Effect of vedolizumab dose intensification on serum drug concentrations and regain of response in inflammatory bowel disease patients with secondary loss of response

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Background and Aims: Dose intensification of vedolizumab (VDZ) for moderate-to-severe ulcerative colitis (UC) and Crohn's disease (CD) may be effective in patients losing response. We aimed to assess the clinical and pharmacokinetic effect of VDZ dose intensification.

Methods: We performed a multicentre open-label prospective study from June 2017 through December 2018 in patients on VDZ losing response, defined as total Mayo score >6 (UC) or Harvey-Bradshaw Index >4 with inflammation (CD). Blood samples and clinical scores were collected at baseline and after VDZ infusion at Weeks 4 and 8. Clinical response was defined as a decrease of partial Mayo score ≥2 points or Harvey-Bradshaw Index ≥3 points. Biological response was defined as a decrease of C-reactive protein to ≤5 mg/L or of >50%.

Results: A total of 59 patients (31 UC and 28 CD) were included. Median (IQR) trough levels (TLs) increased from 8.7 (5.1-12.7) µg/mL (baseline) to 19.1 (12.4-22.4) µg/mL (Week 4) and 23.1 (16.7-28.4) µg/mL (Week 8) (all P < 0.0001). Partial Mayo score decreased with 3 points from baseline to Week 4 (P = 0.001) but stabilised to Week 8 (P = 0.16). Harvey-Bradshaw Index decreased with 4 points from baseline to Week 4 (P = 0.001) and 1 point to Week 8 (P = 0.04). Recapture of clinical and biological response was achieved in 49% and 27% at Week 4, and 54% and 37% at Week 8 respectively.

Conclusion: Dose escalation to VDZ every 4 weeks after loss of response resulted in higher TLs with regain of clinical response in half of the patients.
1 | INTRODUCTION

Vedolizumab (Entyvio®) is an approved biological treatment for moderate-to-severe ulcerative colitis (UC) and Crohn's disease (CD). Vedolizumab (VDZ) prevents the interaction of α4β7 integrin, expressed by a subset of gastrointestinal-homing T-lymphocytes, with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) present on the surface of mucosal endothelial cells. As a result, VDZ inhibits the mucosal addressin cell adhesion molecule-1 (MAdCAM-1) present on the surface of mucosal endothelial cells. As a result, VDZ inhibits the migration of T-lymphocytes into the bowel tissue. VDZ might also modulate the innate immune system with additional therapeutic effect. The recommended dose regimen of VDZ is 300 mg administered by intravenous (IV) infusion at 0, 2 and 6 weeks followed by infusions every 8 weeks (Q8W) thereafter. Patients with CD who have not shown an adequate clinical response after induction may benefit from an additional dose at 10 weeks.

Long-term studies have shown sustained efficacy over time, although loss of response was seen in 26%, 22% and 54% of UC patients and in 29%, 31% and 57% of CD patients after 1, 2 and 3 years of treatment respectively. Loss of response to biological agents is a well-known phenomenon and for anti-tumour necrosis factor (TNF)-α biologicals it is typically managed by increasing dose and/or shortening interval. For anti-TNFs, it has been shown that therapeutic drug monitoring (TDM) is useful in guiding physicians on the most optimal therapeutic strategy in the situation of loss of response. TDM involves measuring drug levels with adjustment of the dose when needed, and is particularly of interest because drug exposure, rather than the administered dose, is related to response to biologicals. Several studies have also suggested an exposure-efficacy relationship with VDZ, however, solid data supporting a role for monitoring of VDZ trough concentrations are lacking.

Since the effect of dose escalation on serum drug concentrations of VDZ and clinical outcome in case of loss of response is not known, we investigated the effect of increased dosing frequency to 300 mg every 4 weeks (Q4W) on drug exposure and clinical and biological outcomes in patients with loss of response during maintenance therapy.

2 | METHODS

2.1 | Patients

We performed an open-label prospective study from June 2017 through December 2018 in 14 centres including IBD patients with secondary loss of response to VDZ Q8W maintenance therapy and who would benefit from a dose escalation to VDZ Q4W. All patients provided written informed consent and the study was approved by the Ethics Committee of all participating centres (Study approval number UZ Leuven Central Ethics Committee: B322201730955). Inclusion criteria were age 18 years or more, current treatment with VDZ 300 mg Q8W maintenance and loss of response to this therapy after showing response to induction treatment by Week 10 for UC and Week 14 for CD.

