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ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

Real-world effectiveness of ustekinumab and vedolizumab in TNF-exposed pediatric patients with ulcerative colitis

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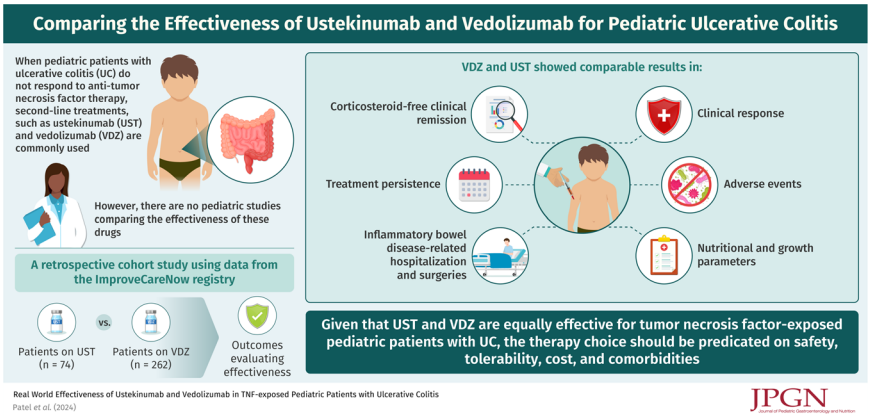
Abstract

Objectives: Vedolizumab (VDZ) and ustekinumab (UST) are second-line treatments in pediatric patients with ulcerative colitis (UC) refractory to antitumor necrosis factor (anti-TNF) therapy. Pediatric studies comparing the effectiveness of these medications are lacking. Using a registry from ImproveCareNow (ICN), a global research network in pediatric inflammatory bowel disease, we compared the effectiveness of UST and VDZ in anti-TNF refractory UC.

Methods: We performed a propensity-score weighted regression analysis to compare corticosteroid-free clinical remission (CFCR) at 6 months from starting second-line therapy. Sensitivity analyses tested the robustness of our findings to different ways of handling missing outcome data. Secondary analyses evaluated alternative proxies of response and infection risk.

Results: Our cohort included 262 patients on VDZ and 74 patients on UST. At baseline, the two groups differed on their mean pediatric UC activity index (PUCAI) ($p = 0.03$) but were otherwise similar. At Month 6, 28.3% of patients on VDZ and 25.8% of those on UST achieved CFCR ($p = 0.76$). Our primary model showed no difference in CFCR (odds ratio: 0.81; 95% confidence interval [CI]: 0.41–1.59) ($p = 0.54$). The time to biologic discontinuation was similar in both groups (hazard ratio: 1.26; 95% CI: 0.76–2.08) ($p = 0.36$), with the reference group being VDZ, and we found no differences in clinical response, growth parameters, hospitalizations, surgeries, infections, or malignancy risk. Sensitivity analyses supported these findings of similar effectiveness.

Conclusions: UST and VDZ are similarly effective for inducing clinical remission in anti-TNF refractory UC in pediatric patients. Providers should consider safety, tolerability, cost, and comorbidities when deciding between these therapies.



KEYWORDS

biologic therapy, children, clinical data science, comparative effectiveness, inflammatory bowel disease

1 | INTRODUCTION

In contrast to its adult-onset disease, pediatric patients with ulcerative colitis (pUC) commonly present with extensive disease associated with higher rates of hospitalization, corticosteroid failure, colorectal cancer risk, and up to 20% colectomy rate within 5-year of diagnosis.[1–5] Antitumor necrosis factor (anti-TNF) medications are first-line treatments for moderate to severe pUC, with adalimumab and infliximab being the only Food and Drug Administration (FDA) approved biologics for children.[5,6] However, up to 30% of patients do not respond to anti-TNF induction doses, and as many as 45% of responders subsequently lose response within the first year.[1,6] Patients who are refractory to or intolerant of these drugs usually require treatments with different mechanisms of action, with providers and families having to decide between off-label therapies with less available information about treatment efficacy.

Typical options for these patients include vedolizumab (VDZ), an inhibitor of leukocyte trafficking to the intestinal tract,[7] and ustekinumab (UST), an inhibitor of interleukins-12 and -23.[8] Despite how commonly these medications are needed and applied, an evidence gap exists regarding how to optimally select between these options. At present, no published studies compare efficacy in children. Furthermore, evidence extrapolated from adult studies is inconsistent. A meta-analysis in adult patients with ulcerative colitis (UC) showed that both were effective at inducing clinical remission and endoscopic response, while a systematic review in adults with Crohn's disease favored sustained corticosteroid-free clinical remission (CFCR) with UST.[9,10] While some comparative effectiveness studies indicate no difference in adults with Crohn's disease, one favored VDZ for clinical remission, while another suggested UST was superior for CFCR.[11–15] It is possible that these conflicting findings may be due in part to differences in outcome measures and methods applied for handling missing data.

