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Impact of Vedolizumab on Extraintestinal Manifestations in Inflammatory Bowel Disease: Results From a Descriptive, Retrospective, Real-world Study

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Background: Patients with inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, may develop extraintestinal manifestations (EIMs). The EMOTIVE study aimed to analyze the effect of vedolizumab on EIMs in a real-world cohort of patients with IBD.

Methods: This multicenter, descriptive, retrospective study was conducted in Belgium, Denmark, Israel, the Netherlands, and Switzerland in adults with moderately to severely active IBD and concurrent active EIMs at vedolizumab initiation (index date), with a ≥6-month follow-up after the index date. The primary endpoint was resolution of all EIMs within 6 months of vedolizumab initiation.

Results: In 99 eligible patients, the most frequent EIMs were arthralgia (69.7%), peripheral spondyloarthritis (21.2%), and axial spondyloarthritis (10.1%). Within 6 and 12 months of vedolizumab initiation, 19.2% and 25.3% of patients reported resolution of all EIMs, while 36.5% and 49.5% of all EIMs were reported to be improved (combination of resolution and partial response), respectively. Vedolizumab treatment persistence at 12 months was 82.8%. Adverse events were reported in 18.2% of patients, with the most frequent being arthralgia (4.0%).

Conclusions: This real-world study showed resolution of all EIMs in up to one-fourth of patients with IBD and improvement in up to half of EIMs within 12 months of vedolizumab treatment. Overall, vedolizumab was effective on EIMs in patients with IBD and showed a good safety profile.

Key Words: Crohn's disease, extraintestinal manifestations, real-world study, ulcerative colitis, vedolizumab

Introduction

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract.[1] Along with the effects of IBD on the gastrointestinal tract, a large proportion of patients experience extraintestinal manifestations (EIMs). Up to 50.0% of patients with IBD develop at least 1 EIM during the course of the disease,[2] with an estimated prevalence of 20.0% to 40.0% and 15.0% to 20.0% in patients with CD and UC, respectively.[3] The most frequent EIMs present as musculoskeletal, ophthalmic, dermatological, and hepatobiliary disorders, with or without a link to disease activity, and impact the quality of life and morbidity in patients with IBD.[2,4]

The first consensus document on the management of EIMs in patients with IBD was published by the European Crohn's and Colitis Organisation in 2016.[2] Extraintestinal manifestations are best managed by a multidisciplinary team, and treatment options, based on symptom severity and association with IBD activity, include the use of nonsteroidal anti-inflammatory drugs, anti–tumor necrosis factor (anti-TNF) agents, biologics, and small molecules.[2,3,5,6] A review by Greuter et al summarizing the current treatment options has highlighted the importance of diagnosing, monitoring, and treating EIMs in patients with IBD.[5] However, the lack of clearly defined pathogenic mechanisms or definition of treatment response/remission for many EIMs, standardized diagnostic approaches, and high-quality evidence supporting different treatment strategies for EIMs in IBD indicate the need for determining the optimal treatment for EIMs.[7,8]

Vedolizumab, a gut-selective anti–lymphocyte trafficking humanized monoclonal antibody that specifically binds to

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Key Messages

What is already known?

Vedolizumab has established efficacy in treating moderate-to-severe inflammatory bowel disease (IBD). However, its role in the treatment of extraintestinal manifestations (EIMs) remains largely unknown.

What is new here?

This real-world study showed resolution and improvement of EIMs with vedolizumab treatment in patients with IBD.

How can this study help patient care?

This study suggests that vedolizumab is effective for the treatment of EIMs in patients with IBD while demonstrating a good safety profile.

the α4β7 integrin, has constituted an addition to the treatment armamentarium for adult patients with CD and UC since its approval by the European Medicines Agency and the United States Food and Drug Administration in 2014.[9,10] Contrary to anti-TNF-α treatments that elicit systemic immunosuppression, the mode of action of vedolizumab is characterized by its gut-selective lymphocyte trafficking inhibition.[11] Although vedolizumab has been proven effective in treating moderate-to-severe IBD in clinical trials and real-world studies,[12–15] its efficacy with regard to EIMs remains unclear due to the lack of large controlled trials.[16,17] Evidence of the role of vedolizumab in managing EIMs is limited to post hoc analyses of pivotal randomized controlled trials or real-world cohort studies in a subgroup of patients with EIMs in IBD.[18–24] Moreover, the existing data do not provide strong evidence on the efficacy of vedolizumab in patients with IBD with preexisting EIMs.

Given this paucity of evidence on the impact of vedolizumab on EIMs in IBD, the EMOTIVE study aimed to analyze the effect of vedolizumab on the activity of EIMs in a real-world cohort of patients with IBD (EU PAS Register Number EUPAS25761).

Materials and Methods

The protocol, any amendments thereto, and the patient information sheet/informed consent form were submitted to the relevant independent ethics committees or institutional review boards according to local requirements. Patients provided written informed consent for data collection, if applicable per country regulations.

