

Ustekinumab and Janus Kinase Inhibitors Outperform Vedolizumab as Second-Line Therapy in Anti-Tumor Necrosis Factor-Experienced Patients With Ulcerative Colitis



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Abbreviations used in this paper: AE, adverse event; aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; ASMD, absolute standardized mean difference; CI, confidence interval; CLMM, cumulative link mixed model; CRP, C-reactive protein; EBW, energy balancing weight; ECCO, European Crohn's and Colitis Organization; eMS, endoscopic Mayo Score; FCP, fecal calprotectin; HR, hazard ratio; IL, interleukin; IQR, interquartile range; IRR, incidence rate ratio; JAKi, Janus kinase inhibitor; OR, odds ratio; RB, rectal bleeding; SD, standard deviation; SF, stool frequency; SFCR, steroid-free clinical remission; TNF, tumor necrosis factor; UC, ulcerative colitis.

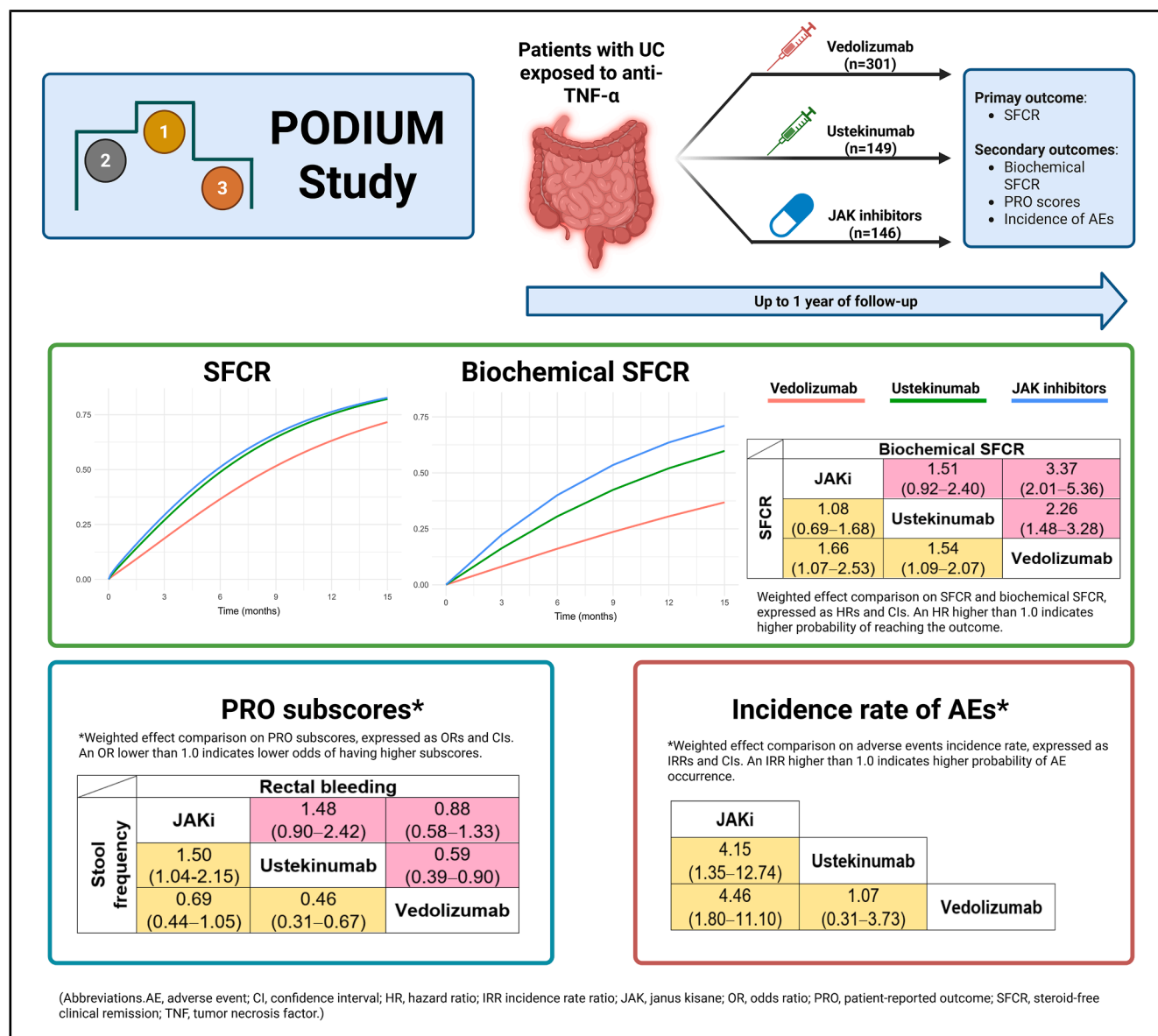


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**BACKGROUND & AIMS:**

With the advent of agents targeting distinct inflammatory pathways, therapeutic sequencing after anti-tumor necrosis factor alpha (TNF- α) failure in ulcerative colitis (UC) represents a major challenge. We compared the real-world effectiveness and safety of vedolizumab, ustekinumab, and Janus kinase inhibitors (JAKi) in anti-TNF- α -exposed patients.

METHODS:

In this retrospective, multicenter European study, adults with UC initiating second-line vedolizumab, ustekinumab, or a JAKi after anti-TNF- α were evaluated. Baseline confounding was addressed by applying energy balancing weights (EBWs). Effectiveness outcomes included probability of steroid-free clinical remission (SFCR) and biochemical SFCR at 12 months, analyzed using EBW-weighted Royston-Parmar survival models to derive adjusted time-averaged hazard ratios (aHRs). Adverse event (AE) rates were compared using EBW-weighted Poisson regression.