2.2 | Definitions

Loss of response was defined as a total Mayo score >6 for UC and a Harvey-Bradshaw Index (HBI) score >4 with objective signs of inflammation detected by endoscopy, ultrasound, radiography, C-reactive protein (CRP) >5 mg/L or faecal calprotectin >250 μg/g for CD.

Clinical response was defined as a decrease of partial Mayo score with ≥2 points for UC or a decrease of HBI score with ≥3 points for CD. Biological response was defined as a CRP ≤5 mg/L or a decrease in CRP of ≥50% in patients with a CRP >5 mg/L at baseline. Patients who prematurely discontinued the study or had missing data were considered as nonresponders in the statistical analyses for clinical and/or biological response.

2.3 | Study procedures and outcomes

We collected demographic, clinical and laboratory variables for each patient who met the inclusion criteria at baseline (last infusion of 8-weekly dosing and start of 4-weekly dosing), Week 4 after dose escalation and Week 8 after dose escalation.

The primary outcome was the effect of 4-weekly dosing on serum concentrations and the association of higher serum concentrations with regained response.

The secondary outcomes were the proportion of UC and CD patients who recaptured biological and/or clinical response after increasing to 4-weekly dosing.

2.4 | Vedolizumab serum concentrations

Vedolizumab serum trough levels (TLs) were determined using ELISA with MA-VDZ6F3 as coating and biotinylated MA-VDZ6E6 for detection, allowing the detection of VDZ concentrations from 3.0 μg/mL up to 100.0 μg/mL. This home-made VDZ enzyme-linked immunosorbent assay was converted into a CE-marked kit and is distributed by apDia as apDia Vedolizumab Elisa kit and as RIDASCREEN Vedolizumab Monitoring by R-Biopharm AG. Anti-drug antibodies were not measured.

2.5 | Statistics

Continuous variables were summarised as medians with interquartile ranges (IQR) and categorical data as percentages. The evolution in biological and clinical response was studied within patient groups (CD, UC or both) with nonparametric paired (Wilcoxon signed-rank)
tests. Comparison between patient groups was done with nonparametric unpaired (Mann-Whitney U) tests. Fisher exact or Chi-square test was used for the analysis of proportions. In addition, VDZ levels were categorised into quartiles, and rates of remission were compared across quartiles using the Chi-square test of trend. Two-tailed $P$ values were used in all analyses to determine statistical significance (threshold $<0.05$). Statistical analyses were performed with Prism version 8 (GraphPad Software).

2.6 | Availability of data

The data underlying this article will be shared on reasonable request to the corresponding author.

3 | RESULTS

3.1 | Patient population

A total of 70 IBD patients were assessed for eligibility in the study. Ten patients did not meet the inclusion criteria and TLs from one patient were unavailable, resulting in an overall study population of 59 patients (Figure 1). By Week 4, three patients prematurely discontinued the study and data were missing for three more patients at Week 8. Baseline demographics and clinical characteristics are depicted in Table 1.

3.2 | Trough level evolution

After dose escalation, median (IQR) TL increased from 8.7 (5.1-12.7) $\mu$g/mL at baseline to 19.1 (12.4-22.4) $\mu$g/mL at Week 4, and 23.1 (16.7-28.4) $\mu$g/mL at Week 8 (all $P < 0.0001$) (Figure 2) with a similar evolution in UC and CD (Table 2).

3.3 | Clinical and biological response to VDZ dose escalation

In patients with UC, partial Mayo score significantly decreased from baseline to Week 4 ($P = 0.001$), but no further decrease from Week 4 to Week 8 ($P = 0.16$) was observed. In patients with CD, HBI significantly decreased from baseline to Week 4 ($P = 0.001$) and further from Week 4 to Week 8 ($P = 0.04$) (Table 2).

We observed a numerical decrease in CRP from 6.1 (2.2-11.4) mg/L at baseline to 5.6 (2.1-12.6) mg/L at Week 4, and 3.9 (2.7-8.9) mg/L at Week 8, although this was not significant (all $P > 0.05$) and similar in UC and CD (Table 2). For patients with a CRP at baseline of >5 mg/L ($n = 30$), the decrease in CRP from 11.2 (7.5-18.8) mg/L at baseline to 11.1 (5.9-17.8) mg/L at Week 4, and 8.6 (3.7-12.7) at Week 8 was also not significant (all $P > 0.05$) (Figure 3) and similar in UC and CD (Table 2).