Study Design

This noninterventional, multinational, multicenter, retrospective medical chart review study was conducted from January 2018 to May 2020 at 16 sites across 5 countries (Belgium, $n = 3$; Denmark, $n = 2$; Israel, $n = 5$; the Netherlands, $n = 2$; and Switzerland, $n = 4$). Adult patients with moderately to severely active IBD and concurrent active EIMs at vedolizumab initiation (index date) with a ≥6-month follow-up after the index date were enrolled. Data collection spanned over 2 main periods anchored to the date of the index event: the pre-index event period, ranging from the date of the UC/CD diagnosis up to 1 day prior to the index date, and the postindex event period/follow-up period, ranging from the index date up to the date of chart abstraction initiation, loss to follow-up, or death, whichever occurred earlier (Supplementary Figure S1). Retrospective data collected from the medical charts (obtained from other health care providers, if necessary) of eligible patients with EIMs of IBD, who initiated vedolizumab per the inclusion criteria, were abstracted to a web-based data entry tool. Each site was estimated to include approximately 10 patients for a target sample size of 200 patients. To minimize selection bias, patients were identified sequentially starting from those who started vedolizumab 6 months prior to the chart abstraction date and going backward in time until the number of patients required per site was reached.

Study Population

The study population consisted of patients 18 years of age and older with a diagnosis of moderate-to-severe CD or UC (per physician's assessment of disease activity) who had received ≥1 dose of vedolizumab for the treatment of IBD and presented with ≥1 clinically active EIM within 8 weeks prior to vedolizumab initiation that had not resolved at the time of vedolizumab initiation (as documented in patients' medical records). Patients were included if follow-up information was available for ≥6 months after the index date. Patients were excluded if they had participated in an interventional clinical trial at the index date or during the follow-up period, had a diagnosis of indeterminate/an unspecified type of IBD, or had initiated vedolizumab treatment as part of a combination therapy with other biological agents.

Study Outcomes

The primary outcome was the percentage of patients treated with vedolizumab experiencing resolution of all EIMs within 6 months post-treatment initiation, defined as the clinical absence of EIM-related symptoms based on the last available clinical assessment; for primary sclerosing cholangitis (PSC), resolution was defined as the normalization of liver enzymes. As a patient could experience ≥1 EIM at the index date, the primary outcome assessed the resolution of all EIMs in the same patient; therefore, if a patient had 2 EIMs, then both of these had to be resolved to be included. The secondary outcomes were as follows: (1) course and outcome of EIMs at 6 and 12 months post-treatment initiation, including resolution; partial response, defined as clinical improvement in EIM symptoms; no response, defined as no change in EIM symptoms; or worsening, defined as clinical exacerbation of EIM symptoms; (2) resolution of EIMs within 12 months post-treatment initiation; (3) new onset of EIMs during the postindex period, defined as any EIM that was not active at the index date (newly diagnosed/de novo EIM, or reactivated historical EIM during the postindex period that was nonactive at the index date); (4) vedolizumab treatment persistence at 12 months post-treatment initiation (based on the percentage of patients who continued with a vedolizumab prescription at 12 months post-treatment initiation, independent of the reason; patients with dose or frequency adjustments but continuing on treatment were considered treatment persistent); and (5) clinical effectiveness of vedolizumab at 14 weeks and at 6 and 12 months post-treatment initiation, defined by the partial Mayo score (PMS) in patients with UC

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(PMS reduction of ≥3 points and a decrease of ≥30.0% from baseline for clinical response and a PMS of ≤1 for clinical remission) and the Harvey-Bradshaw Index (HBI) score in patients with CD (HBI score reduction of ≥3 points for clinical response and an HBI score of ≤4 for clinical remission). Due to a lack of study visits, the time windows defined for each time point to select the closest assessment were 14 ± 2 weeks, 6 ± 1 months, and 12 ± 2 months.

Safety Analyses

Adverse events (AEs) were recorded and safety data reported from the medical records of patients who had received at least 1 dose of vedolizumab. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 20.0.[25]

Statistical Analysis

In this study, the "all patients enrolled" set comprising all patients who provided informed consent was analyzed. Due to the descriptive nature of the study, all results are presented for the overall sample and stratified by diagnosis (UC vs CD). The demographic and clinical characteristics of the patients are presented descriptively. Continuous variables are expressed as mean ± standard deviation (SD) or median (quarter [Q1-Q3]), and categorical variables are expressed as frequency (%). The percentage of patients with resolution of all EIMs within 6 and 12 months post-treatment initiation with vedolizumab are reported for the overall sample. Course and outcome of EIMs at 6 and 12 months post-treatment initiation for each EIM type were described using the response categories defined for data collection (eg, resolution, partial response, no response, and worsening). We conducted analyses per type of EIM, where possible, and globally considered all EIMs together. Crude and adjusted parameter estimates were calculated with 95% confidence intervals (CIs) derived using the Clopper Pearson method. Patients who discontinued vedolizumab prior to 6 months post-treatment initiation were included in the analysis of resolution of EIMs, and lack of response was imputed. For patients who did not complete a visit 6 months post-treatment initiation with vedolizumab, the last available outcome was carried forward to the measure at 6 months. We used Kaplan-Meier curves to estimate the time to EIM resolution per type of EIM, where possible, and globally considered all EIMs together. The persistence rate with vedolizumab treatment at 12 months after the index date was described for all patients included in the study; patients with missing information at 6 months and no information available regarding treatment continuation after 6 months were considered to lack persistence (treatment discontinuation). All statistical analyses were conducted using Statistical Analysis System (SAS) version 9.4 or higher (SAS Institute Inc., Cary, North Carolina).

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki (and its amendments), the International Conference on Harmonisation Good Clinical Practice E6 guidelines, Good Pharmacoepidemiology Practices (GPP), the International Society for Pharmacoepidemiology Guidelines for GPP, and any local regulations.

