NON-INTERVENTIONAL PROTOCOL ABSTRACT

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

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Keywords: Comparative effectiveness; biologic; small molecule; inflammatory bowel disease

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 in the United States are needed.

The tofacitinib-treated patients in this protocol were derived from the same patient population in final study report A3921416.

Research question and objectives:

Primary objectives:

1. Compare proportions of steroid-free clinical remission (SFCR; 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 SFCR 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 were included. Because the cohort of vedolizumab-treated patients is more than 4 times the size of the cohort of tofacitinib-treated patients, 2:1 frequency matching by age (±3 years) and sex was used to define the vedolizumab cohort using data automatically extracted from the RPDR. The ustekinumab cohort was anticipated to be similar in size to the tofacitinib cohort, therefore, all eligible ustekinumab-treated patients will be included. Researchers performed manual chart review to collect other baseline independent variables, relevant confounders, and outcome data. Outcomes were assessed at clinic visits 8-12 weeks and 12 months after drug initiation. Drug survival was also 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 were censored at total colectomy due to dysplasia/cancer or the last available gastroenterology encounter through 01 April 2022. Independent variables abstracted were baseline characteristics present at the time of drug initiation (or most recent available values within 3 months of initiation).

Setting: Mass General Brigham health system in Boston, MA, USA.

Subjects and study size, including dropouts: For tofacitinib vs ustekinumab, 69 patients initiated tofacitinib and 97 patients initiated ustekinumab. For tofacitinib vs vedolizumab, 68 patients who initiated tofacitinib were matched to 136 patients who initiated vedolizumab (1 tofacitinib patient could not be matched, hence reduction in tofacitinib sample from 69 to 68).

Variables and data sources: Variables included 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. The data source was Epic, the electronic

medical record of Mass General Brigham (MGB) and the MGB Research Patient Data Registry (RPDR).

Results: For tofacitinib vs ustekinumab: At 12 weeks, 53% of tofacitinib vs 32% of ustekinumab patients were in SFCR. At 52 weeks, 56% of tofacitinib vs 49% of ustekinumab patients were in SFCR. After inverse probability of treatment-weighted logistic regression, there was no association of tofacitinib vs ustekinumab with SFCR at 12 weeks (OR 1.65, 95% CI 0.79-3.41) or 52 weeks (OR 1.14, 95% CI 0.55-2.34). During all available follow-up, 17 AEs were reported for tofacitinib (most commonly shingles, n=4) and 10 AEs were reported for ustekinumab (most commonly arthralgia and rash, each n=2). Two patients discontinued treatment due to AEs (one tofacitinib for elevated liver enzymes, one ustekinumab for arthralgia).

For tofacitinib vs vedolizumab: At 12 weeks, 54% of tofacitinib vs 46% of vedolizumab patients achieved SFCR. At 52 weeks, 59% vs 45% achieved SFCR. After logistic regression analysis, tofacitinib had a non-significantly higher odds of SFCR 12 (OR 1.66, 95% CI 0.77-3.62) and a significantly higher odds of SFCR 52 (aOR 2.15, 95% CI 1.01-4.61) and ER within 52 weeks (aOR 3.42, 95% CI 1.08-10.80) vs vedo. During available follow-up, the most common AEs (reported among ≥1% of total cohort) included rash (0% tofa vs 4% vedo), C. difficile infection (1% vs 2%), shingles (2% vs 1%), COVID-19 (1% vs 2%), other infection (2% vs 4%), and elevated liver enzymes (1% vs 2%).

Discussion:

In a real-world UC cohort, tofacitinib and ustekinumab demonstrated similar effectiveness at 52 weeks. AEs were consistent with the known safety profiles of these agents. Tofacitinib was associated with higher odds of SFCR at 52 weeks vs vedolizumaba for UC. AEs were also consistent with known safety profiles. Due to limited sample sizes, larger cohort studies are needed to confirm these findings.

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