



Predictors of Response to Vedolizumab in Patients with Ulcerative Colitis: Results from the Greek VEDO-IBD Cohort

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Abstract

Background Optimization of treatment with biologics is currently an unmet need for patients with ulcerative colitis (UC). Real-world studies provide neutral estimates of drug efficacy and safety within unselected patient populations and allow for the recognition of specific characteristics that affect response to therapy.

Aims We aimed to depict the efficacy of vedolizumab in patients with UC in a real-world setting and identify prognosticators of improved outcomes.

Methods Patients with active UC who commenced treatment with vedolizumab were prospectively followed up. Patient-reported outcomes (PROs) and clinical/endoscopic-reported outcomes were recorded at baseline and at weeks 14 and 54. Predefined endpoints of early and persistent efficacy were analyzed against clinical characteristics to identify prognostic factors for response.

Results We included 96 patients (anti-TNF-exposed = 38.5%). At week 14, 73 patients (76%) had clinical response and 54 (56.3%) clinical remission. At week 54, the primary endpoint of vedolizumab persistence was met by 72 patients (75%), whereas steroid-free clinical remission by 59.4%. Among patients who had endoscopy, rates for mucosal healing (Mayo endoscopic score of 0) were 29.8% at week 14 and 44.6% at week 54, respectively. Vedolizumab treatment led to significant improvements in quality of life. Corticosteroid-refractory or anti-TNF-refractory disease, articular manifestations, and high baseline UC-PRO2 were associated with decreased efficacy of vedolizumab in the primary and secondary outcomes.

Conclusions Vedolizumab is characterized by high efficacy and long-term treatment persistence in UC. More aggressive disease, as indicated by refractoriness to steroids or anti-TNFs and elevated baseline PROs, may predict suboptimal response and help pre-treatment prognostic stratification of patients.

Keywords Efficacy · Clinical remission · Treatment persistence · Mucosal healing

Introduction

In recent years, significant advancements in basic and translational research and improvements in clinical trial design have revolutionized therapeutic approaches to Ulcerative colitis (UC). The realization of the considerable burden that UC imposes on patients' well-being led to the

introduction of more demanding treatment targets, which predict more favorable long-term outcomes [1]. Accordingly, combinations of patient-reported outcomes (PROs) and mucosal healing (verified via endoscopy and/or histology) are increasingly applied as essential endpoints in inflammatory bowel disease (IBD) studies [2]. On the other hand, continuous exploration of underlying inflammatory pathways has led to discovery of pivotal pathogenic molecules, the pharmacological targeting of which has translated to the current availability of four discrete therapeutic choices [3]. Those include neutralization of the

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proinflammatory cytokine tumor necrosis factor (TNF)- α , blockade of interleukin (IL)-23/IL-12-mediated immunity, inhibition of Janus-kinase activity, and inhibition of inflammatory cell recruitment into affected mucosal areas [4].

Vedolizumab (Takeda®, Minnesota, USA) is a humanized, IgG1 monoclonal antibody against the $\alpha 4\beta 7$ integrin heterodimer that is, currently, approved for the treatment of active UC and Crohn's disease (CD) [5]. Vedolizumab prevents $\alpha 4\beta 7$, expressed on lymphocytes, to bind to its endothelial ligand, mucosal addressin cell adhesion molecule-1 (MAdCAM-1), whose expression is confined to the gut [6]. Thus, vedolizumab is predicted to selectively prevent mucosal influx of inflammatory leukocytes to the intestine, leading to enhanced local efficacy and superior safety due to minimal systemic effects. The pivotal GEMINI 1 trial demonstrated significantly higher clinical effectiveness of vedolizumab as induction and 54-week maintenance therapy in patients with UC in comparison with placebo [7]. Long-term follow-up of patients also confirmed persistence of the clinical benefit and a favorable safety profile of vedolizumab [8–10].

Although regulatory trials are indispensable for initial approval of any novel drug, the very strict patient selection process usually results in a study population that may not be truly representative of average individuals of everyday clinical practice [11]. Real-world studies bridge this gap by providing neutral estimates for performance characteristics of the drug within the general patient pool. Moreover, they allow for recognition of specific characteristics that may be associated with increased or decreased responsiveness to the drug, which is very important for pre-treatment prognostic stratification of patients. Such studies on the use of vedolizumab in UC have confirmed its efficacy and safety [12, 13]. Nevertheless, real-world studies vary considerably in several aspects, including number of patients, retrospective versus prospective design, outcome definitions, comorbidities and concomitant treatments, and whether IBD patients are analyzed as a whole or CD and UC are considered separately. Such variability often underlies dissimilar or even conflicting results in the literature.

In the present multi-center nationwide study, we aimed to analyze our real-world experience in patients with active UC who commenced therapy with vedolizumab and were followed prospectively for up to 54 weeks. Our specific goals were to: (a) capture the persistence of vedolizumab treatment through week 54 and illustrate the rates of clinical remission at this timepoint; (b) characterize the early (week 14) response to vedolizumab; (c) examine the effect of vedolizumab on up-to-date treatment outcomes, including PROs and mucosal healing; (d) identify predictors for early and persistent response to vedolizumab in patients with UC.

