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**Observations and Research**

# Comparing Patient-Reported Outcomes Among Anti-TNF Experienced Patients With Ulcerative Colitis Initiating Vedolizumab Versus Tofacitinib

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**Background:** Primary and secondary nonresponse to anti-tumor necrosis factor (TNF) therapy is common in patients with ulcerative colitis (UC), yet limited research has compared the effectiveness of subsequent biological therapy.

**Objective:** We sought to compare the effectiveness of vedolizumab and tofacitinib in anti-TNF experienced patients with UC, focusing on patient-prioritized patient-reported outcomes (PROs).

**Methods:** We conducted a prospective cohort study nested within the Crohn's & Colitis Foundation's IBD Partners and SPARC IBD initiatives. We identified anti-TNF experienced patients with UC initiating vedolizumab or tofacitinib and analyzed PROs reported approximately 6 months later (minimum 4 months, maximum 10 months). Co-primary outcomes were Patient Reported Outcome Measurement Information System (PROMIS) domains of Fatigue and Pain Interference. Secondary outcomes included PRO2, treatment persistence, and need for colectomy.

**Results:** We compared 72 vedolizumab initiators and 33 tofacitinib initiators. At follow-up, Pain Interference ($P = .04$), but not Fatigue ($P = .53$) was lower among tofacitinib initiators. A trend toward higher Social Role Satisfaction was not significant. The remainder of secondary outcomes (PRO2, treatment persistence, colectomy) did not differ between treatment groups.

**Conclusions:** Among anti-TNF experienced patients with UC, Pain Interference 4–10 months after treatment initiation was lower among tofacitinib users as compared with vedolizumab users. Many, but not all, secondary endpoints and subanalyses also favored tofacitinib. Future studies with larger sample sizes are needed to further evaluate these findings.

## Lay Summary

In this prospective study comparing the effectiveness of tofacitinib and vedolizumab in ulcerative colitis patients previously treated with anti-tumor necrosis factor therapy, we found lower pain interference 4–10 months after treatment among tofacitinib users but no significant differences in fatigue scores.

**Key Words:** Ulcerative colitis, comparative effectiveness research, patient-reported outcomes, tofacitinib, vedolizumab

## Background

Ulcerative colitis (UC) affects approximately 600 000 individuals in the United States,[1] costs over $3 billion annually,[2] and causes substantial patient morbidity,[3] missed work[4] and school,[5] and diminished quality of life.[6] Currently, anti-tumor necrosis factor (TNF) therapy is considered first-line treatment for moderate to severe disease.[7,8] Yet, primary nonresponse occurs in up to 40% of patients with inflammatory bowel disease, and secondary loss of response is observed in up to 50% of initial responders.[9]

When anti-TNF therapy fails, subsequent treatment options for UC include vedolizumab, an antibody to α4β7 integrin, tofacitinib (janus kinase inhibitor), ustekinumab (antibody to IL-12/23), upadacitinib (selective janus kinase 1 inhibitor), and ozanimod (sphingosine-1-phosphate

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receptor modulator). Unfortunately, anti-TNF refractory patients respond less well to subsequent treatments,[10,11] underscoring the importance of selecting the most effective second-line agent. Yet, there is a paucity of comparative effectiveness research (CER) to guide this challenging clinical decision faced by many patients and their providers.[12,13] A systematic review and network meta-analysis of randomized, placebo-controlled trials found tofacitinib and ustekinumab to be superior to vedolizumab for the induction of remission and endoscopic improvement in patients with prior exposure to anti-TNF antagonists; however, vedolizumab had the lowest risk of infections in maintenance trials. The authors concluded that more direct comparisons are needed to inform clinical decision making with greater confidence.[14] An updated network meta-analysis including newer agents concluded that upadacitinib was superior to other medications among anti-TNF experienced patients, and again found vedolizumab to be associated with a lower risk of infection.[15] Over the last year, a few multicenter European studies have compared the effectiveness of vedolizumab and tofacitinib, with results suggesting improved effectiveness of tofacitinb.[16,17] Real-world comparative effectiveness studies from the United States are lacking. Furthermore, these prior studies have all focused on clinical and endoscopic outcomes and none have reported on patient-reported outcomes (PROs) which are direct measures of how patients feel and function.

