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Alimentary Tract

Effectiveness and safety of vedolizumab for maintenance treatment in inflammatory bowel disease—The Israeli real world experience

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SUMMARY

Introduction: Several real-world experience (RWE) studies with vedolizumab (VDZ) for induction of remission in inflammatory bowel diseases (IBD) have been published; however, long-term RWE data is scarce.
Aims: To describe the effectiveness and safety of VDZ in maintenance treatment of IBD.
Methods: A multicenter retrospective national study. The primary outcome of was clinical response at week 52; main secondary aims included clinical remission at week 52, rates of secondary loss of response and treatment discontinuation.
Results: We included 193 (133—CD; 60—UC) patients from 9 Israeli IBD centers. At week 52, response was observed in 62/133 (46.7%) CD patients, including 28 (21%) in clinical remission; 71 (53.3%) discontinued treatment or did not respond. For UC, response at week 52 was observed in 27/60 (45%), including 20 (33%) in clinical remission; 33 (55%) discontinued treatment or did not respond. Secondary non-response by week 52 occurred in 19.4% and 23.5% of week 14 responders in CD and UC, respectively. Week 14 response was associated with treatment continuation at week 52: no predictors of secondary loss of response were identified.
Summary: VDZ is safe and effective for maintenance of response and remission in IBD; week 14 response is positively associated with long-term response in both UC and CD.

1. Introduction

Vedolizumab (VDZ) is a humanized monoclonal antibody that targets the alpha 4 beta 7 integrin, characteristically expressed by gut-homing lymphocytes and recognized by mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1) on endothelial cells. The efficacy of VDZ in patients with Crohn's disease (CD) and ulcerative colitis (UC) was demonstrated in the GEMINI trials [1–4]. Since the approval of VDZ for both UC and CD, several real-world experience (RWE) studies were published [5–14]. The majority of the published studies addressed short-term effectiveness of VDZ; however RWE of long-term effectiveness and safety are scarce. In the GEMINI 1 study, 41.8% and 44.8% of UC patients who continued to receive VDZ every 8 and 4 weeks, respectively were in clinical remission at week 52, as compared with 15.9% of patients who switched to placebo [15]. In GEMINI 2, 39.0% and 36.4% of CD patients assigned to VDZ every 8 weeks and every 4 weeks, respec-

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tively, were in clinical remission at week 52, as compared with 21.6% assigned to placebo [3]. In RWE studies assessing VDZ effectiveness after 1 year clinical remission rates varied between 21% and 35% [14].

The aims of the current study were to describe the effectiveness of VDZ for maintenance of response and remission in IBD patients, and to evaluate the prevalence and the clinical/demographic factors associated with secondary loss of response and drug discontinuation. The current study is the extension of the previously published Israeli multicenter RWE series that focused on effectiveness and safety during induction (up to 14 weeks) VDZ therapy.

2. Methods

This was a retrospective, observational pooled national multicenter study including patients from major IBD Centers in Israel. Eligible IBD patients were identified in the databases of the participating centers. All adult IBD patients who received VDZ for active disease at treatment onset (week 0) and accumulated 52 weeks of follow-up (unless the treatment was discontinued before week 52) were eligible for inclusion. All patients that discontinued treatment after receiving even single VDZ infusion were included. Patients not yet reaching 52 weeks of follow-up while still on active VDZ treatment were excluded. Active disease at treatment onset (week 0) was defined as any of the following: for CD—Harvey Bradshaw Index (HBI) >4, Crohn's disease activity index (CDAI) >150; for UC—Lichtiger score >4; simple clinical colitis activity index (SCCAI) >2, partial Mayo score >2 as per availability in each in the participating centers.

VDZ was administered intravenously at a standard dosing regimen (300 mg at week 0, 2, 6 followed by q8w maintenance dosing). Interval between VDZ infusions could be shortened (to q4/q6 weeks) in some of the patients as per discretion of the treating physician.

Retrospective data collection for the current study was approved by the local ethics review board.