Methods

Patient Population

This was a collaborative, prospective observational study in adult patients with regular follow-up in 9 Greek tertiary GI-IBD centers and established active UC (Mayo score ≥ 3), who commenced treatment with vedolizumab between November 2015 and May 2019. The decision to receive vedolizumab was made by the treating GI-specialists, as was consequent follow-up. Baseline characteristics were collected from the patients' medical records. Patients were prospectively evaluated at study entry, and at weeks 14 (short-term response) and 54 (persistent response) of follow-up and predefined clinical and laboratory evaluations were recorded. Endoscopies were uniformly performed at baseline and according to decisions by the treating gastroenterologists at 14 and 54 weeks.

Treatment and Outcomes

All participating patients received vedolizumab according to standard protocol, consisting of intravenous, 30-min infusions of 300 mg of vedolizumab at weeks 0–2–6 (induction regimen), followed by 8-weekly infusions of the same dose (maintenance regimen). Prior and concomitant therapies were also recorded. Dose escalation (shorter infusion intervals) due to suboptimal response was also recorded. Patients who stopped treatment due to safety concerns were analyzed as failures.

Disease activity was assessed by calculating the Mayo score at the relevant time points (full score at baseline and partial score at 14 and 54 weeks). In addition, PROs for UC were separately recorded and analyzed (UC-PRO1, rectal bleeding, UC-PRO2, stool frequency, definitions are shown in Fig. 2) [14]. The Mayo endoscopic sub-score was applied for demonstrating endoscopic outcomes.

The primary outcome of our study was persistence of vedolizumab administration at week 54. Secondary outcomes were: corticosteroid-free persistence of vedolizumab administration at week 54, clinical remission at week 54, corticosteroid-free clinical remission at week 54, endoscopical improvement at week 54, mucosal healing at week 54 and deep remission at week 54. We also included evaluations of patients at week 14 to capture the effect of induction therapy. We studied the following secondary outcomes for this early timepoint: clinical response, clinical remission, corticosteroid-free clinical response and clinical remission, endoscopical improvement, mucosal healing, deep remission.

Persistence of vedolizumab administration was defined as the uninterrupted administration of the drug throughout the 54-week follow-up period. Clinical response was defined as Partial Mayo score (PMS) < 4 or ≥ 30% reduction of baseline PMS; clinical remission as PMS = 0–2; endoscopic improvement as any decrease from baseline in the Mayo endoscopic score; mucosal healing as Mayo endoscopic score of 0; and deep remission as combined corticosteroid-free clinical remission with mucosal healing. Secondary loss of response was defined as vedolizumab discontinuation for patients with clinical response at week 14. In all timepoints, the Short Inflammatory Bowel Disease Questionnaire (sIBDQ) was completed by study participants for evaluation of the effect of vedolizumab treatment on quality of life (QoL). Laboratory tests were also performed as part of the regular follow-up of patients at the study timepoints.

Statistical Analysis

Statistical analysis was performed with the statistical package SPSS 23 (IBM, Armonk, NY, USA). For categorical variables, total count and percentages are presented. For continuous variables that are normally distributed, mean value and standard deviation while for those not normally distributed median and range are presented. For the comparison of continuous variables, the parametric paired-sample t-test and the nonparametric Wilcoxon and Mann–Whitney U tests were performed. The nonparametric X² test was used for the comparison of categorical outcomes. Univariate logistic regression models were performed for the identification of potential clinical predictors with a cut-off *P*-value = 0.1. Factors of potential significance were later included in a multiple logistic regression to identify independent associations. A *P* value = 0.05 was used as threshold of statistical significance.

Results

Baseline Patient Characteristics

In total, 104 patients with UC who commenced treatment with vedolizumab were enrolled in the study. We excluded from further analysis 4 patients with incomplete follow-up and 4 patients without active disease who received vedolizumab because they developed adverse effects to their maintenance regimen, while in remission (Suppl. Figure 1). Thus, final data analysis was performed for the cohort of 96 patients who received vedolizumab due to active disease at baseline and had appropriate follow-up. Table 1 depicts the demographic and clinical characteristics of the study population. Indications for vedolizumab treatment included

Table 1 Clinical and epidemiological characteristics of disease in patients with active ulcerative colitis who received vedolizumab treatment (*n* = 96)

Male [<i>n</i> (%)]	56 (58.3%)
Age, years [median (range)]	44.8 (17.2–78.5)
Disease duration, years [median (range)]	5.6 (0.1–45)
Montreal classification [<i>n</i> (%)]	
E1	1 (1.1%)
E2	39 (40.6%)
E3	55 (57.3%)
Unknown	1 (1.1%)
Smoking status [<i>n</i> (%)]	
Never	44 (45.8%)
Former	40 (41.7%)
Active	11 (11.5%)
Extra-intestinal manifestations [<i>n</i> (%)]	
Arthritic	29 (30.2%)
Ocular	2 (2.1%)
Liver	3 (3.1%)
Skin	11 (11.5%)
Other	5 (5.2%)
BMI kg/m ² [mean (SD)]	25.3 (5.5)
WBC [mean (SD)]	9400 (3850)
Platelets [mean (SD)]	332 (126)
Hemoglobin [mean (SD)]	12.7 (1.8)
Albumin [mean (SD)]	4.05 (0.69)
Amylase [mean (SD)]	58.4 (23.9)
Mayo score [median (range)]	8 (3–12)

Normal values are: WBC 4000–11,000/μL; platelets 150,000–400,000/μL; hemoglobin 13–17 g/dL for men, 12–16 g/dL for women; albumin 3.5–5.5 g/dL; amylase 23–85 U/L

BMI body mass index, *WBC* white blood cells

Table 2 Previous and concomitant therapies [*n* (%)]

