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Efficacy and Safety of Second-Line Advanced Therapy After Vedolizumab in Ulcerative Colitis: A Multicenter Cohort Study From the GETAID

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All the members of the GETAID-AFTER-VEDO study group are listed in the appendix.

ABSTRACT

Background and Aims: Vedolizumab has become the preferred first-line advanced therapy in ulcerative colitis (UC). However, the optimal second-line treatment following vedolizumab failure remains unclear. We aimed to evaluate the effectiveness and safety of second-line therapies after first-line vedolizumab.

Methods: We conducted a multicenter retrospective study including UC patients from 31 centers who received infliximab (IFX), subcutaneous (SC) anti-TNFs, or ustekinumab after vedolizumab failure. The primary endpoint was steroid-free clinical remission (SFCR) at week 14. Predictors of remission were identified using multivariate logistic regression.

Results: Among 196 patients, 99 received IFX, 27 anti-TNF SC, and 70 ustekinumab. At week 14, SFCR was achieved in 78 patients (39.8%): 38 (38.4%) with IFX, 8 (29.6%) with anti-TNF SC, and 32 (45.7%) with ustekinumab, with no significant difference between groups ($p = 0.32$). Median treatment persistence ranged from 8 to 9.2 months. Baseline corticosteroid use was associated with lower odds of SFCR (OR = 0.37, 95% CI [0.18–0.73]). Adverse events occurred in 15.8% of patients, including 12.2% serious events. Overall adverse events were less frequent with ustekinumab than with IFX (10.0% vs. 24.2%, $p = 0.02$), while serious events were comparable (5.7% vs. 16.1%, $p = 0.08$). Discontinuation due to adverse events was more frequent with IFX (12.1%) and anti-TNF SC (14.8%) than with ustekinumab (2.9%, $p = 0.045$ and 0.049).

Conclusion: In UC patients failing vedolizumab, second-line IFX, anti-TNF SC, and ustekinumab showed similar effectiveness and persistence. Infliximab remains a robust option for rapid control in high inflammatory burden, whereas ustekinumab may be preferred for its superior safety profile in high-risk patients.

1 | Introduction

Vedolizumab is widely used as a first-line biological therapy for ulcerative colitis (UC) owing to its favorable safety profile and effectiveness in inducing and maintaining clinical remission. Randomized controlled trials and real-world studies have reported superior or comparable clinical effectiveness between vedolizumab and anti–tumor necrosis factor (TNF) agents in biologic-naïve patients [1–4] with higher treatment persistence [5–8] and fewer adverse events [9, 10] in some settings. As a result, vedolizumab is increasingly prescribed as first-line therapy for UC in routine clinical practice. Response to a second-line agent may vary depending on the mechanism of action of the first-line therapy, potential immunogenicity, and disease progression before switching. With the increasing number of advanced therapies available, including subcutaneous anti-TNF agents (anti TNF SC - adalimumab, golimumab) and interleukin-12/23 inhibitors (ustekinumab), optimizing treatment sequencing has become a critical aspect of UC management [11, 12]. While treatment algorithms after anti-TNF failure are increasingly informed by recent studies such as the EFFICACI trial [13], which demonstrated the effectiveness of vedolizumab after anti-TNF exposure, evidence guiding treatment choices after vedolizumab failure remains scarce. Most clinical trials and real-world studies have focused on treatment-naïve patients or those previously exposed to anti-TNFs, leaving clinicians with limited evidence to guide treatment sequencing after vedolizumab failure [12, 14]. Head-to-head comparisons between advanced therapies in this specific clinical setting remain scarce. Current real-world evidence is characterized by significant heterogeneity, with reported one-year treatment persistence rates ranging from 44% for infliximab to 75% for ustekinumab [14, 15]. This variability highlights the lack of consensus and underscores the need for further studies to define the optimal therapeutic sequence for these patients. Therefore, we conducted a study that aimed to assess and compare the effectiveness of infliximab, anti-TNF SC, and ustekinumab as second-line therapies in UC following first-line vedolizumab treatment.

2 | Methods

2.1 | Study Design and Patients

This multicenter retrospective cohort included UC patients from 31 GETAID centers in France and Belgium treated with infliximab, SC anti-TNFs, or ustekinumab after vedolizumab failure between March 2016 and June 2024. The inclusion date corresponded to the first day of treatment by the second-line advanced therapy and a minimum follow-up of 14 weeks was required. JAK inhibitors, S1P modulators, and IL-23 antagonists were excluded as second-line therapies due to reimbursement restrictions. In each participating center, patients were identified through a systematic query of local institutional IBD databases to retrieve all UC patients who initiated a second-line advanced therapy after vedolizumab discontinuation during the study period. In AP-HP centers, which provided the largest subgroup of the cohort ($n = 69/196$, 35.2%), patients were identified via SUViMIC. This secure, IBD-specific electronic medical record platform, established in 2016, currently manages data for approximately 10,000 patients and facilitates systematic data extraction through targeted database queries. Patients with Crohn's disease, a combination of advanced therapy and a history of colectomy were excluded. The study protocol was reviewed and approved by the GETAID Scientific Committee prior to study initiation. In accordance with French regulations, patients were informed and did not object to the use of their data for research. All data were retrieved from patients' medical files, including clinical, biological, and endoscopy results. Data were entered by each center into a secure standardized electronic case report form (eCRF) hosted on the Doqboard platform. Baseline characteristics collected at inclusion included

Key Summary

- Summarise the established knowledge on this subject
  - Vedolizumab is commonly used as a first-line advanced therapy in ulcerative colitis.
  - Data on the effectiveness and safety of second-line advanced therapies after vedolizumab are limited.
- What are the significant and/or new findings of this study?
  - No statistically significant difference was observed in the effectiveness of second-line advanced therapies including infliximab, antiTNF SC and ustekinumab, following vedolizumab at week 14.
  - Infliximab, anti-TNF SC and ustekinumab showed similar treatment persistence, remission and response rates at 52 weeks.
  - Baseline use of corticosteroids was associated with poorer outcomes at week 14.
  - The overall adverse event rate was lower with ustekinumab than with infliximab. Treatment discontinuation due to adverse events was more frequent with infliximab and anti-TNF SC compared with ustekinumab.
  - Ustekinumab offers a safety advantage in high-risk patients, while infliximab remains a robust option in the setting of high baseline inflammation.

age, sex, disease severity assessed by the Mayo score, treatment types, concomitant treatments, and routine blood tests. Follow-up extended from inclusion to the last available visit. Treatment discontinuation before evaluation timepoints (weeks 14 and 52) was considered as treatment failure at the corresponding timepoint (e.g., patients who discontinued between weeks 14 and 52 were classified as non-responders at week 52).