RESULTS:

A total of 596 patients were included (301 vedolizumab, 149 ustekinumab, 146 JAKi); 54.7% were male, with a mean age of 43.9 ± 15.5 years. Clinical activity, endoscopic scores, and biomarker levels were broadly comparable across treatment groups. Infliximab was the most common prior anti-TNF- α (74.8%), and secondary failure was the predominant discontinuation reason (47.3%). Compared with vedolizumab, both ustekinumab and JAKi showed significantly higher probability of SFCR (aHR, 1.54; 95% confidence interval [CI], 1.09–2.07;

and aHR, 1.66; 95% CI, 1.07–2.53, respectively) and biochemical SFCR (aHR, 2.26; 95% CI, 1.48–3.28 and 3.37; 95% CI, 2.01–5.36, respectively) at 12 months, with no differences between them. JAKi recipients experienced an approximately 4-fold higher incidence of AEs, compared with both vedolizumab and ustekinumab, with no differences between ustekinumab and vedolizumab.

CONCLUSIONS:

Ustekinumab and JAKi were more effective than vedolizumab in inducing steroid-free and biochemical remission following anti-TNF- α failure. Safety concerns with JAKi warrant careful patient selection in clinical practice.

[ClinicalTrials.gov](https://clinicaltrials.gov), Number: NCT06691061.

Keywords: Anti-TNF-A; Bioexposed Patients; Comparative Effectiveness; Treatment Sequencing; Ulcerative Colitis.

Over the past 2 decades, anti-tumor necrosis factor (TNF)- α agents have shaped the management of moderate-to-severe ulcerative colitis (UC). More recently, the therapeutic landscape has expanded, including novel agents with distinct mechanisms of action. The anti- $\alpha 4\beta 7$ integrin vedolizumab inaugurated this new era as the first non-anti-TNF- α advanced therapy licensed for the treatment of moderate-to-severely active UC,¹ exerting its effects via selective inhibition of lymphocyte trafficking to the gut.² The introduction of the pan-Janus kinase inhibitor (JAKi) tofacitinib² broadened the therapeutic armamentarium, as the first oral small molecule approved for UC,³ followed by the JAK1-selective inhibitors upadacitinib⁴ and filgotinib.⁵ Finally, anti-interleukin (IL)-23 agents joined the pipeline—initially with ustekinumab⁶ (that blocks the p40 subunit, common to IL-12 and IL-23²), and subsequently with the IL-23-selective agents targeting the p19 subunit.²

The proliferation of effective but mechanistically different therapies has outpaced our ability to define their optimal positioning after anti-TNF- α exposure. Comparative data are mostly limited to network meta-analyses and observational 2-arm cohorts, overall suggesting that JAKi and ustekinumab may outperform vedolizumab as second-line agents after anti-TNF- α , a line of evidence which has also been incorporated in some recent guidelines.^{7,8} In routine clinical practice, treatment selection is largely driven by empirical judgment—balancing efficacy, safety (with a specific focus on age and comorbidities), and patient preference. Ideally, evidence from head-to-head trials would inform sequencing; however, they are time-consuming, resource-intensive, and sometimes limited in generalizability.⁹ In that regard, well-designed observational studies offer complementary, non-renounceable real-world insights that support clinical decision-making.

Notably, direct, multicenter comparisons that include all 3 non-anti-TNF classes (vedolizumab, anti-IL-23, and JAKi) are lacking. To address this critical knowledge gap, we conducted the first multicenter, 3-arm observational study comparing the real-world effectiveness and safety of second-line vedolizumab, ustekinumab, and JAKi in patients with UC previously exposed or intolerant to anti-TNF- α agents.

Materials and Methods

Study Design and Participants

This was a real-world, observational, retrospective cohort study including anti-TNF- α -experienced patients with UC who started vedolizumab, ustekinumab, or JAKi as second-line advanced therapy at 17 centers across Europe. Investigators screened local databases and included all consecutive patients between January 2014 and December 2024. Main inclusion criteria were: (1) Age ≥ 18 years old; (2) Diagnosis of UC according to European Crohn's and Colitis Organization (ECCO) guidelines¹⁰; (3) Previous exposure to at least 1 anti-TNF- α agent as first-line advanced therapy approved for the treatment of UC; (4) No prior exposure to vedolizumab, ustekinumab, and JAKi before baseline; (5) Initiation of vedolizumab, ustekinumab, or JAKi as second-line advanced therapy. Patients with prior exposure to one of the study drugs, pregnancy, previous partial or total colectomy, or a current/recent (< 5 years) history of malignancy were excluded. The date of the first prescription of vedolizumab, ustekinumab, or JAKi was defined as baseline. All patients received the standard induction regimen for the assigned therapy. Only patients with at least 1 follow-up visit after treatment initiation were included in the analysis.

Data Collection

Data were retrospectively extracted from medical records. Baseline variables included demographic data (sex, age, smoking status, body mass index), comorbidities (Charlson comorbidity index¹¹ excluding age), disease characteristics (duration and extent, according to the Montreal Classification for UC¹⁰), previous and concomitant non-advanced therapies for UC (aminosalicylates, steroids, immunosuppressants), and details of previous anti-TNF- α treatments (agents, duration and reason for discontinuation—classified as “primary failure,” “secondary failure,” “intolerance,” and “others”).

