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Short and long-term effectiveness and safety of vedolizumab in inflammatory bowel disease: results from the ENEIDA registry

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Summary

Background: Effectiveness of vedolizumab in real world clinical practice is unknown.

Aim: To evaluate the short and long-term effectiveness of vedolizumab in patients with inflammatory bowel disease (IBD).

Methods: Patients who received at least 1 induction dose of vedolizumab were included. Effectiveness was defined based on Harvey-Bradshaw index (HBI) in Crohn's disease (CD) and Partial Mayo Score (PMS) in ulcerative colitis (UC). Short-term response was assessed at week 14. Variables associated with short-term remission were identified by logistic regression analysis. The Kaplan-Meier method was used to evaluate the long-term durability of vedolizumab treatment. Cox model was used to identify factors associated with discontinuation of treatment and loss of response.

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Results: 521 patients were included (median follow-up 10 months [interquartile range 5-18 months]). At week 14, 46.8% had remission and 15.7% clinical response. CD (vs UC), previous surgery, higher CRP concentration and disease severity at baseline were significantly associated with impaired response. The rate of vedolizumab discontinuation was 37% per patient-year of follow-up (27.6% in UC and 45.3% in CD, $P < 0.01$). CD (vs UC), anaemia at baseline, steroids during induction and CRP concentration were associated with lower durability of treatment. Seven per cent of patients developed adverse events, infections being the most frequent.
Conclusions: Over 60% of IBD patients respond to vedolizumab. Many patients discontinue treatment over time. CD and disease burden impair both short- and long-term response. Vedolizumab seems to be safe in clinical practice.

1 | INTRODUCTION

Anti-tumour necrosis factor alpha (anti-TNF) drugs have dramatically changed the treatment of inflammatory bowel disease (IBD). A proportion of patients treated with anti-TNF drugs will not respond (primary nonresponse) to this therapy or lose response (secondary nonresponse) over time.[1-3] For these reasons, the development of new treatments for IBD directed against different therapeutic targets, based on drugs with more specific mechanism for local effect in the inflamed organ, is an unmet need.

Vedolizumab, a monoclonal antibody that blocks leucocyte trafficking to the gut mucosa through inhibition of $\alpha4\beta7$ integrins,[4] was approved by the Food and Drug Administration and by the European Medicines Agency in 2014 for the treatment of moderate-to-severe ulcerative colitis (UC) and Crohn's disease (CD). The efficacy of vedolizumab for the induction and maintenance of remission in patients with IBD has been proved in the GEMINI clinical trials.[5-10] In addition, long-term safety studies (GEMINI-LTS), which include patients from the GEMINI trials, provide information of the long-term efficacy and safety of vedolizumab.[9,10] However, patients included in clinical trials might not be representative of what happens in real life—for example, only about one-third of patients would fulfil the eligibility criteria of the GEMINI trials.[11]

To date, limited information on the effectiveness and safety of this drug in clinical practice is available[11-19] (Table 1). Furthermore, the long-term benefit of vedolizumab in clinical practice is barely known, as there are only three studies that have evaluated the effectiveness of this agent after approximately 1 year follow-up.[14,17,19] Therefore, additional post-marketing data are required to know the durability and to confirm the long-term benefit and safety of this drug in the clinical practice setting.

Through this multicentre nationwide study we aimed to evaluate the real effectiveness of vedolizumab for the induction of clinical remission at week 14 in a large IBD population and to identify predictors of response. In addition, we aimed to assess the long-term effectiveness of vedolizumab and to determine the safety of this drug in a large multicentre nationwide cohort of IBD patients. We anticipate that our results will help to understand the usefulness of vedolizumab in clinical practice and to select the subset of patients who will benefit most from this agent.

2 | METHODS

2.1 | Study protocol

IBD patients (CD, UC, and IBD unclassified) of the ENEIDA registry that had received at least one dose of vedolizumab due to active disease (Partial Mayo Score [PMS][20] ≥2 or Harvey-Bradshaw [HBI][21] >4) were included. ENEIDA is a large prospectively maintained Spanish database promoted by the Spanish Working Group in Crohn's and Colitis (GETECCU), initiated in 2007, which in December 2017 included over 45 000 patients from 86 centres. Patients who were in clinical remission at the time of starting vedolizumab and those who were still receiving the induction doses and had not reached week 14 at the time of analysis were excluded.