As this was a retrospective study, vedolizumab failure was based on treating physicians' decisions and could be related to either primary non-response (absence of response at week 14), secondary loss of response (response at week 14 followed by discontinuation), or safety issues. All treatment discontinuations were systematically reviewed after data collection to ensure consistency with the clinical course, particularly for cases initially classified as secondary loss of response. Early discontinuations without documented initial response were reclassified as primary non-response when appropriate. In case of uncertainty, final adjudication was performed by a senior investigator.

Given the retrospective nature of the study, second-line treatment decisions were made at the discretion of the treating clinicians. All patients could continue non-biologic treatments including 5-ASA, corticosteroids and immunosuppressive agents according to the standard of care.

2.2 | Outcome Measures

The primary outcome measure was steroid-free clinical remission at induction (SFCR, week 14) defined by a partial Mayo Clinic score of 2 or less, with no sub-score greater than 1 and without treatment discontinuation. Secondary outcomes included remission and response, defined as a decrease in partial Mayo score of at least 30%, at weeks 14 and 52, drug persistence, rates of adverse events and serious adverse events, hospitalization related to UC, and colectomy rates.

Outcomes were retrospectively collected from medical records using the standardized eCRF. Partial Mayo scores were either directly retrieved when explicitly documented or reconstructed from contemporaneous, structured clinical information corresponding to each score component, regardless of the mode of clinical follow-up. In case of uncertainty, adjudication was performed by a senior investigator. To account for real-life variation in visit scheduling, week-14 and week-52 assessments were accepted within a 4-week window.

Adverse events (AEs) were collected from medical records using prespecified categories in the eCRF. After data collection, AEs were classified as serious if they resulted in death, a life-threatening condition, hospitalization or prolongation of hospitalization, significant disability, congenital anomaly, or led to treatment discontinuation. In case of uncertainty regarding severity classification, adjudication was performed by a senior investigator. Infections were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (2025), and serious infections were defined as grade ≥ 3.

2.3 | Statistical Analysis

Qualitative variables were expressed as number and percentages, while quantitative variables were given with mean and standard deviation or median and interquartile range (IQR). The proportions between the groups were compared using a chi^2 test or Fisher's exact test. Persistence was analyzed using Kaplan-Meier and log-rank tests; hazard ratios (HRs) used infliximab as reference. A crude logistic regression was first performed to assess the unadjusted association of each factor with corticosteroid-free remission at week 14. Variables with a p-value ≤ 0.20 in univariate analysis, along with treatment groups, were then included in a multivariate binary logistic regression model. Missing data were systematically assessed. Continuous variables were imputed using their respective medians. Factors with more than 15% missing data were excluded from regression analyses to limit unstable estimates. Sensitivity analyses assessed CRP dichotomization, immunosuppressant use, and corticosteroid–treatment interaction. To determine whether baseline corticosteroid use affected treatment success differently across therapies, we tested an interaction between corticosteroid use and treatment type in a multivariate model using a likelihood ratio test. Analyses were done with R (version 4.4.2). Statistical significance was interpreted by 95% CIs and p-values < 0.05.

3 | Results

3.1 | Patients' Baseline Characteristics

Data collection was performed between December 2022 and October 2024 across 31 GETAID centers. Of 230 eligible patients, 196 were included: 99 (50.5%) infliximab, 70 (35.7%)

ustekinumab, and 27 (13.8%) SC anti-TNFs (24 adalimumab, 3 golimumab) (Figure S1). Vedolizumab was discontinued due to primary non-response in 78 patients (39.8%), secondary loss of response in 105 patients (53.6%), and adverse events in 14 patients (7.1%). The cause of vedolizumab discontinuation differed across treatment groups, with a higher proportion of primary non-response in patients treated with infliximab compared with subcutaneous anti-TNF agents and ustekinumab ($p < 0.001$).

Among the 99 patients treated with infliximab, 61 (61.6%) received combination therapy, including 52 with thiopurines (85.2% of all infliximab combination therapies), 9 with methotrexate (14.8%), and 7 received the subcutaneous formulation (7.1%). Patients in the infliximab group had significantly higher CRP levels (median [IQR]: 9.8 [3–28.1] mg/L) and fecal calprotectin levels (median [IQR]: 2088 [766–2940] µg/g) compared with the rest of the cohort (CRP: 6 [2.2–21] mg/L; $p = 0.040$, calprotectin: 1225 [455–2658] µg/g; $p = 0.040$). Within the infliximab group, patients on combination therapy had a higher baseline partial Mayo score ($p = 0.005$), CRP levels ($p = 0.04$), and fecal calprotectin levels ($p = 0.005$) compared to those on monotherapy. The baseline characteristics of the entire cohort, as well as those of the individual treatment groups are presented in Table 1.

3.2 | Outcome Results at 14 weeks

Overall, 78 patients (39.8%, 95% CI [32.90%–46.6%]) reached SFCR at week 14. SFCR rates were 38.4% (38/99) with infliximab, 29.6% (8/27) with anti-TNF SC, and 45.7% (32/70) with ustekinumab (Figure 1A). Differences between treatment groups were not statistically significant (χ^2 test, $p = 0.32$). Rates of clinical remission and (steroid-free) clinical response in each treatment group at week 14 are presented in Figure 1B–D.