At baseline, clinical disease activity (assessed by Stool Frequency [SF] and Rectal Bleeding [RB] subscores), urgency (present or absent), concomitant oral

therapies (aminosalicylates, steroids and immunosuppressants), C-reactive protein (CRP) serum levels, fecal calprotectin (FCP) levels, and endoscopic activity (according to Mayo endoscopic subscore¹²)—if endoscopy performed within 3 months before baseline—were recorded. Follow-up data were collected for each outpatient visit performed within 12 months (with a 3-month tolerance) following baseline, or until drug discontinuation (when occurring earlier). At each visit, data collected included: SF and RB scores, optimization of study drug regimen, concomitant oral therapies for UC, CRP and FCP levels, endoscopic activity (if available), treatment-related adverse events (AEs) requiring medical intervention or therapy discontinuation, and reasons for discontinuation. Reasons for discontinuation—applied both to prior anti-TNF- α and study drugs—were classified as: (1) Primary failure: lack of efficacy or worsening during induction, leading to discontinuation; (2) Secondary failure: worsening after initial improvement during maintenance; (3) Intolerance: drug-related AE at any time causing permanent discontinuation; or (4) Other: any reason not included above.

Outcome Definitions

The primary endpoint was achievement of steroid-free clinical remission (SFCR), defined as SF ≤ 1 and RB = 0 combined with no steroid therapy in the previous 3 months, within 12 months. Secondary endpoints included: (1) Achievement of biochemical SFCR within 12 months (SFCR associated with biomarker normalization: FCP $< 250 \mu\text{g/g}$ or CRP $< 5 \text{ mg/L}$ —if discordant, FCP was considered the reference biomarker); (2) Improvement in SF and RB (reduction in subscores during follow-up); (3) Occurrence of AEs; (4) Endoscopic improvement (a decrease of at least 1 point in endoscopic Mayo Score [eMS] between 2 endoscopic assessments from baseline to last follow-up, descriptive endpoint); (5) Endoscopic remission (eMS = 0 at any follow-up visit, descriptive endpoint); and (6) Treatment persistence (descriptive endpoint).

Statistical Analysis

Baseline characteristics were summarized as means with standard deviations (SD) for continuous variables and as frequencies with proportions for categorical variables. Normality of distributions was assessed using the Shapiro-Wilk test; between-group differences were tested using Kruskal-Wallis or χ^2 tests, as appropriate. Crude incidence rates of SFCR were estimated using Kaplan-Meier analysis.

To address baseline imbalances, energy balancing weights (EBWs) were applied using the average treatment effect as estimand. EBW is a direct covariate-balancing method that minimizes a multivariate ‘energy’ distance between groups and does not require

What You Need to Know

Background

The optimal sequencing of advanced therapies for ulcerative colitis after anti-tumor necrosis factor alpha (TNF- α) exposure remains uncertain. Comparative real-world data on the efficacy and safety of vedolizumab, ustekinumab, and Janus kinase (JAK) inhibitors are limited.

Findings

Ustekinumab and JAK inhibitors achieved higher rates of steroid-free clinical remission than vedolizumab over 1 year. JAK inhibitors were linked to a 4-fold higher risk of infection-related adverse events.

Implications for patient care

Ustekinumab and JAK inhibitors represent effective second-line options in anti-TNF- α -exposed ulcerative colitis. JAK inhibitors require caution in frail or comorbid patients due to their higher infection risk.

modeling treatment probabilities. In multi-arm settings, multinomial or pairwise propensity-score models can be difficult to specify and may not achieve joint balance. EBW generalizes naturally to more than 2 treatment groups and can provide more stable weights and improved covariate balance when treatment assignment is complex.¹³ Covariates included in the weighting model were selected a priori to capture the key prognostic and confounding factors, while maintaining a parsimonious and stable model, and included age, sex, disease duration and extent, comorbidity, oral steroid use, SF and RB subscores, and reason for prior anti-TNF- α discontinuation. Covariate balance was assessed using absolute standardized mean differences (ASMD < 0.10) and variance ratios (0.5–2.0). No imputation of missing data was performed. Patients with missing outcome data were excluded from each specific analysis.

Comparative effectiveness was evaluated using weighted time-to-event analyses. Time to SFCR and biochemical SFCR was analyzed with Royston-Parmar flexible parametric survival models, which allow time-varying effects. Treatment group was the primary exposure, and models were double robust by including the same baseline covariates used for weighting. Non-parametric bootstrapping with 1000 replicates was performed to derive survival-weighted, time-averaged hazard ratios (HRs) and 95% confidence intervals (CIs). Weighted cumulative incidence curves were generated up to 12 months. For biochemical SFCR, 1 patient with missing data was excluded, requiring recalculation of EBWs for this subgroup. Improvement in SF and RB subscores was analyzed using EBW-weighted cumulative link mixed models (CLMMs), which account for repeated measures and within-patient correlation. Odds ratios (ORs) with 95% CIs were estimated for all

pairwise treatment comparisons. Endoscopic outcomes (eMS improvement and endoscopic remission) were analyzed descriptively in patients with available data; as data availability likely resulted from informative selection, no formal comparison was performed. Safety outcomes were evaluated by calculating the incidence rates of treatment-related AEs. A weighted Poisson regression model with generalized estimating equations was used, incorporating EBWs and adjusting for the same baseline covariates as in the primary models. Follow-up time was included as an offset. Incidence rate ratios (IRRs) and reasons for treatment discontinuation were reported by treatment group.

Sensitivity analyses tested the robustness of findings by re-estimating the main models while accounting for treatment optimization during follow-up. Optimization was included as a time-dependent covariate for time-to-event outcomes, and as a fixed covariate for repeated-measures and safety analyses. All analyses were conducted in R (version 4.4.2) using standard packages for weighting, survival, ordinal regression, and generalized estimating equations. Comparative results were summarized in league tables. A 2-sided $P < .05$ was considered statistically significant.

Further methodological details, including model specifications, weighting diagnostics, and bootstrapping procedures, are provided in the [Supplementary Materials](#).

