ORIGINAL ARTICLE

Comparative Long-Term Drug Survival of Vedolizumab, Adalimumab, and Infliximab in Biologic-Naïve Patients with Ulcerative Colitis

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Abstract

Background The comparative long-term survival of first-line biologics for UC and reasons for drug discontinuation are poorly understood. We sought to compare the long-term drug survival related to non-response (NR) and adverse effects (AEs) for vedolizumab, adalimumab, and infliximab among biologic-naïve patients with UC.

Methods This was a retrospective cohort study of adult biologic-naïve patients with moderate-to-severe UC initiating vedolizumab, adalimumab, or infliximab 6/1/14–12/31/20 at a large academic medical center. The primary outcome was time to biologic discontinuation for primary or secondary NR (including colectomy). The secondary outcome was time to biologic discontinuation due to AEs. Inverse probability of treatment-weighted (IPTW) Cox regression was used to perform three pair-wise comparisons of drug survival.

Results The cohort included 805 patients with UC who initiated vedolizumab ($n = 195$), adalimumab ($n = 278$), or infliximab ($n = 332$). The adjusted hazard of biologic discontinuation for NR was significantly lower for vedolizumab vs adalimumab (HR 0.51, 95% CI 0.34–0.75), similar for vedolizumab vs infliximab (HR 1.32, 95% CI 0.79–2.18), and greater for adalimumab vs infliximab (HR 2.07, 95% CI 1.51–2.86). The adjusted hazard of discontinuation for AEs was significantly lower for vedolizumab vs adalimumab (HR 0.25, 95% CI 0.09–0.64), lower for vedolizumab vs infliximab (HR 0.21, 95% CI 0.10–0.46), and similar for adalimumab vs infliximab (HR 0.85, 95% CI 0.53–1.35).

Conclusions There was greater survival of vedolizumab compared to adalimumab for clinical response and greater survival of vedolizumab compared to both adalimumab and infliximab for AEs. These long-term data support the use of vedolizumab as a first-line biologic over adalimumab for biologic-naïve patients with UC.

Keywords Inflammatory bowel disease · Anti-TNF · Anti-integrin · Survival · Remission · Failure

Introduction

Biologic therapy is essential to the management of moderate-to-severe ulcerative colitis (UC) [1]. According to clinical guidelines, first-line biologic agents for UC include vedolizumab, a gut-selective integrin antagonist, and the more systemically active anti-tumor necrosis factor α (TNFα) agent infliximab [2]. Adalimumab can be considered as an alternative first-line anti-TNFα agent [2]. This positioning was influenced by the only head-to-head clinical trial of biologics in UC, which demonstrated the superiority of vedolizumab to adalimumab in achieving clinical remission, but not corticosteroid-free clinical remission, at 52 weeks [3]. Singh and colleagues [4] conducted a systematic review and network meta-analysis of clinical trials that identified infliximab as the preferred biologic for induction of remission in biologic-naïve patients with UC. However, when considering diverse patient characteristics and risk factors that are poorly represented in clinical trials, the optimal real-world positioning of these agents is unclear.

In contrast to Singh et al. [4], real-world comparative data of first-line biologics in UC suggest similar or better clinical efficacy of vedolizumab compared to anti-TNFα agents. Several small, retrospective studies with 12 or fewer months of follow-up reported no differences in clinical efficacy [5–8]. A recent multinational study of biologic-naïve patients found greater treatment persistence,

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fewer disease exacerbations, and similar rates of adverse events at 24 months with vedolizumab compared to anti-TNFα agents [9]. However, most real-world studies with long-term follow-up have not analyzed infliximab and subcutaneous anti-TNFα agents separately, likely due to sample size limitations [5, 9–14].

A growing body of evidence suggests that vedolizumab is more clinically effective and safer in the biologic-naïve than in individuals with prior anti-TNFα exposure [15–19]. Therefore, a better understanding of the relative long-term durability of vedolizumab as a first-line agent is imperative to optimize its positioning and therapeutic potential. To address this need, we performed a real-world retrospective cohort study comparing the long-term drug survival of vedolizumab, adalimumab, and infliximab initiated between 2014 and 2020 among biologic-naïve patients with UC. We separately assessed drug survival related to non-response (NR) and drug survival related to adverse effects (AEs). We also compared reasons for biologic discontinuation and proportions of clinical and endoscopic remission at 24 and 48 months.

Materials and Methods

Study Design and Patient Selection

This was a retrospective cohort study of adult biologic-naïve patients with UC (ICD-10-CM 51x) who initiated vedolizumab, adalimumab, or infliximab between 6/1/2014–12/31/3020 at Brigham and Women's Hospital (Boston, MA, USA), Massachusetts General Hospital (Boston, MA, USA), or affiliate hospitals (MA, USA). Electronic health records were manually reviewed for clinical, endoscopic, prescription, and laboratory data. Patients were initiated on biologic therapy per provider assessment of moderate-to-severe UC, which could include endoscopic, biochemical, and/or clinical parameters. Patients with Crohn's disease, inflammatory bowel disease unclassified (IBDU), prior biologic exposures or colectomy, and those who initiated biologic agents for non-UC indications were excluded. Patients were followed until biologic discontinuation or the last available gastroenterology encounter through 8/1/21, which was the preset end date of eligible clinical data for chart review. The date of biologic discontinuation was defined as the earliest of the following: the first missed due date of biologic administration among those with at least two consecutive missed doses, the date of switch to a new biologic agent, or colectomy. The primary documented reason for biologic discontinuation was extracted from gastroenterology clinic notes (Supplementary Methods).