Of note, at week 14, anti-drug antibodies were available for 61/99 (61.6%) infliximab patients; only one (on combination therapy) was positive. Among 35 antibody-negative patients, 24 (68.6%) received combination therapy. Assessments were unavailable for 38 patients, primarily due to early discontinuation ($n = 25$) or routine monitoring gaps.

3.3 | Outcome Results at 52 weeks

At week 52, 56 out of 196 patients (28.6%, 95% CI [22.2%–34.9%]) reached SFCR, including 30 out of 99 (30.3%) on infliximab, 6 out of 27 (22.2%) on anti-TNF SC, and 20 out of 70 (28.6%) on ustekinumab, with no statistically significant difference (χ^2 test, $p = 0.74$) (Figure 2A). Rates of clinical remission and (steroid-free) clinical response in each treatment group at week 52 are presented in Figure 2B–D.

3.4 | Treatment Persistence

With a median follow-up duration in the whole cohort of 16.2 months (95% CI: 13.8 –8.5), the overall median survival without drug discontinuation was 8.5 months (IQR: 4.2–64.6). The median persistence was 8.2 months (IQR: 3.4–not reached during a maximum follow-up of 60.2 months) for infliximab, 8 months (IQR: 3.0–64.6) for TNF SC, and 9.2 months (IQR: 5.2–33.0) for ustekinumab, without significant difference (Figure 3, log-rank $p = 0.53$).

The rates of survival without treatment discontinuation at 6 months and 1 year varied across treatment groups. For infliximab, survival without discontinuation was 56.3% (95% CI [45.6%–65.8%] at 6 months and 44.4% (95% CI [33.6%–54.6%]) at 1 year. In the anti-TNF SC group, it was 51.9% (95% CI [31.9%–68.5%]) at 6 months and 43.8% (95% CI [24.7%–61.3%]) at 1 year. Among ustekinumab-treated patients, the persistence rate was 67.2% (95% CI [53.4%–77.8%]) and 47.0% (95% CI [33.1%–59.7%]) at 6 months and 1 year, respectively.

Hazard Ratios (HRs) for treatment discontinuation compared with infliximab were as follows: anti-TNF SC (HR = 0.95, 95% CI: 0.54–1.7, $p = 0.86$), ustekinumab (HR = 0.78, 95% CI: 0.50–1.2, $p = 0.27$) (Figure S2). Discontinuation due to primary non-response was lower with ustekinumab (7.1%) than with infliximab (25.3%, $p = 0.002$). Secondary loss of response was higher with ustekinumab (31.4%) and SC anti-TNFs (29.6%) than with infliximab (12.1%, $p = 0.003$ and 0.02) (Table S1).

3.5 | Factors Associated With Corticoid-Free Clinical Remission at Week 14

We first performed a univariate logistic regression analysis to identify factors associated with SFCR. Fecal calprotectin was missing in more than 70% of patients and was therefore excluded from regression analyses. Left-sided colitis (OR = 1.89, 95% CI [1.04–3.43], $p = 0.04$), baseline corticosteroid use (OR = 0.43, 95%CI [0.24–0.80], $p = 0.01$), and higher CRP levels (OR = 1.01, 95%CI [1.00–1.03], $p = 0.03$) were identified as potential predictors of SFCR. These variables were then included in a multivariate logistic regression analysis (Table 2, Figure S3). Given baseline differences across treatment groups, the association between primary non-response to vedolizumab and week-14 SFCR was specifically assessed and found to be non-statistically significant (Fisher's test, $p = 1.00$). Left-sided colitis was associated with week-14 SFCR (OR = 2.36, $p = 0.01$ compared to pancolitis), whereas baseline corticosteroid use was negatively associated with week-14 SFCR (OR = 0.37, $p = 0.006$). Regarding the type of second-line therapy, no significant differences were observed for ustekinumab (OR = 1.80, $p = 0.11$) or subcutaneous anti-TNF (OR = 0.58, $p = 0.32$) compared with infliximab. These findings were consistent across all three sensitivity analyses (Tables S2–S4).

Higher CRP levels at baseline were associated with an increased likelihood of treatment success (OR = 1.02, $p = 0.04$). However, in a sensitivity analysis, after inclusion of CRP–treatment interaction terms, no significant interaction was detected ($p = 0.37$ for TNF SC and $p = 0.72$ for ustekinumab), and the association between CRP and SFCR was no longer significant ($p = 0.19$) (Table S4).

TABLE 1 | Patients' characteristics.