Ethical Considerations

The study protocol (version 1.0, March 31, 2023) was approved by the Ethics Committee “Lombardia 5” on July 18, 2023. All procedures were conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Results

Patient Characteristics

A total of 596 patients with UC who initiated a second-line therapy with vedolizumab, ustekinumab, or JAKi following failure or intolerance to first-line anti-TNF- α agents were included in the primary efficacy analysis. [Supplementary Figure 1](#) illustrates patient disposition, including numbers included and excluded for each efficacy analysis.

Baseline demographic and clinical characteristics of the unadjusted cohorts are summarized in [Table 1](#). Overall, 54.7% of patients were male, with a mean age of 43.9 ± 15.5 years. Among the 596 patients, 301 (50.5%) received vedolizumab, 149 (25.0%) ustekinumab, and 146 (24.5%) JAK inhibitors (114 tofacitinib, 28 upadacitinib, 5 filgotinib). Mean disease duration was slightly longer in the ustekinumab group (11.0 ± 10.2 years) compared with vedolizumab (8.9 ± 7.8 years) and JAKi (8.3 ± 8.1 years), and this group had a lower proportion

of extensive colitis (47.0% vs 59.8% in vedolizumab and 51.4% in JAKi). Comorbidities were most frequent in ustekinumab (24.2%) and vedolizumab (20.9%) cohorts, whereas baseline oral steroid use was highest in the JAKi group (48.6%). Clinical activity—assessed by SF, RB, and urgency—was broadly similar across groups, as were endoscopic activity and inflammatory biomarkers (FCP and CRP). Regarding prior anti-TNF- α therapy, infliximab was the most frequently used agent in all groups (74.8% overall), followed by adalimumab (18.5%); the mean duration of prior anti-TNF- α therapy was slightly longer in the ustekinumab group (21.4 ± 31.9 months) vs vedolizumab (17.9 ± 22.3 months) and JAKi (13.6 ± 18.4 months). Secondary failure was the most common reason for anti-TNF- α discontinuation across all groups (47.3%); of note, anti-TNF- α primary failure was more frequent among JAKi recipients (41.0%), compared with patients treated with vedolizumab (29.2%) and ustekinumab (26.9%). Total follow-up was 348.4 person-years: 201.3 for vedolizumab, 70.9 for ustekinumab, and 76.2 for JAKi. Baseline covariates were well-balanced across treatment groups after EBW, with ASMDs below 0.10 and variance ratios for continuous variables between 0.5 and 2.0 ([Supplementary Table 1](#) and [Figure 1](#)).

Primary Outcome

During an average follow-up of 7 months, 391 patients achieved SFCR, corresponding to an estimated 12-month probability of 73.4% (95% CI, 69.0%–77.6%). The crude IR of SFCR at 12 months was 65.3% (95% CI, 59.2%–71.4%) for vedolizumab, 87.0% (95% CI, 79.3%–92.9%) for ustekinumab, and 80.2% (95% CI, 70.5%–88.2%) for JAKi.

Weighted Royston-Parmar flexible parametric survival models were used to compare the effectiveness of vedolizumab, ustekinumab, and JAKi for the achievement of SFCR over 12 months. Pairwise comparisons showed that patients treated with ustekinumab had a 54% higher average hazard of achieving SFCR at 12 months compared with those treated with vedolizumab (time-averaged adjusted HR [aHR], 1.54; 95% CI, 1.09–2.07). Similarly, treatment with JAKi was associated with a 66% higher average hazard of achieving SFCR at 12 months compared with vedolizumab (time-averaged aHR, 1.66; 95% CI, 1.07–2.53). No statistically significant difference was observed between JAKi and ustekinumab (time-averaged aHR, 1.08; 95% CI, 0.69–1.68) over time ([Table 2](#)). Accordingly, weighted cumulative incidence curves ([Figure 2A](#)) show a higher probability of achieving SFCR over time with ustekinumab and JAKi compared with vedolizumab, with similar outcomes between the two.

Secondary Effectiveness Outcomes

Over 12 months, both ustekinumab and JAKi were associated with higher hazards of achieving biochemical

Table 1. Baseline Characteristics and Follow-Up Events of the Overall Cohort, Stratified by Treatment Group