2.1. Study definitions

The clinical, endoscopic and laboratory data (as per availability) per each time point was extracted from the patients' clinical charts and electronic records. Clinical remission was defined as HBI $\leq$4, CDAI <150; for UC–SCCAI <2, partial Mayo score $\leq$2 [16]. Clinical response was defined as improvement in HBI or SCCAI $\geq$3, or improvement in partial Mayo score $\geq$2. Use of corticosteroids at week 52 was considered as non-response in all cases. In absence of clinical scores, physician's global assessment (PGA) could be used.

C-reactive protein (CRP) levels were defined as elevated if above the limit of normal as defined by the laboratory of the corresponding participating center.

The main outcome was VDZ discontinuation at week 52. Secondary outcomes included clinical response, clinical remission and corticosteroid-free remission at week 52. Secondary loss of response (LOR) was defined as clinical exacerbation following initial clinical response achieved by week 14 (induction). Need for surgery, initiation of corticosteroids or immunomodulators during the course of treatment were also considered as LOR. Dose adjustments for VDZ were not considered as LOR as long as other definitions of secondary LOR were not met and the patient maintained clinical response at the next time point.

2.2. Statistical analysis

Descriptive statistics were presented as means $\pm$ standard deviations for parametric variables and medians with interquartile ranges (IQR) for non-parametric continuous variables and percentages for categorical variables. Categorical variables were analyzed by Chi Square/Fisher's exact test and continuous variables-by T-test/Mann Whitney test as appropriate. A two-tailed p value <0.05 was considered statistically significant. We constructed a multivariate logistic regression model to identify the independent predictors VDZ discontinuation at week 52. Variables with significance level <0.1 on the univariate analysis were included in the model. To investigate the effect of the variables on duration of continued VDZ treatment, we performed a survival analysis using Cox multivariate proportional hazard model for patients that continued treatment after week 14. The model included baseline and week 14 variables with significance level <0.1 on univariate analysis. The analysis was performed using IBM SPSS statistic (Version 20.0) (Armonk, NY, USA).

3. Results

A total of 193 (133—CD; 60—UC) were enrolled and followed for up to 52 weeks from treatment onset. Baseline clinical and demographic characteristics (Supplementary Tables 1 and 2), effectiveness of induction therapy with VDZ (week 14) and predictors of initial response and adverse events during induction were previously described in detail elsewhere [12]. Fifteen patients (6/133 (4.5%)—CD, 9/60 (15%)—UC)) were anti-TNF naïve. At week 14, 108/133 (81.2%) CD and 48/60 (80%) of UC patients continued treatment (Fig. 1). Fifteen patients (10—CD, 5—UC) received the week 10 dose and all but one continued to receive VDZ q4 weeks; 7/15 of the week 10 dose recipients were considered responsive at week 14. Out of 37 IBD patients that stopped treatment before or at week 14, 35/37 (94.5%) discontinued treatment due to primary non-response; 2 patients wished to discontinue VDZ due to pregnancy and 1-for adverse event (hearing loss) (Fig. 1).

Characteristics of patients continuing VDZ treatment after week 14 are detailed in Tables 1 and 2.

3.1. CD

3.1.1. Induction data (week 14)

At week 14, 70/133 (52,3%) of patients responded to treatment including 31 (23.3)% who were in clinical remission; 108/133 (81.2%) patients continued VDZ treatment after week 14. Out of 38 patients that continued treatment at week 14 despite non-response, 23 continued to be non-responsive and 15 gained clinical response at a later date (2 were in clinical remission by the end of the follow-up).

3.1.2. Maintenance data (week 52)

At week 52, 62/133 (46.7%) were responding to treatment (including 28 (21%) in clinical remission), and 71 (53.3%) discontinued treatment or did not respond. Twenty eight patients discontinued treatment between week 14 and 52; the reason for discontinuation was non-response in 27/28 and adverse event (ITP) in 1 patient. Out of patients that discontinued treatment for non-response between weeks 14 and 52, 15/27 were patients that continued treatment despite primary non-response and 12 developed secondary LOR after a median of 23 (12–33) weeks. Overall, secondary LOR by week 52 was experienced by 12/62 (19.4%) of week 14 responders.