Results

Baseline and Clinical Characteristics

A total of 99 patients (CD, *n* = 55, 55.6%; UC, *n* = 44, 44.4%) were recruited in this study: 30 (30.3%), 30 (30.3%), 19 (19.2%), 15 (15.2%), and 5 (5.1%) from Israel, Switzerland, Denmark, Belgium, and the Netherlands, respectively. The demographic and clinical characteristics of the patients at the index date are listed in Table 1. The mean (SD) time since IBD diagnosis was 12.4 (10.8) years (CD, 13.4 [11.8] years; UC, 11.0 [9.2] years). Physician's assessment of disease activity was moderate in 58.9% (33 of 56) and severe in 17.9% (10 of 56) of patients. Approximately half (51.5%, 51 of 99) of the patients did not have any chronic comorbidities, whereas the most frequent comorbidities, based on physician's diagnosis affecting 5.0% to 9.0% of the patients, were diabetes, hypertension, renal disease, and rheumatic disease. At the index date, the mean (SD) Charlson Comorbidity Index score was 0.7 (2.0) for the overall population. The mean (SD) and median (Q1-Q3) HBI score for patients with CD was 10.2 (4.1) and 9.5 (6.2-12.8), respectively. The mean (SD) and median (Q1-Q3) PMS for patients with UC was 5.8 (2.0) and 6.0 (5.0-7.0), respectively.

Prior to the index date, approximately one-fourth (23.2%, *n* = 23) of the patients were biologic-naïve; the most common nonbiological drug therapies included corticosteroids (18.2%, *n* = 18), azathioprine (12.1%, *n* = 12), and aminosalicylates (11.1%, *n* = 11); and biological drug therapies included infliximab (63.6%, *n* = 63) and adalimumab (32.3%, *n* = 32). At the index date, the most common concomitant nonbiological IBD-related drug therapies included corticosteroids (36.4%, *n* = 36) and aminosalicylates (18.2%, *n* = 18) and concomitant medications for treating IBD-related EIMs included analgesics (26.3%, *n* = 26; Supplementary Table S1).

All patients in this study had ≥1 EIM, and the most common active EIMs reported at the index date (Table 2) were articular manifestations, including arthralgia (69.7%, *n* = 69), peripheral spondyloarthritis (21.2%, *n* = 21), and axial spondyloarthritis (10.1%, *n* = 10). The most common EIM-related concomitant medications included analgesics (cyclooxygenase-2 [COX-2] inhibitors and aspirin) for peripheral spondyloarthritis (17.2%, *n* = 17), analgesics (COX-2 inhibitors) for axial spondyloarthritis (8.1%, *n* = 8), ursodeoxycholic acid for PSC (4.0%, *n* = 4), topical skin steroids for erythema nodosum (3.0%, *n* = 3), and topical eye steroids for uveitis (1.0%, *n* = 1; Supplementary Table S2).

EIM Response to Vedolizumab Treatment

Within 6 and 12 months of vedolizumab initiation, resolution of all EIMs was reported in approximately one-fifth (19.2%; 19 of 99; 95% CI, 12.0-28.3) and one-fourth (25.3%; 25 of 99; 95% CI, 17.1-35.0) of the patients, respectively (Figure 1). In patients with the corresponding EIM at baseline, the EIMs that resolved at 6 and 12 months, respectively, were arthralgia (20.3% [*n* = 14 of 69] and 26.1% [*n* = 18 of 69]), peripheral spondyloarthritis (28.6% [*n* = 6 of 21] and 33.3% [*n* = 7 of 21]), erythema nodosum (42.9% [*n* = 3 of 7] and 42.9% [*n* = 3 of 7]), PSC (16.7% [*n* = 1 of 6] and 33.3% [*n* = 2 of 6]), and oral aphthous ulcers (0% [*n* = 0 of 3] and 33.3% [*n* = 1 of 3]; Table 3). No resolution was observed in patients with axial spondyloarthritis and uveitis. Overall EIM outcomes (resolution, partial response, no response, worsening, or missing response), as summarized in

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Table 1. Baseline and clinical characteristics at the index date.