Outcomes

The primary outcome was time from biologic initiation to discontinuation due to primary or secondary NR. For this outcome, patients who required colectomy for refractory UC within 6 weeks after biologic initiation (i.e., prior to completion of induction) were excluded. This strategy eliminates bias from the most refractory cases of acute severe UC where infliximab is disproportionately utilized in our health system. The secondary outcome was time to biologic discontinuation due to an adverse effect (AE), which was extracted from gastroenterology clinic notes. Specific AEs that led to biologic discontinuation were characterized as any of the following: acute reaction (onset of symptoms within 24 h of administration, including anaphylaxis), joint/soft tissue (arthralgia, arthritis, myalgias, soft tissue swelling, or lupus-like reactions), subacute rash (onset > 24 h after administration), infection, elevated liver enzymes, neurologic (headache, seizure, or sensory disturbance), malignancy, pulmonary (pneumonitis or interstitial lung disease), renal (interstitial nephritis), vascular (vasculitis or thromboembolism), weight gain, and other non-acute signs or symptoms reported.

Additional outcomes included corticosteroid-free clinical remission (CFCR) and deep remission (DR; defined as CFCR with endoscopic mucosal healing with Mayo endoscopic subscore ≤ 1) at 24 months and 48 months after biologic initiation. CFCR was defined as no use of systemic corticosteroids or oral budesonide for at least 30 days after achieving clinical remission (simple clinical colitis activity index [SCCAI] ≤ 2, 9-point Mayo score ≤ 2, or gastroenterology provider documentation of "remission" when the aforementioned indices were not documented). Due to variability in timing of clinical and endoscopic assessments, 24 and 48 month outcomes were based on the closest available data within 6 months of these endpoints. However, only patients with a minimum of 24 and 48 months of potential follow-up between biologic initiation and 8/1/21 were eligible for these outcome assessments. Patients who discontinued therapy due to an AE prior to these time points and those who underwent colectomy for refractory disease within 6 weeks after biologic initiation were ineligible for these outcomes. Lastly, data were obtained regarding the primary documented reason for biologic discontinuation (Supplementary Methods) and regarding dose escalation, defined as any dose increase or dose interval reduction of the biologic for at least two consecutive doses.

Independent Variables

The primary exposure was choice of biologic (vedolizumab, adalimumab, or infliximab). Other baseline independent variables included demographics, concomitant medications (corticosteroids and immunomodulators), Mayo endoscopic subscore, disease extent, and other factors related to IBD severity (Supplementary Methods).

Statistical Analysis

Continuous and categorical data were compared using the Kruskal–Wallis and Chi-squared tests, respectively. Kaplan–Meier (KM) analyses with log-rank tests stratified by biologic therapy were performed for overall drug survival and time to discontinuation for NR and AEs. Patients were censored at loss of follow-up, biologic discontinuation for reasons other than the outcome being assessed, colectomy, or death.

To adjust for treatment selection bias, inverse probability of treatment weighting (IPTW) using propensity scores was performed for the three pairwise comparisons of vedolizumab vs adalimumab, vedolizumab vs infliximab, and adalimumab vs infliximab. IPTW was preferred over propensity score matching in order to maximize the statistical power for each comparison. Propensity scores were calculated using logistic regression of biologic choice on the following covariates selected a priori: age, sex, Caucasian race, BMI, disease duration > 5 years (dichotomized using median value), concomitant corticosteroid use (prednisone, methylprednisolone, or oral budesonide) at the time of biologic initiation, concomitant immunomodulator use, any UC-related hospitalization within the prior 12 months, last Mayo endoscopic subscore (3 versus < 3), last Montreal disease extent (> E1 versus ≤ E1), serum albumin, and history of malignancy. Covariate balance was assessed using standardized mean differences. SCCAI was excluded from propensity score calculations due to missing data in > 20% of the sample; however a sensitivity analysis was performed with SCCAI added as a separate covariate to the IPTW Cox regression models for NR. Propensity scores involving vedolizumab also incorporated biologic initiation two years after the date of FDA approval (May 20, 2014) of vedolizumab as a binary covariate to account for the delay in uptake of vedolizumab prescribing. Two years was specifically chosen as more than 90% of vedolizumab-treated patients in the cohort were prescribed the biologic after this time. The proportional hazards assumption was confirmed using Schoenfeld residuals.

Unadjusted and adjusted odds ratios were calculated using logistic regression of unweighted and IPT-weighted samples to determine the associations between choice of biologic with CFCR and DR at 24 and 48 months. P-values below 0.05 were considered statistically significant. Data regarding treatment discontinuation, types of AEs, and dose escalation are intended to be descriptive, and therefore p-values were not calculated. STATA/SE 17.0 (College Station, TX) was used for all analyses.