At week 14, 32 (29.6%) and at week 52, 11 (13.8%) patients were receiving corticosteroids, respectively. Of the latter, 5 were on corticosteroids at treatment onset and 6 required addition of

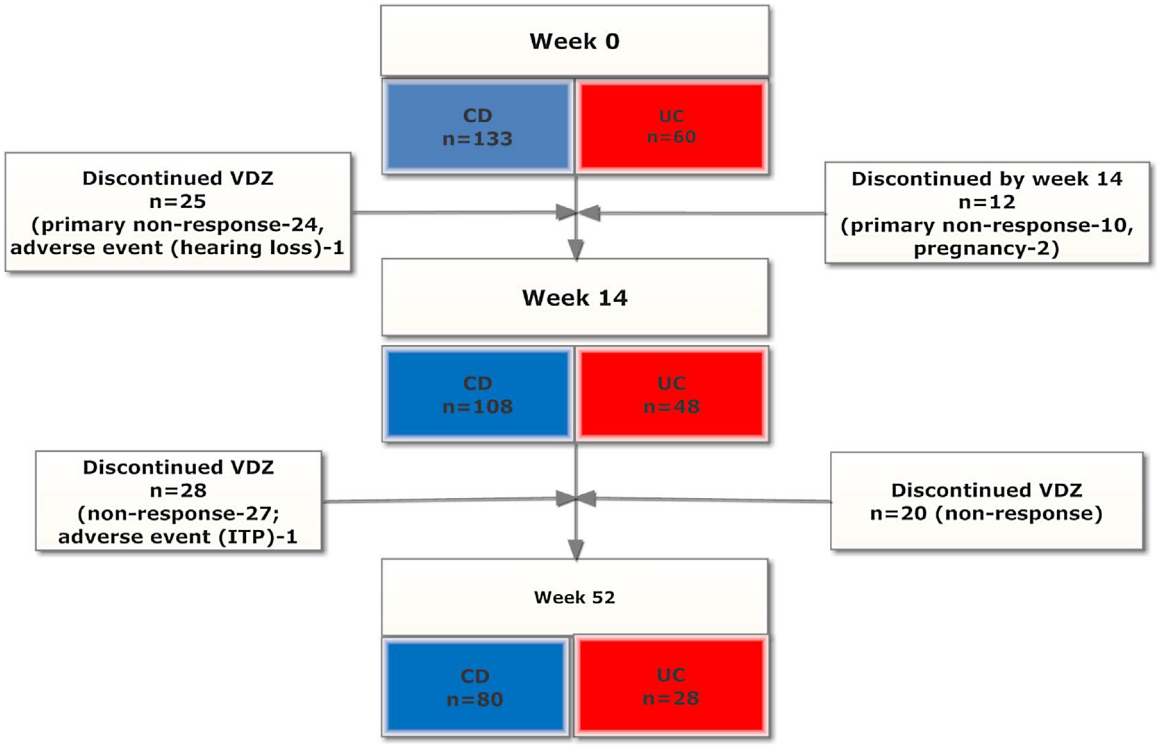

Fig. 1. Treatment discontinuation by week 14 and 52.

Table 1
Clinical and demographic characteristics of IBD [atients starting Vedolizumab therapy.

