European Journal of Internal Medicine 66 (2019) 85–91

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Vedolizumab is effective and safe in real-life treatment of inflammatory bowel diseases outpatients: A multicenter, observational study in primary inflammatory bowel disease centers

Antonio Tursi[a,*], Giammarco Mocci[b], Roberto Faggiani[c], Leonardo Allegretta[d], Nicola Della Valle[e], Antonio de Medici[f], Giacomo Forti[g], Marilisa Franceschi[h], Antonio Ferronato[h], Sara Gallina[c], Giuseppina Grasso[d], Tiziana Larussa[i], Francesco Luzza[i], Roberto Lorenzetti[j], Antonio Penna[k], Stefano Rodino[l], Ladislava Sebkova[l], Angelo Lauria[m], Simona Piergallini[n], Giuseppe Pranzo[o], Stefano Scorza[d], Costantino Zampaletta[c], Marcello Picchio[p], Walter Elisei[q]

[a] Territorial Gastroenterology Service, ASL BAT, Andria, Italy
[b] Division of Gastroenterology, "Brotzu" Hospital, Cagliari, Italy
[c] Division of Gastroenterology, "Belcolle" Hospital, Viterbo, Italy
[d] Division of Gastroenterology, "Santa Caterina Novella" Hospital, Galatina (LE), Italy
[e] Division of Gastroenterology, A.O. "Ospedali Riuniti", Foggia, Italy
[f] Territorial Gastroenterology Service, PST Catanzaro Lido, Catanzaro, Italy
[g] Division of Digestive Endoscopy, "S. Maria Goretti" Hospital, Latina, Italy
[h] Digestive Endoscopy Unit, ULSS7 Pedemontana, Santorso (VI), Italy
[i] Department of Health Science, University of Catanzaro, Catanzaro, Italy
[j] Division of Gastroenterology, "Nuovo Regina Margherita" Territorial Hospital, Roma, Italy
[k] Division of Gastroenterology, "S. Paolo" Hospital, Bari, Italy
[l] Division of Gastroenterology, "Ciaccio-Pugliese" Hospital, Catanzaro, - Italy
[m] Division of Gastroenterology, A.O. "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy
[n] Division of Gastroenterology, IBD Unit, "A. Murri" Hospital, Fermo, Italy
[o] Ambulatory for IBD Treatment, "Valle D'Itria" Hospital, Martina Franca (TA), Italy
[p] Division of General Surgery, "P. Colombo" Hospital, ASL Roma 6, Velletri, Roma, Italy
[q] Division of Gastroenterology, ASL Roma 6, Albano Laziale, Roma, Italy

ARTICLE INFO

Keywords:
Crohn's disease
Ulcerative colitis
Vedolizumab
Remission
Safety

ABSTRACT

Background: Italian data currently available in managing ulcerative colitis (UC) and Crohn's disease (CD) patients with vedolizumab (VDZ) are coming just from secondary and tertiary centers. The present study aimed to assess the real-life efficacy and safety of VDZ to achieve remission in inflammatory bowel diseases (IBD) outpatients in primary gastroenterology centers.

Methods: Clinical activity was scored according to the Mayo score in UC and to the Harvey-Bradshaw Index (HBI) in CD. The primary endpoints were the achievement of clinical remission and safety. Secondary endpoints were clinical response to treatment, achievement of mucosal healing (MH), and steroid discontinuation.

Results: One hundred and thirty-six pts. were enrolled (91 UC and 45 CD pts). During an 18-month median follow-up, clinical remission was present in 63 (46.3%) pts.: in particular, it occurred in 48 (52.7%) patients in UC group and in 15 (33.3%) patients in CD group ($p = 0.003$).

more in UC group. Fecal calprotectin ≥400 μg/g and presence of comorbidities were factors significantly related to the failure of remission in UC and CD, respectively.

Ten (7.3%) cases of adverse events were recorded (2 required suspension of treatment).

Clinical response was present in 105 (72.2%) pts.: 71 (78.0%) in UC and 34 (75.5%) in CD group. MH

* Corresponding author at: Territorial Gastroenterology Service, Via Torino, 49, 76123 Andria, Italy.
E-mail address: antotursi@tiscali.it (A. Tursi).

https://doi.org/10.1016/j.ejim.2019.06.006
Received 19 March 2019; Received in revised form 7 June 2019; Accepted 10 June 2019
Available online 14 June 2019

occurred in 47 (62.7%) UC and in 9 (50.0%) CD patients. Steroids discontinuation occurred in 92 (67.6%) pts.; 61 (67.0%) UC and 31 (68.9%) CD pts.
Conclusion: VDZ is effective and safe in IBD outpatients, especially in UC patients.