Results

Cohort Characteristics

The cohort included 805 patients with UC who initiated vedolizumab ($n = 195$), adalimumab ($n = 278$), or infliximab ($n = 332$). There were significant differences in age, BMI, malignancy history, concomitant immunomodulator and corticosteroid use, endoscopic inflammation and extent, albumin, CRP, bowel frequency, SCCAI, and UC hospitalizations within 12 months prior to biologic initiation (Table 1).

Drug Survival

The proportions of patients who discontinued therapy during follow-up were 76/195 (39.0%) for vedolizumab, 180/278 (64.8%) for adalimumab, and 175/332 (52.7%) for infliximab. Median time until discontinuation or censoring was 587 (IQR 254–956) days for vedolizumab, 286.5 (119–1132) days for adalimumab, and 473.5 (IQR 165–1063.5) days for infliximab. Among those who discontinued therapy (431/805), the common reasons were NR (63.8%), AEs (26.0%), and non-adherence (5.3%) (Fig. 1).

KM analysis of overall drug survival demonstrated the greatest drug survival for vedolizumab (log-rank test $p < 0.01$; Fig. 2a). KM analysis for NR demonstrated greater drug survival of vedolizumab and infliximab relative to adalimumab (log-rank test $p < 0.01$; Fig. 2b) and KM analysis for AEs demonstrated the greatest drug survival for vedolizumab (log-rank test $p < 0.01$; Fig. 2c). Among those who discontinued therapy for AEs ($n = 112$), the most common reported AEs were joint/soft tissue (21.4%), acute reaction (18.8%), and subacute rash (18.8%) (Fig. 3). No adverse effects in this study were associated with patient death.

There were complete covariate data for 728/805 (90.4%) patients. Covariate balance after IPTW was confirmed with < 10% absolute standardized differences across all covariates (Fig. 4). For the NR analysis, an additional 13 patients (1 vedolizumab, 1 adalimumab, 11 infliximab) were excluded due to colectomy within 6 weeks after biologic initiation. The IPTW Cox models demonstrated a significantly lower hazard of discontinuation for NR for vedolizumab vs adalimumab (HR 0.51, 95% CI 0.34–0.75), greater hazard for adalimumab vs infliximab (HR 2.08, 95% CI 1.51–2.86), and similar hazard for vedolizumab vs infliximab (HR 1.32, 95% CI 0.79–2.18). The sensitivity analysis for NR, which added SCCAI as a covariate in the IPTW Cox models,

Table 1 Baseline characteristics

| Characteristic	Vedolizumab	Adalimumab	Infliximab	P-value
N†	195	278	332	
Follow-up time until discontinuation/censoring, d, median (IQR)	587 (254, 956)	286.5 (119, 1132)	473.5 (165, 1063.5)	
Age, y, median (IQR)	48 (31, 64)	36 (26, 50)	34 (26, 51)	<0.001
Female sex	108 (55.4%)	148 (53.2%)	185 (55.7%)	0.81
Race				
White, non-Hispanic	177 (90.8%)	243 (87.4%)	286 (86.1%)	0.51
Hispanic	5 (2.6%)	6 (2.2%)	10 (3.0%)	
Black, non-Hispanic	5 (2.6%)	6 (2.2%)	15 (4.5%)	
Asian, non-Hispanic	4 (2.1%)	11 (4.0%)	10 (3.0%)	
Native American or Hawaiian	1 (0.5%)	0 (0.0%)	1 (0.3%)	
Unknown	3 (1.5%)	12 (4.3%)	10 (3.0%)	
BMI, kg/m2, median (IQR), n = 194, 268, 316	24.5 (21.8, 27.6)	25.4 (22.2, 28.75)	24.0 (21.1, 27.5)	0.013
Disease duration, y, median	7 (2, 18)	5 (2, 11)	3 (1, 10)	<0.001
History of malignancy	61 (31.3%)	25 (9.0%)	33 (9.9%)	<0.001
Concomitant immunomodulator				
None	172 (88.2%)	221 (79.5%)	286 (86.1%)	0.022
Thiopurine	18 (9.2%)	53 (19.1%)	42 (12.7%)	
Methotrexate	5 (2.6%)	4 (1.4%)	4 (1.2%)	
Concomitant corticosteroids				
None	77 (39.5%)	64 (23.0%)	40 (12.0%)	<0.001
Systemic (prednisone or methylprednisolone)	84 (43.1%)	164 (59.0%)	266 (80.1%)	
Oral budesonide	26 (13.3%)	42 (15.1%)	20 (6.0%)	
Corticosteroid enemas only	8 (4.1%)	8 (2.9%)	6 (1.8%)	
Current smoking	3 (1.5%)	11 (4.0%)	16 (4.8%)	0.15
Current cannabis	16 (8.2%)	44 (15.8%)	31 (9.3%)	0.012
Current opioids	10 (5.1%)	15 (5.4%)	29 (8.7%)	0.16
Mayo endoscopic subscore, n = 193, 273, 327				
0 (remission)	12 (6.2%)	11 (4.0%)	9 (2.8%)	<0.001
1 (mild)	47 (24.4%)	64 (23.4%)	30 (9.2%)	
2 (moderate)	95 (49.2%)	151 (55.3%)	138 (42.2%)	
3 (severe)	39 (20.2%)	47 (17.2%)	150 (45.9%)	
Montreal disease extent > E1 (proctitis), n = 194, 276, 328	158 (81.4%)	240 (87.0%)	304 (92.7%)	<0.001
Albumin, g/dL, median (IQR), n = 188, 255, 311	4.2 (3.8, 4.5)	4.2 (3.7, 4.5)	3.8 (3.2, 4.2)	<0.001
CRP, mg/dL, median (IQR), n = 171, 213, 283	2.7 (1, 8.5)	3.6 (1.3, 13.8)	10.6 (2.3, 48.6)	<0.001
Fecal calprotectin > 120 ug/g, n = 74, 56, 90	59 (80%)	46 (82%)	81 (90%)	0.16
Daily bowel frequency, median (IQR), n = 170, 207, 263	4 (2, 6)	5 (3, 9)	8 (5, 11)	<0.001
SCCAI, median (IQR), n = 168, 204, 248	4 (2, 6)	4 (2, 7)	8 (4, 10)	<0.001
UC hospitalization within prior 12 months	27 (13.8%)	70 (25.2%)	186 (56.0%)	<0.001