The two principal variables in our study were: the proportion of patients that reached clinical remission at week 14 and the proportion of patients that maintained the treatment with either the

TABLE 1 Population-based studies assessing the effectiveness of vedolizumab in inflammatory bowel disease patients

	N	Study design	Follow-up (weeks)	End-points	Effectiveness	Predictors of response
Shelton et al[11]	172 IBD (107 CD)	Retrospective and prospective	14	Clinical response (decrease in HBI ≥3 or SCCAI ≥3) and remission (HBI ≤4 or SCCAI ≤2)	CD: 48.9% response and 23.9% remission UC: 53.9% response and 29.3% remission	Elevated CRP at baseline (impaired response)
Baumgart et al[12]	212 active IBD (97 CD)	Prospective	14	Clinical remission (HBI ≤4 or PMS ≤1)	CD: 60.8% response and 19.6% remission UC: 57.4% response and 19.1% remission	Low HBI score and no hospitalisation in past 12 months, better effectiveness in CD
Amiot et al[13]	294 active IBD (173 CD)	Prospective	14	Steroid-free remission Clinical remission (HBI ≤4 or PMS <3)	CD: 51% response and 31% remission UC: 50% response and 36% remission	CD: Clinical response at week 6 (better response) and concomitant steroids and HBI score >10 (impaired response) UC: Clinical response at week 6 (better response) and CRP >20 g/dL and PMS >10 (impaired response)
Dulai et al[14]	212 active CD	Retrospective	39 (median)	Clinical remission (complete resolution of CD symptoms) Mucosal healing (no erosions)	35% cumulative clinical remission 63% cumulative mucosal healing	Prior anti-TNF use, smoking history, severe disease activity and active perianal disease associated with impaired response.
Kopylov et al[15]	204 IBD (130 CD)	Prospective	14	Clinical remission (HBI ≤4 or PMS <2 or SCCAI ≤3). PGA when scores were not available	CD: 53% response and 34.6% remission UC: 43% response and 28.4% remission	CD: Mild activity at treatment onset (better response) UC: Mild activity at treatment onset (better response)
Stallmach et al[16]	127 active IBD (67 CD)	Prospective	54	Clinical remission (HBI ≤4 or PMS ≤1)	CD: 15% steroid-free remission (NRI) UC: 22% steroid-free remission (NRI)	CD: Response and remission at week 14 and lower CRP in comparison with baseline (better response) CD: No prior anti-TNF, use of steroids less than 25% within the last 6 months, response and remission at week 14, lower CRP in comparison with baseline and lower faecal calprotectin at week 14 (better response)
Allegretti et al[17]	136 IBD	Retrospective Patients with response at week 14 were included	54	Clinical response (decrease in HBI ≥3 or SCCAI ≥3) and remission (HBI ≤4 or SCCAI ≤2)	73% remained in remission at week 54 CD: 67% in remission UC: 88% in remission	CD: Immunomodulator during induction UC: Not identified
Eriksson et al[18]	246 IBD (147 CD)	Retrospective	68	Drug discontinuation rate (due to lack of or loss of response)	58% remained on vedolizumab after median 17 months	Previous anti-TNF and elevated CRP at baseline (discontinuation due to lack of response). Female sex (discontinuation due to intolerance)

(Continues)

TABLE 1 (Continued)

	N	Study design	Follow-up (weeks)	End-points	Effectiveness	Predictors of response
Amiot et al[19]	272 IBD (161 CD)	Prospective	54	Steroid-free remission (HBI ≤4 or PMS <3) at week 54	CD: 27% steroid-free remission UC: 40.5% steroid-free remission	CD: Clinical response at week 6 (better response). Concomitant steroids at induction and HBI≥10 (impaired response) UC: Clinical response at week 6 (better response). Concomitant steroids at induction, leucocytes >9.000/mm^3 and HBI ≥10 (impaired response)

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; HBI, Harvey-Bradshaw index; PMS, Partial Mayo Score; CRP, C-reactive protein; SCCAI, Simple Clinical Colitis Activity Index.

standard or the escalated regimen (other than 300 mg every 8 weeks). As secondary end-points, we analysed the rate of loss of response during follow-up and the safety of the drug.

Short-term response was evaluated at week 14. To assess the durability of response to vedolizumab all the patients were included. To evaluate the cumulative incidence of loss of response, only patients with primary response or remission at week 14 (after the induction doses) were considered. Patients were evaluated for clinical activity and adverse events at each vedolizumab infusion during follow-up.

ENEIDA registry was approved by Research Ethic Committees in all participating centres. All co-authors had access to the study data and had reviewed and approved the final manuscript.

2.2 | Data collection

ENEIDA registry prospectively records the use, effectiveness and adverse events of immunomodulators and biological therapies in IBD patients. Variables collected for this study were sex, age, smoking status, age at diagnosis, type of IBD (CD, UC, IBD unclassified), location, disease behaviour (inflammatory, stenosing or fistulising), perianal disease, extraintestinal manifestations, previous surgery for IBD, concurrent use of immunomodulators, previous treatments for IBD, starting date of vedolizumab therapy, response to vedolizumab, date of loss of response (when it occurred), treatment option after loss of response, response to escalated vedolizumab dose and adverse events with standard and escalated treatment. ENEIDA registry is a prospectively maintained database. Practitioners include the information from face-to-face appointments while patients are in the IBD clinic. Patients receive vedolizumab infusion in the hospital; therefore, the clinicians have the opportunity to assess the patients' status and select those who fulfil ENEIDA registry requirements. Additional information such as endoscopic assessment or biological markers such as C-reactive protein (CRP) was requested from the treating practitioners, when available. All adverse events during the follow-up period were recorded. The database was monitored and queries were resolved by contacting practitioners to ensure data quality.