Characteristic	CD—n = 133		UC—n = 60
Median (IQR) age—yr	40 (29–57)		36 (30–49)
Median (IQR) age at disease onset—yr	27 (20–41)		27 (21–37)
Gender			
Male—n(%)	62 (46.6%)		30 (50%)
Female—n(%)	71 (53.4%)		30 (50%)
CD location			
Ileal—n(%)	52 (39.6%)	Rectum—n(%)	1 (1.7%)
Colonic—n(%)	21 (16%)	Left-sided—n(%)	27 (45%)
Ileocolonic—n(%)	58 (44.3%)	Extensive—n(%)	31 (52.7%)
CD behavior			
Non-stricturing non-penetrating n(%)	72 (54.1%)		
Structuring—n(%)	26.3 (35.4%)		
Penetrating—n(%)	26 (19.5%)		
History of perianal disease—n(%)	41 (30.8%)		
Prior surgery for Crohn's disease—n(%)	57 (43.2%)		
Smoking status			
Never—n(%)	85 (63.9%)		52 (86.7%)
Current—n(%)	39 (29.3%)		2 (3.3%)
Past—n(%)	9 (6.8%)		6 (10%)
Elevated CRP—n(%)	89/115 (77.4%)		37/55 (67.3%)
Biologic-naïve—n (%)	6/133 (4.5%)		9 (15.1%)
Systemic corticosteroids at treatment onset—n(%)	49 (36.8%)		9 (15.1%)
Concomitant immunomodulators at treatment onset—n(%)	20 (15.2%)		14 (23.3%)

VDZ—vedolizumab; CD—Crohn's disease: UC—ulcerative colitis; CRP-C—reactive protein.

corticosteroids. C-reactive protein (CRP) levels at week 14 were available in 92/108 patients that continued treatment after week 14 and were elevated in 68/92 (74%) of them. In 46/68, CRP levels were available at both week 14 and week 52 and normalized in 7/46 (15.2%). Thirty one (28.7%) patients required VDZ dose escalation during the course of treatment, of them 19/31 (61.3%) were responsive at the end of follow-up.

3.1.3. Predictors of VDZ discontinuation and loss of response

The only variable that was positively associated with continued VDZ treatment at week 52 was clinical response at week 14: 12 (42.9%) vs 58 (72.5%) patients, odds ratio (OR)—3.5 (95% CI (1.4–8.6), p = 0.006). Multivariate analysis was not performed as no other variable reached the threshold p value for inclusion in the model ($p \leq 0.1$) (Table 1).

Table 2
Association of clinical and demographic characteristics with continuation of vedolizumab treatment at week 52.

CD (continued VDZ after week 14—n = 108)	Discontinued VDZ by week 52 (n = 28)	Discontinued VDZ by week 52 (n = 80)	P	UC—(continued VDZ after week 14—n = 48)	Discontinued VDZ by week 52(n = 20)	Continued VDZ at week 52 (n = 28)	P
Gender							
Male—n(%)	12 (42.9%)	38 (47.5%)	0.7		9 (45.0%)	19 (67.9%)	0.11
Female—n(%)	16 (57.1%)	42 (52.5%)			11 (55.0%)	9 (32.1%)	
Disease location							
Ileal—n(%)	12 (42.9%)	28 (36.8%)	0.7	Rectum—n(%)	1 (5.0%)	1 (3.6%)	0.32
Colonic—n(%)	5 (17.9%)	11 (14.3%)		Left-sided—n(%)	11 (55.0%)	11 (39.3%)	
Ileocolonic—n(%)	11 (39.3%)	38 (49.4%)		Extensive—n(%)	8 (40.0%)	16 (57.1%)	
CD behavior							
Non-stricturing non-penetrating—n(%)	11 (39.3%)	45 (56.3%)	0.3				
Stricturing—n(%)	9 (32.1%)	19 (23.8%)					
Penetrating	8 (28.6%)	16 (20.0%)					
History of perianal disease—n(%)	13 (46.4%)	23 (28.8%)	0.9				
Smoking status							
Never—n(%)	21 (75.0%)	47 (58.8%)	0.16		18 (90.0%)	22 (78.6%)	0.41
Current—n(%)	7 (25.0%)	26 (32.5%)			0 (0.0%)	2 (7.1%)	
Past—n(%)	0 (0.0%)	7 (8.8%)			2 (10.0%)	4 (14.3%)	
Disease severity at baseline—n (%)							
Mild—n(%)	5 (17.9%)	18 (22.5%)	0.8		5 (25.0%)	7 (25.0%)	
Moderate—n(%)	17 (60.7%)	48 (60.0%)			11 (55.0%)	10 (35.7%)	0.35
Severe—n(%)	6 (21.4%)	14 (17.5%)			4 (20.0%)	11 (39.3%)	
Biologic-naïve—n (%)	0 (0%)	5 (4%)	0.23		2 (10%)	6 (21.4%)	0.37
Elevated CRP at treatment onset—n(%)	19 (79.2%)	54 (78.3%)	0.47		14 (70.0%)	16 (64.0%)	0.67
Systemic corticosteroids at treatment onset, baseline—n(%)	8 (28.6%)	24 (30.0%)	0.89		12 (60.0%)	9 (32.1%)	0.06
Concomitant immunomodulators at treatment onset—n(%)	3 (10.7%)	14 (17.7%)	0.38		4 (20.0%)	8 (26.8%)	0.59
Response at week 14—n(%)	12 (42.9%)	58 (72.5%)	0.01		9 (45%)	24 (85.2%)	0.004
Elevated CRP, week 14—n(%)	14 (70%)	54 (75.0%)	0.75		12 (66.7%)	14 (60.9%)	0.75
Systemic corticosteroids, week 14—n(%)	4 (14.3%)	8 (10.0%)	0.50		4 (20.0%)	3 (10.7%)	0.46