	Population (n = 196)	Infliximab (n = 99)	TNF SC (n = 27)	Ustekinumab (n = 70)
Female—n (%)	102 (52)	51 (51.5)	20 (74.1)	31 (44.3)
Age (years)—median [IQR]	46.6 [29.2–62.3]	36.8 [25.4–57.8]	43.9 [31.3–59.5]	58.5 [39.1–70.1]
Smoking status—n (%)				
Current smoker	10 (5.1)	5 (5.1)	1 (3.7)	4 (5.7)
Former smoker	57 (29.1)	22 (22.2)	12 (44.4)	23 (32.9)
Never smoked	129 (65.8)	72 (72.7)	14 (51.9)	43 (61.4)
Disease duration (months)—median [IQR]	39.7 [16.8–141.6]	27.0 [14.1–116]	78.7 [37.2–154]	47.1 [23.5–156]
Extension—n (%)				
E1	11 (5.6)	5 (5.1)	4 (14.8)	2 (2.86)
E2	90 (45.9)	44 (44.4)	14 (51.8)	32 (45.7)
E3	95 (48.4)	50 (50.5)	9 (33.3)	36 (51.4)
Previous treatment exposure before vedolizumab—n (%)				
Oral 5-ASA	171 (87.2)	86 (86.9)	24 (88.9)	61 (87.1)
Thiopurines	66 (33.7)	35 (35.4)	7 (25.9)	24 (34.3)
Oral corticosteroids	153 (78.1)	80 (80.8)	21 (77.8)	52 (74.3)
Steroid dependent	67 (34.1)	37 (37.4)	10 (37.0)	20 (28.6)
Steroid resistant	17 (8.7)	8 (8.1)	4 (14.8)	5 (7.1)
Cause of vedolizumab discontinuation				
Primary non-response	78 (39.8)	54 (54.5)	7 (25.9)	17 (24.3)
Secondary loss of response	105 (53.6)	42 (42.4)	16 (59.3)	47 (67.1)
Adverse events	14 (7.1)	6 (6.1)	3 (11.1)	5 (7.1)
Patients' preference	3 (1.5)	0	2 (7.4)	1 (1.4)
Concomitant treatment at initiation				
Oral 5-ASA	49 (25.0)	17 (17.2)	11 (40.7)	21 (30.0)
Thiopurines	59 (30.1)	52 (52.5)	5 (18.5)	2 (2.9)
Methotrexate	10 (5.1)	9 (9.1)	0	1 (1.5)
Steroid use on induction—n (%)	78 (39.8)	40 (40.4)	9 (33.3)	29 (41.4)
Baseline CRP—median [IQR]	6 [2.2–21]	9.7 [3–26]	2 [1–18.2]	4.39 [2.8–9]
Baseline fecal calprotectin—median [IQR]	1225 [455–2658]	2088 [766–2940]	1400 [738–1976]	689 [397–2364]
Missing—number (%)	150 (76.5%)	72 (72.7%)	23 (85.1%)	55 (78.6%)
Baseline partial mayo score—median [IQR]	6 [4–7]	6 [5–8]	5 [4–6]	5 [3–6]

Note: Data are presented as n (%) for categorical variables and median [interquartile range] for continuous variables.

Finally, we explored whether the impact of baseline corticosteroid use differed across treatment groups. Corticosteroid use was significantly associated with lower remission in the ustekinumab group (OR = 0.35, $p = 0.006$), but not in the infliximab (OR = 0.65, $p = 0.39$) or subcutaneous anti-TNF groups (OR = 0.27, $p = 0.09$), and the global interaction test was not statistically significant (likelihood ratio test $p = 0.08$).

3.6 | Safety

A total of 36 adverse events (excluding UC flares) were reported, occurring in 31/196 patients (15.8%), mainly infections (n = 19, 9.7%) and allergic reactions, including infusion reactions (n = 6, 3.1%). When analyzed as total events, overall adverse events were less frequent with ustekinumab than with infliximab (10.0% vs. 24.2%, Fisher's exact test, $p = 0.02$), whereas rates of serious adverse events and infections, including serious infections, were comparable across treatment groups (all $p > 0.05$; Table 3). Treatment was discontinued due to adverse events in 12 patients receiving infliximab (12.1%), 4 patients receiving subcutaneous anti-TNF agents (14.8%), and 2 patients receiving ustekinumab (2.9%). Discontinuation related to safety was more frequent with infliximab and anti-TNF SC compared with ustekinumab ($p = 0.045$ and $p = 0.049$, respectively). Infections leading to treatment discontinuation occurred in 6 infliximab-