We sought to compare the effectiveness of vedolizumab and tofacitinib, the first 2 non-anti-TNF advanced therapies approved to treat UC, among anti-TNF experienced patients from across the United States, focusing on PROs prioritized by patients living with IBD. To accomplish this, we conducted a prospective cohort study in a geographically diverse population of patients cared for in a variety of practice settings.

## Materials and Methods

### Overall Study Design

We conducted a prospective cohort study by combing data collected through 2 independent cohorts sponsored by the Crohn's & Colitis Foundation. Our overall study design utilizes an analytical framework created for a parallel study in Crohn's disease that was funded through the same award mechanism.

### Study Population

IBD Partners is an internet-based cohort study of over 16 000 adult patients with IBD. Participants complete a baseline survey, and receive follow-up surveys every 6 months. Participants can also update their treatment and outcome information "on demand" through a web portal. Descriptions of the methods of cohort recruitment, follow-up, and data capture have been previously published.[18,19] Overall, IBD Partners inclusion criteria includes age ≥18 years, a self-reported diagnosis of IBD, internet access, and the ability to complete surveys in English. A prior validation study of IBD Partners participants indicated that self-reported diagnoses of IBD were highly accurate, with 97% of participants having their diagnosis confirmed by their treating physicians.[20] For the present study, we evaluated the outcomes of a subcohort of IBD Partners participants with UC who reported new initiation of following treatment with anti-TNF therapy. We supplemented enrollment through a collaboration with the Anthem and Humana health plans. These health plans reviewed claims of enrolled members on a monthly basis to identify anti-TNF experienced patients with UC initiating vedolizumab or tofacitinib and refer them to IBD Partners by US mail, email, and telephone calls.

Study of Prospective Adult Research Cohort with IBD (SPARC IBD) is a prospective, multi-center cohort of over 4000 adult patients with longitudinal collection of clinical and patient-reported data and biosamples.[21] The overall objective is to identify predictors of response to IBD therapy and relapse of disease. Clinical and demographic characteristics of all participants are captured at the time of enrollment and updated during follow-up visits and hospitalizations. Data elements include disease phenotype, duration of disease, selected laboratory data, prior surgeries, and prior medication use. Data on validated endoscopic severity scores are also captured.[22,23] Most clinical data are captured at the point of care through the Electronic Health Record at each site. These clinical data are supplemented by PROs collected quarterly through electronic surveys.

### Study-Specific Eligibility Criteria

In addition to the general eligibility criteria for both parent cohorts, inclusion criteria for this study were as follows: (1) initiation of tofacitinib or vedolizumab), (2) prior use of 1 or more anti-TNF agents, (3) a reported diagnosis of UC at or immediately prior to date of tofacitinib or vedolizumab initiation, and (4) no colectomy prior to date of treatment initiation. As tofacitinib received FDA approval for UC on May 30, 2018, we only considered participants who initiated vedolizumab or tofacitinib after September 1, 2018 in order to maximize equal comparisons. For participants who initiated both vedolizumab and tofacitinib, only the first treatment following anti-TNF therapy was considered.

### Primary Comparison

We compared new initiators of vedolizumab versus tofacitinib. The first of these medications used following anti-TNF was assigned as the index treatment. The date of first reported use was assigned as the index date.

### Follow-up

Participants were followed until the outcome assessment date, defined as the survey date closest to 6 months following the index date (no earlier than 4 months and no later than 10 months following index date). This timeframe was selected a priori based on our clinical judgment that responders to either treatment should have achieved steroid-free clinical remission by this point. We encouraged follow-up with patient-centered messaging developed by our patient co-investigators regarding the importance of the research question and provided a $25 incentive for completing the 6-month follow-up survey.

### Outcomes

Prespecified, co-primary outcomes included NIH Patient Reported Outcome Measurement and Information System (PROMIS) measures of Fatigue and Pain Interference. These domains were selected based on (1) prioritization by 2 patient co-investigators (J.B. and J.E.D.) and the broader IBD Partners Patient Governance Committee following review of multiple

potential PRO measures and (2) prior evidence demonstrating construct validity and responsiveness to changes over time in the Simple Clinical Colitis Index (SCCAI) and the Short IBD Questionnaire, a disease-specific quality of life measure.[24] PROMIS scales are continuous measures, calibrated using a *T*-score metric to the US general population with a mean of 50 and SD of 10. Minimal important differences have been reported to be in the range of 2–6.[25] Secondary outcomes measured at the same time point included PRO2,[26] a patient-reported measure of stool frequency and bleeding, the PROMIS domain of Social Satisfaction, continued use of the index medication (persistence), and need for colectomy.