VDZ—vedolizumab; CD—Crohn's disease: UC—ulcerative colitis; CRP-C—reactive protein.

We also performed a Cox proportional hazards regression analysis to identify factors associated with secondary LOR to VDZ in CD patients; no significant associations were demonstrated (Supplementary Table 1).

3.2. UC

3.2.1. Induction data (week 14)

Forty eight of 60 (80%) patients continued treatment after week 14. At week 14, 34/60 (56.7%) patients responded to treatment, including 14 (23.3%) in clinical remission (p = 0.67 in comparison to CD). Out of 15 patients continuing treatment despite clinical non-response by week 14, 11 discontinued VDZ before week 52 and 4 continued treatment at week 52; 3 of those achieved response between week 14 and 52.

3.2.2. Maintenance data (week 52)

At week 52, 27/60 (45%) patients were responding to treatment (p = 0.8 compared to CD), including 20 (33%) in clinical remission; 33 (55%) discontinued treatment or did not respond; 28/48 (58.3%) patients that continued VDZ at week 14 were still on active VDZ treatment and 20 discontinued for non-response: 12-primary and 8-secondary LOR after 30 (18–37) weeks from initial response. Secondary LOR by week 52 occurred in 8/34 week 14 responders (23.5%).

At week 14, 7/48 (14.6%) of the patients that continued treatment were on systemic corticosteroids; at week 52, 1/28 (3.6%) patients continuing treatment were receiving corticosteroids.

CRP levels at week 14 were available in 41/48 of patients that continued treatment at week 14 and were elevated in 26/41 (63.4%). CRP levels at week 52 were available in 13 out 30 patients with elevated week 14 CRP levels and normalized in 5/13 (38.5%). Dose escalation to q4w was required in 17 (33.3%); 11/17 (64.7%) patients were responding to treatment by week 52.

3.2.3. Predictors of VDZ discontinuation and loss of response

On univariate analysis, the only variable that was positively associated with continued VDZ treatment at week 52 was clinical response at week 14 (9/20 (45%) vs/28 (85.2%), OR—7.3, CI 95% (1,8–29.1), p = 0.004). Multivariate analysis was not performed as no other variable reached the threshold p value for inclusion in the model ($p \leq 0.1$) (Table 2).

We also performed a Cox proportional hazards regression analysis to identify factors associated with secondary LOR to VDZ in IC/IBD-U patients; no significant associations were demonstrated (Supplementary Table 2). In addition, there were no significant differences in VDZ LOR–free survival between CD and UC/IBD-U (Fig. 2, Fig. 3).