Characteristic	CD (N = 55)	UC (N = 44)	Overall Population (N = 99)
Country, *n* (%)			
Israel	19 (34.5)	11 (25.0)	30 (30.3)
Switzerland	16 (29.1)	14 (31.8)	30 (30.3)
Denmark	9 (16.4)	10 (22.7)	19 (19.2)
Belgium	10 (18.2)	5 (11.4)	15 (15.2)
The Netherlands	1 (1.8)	4 (9.1)	5 (5.1)
Age (years)			
Mean (SD)	45.6 (13.5)	42.0 (15.9)	44.0 (14.7)
Sex, *n* (%)			
Female	36 (65.5)	28 (63.6)	64 (64.6)
Male	19 (34.5)	16 (36.4)	35 (35.4)
Ethnicity, *n* (%)			
Caucasian	49 (90.7)	42 (97.7)	91 (93.8)
Asian	0 (0.0)	1 (2.3)	1 (1.0)
Other	5 (9.3)	0 (0.0)	5 (5.2)
Unknown/missing	1 (1.8)	1 (2.3)	2 (2.0)
Weight (kg), *n* (%)	52 (94.6)	36 (81.8)	88 (88.9)
Mean (SD)	71.0 (18.8)	66.7 (14.2)	69.2 (17.1)
BMI (kg/m^2), *n* (%)	50 (90.9)	35 (79.6)	85 (85.9)
Mean (SD)	24.7 (5.9)	23.2 (4.2)	24.1 (5.3)
Smoking status, *n* (%)	48 (87.3)	40 (90.9)	88 (88.9)
Nonsmokers	26 (54.2)	23 (57.5)	49 (55.7)
Current smokers	13 (27.1)	4 (10.0)	17 (19.3)
Ex-smokers	9 (18.8)	13 (32.5)	22 (25.0)
Time since IBD diagnosis (years), *n* (%)	52 (94.6)	38 (86.4)	90 (90.9)
Mean (SD)	13.4 (11.8)	11.0 (9.2)	12.4 (10.8)
Chronic comorbidities,[a] *n* (%)			
None	24 (43.6)	27 (61.4)	51 (51.5)
Asthma	1 (1.8)	1 (2.3)	2 (2.0)
Cerebrovascular disease	2 (3.6)	0 (0.0)	2 (2.0)
Chronic liver disease	0 (0.0)	1 (2.3)	1 (1.0)
Chronic lung disease	0 (0.0)	3 (6.8)	3 (3.0)
Depression	4 (7.3)	0 (0.0)	4 (4.0)
Diabetes	6 (10.9)	3 (6.8)	9 (9.1)
Eye disorder	2 (3.6)	1 (2.3)	3 (3.0)
Gastric or peptic ulcers	1 (1.8)	0 (0.0)	1 (1.0)
Hypertension	3 (5.5)	2 (4.5)	5 (5.1)
Hypo/hyperthyroidism	3 (5.5)	1 (2.3)	4 (4.0)
Renal disease	3 (5.5)	2 (4.5)	5 (5.1)
Rheumatic disease	3 (5.5)	2 (4.5)	5 (5.1)
Skin ulcer	1 (1.8)	0 (0.0)	1 (1.0)
Solid tumor	3 (5.5)	0 (0.0)	3 (3.0)
Other	21 (38.2)	17 (38.6)	38 (38.4)
Charlson Comorbidity Index			
Mean (SD)	0.7 (2.0)	0.6 (2.0)	0.7 (2.0)
Physician assessment of disease activity at diagnosis, *n* (%)	33 (60.0)	23 (52.3)	56 (56.6)
Remission	4 (12.1)	2 (8.7)	6 (10.7)
Mild	3 (9.1)	4 (17.4)	7 (12.5)
Moderate	21 (63.6)	12 (52.2)	33 (58.9)
Severe	5 (15.2)	5 (21.7)	10 (17.9)

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Table 1. Continued

Characteristic	CD (N = 55)	UC (N = 44)	Overall Population (N = 99)
Presence of fistula, *n* (%)	52 (94.5)	39 (88.6)	91 (91.9)
No fistula	46 (88.5)	38 (97.4)	84 (92.3)
Perianal fistula	5 (9.6)	0 (0.0)	5 (5.5)
Entero-enteric or entero-colonic fistula	1 (1.9)	1 (2.6)	2 (2.2)
Disease localization/extent at diagnosis, *n* (%)	52 (94.5)	42 (95.5)	NA
Ulcerative proctitis (E1)	NA	5 (11.9)	NA
Left-sided UC—distal UC (E2)	NA	16 (38.1)	NA
Extension UC—pancolitis (E3)	NA	21 (50.0)	NA
Ileal (L1), possibly involving cecum	13 (25.0)	NA	NA
Colonic (L2)	14 (26.9)	NA	NA
Ileocolonic (L3)	24 (46.2)	NA	NA
Upper gastrointestinal tract involvement (L4)	1 (1.9)	NA	NA

The percentage of patients for each characteristic is calculated using the total patient population analyzed in that category. The number of patients analyzed for each category is shown if different from the total number of patients.
[a] A patient could have experienced more than 1 chronic comorbidity.
Abbreviations: BMI, body mass index; CD, Crohn's disease; E, extent of UC; IBD, inflammatory bowel disease; L, location of disease; NA, not applicable; SD, standard deviation; UC, ulcerative colitis.

Table 2. EIMs reported at the index date.

EIM Type, *n* (%)	CD (N = 55)	UC (N = 44)	Overall Population (N = 99)
Arthralgia	37 (67.3)	32 (72.7)	69 (69.7)
Peripheral spondyloarthritis[a]	14 (25.5)	7 (15.9)	21 (21.2)
Axial spondyloarthritis	6 (10.9)	4 (9.1)	10 (10.1)
Erythema nodosum	5 (9.1)	2 (4.5)	7 (7.1)
PSC	2 (3.6)	4 (9.1)	6 (6.1)
Oral aphthous ulcers	1 (1.8)	2 (4.5)	3 (3.0)
Uveitis	1 (1.8)	0 (0.0)	1 (1.0)

[a]Arthralgia and peripheral spondyloarthritis could be reported simultaneously.
Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Supplementary Table S3, showed an improvement (combination of resolution and partial response per EIM) in 36.5% (38 of 104) and 49.5% (49 of 99) of EIMs with 6 and 12 months of vedolizumab treatment, respectively. The 38 and 49 EIMs observed were calculated by adding the number of different EIMs with resolution and partial response at months 6 and 12, respectively. Overall, in 99 patients, 104 and 99 EIMs were reported at months 6 and 12, respectively, and these included resolution, partial response, no response, worsening, or missing response. For the new onset of EIMs (de novo or reactivated), 1% of patients each reported the new onset of arthralgia, peripheral spondyloarthritis, PSC, and uveitis (Supplementary Table S4).