	Previous	Week 0	Week 14	Week 54
5-asa	95 (99)	59 (61.5)	61 (67)	50 (69.4)
Steroids	91 (94.8)	62 (64.6)	31 (34.1)	5 (6.9)
Thiopurines	57 (59.4)	18 (18.8)	15 (16.5)	10 (13.9)
anti-TNF	37 (38.5)			
Infliximab	27 (28.1)			
Adalimumab	10 (10.4)			
Golimumab	11 (11.5)			

Percentages refer to 96 patients for previous treatments and week 0, 91 patients for week 14, and 72 patients for week 54

steroid-refractory disease (*n* = 12), steroid-dependent (*n* = 25), thiopurine-refractory (*n* = 21), and anti-TNF-refractory (*n* = 34), whereas in 4 patients the reason could not be clearly defined. In Table 2, previous treatments and concomitant therapies during the follow-up period are shown.

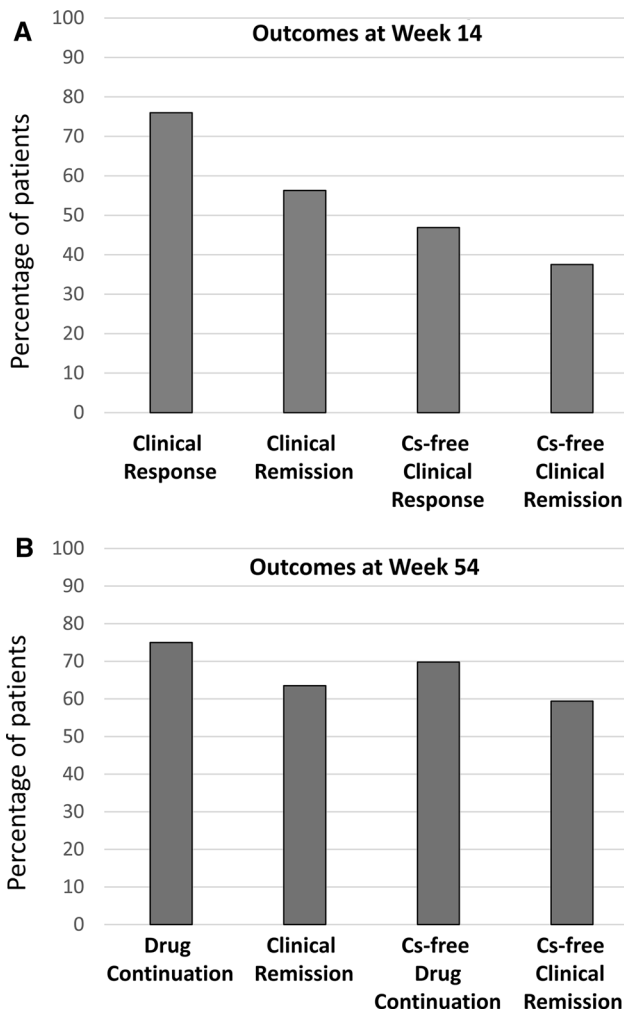


Figure 1 Clinical study outcomes at weeks 14 (a) and 54 (b). Drug continuation through week 54 was the primary outcome

In particular, 37 (38.5%) patients had received biologic therapy in the past, among whom 26 (27.1%) one anti-TNF and 11 (11.5%) 2 anti-TNF agents. Almost 2/3 (64.5%) of patients were on therapy with steroids during induction with vedolizumab.

Short-Term Outcomes (14 Weeks)

The proportions of patients who met the short-term endpoints are shown in Fig. 1A. Clinical response at week 14 was accomplished by 73 patients (76%) and clinical remission by 54 (56.3%). At week 14, 34% of patients were still receiving steroids, as opposed to 64% at baseline (Table 2). In all, 36 patients (37.5%) were in steroid-free remission at this early timepoint.

We also evaluated changes in UC-PRO 1&2 in our cohort and found significant decreases for both at week 14 (Fig. 2A). In particular, the percentage of patients with a value of 2 or 3 for UC-PRO1 (indicative of high mucosal damage) decreased from 46.9% at baseline to 7.8% at week 14. There was a corresponding increase in the proportion of patients with no bleeding (UC-PRO1 value of 0) from 30.2% at baseline to 75.6% at week 14. Similarly, for UC-PRO2, patients with a value of 2 or 3 (≥ 3 stools per day above normal) decreased from 56.3% at baseline to 12.2% at week 14, while those with normal stools per day (UC-PRO2 value of 0) increased from 14.6% at baseline to 61.1%. We also observed changes in the laboratory markers in patients treated with vedolizumab with both white blood cells (WBC) and platelets (PLT) numbers being significantly decreased at week 14 in comparison with baseline ($P < 0.001$ for both markers, data not shown).