Baseline characteristics	All study population (N = 596)	Vedolizumab (n = 301)	Ustekinumab (n = 149)	JAKi (n = 146; tofacitinib n = 114; upadacitinib n = 28; filgotinib n = 5)	P value
Age, y	43.9 ± 15.5	45.7 ± 16.2	45.7 ± 16.0	38.5 ± 11.9	<.001
Male sex	329 (54.7)	166 (55.1)	76 (51.0)	54 (57.5)	.52
BMI, kg/m ² (n = 347)	24.7 ± 4.8	24.6 ± 4.6	25.5 ± 5.3	24.0 ± 4.5	.16
Smoking (n = 562)					
Active smokers	56 (10.0)	28 (10.4)	20 (13.7)	8 (5.5)	.045
Non-smokers	370 (65.8)	187 (69.3)	86 (58.9)	97 (66.4)	
Former smokers	136 (24.2)	55 (20.3)	40 (27.4)	41 (28.1)	
Disease duration, y	9.3 ± 8.6	8.9 ± 7.8	11.0 ± 10.2	8.3 ± 8.1	.03
Disease extent					
Proctitis	50 (8.4)	27 (9.0)	10 (6.7)	13 (8.9)	.03
Left-sided colitis	221 (37.1)	94 (31.2)	69 (46.3)	58 (39.7)	
Extensive colitis	325 (54.5)	180 (59.8)	70 (47.0)	75 (51.4)	
Presence of any comorbidity ^a	112 (18.8)	63 (20.9)	36 (24.2)	13 (8.9)	<.001
Oral steroid use	235 (39.4)	111 (36.9)	53 (35.6)	71 (48.6)	.03
SF subscore					
0	82 (13.8)	41 (13.6)	28 (18.8)	13 (8.9)	.13
1	134 (22.5)	74 (24.6)	31 (20.8)	29 (19.9)	
2	188 (31.5)	92 (30.6)	49 (32.9)	47 (32.2)	
3	192 (32.2)	94 (31.2)	41 (27.5)	57 (39.0)	
RB subscore					
0	209 (35.1)	103 (34.2)	65 (43.6)	41 (28.1)	.15
1	221 (37.1)	113 (37.5)	52 (34.9)	56 (38.4)	
2	143 (24.0)	74 (24.6)	27 (18.1)	42 (28.8)	
3	23 (3.9)	11 (3.6)	5 (3.4)	7 (4.8)	
Urgency	373 (62.6)	177 (58.8)	95 (63.8)	101 (69.2)	.10
Mayo endoscopic subscore (n = 448)					
0	22 (4.9)	11 (5.2)	6 (5.1)	5 (4.2)	.21
1	56 (12.5)	32 (15.2)	15 (12.8)	9 (7.5)	
2	151 (33.7)	77 (36.5)	38 (32.5)	36 (30.0)	
3	219 (48.9)	91 (43.1)	58 (49.6)	70 (58.3)	
Previous anti-TNF-α therapy					
Infliximab	446 (74.8)	244 (81.1)	96 (64.4)	106 (72.6)	<.001
Adalimumab	110 (18.5)	33 (10.9)	42 (28.2)	35 (24.0)	
Golimumab	40 (6.7)	24 (8.0)	11 (7.4)	5 (3.4)	
Duration of previous anti-TNF-α therapy, mo	17.7 ± 24.1	17.9 ± 22.3	21.4 ± 31.9	13.6 ± 18.4	.02
Reason for anti-TNF-α discontinuation					
Primary failure	188 (31.5)	88 (29.2)	40 (26.9)	60 (41.0)	.01
Secondary failure	282 (47.3)	141 (46.8)	73 (49.0)	68 (46.6)	
Intolerance	98 (16.5)	52 (17.3)	30 (20.1)	16 (11.05)	
Other	28 (4.7)	20 (6.7)	6 (4.0)	2 (1.4)	
FCP (n = 349), μg/g	1282 ± 1677	1374 ± 1930	1011 ± 1205	1400 ± 1604	.16
CRP (n = 474), mg/dL	12.7 ± 22.7	11.9 ± 18.3	12.1 ± 26.4	14.7 ± 25.6	.08

NOTE. Data are presented as means ± standard deviations or number (%) as appropriate.

NOTE. Continuous variables were compared using Kruskal-Wallis; categorical variables were compared by χ^2 test.

NOTE. Total number of patients achieving SFCR during follow-up was 191 (63.5%) in the vedolizumab cohort, 110 (73.8%) in the ustekinumab cohort, and 90 (61.6%) in the JAKi cohort.

BMI, body mass index; CRP, C-reactive protein; FCP, fecal calprotectin; JAKi, Janus kinase inhibitor; RB, rectal bleeding; SF, stool frequency; SFCR, steroid-free clinical remission; TNF, tumor necrosis factor.

^aCharlson Comorbidity Index (CCI) score without age >0.