1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) represent the main form of inflammatory bowel diseases (IBD). A complex interaction between genetic and environmental factors is the background of these diseases, and a specific trigger for the occurrence of the disease is still unknown [1]. Both these diseases are characterized by a relapsing and remitting course, sometimes requiring an aggressive therapeutic approach in order to prevent complications [2]. More than twenty years ago, tumor necrosis factor α (TNFα) was identified as an important player in the pathogenesis of IBDs [1], and the introduction of monoclonal anti-TNFα antibodies has greatly improved treatment options in IBD patients refractory or intolerant to standard therapies [2,3], either in CD or in UC [1].

Vedolizumab (VDZ) is a biologic agent, which targets the integrin receptor and is approved for the treatment of patients with moderate-severe UC and CD [4]. VDZ inhibits the interaction between a4b7 integrin and mucosal addressing cell adhesion molecule-1 (MAdCAM–1), which is selectively expressed by the vascular endothelium in the gastro-intestinal tract [5].

Two pivotal trials, GEMINI 1 and GEMINI 2, have led to the approval of VDZ for CD and UC [6,7]. Since clinical trials in inflammatory bowel diseases rarely represent the real-world patient population [8], several real-life reports have recently described the efficacy and safety of this drug in real-life [9–17].

VDZ reimbursement for CD and UC was approved in Italy in 2016 [18], but real-life Italian data currently available in managing those patients are coming just from secondary and tertiary centers [18]. The aim of the present study was to assess the efficacy and safety of VDZ to treat a large IBD outpatient population in some Italian primary IBD centers after approval of VDZ reimbursement for IBD by Italian Regulatory Authorities.

2. Materials and methods

This study consisted of a retrospective, observational, multicenter study on UC and CD outpatients unresponsive to standard treatments and treated with VDZ (Entyvio™) in 14 Italian primary IBD centers (namely centers identified by The Italian National and Regional Health Systems as able to manage uncomplicated IBD patients). We assessed patients enrolled from 1st May 2017 to 31st December 2018, who completed at least the induction treatment.

Eligible patients included men and women, at least 18 years old, with an established diagnosis of UC and CD according to standard endoscopic and/or radiology and/or histological criteria [1].

A shared common database was used to collect demographic and clinical data. Data collected at baseline were gender, age at diagnosis, disease duration, smoking status, presence of comorbidities, appendectomy, disease extension, previous immunosuppressive and anti-TNFα therapies, concomitant medications at baseline, C-Reactive Protein (CRP) and fecal calprotectin (FC) levels, Mayo score and Mayo subscore for endoscopy for UC patients, Harvey-Bradshaw Index (HBI) for CD patients. Patients were clinically assessed at entry, after 2, 3, 6, and thereafter every 6 months.

The study was conducted according to the clinical practice guidelines. All patients gave written informed consent before undergoing to endoscopy and VDZ treatment. The present study follows the principles of the Declaration of Helsinki. Since the study was retrospective, no Ethic Committee approval was requested by current law.

2.1. Study treatment

All patients were eligible for infusion of VDZ after exclusion of active hepatitis B virus infection, active cytomegalovirus infection, and tuberculosis infection.

VDZ (Entyvio™) was administered at a dose of 300 mg via 30-min intravenous infusion at weeks 0, 2, and 6 in order to obtain remission, and thereafter every 8 weeks in order to maintain remission.

The need of treatment discontinuation was left to the investigators' judgement, as well as concomitant medications including oral and topical aminosalicylates, steroids, and immunosuppressants.

2.2. Clinical assessment

Disease extension was assessed according to the Montreal classification [19]. Severity was assessed according to the Mayo score [20] in UC patients and to Harvey-Bradshaw Index (HBI) [21] score in CD patients. All included patients had active disease in spite concomitant treatment, defined as a Mayo score ≥ 3 points [20] for UC patients, and as HBI score > 5 points [11] in CD patients.

As stated, patients were clinically assessed at entry, after 2, 3, 6, and thereafter every 6 months.

2.3. Endoscopy

As standard protocol in the participating centers regarding patients under treatment with biologics, ileo-colonoscopy was performed in all the enrolled patients at entry, after 6, 12 and thereafter every 12 months during follow-up. CD patients with upper gastrointestinal location underwent both esophagogastroduodenoscopy and ileo-colonoscopy: in all of them upper gastrointestinal location was the only location, so the patients only underwent esophagogastroduodenoscopy during follow-up.

Endoscopic severity in UC patients was assessed according to Mayo subscore for endoscopy [20]. Endoscopic severity in CD patients was assessed by Simple Endoscopic Score for CD (SES-CD) [22,23].

