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Long-Term Safety of Vedolizumab in Patients With Ulcerative Colitis/Crohn's Disease: A Prospective Observational Study

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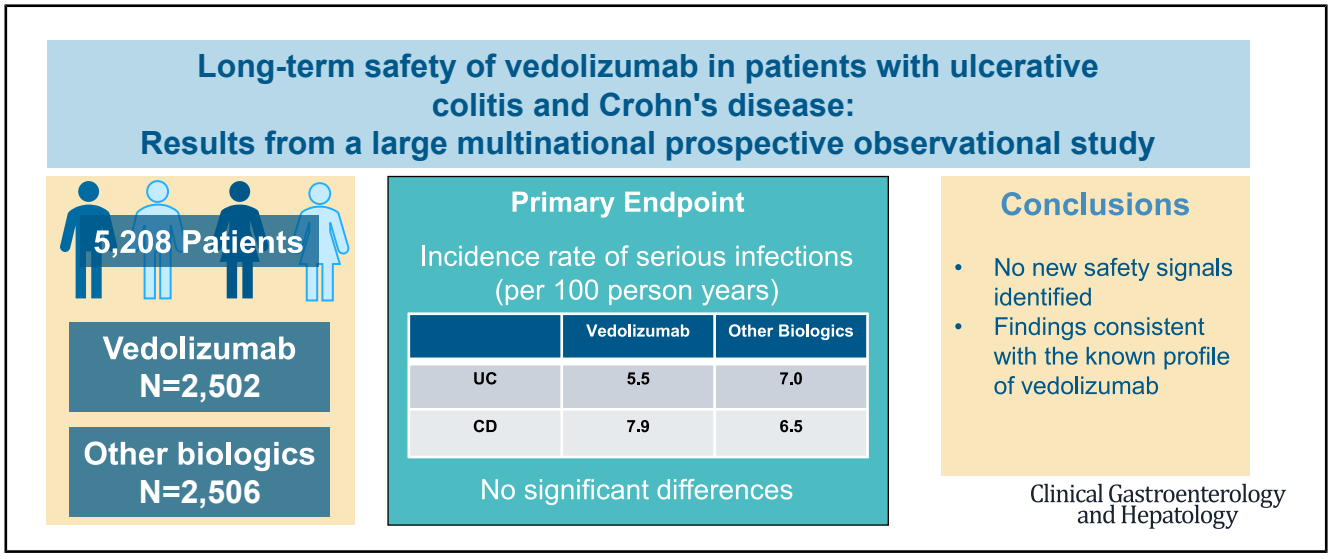

BACKGROUND & AIMS: This postauthorization safety study compared long-term safety of vedolizumab or other biologics in patients with ulcerative colitis (UC) or Crohn's disease (CD).

METHODS: This was a prospective, observational, multicenter cohort study in patients with UC or CD starting treatment with vedolizumab or other biologics (NCT02674308, EUPAS6469). The primary safety outcome was serious infections compared between cohorts using a Cox proportional hazards model adjusted by propensity score. Clinical effectiveness was a secondary outcome.

Abbreviations used in this paper: AE, adverse event; CD, Crohn's disease; CI, confidence interval; HBI, Harvey-Bradshaw Index; HR, hazard ratio; IBD, inflammatory bowel disease; IRR, incidence rate ratio; PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TNF-α, tumor necrosis factor α; UC, ulcerative colitis.

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RESULTS: **The full analysis set comprised 5008 patients (vedolizumab: n = 2502; other biologic: n = 2506) and mean follow-up duration was 37.4 ± 14.1 months. Patients in the vedolizumab group had greater age, duration of disease, and concomitant medication use at baseline, indicating more advanced disease. In patients with UC, the incidence rate per 100 person-years of serious infections was 5.5 (95% confidence interval [CI], 4.7–6.5) (vedolizumab) and 7.0 (95% CI, 5.8–8.5) (other biologic), with an adjusted hazard ratio of 0.89 (95% CI, 0.69–1.15) ($P = .38$). In patients with CD, corresponding findings were 7.9 (95% CI, 6.8–9.1) (vedolizumab) and 6.5 (95% CI, 5.7–7.3) (other biologic) with adjusted hazard ratio of 1.15 (95% CI, 0.95–1.40) ($P = .16$). There were no safety issues relating to pregnancy, and no cases of progressive multifocal leukoencephalopathy were observed. There were 18 deaths in the vedolizumab group and 13 in the other biologics group. Clinical effectiveness was comparable between cohorts and was similar to the levels seen in other prospective observations of vedolizumab.**

CONCLUSIONS: **There was no new safety signal identified in relation to vedolizumab. Results regarding safety and effectiveness were consistent with the known profile of vedolizumab.**

Keywords: Ulcerative Colitis; Crohn's Disease; Safety; Vedolizumab.

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a complex, lifelong, disorder of the gastrointestinal tract causing considerable morbidity with increasing incidence and prevalence worldwide.[1,2] Both UC and CD are chronic, relapsing, remitting inflammatory diseases with abnormal immune activation and include symptoms such as diarrhea, rectal bleeding, and abdominal pain or weight loss.[1,3] Patients with UC and CD have significant physical, psychosocial, and economic burdens related to the high risk of adverse health outcomes, including morbidity, hospitalization, surgery, and even mortality.[3–6]

Currently available treatments for UC and CD include mesalamine; corticosteroids; immunosuppressants such as azathioprine, mercaptopurine, and methotrexate; biological therapies such as tumor necrosis factor α (TNF-α) antagonists and interleukin-12 and/or interleukin-23 antagonists; and small molecules such as Janus kinase inhibitors and sphingosine-1-phosphate receptor modulators. Vedolizumab is a humanized monoclonal anti-$\alpha4\beta7$ integrin antibody for the treatment of UC and CD. The $\alpha4\beta7$ integrin mediates lymphocyte trafficking to gastrointestinal mucosa and gut-associated lymphoid tissue and impacts on the innate immune system.[7–9]

This study was a prospective, multinational observational study to assess the safety of vedolizumab vs other biologics in the real-world clinical setting as part of a postmarketing requirement for the U.S. Food and Drug Administration and a required additional pharmacovigilance activity in the European Union risk management plan for the European Medicines Agency. The study was designed to accommodate the use of products according to approved product labels in all participating countries. The primary objective of the study was to evaluate the long-term safety of vedolizumab vs other biologics in patients with UC or CD. Secondary objectives were to describe changes in UC/CD disease activity, using disease activity scores, and the number of hospitalizations and surgeries over the course of the study.