†Total sample size unless otherwise specified due to missing data

TNF = tumor necrosis factor, IQR = interquartile range, BMI = body mass index, CRP = C-reactive protein, SCCAI = simple clinical colitis activity index

demonstrated similar results for vedolizumab vs adalimumab (HR 0.53, 95% CI 0.35–0.82) and adalimumab vs infliximab (2.62, 95% CI 1.78–3.86), but a significantly greater hazard for vedolizumab vs infliximab (2.14, 95% CI 1.17–3.93).

For the AE analysis, IPTW Cox models demonstrated significantly lower hazard of discontinuation for vedolizumab vs adalimumab (HR 0.25, 95% CI 0.09–0.64), similar hazard for adalimumab vs infliximab (HR 0.85, 95% CI 0.53–1.35), and lower hazard for vedolizumab vs infliximab (HR 0.21, 95% CI 0.10–0.46). The complete unweighted and weighted Cox proportional hazard models for NR and AEs are presented in Table 2.
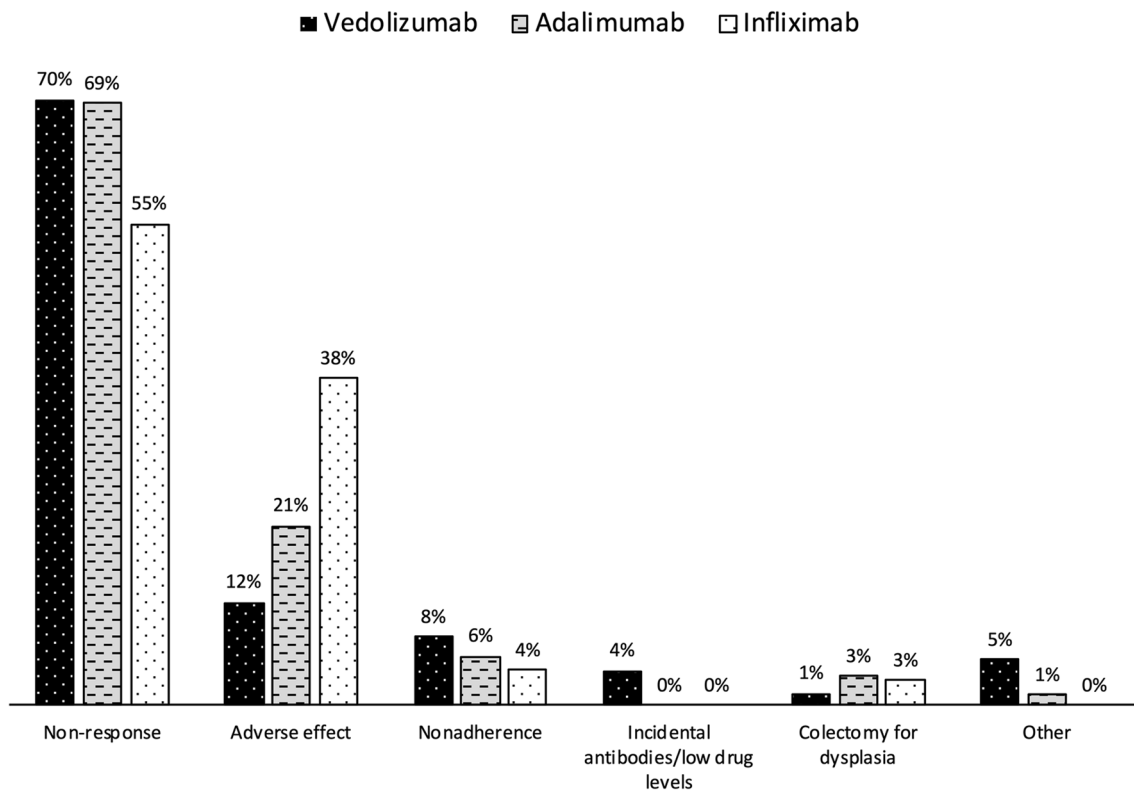
Fig. 1 Reasons for biologic discontinuation. Percentages are derived from the sums of patients who discontinued each biologic agent separately (*n* = 76 vedolizumab, 180 adalimumab, 175 infliximab)