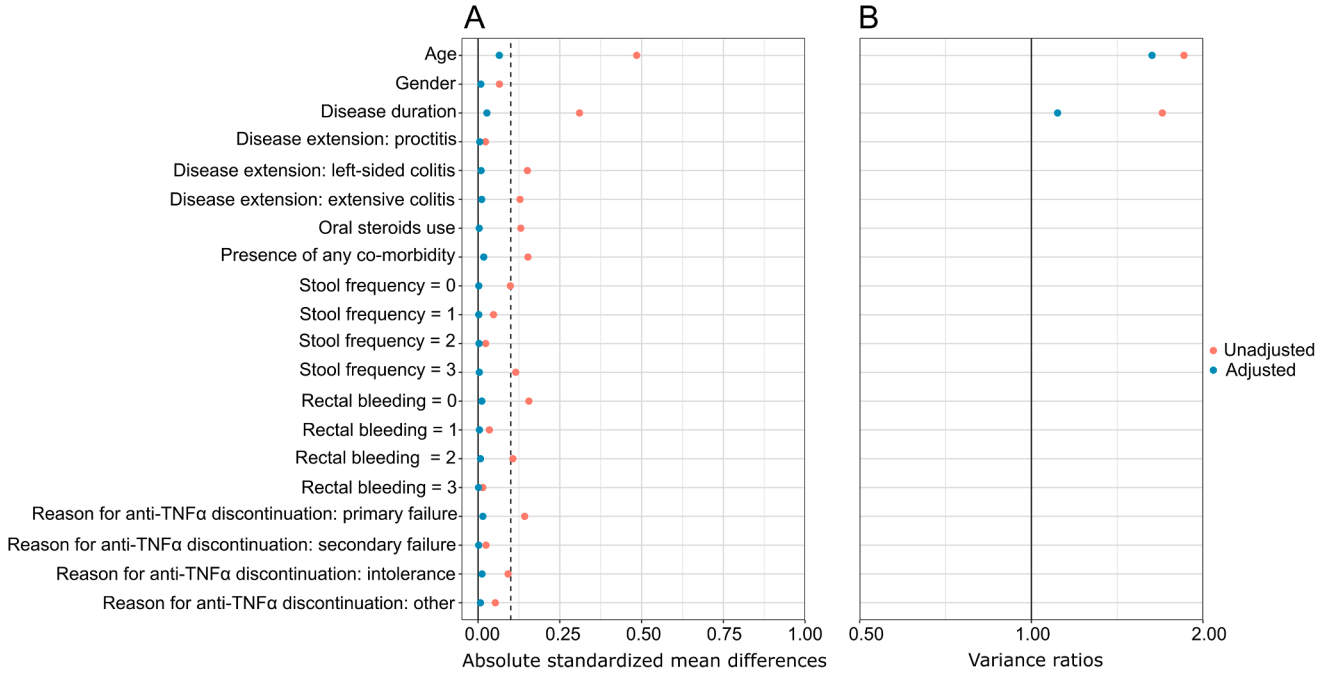


Figure 1. Covariate balance before (red) and after (blue) the application of the EBWs method; all the categorical covariates included were transformed, creating a binary variable for each category. (A) ASMD: values closer to 0 (solid line) have better balance, values <0.1 (dashed line) are considered indicative of acceptable balance. (B) Variance ratios only for continuous variables: optimal value is 1 (solid line), but values between 0.5 and 2.0 are considered indicative of acceptable balance.

SFCR compared with vedolizumab (time-averaged aHR, 2.26; 95% CI, 1.48–3.28 and time-averaged aHR, 3.37; 95% CI, 2.01–5.36, respectively), with no significant difference between the 2 (time-averaged aHR, 1.51; 95% CI, 0.92–2.40) (Table 2). The corresponding weighted cumulative incidence curves (Figure 2B) confirmed a higher cumulative incidence of biochemical SFCR for ustekinumab and JAKi compared with vedolizumab, with JAKi showing the numerically highest probability over the study period.

Weighted repeated-measures ordinal regression of SF and RB subscores showed that ustekinumab reduced the odds of more severe SF (OR, 0.46; 95% CI, 0.31–0.67) and RB (OR, 0.59; 95% CI, 0.39–0.90)

compared with vedolizumab. No significant differences were observed between JAKi and vedolizumab. However, patients on JAKi had higher odds of more severe SF than those on ustekinumab (OR, 1.50; 95% CI, 1.04–2.15), whereas RB severity did not differ significantly (OR, 1.48; 95% CI, 0.90–2.42) (Table 3).

Endoscopic Outcomes and Treatment Persistence (Descriptive Analysis)

Endoscopic outcomes were evaluated descriptively in patients with available endoscopic evaluations, which were performed after a median time of 7.5 months (interquartile range [IQR], 3.5–11.5 months)—specifically,

Table 2. League Table of Time-Averaged Treatment Effects Comparison on Achievement of SFCR (Bottom Left; Light Blue Squares) and Biochemical SFCR (Top Right; Light Orange Squares) at 12 Months

		Biochemical SFCR	
SFCR	JAKi	1.51 (0.92–2.40); .10	3.37 (2.01–5.36); <.001
	1.08 (0.69–1.68); .73	Ustekinumab	2.26 (1.48–3.28); <.001
	1.66 (1.07–2.53); .021	1.54 (1.09–2.07); .008	Vedolizumab

NOTE. Comparisons read from left to right.
NOTE. Treatment effects are indicated as time-averaged HR, 95% CI, and *P* value. An HR higher than 1.0 indicates the top-left treatment being better. Results come from EBW (weighted by age, sex, disease duration, disease extension, presence of any comorbidity, oral steroids use, SF subscore, RB subscore, and reason for prior anti-TNF- α discontinuation) Royston-Parmar flexible parametric survival model using the double robust approach. CI, confidence interval; EBW, energy balancing weight; HR, hazard ratio; JAKi, Janus kinase inhibitors; RB, rectal bleeding; SF, stool frequency; SFCR, steroid-free clinical remission; TNF, tumor necrosis factor.

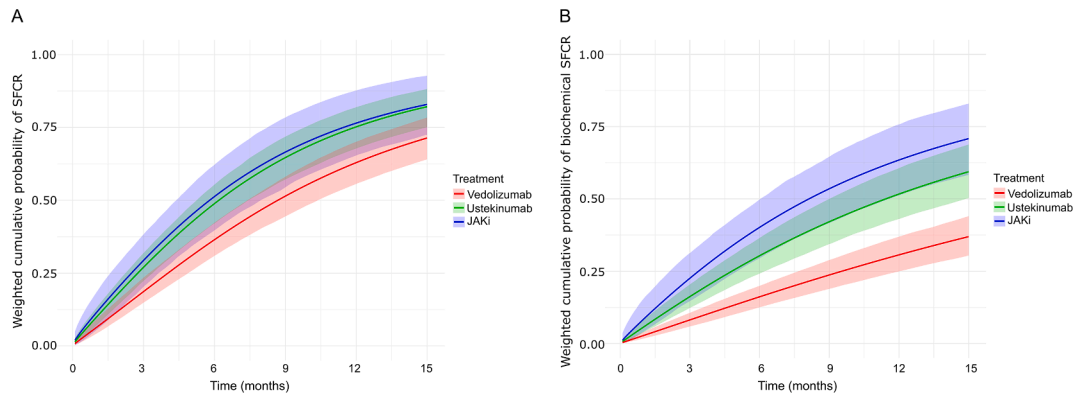


Figure 2. Cumulative incidence probabilities of SFCR (A), and biochemical SFCR (B), by treatment group over 12 months (including any delayed visit up to 15 months). Cumulative incidence probabilities were estimated using an EBW Royston-Parmar flexible parametric survival model, weighted for age, sex, disease duration, disease extension, presence of any comorbidity, oral steroid use, SF subscore, RB subscore, and reason for prior anti-TNF- α discontinuation, using the double-robust approach. Cumulative incidence curves were derived from 1000 bootstrap samples, and shaded areas represent the corresponding 95% CIs. Numerical results of pairwise treatment comparisons, including point estimates and 95% CIs, are reported in the text and summarized in the corresponding league tables.