3.3. Safety

Adverse events during the first 14 weeks of therapy are described in detail elsewhere [12]. Overall, 18 patients reported adverse effects during the entire course of follow-up (week 0–52) (Table 3). Six patients reported adverse events during the course of maintenance therapy (ITP, miscarriage, skin eruption, infusion reaction, cough, arthralgia—1 case of each); VDZ was discontinued in 1 patient due to an adverse event (ITP). Notably, there was one death during the induction phase. This was a 69-year old patient that received VDZ and full dose prednisone for severe pancolitis; after his second infusion of VDZ he developed necrotizing fasciitis followed by perforation after colonoscopy. After surgery the patient developed multi-organ failure that resulted in death. In

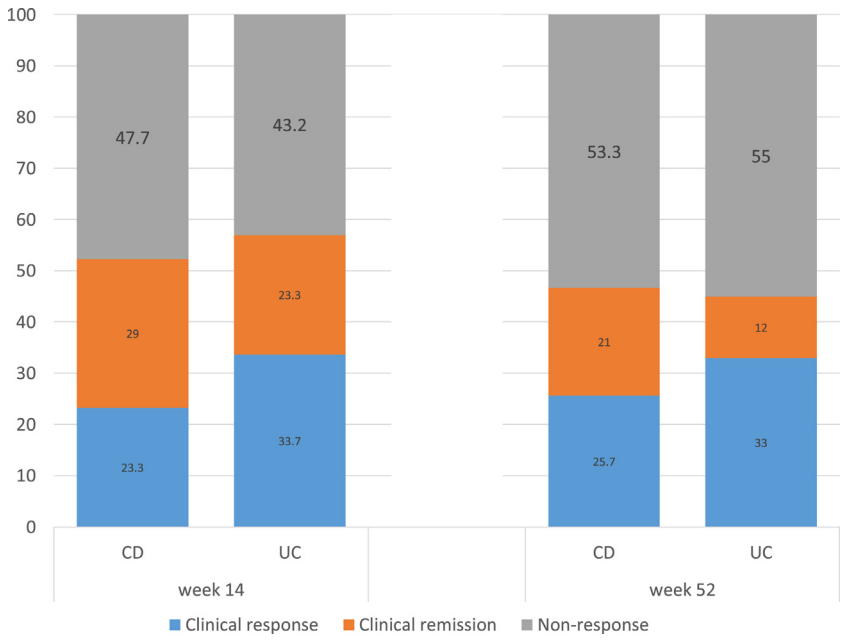

Fig. 2. Response to vedolizumab at week 14 and 52.