We sought to address this evidence gap and study the comparative effectiveness of VDZ and UST in anti-TNF-refractory pUC using the ImproveCareNow (ICN) registry. We evaluated multiple measures of effectiveness including CFCR, clinical response, growth and nutritional status, inflammatory bowel disease (IBD)-related hospitalizations, or surgery at 6 months, and

What is Known

- Antitumor necrosis factor (anti-TNF) medications are first-line therapy for pediatric patients with moderate to severe ulcerative colitis.
- A significant proportion of patients will be primary nonresponders or experience loss of response to anti-TNFs.
- Vedolizumab (VDZ) and ustekinumab (UST) are common second-line treatments for these patients.

What is New

- UST and VDZ have similar effectiveness in this cohort, with equivalent rates of corticosteroid-free clinical remission, clinical response, hospitalizations, surgeries, and biologic persistence.
- These results are consistent across multiple methods of correcting for missing data in the ImproveCareNow registry.

time to treatment discontinuation, up to 1 year. We also evaluated safety outcomes at 6 months by comparing rates of severe infections and malignancies. Furthermore, we tested the robustness of our results across different potential explanations for missing outcome measures in the context of routine clinical care.

2 | METHODS

2.1 | Data source

We used prospectively collected data from the ICN Registry to conduct a retrospective cohort study of pUC initiating VDZ or UST therapy as a second-line therapy after failure of an anti-TNF drug between October 1, 2006, and April 5, 2023. ICN is a pediatric IBD research network initiated in 2006 and has captured data on over 32,000 patients treated across >100 centers. It functions as a learning health system, with a continuously updated database that facilitates patient-centered research to optimize outcomes.[16] Institutional review board (IRB) approval is obtained, and participants are enrolled under informed consent at each site. Data are collected at each clinic visit and hospitalization. The captured information includes demographics, disease characteristics, serum and stool tests, medication history, IBD-related surgical history, growth measures, and disease activity scores.

2.2 | Cohort selection criteria

We queried the ICN database to identify pediatric patients (<21 years old) meeting the following criteria: (1) a documented, confirmed diagnosis of UC based on the diagnosis at registration and the most recent visit, (2) anti-TNF exposure based on medications documented during clinic visits, and (3) VDZ or UST exposure documented in the clinic visit medication list, without previous exposure documented to either drug (i.e., VDZ or UST as third-line therapy were excluded). Concomitant medications such as immunomodulators or antibiotics were allowed. We excluded patients with a diagnosis of CD or IBD unclassified, history of colectomy, and those who were started on VDZ or UST before anti-TNF therapy. These queries identified 381 pUC who failed anti-TNFs and were subsequently treated with UST or VDZ. Anti-TNF failure was defined as anti-TNF use and cessation before treatment with VDZ or UST. Patients must have exhibited active disease at the visit before the first recorded visit on VDZ or UST, defined as a Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥ 10[17] or a physician global assessment (PGA) > 1 (if PUCAI not available), or current corticosteroid use, or abnormal inflammatory markers (C-reactive protein ≥ 5 mg/L). These markers were selected in alignment with guideline-based early treat-to-target goals.[18]

2.3 | Baseline and outcome periods

The timing of clinic visits and data capture in real-world settings commonly differs from those in controlled studies due to a variety of factors, including provider practice patterns, patients' state of illness or health, and social determinants of health impacting the ability to follow-up.[19] ICN is a learning collaborative that disseminates best practice recommendations,[20] but there are no formal guidelines on monitoring pediatric patients on UST or VDZ. Therefore, patients in our study were monitored based on individual center protocols and provider recommendations. To emulate a hypothetical trial with planned study visits and to minimize the effects of missing data and selection bias, we performed an exploratory data analysis and retrospectively defined time windows corresponding to the baseline and outcome periods.