2.3 | Definitions

2.3.1 | Active disease

Active disease was defined as an HBI >4 for CD.[21] In the case of UC, active disease was defined as a score ≥2 points in the PMS.[22] When endoscopy was available, the severity was graded as quiescent, mild, moderate or severe by local site investigators. Neither the SES-CD nor the Mayo endoscopic score were available as their use in clinical practice is highly uncommon.

2.3.2 | Severity of clinical activity

The severity of clinical activity was rated based on HBI in CD (<5: remission, 5-7: mild, 8-16: moderate and >16: severe activity)[21] and on the PMS in UC (<2: remission, 2-4: mild; 5-7: moderate and >7: severe activity).[22]

2.3.3 | Evaluation of response

When response to induction was evaluated, clinical remission/response was determined by the above-mentioned clinical indexes calculated both at baseline and at week 14. Clinical remission was defined as a PMS <2 for UC and an HBI score <5 for luminal CD. For UC, clinical response was defined as a reduction in the PMS ≥3 points and a decrease of at least 30% from baseline, with a decrease ≥1 point on the rectal bleeding subscale (absolute score 0-1). For luminal CD, response was defined as a decrease in the HBI ≥3 points without reaching remission.

2.3.4 | Loss of efficacy

Loss of efficacy was defined as worsening of patient's symptoms combined with endoscopic, radiographic and/or serologic (elevated CRP) evidence of inflammation, which led the physician to escalate the dose of treatment, to add or change to another drug or to change to surgery.

2.3.5 | Dose escalation

Dose escalation was defined as a decrease in vedolizumab infusion interval, for example, 300 mg every 4 weeks.

2.3.6 | Durability of vedolizumab

Durability of vedolizumab was calculated considering the entire period under vedolizumab treatment: from the first to the last dose. In addition, time to loss of efficacy (see above) was also calculated.

2.4 | Statistical analysis

For categorical variables percentages were calculated (with their 95% confidence intervals [95% CI]). The descriptive analysis of quantitative variables calculated the mean and standard deviation (SD), or the median and interquartile range (IQR), depending on whether they were normally distributed or not. In the univariate analysis, categorical variables were compared using Chi-square (χ^2) test and quantitative variables using the appropriate test. The variables associated with short-term remission were identified by logistic regression analysis.

A Kaplan-Meier analysis, where patients who discontinued vedolizumab for any reason were rightly censored at the time of discontinuation, was used to evaluate the long-term durability of vedolizumab treatment, and any differences between survival curves were evaluated with the log-rank test. As a secondary end-point, the Kaplan-Meier method was used to evaluate the time to loss of efficacy of the treatment; in this case, patients who lost response to vedolizumab were rightly censored at the time of loss of efficacy. Any differences between survival curves were evaluated with the log-rank test. Stepwise multivariable analysis using the Cox model was used to investigate factors potentially associated with vedolizumab discontinuation. In the log-rank test and in the multivariable analysis, statistical significance was considered when $P < 0.05$. In addition, variables associated with loss of response to the standard dose of vedolizumab were studied with the same statistical methods.

3 | Results

Up to December 2017, 828 patients that had received at least one vedolizumab infusion were included in ENEIDA registry. A total of 521 (63%) of them had active disease when they started vedolizumab. Thirteen patients were excluded because they were still receiving the induction doses and had not reached week 14 at the time of data extraction. Finally, 508 patients were included (Figure 1).