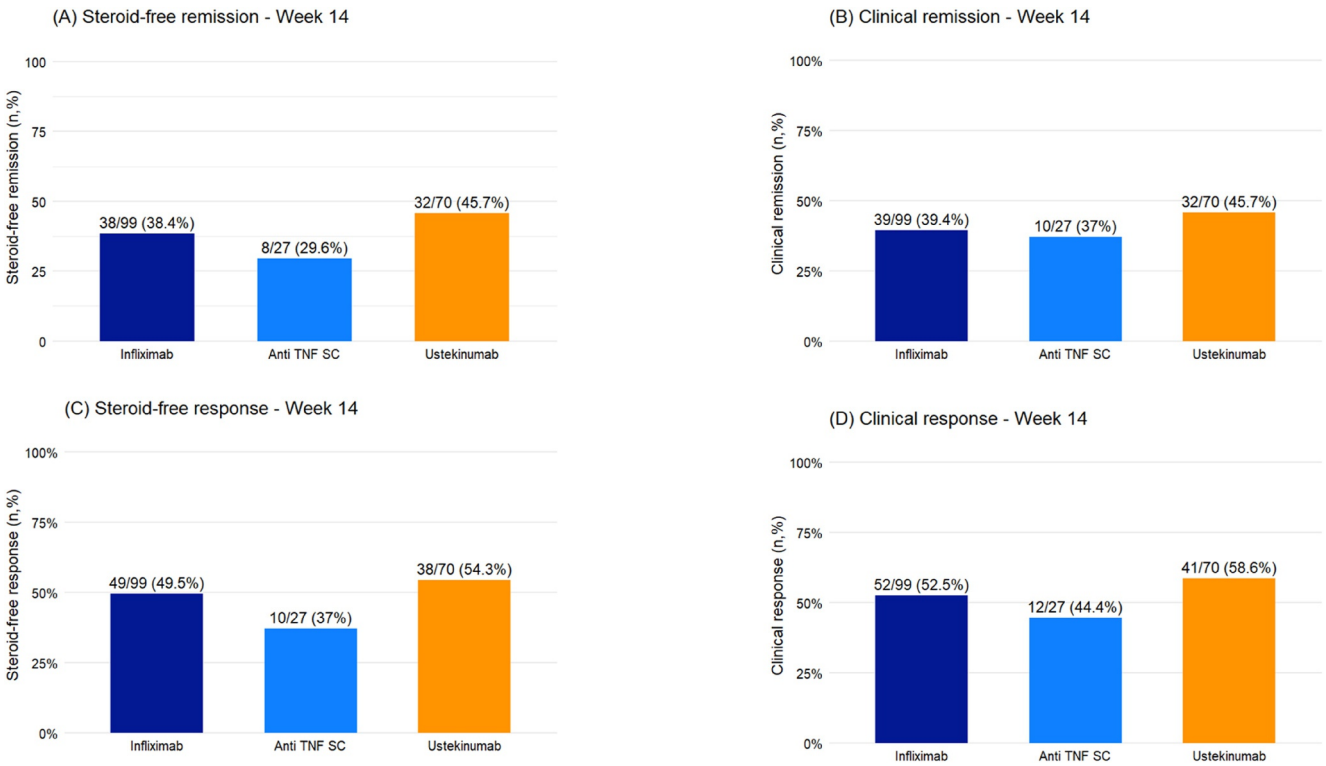

FIGURE 1 | Remission and response rates at 14 weeks across treatment groups. (A) Steroid-free remission, (B) Clinical remission, (C) Steroid-free response, and (D) Clinical response. Data are expressed as n/N (%). Statistical comparisons between treatment groups (Infliximab, anti-TNF SC, and Ustekinumab) were performed using the chi-squared test. *p*-values were as follows: (A) $p = 0.321$, (B) $p = 0.645$, (C) $p = 0.317$, and (D) $p = 0.455$.

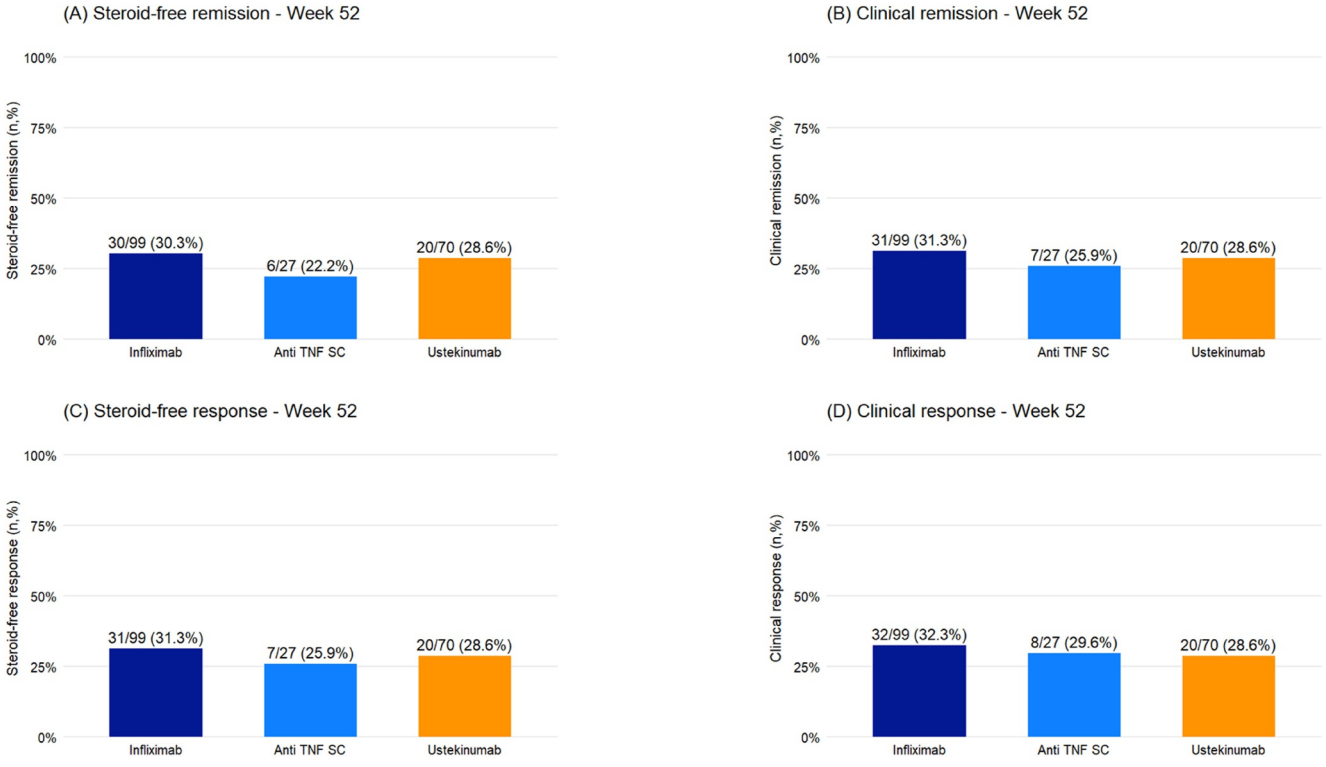

FIGURE 2 | Remission and response rates at 52 weeks across treatment groups. (A) Steroid-free remission, (B) Clinical remission, (C) Steroid-free response, and (D) Clinical response. Data are expressed as n/N (%). Comparisons between treatment groups were performed using the chi-squared test. *p*-values were as follows: (A) $p = 0.740$, (B) $p = 0.864$, (C) $p = 0.866$, and (D) $p = 0.886$.