Clinical and biological response was achieved by Week 4 in 49% and 27% of patients and by Week 8 in 54% and 37% of patients respectively. In UC, clinical and biological response was achieved by Week 8 in 48% and 40% of patients respectively. In CD, clinical and biological response was achieved by Week 8 in 61% and 40% of patients respectively. There was no significant difference in disease duration between clinical and biological responders and nonresponders ($P = 0.57$ and $P = 0.08$ respectively). Looking into anti-TNF experienced versus naïve patients, there was no significant difference between clinical and biological responders and nonresponders. As there were only six patients with a combined clinical and biological response, we did not further study this subgroup.

3.4 | Relation between VDZ drug exposure at baseline and clinical and biological response

When considering the optimal VDZ TL of 14 $\mu$g/mL, a similar proportion of clinical and biological responders was seen in patients with TL above 14 $\mu$g/mL or below 14 $\mu$g/mL at baseline (Figure 4). Quartile analysis looking at VDZ TL at baseline showed no difference in clinical and biological responders at Week 4 or 8 (all $P > 0.05$) (Figure 5 and Table S1). Also partial Mayo score, HBI, serum albumin and body mass index (BMI) at baseline did not differ between clinical and biological responders and nonresponders, and were similar in UC and CD (all $P > 0.05$) (Table S2).
3.5 | Relation between VDZ drug exposure at Week 8 and clinical and biological response

At Week 8, median (IQR) VDZ TLs were significantly higher in clinical and biological responders (24.7 (21.0-30.6) and 18.3 (15.7-24.2)) compared to nonresponders (18 (13.4-23.1) and 5.9 (3.1-9.7)) (P = 0.006 and <0.0001 respectively) (Figure 6). These observations were seen in all IBD patients, as well as UC and CD patients with lack of significance in CD (P = 0.17) (Table S3). There was also a significant difference in median (IQR) CRP at Week 8 between clinical responders (2.9 (2.4-5.5)) and nonresponders (9 (3.4-15.2)) (P = 0.003) (Figure 7). Data in UC and CD separately followed the same numerical trend, although these lacked significance (Table S3).

The changes in VDZ serum concentrations from baseline to Week 8 did, however, not correlate significantly with the observed changes in CRP, partial Mayo score or HBI.

When considering potential associations between clinical and biological variables at Week 8, we only found a significant correlation between partial Mayo score and TL (r = −0.56, P = 0.004) and CRP (r = 0.49, P = 0.008) in UC and not between HBI and TL (r = 0.02, P = 0.394) or CRP (r = 0.19, P = 0.38) in CD.

ROC curves were constructed to assess the correlation between clinical and biological response at Week 8 and VDZ TLs either at baseline or Week 8 (Figure 8). Whereas this ROC analysis did not show a significant area under the curve for clinical (P = 0.26) and biological response (P = 0.27) with TL at baseline, the area under the curve was

### TABLE 1 Baseline demographics and clinical characteristics

| Patient characteristic                             | Total n = 59 | Ulcerative colitis n = 31 | Crohn's disease n = 28 |
|---------------------------------------------------|--------------|---------------------------|------------------------|
| Sex, women, n (%)                                 | 38 (64%)     | 18 (58%)                  | 20 (71%)               |
| Age at diagnosis, median (IQR), y                 | 27.6 (18.4-37.5) | 33.2 (21.5-41.2) | 25.2 (17.5-30.1) |
| Age at dose escalation, median (IQR), y           | 39.2 (29.1-50.4) | 42.4 (31.6-49.8) | 36.5 (28.7-51.8) |
| Disease duration, median (IQR), y                 | 6.6 (4.6-12.7) | 5.9 (3.5-12.5) | 8.2 (5.4-14.7) |
| Body mass index, median (IQR), kg/m²              | 25.7 (22.4-28.0) | 25.7 (22.9-27.7) | 25.8 (22.3-28.9) |
| Active smoker, n (%)                              | 7 (12%)      | 1 (3%)                    | 6 (21%)                |
| Previous anti-TNF exposure, n (%)                 | 45 (76%)     | 23 (74%)                  | 22 (79%)               |
| Concomitant corticosteroid therapy, n (%)         | 16 (27%)     | 10 (32%)                  | 6 (21%)                |
| Concomitant immunomodulatory therapy, n (%)       | 7 (12%)      | 3 (10%)                   | 4 (14%)                |
| Haemoglobin, median (IQR), g/dL                   | 13.3 (12.2-14.4) | 13.9 (12.0-14.8) | 13.1 (12.5-13.8) |
| Haematocrit, median (IQR), %                      | 40.2 (37.1-42.7) | 41.6 (37.4-43.5) | 39.5 (36.8-41.5) |
| White blood cell count, median (IQR), ×10⁹/L      | 8.3 (6.7-10.4) | 8.1 (6.7-10.4) | 8.3 (6.8-10.3) |
| Lymphocytes, median (IQR), ×10⁹/L                 | 1.9 (1.4-2.3) | 1.9 (1.4-2.2) | 2.0 (1.4-2.9) |
| C-reactive protein, median (IQR), mg/L            | 6.05 (2.15-11.40) | 5.05 (1.43-8.65) | 7.00 (2.88-14.20) |
| Serum albumin, median (IQR), g/L                  | 41.0 (39.6-43.8) | 42.0 (38.7-44.2) | 40.5 (40.0-43.2) |