24- and 48-Month Outcomes

Proportions of eligible patients achieving CFCR at 24 months were 61/104 (58.7%) for vedolizumab, 74/182 (40.7%) for adalimumab, and 112/178 (62.9%) for infliximab (*p* < 0.01). Proportions for deep remission at 24 months proportions were 38/89 (41.8%) for vedolizumab, 61/177 (34.5%) for adalimumab, and 76/153 (49.7%) for infliximab (*p* = 0.021). Proportions for CFCR at 48 months were 12/23 (52.2%) for vedolizumab, 31/103 (30.1%) for adalimumab, and 45/87 (51.7%) for infliximab (*p* < 0.01). Proportions for deep remission at 48 months were 10/22 (45.5%) for vedolizumab, 18/90 (20.0%) for adalimumab, and 28/73 (38.4%) for infliximab (*p* < 0.01) (Fig. 5).

For vedolizumab vs adalimumab, IPTW logistic regression demonstrated significantly greater odds of CFCR at 24 months (OR 1.99, 95% CI 1.11–3.54) and deep remission at 48 months (OR 4.06, 95% CI 1.28–12.94). For adalimumab vs infliximab, there was significantly lower odds of CFCR at 24 months (OR 0.39, 95% CI 0.24–0.64), DR at 24 months (0.50, 95% CI 0.30–0.83), CFCR at 48 months (OR 0.44, 95% CI 0.22–0.86), and DR at 48 months (OR 0.34, 95% CI 0.16–0.76). Other biologic comparisons for CFCR and DR at 24 months and 48 months (Supplementary Table) were not statistically significant.

Dose Escalation

Proportions of patients who underwent dose escalation during follow-up were 79/195 (40.5%) after a median of 110 days (IQR 57–274 days) for vedolizumab, 101/278 (36.3%) after a median of 138 days (IQR 65–358 days) for adalimumab, and 210/332 (63.3%) after a median of 207 days (IQR 133.5–410 days) for infliximab.