### Covariates

We assessed age, sex, race, Hispanic ethnicity, and years from IBD diagnosis using baseline data from each cohort. Current smoking status and body mass index were ascertained at the collection date immediately preceding the index date. Baseline measures of PRO2 and PROMIS domains of Pain Interference, Fatigue, and Social Satisfaction were ascertained only if available within the 6 months prior to the index date. The number of prior anti-TNF agents, use of prior medications [immunomodulators (6-mercaptopurine, azathioprine, and methotrexate), calcineurin inhibitors (tacrolimus and cyclosporine), and corticosteroids], and prior hospitalization and surgery were evaluated based on all data recorded prior to the index date.

### Sample Size

To detect a clinically relevant effect size (difference in PROMIS *T* scores ≥ 5 with an SD of 10), we estimated that a total of 144 participants would be needed to achieve 80% power with a 2-sided α of 0.05, assuming no more than a 2:1 imbalance in treatment group size and no more than 20% loss to follow-up. However, based upon preset project milestones and timeline, we ended enrollment in December 2021 with a total of 105 participants, falling short of our target enrollment.

### Statistical Analysis

We used standard descriptive and bivariate statistics to characterize the study population and compare demographic and baseline characteristics between users of the 2 treatments. We also compared the characteristics of retained participants versus those lost to follow-up within each treatment group. We conducted unadjusted analyses for primary and secondary outcomes using 2-sample *t*-tests for continuous variables and chi-squared tests for categorical variables. As prespecified in our study protocol, our primary analyses utilized outcome data collected at follow-up, regardless of whether or not patients continued on their index treatment at the time of follow-up. We used an intention-to-treat analysis because this comparative effectiveness study aimed to evaluate the effectiveness of initiating vedolizumab versus tofacitinib rather than compare the biological efficacy of the medications themselves.

Next, we conducted adjusted analyses (linear regression for PROMIS measures and PRO2 and logistic regression for persistence and colectomy) using inverse probability treatment weights (IPTW) to assess average treatment effects while controlling for age, sex, and number of prior anti-TNF agents. We also adjusted for the overall cohort effect (IBD Partners vs SPARC) and evaluated for its potential interaction effect with age and the number of prior anti-TNF therapies. The interaction effect with the number of prior anti-TNF therapies was significant and thus included in the final model. The test statistics were then weighted by the IPTW, calculated by inverse the predicted probability derived from the logistic regression model. We reported weighted mean differences between the treatment groups for continuous outcomes and odds ratios for binary outcomes, with 95% CIs and Wald-type *P* values. Prior medication use, baseline PROMIS measures and PRO2 were missing in many participants since the follow-up schedule for both cohorts does not often align with treatment initiation. Thus, we were unable to adjust for these in our primary analyses.

### Subgroup and Sensitivity Analyses

We conducted a sensitivity analysis including only participants with nonmissing PRO2 and PROMIS measures within the 6 months prior to index date. We compared baseline characteristics and co-primary outcomes across the 2 treatment groups using standard bivariate statistics and compared change in PROMIS measures and PRO2 scores between baseline and follow-up using paired *t*-tests.

All statistical analyses were conducted using SAS 9.4.

## Ethical Considerations

The study protocol was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

## Results

### Study Population

Overall, 72 vedolizumab initiators and 33 tofacitinib initiators were included in our analysis. Demographic and clinical characteristics of vedolizumab and tofacitinib are shown in Table 1, and standardized mean differences before and after IPTW are provided in Supplementary Table S1. The mean ages of vedolizumab and tofacitinib initiators were 45.1 and 40.4 years, respectively. Females represented 67% of vedolizumab and 52% of tofacitinib users. The study sample was primarily White. The mean number of prior anti-TNF agents recorded was 1.4 in both groups. Of vedolizumab initiators, prior anti-TNF therapy included 28% infliximab only, 28% adalimumab only, 4% other anti-TNF, 36% ≥2 anti-TNF agents, 7% ≥3 anti-TNF agents, and 4% unknown. Of tofacitinib initiators, prior anti-TNF therapy included 30% infliximab only, 36% adalimumab only, 30% ≥2 anti-TNF agents, 6% ≥3 anti-TNF agents, and 3% unknown.