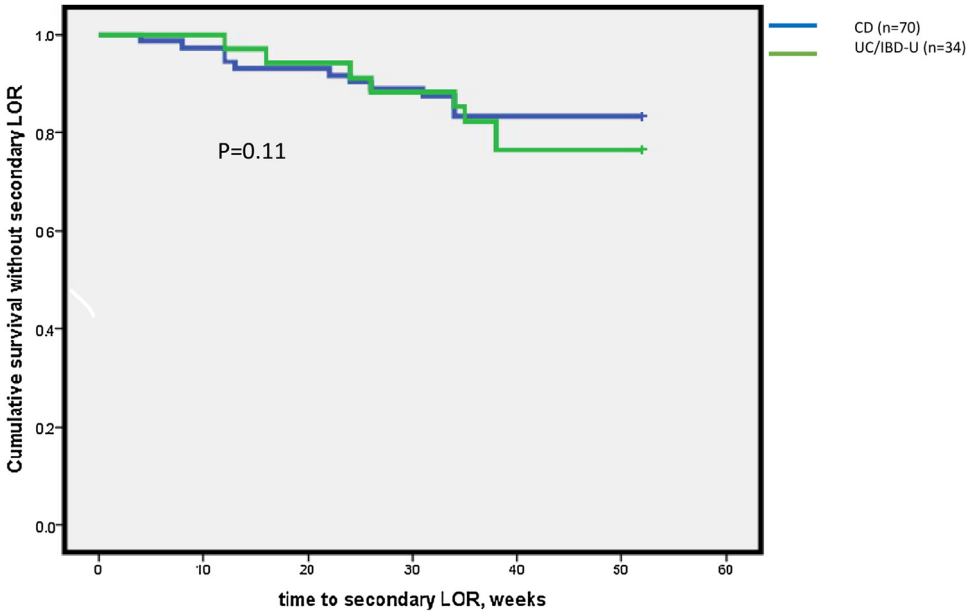

Fig. 3. Kaplan–Meier survival analysis for development of secondary loss of response in patients that responded to treatment at week 14.

Table 3
Adverse effects during vedolizumab treatment.

	CD	UC
Arthralgia	2	0
Dyspnea	0	1
Encephalitis	1	0
Headache	1	0
Hearing loss	1	0
Idiopathic thrombocytopenic purpura	1	0
Infusion reaction	0	1
Line sepsis	1	0
Miscarriage	2	0
Nasopharingytis	3	0
Peripheral edema	1	0
Psychosis	1	0
Sepsis (resulting in death)	0	1
Skin eruption	1	0

addition, one case of encephalitis occurred; VDZ was reinstituted after progressive multifocal leukoencephalopathy was ruled out.

Twenty six (24.1%) CD patients required hospitalization during the course of follow-up, including 10 (9.8%) that required surgery. For UC/IBD—13 (25.5%) required hospitalization, of them 3 were hospitalized for total colectomy.

4. Discussion

This is a report of RWE of the effectiveness and safety of VDZ in a national multicenter Israeli cohort The current study is the extension of the previously published Israeli multicenter RWE series that focused on induction VDZ therapy. At week 52, response was observed in 62/133 (46.7%) CD patients, and in 27/60 (45%) UC/IBDU patients. Similarly to other RWE studies, our cohort was comprised

of patients with complicated disease who failed previous treatment lines including at least one anti-TNF (93%). Of note, we included only patients with active disease at treatment onset, thus demonstrating the potential of VDZ to induce and maintain remission in patients with active IBD. By week 52, 46.7% of CD and 42.6% of UC/IBD-U patients were responding to treatment; secondary LOR by week 52 occurred in 17% and 22% of week 14 responders in UC and CD, respectively. These response rates are in line with the reports of previous real-world cohorts in adult population (25–58%) [7,8,10,14]. Stallmach et al. reported a 21% remission rate in CD and 25% in UC after 54 weeks; clinical response rates were at week 54 were 25% in CD and 38% in UC, respectively [8]. Eriksson et al. reported drug continuation rate of 61% by week 52 in CD; 41/147 (27.8%) of the patients started on VDZ were in clinical remission and 36 (24.5%) were responding to treatment. For UC, the continuation rate was 65%; 28 (30.4%) were in clinical remission and 29 (31.5%) at week 52 (out of 92 UC patients included) [11]. In recent reports form a large multicenter American cohort (VICTORY), 35% of the included 212 CD patients were in clinical remission at week 52 [7]. In UC, 12-month cumulative rates of clinical remission and endoscopic remission were 51% and 41%, respectively. Corresponding rates for corticosteroid-free remission and deep remission were 37% and 30%, respectively [17] (Supplementary Table 5). In a recent systematic review, the pooled incidence rates of loss of response were 47.9 per 100 person-years of follow up (95% CI, 26.3–87.0; I2 = 74%) among patients with CD and 39.8 per 100 person-years of follow up (95% CI, 35.0–45.3; I2 = 0%) among patients with UC. Dose intensification restored response to the drug in 53.8% of secondary non-responders (95% CI, 21.8%–82.9%; I2 = 77%) [18].

No significant difference in response/remission rate between UC and CD was detected in our study. The only predictor of maintenance of response was clinical response by week 14. In contrast with the Massachusetts cohort described by Allegretti et al. [10], concomitant immunomodulators therapy did not have an impact on treatment outcomes in our study. Similarly, there was no association of previous anti-TNF exposure [7] with treatment outcomes at week 52; however, only 7% of the patients in our cohort were anti-TNF naïve.