Treatment Persistence with Vedolizumab

Most patients (70.7%, *n* = 70) received an induction treatment of intravenous vedolizumab 300 mg at 0, 2, and 6 weeks, followed by a maintenance dose every 8 weeks, whereas 23.2% (*n* = 23) of the patients received 1 extra vedolizumab dose at 10 weeks before starting the maintenance dose every 8 weeks (Supplementary Table S5). Over one-fourth (27.3%, *n* = 27) of the patients had recorded changes to their vedolizumab treatment regimen within the 12-month follow-up period, with a mean (SD) time to the first treatment regimen change of 9.7 (6.9) months. The primary changes in the treatment regimen included increased dosing frequency (21.2%, n = 21), reduced dosing frequency/extended interval (2.0%, n = 2), and increased dose (2.0%, *n* = 2). The reasons for dose increase or increased dosing frequency, as recorded by the physician in the patient's medical chart, included partial treatment response (IBD management, 10.1%, *n* = 10; EIM management, 2.0%, *n* = 2) and lack of effectiveness (IBD management, 9.1%, *n* = 9; EIM management, 1.0%, *n* = 1).

The treatment persistence rate of vedolizumab at 12 months was 82.8% (82 of 99; 95% CI, 73.9-89.7; CD, 78.2% [43 of 55]; 95% CI, 65.0-88.2 and UC, 88.6% [39 of 44]; 95% CI, 75.4-96.2). The time from vedolizumab initiation to the first EIM resolution and the last EIM resolution for up to 12 months is shown in Supplementary Figure S2A and S2B, and the time to vedolizumab discontinuation is shown in Figure 2. Over the complete follow-up period, the estimated median time to vedolizumab discontinuation among patients with UC was 45.1 months. The lower limit of the 95% CI was 25.1 months, but the upper limit was not reached due to

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the limited follow-up period (at the time of data collection, less than 75% of the patients had discontinued treatment). Median time to discontinuation could not be estimated for patients with CD, as fewer than 50% of them discontinued vedolizumab (Figure 2).

Real-world Clinical Effectiveness of Vedolizumab

Patients' data on clinical outcomes of IBD were limited. At 14 (±2) weeks after vedolizumab initiation, clinical response and clinical remission were achieved in 33.3% (4 of 12) and 58.3% (7 of 12) of the patients with available data, respectively. At 6 (±1) months after vedolizumab initiation, clinical response and clinical remission were achieved in 20.0% (3 of 15) and 46.7% (7 of 15) of the patients, respectively. At 12 (±2) months after vedolizumab initiation, clinical response and clinical remission were achieved in 23.1% (3 of 13) and 30.8% (4 of 13) of the patients, respectively.

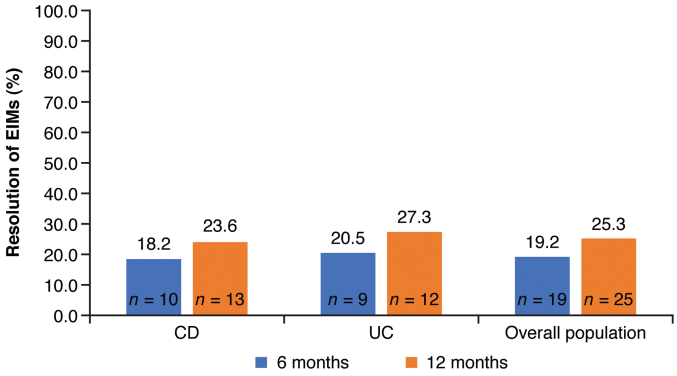

Figure 1. Resolution[a] of EIMs within 6 and 12 months of vedolizumab initiation at the index date by disease subgroup. [a] Resolution was defined as the clinical absence of EIM-related symptoms (or normalization of liver enzymes for PSC). Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Safety Results

Of the 33 AEs (CD, 21; UC, 12) reported, the most frequent AE was arthralgia in 4.0% of the patients, followed by back pain, constipation, eczema, and headache, each in 2.0% of the patients, and bronchitis, dyspepsia, erythema, gastroenteritis, hypertension, muscular weakness, and paresthesia, each in 1.0% of the patients (Table 4). Of the 27 patients with available data for seriousness of AEs, 96.3% (26 of 27) had AEs that were nonserious. Pulmonary embolism was the only serious AE reported in 1 patient with CD and was not related to vedolizumab as assessed by the investigator.

Discussion

The current EMOTIVE study adds to the growing body of real-world studies on the effectiveness of vedolizumab in the subgroup of patients with IBD and concurrent EIMs. To date, few studies have evaluated the course and outcome of vedolizumab-treated IBD patients with EIMs in a real-world setting.[20,22–24,26–29] The results of a French national multicenter cohort study (OBSERV-IBD) showed that vedolizumab treatment was associated with successful resolution of or at least improvement in EIMs such as arthritis/arthralgia.[19] A recent systematic review on vedolizumab treatment for EIMs in IBD found that for most EIMs (apart from PSC and arthralgia), no analysis could be performed due to the limited number of events.[30] Furthermore, outcome measures, clinical definition, and characteristics of EIMs were different across the studies.[30] Altogether, the review lacked strong evidence to suggest

Table 3. Resolution[a] of EIMs within 6 and 12 months of vedolizumab initiation at the index date by EIM type.