In the subgroup of patients with available baseline PROs, Pain Interference was significantly higher in tofacitinib versus vedolizumab initiators. Fatigue and PRO2 scores were numerically higher and Social Satisfaction scores numerically lower among tofacitinib users, but these differences were not statistically significant. Other baseline characteristics are summarized in Table 1.

### Main Findings

Our unadjusted results are shown in Table 2. Our co-primary endpoints of Fatigue and Pain Interference at 6 months did not differ between vedolizumab- and tofacitinib-treated patients [mean *T* scores 52.7 vs 50.6 (*P* = .36) and 50.1 vs 48.2.4 (*P* = .37), respectively]. Regarding secondary outcomes, we

**Table 1.** Demographic and baseline characteristics of patients with ulcerative colitis initiating treatment with vedolizumab versus tofacitinib following anti-TNF therapy.

| | Vedolizumab (*n* = 72) | | | Tofacitinib (*n* = 33) | | | *P* |
|---|---|---|---|---|---|---|---|
| | *N* | *n*/mean | %/SD | *N* | *n*/mean | %/SD | |
| Index year (*N*, %) | | | | | | | .331 |
| 2018 | | 2 | 3% | | 0 | 0% | |
| 2019 | | 29 | 40% | | 18 | 55% | |
| 2020 | | 23 | 32% | | 7 | 21% | |
| 2021 | | 18 | 25% | | 7 | 21% | |
| 2022 | | 0 | 0% | | | | |
| Age (mean, SD) | 72 | 45.1 | 15.3 | 33 | 40.4 | 16.2 | .150 |
| Sex (*N*, %) | | | | | | | .126 |
| Male | | 20 | 28% | | 14 | 42% | |
| Female | | 48 | 67% | | 17 | 52% | |
| Race/ethnicity (*N*, %) | | | | | | | .456 |
| White | | 58 | 81% | | 28 | 85% | |
| Black | | 3 | 4% | | 1 | 3% | |
| Other | | 3 | 4% | | 1 | 3% | |
| Missing/unknown | | 8 | 11% | | 3 | 9% | |
| Years from diagnosis (mean, SD) | 72 | 13.5 | 10.0 | 33 | 12.1 | 9.9 | .499 |
| Number of prior anti-TNF (*N*, %) | 72 | 1.4 | 0.7 | 33 | 1.4 | 0.6 | .624 |
| Smoking status (*N*, %) | | | | | | | n/a |
| Nonsmoker | | 51 | 71% | | 25 | 76% | |
| Former smoker | | 0 | 0% | | 0 | 0% | |
| Current smoker | | 21 | 29% | | 8 | 24% | |
| BMI prior to index (mean, SD) | | 25.3 | 6.45 | | 25.4 | 5.85 | .018 |
| Prior use of steroids (pred, bud) (*N*, %) | 37 | 26.6 | 4.7 | 18 | 28.6 | 9.0 | .282 |
| Prior use of 6MP/AZA (*N*, %) | 53 | 45 | 85% | 26 | 24 | 92% | .353 |
| Prior use of MTX (*N*, %) | 49 | 29 | 59% | 24 | 9 | 38% | .081 |
| Prior use of tacrolimus/cyclosporine (*N*, %) | 49 | 5 | 10% | 24 | 5 | 21% | .215 |
| Baseline PRO2[a] | 30 | 2.1 | 2.0 | 19 | 2.7 | 1.8 | .310 |
| Baseline PROMIS Measures[a] | | | | | | | |
| Fatigue | 26 | 52.4 | 11.0 | 15 | 55.1 | 10.9 | .455 |
| Pain Interference | 26 | 50.9 | 10.2 | 15 | 57.7 | 6.0 | .023 |
| Social Role Satisfaction | 26 | 49.4 | 12.3 | 15 | 43.6 | 5.9 | .095 |

Abbreviation: BMI, body mass index.
[a]Baseline measures of PRO2 and Patient Reported Measurement Information System (PROMIS) measures were evaluated within the 6 months prior to index date.