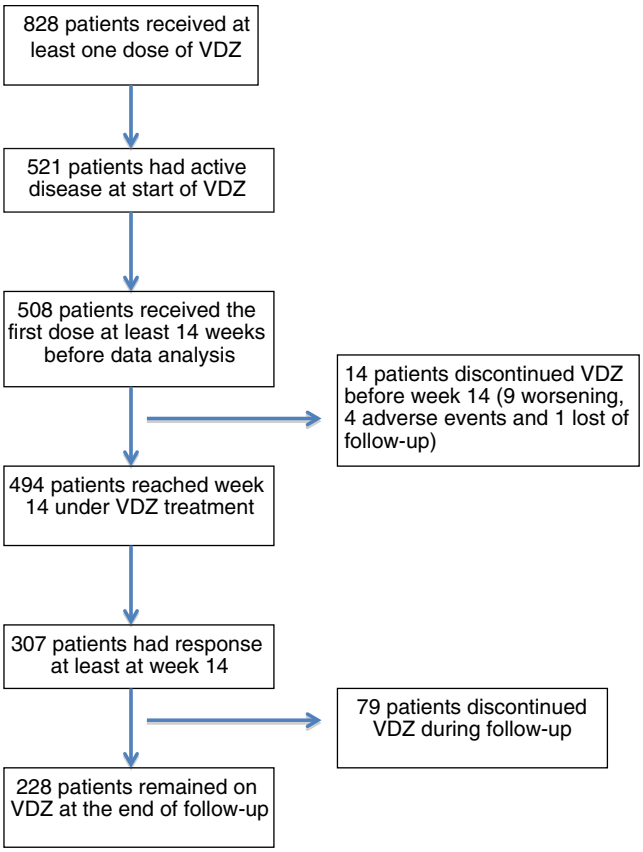

FIGURE 1 Flow chart of patients treated with vedolizumab (VDZ)

3.1 | Short-term effectiveness

The main characteristics of the study population are summarised in Table 2. The majority of patients had been exposed to prior anti-TNF agents (93%), and the median number of previous anti-TNF agents was 2. Almost 50% of patients had anaemia, median CRP was high (1.2 mg/dL) and 66% of patients had moderate-severe disease at baseline. Two-thirds of the patients were under immunomodulators and 60% received steroids when they started vedolizumab treatment. Finally, 31.8% of patients had undergone intestinal resection before starting vedolizumab treatment.

Fourteen patients dropped out before week 14 because of several reasons: severe disease activity despite vedolizumab treatment (9), adverse events (4) and missed follow-up (1). At week 14, 230 patients (46.8%) reached remission, 77 (15.7%) clinical response and 184 (37.5%) were primary nonresponders. Among UC patients, 118 (49.8%) had remission and 41 (17.3%) clinical response at week 14. With respect to CD patients, 111 (44.6%) had remission and 35 (24%) clinical response at week 14.

Basal CRP concentration was lower among remitters at week 14. In addition, the proportion of patients with previous surgery and the proportion of patients with severe disease were higher among non-remitters at week 14. In the multivariable analysis, CD (instead of UC), higher CRP concentration at baseline, previous intestinal resection and higher severity of the disease were significantly associated with impaired response to vedolizumab treatment (Table 3). Other variables, such as concomitant immunomodulators, steroids at induction and previous anti-TNF exposure, were not associated with remission at week 14.

TABLE 2 Characteristics of the study population

Median age (IQR) (years)	42 (34-54)
Median disease duration (IQR) (months)	119 (53-184)
Female gender (%)	279 (54.8)
Smoking status (%)	80 (15.7)
Extraintestinal manifestations (%)	154 (30.3)
Crohn's disease (%)	259 (50.9)
Isolated ileal location (%)	63 (26.5)
Isolated colonic location (%)	36 (15.1)
Ileocolonic disease (%)	139 (58.4)
Upper gastrointestinal tract (%)	31 (12)
Inflammatory (%)	134 (53.2)
Stricturing (%)	62 (24.6)
Penetrating (%)	56 (22.2)
Perianal disease (%)	84 (16)
Ulcerative colitis (%)	244 (47.9)
Extensive (%)	146 (60.8)
Left-sided (%)	84 (35)
Median Harvey-Bradshaw Index score (IQR)	8 (6-10)
Median Partial Mayo Score (IQR)	6 (5-7)
Median CRP (mg/dL) (IQR)	1.2 (0.39-2.8)
Mean haemoglobin (g/dL) (SD)	12.7 (0.07)
Anaemia (%)	222 (43.6)
Concomitant immunosuppresants (%)	332 (65)
Steroids during induction (%)	306 (60.6)
Prior anti-TNF treatment (%)	474 (93)
Median number of previous biologics (IQR)	2 (1-3)
Prior surgery for IBD (%)	162 (31.8)

IQR, interquartile range; CRP, C-reactive protein; SD, standard deviation; IBD, inflammatory bowel disease.

Our cohort comprised 237 UC patients. Ninety-eight (41%) had severe activity and 85 (36%) had moderate activity of the disease. At week 14, 159 (67%) had response (49.8% remission). In the univariate analysis, PMS at baseline was significantly higher in non-remitters. In the multivariable analysis, higher CRP at baseline (OR = 0.8 [95% CI = 0.8-0.9]) and mild (vs severe) activity (OR = 6.6 [95% CI = 3-14.7]) were significantly associated with remission at week 14.

In our cohort, 249 patients had CD. Ninety-eight per cent had mild to moderate disease at baseline. At week 14, 146 patients (58.7%) had response (44.6% remission). In the univariate analysis, remitters at week 14 had lower HBI and CRP at baseline than non-remitters. In the multivariable analysis, higher HBI score at baseline was the only variable associated with lower probability of achieving remission (OR = 0.6 [95% CI = 0.5-0.7]).