Materials and Methods

Study Design

This was a prospective, multicenter, observational cohort study in patients with UC or CD starting treatment with at least 1 dose of vedolizumab or other biologics (NCT02674308, EUPAS6469). The study was conducted in 344 sites in 21 countries (Supplementary Table 1). As an observational study, patients were treated under their usual standard of care as directed by their physician. For both cohorts, the decision to modify treatment, including dose intensification, was made by the treating physician. The treatment decision triggered eligibility for inclusion in the study. Patients were followed for up to 7 years, with no minimum time limit for follow-up. All patients provided written informed consent prior to participation and the study was approved by the Institutional Review Board or Independent Ethics Committee at each site.

Study Participants

Eligible patients were 18 years of age or older (no upper age limit), with UC or CD, and initiating or switching biologics. Patients may have had prior exposure to biologics or may have been naïve to biologic treatment, but they had no prior exposure to vedolizumab at study entry. Patients, or their legally acceptable representatives provided signed informed consent before any study-related activities were performed.

Study Treatment

Patients with UC or CD who initiated vedolizumab therapy were recruited into the vedolizumab group and

those who initiated therapy with another biologic agent indicated for UC or CD were recruited into the other biologics group. As with patients in the vedolizumab group, patients recruited to the other biologics group were allowed to change treatment at cohort entry (switching from a branded TNF-α antagonist to a biosimilar of the same TNF-α antagonist was not considered a treatment change in this study). Patients were prescribed vedolizumab or other biologics according to the local prescribing information in the participating countries.

Study Assessments and Endpoints

Primary Safety Outcome. The primary safety outcome was development of serious infections and opportunistic infections, including progressive multifocal leukoencephalopathy (PML). Serious infections were defined as any event coded to a MedDRA (Medical Dictionary for Regulatory Activities) v23.0 Preferred Term within the MedDRA system organ class of "infections and infestations" that met the definition of seriousness. Opportunistic infections were defined as any treatment-emergent adverse event (TEAE) coded to the Standardized MedDRA Query "opportunistic infections" plus the MedDRA Preferred Term "leukoencephalopathy."

Secondary Safety Outcomes. Predefined secondary safety outcomes were adverse events (AEs) of special interest and included the following: PML, gastrointestinal infections, lower and upper respiratory infections, other clinically significant infections, and malignancies (malignant and benign neoplasms). Investigators sought all available clinical and histopathology information on the malignancy, including site, cell type, size, stage and grade (including nodal status and metastases), clinical history, prior history of malignancy or premalignant disorders, family history, history of screening and diagnostic tests, and history of risk factors and concomitant medication history. Follow-up for malignancies began 6 months after cohort entry to minimize the likelihood of including pre-existing malignancies. The following were considered as suspected reports of drug-induced liver injury: cholestasis and jaundice of hepatic origin; hepatic failure; fibrosis and cirrhosis and other liver damage-related conditions; noninfectious hepatitis; and liver infections. Investigators sought all relevant information on the hepatic injury, including signs and symptoms, initial and follow-up laboratory results (including serology results), time course of the hepatic injury, diagnosis, concurrent medications and doses, pre-existing liver disease, infections, suspected etiology, and outcome.

Other AEs. Other safety endpoints included all other serious adverse events (SAEs) not included in the aforementioned AEs of special interest, adverse drug reactions including all serious and nonserious events considered to be related to vedolizumab or to other biologics, and pregnancy with the outcomes.

What You Need to Know

Background

This was a postauthorization study of the safety of vedolizumab (n = 2502) vs other biologics (n = 2506) in patients with ulcerative colitis or Crohn's disease.

Findings

There were no significant differences in the incidences of the primary endpoint of serious infections between the vedolizumab and other biologic cohorts.

Implications for patient care

No new safety signals were identified, and safety and effectiveness were consistent with the known profile of vedolizumab.

Disease Activity and Effectiveness Outcomes. UC disease activity was measured at baseline and each follow-up visit using the partial Mayo score.[10] The full Mayo score was determined for patients who had a recent endoscopy, but endoscopy was not mandatory for all patients in the study. Clinical remission was defined as a partial Mayo score of $\leq$2 with no individual subscore $>$1. Symptomatic response was defined as a reduction in the partial Mayo score of $\geq$2 points and $\geq$25% from baseline, plus either a decrease in the rectal bleeding subscore of $\geq$1 point or an absolute rectal bleeding score of $\leq$1.

CD activity was measured at baseline and each visit using the Harvey-Bradshaw Index (HBI).[11,12] The scale consists of 5 questions, each with a numeric score. Clinical remission was defined as a HBI of $\leq$4. Clinical response was defined as a 3-point decrease or a 30% decrease from the baseline HBI.

Mucosal healing was assessed for patients with UC using a Mayo endoscopy finding of 0 or 1. For patients with CD, mucosal healing was reported as a Simple Endoscopy Score for Crohn's Disease of $\leq$2.

IBD-related hospitalization and surgery rates and time to first hospitalization and surgery were compared in patients with UC or CD initiating vedolizumab and other biologics.

Treatment Failure and Discontinuation. Treatment failure up to 36 months was defined as 1 or more of biologic discontinuation, primary IBD surgery, nonsurgical IBD hospitalization, or corticosteroid initiation. In addition, dose modifications at any time during the study were analyzed in biologic-naïve and biologic-experienced patients with CD.

Statistical Analyses

Statistical analysis was carried out using SAS version 9.4 (SAS Institute). The full analysis (safety) set

consisted of all enrolled patients who provided valid informed consent date, received at least 1 dose of vedolizumab or other biologic agent prior to or on June 30, 2021, had a UC or CD diagnosis, had nonmissing prior exposure to biologics, and had their forms signed by the principal investigator.

Results were reported for UC and CD patients combined and separately. The primary safety outcome of serious infections was compared between cohorts using a Cox proportional hazards model adjusted by propensity score (with other biologics as reference) to minimize the differences in baseline characteristics between the two groups.