**Table 2.** Unadjusted outcomes at 6 months among patients with ulcerative colitis initiating treatment with vedolizumab versus tofacitinib following anti-TNF therapy.

| | Vedolizumab (*n* = 72) | | Tofacitinib (*n* = 33) | | *P* |
|---|---|---|---|---|---|
| | *n*/mean | %/SD | *n*/mean | %/SD | |
| Primary outcomes | | | | | |
| PROMIS Fatigue[a] (mean, SD) | 52.7 | 11.8 | 50.6 | 9.4 | .357 |
| PROMIS Pain interference[a] (mean, SD) | 50.1 | 10.2 | 48.2 | 9.0 | .372 |
| Secondary outcomes | | | | | |
| PRO2 (mean, SD) | 1.7 | 1.8 | 1.2 | 1.5 | .200 |
| Index medication persistence (*N*, %) | 63 | 88% | 29 | 88% | .956 |
| PROMIS Social satisfaction (mean, SD)[a] | 47.5 | 11.0 | 50.4 | 10.6 | .204 |
| Colectomy (*n*, %) | 3 | 4% | 2 | 6% | .672 |

[a]Patient Reported Measurement Information System.

observed no significant differences in index medication persistence, PRO2, Social Satisfaction, or colectomy.

In adjusted analyses of our co-primary endpoints, Pain Interference scores at follow-up were lower in initiators of tofacitinb as compared with vedolizumab (mean difference 4.2, $P$ = .04) (Table 3). Fatigue scores did not differ between groups. Regarding secondary outcomes, a trend toward higher Social Role Satisfaction was not significant. The remainder of secondary outcomes (PRO2, treatment persistence, colectomy) did not differ between treatment groups.

In a sensitivity analysis including only participants with nonmissing PRO2 and PROMIS measures within the 6 months prior to index date ($n$ = 40), we compared change in these measures between baseline and follow-up using paired $t$-tests (Table 4). Tofacitinib users improved in all measured domains (less Fatigue, less Pain Interference, more Social Role Satisfaction, and lower PRO2 scores) and vedolizumab users improved in all domains with the exception of Social Role Satisfaction. The magnitude of improvement was statistically greater among tofacitinib users for secondary outcomes of Social Role Satisfaction and PRO2 scores. We observed a nonsignificant trends toward greater improvement among tofacitinib users for the primary outcome of Pain Interference, but not Fatigue.

**Table 3.** Adjusted outcomes at 6 months among patients with ulcerative colitis initiating treatment with vedolizumab versus tofacitinib following anti-TNF therapy.

| | Reference group | Point estimate | LCL mean | UCL mean | *P* |
|---|---|---|---|---|---|
| Primary outcomes | | | | | |
| Pain Interference[a] | Vedolizumab | −4.21 | −8.30 | −0.11 | .044 |
| Fatigue[a] | Vedolizumab | −1.25 | −5.16 | 2.66 | .531 |
| Secondary outcomes | | | | | |
| Social Role Satisfaction[a] | Vedolizumab | 3.98 | −0.18 | 8.15 | .061 |
| PRO2[a] | Vedolizumab | −0.32 | −0.99 | 0.35 | .349 |
| | | **Odds ratio** | **95% Wald confidence limits** | | *P* |
| Colectomy[b] | Vedolizumab | 0.69 | 0.191 | 2.526 | .580 |
| Index medication persistence[b] | Vedolizumab | 1.22 | 0.556 | 2.657 | .625 |

[a]Estimates for Patient Reported Measurement Information System (PROMIS) measures of Fatigue, Pain Interference, and Social Satisfaction and the PRO2 represent adjusted mean differences comparing treatment with vedolizumab versus tofacitinib.
[b]Estimates for persistence and colectomy represent adjusted odds ratios for treatment for vedolizumab versus tofacitinib.