Discussion

In this real-world study with up to 6 years of clinical follow-up, vedolizumab demonstrated the greatest overall drug survival for biologic-naïve patients with UC. When considering drug survival related only to NR, vedolizumab was superior to adalimumab, infliximab was superior to adalimumab, and vedolizumab was similar to infliximab after IPTW to control for treatment selection bias. In our sensitivity analysis that also controlled for baseline SCCAI (for the subset of patients with this data available), results were similar except infliximab was found to be superior to vedolizumab, which could represent residual confounding by indication for this comparison of NR. However, like other clinical disease activity scores, the SCCAI is comprised of
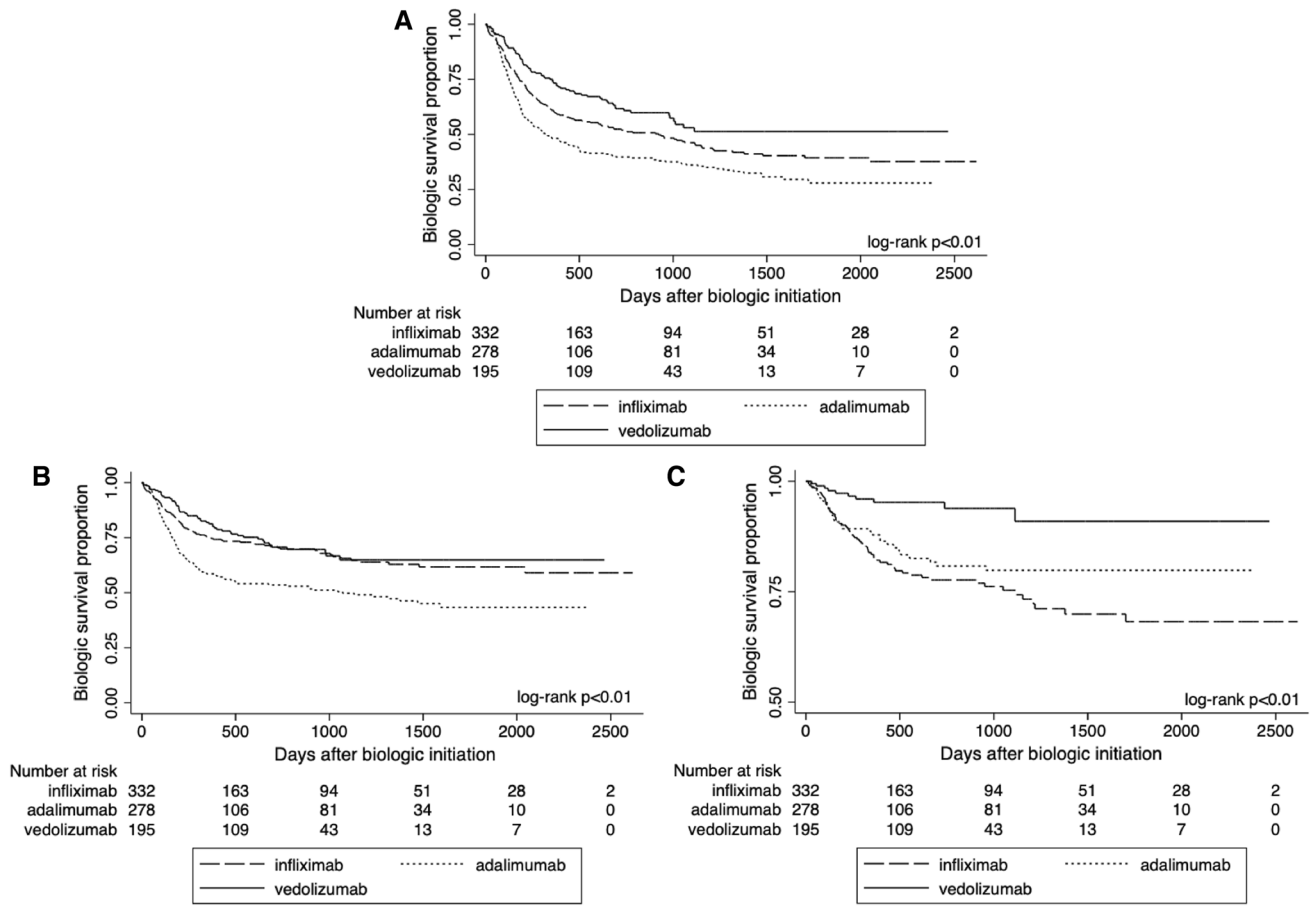
Fig. 2 Kaplan–Meier analyses for biologic survival. **A** Overall survival. **B** Survival related to non-response. **C** Survival related to adverse effects. Patients were censored at loss of follow-up, biologic discontinuation for reasons other than the outcome assessed, colectomy, or death
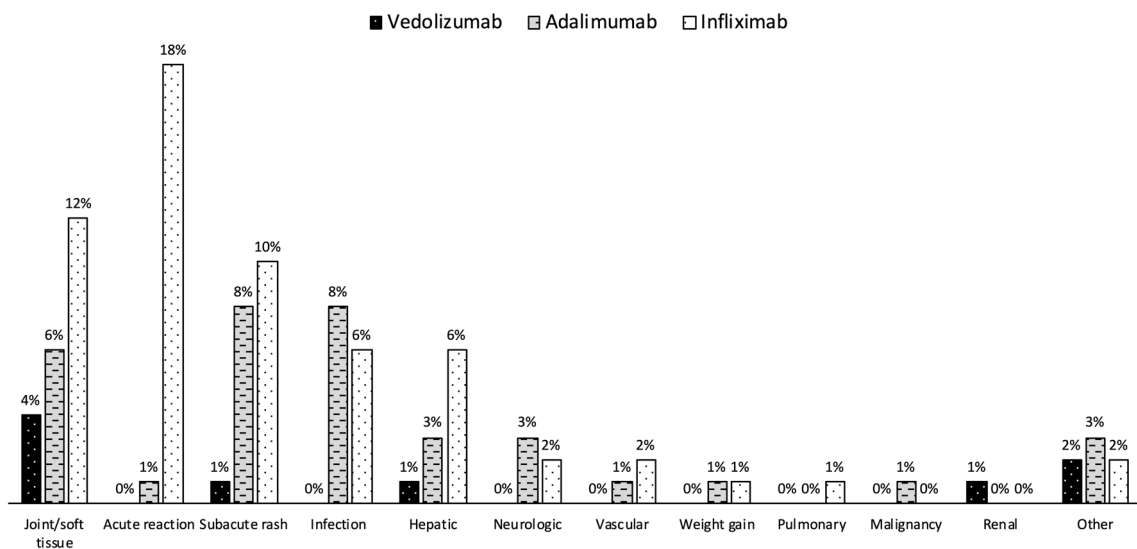
Fig. 3 Distribution of adverse effects. Percentages are derived from the sum of all adverse effects in the cohort ($n = 112$)
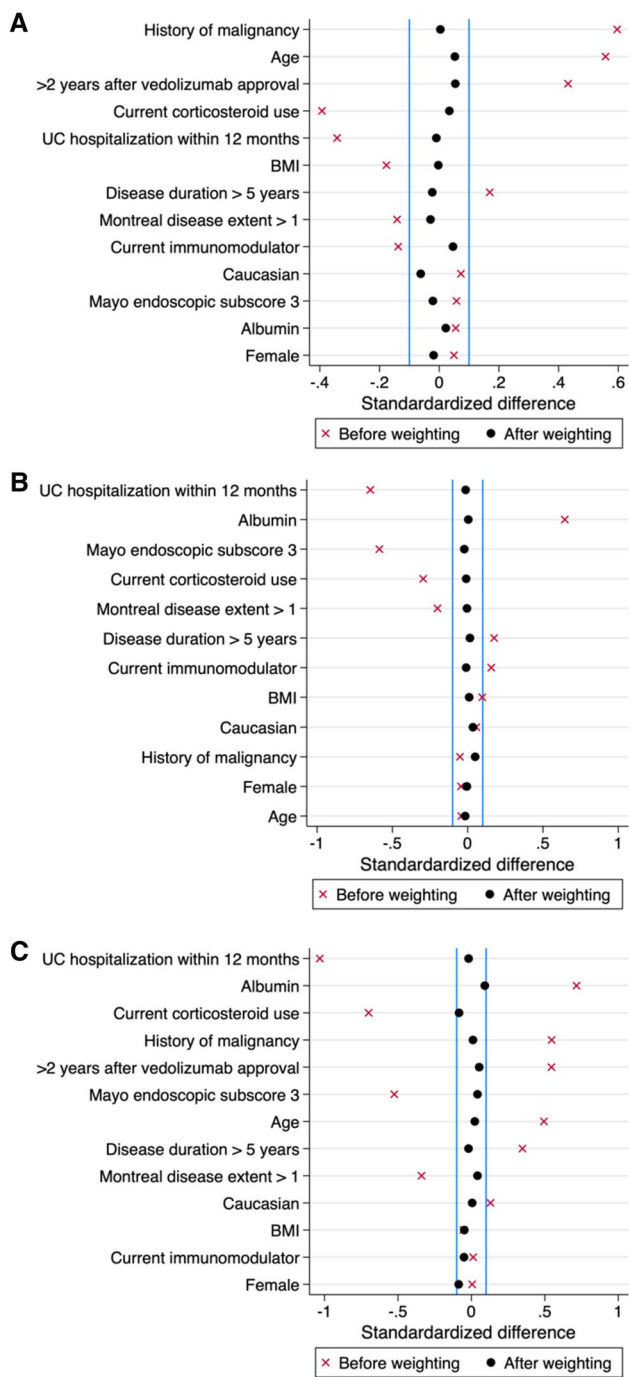
Fig. 4 Standardized mean differences of covariates before and after inverse probability of treatment weighting. **A** Vedolizumab vs adalimumab. **B** Adalimumab vs infliximab. **C** Vedolizumab vs infliximab. Abbreviations: BMI = body mass index