3.2 | Long-term survival of vedolizumab treatment

A total of 194 patients discontinued vedolizumab treatment during follow-up (median 10 months [IQR = 5-18 months]). The proportion of patients that remained under vedolizumab treatment was 66% after 12 months, and 49% after 24 months of follow-up. The incidence rate of vedolizumab discontinuation was 37% per patient-year of follow-up. The most frequent reason for vedolizumab discontinuation was primary nonresponse (48.5%), followed by loss of response (29%) (Table 4). Among UC patients, 68 (27%) discontinued the treatment with vedolizumab during follow-up (median 10 months [IQR = 5-18 months]); the incidence rate of vedolizumab discontinuation was 27.6% per patient-year of follow-up. The incidence rate of vedolizumab discontinuation was significantly higher among CD patients (Figure 2). Among CD patients, 126 (47.9%) discontinued the treatment during follow-up (median 11 months [IQR = 5-18 months]); the incidence rate of discontinuation was 45.3% per patient-year of follow-up.

In the multivariable analysis, CD (vs UC), CRP concentration, the presence of anaemia and the use of steroids during induction were significantly associated with higher risk of discontinuation of vedolizumab (Table 5).

A total of 307 patients had response at week 14 (75% of them remission) and were included in the analysis to assess the incidence rate of loss of response (Table S1). Ninety-four of these patients lost response during follow-up (median 12 months [IQR = 6-18 months]); the incidence rate of loss of response was 28.8% patient-year of follow-up (Figure S1). The treatment was escalated in 57 patients (60%); after the first escalated dose 28.6% of patients regained remission and 30.6% clinical response.

TABLE 3 Predictive factors of remission at week 14 in inflammatory bowel disease patients treated with vedolizumab

Variable	Odds ratio	95% confidence interval	*P*-value
Crohn's disease (vs ulcerative colitis)	0.36	0.33-0.95	<0.01
C-reactive protein (mg/dL)	0.9	0.8-0.9	<0.01
Previous surgery	0.04	0.3-0.9	<0.05
Severity at baseline			
Mild vs severe	8.6	4.5-16	<0.01
Moderate vs severe	1.6	0.9-2.8	>0.05

TABLE 4 Reasons for discontinuation of vedolizumab during follow-up

Reasons for discontinuation	N (%)
Primary nonresponse	97 (48.5)
Loss of response	58 (29)
Clinical response	4 (2)
Worsening of extraintestinal manifestations	3 (1.5)
Patient's choice	3 (1.5)
Adverse events	12 (6)
Others	10 (5)

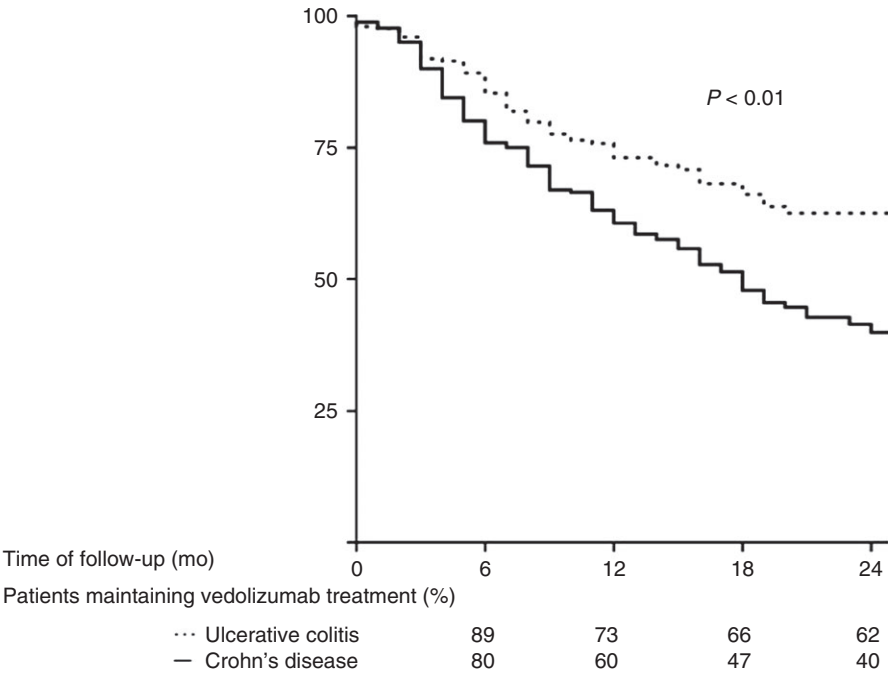

FIGURE 2 Survival curves of patients under vedolizumab treatment based on disease type (Crohn's disease vs ulcerative colitis)

The incidence rate of loss of response was significantly higher in CD than in UC patients (Figure S2). In the multivariable analysis, CD (vs UC) (HR = 1.9 [95% CI = 1.2-2.9]) and higher CRP (mg/dL) at week 14 (HR = 1.04 [95% CI = 1.008-1.09]) were significantly associated with the incidence rate of loss of response. Other variables such as concomitant immunomodulators, previous anti-TNF exposure or clinical response (vs remission) at week 14 were not associated with the risk of loss of response.