**Table 4.** Sensitivity analysis of patients with available baseline data.

| | Vedolizumab ($n$ = 25) | | Tofacitinib ($n$ = 15) | | *P* |
|---|---|---|---|---|---|
| | *n*/mean | %/SD | *n*/mean | %/SD | |
| Baseline measures[a] | | | | | |
| Fatigue | 52.6 | 11.2 | 55.1 | 10.9 | .490 |
| Pain Interference | 51.3 | 10.2 | 57.7 | 6.0 | .033 |
| Social Role Satisfaction | 49.3 | 12.6 | 43.6 | 5.9 | .107 |
| PRO2 | 2.1 | 2.0 | 3.0 | 1.8 | .156 |
| Follow-up measures | | | | | |
| Fatigue | 50.8 | 11.9 | 52.3 | 7.9 | .674 |
| Pain Interference | 49.2 | 9.7 | 50.4 | 10.0 | .712 |
| Social Role Satisfaction | 46.2 | 12.9 | 47.8 | 9.0 | .677 |
| PRO2 | 1.8 | 1.8 | 0.9 | 1.0 | .086 |
| Fatigue | 52.6 | 11.2 | 55.1 | 10.9 | .490 |
| Index Medication Persistence | 22 | 88% | 14 | 93% | .586 |
| Colectomy | 0 | 0% | 0 | 0% | — |
| Change in measures | | | | | |
| Fatigue | −1.7 | 9.0 | −2.8 | 12.6 | .758 |
| Pain Interference | −2.1 | 9.1 | −7.3 | 10.8 | .109 |
| Social Role Satisfaction | −3.1 | 11.5 | 4.2 | 8.9 | .042 |
| PRO2 | −0.2 | 2.7 | −2.1 | 2.0 | .028 |

[a]Baseline measures of PRO2 and Patient Reported Measurement Information System (PROMIS) measures were evaluated within the 6 months prior to index date.

## Discussion

We conducted a prospective cohort study to compare patient-prioritized PROs among anti-TNF experienced patients with UC initiating treatment with either vedolizumab or tofacitinib. We consider this study to be exploratory in nature based on the relatively small sample size. In our adjusted analyses, we observed lower Pain Interference among initiators of tofacitinib. Fatigue scores did not differ between treatment groups. A trend of higher Social Role Satisfaction, a secondary outcome, did not reach statistical significance. In a subanalysis of participants with baseline scores available, improvement in Social Role Satisfaction and PRO2 were greater among tofacitinib than vedolizumab users; with a nonsignificant trend toward greater improvement in Pain Interference.

While these data represent the first comparative effectiveness data focusing on PROs and from a US population, they must be taken in the context of emerging data from European studies. Straatmijer et al recently published a report of 83 vedolizumab- and 65 tofacitinib-treated patients with UC who were refractory to anti-TNF treatment and found superior effectiveness of tofacitinib for outcomes of corticosteroid-free clinical remission and biochemical remission at weeks 12, 24, and 52.[17] Additionally, a Dutch cohort demonstrated similar rates of corticosteroid-free clinical remission at week 16 for vedolizumab and tofacitinb users, though higher rates of endoscopic improvement in tofacitinb users, concluding that tofacitinib seems to be more effective than vedolizumab.[16] Our study complements these recent studies by focusing on PROs, direct measures of how patients feel and function. Although only some of our analyses reached statistical significance, the overall direction of nearly all of our finding seemed to favor tofacitinib. Thus, results from this study are consistent with and reinforce prior literature.