Logistic Regression to Select Predictors for Propensity Score Model. Predictor variables for the propensity score model were selected by stepwise logistic regression with the baseline treatment group as the dependent variable. Candidate variables included: baseline visit year, baseline age, sex, time from UC/CD diagnosis to baseline, ongoing baseline comorbidities, prior anti-TNF therapy, prior biologic use, Short Inflammatory Bowel Disease Questionnaire bowel domain and total scores, and disease status (UC vs CD). Variables were considered for inclusion at $P \leq .1$ and retained at $P \leq .2$.

Multiple Imputation. Missing values were imputed for all patients by multiple imputation with imputed datasets specified as 10 to reduce sampling variability. Minimum and maximum imputed values were set and rounded to possible values (e.g., $\geq$18 to $\leq$90 years of age at baseline, $\geq$0 to $\leq$70 years since diagnosis, baseline Short Inflammatory Bowel Disease Questionnaire domain $\geq$0 to $\leq$14).

Propensity Score Model. Final imputed predictor variables were used to generate a propensity score for every patient in each group for every imputation. To reduce variability, "stabilized" weights were calculated by using weights (created based on propensity score using the inverse probability of receiving treatment given the predictor variables), multiplied by the probability of receiving the given treatment for each group.

Cox Proportional Hazards Model. For serious infections, the Cox proportional hazard regression was performed to generate unadjusted and adjusted hazard ratios (HRs). Serious infections were defined on the date of first occurrence following baseline. If patients did not experience the event, they were censored at the end of follow-up. The estimates were produced by imputation with the pooled HRs calculated based on Rubin's rule.

Kaplan-Meier Analysis. For Kaplan-Meier estimates of rate of discontinuation, the first event was considered. for patients not discontinuing treatment, time to discontinuation was treated as censored at the patient's end of follow-up.

Results

Patient Characteristics

A total of 5208 patients were enrolled across 344 sites in 21 countries, with data collected between March 2015 and December 2021 (Table 1). The full analysis set comprised 5008 patients (vedolizumab cohort: n = 2502; other biologics cohort: n = 2506), and the mean study duration was 37.4 ± 14.1 months. Overall, 3840 (76.7%) patients completed the study, with discontinuation rates of 25.4% in the vedolizumab group and 21.2% in the other biologics group. The most common reasons for study discontinuation were that the patient withdrew consent (5.3%), that the patient enrolled in a clinical trial (2.2%), administrative reasons (2.2%), physician determination (1.8%), death (1.1%), lost to follow-up (0.3%), and other reasons (12.3%).

Consistent with the observational nature of the study and evolution of standard of care, the baseline characteristics in the two cohorts were imbalanced (Table 2). Patients were more likely to have had prior biologics in the vedolizumab vs other biologics cohort (65.3% vs 35.4%). The other biologics cohort consisted primarily, though not exclusively, of patients treated with an anti-TNF agent (Table 2). Compared with the other biologics group, patients in the vedolizumab group had greater average age, duration of IBD, and increased use of concomitant medications, which indicated more advanced and clinically complex disease. The percentages of patients with a history of infection, hepatic injury, infusion-related reaction, and malignancy were numerically greater in the vedolizumab cohort than the other biologics cohort.

Infections

Incidence rates of serious and opportunistic infections, gastrointestinal infections, and respiratory infections were similar in the vedolizumab vs other biologics group in patients with UC and CD (Table 3). Overall, the incidence rate per 100 person-years for serious and opportunistic infections was 6.5 (95% confidence interval [CI], 5.9–7.3) in the vedolizumab group and 6.6 (95% CI, 6.0–7.4) in the other biologics group. The unadjusted incidence rate ratio (IRR) for vedolizumab/other biologics was 0.99 (95% CI, 0.85–1.15). The propensity score–adjusted Cox model showed no difference in risk of serious and opportunistic infections in patients exposed to vedolizumab vs other biologics (HR, 1.04; 95% CI, 0.90–1.21; $P = .60$).

In patients with UC, the incidence rate per 100 person-years of serious and opportunistic infections was: 5.5 (95% CI, 4.7–6.5) for the vedolizumab group and 7.0 (95% CI, 5.8–8.5) for the other biologics group, with an HR of 0.89 (95% CI, 0.69–1.15) ($P = .38$). In patients with CD, the incidence rates of serious and opportunistic infections were 7.9 (95% CI, 6.8–9.1) for the vedolizumab group and 6.5 (95% CI, 5.7–7.3) for the other biologics group, with an HR of 1.15 (95% CI, 0.95–1.40) ($P = .16$) (Table 3).

The incidence rate per 100 person-years for gastrointestinal infections was 3.6 (95% CI, 3.1–4.1) in the

Table 1. Patient Disposition

	All Patients			Patients With UC			Patients With CD		
	All Patients	Vedolizumab	Other Biologics	All Patients With UC	Vedolizumab	Other Biologics	All Patients With CD	Vedolizumab	Other Biologics
Enrolled patients[a]	5208	2568	2640	2175	1377	798	2961	1157	1804
Eligible patients[b]	5094	2544	2550	2144	1373	771	2898	1143	1755
Full analysis set[c]	5008	2502	2506	2127	1361	766	2881	1141	1740
Completed study	3840 (76.7)	1866 (74.6)	1974 (78.8)	1619 (76.1)	1012 (74.4)	607 (79.2)	2221 (77.1)	854 (74.8)	1367 (78.6)
Discontinued study[d]	1168 (23.3)	636 (25.4)	532 (21.2)	508 (23.9)	349 (25.6)	159 (20.8)	660 (22.9)	287 (25.2)	373 (21.4)
Reason for study discontinuation									
Administration reasons	108 (2.2)	47 (1.9)	61 (2.4)	51 (2.4)	24 (1.8)	27 (3.5)	57 (2.0)	23 (2.0)	34 (2.0)
Lost to follow-up	14 (0.3)	7 (0.3)	7 (0.3)	6 (0.3)	5 (0.4)	1 (0.1)	8 (0.3)	2 (0.2)	6 (0.3)
Enrolled in clinical trial	109 (2.2)	58 (2.3)	51 (2.0)	53 (2.5)	38 (2.8)	15 (2.0)	56 (1.9)	20 (1.8)	36 (2.1)
Withdrew consent	264 (5.3)	150 (6.0)	114 (4.5)	116 (5.5)	80 (5.9)	36 (4.7)	148 (5.1)	70 (6.1)	78 (4.5)
Physician determination	89 (1.8)	49 (2.0)	40 (1.6)	40 (1.9)	28 (2.1)	12 (1.6)	49 (1.7)	21 (1.8)	28 (1.6)
Death[e]	57 (1.1)	38 (1.5)	19 (0.8)	20 (0.9)	17 (1.2)	3 (0.4)	37 (1.3)	21 (1.8)	16 (0.9)
Other	616 (12.3)	332 (13.3)	284 (11.3)	269 (12.6)	180 (13.2)	89 (11.6)	347 (12.0)	152 (13.3)	195 (11.2)
Study duration, months[d,f]	37.42 ± 14.06	37.06 ± 14.32	37.78 ± 13.79	37.05 ± 14.16	36.19 ± 14.02	38.58 ± 14.30	37.70 ± 13.98	38.11 ± 14.61	37.43 ± 13.54