We defined the baseline as the clinic visit before the first documentation of VDZ or UST use for a patient. Although this corresponds to a date before the true date of treatment induction (which is not well-captured across the data set), we chose this definition because it most accurately reflects the patient's clinical status at the time of deciding between second-line therapies. To address missing baseline data, we used the *sklearn* implementation of Iterative Imputation, a method that iteratively imputes each missing variable as a function of all other variables until convergence is achieved.[21]

Our outcome period was Month 6 2 months after baseline. This minimized missing data, accounted for differences in medication time to onset, and was in-line with previous IBD comparative effectiveness literature.[13] For those who had multiple clinic visits during the outcome period, we selected data from the visit closest to Day 183 relative to baseline.

2.4 | Study endpoints

Our primary endpoint was CFCR, a composite binary variable defined as a PUCAI < 10 or PGA $= 1$, in addition to the absence of all of the following during the outcome period: therapy discontinuation, IBD-related hospitalization or surgery (predefined variables in ICN), or continued corticosteroid use (including budesonide) at the outcome visit.[1,22] PGA was used in visits where a complete PUCAI was not documented. As fecal calprotectin was collected in only 10% of visits during the outcome window, we did not incorporate it into our primary endpoint.

Our secondary endpoints included corticosteroid-free clinical response, IBD-related hospital admissions

and surgeries, growth, nutrition, infections, malignancies, and biologic durability. Clinical response was a binary outcome that included patients in remission, and as per the STRIDE-II guidelines included those with a decrease in PUCAI ≥ 20,[18] or a PGA indicating mild or quiescent disease. Growth and nutritional status were evaluated based upon predefined ordinal variables in the ICN database. Nutritional is categorized as "in failure" (decrease in weight by two isobars, weight loss of ≥10%, or weight <3rd percentile for age); "at risk" (decrease in weight by one isobar, weight loss of 1%–9%, or weight ≤10th percentile for age; or "satisfactory" if not meeting the above conditions. Growth is categorized as "in failure" (drop in height by two isobars, or height <3rd percentile for age, or height velocity <3rd percentile); "at risk" (drop in height by one isobar, or height <10th percentile for age, or height velocity <10th percentile); or "satisfactory" if not meeting the above conditions. Serious infection, a predefined ICN variable, encompassed any infection that required hospitalization or intravenous treatment. As an alternative measure of effectiveness, we evaluated time to treatment discontinuation. This was determined through the current medications documented at each visit after the baseline visit.

2.5 | Statistical methods

2.5.1 | Primary outcomes

We used a stabilized inverse probability of treatment weighted (sIPTW) logistic regression model to compare the likelihood of CFCR between treatment groups. Baseline differences were assessed using traditional significance testing (Fisher's exact test, Student's *t*-test, Mann–Whitney *U* as appropriate) as well as standardized mean differences (SMDs) given the disparity in cohort sizes. We used >0.2, >0.5, and >0.8 cutoffs for SMD to represent small, moderate, and large differences.[23,24] For this sIPTW model, the numerator for the weights was the probability of treatment selection irrespective of the covariates, and the denominator represented the probability of treatment selection based on all baseline variables in Table 1.[25]

We performed a complete case analysis as our primary approach to analyzing the data. This approach assumes that the patients with captured outcomes are representative of the study population. We considered this assumption reasonable with the understanding that many missing outcome measurements at month 6 may reflect idiosyncratic practice styles around the timing of follow-up, patient preferences, and other factors that are independent of a patient's clinical status. However, given the possibility of alternative explanations for missing data in real-world contexts, we performed sensitivity analyses to test the robustness of our primary findings, as detailed in our supplemental methods.

2.5.2 | Secondary outcomes

We used a logistic regression analysis adjusted for baseline differences in our treatment cohorts to compare the odds of patients achieving a clinical response at Month 6. We also used Fisher's exact testing to compare growth status, nutritional status, prevalence of hospitalizations, surgeries, malignancies, and serious infections between the treatment groups from baseline until the Month 6 follow-up visit.

To compare the rates of medication discontinuation for up to 1 year of follow-up, we conducted a Cox regression that controlled for baseline differences noted in Table 1. Follow-up was censored at the date of medication change. Patients who had been followed for <1 year after starting their second-line therapy were censored at the time of their last visit.

2.5.3 | Ethics

The Human Research Protection Program IRB at the University of California San Francisco (IRB#21-34392) approved this study. At each participating center, patients were consented for their data to be shared with ICN and used for research.

3 | RESULTS

3.1 | Data capture

At baseline, disease characteristics such as Paris Classification, extra-intestinal manifestations, growth status, and current medications were captured in >95% of patients. Serum lab values were documented in 80%–94% of patients and were similar across the two groups at baseline (Table S1).