Strengths of this study include the novel focus on highly relevant and patient-prioritized PROs, capturing not only traditional gastrointestinal symptoms but also nontraditional symptoms such as fatigue and social satisfaction that are central drivers of patient well-being. The geographic diversity of participants across the United States cared for in many practice settings is another strength of our study. We also note a number of limitations. The sample size of our study was less than we had initially planned due, as recruitment into the SPARC cohort was impacted by the COVID-19 pandemic and real-world adoption of tofacitinib was slower than expected. Thus, we acknowledge the possibility of Type II error, and consider these findings as exploratory. We recommend cautious interpretation of results, taking in to account other emerging studies as discussed above. Another limitation is that our study compared treatments that were FDA approved at the time the study was conceived and funded. Since then, additional treatment options are now available for treatment refractory patients with UC including upadacitinib and ustekinumab. Thus, this study has laid a foundation for future to compare the effectiveness of second-line therapies with a focus on patient-prioritized PROs. In the IBD Partners component of our cohort, we relied on with self-reported rather than physician-confirmed UC raising the potential for misclassification of IBD status or type (CD vs UC). However, a prior validation study within IBD Partners has demonstrated the high validity of self-reported diagnoses in the overall cohort[20] and we anticipate even greater validity in this subcohort of treatment-experienced individuals who have reported prior anti-TNF therapy as well as current treatment with either vedolizumab or tofacitinib. Additionally, loss to follow-up in IBD Partners and other internet-based cohorts is relatively high given the lack of direct participant engagement and may not have occurred at random, thus introducing a potential source of bias. Similarly, within SPARC IBD, completion of PRO surveys was optional and differential reporting by clinical status may have resulted in similar bias. We also acknowledge that our study population is a convenience sample rather than a representative sample and is not fully generalizable to the broader US population of patients with UC. In particular, our cohort lacks robust participation from minority populations frequently underrepresented in health research. Finally, we also acknowledge the possibility of confounding in this observational study. Due to the small sample size, we could not adjust for all measured confounders and missing data prohibited adjustment for baseline measures disease symptoms and other PROs. Unmeasured confounders may also contribute to residual confounding.

## Conclusions

In conclusion, this first-of-its-kind comparative effectiveness study of anti-TNF experienced patients with UC initiating vedolizumab or tofacitinib showed lower pain interference 4–10 months after treatment among tofacitinib users but no significant differences in fatigue or other secondary outcomes. However, due to a smaller than anticipated sample size, our study may have been underpowered to identify clinically meaningful differences. We observed consistent trends in nearly all outcomes, suggesting the possibility that tofacitinib may have superior effectiveness in anti-TNF experienced patients. Thus, these findings are consistent with, and complement, emerging European studies focused on clinical endpoints. Thus, the results of this study should be interpreted in the context of all available literature and should encourage further CER of emerging therapeutics focusing on patient-centered outcomes.

## Supplementary Data

Supplementary data is available at *Crohn's and Colitis 360* online.

## Author Contributions

M.D.K.: conception, funding acquisition, investigation, methodology, writing original draft. M.D.L. and J.D.L.: conception, funding acquisition, investigation, methodology, writing review & editing. X.Z. and F.-C.L.: formal analysis, methodology, writing review & editing. L.W.: project administration, investigation, writing review & editing. W.C., L.E.P., K.H., V.N., and A.F.K.: investigation, writing review & editing. J.B. and J.E.D.: funding acquisition, investigation, writing review & editing. T.F. and C.M.B.: analysis, writing review & editing. A.D.: funding acquisition, project administration, writing review & editing.

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## Conflicts of Interest

M.D.K. has consulted for AbbVie, Janssen, Pfizer, Takeda, and Lilly, is a shareholder in Johnson & Johnson, and has received research support from Pfizer, Takeda, Janssen, AbbVie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion, and Arenapharm. M.D.L. consulting for AbbVie, Janssen, Pfizer, Takeda, Lilly, BMS, Prometheus, Target Pharmasolutions, Calibr, Roche, Genentech, Theravance, Research support Takeda, and Pfizer. X.Z., F.-C.L., L.W., W.C., J.B., C.M.B., V.N., A.F.K., and A.D. report no conflicts of interest. J.D. is a shareholder in Pfizer. L.E.P. is employed by HealthCore/Anthem. K.H. was employed by Anthem at the time of the research and is currently an employee of Janssen Research & Development. J.D.L. has served as a consultant for Janssen Pharmaceuticals, Samsung Bioepis, Bristol-Myers Squibb, Merck, Celgene, AbbVie, Entasis Therapeutics, and Bridge Biotherapeutics. J.D.L. has served as a paid member of a data monitoring committee for Pfizer, UCB, Gilead, Galapagos, Arena Pharmaceuticals, Protagonist Therapeutics, Sanofi, and Amgen. J.D.L. has received research funding from Janssen Pharmaceuticals, AbbVie, and Takeda Pharmaceuticals. J.D.L. has received educational grant funding from Takeda Pharmaceuticals and Janssen.

## Data Availability

IBD Partners and SPARC IBD data can be made available, upon request, by contacting the IBD Plexus program at the Crohn's & Colitis Foundation. https://www.crohnscolitisfoundation.org/research/grants-fellowships/ibd-plexus.

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