Values are n, n (%), or mean ± SD.
CD, Crohn's disease; UC, ulcerative colitis.
[a]Patients who had signed informed consent and received either vedolizumab or other biologic treatment.
[b]Enrolled patients who met/did not meet the study inclusion/exclusion criteria.
[c]Enrolled patients who had nonmissing informed consent date, had no informed consent form issues, received at least 1 dose of vedolizumab or other biologics agent prior to or on June 30, 2021, had UC or CD inflammatory bowel disease diagnosis, had nonmissing prior exposure to biologics, and had their forms signed by the principal investigator.
[d]Denominator for percentages was defined by the full analysis set population.
[e]Death was either the outcome of an adverse event or other reason.
[f]Date of follow-up period end date minus first study dose date +1 divided by 30.4375.

Table 2. Baseline Demographics and Clinical Characteristics

Parameter	All Patients			UC		CD	
	All Patients (n = 5008)	Vedolizumab (n = 2502)	Other Biologics (n = 2506)	Vedolizumab (n = 1361)	Other Biologics (n = 766)	Vedolizumab (n = 1141)	Other Biologics (n = 1740)
Age, y	42.5 ± 15.51	44.5 ± 16.33	40.4 ± 14.37	44.2 ± 16.5	41.7 ± 14.4	44.8 ± 16.1	39.9 ± 14.3
Female	52.4	52.4	52.4	47.2	49.3	58.6	53.8
Disease duration, y	11.4 ± 10.54	12.5 ± 10.85	10.4 ± 10.12	10.6 ± 9.67	8.8 ± 8.67	14.7 ± 11.74	11.2 ± 10.62
Partial Mayo score	—	—	—	4.6 ± 2.3	4.8 ± 2.3	—	—
Harvey-Bradshaw Index score	—	—	—	—	—	5.9 ± 4.8	5.4 ± 4.5
Prior therapy	4513 (90.1)	2335 (93.3)	2178 (86.9)	1258 (92.4)	670 (87.5)	1077 (94.4)	1508 (86.7)
Corticosteroids	2913 (58.2)	1536 (61.4)	1377 (54.9)	851 (62.5)	470 (61.4)	685 (60.0)	907 (52.1)
Immunomodulators	2267 (45.3)	1275 (51.0)	992 (39.6)	611 (44.9)	259 (33.8)	664 (58.2)	733 (42.1)
Biologics	2521 (50.3)	1,634 (65.3)	887 (35.4)	805 (59.1)	173 (22.6)	829 (72.7)	714 (41.0)
Biologic administered at study entry							
Vedolizumab		2502 (100.0)	0 (0.0)	1361 (100.0)	0 (0.0)	1141 (39.6)	0 (0.0)
Infliximab		0 (0.0)	1294 (51.6)	0 (0.0)	524 (68.4)	0 (0.0)	770 (44.3)
Adalimumab		0 (0.0)	731 (29.2)	0 (0.0)	166 (21.7)	0 (0.0)	565 (32.5)
Ustekinumab		0 (0.0)	390 (15.6)	0 (0.0)	3 (0.4)	0 (0.0)	387 (22.2)
Golimumab		0 (0.0)	76 (3.0)	0 (0.0)	73 (9.5)	0 (0.0)	3 (0.2)
Certolizumab		0 (0.0)	14 (0.6)	—	—	0 (0.0)	14 (0.8)
Natalizumab		0 (0.0)	1 (0.0)	—	—	0 (0.0)	1 (0.1)

Values are mean ± SD or n (%).
CD, Crohn's disease; UC, ulcerative colitis.

vedolizumab group and 3.2 (95% CI, 2.8–3.7) for the other biologics group, with an IRR of 1.11 (95% CI, 0.90–1.36). In UC patients, incidence rates were similar between the vedolizumab and other biologics groups whereas in CD patients the incidence rate per 100 patient years was 5.1 (95% CI, 4.3–6.2) in the vedolizumab group and 3.5 (95% CI, 3.0–4.2) in the other biologics group (Table 3).

For lower and upper respiratory tract infections, the incidence rate per 100 person-years was 9.2 (95% CI, 8.3–10.1) for the vedolizumab group and 7.6 (95% CI, 6.9–8.4) for the other biologics group, with an IRR of 1.21 (95% CI, 1.06–1.39). In UC patients, the incidence rates per 100 patient years were 8.4 (95% CI, 7.3–9.5) and 6.9 (95% CI, 5.7–8.3) in the vedolizumab and other biologics groups, respectively. In CD patients, the incidence rate per 100 patient years was 10.2 (95% CI, 8.9–11.7) in the vedolizumab group and 7.9 (95% CI, 7.0–8.8) in the other biologics group (Table 3).

There were 5 cases of latent tuberculosis reported during the study, all of which were deemed as nonserious: 2 cases in the vedolizumab group and 3 cases in the other biologics group. Additionally, there was 1 case of tuberculosis (nonserious) in the other biologics cohort and 1 case of tuberculous meningitis (serious) in the vedolizumab group. There were no cases of PML observed and no other clinically significant infections.

Adverse Events

TEAEs were reported in 61.3% (vedolizumab) and 59.5% (other biologics) of patients, respectively, with incidence rates per 100 patient years of 8.9 (95% CI, 8.1–9.8) in the vedolizumab group and 12.1 (95% CI, 11.2–13.1) in the other biologics group. SAEs were reported in 27.5% (vedolizumab) and 25.7% (other biologics) of patients (Table 4). Overall, the most frequently reported SAEs were gastrointestinal disorders (15.4%; including CD [4.6%], UC [3.8%], small intestinal obstruction [1.2%], abdominal pain [0.9%], and intestinal obstruction [0.8%]), infections and infestations (8.0%; including anal abscess [0.9%], pneumonia [0.7%], and sepsis [0.6%]), and renal and urinary disorders (1.3%; including acute kidney injury [0.5%]).