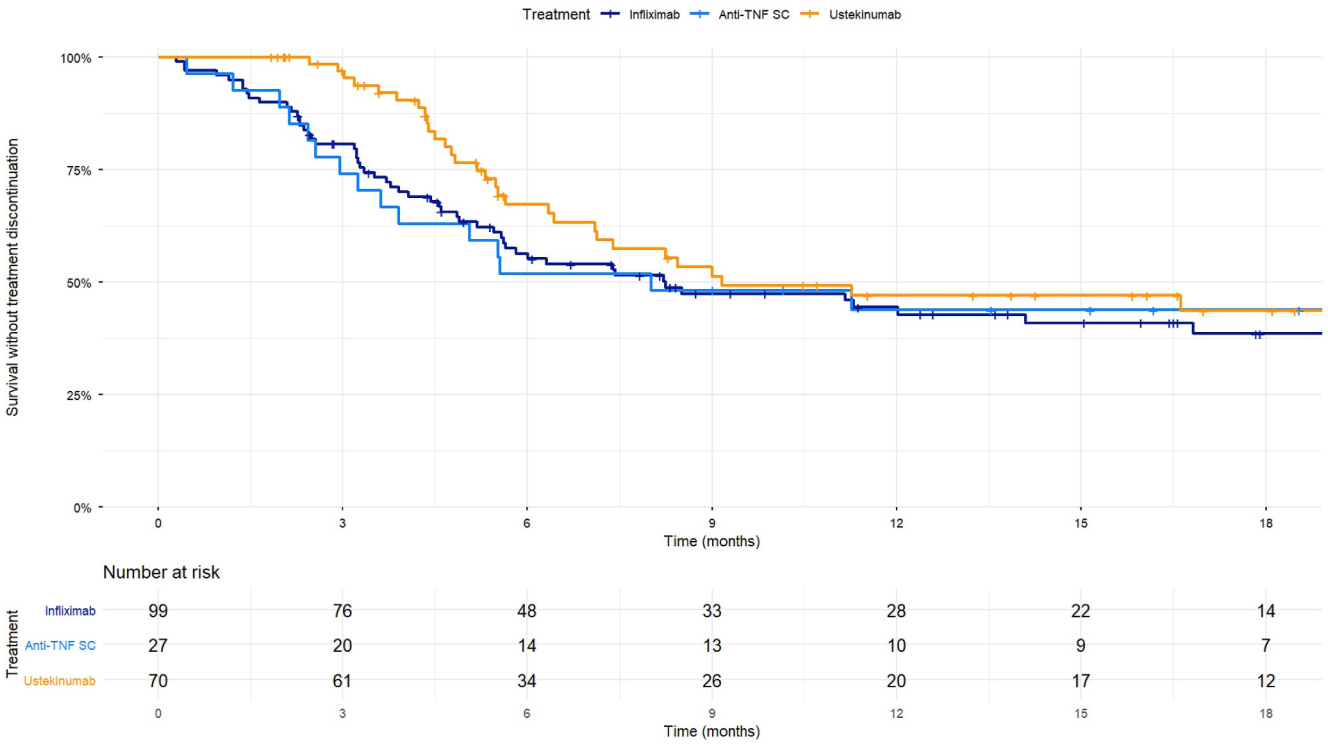

FIGURE 3 | Survival without treatment discontinuation. Kaplan-Meier curves for Infliximab (dark blue), subcutaneous anti-TNF (light blue), and Ustekinumab (orange). The overall median survival was 8.5 months (IQR: 4.2–64.6), with no significant difference between the groups (Log-rank $p = 0.53$). The table indicates the number of patients at risk at each 3-month interval.

treated patients (6.1%), 1 patient on subcutaneous anti-TNF (3.7%), and 1 patient on ustekinumab (1.4%). Serious adverse events occurred in 24 patients (12.2%): 16 receiving infliximab (16.1%, including one COVID-19-related death), 4 receiving subcutaneous anti-TNF (14.8%), and 4 receiving ustekinumab (5.7%), with no statistically significant differences between groups ($p > 0.05$ for all comparisons). Hospitalizations for UC flares occurred in 22.2% of patients treated with infliximab, 22.2% with anti-TNF SC, and 8.6% with ustekinumab. Hospitalization rates were significantly lower with ustekinumab compared with infliximab ($p = 0.02$), with a non-significant trend compared with anti-TNF SC ($p = 0.09$). Four patients (2.0%) underwent colectomy.

4 | Discussion

In this large multicenter real-world cohort, we observed no statistically significant difference in steroid-free clinical remission at week 14 or treatment persistence between infliximab, subcutaneous anti-TNF agents, and ustekinumab when used as second-line therapies after vedolizumab failure in ulcerative colitis. These findings suggest that several advanced therapies may remain effective after vedolizumab failure and that no single option clearly outperforms the others in routine clinical practice.

Our results add to the scarce existing data available in other smaller real-world studies. In a retrospective study of 59 patients with UC, clinical remission on second-line infliximab after vedolizumab was reached in 42% of patients [11]. SFCR at week 52 was also comparable (28.6% for ustekinumab vs. 28.3% for infliximab), suggesting similar effectiveness and persistence between ustekinumab and infliximab as second-line options after vedolizumab failure, consistent with observations in Crohn's disease [12]. In another study comparing persistence rates of vedolizumab or infliximab as first- or second-line treatments in UC, the persistence rate of infliximab at week 52 after vedolizumab failure was 44%, similar to our rate of 44.4% [14]. Chiu et al. reported higher persistence with ustekinumab than with anti-TNFs after vedolizumab (75% vs. 35%; HR = 0.28, 95% CI 0.08–0.996, $p = 0.049$) [15]. Differences likely reflect variations in patient profiles and access to biologics, as our cohort showed higher baseline severity. In contrast, our similar persistence rates for ustekinumab and infliximab suggest that both remain valid second-line options, guided by individual patient factors.

In our multivariate analysis, baseline corticosteroid use was independently associated with a lower likelihood of remission, likely reflecting more severe or refractory disease. Although higher baseline CRP was initially associated with remission, this association was not consistent across sensitivity analyses, suggesting that its predictive value may depend on treatment choice and underlying disease severity rather than acting as an independent marker. These findings underscore the complexity of managing patients after vedolizumab failure, where both patient-specific factors and treatment interactions play a crucial role in determining outcomes.

Adverse events were not uncommon, occurring in 15.8% of patients, and consisted mainly of infections and infusion or allergic reactions. The overall number of adverse events was

TABLE 2 | Univariate and multivariate analysis results for SFCR at week 14.