2.4. End-points

Primary end-points were:

- reaching of remission, defined as Mayo score ≤ 2 in UC patients and HBI < 5 in CD patients, associated with steroid discontinuation;
- safety of VDZ, defined as absence of adverse events (AE) during treatment;

The AEs were subdivided as early (occurring during infusion), and late (occurring at least one week after infusion) events, and graded as mild (not requiring to stop treatment) and severe (requiring to stop treatment). Occurrence of opportunistic infections was also considered as an AE. It was defined as any infection caused by microorganisms, which have limited pathogenic capacity under normal circumstances, but have been able to cause disease because of the predisposing effect of another disease or its treatment [6,7].

Secondary end-points were:

- clinical response, defined as reduction of at least 2 points in the Mayo score in UC patients and at least 3 points in the HBI in CD;
- reaching of mucosal healing (MH), defined as Mayo subscore for endoscopy ≤1 in UC and SES-CD score ≤ 2 in CD;

- reduction of steroid use during the study;
- assessment of CRP and FC during the follow-up.
- occurrence of colectomy in UC and any surgical procedure related to the disease in CD.

2.5. Statistical analysis

Data were analyzed using MedCalc® Release 14.8.1. The characteristics of the study group were analyzed as median and interquartile range (IQR) for continuous non-parametric variables and as number (percentage) for categorical variables. Fisher's exact test was used to compare categorical variables. Clinical remission was considered as the primary end-point. The prognostic value of clinical parameters was evaluated using time-to-event methods for censored observations, because of the varying length of follow-up. Follow-up times were calculated from the date of diagnosis to the date of event or censorship. Time-to-event analysis was carried out using Kaplan–Meier estimates to draw the cumulative incidence curves, compared by logrank tests, as well as by univariate and multivariate Cox's proportional hazards (PH) models of prognostic variables. The hazards ratios (HR) are presented with 95% confidence intervals (CI) and *p*-values. A ratio higher than unity implies a higher probability of event compared to the reference group. *P*-values of < 0.05 were considered to be statistically significant. The Friedman test was used to investigate any change of CRP and FC levels during follow-up. *P* values < 0.05 were considered statistically significant.

3. Results

One hundred and thirty-six patients were enrolled according to the inclusion criteria. The characteristics of the study group according to UC and CD disease are reported in Table 1. Both groups were similar with respect to demographic and clinical characteristics.

The median (IQR) follow-up was 18 [6–24] months.

3.1. Primary end-points

Overall, clinical remission was present in 63 (46.3%) patients. Clinical remission in the two study groups during follow up is reported in Fig. 1. In particular clinical remission occurred in 48 (52.7%) patients in UC group and in 15 (33.3%) patients in CD group ($p = 0.003$, logrank test).

Both at univariate and at multivariate analysis a value of FC ≥ 400 μg/g was the only factor related to the absence of remission in UC patients (Table 2a). In CD, at univariate analysis both a CRP value ≥ 15 mg/dL and the presence of comorbidities were factor significantly related to the absence of remission; at multivariate analysis the presence of comorbidities was the only independent factor related to the absence of remission (Table 2b).

Overall, 10 (7.3%) AEs were recorded. In particular, there were two cases of fungal pneumonia, occurring in one UC and in one (CD patient respectively), which required suspension of treatment. Eight other cases of mild AEs also occurred, not requiring treatment suspension: 5 were related to VDZ (3 cases of hypertension and 2 cases of Herpes Zoster), and 3 were not related to VDZ (2 cases of migraine and 1 case of cough).

3.2. Secondary end-points

Overall, clinical response was present in 105 (72.2%): it was achieved in 71 (78.0%) in UC group and in 34 (75.5%) in CD group ($p = 0.981$).

MH occurred in 47/75 (62.7%) patients in UC group and in 9/18 (50.0%) in CD group ($p = 0.327$).

Steroids discontinuation occurred in 92 (67.6%) patients, in particular in 61 (67.0%) UC patients and in 31 (68.9%) CD patients ($p = 0.847$). In the remaining 44 patients, steroids were tapered in 40 (90.9%) patients.

Both CRP and FC values decreased significantly during follow-up (Fig. 2A, B).

One patient in UC group underwent colectomy. No surgical procedures for CD patients were recorded during the follow-up.

4. Discussion

To our knowledge, this is the first cohort follow-up of IBD Italian outpatients treated with VDZ in primary IBD centers, and this fact allowed us to obtain several key results about VDZ treatment in clinical practice.