subjective, patient-reported data that may be less reliable than other covariates.

When considering drug survival related only to AEs, which is likely less susceptible to confounding by indication, vedolizumab was superior to both adalimumab and infliximab. Vedolizumab therapy was also associated with

a greater weighted odds of CFCR at 24 months and DR at 48 months when compared to adalimumab but performed similarly to infliximab. Adalimumab was associated with a lower weighted odds of CFCR and DR compared to infliximab at both time points. The lower rate of AEs with vedolizumab compared to adalimumab is not felt to be related to the higher rate of CFCR with vedolizumab, as patients who discontinued therapy due to an AE prior to 24 or 48 months were not eligible for the analysis of the corresponding CFCR and DR outcomes.

Few real-world UC studies to-date have examined differences in long-term efficacy between vedolizumab and specific anti-TNFα therapies for the biologic-naïve [10, 12, 19]. In the multicenter cohort study by Lukin et al. [10], vedolizumab-treated patients achieved CFCR and DR at higher rates compared to infliximab and sub-cutaneous anti-TNFα therapies. However, only 303/722 (41.9%) patients were biologic-naïve, limiting conclusions that can be drawn for this population. CFCR and DR were also assessed as time-to-event analyses, which may introduce bias. Retrospective study designs are subject to inaccuracies in the time of remission outcomes, as they depend entirely on the scheduling of follow-up clinical assessments that may vary due to patient, provider, and institutional factors. Patients may therefore achieve clinical remission several weeks before it is documented in a clinic visit. For this reason, we chose discrete events (i.e., date of biologic discontinuation) for our survival analyses that maximized precision.

A recent population-based registry study in Australia compared the 12-month persistence of vedolizumab, adalimumab, and infliximab among 864 patients with UC, among which 632 were biologic-naïve [19]. Similar to our findings, vedolizumab demonstrated the greatest treatment persistence. However, in line with the limitations of other database studies, the authors were unable to determine the specific reasons for drug discontinuation and baseline disease severity variables with known prognostic impact, such as corticosteroid use, endoscopic inflammation, disease activity scores, or biochemical markers, which may confound their results [20, 21].

Our study has several strengths. We include separate comparisons of treatment persistence for vedolizumab versus specific anti-TNFα agents, whereas many similar studies to-date have compared only classes of biologic therapy [5, 9, 11, 14]. Consequently, our study identified differential treatment persistence by specific agents within the anti-TNFα class. Unlike other studies of overall treatment persistence, this study also distinguished persistence related to NR and persistence related to AEs. We were able to include specific variables related to baseline UC activity such as endoscopic severity and extent, BMI, and albumin, among other factors which were not available in prior database studies that have attempted to answer similar questions [5, 12]. While there

Table 2 Cox proportional hazard models of biologic survival

Non-response models	Unweighted HR (95% CI)	*P*-value	Weighted HR (95% CI)	*P*-value
Vedolizumab vs adalimumab	0.48 (0.35–0.67)	<0.001	0.50 (0.34–0.75)	0.001
Adalimumab vs infliximab	1.95 (1.46–2.57)	<0.001	2.08 (1.51–2.86)	<0.001
Vedolizumab vs infliximab	0.96 (0.68–1.36)	0.827	1.32 (0.79–2.18)	0.287
Non-response with SCCAI models (sensitivity analysis)	Unweighted HR (95% CI)	*P*-value	Weighted HR (95% CI)	*P*-value
Vedolizumab vs adalimumab	–	–	0.54 (0.35–0.82)	0.004
SCCAI	–	–	1.09 (1.03–1.16)	0.002
Adalimumab vs infliximab	–	–	2.62 (1.78–3.86)	<0.001
SCCAI	–	–	1.06 (1.01–1.12)	0.022
Vedolizumab vs infliximab	–	–	2.14 (1.17–3.93)	0.014
SCCAI	–	–	1.12 (1.04–1.21)	0.002
Adverse effect models	Unweighted HR (95% CI)	P-value	Weighted HR (95% CI)	P-value
Vedolizumab vs adalimumab	0.32 (0.16–0.65)	0.001	0.25 (0.09–0.64)	0.004
Adalimumab vs infliximab	0.75 (0.50–1.13)	0.167	0.85 (0.53–1.35)	0.483
Vedolizumab vs infliximab	0.25 (0.13–0.48)	<0.001	0.21 (0.10–0.46)	<0.001