3.3 | Safety

A total of 36 patients (7.1%) developed 42 adverse events from an exposure to vedolizumab of 527 patient-years, leading to the discontinuation of the treatment in 15 patients (2.9%) (Table 6). Median follow-up was 10 months (IQR = 5-18 months). The most frequent adverse events were infections, which occurred in 14 patients; among infections, the most prevalent were sinopulmonary infections followed by infections of the gastrointestinal tract (two patients had *Clostridium Difficile* infection). Two patients in our cohort suffered from bowel perforation; both of them were patients with severe disease; one of the bowel perforations occurred few days after initiating vedolizumab, and the other after 2 months of treatment. One patient was diagnosed with colon cancer during follow-up; the case was a 36-year old male with long-standing UC and primary sclerosing cholangitis that was diagnosed in 2006. The patient had maintained active disease for years; he was refractory to adalimumab and infliximab and had undergone several colonoscopies that demonstrated severe activity and lack of response to the treatments. The patient improved with vedolizumab (he had a colonoscopy showing severe disease before starting the treatment) and after 7 months, he underwent colonoscopy because he had clinical response but maintained rectal bleeding. The colonoscopy confirmed the improvement but two suspicious lesions were seen both in the right and sigmoid colon. Histology confirmed that they were adenocarcinomas. Genetic tests ruled out the presence of colorectal family syndrome in this patient. No patient developed progressive multifocal leukoencephalopathy under vedolizumab treatment.

TABLE 5 Multivariable analysis of factors associated with discontinuation of vedolizumab treatment

Variable	Hazard ratio	95% confidence interval	*P*-value
Crohn's disease (vs ulcerative colitis)	1.6	1.3-2.1	<0.01
C-reactive protein (mg/dL) at baseline	1.02	1.01-1.03	<0.01
Anaemia at baseline	1.5	1.1-2	<0.01
Steroids at baseline	1.5	1.1-2.1	<0.05

Finally, there were two deaths in our cohort of patients, both with severe comorbidities. The first case was a 72-year old male with CD that had also been diagnosed with cirrhosis, heart and renal failure, who died due to septic arthritis 2 months after starting vedolizumab. The second case was a 60-year old male admitted due to UC refractory to both steroids and anti-TNF drugs. He also had atrial fibrillation and ischaemic heart disease. During admission, he suffered a complex cardiac arrhythmia that required amiodarone. Amiodarone caused severe hyperthyroidism, which precluded colectomy (due to high risk of surgery). Vedolizumab was then prescribed without improvement. Severe hyperthyroidism persisted with hemodynamic instability. The patient was admitted to the intensive care unit where he suffered upper gastrointestinal bleeding due to a gastric ulcer that could not be treated endoscopically; the patient required urgent surgery. After surgery, he had to be operated on again due to wound dehiscence, and he finally died due to hypovolemic shock.

TABLE 6 Adverse events during vedolizumab treatment

Adverse events	N	Event rate per 100 patient-years
Infections	14	2.6
Sinopulmonary	6	1.3
Gastrointestinal	3	0.5
Conjunctivitis	1	0.2
Chickenpox	1	0.2
Herpes-zoster reactivation	1	0.2
Osteomyelitis	1	0.2
Otitis	1	0.2
Skin reactions	6	1.3
Infusional reactions	5	0.9
Heart failure	3	0.5
Bowel perforation	2	0.4
Deaths	2	0.4
Dizziness	2	0.4
Headache	2	0.4
Worsening of perianal disease	2	0.4
Athralgia	1	0.2
Colon cancer	1	0.2
Fever of unknown cause	1	0.2
Neurological symptoms	1	0.2

4 | DISCUSSION

To our knowledge, this is the largest cohort with the longest follow-up of IBD patients treated with vedolizumab in real life, and this fact allowed us to obtain several key results about vedolizumab treatment in clinical practice. First, our results support that vedolizumab is effective in clinical practice, even in a refractory IBD population. After the induction, two-thirds of the patients responded to the treatment and over 40% had clinical remission. In addition, we could identify predictive factors of remission at week 14, which could allow identify the subset of patients who would benefit the most from the treatment. In this respect, we observed that patients with CD (instead of UC) and those with more severe disease at baseline (previous surgery, higher CRP concentration and more severely active disease) were less likely to achieve remission at week 14. Second, we observed that almost 30% of patients that responded to the induction doses suffered from loss of response during follow-up and that after the escalation of treatment approximately 60% of the patients regained response. Third, CD instead of UC and higher CRP after the induction were factors independently associated with loss of response over time.