First, our results confirm that VDZ is effective in clinical practice, even in primary IBD centers. After induction, about two thirds of the patients had clinical response to the treatment and over 40% had sustained clinical remission. This result seems to be better that the one achieved by pivotal studies GEMINI 1 and GEMINI 2, which reached clinical response and clinical remission in less the half of patients [6,7]. Comparing our results with other experiences from clinical practice, the overall response rate in our study seems similar the one reported in other published cohorts, while our remission rate is slightly higher [9–17]. These results was reached despite our enrolled population included patients with at least moderate disease, with a mean partial Mayo score of 6 in UC and a mean HBI of 10 in CD (Table 1). Different inclusion criteria and methods for the assessment of response to treatment might be responsible for the reported differences [9–17].

In addition, we found that UC patients had higher remission rates than CD patients. Our findings are in agreement with both GEMINI 1

Table 1
Demographics, disease characteristics, and concomitant medications.

	UC ($n = 91$)	CD ($n = 45$)
Gender, male	50 (54.9)	29 (64.4)
Media (IQR) age, years	49.9 (40.3–60.6)	49.5 (37.6–64.3)
Median (IQR) disease duration, years	9.3 (3.5–12.6)	6.4 (2.5–14.3)
Smoke	7 (7.7)	8 (17.8)
Presence of comorbidities	26 (28.6)	19 (42.2)
Appendectomy	9 (9.9)	16 (35.6)
Previous therapy		
Mesalazine	86 (94.5)	36 (80.0)
Steroids	90 (98.9)	43 (95.6)
Tiopurine	28 (30.8)	18 (40.0)
Previous exposure to anti-TNFα	75 (82.4)	28 (62.2)
Infliximab	23 (30.7)	7 (15.5)
Adalimumab	5 (6.7)	7 (15.5)
Golimumab	26 (34.7)	–
Infliximab and adalimumab	11 (14.7)	13 (28.9)
Infliximab and golimumab	10 (13.2)	1 (2.1)
Montreal classification of extent of UC		
Left-sided colitis	38 (41.8)	–
Extensive colitis	53 (58.2)	–
Montreal classification of CD		
Isolated ileal disease	–	20 (44.4)
Isolated colonic disease		3 (6.7)
Ileocolonic disease		21 (46.7)
Isolated UGI disease		1 (2.2)
Concomitant perianal disease		10 (22.2)
Non structuring, non-penetrating		20 (44.4)
Stricturing	–	19 (42.2)
Penetrating	–	6 (13.3)
Median (IQR) CRP, (mg/L)	18 (10–34)	16 (12 – 31)
Median (IQR) calprotectin (μg/g)	451 (300–779)	360 (217–921)
Median (IQR) partial Mayo score	6 (4–8)	–
Median (IQR) Mayo subscore for endoscopy	3 (2–3)	
Median (IRQ) HBI	–	10 (5–14)
Median (IRQ) SES-CD	–	10 (9–12)

Data are given as number (percentage) of patients unless otherwise indicated. UC, ulcerative colitis; CD Crohn's disease; TNF, tumor necrosis factor; IQR, interquartile range; CRP, C-reactive protein; HBI, Harvey-Bradshaw index; SES-CD, simple endoscopic score for Crohn's disease.

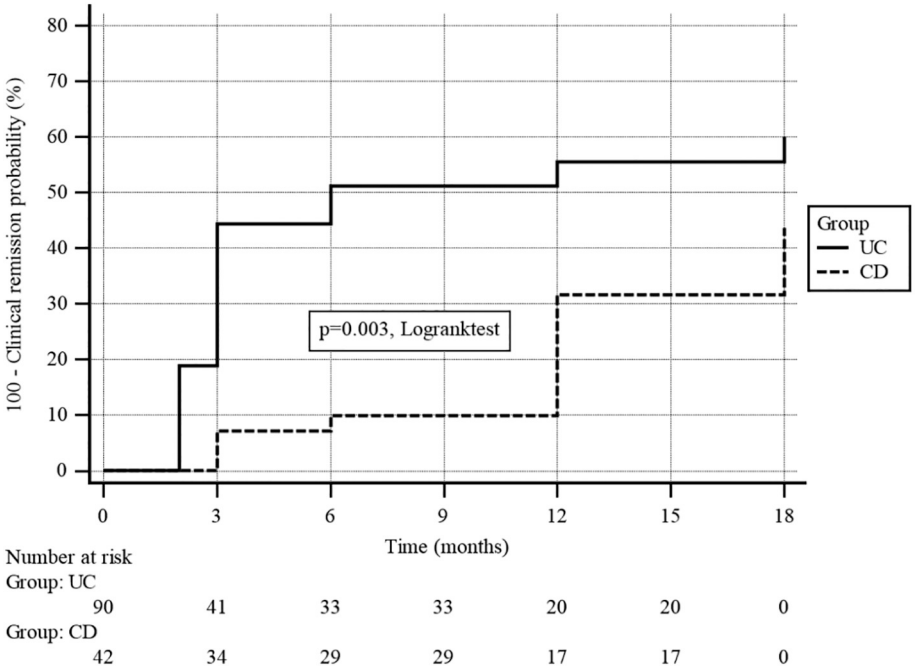

Fig. 1. Estimated cumulative clinical remission probability during follow-up by ulcerative colitis (UC) patients and Crohn's disease (CD) patients. Logrank test.

