's disease or indeterminate colitis, those on dual therapy with tofacitinib and a biologic or vedolizumab/ ustekinumab and a second biologic, or non-UC indications for drug treatment 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 or small molecule 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: Corticosteroid-free clinical remission and corticosteroid-free clinical response at 8-12 weeks after initiation of tofacitinib, ustekinumab or vedolizumab, drug survival (i.e. treatment persistence during all available follow-up), endoscopic response and remission, biochemical response and remission, colectomy, hospitalization, corticosteroid use, improvement in extraintestinal manifestation, adverse effects/complications, tofacitinib or vedolizumab discontinuation.

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

Study size: The sample size that meets inclusion criteria is estimated to be 70 patients in the tofacitinib group, 70 patients in the ustekinumab group, and 500 patients in the vedolizumab group per the RPDR. For the tofacitinib vs vedolizumab comparison, two vedolizumab patients will be frequency matched by age and sex for every one tofacitinib patient (estimated total sample of 210 patients). For the tofacitinib vs

ustekinumab comparison, all eligible patients will be included (estimated total sample of 140 patients).

Data analysis: Two propensity scores will be calculated using a logistic regression model to predict treatment of tofacitinib versus ustekinumab and tofacitinib versus vedolizumab using the following *a priori* covariates (i.e. confounders): age, sex, race, last Mayo endoscopic subscore, disease extent, serum albumin, disease duration, current corticosteroid use, current immunomodulator use, number of prior biologic or small molecule therapies, and UC hospitalization within the prior 12 months. The propensity scores will then be used to calculate inverse probability of treatment weights (IPTW) for each comparison. The IPT-weighted samples will then be utilized in two logistic regression models determining the association between tofacitinib versus ustekinumab and vedolizumab therapy on remission at 8-12 weeks and 12 months.

A survival analysis of time to treatment discontinuation or colectomy due to non-response will also be conducted. First, two unweighted Kaplan-Meier analyses with log-rank test stratified by treatment will be performed. Subsequently, two IPTW Cox proportional hazards models will be built to determine the association of tofacitinib versus ustekinumab and vedolizumab therapy with time to treatment discontinuation or colectomy due to non-response.

Milestones.

Milestone	**Planned date**
Start of data collection	24 February 2022
End of data collection	30 April 2022
Registration in the European Union (EU) PAS register	23 February 2022
Final study report	30 March 2023