We performed endoscopy in 57 patients at week 14 (Fig. 3A). Among those, we observed mucosal healing

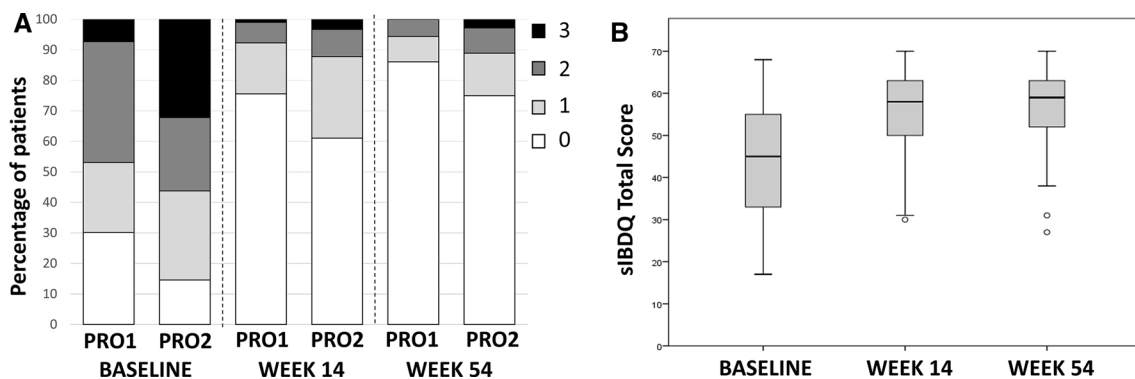
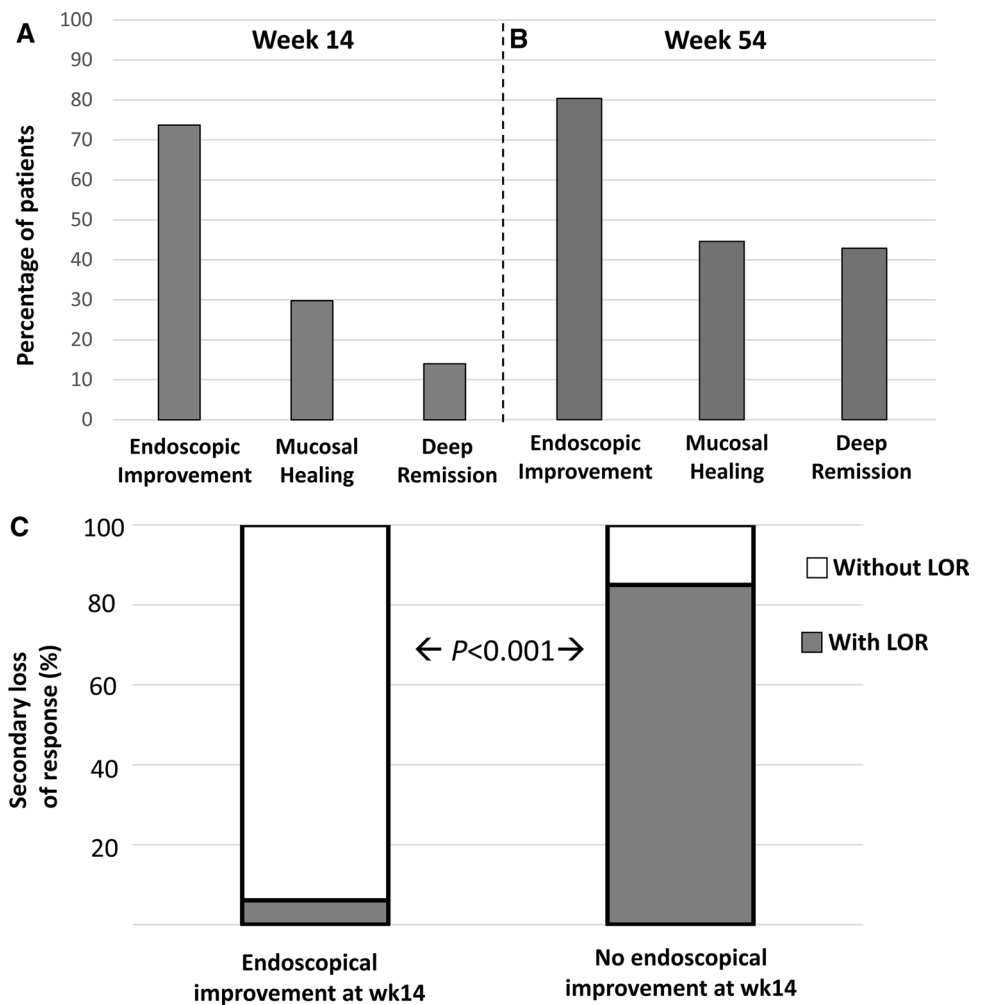


Figure 2 a Distribution of patient-reported outcomes at weeks 0, 14 and 54. UC-PRO1 depicts the rectal bleeding (0 = no bleeding, 1 = streaks of blood with stools less than 50% of the time, 2 = obvious blood with stool most of the time, 3 = passes blood without stool) and UC-PRO2 depicts the stool frequency (0 = normal number of stools for patient, 1 = 1–2 more stools than normal, 2 = 3–4 more stools than

normal, 3 = 5 + more stool than normal). **b** Improvement of QoL of patients treated with vedolizumab. The sIBDQ was completed by study participants at baseline, as well as at the 14- and 54-week evaluations. There was statistically significant improvement of patients' QoL following treatment with vedolizumab in comparison with the baseline evaluation (paired-sample t test $P < 0.001$ for both analyses)

Figure 3 Endoscopic study outcomes at weeks 14 (a) and 54 (b) were calculated for 57 and 56 patients, respectively, that were subjected to endoscopy at the respective study evaluation points. c Secondary loss of response (LOR) among patients with or without endoscopic improvement at week 14. Endoscopic improvement was defined as any decrease of the Mayo endoscopy sub-score in comparison with the baseline assessment. Patients without endoscopic improvement are at increased risk of secondary loss of response ($X^2 P<0.001$)



(Mayo 0) in 17 (29.8%), whereas an additional 23 patients (40.4%) had a Mayo score of 1. Overall, endoscopic improvement from baseline was observed in 42 patients (73.7%) who had an early endoscopic evaluation. No statistically important difference was observed on the PMS between patients underwent endoscopy and those who did not at week 14 (Mann–Whitney U test $P=0.198$).