	Resolution Within 6 Months of the Index Date			Resolution Within 12 Months of the Index Date		
EIM Type, *n*/N (%)	CD	UC	Overall Population	CD	UC	Overall Population
Arthralgia	5/37 (13.5)	9/32 (28.1)	14/69 (20.3)	6/37 (16.2)	12/32 (37.5)	18/69 (26.1)
95% CI	4.5-28.8	13.7-46.7	11.6-31.7	6.2-32.0	21.1-56.3	16.3-38.1
Peripheral spondyloarthritis	5/14 (35.7)	1/7 (14.3)	6/21 (28.6)	6/14 (42.9)	1/7 (14.3)	7/21 (33.3)
95% CI	12.8-64.9	0.4-57.9	11.3-52.2	17.7-71.1	0.4-57.9	14.6-57.0
Axial spondyloarthritis	0/6 (0.0)	0/4 (0.0)	0/10 (0.0)	0/6 (0.0)	0/4 (0.0)	0/10 (0.0)
95% CI	0.0- 45.9	0.0-60.2	0.0-30.8	0.0-45.9	0.0-60.2	0.0-30.8
Erythema nodosum	3/5 (60.0)	0/2 (0.0)	3/7 (42.9)	3/5 (60.0)	0/2 (0.0)	3/7 (42.9)
95% CI	14.7-94.7	0.0-84.2	9.9-81.6	14.7-94.7	0.0-84.2	9.9-81.6
PSC	0/2 (0.0)	1/4 (25.0)	1/6 (16.7)	1/2 (50.0)	1/4 (25.0)	2/6 (33.3)
95% CI	0.0-84.2	0.6-80.6	0.4-64.1	1.3-98.7	0.6-80.6	4.3-77.7
Oral aphthous ulcers	0/1 (0.0)	0/2 (0.0)	0/3 (0.0)	1/1 (100.0)	0/2 (0.0)	1/3 (33.3)
95% CI	0.0-97.5	0.0-84.2	0.0-70.8	2.5-100.0	0.0-84.2	0.8-90.6
Uveitis	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)	0/1 (0.0)	0/0 (0.0)	0/1 (0.0)
95% CI	0.0-97.5	NA	0.0-97.5	0.0-97.5	NA	0.0-97.5
All EIMs	10/55 (18.2)	9/44 (20.5)	19/99 (19.2%)	13/55 (23.6)	12/44 (27.3)	25/99 (25.3)
95% CI	9.1-30.9	9.8-35.3	12.0-28.3	13.2-37.0	15.0-42.8	17.1-35.0

[a]Resolution was defined as the clinical absence of EIM-related symptoms (or normalization of liver enzymes for PSC). Percentages calculated using the total number of patients, with the corresponding EIM at baseline visit (valid n) as the denominator.
Abbreviations: CD, Crohn's disease; CI, confidence interval; EIM, extraintestinal manifestation; NA, not applicable; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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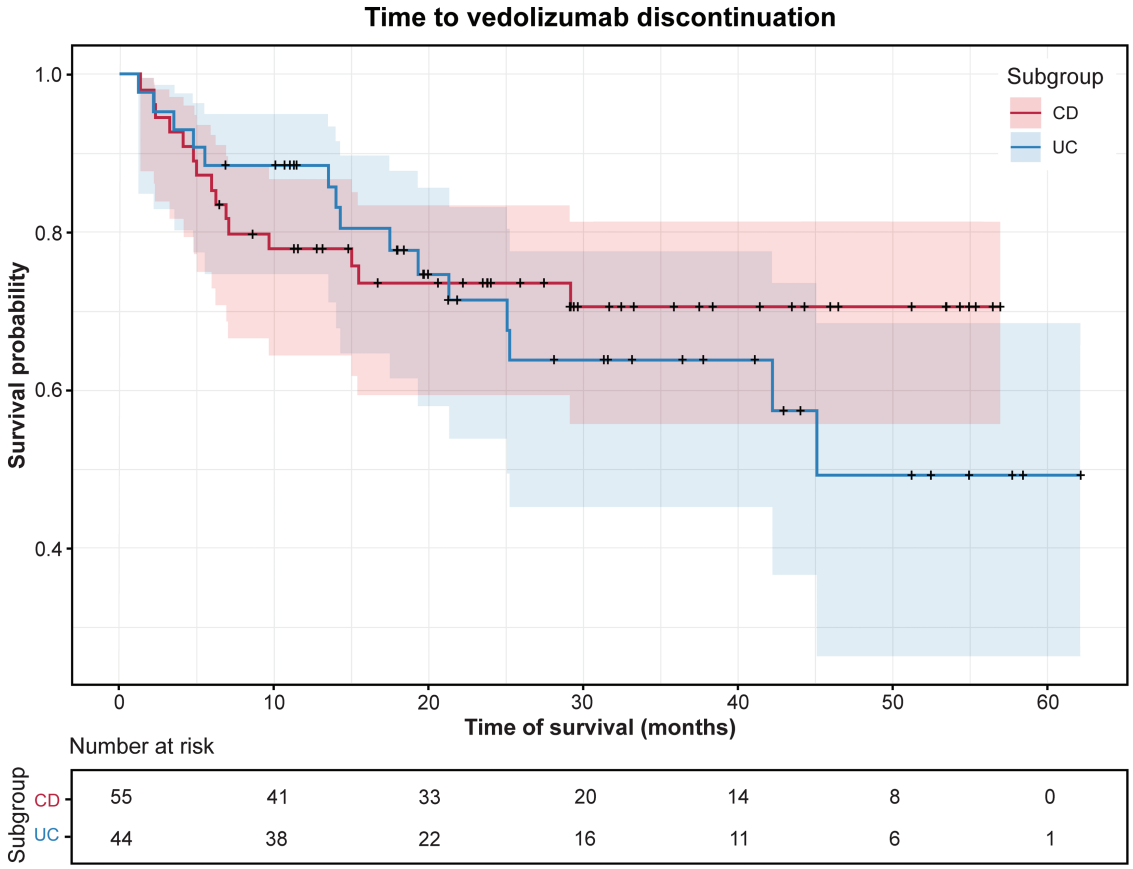