Table 2a
Predictors of clinical remission in UC patients.

	Remission	No remission	*p*	Hazard radio (95% CI) multivariate analysis	*p*
Number	48	42			
Sex, male	27 (56.2)	23 (54.8)	0.922		
Age ≥ 50 years	22 (45.8)	22 (52.3)	0.425		
Disease duration ≥10 years	19 (39.5)	18 (42.8)	0.925		
Smoke	5 (10.4)	2 (4.8)	0.186		
Appendectomy	3 (6.2)	6 (14.3)	0.219		
Presence of comorbidities	15 (31.2)	10 (23.8)	0.466		
Previous exposure to anti-TNFα	42 (87.5)	32 (72.2)	0.274		
CRP ≥ 15 mg/dL	28 (58.3)	27 (64.3)	0.145		
Fecal calprotectin ≥400 μg/g	21(43.7)	32 (76.2)	0.003	0.458 (0.239 to 0.878)	0.019

Values are expressed as number (percentage) of patients. CI, confidence interval; CRP, C-Reactive Protein.

Table 2b
Predictors of clinical remission in CD patients.

	Remission	No remission	*p*	Hazard radio (95% CI) multivariate analysis	*p*
Number	15	28			
Sex, male	8 (53.3)	8(28.5)	0.387		
Age ≥ 50 years	6 (40.0)	15 (53.5)	0.453		
Disease duration ≥10 years	5 (33.3)	13 (46.4)	0.637		
Smoke	5 (33.3)	3 (10.7)	0.162		
Appendectomy	7 (46.7)	8 (28.6)	0.199		
Presence of comorbidities	2 (31.2)	16 (57.1)	0.003	0.037 (0.003 to 0,466)	0.011
Previous exposure to anti-TNFα	11 (73.3)	16 (57.1)	0.144		
CRP ≥ 15 mg/dL	7 (46.7)	22 (78.5)	0.049		
Fecal calprotectin ≥400 μg/g	5 (33.3)	10 (35.7)	0.919		

Values are expressed as number (percentage) of patients. CI, confidence interval; CRP, C-Reactive Protein.

and GEMINI 2 trials and with other trials assessing VDZ in the clinical practice setting [6,7,9–17]. We could identify just two predictive factors significantly related to the failure of remission. First, we observed that patients with higher FC values, namely with more severe disease at baseline, were less likely to achieve and maintain remission in UC patients, but not in CD patients. This could mean that, similar to what happens in our experience when using anti-TNFα [24–26], more severe disease activity may be a predictor of failure of therapy with respect to obtaining/maintaining remission. Our result seem to confirm that FC is a reliable predictor of UC recurrence even under treatment with VDZ, probably because of a strong better relationship between FC and colonic inflammation [27]. On the contrary, the role of FC in detecting a significant ileal damage in CD is still under debate [28], and some authors still advise the use of CRP in monitoring CD patients with ileal localization of the disease [29]. Our results seem also to confirm a role of CPR in monitoring those patients even under treatment with VDZ at univariate analysis (the multivariate analysis did not reach statistically significance probably because of lack of statistical power in this