The primary outcome of CFCR was captured in 89% of the cohort (299/336). This degree of outcome capture was similar in both the VDZ (88.9%; 233/262) and UST (89.1%; 66/74) subcohorts ($p = 0.95$).

3.2 | Baseline characteristics

Our study included 336 patients started on either VDZ (262) or UST (74). Patients were seen at 76 ICN centers, all in the United States. The treatment groups differed slightly on PUCAI scores (VDZ 26.8; interquartile range [IQR: 10–40] vs. UST 20.0 [IQR: 5–30]; SMD = 0.29) and concomitant immunomodulator use (VDZ 21.4% vs. UST 12.2%; SMD = 0.23) (Table S1,

TABLE 1 Baseline characteristics after imputation.

	Vedolizumab	Ustekinumab	*p*-Value	Standardized mean difference
N	262	74	-	-
Female	128 (48.9%)	33 (44.6%)	0.60	0.08
Age at diagnosis (years), median (interquartile range [IQR])	13.5 [10.3–15.6]	13.1 [11.6–16.5]	0.25	0.15
Age at baseline visit (years), median [IQR]	16.2 [13.5–18.3]	16.6 [14.0–18.5]	0.38	0.12
Disease duration at baseline visit (years), median [IQR]	2.0 [1.0–3.7]	1.5 [0.8–4.1]	0.74	0.04
Paris classification				
Extent (pancolitis)	186 (71.0%)	53 (71.6%)	0.41	0.06
Severity (S1)	124 (47.3%)	32 (43.2%)	0.24	0.18
Immunomodulators	56 (21.4%)	9 (12.2%)	0.13	0.23
Corticosteroids	112 (42.7%)	25 (33.8%)	0.20	0.17
Labs, median [IQR]				
Hematocrit (%)	37.9 [34.6–40.9]	37.3 [33.4–40.6]	0.66	0.06
C-reactive protein (mg/L)	1.8 [0.5–5.5]	2.2 [0.5–6.2]	0.79	0.03
Sedimentation rate (mm/h)	17.0 [9.0–29.0]	16.0 [9.0–26.0]	0.58	0.07
Albumin (g/dL)	4.0 [3.7–4.3]	4.1 [3.7–4.4]	0.78	0.04
Growth (satisfactory)[a]	225 (85.6%)	65 (87.8%)	0.32	0.13
Nutrition (satisfactory)[a]	192 (73.3%)	58 (78.4%)	0.48	0.14
Pediatric Ulcerative Colitis Activity Index, median [IQR]	26.8 [10–40]	20 [5–30]	0.03	0.29
Extra-intestinal manifestations[b]	<10	<10	0.76	0.06

[a]Predefined ImproveCareNow variables.

[b]Extra-intestinal manifestations include arthritis, fevers, pyoderma gangrenosum, erythema nodosum, and uveitis.

Figure S1). Otherwise, the groups were well-balanced with no differences were found in gender, age at diagnosis, age at initiating second-line biologic therapy, corticosteroid use, baseline serum labs, growth trajectories, nutritional status, PGA, or extra-intestinal manifestations (Table S1). Descriptive characteristics of the cohort remained stable after imputation (Table 1), and sIPTW ensured appropriate balance across all baseline variables during modeling.

3.3 | Primary endpoint

We performed a complete case analysis as our primary method for analyzing the data. In the study cohort, the proportions of CFCR were similar across treatment arms: 28.3% (VDZ) versus 25.8% (UST). An unadjusted odds ratio (OR) showed no difference between the two medications; OR = 0.88 (95% confidence interval [CI]: 0.47–1.63) ($p = 0.68$). In the sIPTW model, the differences remained nonsignificant; OR = 0.81 (0.41–1.59) ($p = 0.54$, Table 2), suggesting similar effectiveness.

3.4 | Sensitivity analyses

We performed two sensitivity analyses to test whether our findings would remain stable under alternative methods for handling missing outcomes, an issue that affected 11% of our cohort. These included: (1) nonresponder imputation (patients missing outcomes were assumed to be nonresponders) to model scenarios where patients who are too ill to follow-up, and (2) responder imputation (patients missing outcomes were assumed to be responders) to model scenarios where patients who are well are less inclined to follow-up. These analyses supported the conclusion of similar effectiveness between UST and VDZ (Table 2).

TABLE 2 Results for corticosteroid-free clinical remission.