Figure 2. Kaplan-Meier plot to depict time to vedolizumab discontinuation. +Indicates censored data. Abbreviations: CD, Crohn's disease; EIM, extraintestinal manifestation; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

Table 4. AEs during vedolizumab treatment.

	CD (N = 55)	UC (N = 44)	Overall Population (N = 99)
AEs, *n* (%)			
Arthralgia	2 (3.6)	2 (4.5)	4 (4.0)
Back pain	1 (1.8)	1 (2.3)	2 (2.0)
Bronchitis	1 (1.8)	0 (0.0)	1 (1.0)
Constipation	1 (1.8)	1 (2.3)	2 (2.0)
Dyspepsia	1 (1.8)	0 (0.0)	1 (1.0)
Eczema	0 (0.0)	2 (4.5)	2 (2.0)
Erythema	1 (1.8)	0 (0.0)	1 (1.0)
Gastroenteritis	1 (1.8)	0 (0.0)	1 (1.0)
Headache	2 (3.6)	0 (0.0)	2 (2.0)
Hypertension	0 (0.0)	1 (2.3)	1 (1.0)
Muscular weakness	1 (1.8)	0 (0.0)	1 (1.0)
Paresthesia	1 (1.8)	0 (0.0)	1 (1.0)
Other	6 (10.9)	4 (9.1)	10 (10.1)
Serious AEs, *n* (%)			
Pulmonary embolism	1 (1.8)	0 (0.0)	1 (1.0)

Abbreviations: AE, adverse event; CD, Crohn's disease; UC, ulcerative colitis.

the efficacy of vedolizumab in the treatment of preexisting EIMs.[30] The current descriptive study supports the impact of vedolizumab on EIMs in patients with IBD, recognizing that the study was not designed to establish the effectiveness of vedolizumab treatment on EIM outcomes observed during the study period. Although the mechanism of action remains to be fully elucidated, vedolizumab may be particularly effective in EIMs associated with active luminal disease, and the general treatment of IBD through vedolizumab-mediated integrin α4β7-blockade results in concomitant resolution of those EIMs.[31,32] The most frequent EIMs in our study population were articular manifestations, including arthralgia, peripheral spondyloarthritis, and axial spondyloarthritis, and the less frequent EIMs included erythema nodosum, PSC, oral aphthous ulcers, and uveitis at the index date. No patients had Sweet's syndrome, pyoderma gangrenosum, or episcleritis. This may be attributed to the limited number of patients included and the overall low prevalence of these EIMs in the IBD population.[4,33]

Although several studies have suggested a risk of developing skin and articular manifestations after initiating vedolizumab,[16] it is not clear from the existing evidence if "new onset of EIMs" under vedolizumab are de novo EIMs or a consequence of transitioning from a previous systemic immunosuppressive treatment (under which the EIM was nonactive) to vedolizumab, leading to the reactivation of an existing EIM.[31] In the current study, the EIM status changed from "nonactive" at the index date to "active" within 12 months of vedolizumab initiation in a small percentage of

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patients; however, firm conclusions regarding the association between these new onset EIMs and vedolizumab treatment are unable to be drawn.

Prior to vedolizumab initiation, most patients had received at least 1 other biological therapy, most commonly infliximab and adalimumab, and approximately one-fourth of the patients were biologic-naïve. Among patients who reported changes in vedolizumab treatment within the 12-month follow-up period, most reported an increased vedolizumab administration frequency due to partial response or lack of effectiveness for the management of IBD. Increased treatment frequency in the administration of vedolizumab has been previously associated with improved IBD outcomes, including clinical remission and clinical response.[34] Interestingly, in the current study, the reason for dose increase or increased dosing frequency was mainly related to IBD management, although dose increase or increased dosing frequency related to EIM management was reported in a very low proportion of patients.

Anti-TNFs are the main biological treatments for EIMs in IBD and are confirmed to be effective, with clinical response in over 50% of patients.[8] For example, a retrospective analysis of the Swiss IBD Cohort Study reporting the use of 3 anti-TNF agents in patients with IBD presenting with EIMs showed improvement rates of 71.8% in the underlying EIM.[35] The current study provides some evidence on the efficacy of the gut-selective agent vedolizumab on EIMs. Over one-third (36.5%) and half (49.5%) of all EIMs showed improvement (resolution and partial response) at 6 and 12 months of vedolizumab treatment, respectively. Moreover, the percentage of patients with improvements in articular manifestations such as arthralgia, peripheral spondyloarthritis, and axial spondyloarthritis increased from 31.0%, 60.0%, and 22.2% at 6 months from vedolizumab initiation to 42.6%, 70.0%, and 33.3% at 12 months from vedolizumab initiation, respectively.