Variable	OR—univariate [95% CI]	*p*-value - univariate	OR—multivariate [95% CI]	*p*-value - multivariate
Female	1.34 [0.75–2.38]	0.32		
Age at week 0 (+1 year)	1 [0.98–1.01]	0.74		
Smoking status				
Never smoker	Reference			
Active smoker	1.11 [0.30–4.12]	0.88		
Former smoker	1.30 [0.69–2.45]	0.42		
Duration of disease (months)	1.00 [1.00–1.00]	0.19	1.02 [1.00–1.04]	0.29
Disease extent				
E3	Reference		Reference	
E1	1.03 [0.24–4.40]	0.97	1.60 [0.30–7.22]	0.55
E2	**1.89 [1.04-3.43]**	**0.04**	**2.36 [1.23-4.62]**	**0.01**
Cause of vedolizumab discontinuation				
Primary non-response	Reference	Reference	Reference	Reference
Adverse events	3.41 [0.97–12.05]	0.06	3.45 [0.85–16.3]	0.10
Secondary loss of response	0.86 [0.47–1.57]	0.62	0.80 [0.39–1.62]	0.54
Immunosuppressants at baseline	0.87 [0.48–1.59]	0.66		
Corticosteroids at week 0	**0.43 [0.24-0.80]**	**0.01**	**0.37 [0.18-0.73]**	**0.006**
CRP (+1 mg/L)	**1.01 [1.00-1.03]**	**0.03**	**1.02 [1.00-1.04]**	**0.04**
Hemoglobin (+1 g/dL)	0.89 [0.76–1.04]	0.16	0.93 [0.76–1.12]	0.43
Albumin (+1 g/L)	1.00 [0.94–1.06]	0.95		
Mayo score at week 0 (+1 point)	1.04 [0.92–1.18]	0.51		
Treatment				
Infliximab	Reference	Reference	Reference	Reference
TNF SC	0.68 [0.27–1.70]	0.40	0.58 [0.19–1.63]	0.32
Ustekinumab	1.35 [0.73–2.51]	0.34	1.80 [0.87–3.78]	0.11

Note: Factors associated with steroid-free clinical remission (SFCR) were assessed using logistic regression. Only variables with a p-value < 0.2 in the univariate analysis and the treatment groups were included in the multivariate model. Statistically significant predictors in the multivariate analysis ($p < 0.05$) are highlighted in bold.

higher in the infliximab group, likely reflecting its preferential use in patients with more severe disease and higher inflammatory burden, as well as the need for combination therapy. In contrast, the lower frequency of overall adverse events and treatment discontinuations with ustekinumab may be clinically relevant in patients with comorbidities, prior safety issues, or lower tolerance for treatment-related complications. However, the similar rates of serious adverse events and infections across treatments underscore the importance of individualized risk–benefit assessment.

Our study has several strengths including real-world data on a large number of patients in more than 30 centers, increasing external validity and limited selection bias. We provide insights from a follow-up period of 1 year or more, offering valuable long-term perspectives. We provide direct comparisons of second-line therapies after vedolizumab, an approach that is not addressed in randomized controlled trials. Our multivariate analysis identified independent predictors of and incorporated disease severity markers, accounting for complex interactions such as those between treatment and baseline inflammatory markers. However, our study has some limitations. Despite the use of predefined outcome definitions and standardized data collection using an eCRF, its retrospective design resulted in missing data, particularly for fecal calprotectin, endoscopic assessments, and infliximab immunogenicity. Regarding the latter, available results at week 14 revealed a very low rate of detectable antibodies, likely associated with the high rate of combination therapy in this group. In real-world settings, these investigations are more frequently undertaken in patients with ongoing symptoms or suspected active disease, whereas patients in clinical remission are less likely to undergo invasive or repeated assessments. Consequently, their availability data could be influenced by disease severity, introducing a potential bias. For this reason, these variables could not be incorporated into multivariable regression analyses, and study outcomes were primarily defined using validated clinical indices. Additionally, baseline

TABLE 3 | Treatment-related adverse events.

Adverse events	Overall $N = 196$ n (%)	Infliximab $N = 99$ n (%)	TNF SC $N = 27$ n (%)	Ustekinumab $N = 70$ n (%)
Overall events	36 (18.3%)	24 (24.2%)	5 (18.5%)	7 (10%)
Overall patients	31 (15.8%)	19 (19.1%)	5 (18.5%)	7 (10%)[a]
Allergies/Infusion reactions	6 (3.1%)	5 (5.1%)	1 (3.7%)	0 (0%)
Infections				
Including:	19 (9.7%)	12 (12.1%)	3 (11.1%)	4 (5.8%)
Serious[b]	12 (6.1%)	8 (8.1%)	1 (3.7%)	3 (4.3%)
Non-digestive infections	12 (6.1%)	8 (8.1%)	2 (7.4%)	2 (2.9%)
Digestive infections	7 (3.6%)	4 (4.0%)	1 (3.7%)	2 (2.9%)
Cutaneous	4 (2.0%)	3 (3.0%)	1 (3.7%)	0 (0%)
Arthralgia	1 (0.5%)	0 (0%)	0 (0%)	1 (1.4%)
Other	7 (3.6%)	6 (6.1%)	1 (3.7%)	0 (0%)
Serious adverse events[c]	24 (12.2%)	16 (16.1%)	4 (14.8%)	4 (5.7%)
Including deaths[d]	1 (0.5%)	1 (1.0%)	0 (0%)	0 (0%)
Colectomy	4 (2.0%)	2 (2.0%)	0	2 (2.9%)

Note: Safety data for the cohort ($N = 196$) starting second-line therapy. Data are presented as n (%). Multiple events could occur in a single patient. Colectomy was not included in overall events.

[a]When analyzed as total events, overall adverse events were less frequent with ustekinumab than with infliximab (10.0% vs. 24.2%, Fisher's test, $p = 0.02$). In contrast, the proportion of patients experiencing at least one adverse event did not differ significantly between the groups (10.0% vs. 19.1%, $p = 0.131$). There were no statistically significant differences between groups for specific events (all $p > 0.05$).