Several studies have assessed the effectiveness of vedolizumab in clinical practice[11-19]; all of them included less than 300 patients with a limited follow-up period (Table 1). Overall, the proportion of patients that responded to the treatment at week 14 in those series was approximately 80%, considering both remission and response.[11-13,15] Although the overall response rate in our study is similar or even lower than in other published cohorts, our remission rate is slightly higher. Different inclusion criteria and methods for the assessment of response to treatment might be responsible for these differences. For instance, Baumgart et al included patients with active disease,[12] defined as an HBI score >7 in CD and a PMS >4 in UC, while we defined active disease as an HBI score >4 and a PMS≥ 2. As a consequence, the population included by Baumgart et al had more severe activity than ours, which could have impacted on our remission rate. In agreement with our results, those studies found that the severity of disease activity at baseline inversely correlated with the probability of achieving remission or response at week 14.[11-13,15] Other variables, such as previous exposure to anti-TNF agents, were not associated with the probability of remission at week 14 either in our study or in other cohorts. Finally, vedolizumab was safe, without any warning signal in clinical practice.

In addition, we found that CD patients were less likely to reach remission than UC patients. Our findings are in agreement with GEMINI trials, where UC patients had higher remission rates than CD patients. To our knowledge, this is the first study to demonstrate that UC patients benefit more from vedolizumab than CD patients in the clinical practice setting. Most of the population-based studies analysed CD and UC patients separately and the numbers were possibly too small to demonstrate this association.

Neither the combination treatment with steroids nor with immunomodulators boosted the response to vedolizumab treatment at week 14, in contrast to results described with anti-TNF treatment.[23,24] Some clinicians suggest starting vedolizumab treatment in combination with steroids to improve response to the induction doses. Of note, in our study, the treatment with steroids during the induction was not associated with better results. Furthermore, Amiot et al and Stallmach et al observed that patients under steroids during the induction had lower response and remission at week 14, suggesting a selection bias for more severe patients among those under steroids.[13,16] In fact, in our study there was a trend towards higher steroid prescription among more severe patients (53%, 62.7% and 67% in patients with mild, moderate and severe disease at baseline respectively [P = 0.045]). Therefore, steroid treatment cannot be recommended during the induction phase in IBD patients, as the benefit of the combination has not been demonstrated yet.

A question arises about the impact of previous exposure to anti-TNF drugs on vedolizumab efficacy. Two post hoc analyses from the GEMINI studies evaluated the efficacy of vedolizumab in CD and UC based on prior anti-TNF exposure.[7,25] They consistently showed benefit from vedolizumab treatment in the induction and maintenance of clinical response and remission in both anti-TNF failure and anti-TNF naïve patients, in comparison with placebo. Authors observed that the rates of response and remission were higher in CD patients not exposed to anti-TNF agents than in patients who had anti-TNF failure.[25] These higher rates persisted at week 52. The same results were found in UC: patients naïve to anti-TNF had higher rates of response (absolute difference: 15.5%), compared to placebo at week 6, than patients with anti-TNF failure (absolute difference: 7%), whereas

during maintenance treatment, the absolute differences with placebo were the same in both groups.[7] No statistical analysis was performed comparing anti-TNF naïve and anti-TNF failure groups. However, anti-TNF failures had higher disease burden given their longer disease duration, higher mean faecal calprotectin concentration at baseline, higher percentage of surgery, higher proportion of patients with extraintestinal manifestations and history of fistulising disease. All these factors have been consistently associated with impaired response to biological agents, including vedolizumab. Therefore, it needs to be clarified whether the lower benefit of vedolizumab in patients with anti-TNF failure was caused by previous exposure to biological agents or by higher disease burden. In addition, authors did not find differences based on the number of prior anti-TNF failures. With respect to our results, we did not observe an impact of previous anti-TNF exposure on short-term response or long-term duration of efficacy (57.6%, 51.2% and 44% of remission at week 14 for patients naïve, with failure to 1 anti-TNF and failure to >1 anti-TNF respectively). However, the proportion of naïve patients in our cohort was very low—only 33 patients naïve to anti-TNF treatment reached week 14 and only 22 of them were followed up in the long-term study.

Some studies have suggested a sustained benefit of vedolizumab treatment over time.[19] Conversely, we observed that a relevant proportion of patients (approximately 30% per patient-year) lost response during follow-up; the incidence rate of loss of response in our cohort was similar to that described in patients treated with anti-TNF agents after failing to a previous anti-TNF drug.[26,27] The GEMINI-LTS study is a continuing phase 3 trial investigating the safety and efficacy of vedolizumab in CD and UC patients from C13004, GEMINI 1, 2 and 3 trials. Interim analyses of the GEMINI-LTS study have been recently published.[9,10] Authors observed that remission rate was stable along 152 weeks of follow-up. However, patients who discontinued the study, for instance due to loss of response, were not included in the analysis. When response and remission rate were conservatively calculated with patients with missing data considered as treatment failures, those figures changed. In the enrolled population of CD patients, 71% were in remission at week 52, 69% at week 104 and 43% at week 152. Corresponding remission rates in UC patients were 74%, 78% and 46% after 52, 104 and 152 weeks of treatment respectively. In addition, similar benefit was demonstrated regardless of prior anti-TNF exposure. In our cohort, neither drug survival nor loss of response over time was associated with previous exposure to anti-TNF drugs.