**FIGURE 2** Evolution of vedolizumab trough level (TL) at baseline and after dose escalation at Weeks 4 and 8
significant for clinical (0.732 (0.584-0.880), \( P = 0.007 \)) but not biological response (\( P > 0.99 \)) with TL at Week 8. This indicated a statistical significant association between TL at Week 8 and clinical response.

### 4 | DISCUSSION

In this article, we present results from a prospective study in 59 VDZ-treated IBD patients with secondary loss of response on Q8W therapy, who received dose escalation to Q4W therapy. Dose escalation resulted in a significantly higher drug exposure at Week 8 and in a recapture of clinical and biological response in, respectively, 54% and 37% of patients at Week 8. These findings confirm already available data; however, these studies are either retrospective or included fewer patients.\(^ {16-20} \)

We also studied the role of TDM in predicting and assessing regain of clinical and biological response after dose escalation. TDM has acquired a significant role in therapeutic decision-making in case of loss of response to biologicals. In anti-TNF-treated patients, reactive TDM has shown to be cost-effective and is associated with improved outcomes.\(^ {6,9,21} \) However, data on the clinical utility of TDM in the setting of VDZ are scarce. Since infliximab therapy uses weight-based dosing, there is more flexibility in dosing compared with VDZ therapy, in which a fixed dose is administered. Also, antibody development against VDZ is a rare event. These reasons make the benefit of TDM for VDZ less clear, and its positioning in the setting of clinical loss of response is yet to be defined.

To our knowledge, this is the largest cohort prospectively evaluating the effect of VDZ dose escalation on serum drug concentrations and the association of higher concentrations with regained response. While we show an association between higher drug exposure after dose escalation and regain of response, baseline VDZ serum concentrations cannot predict successful outcome of treatment escalation. Neither quartile analysis of baseline TL nor

| TABLE 2 | Evolution of vedolizumab trough level (TL), partial Mayo score, Harvey-Bradshaw Index (HBI) and C-reactive protein (CRP) at baseline and at Weeks 4 and 8 after dose escalation |
|----------|-------------------|-------------------|-------------------|
|          | Baseline | Week 4 | Week 8 |
| UC (n = 31) |         |        |        |
| Median (IQR) TL (µg/mL) | 8.1 (4.8-11.0) | 18.0 (12.1-21.3) | 21.3 (14.7-24.9) |
| Median (IQR) partial Mayo score | 6 (5-6) | 3 (3-5) | 3 (2-5) |
| Median (IQR) CRP (mg/L) | 5.1 (1.4-8.6) | 4.4 (1.7-13.6) | 3.9 (2.8-10) |
| Median (IQR) CRP in patients with a CRP >5 mg/L at baseline | 9.0 (6.9-16.3) | 12.6 (7.2-17.8) | 10.0 (4.6-12.8) |
| CD (n = 28) |         |        |        |
| Median (IQR) TL (µg/mL) | 9.1 (5.5-15.1) | 21.2 (12.8-27.2) | 23.6 (19.8-31.0) |
| Median (IQR) HBI | 8 (5-13) | 4 (1-6) | 3 (1-5) |
| Median (IQR) CRP (mg/L) | 7.0 (2.9-14.2) | 5.6 (2.7-10.1) | 3.6 (2.7-8.8) |
| Median (IQR) CRP in patients with a CRP >5 mg/L at baseline | 14.2 (9.5-22.0) | 9.9 (5.5-22.2) | 8.5 (2.8-9.8) |

Abbreviations: Pb, \( P \)-value for comparison with baseline; Pw4, \( P \)-value for comparison with Week 4.