Long-Term Outcomes (54 weeks)

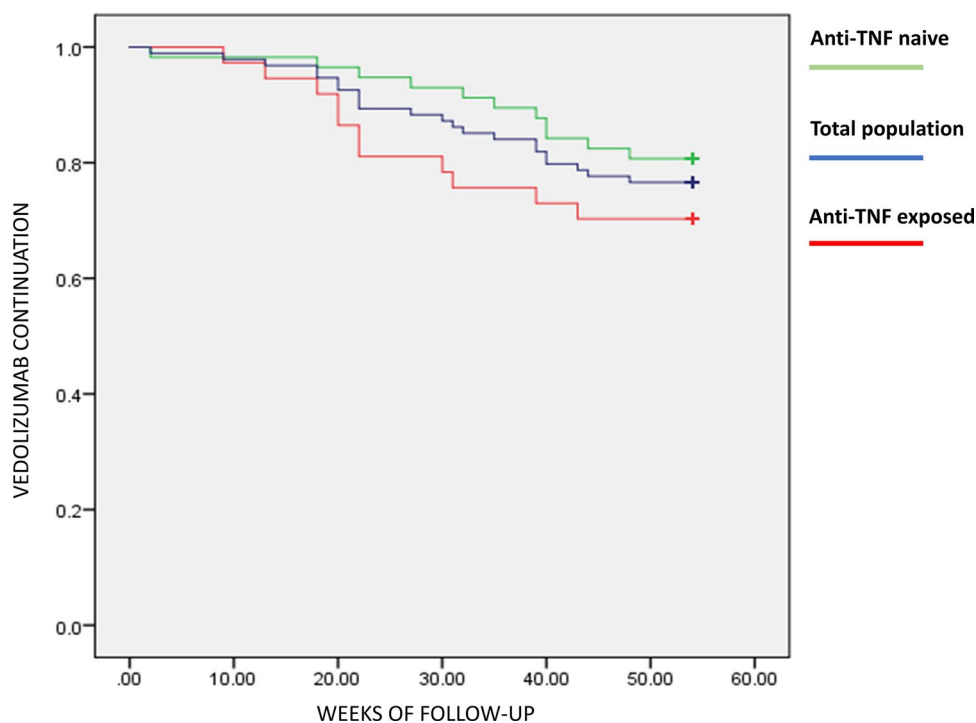
The primary endpoint of persistence of vedolizumab administration at week 54 was met by 72 patients (75%) (Figs. 1B, 4), whereas clinical remission and steroid-free remission were accomplished by 61 (63.5%) and 57 (59.4%) patients, respectively (Fig. 1B). When patients who were exposed to anti-TNF therapies were tested separately from those naïve to biological treatment, we observed a trend toward higher persistence in the latter (Fig. 4). Nevertheless, the difference between the two groups was not statistically significant. Overall, among patients who responded to treatment at week 14, 10 patients (14%) discontinued therapy due to loss of

response (secondary loss of response). On the other hand, among non-responders to vedolizumab at week 14, 18 continued therapy with vedolizumab. Among those, 9 patients completed therapy to week 54, of whom 6 patients were in clinical remission and 5 in corticosteroid-free clinical remission (data not shown).

Regarding PROs (Fig. 2A), the percentage of patients with a value of 2 or 3 for UC-PRO1 further decreased to 5.6%, while the proportion of patients with no bleeding (UC-PRO1 value of 0) increased to 86.1%. Similarly, for UC-PRO2, patients with a value of 2 or 3 decreased to 11.1%, while those with normal stools per day (UC-PRO2 value of 0) increased to 75% at week 54. Mean values for both WBC and PLT remained significantly lower than baseline values ($P<0.001$ for both markers).

Endoscopy was performed at week 54 in 56 patients. Among those, we observed mucosal healing (Mayo 0) in 25 patients (44.6%), whereas an additional 18 patients (32.1%) had a Mayo score of 1 (Fig. 3B). Endoscopic improvement from baseline was observed in 45 patients (80.4%) who underwent endoscopic evaluation at the end of study. No

Figure 4 Kaplan–Meier curve of vedolizumab persistence for the total study population as well as for anti-TNF-naïve and anti-TNF-exposed patients



statistically important difference was observed on the PMS between patients underwent endoscopy and those who did not at week 54 (Mann–Whitney U test $P=0.127$).

Dose escalation (i.e., monthly injections of vedolizumab) was introduced by the treating gastroenterologist in 5 cases. Among those patients, three were still on treatment at week 54, whereas the other discontinued to inability to regain response to vedolizumab. In total, at week 54, 69 patients were receiving vedolizumab every 8 weeks and 3 patients every 4 weeks.

Four patients in our cohort discontinued due to safety concerns which concerned two cases with CMV colitis, one of whom also developed autoimmune hemolytic anemia, one case with ophthalmic vein thrombosis, and one with surgical wound infection by *Pseudomonas aeruginosa*.