A controversy is still ongoing regarding whether biological agents should be prescribed in combination with immunomodulators to prevent loss of response, mainly due to immunogenicity. In this respect, although vedolizumab immunogenicity is low, GEMINI trials showed that concomitant immunomodulators were associated with decreased immunogenicity.[5,6,8] However, in agreement with other studies, we have failed to show a benefit from the combo therapy (vedolizumab plus immunomodulators) in comparison with vedolizumab as monotherapy, both in the induction and for preventing loss of long-term response.

With respect to safety, the rate of adverse events in our cohort was similar to that described both in clinical trials and in other population-based studies.[28] As in other cohorts, the majority of patients could keep the treatment, and less than 3% of patients of our population had to interrupt vedolizumab. The most prevalent adverse events were infections (mainly sinopulmonary and gastrointestinal infections) followed by infusional reactions and skin manifestations, which is also consistent with results previously described for vedolizumab. The GEMINI trials demonstrated that the overall adverse event rate was similar between vedolizumab and placebo, which was also confirmed by a Cochrane review.[29] However, the GEMINI-LTS demonstrated a higher incidence of new perianal abscess formation among CD patients treated with vedolizumab.[10] In our cohort, two CD patients suffered from worsening of the perianal disease. This finding has also been described in other population-based cohorts.[11] Future clinical trials will address the role of vedolizumab specifically in perianal disease.

Our study has some limitations. First of all, although ENEIDA registry is prospectively completed, efficacy outcomes are rated based on clinician subjective assessment. To overcome the potential heterogeneity in clinical assessment, clinicians were asked to provide HBI and PMS score values of every visit. Both indexes and their cut-off values have been recently recommended by a steering committee of 28 IBD experts.[30] Second, we chose week 14 for evaluation, which is different from the GEMINI trials, where the efficacy of vedolizumab induction protocol was assessed at weeks 6 and 10. However, our choice is the consequence of the belief that vedolizumab needs longer time to exert its effect. For example, in the GEMINI 2 trial, vedolizumab failed to induce clinical response at week 6 in comparison with placebo.[8] In the GEMINI 3 trial, including only CD patients refractory to anti-TNF, vedolizumab was more effective than placebo at week 10 but not at week 6.[6] Accordingly, all of the population-based studies have chosen the response at week 14 as primary endpoint. Third, 14-week endoscopy was not available in our cohort; therefore, we could not evaluate mucosal healing at this time point. However, this reflects what happens in clinical practice, where endoscopy studies are generally not carried out if patients have good response after the induction. The majority of patients reported in this study had been exposed to several biological agents; therefore, the study was underpowered to find differences in the effectiveness of the treatment between naïve patients and patients previously exposed to anti-TNF agents. We could not evaluate the correlation between vedolizumab concentrations and response to the treatment because the test to measure vedolizumab serum levels is not available in Spanish hospitals at this time. Finally, detailed information about perianal disease activity was not available; therefore, response to the treatment could not be assessed, mainly because of the wide heterogeneous management and assessment of perianal disease across sites.

Our study has also several strengths. To our knowledge, as previously mentioned, this is the largest cohort with the longest follow-up of IBD patients treated with vedolizumab; therefore, we were

able to identify predictive factors of short-term response and drug survival and to determine the proportion of patients that lose efficacy over time and the incidence rate of discontinuation of the treatment, which have not been previously described in a population-based cohort. In addition to CD patients, we also included UC patients, which allowed us to make comparisons between groups. In contrast to other observational studies, we only included IBD patients with active IBD with the aim to categorise response in a standardised and more objective manner.

In conclusion, vedolizumab seems to be effective even in a refractory cohort of IBD patients, inducing remission or response in over two-thirds of the patients showing a good safety profile. In the long term, a relevant proportion of patients discontinue the treatment, mainly because of loss of response, and this figure is similar to that described in cohorts of refractory patients treated with anti-TNF agents. Finally, CD instead of UC and a more severe activity of the disease impair both short and long-term effectiveness of the drug, while concomitant treatment with immunomodulators seems to have no effect either improving short-term response or preventing loss of efficacy. Further clinical trials are warranted to place vedolizumab in the therapeutic algorithm of IBD patients.

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Author contributions: María Chaparro and Javier P. Gisbert: study design, data collection, data analysis, data interpretation, writing the manuscript. Ana Garre: Data collection and database monitoring. Rest of authors: Patient inclusion and data collection.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

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APPENDIX 2

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