Deaths

There were 18 deaths in the vedolizumab group, 1 of which was considered treatment-related and was due to pneumonia. There were 13 deaths in the other biologics group, 2 of which were deemed treatment related: 1 due to septic shock and pneumonia and the other due to non-small cell lung cancer (Table 4).

Table 3. Treatment-Emergent AEs of Special Interest

	All Patients		UC		CD	
	Vedolizumab (n = 2844)	Other Biologics (n = 3147)	Vedolizumab (n = 1569)	Other Biologics (n = 1068)	Vedolizumab (n = 1275)	Other Biologics (n = 2079)
Serious infections						
Patients with ≥1 event	327 (11.5)	359 (11.4)	155 (9.9)	110 (10.3)	172 (13.5)	249 (12.0)
IR per 100 patient-years (95% CI)	6.5 (5.9–7.3)	6.6 (6.0–7.4)	5.5 (4.7–6.5)	7.0 (5.8–8.5)	7.9 (6.8–9.1)	6.5 (5.7–7.3)
Gastrointestinal infections						
Patients with ≥1 event	184 (6.5)	183 (5.8)	69 (4.4)	41 (3.8)	115 (9.0)	142 (6.8)
IR per 100 patient-years (95% CI)	3.6 (3.1–4.1)	3.2 (2.8–3.7)	2.4 (1.9–3.0)	2.4 (1.8–3.3)	5.1 (4.3–6.2)	3.5 (3.0–4.2)
Lower and upper respiratory tract infections						
Patients with ≥1 event	428 (15.0)	400 (12.7)	221 (14.1)	107 (10.0)	207 (16.2)	293 (14.1)
IR per 100 patient-years (95% CI)	9.2 (8.3–10.1)	7.6 (6.9–8.4)	8.4 (7.3–9.5)	6.9 (5.7–8.3)	10.2 (8.9–11.7)	7.9 (7.0–8.8)
Malignancies—6 mo after first dose						
Patients with ≥1 event	65 (2.3)	58 (1.8)	26 (1.7)	13 (1.2)	39 (3.1)	45 (2.2)
IR per 100 patient-years (95% CI)	1.2 (1.0–1.6)	1.0 (0.8–1.3)	0.9 (0.6–1.3)	0.8 (0.4–1.3)	1.7 (1.2–2.3)	1.1 (0.8–1.4)
Infusion-related reactions and hypersensitivity within the 2-d risk window						
Patients with ≥1 event	15 (0.6)	19 (0.8)	8 (0.6)	8 (1.1)	7 (0.6)	11 (0.6)
IR per 100 patient-years (95% CI)	220.7 (133.0–366.0)	278.4 (177.6–436.4)	215.6 (107.8–431.2)	385.5 (192.8–770.8)	226.7 (108.1–475.4)	231.6 (128.2–418.1)
Hepatic injury within the 5-d risk window						
Patients with ≥1 event	1 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
IR per 100 patient-years (95% CI)	3.7 (0.5–26.1)	7.3 (1.8–29.3)	0	0	8.1 (1.1–57.5)	10.5 (2.6–42.1)
Any other SAE (unrestricted risk window)						
Patients with ≥1 event	526 (18.5)	545 (17.3)	239 (15.2)	155 (14.5)	287 (22.5)	390 (18.8)
IR per 100 patient-years (95% CI)	10.9 (10.0–11.9)	10.4 (9.6–11.3)	8.6 (7.6–9.8)	10.0 (8.5–11.7)	14.1 (12.5–15.8)	10.6 (9.6–11.7)

Values are n (%), unless otherwise indicated.
AE, adverse event; CD, Crohn's disease; CI, confidence interval; IR, incident rate; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