Treatment with Vedolizumab Is Associated with Significant Improvements in QoL of Patients with UC

Next, we examined whether the clinical benefit of vedolizumab treatment affected the QoL of patients with UC. To answer this question, we compared the scores for the sIBDQ questionnaire between baseline (82.3% completion) and at weeks 14 (83.5% completion) and 54 (58.3% completion) as shown in Fig. 2B. When all study participants were included in the analysis, we observed significant increases in the sIBDQ score, indicating improvement, which were statistically significant between baseline (mean score = 44.9) and week 14 (mean score = 55.2, $P < 0.001$) and between

baseline and week 54 (mean score = 56.5, $P < 0.001$). We also separately analyzed the group of long-term responders to vedolizumab and found that again the sIBDQ scores were significantly higher at both study evaluation timepoints (mean scores: baseline = 45.5; week 14 = 56.7, $P < 0.001$; week 54 = 56.5, $P < 0.001$).

Predictors of Response to Vedolizumab

Next, we sought to examine whether we could identify any patient- or disease-related factors that may be associated with the major outcomes of the study and/or secondary loss of response (Table 3). In the univariate logistic regression model, clinical response at week 14 was negatively associated with corticosteroid-refractory disease, anti-TNF-refractory disease, PLT count, and history of tonsillectomy and positively associated with concomitant 5-asa administration. In the multivariate analysis, only corticosteroid-refractory (OR = 0.11, 95% CI = 0.02–0.71) and anti-TNF refractory disease (OR = 0.16, 95% CI = 0.03–0.8) remained independently associated with poorer prognosis, while a tendency was also observed for history of tonsillectomy (OR = 0.21, 95% CI = 0.04–1.06).

Persistence of vedolizumab administration was not associated with any factor in the univariate model, but a tendency was observed with concomitant azathioprine use at baseline. In the multivariate model, we found patients with corticosteroid-refractory disease to experience lower persistence (OR = 0.2, 95% CI = 0.04–0.98), while those who received azathioprine at the beginning tended to continue treatment

Table 3 Univariate and multivariate analysis models for prediction of primary study outcomes and clinical remission at week 54

	Univariate			Multivariate				
	OR	95% C.I. for OR	P	OR	95% C.I. for OR	P		
<i>Response W14</i>								
Tonsillectomy	0.286	0.09	0.905	0.033	0.213	0.043	1.06	0.059
Indication								
Cs refractory	0.166	0.032	0.853	0.032	0.106	0.016	0.705	0.02
Cs dependent	1.896	0.34	10.571	0.466	1.79	0.257	12.483	0.557
IM refractory	0.925	0.218	3.922	0.916	1.161	0.216	6.227	0.862
Anti-TNF refractory	0.127	0.034	0.475	0.002	0.16	0.032	0.796	0.025
Concomitant cs	1.403	0.528	3.729	0.498	1.344	0.382	4.732	0.646
Concomitant 5-asa	3.382	1.279	8.94	0.014	1.384	0.393	4.874	0.613
PLT/1000	0.996*	0.992	0.999	0.024	0.998	0.993	1.003	0.51
<i>Drug continuation W54</i>								
Indication								
Cs refractory	0.309	0.073	1.308	0.111	0.198	0.04	0.98	0.047
Cs dependent	0.736	0.213	2.543	0.628	0.529	0.134	2.096	0.365
IM refractory	2.013	0.512	7.908	0.316	1.136	0.255	5.06	0.867
Anti-TNF refractory	0.56	0.182	1.722	0.312	0.377	0.107	1.329	0.129
Concomitant cs	0.651	0.222	1.905	0.433	0.685	0.107	1.329	0.505
Concomitant AZA	7.173	0.896	57.43	0.063	8.455	0.906	78.88	0.061
<i>Clinical remission W54</i>								
Articular EIMs	0.397	0.162	0.974	0.044	0.288	0.092	0.901	0.032
Indication								
Cs refractory	0.23	0.054	0.98	0.047	0.171	0.029	0.997	0.05
Cs dependent	0.369	0.114	1.195	0.096	0.255	0.062	1.047	0.058
IM refractory	1.052	0.329	3.361	0.932	1.172	0.321	4.726	0.81
Anti-TNF refractory	0.234	0.077	0.704	0.01	0.26	0.065	1.047	0.058
Concomitant cs	1.148	0.471	2.798	0.761	1.201	0.411	4.897	0.738
Concomitant 5-asa	2.341	0.94	5.51	0.052	1.597	0.521	3.507	0.468
PROs								
UC-PRO1	1.213*	0.47	3.104	0.498	1.474	0.782	2.778	0.231
UC-PRO2	0.472*	0.276	0.806	0.006	0.422	0.231	0.768	0.005

Cs corticosteroids, IM immunomodulators, PLT platelets, AZA azathioprine, EIMs extra-intestinal manifestations, OR odds ratio, CI confidence interval, PROs patient-reported outcomes, UC-PRO1 rectal bleeding, UC-PRO2 stool frequency

*Concomitant use of corticosteroids was added to the model because of its effect in those variables

at a higher ratio (OR = 8.46, 95% CI = 0.91–78.88). On the other hand, we identified predictors of clinical remission at week 54. In the univariate model, a negative association was detected for corticosteroid-refractory disease, anti-TNF-refractory disease, articular extra-intestinal manifestations (EIMs) and UC-PRO2. After multivariate logistic regression model, corticosteroid-refractory (OR = 0.17, 95% CI = 0.03–0.99), articular EIMs (OR = 0.29, 95% CI = 0.09–0.9), and UC-PRO2 (OR = 0.42, 95% CI = 0.23–0.77) remained independently associated with lower rates of clinical remission. A trend was also observed for anti-TNF refractory disease, although not reaching statistical significance (OR = 0.26, 95% CI = 0.07–1.05).