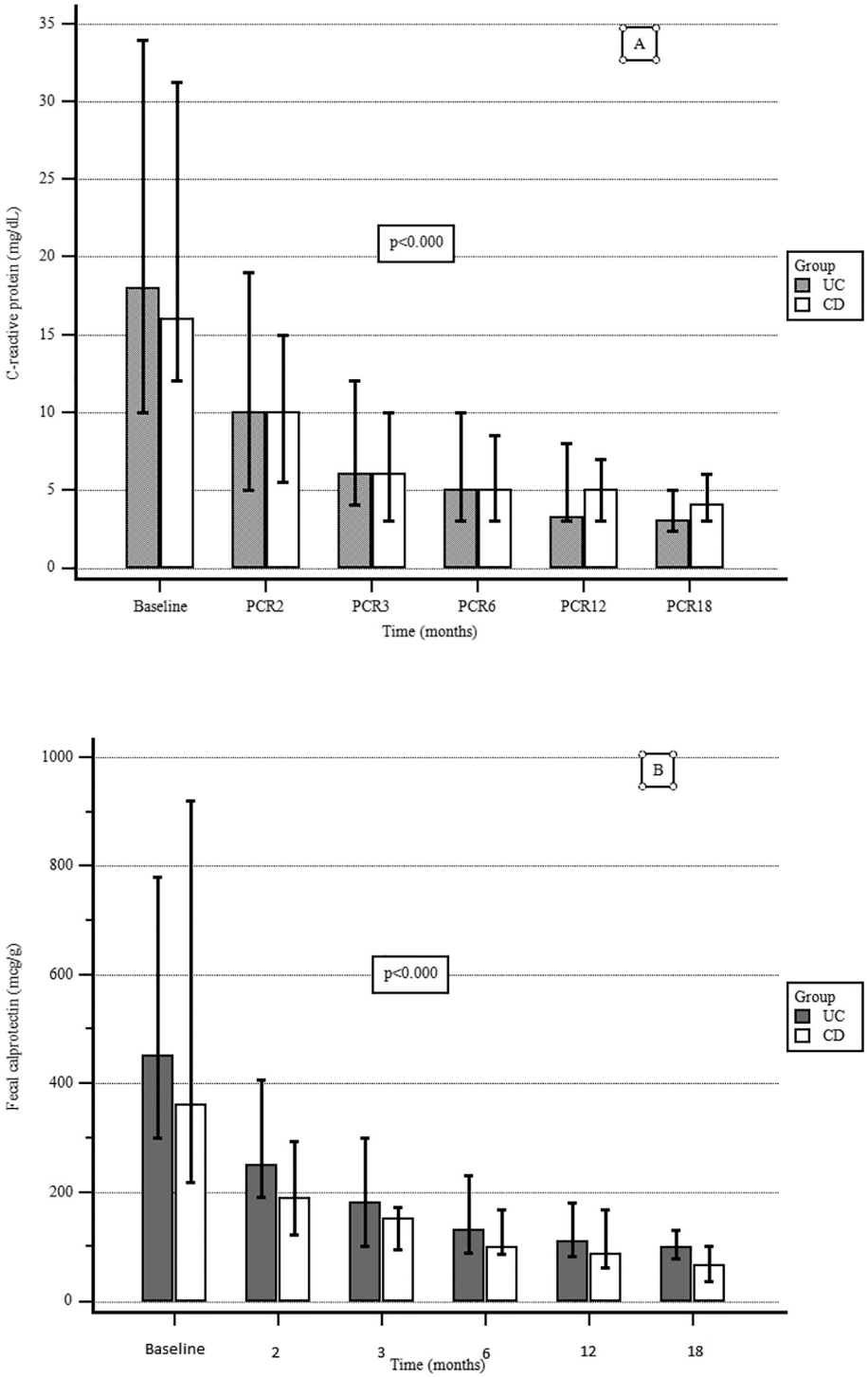

Fig. 2. C-reactive protein (A), and fecal calprotectin (B) values during follow-up by ulcerative colitis (UC) patients and Crohn's disease (CD) patients. Data are expressed as median, interquartile range (error bars). Friedman test.

population). Second, we observed that patients with comorbidities had lower chance to reach remission; even this result was limited to CD patients. Thus, comorbitities seem to influence VDZ response as well as anti-TNFα [30].

With respect to safety, the second primary end-point, the rate of AEs in our cohort was similar to the one described both in clinical trials and in other population-based studies [6,7,9–17]. As in other cohorts, the majority of patients could maintain the treatment, and < 1.5% of patients in our study group had to stop VDZ, confirming that this drug has a very excellent safety profile [31,32]. The most prevalent AE were pulmonary infections, but we recorded also three cases of hypertension and two cases of Varicella-Zoster herpes virus reactivation, even if it was mild and not requiring treatment interruption. These AEs are reported as uncommon when using VDZ [31,32]. While the cases of Varicella-Zoster herpes virus reactivation could be explained by immunosuppression, it is quite difficult to explain how VDZ may cause hypertension. A possible explanation could be a specific individual susceptibility.

With respect to the secondary end-points, we found that VDZ has a significant efficacy also in reaching other important clinical outcomes.

First, MH was achieved in the majority of UC patients and in half of CD ones. This is the first study assessing MH as end-point: our results seems to be significantly better than the ones of pivotal GEMINI 1 study [6], and resembling those obtained in our experience in using anti-TNFα in clinical setting [24–26]. Second, steroids discontinuation occurred in the large majority of patients, and steroid tapering was also obtained in almost all the remaining patients. In addition, these results are significantly better than those reached by both pivotal studies and studies conducted in clinical setting [6,7,9–17]. Moreover, both CRP and FC values decreased significantly during follow-up, and only one UC patient underwent colectomy. With respect to FC, we found that it decreased in parallel to MH. This finding differs from the one reported by a post hoc analysis of GEMINI 1 trial, which showed that a FC concentration after VDZ induction could not be a robust biomarker of mucosal inflammation [33]. We are unable to explain why this difference occurs, but we can hypothesize that this differences may be linked to the own variation of FC expression [34]. Overall, these findings show that VDZ is really effective in reaching other end-point that can influence the outcome of the disease, too [35,36].