The rates of secondary LOR in our cohort are comparable to Allegretti et al. and are in line with anti-TNF data [19]. No difference in rates of secondary LOR between CD and UC was detected. Our data does not provide an insight into the mechanism of secondary LOR to VDZ. While for anti-TNFs, immunogenicity is an important driver of secondary LOR [20–22], antibodies to VDZ are quite rare (up to 17% during induction therapy and 3% of patients during maintenance therapy) and do not correlate with clinical outcomes [21]; moreover, the association of drug levels with clinical outcomes for VDZ appears to be less robust [21,23,24]. Moreover, our data does not support a beneficial effect of combination therapy with thiopurines on the long-term efficacy of VDZ. These results are consistent with GEMINI data and RWE reports [3,14,15]; importantly, such combination therapy is not associated with VDZ trough levels or appearance of anti-VDZ antibodies, contrary to what was demonstrated for anti-TNFs [20–22]. Unfortunately, VDZ levels are available for only a small proportion of patients in this study.

Most of the adverse events occurred shortly after the initiation of treatment; discontinuation of VDZ due to an adverse event occurred in a single patient after week 14 (ITP that was not previously described in association with VDZ treatment). Other AEs reported during the maintenance phase were minor and did not necessitate treatment change.

Our study has several limitations mostly stemming from the retrospective multicenter design. The clinical scores used by the participating centers were not identical; in some patients, only PGA was available. CRP levels were missing for some of the visits, and endoscopic data was available in a small minority of the patients (not described for this reason). In addition, there is a significant discrepancy between clinical response and drug continuation rates. This is best explained by the fact that this study describes a real-world cohort; in daily clinical practice the decisions are usually based on the physician's impression of response that do not necessarily correlate with formal definitions of response by the clinical scores employed in a clinical trial. As 93% of our patients failed previous anti-TNF treatment, and had limited further therapeutic options the treating physician may be more likely to pursue VDZ treatment even when the benefit is not clear-cut in hope for a later response; such delayed response indeed occurred in almost 40% of CD and 20% of UC patients that did not respond by week 14.

In summary, VDZ appears to be safe and effective for maintenance treatment in both CD and UC in a large real-world cohort of complicated IBD patients. The response rate was quite similar for UC and CD. Secondary LOR occurred in a similar proportion to what was described for anti-TNFs. Further studies are merited to further elucidate the mechanisms and the predictors of loss of response to VDZ.

Conflict of interest

UK reports research support form Takeda, Jannsen, Medtronic' speaking fees from Abbvie, Takeda, Jannsen, CTS.

ID reports consulting fees from Takeda, Janssen, Abbvie, Genentech, Pfizer, Ferring, Rafa laboratories, Given Imaging, Protalix, Roche, Celltrion. Speaking and teaching for Takeda, Janssen, Abbvie, Ferring, Falk Pharma, Given Imaging, Genentech, Pfizer, MSD, Neopharm.

ABS reports consulting fees from Takeda, Janssen and Abbvie, speaking and teaching for Takeda, Janssen, Abbvie, Neopharm and Rafa laboratories. Research support from Takeda and Janssen.

SBH reports consultancy and/or Advisory board fees from Abbvie, Schering Plough, Celltrion, Takeda, Janssen, Novartis. Research support from Celltrion and Abbvie.

MW reports speaker and consulting fees JC Healthcare, Israel, Abbvie Israel, Takeda, Israel. Consulting fees Given Imaging, Israel

YC reports grant support Abbvie, Takeda Consultancy: Abbvie, Takeda, Janssen, Medtronics, Protalix Speaker fees: Abbvie, Takeda, Janssen, Ferring.

EZ reports consulting fees from Janssen.

RE reports consulting/speaker fees from Abbvie, Takeda, Janssen, Rafa, Ferring, Medtronics/Given Imaging.

Other authors had no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.07.040.

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