We also compared anti-TNF exposed with anti-TNF naïve patients regarding all studied outcomes. Through univariate logistic regression models, prior treatment with anti-TNF was found to be negatively associated with clinical response (OR = 0.18, 95% CI = 0.06–0.49), clinical remission (OR = 0.24, 95% CI = 0.1–0.57), corticosteroid-free clinical response (OR = 0.31, 95% CI = 0.13–0.75) and corticosteroid-free clinical remission (OR = 0.24, 95% CI = 0.09–0.64) at week 14, while a tendency was observed with clinical remission at week 54 (OR = 0.43, 95% CI = 0.05–1.01).

Finally, we found that secondary loss of response among initial responders highly correlated to endoscopical improvement at week 14. In total, 43 patients with clinical remission

had an endoscopic evaluation at week 14. Among those, secondary loss of response was seen in 2/37 patients (5%) who experienced endoscopic improvement at week 14, whereas it was seen in 5/6 patients (83%) without endoscopic improvement ($P < 0.001$) (Fig. 3C).

Discussion

This is the first real-world data on the effectiveness of vedolizumab treatment in Greek patients with active UC, despite previous administration of conventional and/or anti-TNF therapies. We report that the vast majority of patients remained on treatment through week 54 with significant improvements in clinical and endoscopic parameters and QoL. In particular, 2/3 of patients were in clinical remission at week 54, with 60% not receiving steroids. Those rates are substantially higher than in the regulatory GEMINI 1 trial [7]. In other real-world studies, remission rates vary widely between 20 and 82.5% [15–24]. Differences in the characteristics of study populations and/or definitions of outcomes may underlie these discrepancies. Indeed, the lowest rates were reported in studies with the smallest numbers of patients, which may have skewed results toward worse outcomes [17, 18, 20]. Enrichment with patients reporting multiple anti-TNF failures may be another reason. For example, the French OBSERVE study that reported much lower rates of steroid-free clinical remission at week 54 (40.5%) included only anti-TNF-exposed patients, with 71% having failed more than two agents [15]. Our results are similar to the Scottish and Canadian reports, which, like ours, included mixed anti-TNF-exposed/naïve populations [21, 23]. Finally, different endpoint definitions may also underlie inter-study diversity. This may explain the lower 54-week remission rate (51%) reported in the USA multi-center VICTORY consortium, as remission was defined as cessation of all UC-related symptoms [22].

An important aspect of our work is the incorporation of PROs as treatment outcomes across the study timeframe. Our analysis shows that changes in UC-PRO1 (rectal bleeding) and UC-PRO2 (daily bowel movements) accurately depict the therapeutic benefit of vedolizumab, as both were significantly decreased at week 14 and 54 post-treatment. It has been shown that individual PROs highly correlate with the established UC activity markers, Mayo score and the Simple Clinical Colitis Activity Index (SCCAI) [25, 26]. Thus, our current findings indicate that such simpler and objective, patient-derived indices may be applicable in clinical practice to facilitate disease follow-up and management. This may be of particular importance in the COVID-19 era, as PRO reporting fits well into the e-health paradigm, ascertaining that patients avoid unnecessary hospital visits [27]. PROs should ideally include instruments that directly depict

the patients' well-being [28]. Accordingly, we report that QoL was significantly improved in vedolizumab-treated patients, as shown by increased sIBDQ scores. Furthermore, the current treat-to-target dogma in IBD therapy dictates that PROs should be combined to objective measurements of inflammatory activity, among which endoscopic evaluation has been the first to be incorporated in investigational trials and clinical practice [29]. In our study, vedolizumab treatment positively affected endoscopic outcomes, with 80% of patients showing improvement on paired endoscopic evaluations (baseline vs. 54 weeks). The significance of endoscopic improvement is emphasized by our finding that accomplishing this outcome early (i.e., at week 14) strongly predicted a favorable clinical outcome at week 54. We strictly defined mucosal healing as endoscopic score of 0, and this was accomplished by 46% of the patients who had endoscopy at week 54. This percentage is remarkably similar to studies from Canadian (41%) and US cohorts (47.8%) that used the same endoscopic outcome [21, 22]. In GEMINI 1, mucosal healing was defined as Mayo endoscopic subscore of 0 or 1, which was achieved by 51.6% of patients at week 54 [7]. If we had applied those less stringent criteria in our cohort, the percentage of patients with mucosal healing would increase to 67%, which is similar to the report by Tursi et al. (62.7%, 18-month follow-up) [24], and substantially higher than real-world studies by Kotze (48%, at 12-months), and Christensen (51%, median 6-months) [17, 21]. We propose that the stricter definition of mucosal healing should be sought for in clinical practice, as previous studies have shown that patients with an endoscopic Mayo score of 0 had better outcomes than those with a score of 1 [30, 31]. Overall, our study is distinctive in that it included calculations of both PROs and clinical reported outcomes (ClinROs) to demonstrate high efficacy of a biological treatment in UC (vedolizumab), in line with the current therapeutic treat-to-target dogma which calls for composite treatment endpoints in IBD.