[b]Serious infections were defined as infections graded ≥ 3 according to the Common Terminology Criteria for Adverse Events (CTCAE) v6.0 (2025).

[c]Defined as death. Life-threatening event. Hospital stay (initial or prolonged). Permanent disability. Congenital abnormality or required intervention to avoid permanent damage or event leading to treatment discontinuation.

[d]One patient died of COVID-19 while treated by Infliximab.

characteristics differed across treatment groups. Patients treated with infliximab had a higher clinical and biological disease activity and more frequent use of combination therapy. Primary non-response to vedolizumab was also more frequent in the infliximab group, likely reflecting preferential use of infliximab in patients with more severe or rapidly progressive disease in real-world practice. However, this imbalance did not appear to affect the primary outcome, as primary non-response was not associated with week-14 steroid-free clinical remission. Although propensity score–based methods could theoretically reduce confounding factors, they were not applied due to limited sample sizes and concerns about model stability. Multivariable analyses adjusting for key markers of disease severity and sensitivity analyses yield consistent results, though residual confounding cannot be fully excluded. Furthermore, our study did not include data on dose optimization strategies, which are known to impact treatment outcomes and may contribute to outcome heterogeneity. Finally, we did not include JAK inhibitors, S1P and anti-IL23 p19 as second-line therapies as they were not reimbursed after vedolizumab without anti-TNF in France, leading to a limited use in routine care and limitations of recruitment.

From a clinical perspective, our findings suggest that selection of a second-line advanced therapy after vedolizumab in UC should primarily rely on individual patient characteristics rather than on an assumed hierarchy of efficacy between biologics. Factors such as disease severity, inflammatory burden, comorbidities, prior safety profile, and patient preference are likely to play a central role. The lower overall adverse event rate observed with ustekinumab may be particularly relevant for patients at higher risk of treatment-related complications, whereas infliximab may remain an appropriate option in patients with high inflammatory burden requiring rapid disease control.

Therefore, our study serves as a valuable addition to the findings of randomized controlled trials. Indirect comparisons in meta-analyses and head-to-head randomized controlled trials are required to validate our results.

5 | Conclusion

Infliximab, anti-TNF SC, and ustekinumab demonstrated close effectiveness, and treatment persistence as second-line advanced therapies for UC after vedolizumab failure. Ustekinumab was associated with fewer overall adverse events than infliximab, whereas rates of serious adverse events were comparable across groups. Multivariate analysis identified baseline corticosteroid use as a negative predictor of remission. These findings emphasize the importance of personalized treatment strategies and highlight the need for prospective studies to guide optimal therapy sequencing.

Author Contributions

Louis Calméjane planned and conducted the study, collected and interpreted data, drafted the manuscript, and approved the final manuscript. Catherine Reenaers collected data and approved the final

manuscript. Claire Gay collected data and approved the final manuscript. Aurélien Amiot collected data and approved the final manuscript. Alexandre Nuzzo collected data and approved the final manuscript. Lucine Vuitton collected data and approved the final manuscript. Calina Atanasiu collected data and approved the final manuscript. Carmen Stefanescu collected data and approved the final manuscript. Romain Altwegg collected data and approved the final manuscript. Lucas Guillo collected data and approved the final manuscript. Mélanie Serrero collected data and approved the final manuscript. Guillaume Bouguen collected data and approved the final manuscript. Maria Nachury collected data and approved the final manuscript. Guillaume Le Cosquer collected data and approved the final manuscript. Xavier Roblin collected data and approved the final manuscript. Vered Abitbol collected data and approved the final manuscript. Nassim Hammoudi collected data and approved the final manuscript. Marion Simon collected data and approved the final manuscript. Mathurin Fumery collected data and approved the final manuscript. Guillaume Savoye collected data and approved the final manuscript. Alban Benezech collected data and approved the final manuscript. Maryan Cavicchi collected data and approved the final manuscript. Maeva Charkaoui collected data and approved the final manuscript. Anthony Buisson collected data and approved the final manuscript. Bénédicte Caron collected data and approved the final manuscript. Benoît Coffin collected data and approved the final manuscript. Sophie Geyl collected data and approved the final manuscript. Félix Goutorbe collected data and approved the final manuscript. Marianne Hupé collected data and approved the final manuscript. Mathias Vidon collected data and approved the final manuscript. David Laharie collected data and approved the final manuscript. Julien Kirchgesner collected and interpreted data and approved the final manuscript. Mathieu Uzzan planned and conducted the study, collected and interpreted data, drafted the manuscript, and approved the final manuscript.

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Conflicts of Interest

Louis Calméjane reports no competing interests. Julien Kirchgesner declares lecture fees from Janssen and Lilly; and consulting fees from Roche, Pfizer, Janssen, AbbVie, Takeda, Lilly, Celltrion, Tillots, and Galapagos. Mathieu Uzzan declares board or lecture fees from AbbVie, Janssen, Pfizer, Takeda, Celltrion, Amgen, and Ferring.

All coauthors' competing interests statements are available in Supporting Information S1.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supporting Information S1: ueg270203-sup-0001-suppl-data.docx. **Supporting Information S2:** ueg270203-sup-0002-suppl-data.docx. **Figure S1:** Study flow-chart. **Figure S2:** Hazard ratios for treatment discontinuation. **Figure S3:** Factors associated with clinical remission at week 14 (multivariate analysis). **Table S1:** Causes of second-line treatment discontinuation. **Table S2:** Sensitivity analysis of factors associated with clinical remission at week 14 (CRP threshold at 30 mg/L). **Table S3:** Sensitivity analysis of factors associated with clinical remission at week 14, including baseline immunosuppressant use. **Table S4:** Sensitivity analysis evaluating the interaction between treatment groups and baseline CRP.

Appendix

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