for vedolizumab 8.8 months (IQR, 4.2–12 months), for ustekinumab 9.3 months (IQR, 5.4–12.2 months), and for JAKi 4.6 months (IQR, 2.1–8.3 months). Among the 280 patients with at least 2 endoscopic evaluations, endoscopic improvement was observed in nearly one-half of those treated with vedolizumab (46.6%; 69/148) and JAKi (43.2%; 32/74), and in over one-half of those treated with ustekinumab (58.6%; 34/58). Among the 317 patients who underwent at least 1 follow-up endoscopy, endoscopic remission was achieved in approximately one-quarter of patients receiving vedolizumab (24.3%; 42/173) or ustekinumab (25.8%; 16/62), compared with 14.6% of those receiving JAKi (12/82).

Overall, treatment was discontinued in 44.2% of patients receiving vedolizumab, 27.5% of those receiving ustekinumab, and 41.1% of those treated with JAKi. As shown in [Supplementary Table 2](#), the predominant reason for discontinuation differed across groups: secondary failure was most frequent with vedolizumab (18.9%), whereas primary failure was the leading cause among patients treated with ustekinumab (12.1%) and JAKi (21.9%).

Safety

Treatment-related AEs were reported in 4.0% of patients receiving vedolizumab (12/301; crude IR, 7.9 per 1000 person-years), in 4.0% of those receiving ustekinumab (6/149; crude IR, 12.7 per 1000 person-years), and in 15.1% of those receiving JAKi (22/146; crude IR, 49.2 per 1000 person-years). Infections were the most frequently reported AEs across all treatment groups, whereas mucocutaneous manifestations and cytopenias occurred less frequently. The crude IR of infections was 3.3, 6.4, and 26.9 per 1000 person-years in the vedolizumab, ustekinumab, and JAKi groups, respectively. [Supplementary Table 3](#) summarizes the AEs occurred in each cohort. After applying EBWs, the weighted IR of AEs was highest in the JAKi group (42.8 per 1000 person-years), followed by ustekinumab (10.3 per 1000 person-years) and those in the vedolizumab group (8.7 per 1000 person-years). Weighted Poisson regression showed significantly higher AE rates with JAKi compared with vedolizumab (adjusted IRR [aIRR], 4.46; 95% CI, 1.80–11.10) and ustekinumab (aIRR, 4.15;

Table 3. League Table of Time-Averaged Treatment Effects Comparison on SF (Bottom Left; *Light Blue Squares*) and RB (Top Right; *Light Orange Squares*) Subscores

		RB	
SF	JAKi	1.48 (0.90–2.42); .11	0.88 (0.58–1.33); .53
	1.50 (1.04–2.15); .028	Ustekinumab	0.59 (0.39–0.90); .013
	0.69 (0.44–1.05); .086	0.46 (0.31–0.67); <.001	Vedolizumab

NOTE. Comparisons read from left to right.
NOTE. Treatment effects are indicated as OR, 95% CI, and *P* value. An OR lower than 1.0 indicates lower odds of having higher SF or RB subscore. Results come from EBW (weighted by age, sex, disease duration, disease extension, presence of any comorbidity, oral steroids use, SF subscore, RB subscore, and reason for prior anti-TNF- α discontinuation) repeated-measures ordinal regression model.
CI, confidence interval; EBW, energy balancing weight; JAKi, Janus kinase inhibitors; OR, odds ratio; RB, rectal bleeding; SF, stool frequency; TNF, tumor necrosis factor.

Table 4. League Table of Treatment Effects Comparison on AE Incidence Rate

JAKi			
4.15 (1.35–12.74); .013	Ustekinumab		
4.46 (1.80–11.10); .001	1.07 (0.31–3.73); .91	Vedolizumab	

NOTE. The column-defining treatment is compared with the row-defining treatment.

NOTE. Treatment effects are indicated as IRR, 95% confidence intervals and *P*-value. An IRR higher than 1.0 indicates higher probability of AEs occurrence (ie, top-left treatment being worse). Results come from energy balancing weighted (weighted by age, sex, disease duration, disease extension, presence of any co-morbidity, oral steroids use, SF subscore, RB subscore, and reason for prior anti-TNF- α discontinuation) Poisson regression model with repeated measures using the double robust approach.

AE, adverse event; CI confidence interval; IRR, incidence rate ratio; JAKi, Janus kinase inhibitors; RB, rectal bleeding; SF, stool frequency; TNF, tumor necrosis factor.

95% CI, 1.35–12.74), whereas no difference was observed between ustekinumab and vedolizumab (aIRR, 1.07; 95% CI, 0.31–3.73) (Table 4).

Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of the primary findings. Of 596 patients, 188 (31.5%) received treatment optimization, after a median time of 3.9 months (IQR, 2.1–7.6 months) from baseline. Given the observed imbalance in treatment optimization rate across treatment groups (*P*-value < .001), observed in 37.5% of patients receiving vedolizumab (median time to optimization, 5.4 months [IQR, 3.0–9.6 months]), 32.2% of those receiving ustekinumab (median time to optimization, 2.1 months [IQR, 1.8–3.9 months]), and 18.5% of those receiving JAKi (median time to optimization, 5.1 months [IQR, 1.9–6.6 months]), we conducted sensitivity analyses to assess whether this factor influenced the comparative analysis. All main models were re-estimated with the inclusion of a binary covariate indicating treatment optimization during the outcome-specific follow-up period. The results for all the outcomes remained consistent with the primary analyses, with marginal change in effect estimates and variance, confirming the robustness of the observed treatment effects (Supplementary Material; Supplementary Tables 4–8).