Analysis method	Odds ratio	95% confidence interval	*p*-Value
Unweighted cohort			
Complete case analysis	0.78	0.42–1.48	0.45
Impute missing as nonresponder	0.80	0.43–1.48	0.48
Impute missing as responder	0.80	0.46–1.39	0.43
Propensity-score weighted cohort			
Complete case analysis	0.81	0.41–1.59	0.54
Impute missing as nonresponder	0.94	0.50–1.78	0.85
Impute missing as responder	0.90	0.51–1.60	0.73

TABLE 3 Secondary outcomes.

Outcome measure	Vedolizumab	Ustekinumab	*p*-Value
Clinical response	39.7% ($n = 232$)	30.3% ($n = 66$)	0.20
IBD-related hospitalizations	12.2% ($n = 262$)	<10 ($n = 74$)	0.74
IBD-related surgeries	<10 ($n = 262$)	<10 ($n = 74$)	0.43
Nutritional status (satisfactory)	82.7% ($n = 168$)	84.2% ($n = 38$)	0.83
Growth status (satisfactory)	89.2% ($n = 251$)	94.0% ($n = 67$)	0.24
Infections	<10 ($n = 167$)	<10 ($n = 38$)	0.89
Malignancies	0% ($n = 232$)	0% ($n = 66$)	-

Note: The secondary endpoints of clinical remission, nutritional status, and growth status are assessed during the outcome time window of Month 6 + 2 months. The secondary endpoints of hospitalizations, surgeries, malignancies, and infections were evaluated from baseline until the Month-6 follow-up visit.

3.5 | Secondary endpoints

Clinical response was achieved in 39.7% of patients on VDZ and 30% of patients on UST (Fisher's exact test, $p = 0.20$) (Table 3). In a multivariate regression model that controlled for baseline differences in PUCAI and immunomodulator use, the odds of achieving clinical response remained nonsignificant (OR: 0.65 [0.36–1.15], $p = 0.14$). The only predictor of achieving clinical response (OR: 0.36 [0.21–0.63], $p < 0.001$) or CFCR (OR: 0.33 [0.18–0.62], $p < 0.001$) at Month 6 was not needing corticosteroids at baseline.

At their outcome visit, 82.7% of patients on VDZ and 84.2% of patients on UST had a satisfactory nutritional status ($p = 0.83$) while 89.2% of patients on VDZ and 94.0% of patients on UST had a satisfactory growth status ($p = 0.24$) (Table 3). The proportion of patients hospitalized were similar between the treatment arms —12.2% (VDZ) versus 10.8% (UST) ($p = 0.74$). Surgeries and infections were rare (<10 patients), and no malignancies were reported in either group (Table 3).

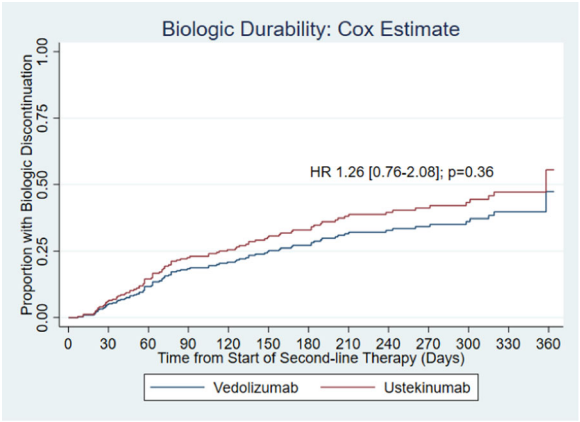


FIGURE 1 Time-to-event analyses for biologic durability. Cox estimate for time to discontinuation of the second-line biologic with a hazard ratio that accounts for control of all baseline covariates.

By 1-year from the start of their second-line biologic, 32% of patients who were started on VDZ and 40% of patients who were started on UST discontinued the medication. We performed a Cox regression that controlled for baseline covariates and found the hazard of medication discontinuation among those on UST was no different than that of patients on VDZ (HR: 1.26 [0.76–2.08], $p = 0.36$) (Figure 1).

4 | DISCUSSION

This is the first comparative effectiveness study of second-line therapies in pediatric patients with UC who failed anti-TNF therapy. Studies on comparative effectiveness in adult populations between these two drugs demonstrated varied results.[10–15] Using the ICN registry, we found that VDZ and UST are similarly effective at inducing CFCR at Month 6. This finding of similar efficacy remained robust under a range of sensitivity analyses and secondary effectiveness and safety endpoints. While there are inherent limitations in research using observational data, our study helps alleviate the uncertainty that accompanies extrapolation from adult cohorts and serves as hypothesis-generating work for future prospective studies that help define treatment positioning in pUC.