Of course, this study has limitations. The first one is the retrospective design, which does not permit to enrol patients having the same timing through the follow-up (both as clinical and endoscopic follow-up). The second one is that only outpatients with mild-to-moderate disease were enrolled. Both these limitations could represent a bias of selection, and might influence the final results.

In conclusion, this is the first Italian real-life cohort study analysing the efficacy and safety of VDZ in primary IBD centres after its approval by the Italian regulatory authorities. We found that it is effective and safe in IBD outpatients in real life, especially in UC patients Since this is a retrospective study, prospective studies are needed to confirm these results.

Funding

None.

Declaration of interest

None.

References

[1] Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis 2012;6:965–90. https://doi.org/10.1016/j.crohns.2012.09.003. [Epub 2012 Oct 3].

[2] Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991–1030. https://doi.org/10.1016/j.crohns.2012.09.002. [Epub 2012 Oct 3].

[3] Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. Gastroenterology 2006;130:940–87.

[4] Armuzzi A, Gionchetti P, Daperno M, et al. GIVI (Gruppo Italiano su Vedolizumab nelle IBD) group. Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe inflammatory bowel disease. Dig Liver Dis 2016;48:360–70. https://doi.org/10.1016/j.dld.2015.12.016.

[5] McLean LP, Shea-Donohue T, Cross RK. Vedolizumab for the treatment of ulcerative colitis and Crohn's disease. Immunotherapy 2012;4:883–98. https://doi.org/10.2217/imt.12.85.

[6] Feagan BG, Rutgeerts P, Sands BE, et al. GEMINI 1 study Group.Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699–710. https://doi.org/10.1056/NEJMoa1215734.

[7] Sandborn WJ, Feagan BG, Rutgeerts P, et al. GEMINI 2 study Group.Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711–21. https://doi.org/10.1056/NEJMoa1215739.

[8] Ha C, Ullman TA, Siegel CA, Kornbluth A. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. Clin Gastroenterol Hepatol 2012;10:1002–7. https://doi.org/10.1016/j.cgh.2012.02.004. [Epub 2012 Feb 15].

[9] Baumgart DC, Bokemeyer B, Drabik A, Stallmach A, Schreiber S. Vedolizumab Germany consortium. Vedolizumab induction therapy for inflammatory bowel disease in clinical practice–a nationwide consecutive German cohort study. Aliment Pharmacol Ther 2016;43:1090–102. https://doi.org/10.1111/apt.13594. [Epub 2016 Apr 1].

[10] Dulai PS, Singh S, Jiang X, Peerani F, et al. The real-world effectiveness and safety of Vedolizumab for moderate-severe Crohn's disease: results from the US VICTORY consortium. Am J Gastroenterol 2016;111:1147–55. https://doi.org/10.1038/ajg.2016.236. [Epub 2016 Jun 14].

[11] Amiot A, Serrero M, Peyrin-Biroulet L, et al. OBSERV-IBD study group and the GETAID. One-year effectiveness and safety of vedolizumab therapy for inflammatory bowel disease: a prospective multicentre cohort study. Aliment Pharmacol Ther 2017;46:310–21. https://doi.org/10.1111/apt.14167. [Epub 2017 Jun 8].

[12] Kopylov U, Ron Y, Avni-Biron I, et al. Efficacy and safety of Vedolizumab for induction of remission in inflammatory bowel disease-the Israeli real-world experience. Inflamm Bowel Dis 2017;23:404–8. https://doi.org/10.1097/MIB.0000000000001039.

[13] Chaparro M, Garre A, Ricart E, et al. GETECCU study group. Short and long-term effectiveness and safety of vedolizumab in inflammatory bowel disease: results from the ENEIDA registry. Aliment Pharmacol Ther 2018;48:839–51. https://doi.org/10.1111/apt.14930.

[14] Narula N, Peerani F, Meserve J, et al. Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY consortium. Am J Gastroenterol 2018;113:1345–54. https://doi.org/10.1038/s41395-018-0162-0. [Epub 2018 Jun 27].

[15] Lenti MV, Levison S, Eliadou E, et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: the Cross Pennine study. Dig Liver Dis 2018;50:1299–304. https://doi.org/10.1016/j.dld.2018.07.007. [Epub 2018 Jul 18].

[16] Kopylov U, Avni-Biron I, Ron Y, et al. Effectiveness and safety of vedolizumab for maintenance treatment in inflammatory bowel disease-The Israeli real world experience. Dig Liver Dis 2019;51:68–74. https://doi.org/10.1016/j.dld.2018.07.040. [Epub 2018 Aug 10].