Table 4. Safety Overview

	All Patients		UC		CD	
	Vedolizumab (n = 2483)	Other Biologics (n = 2493)	Vedolizumab (n = 1355)	Other Biologics (n = 758)	Vedolizumab (n = 1128)	Other Biologics (n = 1735)
Any TEAE[a]	1521 (61.3)	1483 (59.5)	759 (56.0)	443 (58.4)	762 (67.6)	1040 (59.9)
Patients with ≥1 event	428 (15.0)	610 (19.4)	209 (13.3)	199 (18.6)	219 (17.2)	411 (19.8)
IR per 100 patient-years (95% CI)	8.9 (8.1–9.8)	12.1 (11.2–13.1)	7.7 (6.7–8.8)	13.6 (11.8–15.6)	10.5 (9.2–12.0)	11.5 (10.4–12.7)
TEAE reported in ≥3% of patients in either cohort						
Infections and infestations	856 (34.5)	810 (32.5)	417 (30.8)	242 (31.9)	439 (38.9)	568 (32.7)
Upper respiratory tract infection	85 (3.4)	88 (3.5)	50 (3.7)	30 (4.0)	35 (3.1)	58 (3.3)
Urinary tract infection	90 (3.6)	76 (3.0)	41 (3.0)	26 (3.4)	49 (4.3)	50 (2.9)
Nasopharyngitis	80 (3.2)	82 (3.3)	32 (2.4)	17 (2.2)	48 (4.3)	65 (3.7)
Gastroenteritis	65 (2.6)	34 (1.4)	21 (1.5)	11 (1.5)	44 (3.9)	23 (1.3)
Gastrointestinal disorders	650 (26.2)	604 (24.2)	273 (20.1)	180 (23.7)	377 (33.4)	424 (24.4)
CD	154 (6.2)	161 (6.5)	5 (0.4)	9 (1.2)	149 (13.2)	152 (8.8)
UC	143 (5.8)	108 (4.3)	142 (10.5)	108 (14.2)	1 (0.1)	0
Abdominal pain	68 (2.7)	83 (3.3)	25 (1.8)	14 (1.8)	43 (3.8)	69 (4.0)
Diarrhea	52 (2.1)	29 (1.2)	16 (1.2)	4 (0.5)	36 (3.2)	25 (1.4)
Musculoskeletal and connective tissue disorders	273 (11.0)	222 (8.9)	125 (9.2)	73 (9.6)	148 (13.1)	149 (8.6)
Arthralgia	83 (3.3)	91 (3.7)	34 (2.5)	33 (4.4)	49 (4.3)	58 (3.3)
Nervous system disorders	196 (7.9)	158 (6.3)	94 (6.9)	56 (7.4)	102 (9.0)	102 (5.9)
Headache	82 (3.3)	62 (2.5)	36 (2.7)	26 (3.4)	46 (4.1)	36 (2.1)
Treatment-related TEAE	346 (13.9)	478 (19.2)	158 (11.7)	150 (19.8)	188 (16.7)	328 (18.9)
Any SAE	682 (27.5)	641 (25.7)	304 (22.4)	193 (25.5)	378 (33.5)	448 (25.8)
Any SAE reported in ≥0.5% of patients in either cohort						
Gastrointestinal disorders	390 (15.7)	374 (15.0)	159 (11.7)	116 (15.3)	231 (20.5)	258 (14.9)
CD	118 (4.8)	112 (4.5)	0	5 (0.7)	114 (10.1)	107 (6.2)
UC	110 (4.4)	80 (3.2)	110 (8.1)	80 (10.6)	0	0
Small intestinal obstruction	20 (0.8)	39 (1.6)	2 (0.1)	0	18 (1.6)	36 (2.1)
Abdominal pain	15 (0.6)	30 (1.2)	7 (0.5)	7 (0.9)	8 (0.7)	23 (1.3)
Intestinal obstruction	18 (0.7)	21 (0.8)	1 (0.1)	1 (0.1)	17 (1.5)	20 (1.2)
Ileal stenosis	10 (0.4)	23 (0.9)	1 (0.1)	0	9 (0.8)	23 (1.3)
Anal fistula	18 (0.7)	14 (0.6)	2 (0.1)	3 (0.4)	16 (1.4)	11 (0.6)
Colitis	12 (0.5)	9 (0.4)	7 (0.5)	7 (0.9)	5 (0.4)	0
Ileus	11 (0.4)	10 (0.4)	1 (0.1)	3 (0.4)	10 (0.9)	7 (0.4)
Large intestinal stenosis	11 (0.4)	3 (0.1)	2 (0.1)	1 (0.1)	9 (0.8)	2 (0.1)
Subileus	9 (0.4)	7 (0.3)	0	0	9 (0.8)	7 (0.4)
Intestinal stenosis	7 (0.3)	8 (0.3)	0	1 (0.1)	7 (0.6)	7 (0.4)
Infections and infestations	209 (8.4)	190 (7.6)	87 (6.4)	56 (7.4)	122 (10.8)	134 (7.7)
Anal abscess	25 (1.0)	21 (0.8)	6 (0.4)	5 (0.7)	19 (1.7)	16 (0.9)
Pneumonia	20 (0.8)	16 (0.6)	14 (1.0)	8 (1.1)	6 (0.5)	8 (0.5)
Sepsis	14 (0.6)	14 (0.6)	9 (0.7)	5 (0.7)	5 (0.4)	9 (0.5)
Clostridium difficile infection	18 (0.7)	8 (0.3)	10 (0.7)	4 (0.5)	8 (0.7)	4 (0.2)
Abdominal abscess	13 (0.5)	10 (0.4)	4 (0.3)	2 (0.3)	9 (0.8)	8 (0.5)
Gastroenteritis	14 (0.6)	6 (0.2)	3 (0.2)	0	11 (1.0)	4 (0.2)
Appendicitis	0	10 (0.4)	7 (0.5)	4 (0.5)	4 (0.4)	6 (0.3)
Septic shock	2 (0.1)	5 (0.2)	2 (0.1)	4 (0.5)	0	1 (0.1)
Urinary tract infection	7 (0.3)	5 (0.2)	1 (0.1)	2 (0.3)	6 (0.5)	3 (0.2)
Renal and urinary disorders	30 (1.2)	33 (1.3)	13 (1.0)	10 (1.3)	17 (1.5)	23 (1.3)
Acute kidney injury	15 (0.6)	10 (0.4)	5 (0.4)	4 (0.5)	10 (0.9)	6 (0.3)
Treatment-related SAE	79 (3.2)	117 (4.7)	42 (3.1)	37 (4.9)	37 (3.3)	80 (4.6)
Deaths	18 (0.7)	13 (0.5)	5 (0.4)	2 (0.3)	13 (1.2)	11 (0.6)
Treatment-related death	1 (0.0)	2 (0.1)	1 (0.1)	1 (0.1)	0	1 (0.1)

Values are n (%), unless otherwise indicated. Other safety events recorded included progressive multifocal leukoencephalopathy and pregnancy outcomes.
AE, adverse event; CD, Crohn's disease; CI, confidence interval; IR, incident rate; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.
[a]Defined as all AEs that occurred after the first dose date and before the last dose date + 127 days for all episodes.

Neoplasms

Benign or malignant neoplasms were reported in 3.5% of patients. The most frequently reported neoplasms were basal cell carcinoma (23 patients [0.5%]), squamous cell carcinoma (10 patients [0.2%]), skin papilloma (9 patients [0.2%]), and breast cancer (8 patients [0.2%]). The incidence rate of malignancies from 6 months after cohort entry to end of follow-up was comparable between the two cohorts (Table 3). The incidence rate per 100 person-years for malignancies was 1.2 (95% CI, 1.0–1.6) for the vedolizumab group and 1.0 (95% CI, 0.8–1.3) for the other biologics group. The IRR was 1.2 (95% CI, 0.9–1.8).

Infusion/Injection-Related Reactions

The incidence rate of infusion/injection-related reactions was comparable between the groups. The highest incidence rates were observed within the 2-day risk window: 220.7 per 100 person-years in patients exposed to vedolizumab and 278.4 in patients exposed to other biologics (IRR, 0.8; 95% CI, 0.4–1.6) (Table 3).

Pregnancy-Related Safety Parameters

There were no confirmed safety concerns related to pregnancies. There was 1 case of congenital pulmonary airway malformation (cystic adenomatoid) related to vedolizumab and mesalamine, based on investigator's assessment. Pregnancy data in the vedolizumab cohort were comparable to the other biologics cohort.

