Abstract

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

Protocol Number (date and version): A3921415, 08 February 2022, Version 1

Rationale and background: With limited head-to-head clinical trial data of biologic therapies in moderate-to-severe ulcerative colitis (UC), the optimal relative positioning of vedolizumab and tofacitinib 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, real-world comparative data for tofacitinib vs vedolizumab is lacking. We therefore seek to perform a retrospective matched cohort study to compare clinical outcomes of these agents among anti-TNF exposed patients with UC in our health system.

Research question and objectives:

Primary objectives:

1. Compare proportions of corticosteroid-free clinical remission (SCCAI $\leq$2 if not available Mayo $\leq$2 if not available by physician global assessment (PGA)) at 8-12 weeks after tofacitinib or vedolizumab initiation among patients with prior anti-TNF exposure.
2. Compare proportions of corticosteroid-free clinical response (reduction in baseline SCCAI $\geq$2 if not available Mayo score by $\geq$2 points if not available by PGA) at 8-12 weeks.
3. Compare biologic survival (time to treatment discontinuation or colectomy) of tofacitinib vs vedolizumab.

Secondary objectives:

1. Compare proportions of endoscopic response (ie, decrease in Mayo endoscopic subscore by 1 point), endoscopic remission (Mayo endoscopic subscore <1) >8 weeks post-biologic initiation.
2. 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 96, where data is available.
3. Compare proportions of colectomy, IBD-related hospitalization, and corticosteroid use within 52 weeks of biologic initiation.
4. Compare proportions of patient-reported improvement in extraintestinal manifestations at 52 weeks after biologic initiation.
5. Compare proportions of potential complications (eg, infection, thromboembolism, shingles, new malignancy) during available follow-up.
6. Describe reasons for treatment discontinuation.

Study design: This is a matched, retrospective cohort study of patients aged $\geq$18 years with UC who initiate tofacitinib or vedolizumab therapy after 01 October 2018 (month of tofacitinib FDA approval) in the [redacted] health system. Only patients with prior anti-TNF alpha exposure without exposure to other biologic classes

Redacted

will be included. Two vedolizumab patients will be matched for every one tofacitinib patient by age and sex. Outcomes will be assessed at clinic visits 12-16 weeks after biologic initiation. Patients will be followed from the time of biologic initiation to 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 biologic initiation.

Population: Patients of age 18 years or older with UC who initiate tofacitinib or vedolizumab for UC therapy after 01 October 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 biologic therapy (eg, tofacitinib and ustekinumab), or non-UC indications for biologic 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 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 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 60 patients in the tofacitinib group and 300 patients in the vedolizumab group per the RPDR. Two vedolizumab patients will be matched for every one tofacitinib patient by age and sex.

Data analysis: Multivariable logistic regression will be performed to determine the association of tofacitinib vs vedolizumab therapy with corticosteroid-free remission at 8-12 weeks and corticosteroid-free response at 8-12 weeks (two separate models). Confounders for the model will be chosen a priori and will include BMI, Mayo endoscopic subscore, serum albumin, disease duration, current corticosteroid use, current immunomodulator use, and history of malignancy. Multivariable Cox regression will be used to compare drug survival. Propensity scores with inverse probability of treatment weighting may be used to balance baseline covariates if the number of covariates exceeds the number of outcome events/10.

Milestones.

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