[17] Macaluso FS, Orlando R, Fries W, et al. The real-world effectiveness of vedolizumab on intestinal and articular outcomes in inflammatory bowel diseases. Dig Liver Dis 2018;50:675–81. https://doi.org/10.1016/j.dld.2018.02.013. [Epub 2018 Mar 1].

[18] Riclassificazione del medicinale per uso umano «Entyvio» ai sensi dell'art. 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 459/2016). Gazzetta Ufficiale della Repubblica Italiana 2016;157(87):28–9.

[19] Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749–53.

[20] Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalcylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625–9.

[21] Best WR. Predicting the Crohn's disease activity index from the Harvey–Bradshaw index. Inflamm Bowel Dis 2006;12:304–10.

[22] Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505–12.

[23] Moskovitz DN, Daperno M, Van Assche G. Defining and validating cut-offs for the simple endoscopic score for Crohn's disease. Gastroenterology 2007;132:S1097.

[24] Tursi A, Elisei W, Picchio M, et al. Managing ambulatory ulcerative colitis patients with infliximab: a long term follow-up study in primary gastroenterology centers. Eur J Intern Med 2014;25:757–61. https://doi.org/10.1016/j.ejim.2014.02.010. [Epub 2014 Mar 13].

[25] Tursi A, Allegretta L, Buccianti N, et al. Effectiveness and safety of Golimumab in treating outpatient ulcerative colitis: a real-life prospective, multicentre, observational study in primary inflammatory bowel diseases Centers. J Gastrointestin Liver Dis 2017;26:239–44. https://doi.org/10.15403/jgld.2014.1121.263.trs.

[26] Tursi A, Elisei W, Faggiani R, et al. Effectiveness and safety of adalimumab to treat outpatient ulcerative colitis: a real-life multicenter, observational study in primary inflammatory bowel disease centers. Medicine (Baltimore) 2018;97:e11897https://doi.org/10.1097/MD.0000000000011897.

[27] Costa F, Mumolo MG, Ceccarelli L, et al. Calprotectin is a stronger predictive marker of relapse in ulcerative colitis than in Crohn's disease. Gut 2005;54:364–8.

[28] Gecse KB, Brandse JF, van Wilpe S, et al. Impact of disease location on fecal calprotectin levels in Crohn's disease. Scand J Gastroenterol 2015;50:841–7. https://doi.org/10.3109/00365521.2015.1008035. [Epub 2015 Jan 30].

[29] Verdejo C, Hervías D, Roncero Ó, et al. Fecal calprotectin is not superior to serum C-reactive protein or the Harvey-Bradshaw index in predicting postoperative endoscopic recurrence in Crohn's disease. Eur J Gastroenterol Hepatol 2018;30:1521–2152. https://doi.org/10.1097/MEG.0000000000001284.

[30] Singh S, Heien HC, Sangaralingham LR, et al. Comparative effectiveness and safety of anti-tumor necrosis factor agents in biologic-naive patients With Crohn's disease. Clin Gastroenterol Hepatol 2016;14:1120–1129.e6. https://doi.org/10.1016/j.cgh.2016.03.038. [Epub 2016 Apr 4].

[31] Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017;66:839–51. https://doi.org/10.1136/gutjnl-2015-311079. [Epub 2016 Feb 18].

[32] Ng SC, Hilmi IN, Blake A, et al. Low frequency of opportunistic infections in patients receiving Vedolizumab in clinical trials and post-marketing setting. Inflamm Bowel Dis 2018;24:2431–41. https://doi.org/10.1093/ibd/izy153.

[33] Reinisch W, Bressler B, Curtis R, et al. Fecal Calprotectin responses following induction therapy with Vedolizumab in moderate to severe ulcerative colitis: a post hoc analysis of GEMINI 1. Inflamm Bowel Dis 2018 Oct 5. https://doi.org/10.1093/ibd/izy304. [Epub ahead of print].

[34] Calafat M, Cabré E, Mañosa M, Lobatón T, Marín L, Domènech E. High within-day variability of fecal calprotectin levels in patients with active ulcerative colitis: what

is the best timing for stool sampling? Inflamm Bowel Dis 2015;21:1072–6. https://doi.org/10.1097/MIB.0000000000000349.

[35] Cholapranee A, Hazlewood GS, Kaplan GG. Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Aliment Pharmacol Ther 2017;45:1291–302. https://doi.org/10.1111/apt.14030. [Epub 2017 Mar 22].

[36] Siegel CA. Review article: explaining risks of inflammatory bowel disease therapy to patients. Aliment Pharmacol Ther 2011;33:23–33. https://doi.org/10.1111/j.1365-2036.2010.04489.x. Epub. [2010 Oct 26].