Treatment Failure/Discontinuations in Patients With CD

For CD, data were analyzed from 1338 biologic-naïve patients (312 treated with vedolizumab and 1026 treated with other biologics) and 1543 biologic-experienced patients (829 treated with vedolizumab and 714 treated with other biologics). Kaplan-Meier estimates for time to treatment failure in biologic-naive and biologic-experienced patients are shown in Figure 1. Dose modification at any time during the study was less frequently reported in the vedolizumab vs other biologic cohort for both biologic-naïve (4.2% vedolizumab vs 48.9% other biologics) and biologic-experienced (4.1% vedolizumab vs 60.6% other biologics) patients with CD (Figure 2).

In patients with UC, dose modifications at any time during the study occurred in 15 (2.7%) of 556 biologic-naïve patients in the vedolizumab group and 249 (42.0%) of 593 in the other biologics group. For biologic experienced patients, dose modifications occurred in 23 (2.9%) of 805 in the vedolizumab cohort and 87 (50.3%) of 173 in the other biologics cohort (Figure 2).

Clinical Outcomes

Vedolizumab was effective for the duration of the study. Clinical outcomes of remission (Supplementary Figure 1), clinical response (Supplementary Figure 2), and mucosal healing (Supplementary Figure 3) were comparable between the vedolizumab cohort and the cohort of patients receiving other biologics. Fewer biologic-naïve patients with UC or CD receiving vedolizumab had IBD-related hospitalizations and surgeries than patients treated with other biologics (Supplementary Table 2).

Discussion

In this long-term, prospective, real-world observational study of a large multinational IBD patient population under routine standard of care (which may differ based on disease severity or prognosis), there were no new safety signals identified in relation to treatment with vedolizumab, and results are consistent with the known safety profile of vedolizumab. Previously, retrospective real-world studies have suggested a lower risk of serious infections in patients treated with vedolizumab vs anti-TNF agents, particularly in UC patients.[13,14] In our study, the largest such prospective real-world study, the overall rate of serious and opportunistic infections did not allow differentiation between the vedolizumab and other biologics groups and when Cox proportionality methods were applied, there were no significant differences between the vedolizumab group and the other biologics group.

In biologic-naïve and biologic-experienced patients treated with vedolizumab, dose modification was less frequent compared with patients receiving other biologics with rates of 4.2% (biologic-naïve) and 4.1% (biologic-experienced) in the vedolizumab group compared with 48.9% (biologic-naïve) and 60.6% (biologic-experienced) in the other biologics group.

Effectiveness findings from this study are consistent with the established efficacy profile of vedolizumab.[15–17] In patients with CD, vedolizumab was effective at achieving mucosal healing, particularly when used as a first-line biologic treatment. Despite observed differences in baseline demographics and clinical characteristics, rates of clinical response and clinical remission were similar in patients treated with vedolizumab compared with other biologics for both UC and CD.

Limitations of this study should be considered in order to contextualize the findings of the analyses. These constraints include selection bias and confounding due to the absence of randomization with physicians treating patients according to usual standard of care, which may lead to differences in therapy use based on severity of disease or prognosis. Notably this was an observational study with no preprogrammed visits or diagnostic observations. Therefore, assessments regarding