HR = hazard ratio, CI = confidence interval, SCCAI = simple clinical colitis activity index

Fig. 5 24- and 48-month outcomes. For CFCR at 24 months, eligible $n = 104$ vedolizumab, 182 adalimumab, 178 infliximab. For DR at 24 months, eligible $n = 89$ vedolizumab, 177 adalimumab, 153 infliximab. For CFCR at 48 months, eligible $n = 23$ vedolizumab, 103 adalimumab, 87 infliximab. For DR at 48 months, eligible $n = 22$ vedolizumab, 90 adalimumab, 73 infliximab. Abbreviations: CFCR = corticosteroid-free clinical remission, DR = deep remission
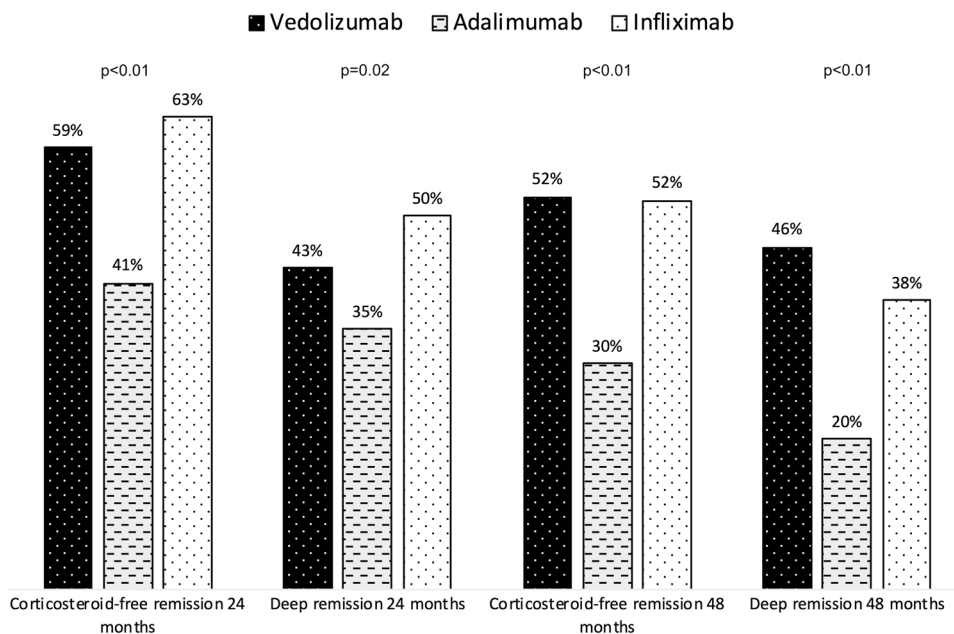
were differences in baseline factors that likely represent clinically significant differences in disease severity, IPTW successfully balanced these covariates to minimize confounding by indication in our regression analyses. We also provided granular detail regarding specific AEs that led to treatment discontinuation, which improves our understanding about the real-world risks associated with first-line biologics. Studies that report serious AEs may utilize inconsistent and subjective definitions for this outcome, whereas AEs leading to biologic discontinuation may be less prone to bias.

Limitations include the retrospective design and potential for missing data, though there were complete covariate data for >90% of the cohort. The study took place at a large, urban academic referral center, and therefore results may be less generalizable to other settings. Assessment of baseline characteristics suggests significantly greater disease severity in the infliximab group compared to adalimumab and vedolizumab. While covariates were balanced after IPTW, unmeasured confounding may still exist. To further mitigate confounding by indication, the NR analysis excluded patients

with failure of therapy within the first 6 weeks. This limits potential bias against infliximab, which, due to its rapid onset of action, is utilized disproportionately for patients with acute severe colitis who may be more likely to fail all medical therapies. While the overall cohort is large ($n = 805$), results of the 48-month outcome analyses are subject to type II error, as only 213 patients were eligible among which 23 were treated with vedolizumab. Finally, the study lacks detailed data regarding therapeutic drug monitoring, which should be prioritized in future prospective studies.

Conclusion

In summary, this study identified greater drug survival of vedolizumab compared to adalimumab but not infliximab for NR and greater drug survival of vedolizumab compared to both adalimumab and infliximab for AEs. Vedolizumab was also associated with greater odds of CFCR at 24 months and DR at 48 months compared to adalimumab but not infliximab. Infliximab was superior to adalimumab for drug survival related to NR and CFCR and DR at 24 and 48 months. These long-term data support the use of vedolizumab as a first-line biologic over adalimumab while suggesting differential durability and efficacy within the anti-TNFα class for biologic-naïve patients with UC.

Declarations

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