A post hoc analysis of the GEMINI 2 trial conducted in patients with CD found a larger proportion of patients with resolved EIMs among those treated with vedolizumab vs placebo (13.0% and 32.0% vs 4.0% and 23.0% at week 26 and week 52, respectively).[21] The results from OBSERV-IBD showed complete remission of inflammatory arthralgia/arthritis in 44.7% of the patients.[19] In the current study, resolution of all EIMs was reported in 19.2% and 25.3% of the patients, whereas resolution of arthralgia was reported in 20.3% and 26.1% of the patients at 6 and 12 months from vedolizumab initiation, respectively. The difference in the rates observed in GEMINI 2, OBSERV-IBD, and the current study could be explained based on how patients were categorized. Specifically, in the GEMINI 2 study, patients were classified by treatment group (vedolizumab vs placebo),[21] whereas in the OBSERV-IBD study, patients were classified by the presence or absence of inflammatory arthralgia/arthritis.[19]

This study also evaluated the real-world clinical effectiveness of vedolizumab in IBD at 14 weeks, 6 months, and 12 months; however, the proportion of patients with IBD response information reported ranged only between 14% and 21%. The overall treatment persistence of vedolizumab at 12 months was 82.8%; the treatment persistence rate of vedolizumab at 12 months was lower among patients with CD (78.2%) vs those with UC (88.6%). The treatment persistence rates for vedolizumab were either similar to or higher than those reported in similar studies, wherein the 6-month vedolizumab persistence ranged between 66% and 88%[36,37] and 67% and 88% at around 12 months (52 and 54 weeks).[38,39]

The safety profile of vedolizumab observed in this study was consistent with that reported in the GEMINI long-term safety study, which reported a low incidence (20%) of serious AEs in an interim analysis after 152 weeks.[34] Of the 33 AEs reported in 18.2% of patients in the present study, 96.3% were reported as a nonserious AE, and arthralgia was reported as an AE in 4.0% of patients. The only serious AE reported was pulmonary embolism in a patient with CD, which recovered/resolved and was assessed by the investigator as being unrelated to vedolizumab treatment.

Our study has several limitations that should be highlighted. Overall, the target sample size was not reached because of the low number of patients meeting the inclusion criteria. Owing to its retrospective nature and the use of patient medical charts as the main data source, there were several missing values such as those related to the evolution of EIMs or IBD. Data on clinical outcomes and endoscopic follow-up were limited. Notably, for this real-world study, variability across the study centers would also be expected in the physicians' interpretation and application of the response and remission criteria, as these outcomes were not predefined. More robust standardization can be explored in future studies. In addition, the effect of concomitant medications on the course and outcome of EIMs cannot be ruled out in this noncomparative study. Additionally, the severity of EIMs was not assessed at baseline. Moreover, because of the retrospective design, there was potential for selection bias based on vedolizumab treatment selection, wherein patients with less severe EIMs may have been included in the study. The absence of supporting radiologic findings to confirm investigator-assessed resolution of PSC in this study is another limitation. Lastly, given that AE data were collected retrospectively from patients' medical records, reporting bias cannot be discounted due to the potential under-registration of less severe AEs.

Conclusion

This real-world multicenter chart review study described the resolution of all EIMs, especially articular manifestations, in approximately one-fifth and one-fourth of patients with IBD with 6 and 12 months of treatment with vedolizumab, respectively. In addition, one-third and half of EIMs improved with 6 and 12 months of treatment with vedolizumab, respectively. Further prospective studies with consistent definitions of response and remission, including standardized assessment of EIMs, are warranted to validate the findings from this study and further understand the impact of vedolizumab on EIMs.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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involved in all operational and study management aspects, including feasibility, selecting the countries and sites, organizing the steering committee meeting at the beginning of the study, and contracting, budgeting, and communicating with the sites. Daniela Bojic, a former employee of Takeda, provided substantial inputs on the study protocol. The statistical analysis was performed by IQVIA. Medical writing assistance was provided by Archana Patkar, PhD, of Cactus Life Sciences (part of Cactus Communications) and funded by Takeda Pharmaceuticals International AG. The authors retained full control of the manuscript content.

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Conflicts of Interest

U.K. has received advisory and speaker fees from AbbVie, BMS, Janssen, MSD, Medtronic, Pfizer, Rafa, and Takeda and research support from Janssen, Takeda, and Medtronic. J.B. has received advisory and/or consulting fees from AbbVie, Janssen-Cilag, Celgene, Pfizer, Samsung Bioepis, MSD, Takeda, Tillotts Pharma, and Pharmacosmos and grants from MSD, Takeda, Tillotts Pharma, Bristol Myers Squibb, and Novo Nordisk. S.B.-H. has received advisory and/or consulting fees from AbbVie, Janssen, Pfizer, Takeda, Celltrion, GSK, Ferring, Novartis, Roche, Gilead, Neopharm, Galmed, and Medial EarlySign and research support from AbbVie, Janssen, Pfizer, Takeda, Celltrion, and Galmed. F.B. was an employee of Takeda Pharmaceuticals International holding Takeda stock options at the time the study was conducted. A.F.-N. is a full-time employee of Takeda Farmacéutica España S.A. and holds Takeda stock options. N.L. and H.S.H. have no conflicts of interest to declare. S.R.V. has received consultancy fees, research grants, and speaker fees from Abbott, Celltrion, Ferring, MSD, Pfizer, Takeda, Sanofi-Aventis, Tillotts Pharma, UCB, Vifor, and Falk Pharma.

Data Availability

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable 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.

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