We found a 25%–30% remission rate and 30%–40% response rate for the two drugs. Clinical trial data for multiple biologic therapies show lower remission rates in TNF-exposed versus TNF-naïve patients.[26–29] Patients who do not respond to anti-TNF

are approximately 25% less likely to respond to second-line biologics, and both UST and VDZ are more effective in anti-TNF naïve patients with UC.[9,30] In a post hoc analysis of the GEMINI trial, 36.1% of anti-TNF refractory UC patients achieved remission with VDZ.[27] A prospective trial in TNF-refractory pUC showed that 24% of the pediatric patients achieved CFCR at 6-months.[31]

We strove to address limitations in existing real-world studies through the analysis of multiple endpoints, use of propensity scores to address bias by indication, and selective measures to address reasons for incomplete data. We utilized both inpatient and outpatient elements in the ICN database, including hospitalizations and surgeries, to define clinical remission. Propensity scoring minimized selection bias while maintaining cohort size and minimizing loss of power.[32] Our results were consistent across multiple models that represented underlying reasons for missingness in real-world settings. Last, we compared alternative proxies of effectiveness, which also showed equivalency. The slightly higher persistence of VDZ was not statistically significant and may be due to its longer time-to-onset or due to lack of other FDA-approved options. Overall, the consistent findings noted throughout our analyses support the hypothesis of similar effectiveness in anti-TNF refractory pUC.

The potential for residual bias exists in retrospective research. Few pediatric resources are as large as ICN, but the nature of collecting data concurrent with clinical care creates heterogeneity in data collection. This is commonly due to practice variation among providers and heterogeneity in patients' disease states, with diagnostics being ordered based on health status rather than a preset schedule as seen in prospective trials. Therefore, patients may not have had a clinic visit during our outcome window, or information from the visit may not have been appropriately documented. PGA scores were used when PUCAI scores were not documented, and this may have increased outcome heterogeneity. Due to variability in the timing of follow-up, our outcome time window was chosen to maximize data capture, but in-turn limited our ability to analyze sustained remission. Additionally, as labs collected outside the treating institution are not routinely uploaded into the database, we were unable to include biomarkers or therapeutic drug monitoring, and therefore could not assess biochemical remission. The ICN database does not accurately capture medication induction dates, dosing changes or reasons for discontinuation, which limits our understanding of biologic durability.

An additional limitation of our study is the sample size discrepancy between the two groups, which may reduce precision. This is likely because VDZ was approved earlier than UST for IBD, and parents may prefer VDZ given its lower systemic immune suppression.[33,34] In a recent ICN study, sequential anti-TNF therapy with infliximab then adalimumab or vice-versa were the most common patterns of biologic use in pediatric IBD, with significantly lower rates of drugs with alternative mechanisms of action.[35] This likely speaks to the limited FDA-approved therapies, and possible provider and/or patient comfort with using off-label biologics. As ICN grows, these imbalances may decrease over time.

Future work should focus on improving data quality so that studies using real-world data can more closely emulate randomized clinical trials. Potential drivers of missing data in ICN include the variation in follow-up timing, differences in clinic note templates across centers, and the large number of data points to collect. To combat variability in free-text information and the burden of information extraction, natural language processing techniques have shown promise in extracting extraintestinal manifestations of IBD from clinical notes, and Mayo scores from colonoscopy reports.[36,37] Future endeavors to automate the extraction of IBD-relevant variables from the electronic health record, including patient symptoms, radiographic, endoscopic, and histologic measures, can improve the completeness of our registries and enhance the quality of downstream research.

In conclusion, we found that VDZ and UST have similar rates of CFCR in anti-TNF refractory pUC. The replicability of our results supports that large disparities do not exist, but physicians should apply these findings cautiously given the inherent limitations of observational work. This study provides preliminary data, and prospective, randomized clinical trials are needed to validate these findings. As treat-to-target goals evolve, the inclusion of biomarkers, endoscopic, and imaging data will improve future comparisons between medications. However, this initial hypothesis-generating study proves that ICN has the potential to provide insight into clinically relevant questions that would otherwise require costly, time-consuming trials. Given the current data, we recommend that clinicians adopt a patient-specific approach to this decision that weights safety, tolerability, cost, route of administration, patient preference, and alternative indications in addition to treatment effectiveness.

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CONFLICT OF INTEREST STATEMENT

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Note: References 38 and 39 are cited in the Supporting Information File 2.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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