Discussion

In this large, multicenter, real-world cohort, both ustekinumab and JAKi demonstrated superior effectiveness compared with vedolizumab in achieving SFCR and biochemical SFCR over 12 months in anti-TNF- α -experienced patients with UC. These results contribute to addressing a critical knowledge gap regarding the

optimal sequencing of advanced therapies in this challenging population.

Optimal sequencing in UC after anti-TNF- α exposure remains an open issue, as direct comparisons are scarce. Overall, our findings are consistent with the network meta-analysis by Lasa et al, which reported superior efficacy of JAKi and ustekinumab compared with vedolizumab in inducing clinical remission and endoscopic improvement in anti-TNF- α -experienced patients.¹⁴ However, these conclusions derive from indirect comparisons across heterogeneous randomized trials. Real-world studies crucially provide complementary evidence with higher external validity, yet most have evaluated only 2 agents at a time. For instance, the Dutch Registry reported superior SFCR and biochemical remission with tofacitinib compared with vedolizumab,¹⁵ and another study confirmed its superiority for endoscopic and histological outcomes¹⁶; conversely, an Italian retrospective study found no significant clinical differences,¹⁷ whereas another work reported lower treatment persistence for tofacitinib compared with vedolizumab without significant differences in other outcomes.¹⁸ Findings on ustekinumab have also been heterogeneous. A 2022 GETAID study found no significant differences compared with vedolizumab,¹⁹ whereas a more recent study reported higher endoscopic and histologic remission rates with ustekinumab.²⁰ Two comparative studies between ustekinumab and tofacitinib reported similar effectiveness following anti-TNF- α failure.^{21,22} Conversely, a 2025 meta-analysis including 3 retrospective cohorts showed superior effectiveness of JAKi in inducing endoscopic remission, with a similar AE rate.²³ Additional evidence also suggests that tofacitinib may perform than ustekinumab better after multiple therapeutic failures or primary failure to any biologic²² and may reduce disease progression when used as third-line therapy.²⁴ Finally, a 2023 registry-based analysis²⁵ and a recent unadjusted 3-arm comparison,²⁶ reported lower colectomy risk with ustekinumab vs vedolizumab or tofacitinib.

In our cohort, weighted analyses showed that ustekinumab and JAKi were associated with significantly similarly higher hazards of achieving SFCR compared with vedolizumab, with time-averaged aHRs of 1.54 and 1.66, respectively; similar trends were observed for biochemical SFCR, with aHRs of 2.26 for ustekinumab and 3.37 for JAKi. No significant differences between ustekinumab and JAK inhibitors were detected for either SFCR or biochemical SFCR. Intriguingly, ustekinumab appeared to confer a more favorable profile in terms of patient-reported outcomes, being associated with lower odds of severe SF and RB compared with vedolizumab and lower SF compared with JAKi, whereas no significant differences were observed between vedolizumab and JAKi. These nuances may reflect differences in symptom perception or reporting, underscoring the value of incorporating patient-reported outcomes alongside

objective measures in comparative effectiveness research. Endoscopic improvement and mucosal healing were observed in approximately 15% to 25% of patients across treatment groups; however, these results should be interpreted descriptively given the variable timing of endoscopy in routine practice and potential indication bias. They provide confirmatory evidence that endoscopic goals can be achieved outside of clinical trials but are not suitable for rigorous pairwise comparisons. From a safety standpoint, JAKi were associated with an approximately 4-fold increase in the incidence rate of treatment-related AEs—primarily infections—compared with both vedolizumab and ustekinumab. These data corroborate the notion of distinct profiles for JAKi compared with the other 2 classes.²⁷ In contrast, both vedolizumab and ustekinumab demonstrated low AE rates, further reinforcing their favorable safety profiles and highlighting the need to weigh JAKi risks.

The strengths of our study include its large, multicenter design reflecting real-world clinical practice across different centers in Europe, the use of objective biomarkers in addition to clinical measures, and the application of advanced statistical methods, including energy balance weighting, double-robust models, and time-dependent survival analyses with bootstrap estimation of time-averaged HRs. Nevertheless, limitations must be acknowledged, including non-random treatment allocation, descriptive-only endoscopic outcomes due to incomplete data, exclusion of IL-23p19-selective agents due to small numbers and follow-up, pooling of inhibitors which precluded in-class comparisons (given the predominance of tofacitinib), lack of anti-TNF- α therapeutic drug monitoring, the inclusion of patients with different reason for anti-TNF- α discontinuation (ie, failure and intolerance), and absence of cost-effectiveness analyses.

Despite these limitations, this first 3-arm real-world comparison provides meaningful evidence that ustekinumab and JAKi are more effective than vedolizumab as second-line therapies in anti-TNF- α -experienced patients with UC. The inclusion of patients who discontinued anti-TNF- α due to either failure or intolerance aligns with the pragmatic aim of guiding second-line decision-making in routine practice: of note, we incorporated the reason for discontinuation both in the weighting procedure and as a covariate in the multivariable models (double-robust approach), thereby minimizing its impact on between-drug comparisons. The distinct safety profile of JAKi should guide treatment decisions in frail or high-risk patients, with ustekinumab—and possibly IL23p19 selective inhibitors—likely offering a more balanced benefit-risk profile.

Conclusion

In conclusion, our findings support the preferential positioning of ustekinumab and JAKi ahead of

vedolizumab as second-line agents in the therapeutic algorithm for UC. Future pragmatic head-to-head trials—ideally incorporating real-world populations, long-term follow-up, and both patient-centered and hard outcomes—will further refine treatment sequencing strategies in UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2026.01.017>.

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Conflicts of interest

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Data Availability

Data can be made available upon request from third parties.