The recent expansion of therapeutic options for UC has brought up the urgent need to outline the profile of the patient with the highest (or lowest) probability to benefit from a certain treatment. Accordingly, in our study, we found that corticosteroid-refractory patients had a significantly lower probability to respond to vedolizumab at week 14 or be in clinical remission at week 54. Similarly, refractoriness to anti-TNF treatment predicted lack of early response and also showed a strong trend toward lack of clinical remission at week 54. Refractoriness to steroids and/or anti-TNF may be indicative of more aggressive disease phenotypes. Very few studies have reported predictors of response to vedolizumab in UC patients, exclusively. Interestingly, findings from those studies are in line with our report. In the VICTORY consortium, prior exposure to TNF α antagonists conferred reduced probability of achieving clinical

remission [22]. In the study by Tursi et al., fecal calprotectin $\geq 400 \mu\text{g/g}$, which indicates higher inflammatory burden, was significantly related to failure of remission in UC [24]. Along the same line, we also found that higher scores of UC-PRO2, reflecting more severe disease, were also predictive of lack of clinical remission at week 54. Taken together, those studies and our current work support the notion that vedolizumab is a suitable option for the treatment of patients with UC, especially for those who present with milder forms of the disease. Further studies, including head-to-head clinical trials, are needed to delineate the proper positioning of currently available biologics (anti-TNF, anti-integrins, anti-IL-12/23) and small molecules (JAK inhibitors) in the therapeutic algorithms for UC. We also found that articular manifestations were a negative predictor of clinical remission at week 54. A possible explanation may be that persistent vedolizumab-resistant joint inflammation may have led to discontinuation of treatment in certain cases. Alternatively, musculoskeletal problems may affect scoring on the Global Medical Assessment indicator, leading to higher final PMS readings.

Our study has limitations. We did not perform endoscopy universally, so rates of mucosal healing refer to a subgroup of patients. Similarly, we do not report measurements of fecal calprotectin because this test is not compensated by the Greek national health system (NHS) and only a small proportion of patients had available records. C-reactive protein (CRP) measurements were not reported because they were not available in full, mainly due to the fact that various laboratories use different units and different cutoffs. This, in association with the fact that many patients with active UC had normal serum CRP, would greatly impact the interpretation of the analysis. Finally, the study was executed in tertiary centers, which may have imposed a bias toward more demanding cases. On the other hand, we believe that our work also has important strengths. First, unlike most published trials that have included both CD and UC cases, ours was focused on the latter exclusively. Second, our study is in line with the highly accepted treat-to-target dogma by systematically combining PROs and ClinROs evaluations. Finally, we applied strict definitions for outcomes, especially for mucosal healing, which ascertains the accomplishment of targets that may be associated with long-term patient benefits.

In conclusion, we demonstrate that vedolizumab is a highly effective treatment for patients with active UC and its use is associated with beneficial clinical results, which eventually lead to improved QoL for the patients. It appears that the best candidates for vedolizumab therapy in UC are patients with milder disease, whereas failure of previous treatments with steroids and/or anti-TNFs may lower the probability of long-term remission. Our results, along with previous and future studies, will further facilitate the search

for defining the optimal profile of patients with UC who will mostly benefit from treatment with vedolizumab and other biologic therapies.

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Declarations

Conflict of interest Bamias G. has served as advisor/lecturer for Janssen, Pfizer, Takeda, Abbvie, MSD, Mylan, Genesis Pharma, Adacety Therapeutics, Amgen, Ferring and Cooper, received funding (Grants/Honoraria) from Pfizer, Takeda, Abbvie and Aenorasis and participated in research/Clinical Trials by Abbvie and Takeda. Karmiris K. has served as advisor/lecturer for Abbvie, Aenorasis, Janssen, MSD, Pfizer, Takeda, Amgen, Ferring, Galenica and Genesis Pharma. Michopoulos S. has served as advisor/Lecturer for Pfizer, Takeda, Abbvie, Ferring, MSD and Janssen. Viazis N. has served as Advisor/lecturer for Janssen, Pfizer, Aenorasis, Takeda, Abbvie, MSD, Mylan, Amgen, Genesis Pharma and Cooper. Tsironi E. has served as lecturer for Ferring and Takeda. Tzouvala M. has served as advisor/lecturer for Janssen, Pfizer, Takeda, Abbvie, MSD, Mylan, Genesis Pharma and Amgen and participated in research/Clinical Trials by AbbVie, Gilead and Takeda. Zampeli E. has served as advisor/lecturer for Pfizer, Takeda, Abbvie, Amgen, Genesis Pharma, Aenorasis and Janssen. KT has served as Lecturer for Takeda and Amgen. Papatheodoridis G. has served as advisor/lecturer for Abbvie, Dicerna, Elpen, Gilead, Glaxo-SmithKline, Ipsen, Janssen, Merck Sharp & Dohme; Roche, Spring Bank and Takeda, received research grants from Abbvie, Gilead and Takeda and participated in clinical trials by Abbvie, Astellas, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, Noorik, Novartis, NovoNordisk, Regulus, Roche and Takeda. Mantzaris G. has served as advisor/lecturer for AbbVie, Celgene, Celtrion, Ferring, Genesis, Hospira, Janssen, Millennium Pharmaceuticals, MSD, Mylan, Pharmacosmos, Pfizer, Takeda, VIANEX, Angelini, Falk Pharma, Galenica, Omega Pharma, consultant for MSD and Takeda and received research support from AbbVie, Galenica, Genesis, Menarini Group, MSD and Pharmathen.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Hospitals' institutional review boards (IRBs), and all patients were informed for the study and signed a consent form for participation.

Informed consent Informed consent was obtained from all individual participants included in the study.


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