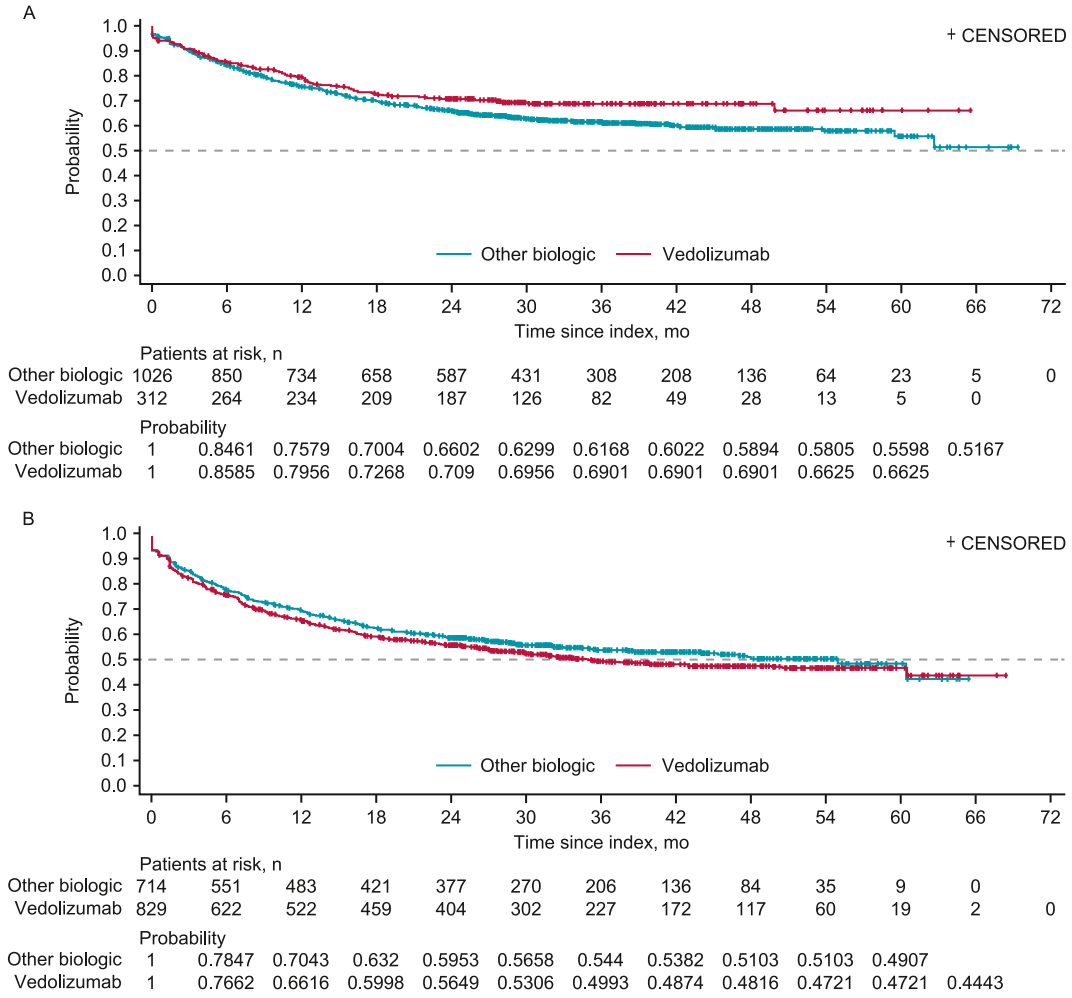

Figure 1. Time to treatment failure in (A) biologic-naïve or (B) biologic-experienced CD patients. (A) Biologic-naïve cohort: for vedolizumab-treated patients, the number of events was 93 (29.8%) and the number censored was 219 (70.2%); for patients treated with other biologics, the number of events was 381 (37.1%) and the number censored was 645 (62.9%). (B) Biologic-experienced cohort: for vedolizumab-treated patients, the number of events was 399 (48.1%) and the number censored was 430 (51.9%); for patients treated with other biologics, the number of events was 316 (44.3%) and the number censored was 398 (55.7%). The analysis set comprised enrolled patients who had received ≥1 dose of vedolizumab or other biologic agent and had data on prior exposure to biologics. Treatment failure included discontinuation of biologic treatment, IBD nonsurgical hospitalization, primary IBD surgery, and corticosteroid initiation.

effectiveness are limited due to the observational nature of the study. Furthermore, a nonrandomized design is limited in its ability to guarantee that characteristics that could influence the outcome of interest are balanced between the populations and that observed differences between the outcomes of the populations can be directly attributed to the intervention. Treatment allocation (channeling) bias may therefore have occurred when drugs were preferentially prescribed to patients with different baseline characteristics and due to the observational nature of the study the investigators prescribed vedolizumab vs other biologics following standard of care. Upon examination of the patient demographics and baseline characteristics of the vedolizumab group, these limitations may apply, as patients who were assigned to vedolizumab were older, had longer duration of disease, and had a higher frequency of prior and concomitant use of steroids, immunomodulators, and biologics than the other biologics group, thus representing a higher risk population for serious infections upfront, as these factors are known to be associated with an increased risk of infection.[18–20] In addition, the distribution of patients with UC and CD differed between treatment cohorts. A propensity score analysis was used to mitigate these baseline differences, but residual bias may remain. Attrition bias is another limitation, with 23.3% of patients discontinuing the study. Additionally, loss to follow-up could have led to over or underestimation of the results of the study.

In conclusion, in this long-term, prospective, real-world observational study of a large multinational population with UC or CD under routine standard of care there was no new safety signal identified in relation to treatment with vedolizumab. There were no new trends or changes of clinical importance for infections (serious

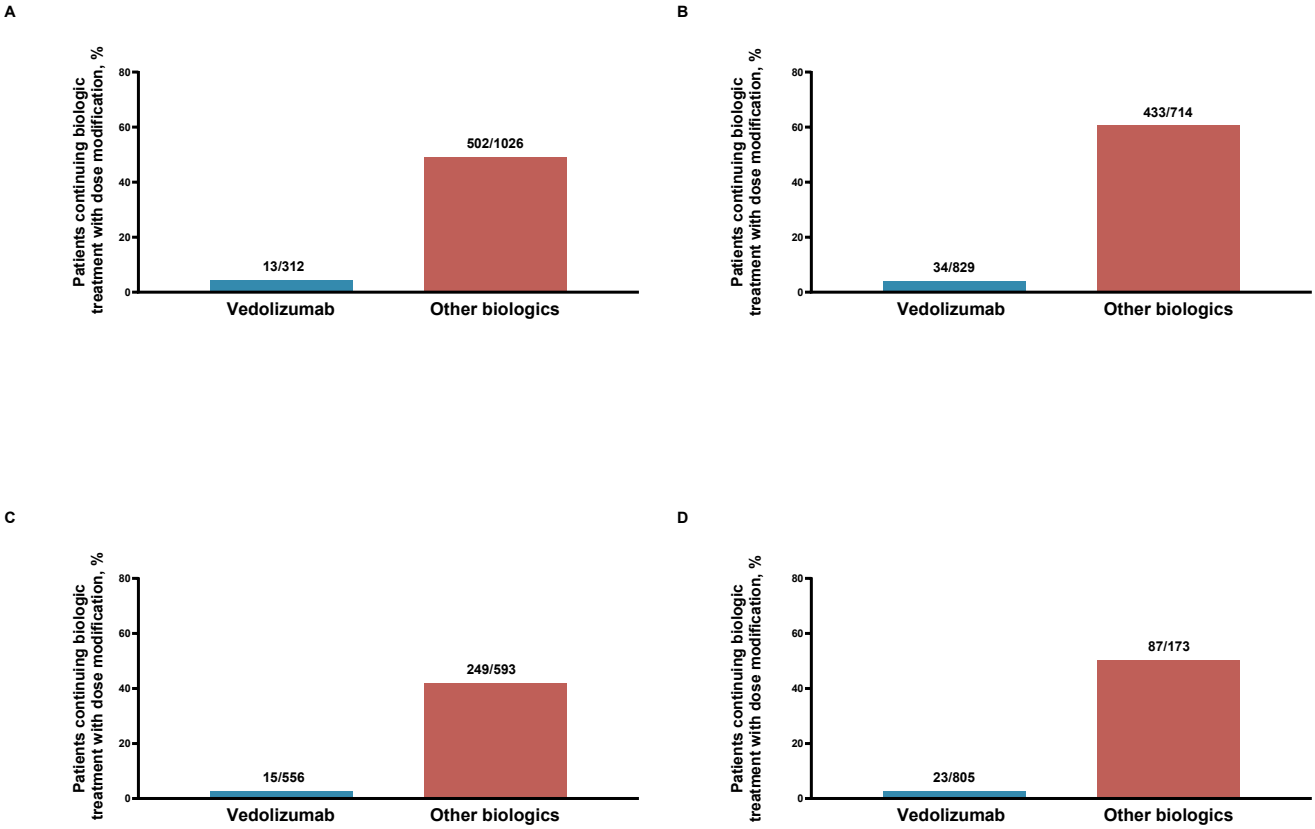

Figure 2. Dose modification of biologic treatment at any time during the study in (A) biologic-naïve or (B) biologic-experienced CD patients and (C) biologic-naïve or (D) biologic-experienced UC patients.

and opportunistic infections, gastrointestinal infections, respiratory tract infections, other infections), malignancies, infusion-related reactions, hepatotoxicity, and pregnancies. No cases of PML were reported. Results are consistent with the known safety and efficacy profile of vedolizumab and support its long-term use.

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.2025.10.006.

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Data Availability
The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.