**FIGURE 3** C-reactive protein (CRP) evolution over time in patients with CRP at baseline of >5 mg/L

**TABLE 2** Evolution of vedolizumab trough level (TL), partial Mayo score, Harvey-Bradshaw Index (HBI) and C-reactive protein (CRP) at baseline and at Weeks 4 and 8 after dose escalation
a baseline TL of <14 µg/mL, as identified in a previous study from our centre, were predictive of response to dose escalation. This is in contrast to Ungaro et al who showed that VDZ TLs were significantly associated with corticosteroid-free remission during maintenance treatment. Patients with VDZ concentrations above 11.5 µg/mL were 2.4 times more likely to be in corticosteroid-free clinical and biochemical remission after adjusting for potential confounders. The authors suggested that if a patient is not responding to VDZ maintenance treatment, dose escalation should be considered in order to achieve a VDZ concentration of at least 11.5 µg/mL. Also, Vaughn et al found that after dose escalation, 74% of those with a VDZ concentration <7.4 µg/mL responded versus 52% of those with a VDZ trough concentration ≥7.4 µg/mL; however, this was not significant (P = 0.08).

From the studies published to date, post-induction VDZ levels appear to show the strongest association with outcomes. Unfortunately, the association between VDZ levels and outcomes during maintenance treatment remains unclear. Plevris et al also
showed no association between VDZ TL and clinical, biological or endoscopic outcomes during maintenance therapy, unlike Dreesen E et al, who looked at induction and maintenance concentrations in 179 patients. Weeks 14, 22 and 30 VDZ concentrations were significantly higher among IBD patients with biological and endoscopic remission, with a higher probability of remission when the VDZ concentration was >14 µg/mL.

In our study, we showed that VDZ serum levels increased significantly and resulted in significantly higher levels at Week 8 in clinical and biological responders than in nonresponders. A previous study suggested that a VDZ serum concentration of 3 µg/mL already induces a near complete saturation of α4β7 on peripheral blood T cells. However, our data and those of others suggest that increasing VDZ concentrations, well above 3 µg/mL, is associated with improved outcomes. Therefore, the mechanism of action of VDZ may not solely depend on complete blockade of peripheral α4β7-expressing T cells. VDZ treatment has been associated with significant changes in innate immune cells, including macrophages, as well as mucosal gene expression of many chemokines, innate immune receptors and T helper 17-associated cytokines.

A new formulation for SC administration of VDZ has been developed and is effective as maintenance therapy in patients with moderate-to-severe ulcerative colitis. The median steady-state trough concentration for VDZ SC at 34.6 µg/mL was higher than for VDZ IV at 11.1 µg/mL. Nevertheless, the new SC formulation showed comparable efficacy to that of the currently available IV formulation. As was seen in our study, the proportion of patients receiving VDZ SC for maintenance who achieved clinical remission at week 52 increased with increasing VDZ exposure from 50% (quartile 1) to 83% (quartile 4).

The still relatively small size of our cohort is one of the main limitations in our study. Due to the lack of associations between the measured variables and response, multivariate analysis was not performed. Also, a small proportion of patients was on concomitant medications, such as steroids, thereby not knowing if these could have an influence on the response rates. A more objective evaluation with faecal calprotectin and endoscopy is lacking. Also, evaluating response 8 weeks after dose escalation may be too soon considering the delayed onset of action of VDZ. However, most studies with VDZ, including the recent VARSITY study, could demonstrate response at Week 6 already. Finally, we only investigated dose escalation by shortening the interval to 4-weekly dosing. We do not know if the same results would be found when increasing the dose from 300 mg to 600 mg with maintaining the 8-weekly interval.

In summary, dose escalation of VDZ from Q8W to Q4W in UC and CD patients with loss of response results in higher TL, and regain of clinical and biological response was observed in, respectively, 54% and 37% of patients. Baseline TL is not predictive of response to dose escalation suggesting that TDM in VDZ-treated patients is
not indicated. However, larger prospective cohorts are needed to further investigate.

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Peer Review
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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