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Original article

Association of Early Vedolizumab Trough Levels with Clinical, Biochemical, Endoscopic Response and Drug Optimization During Maintenance Therapy in Patients with Inflammatory Bowel Diseases

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Short title: Early vedolizumab trough level and effectiveness outcomes

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Abstract

The exposure-response relationship between vedolizumab (VDZ) trough levels (VTLs) and efficacy outcomes has been extensively studied, but data on early VTLs in Asian populations are limited. We assessed clinical outcomes and biochemical response using fecal calprotectin (BioRES[FC]) or C-reactive protein (BioRES[CRP]) at week 14 (W14) and W54, endoscopic healing (EH) at available follow-up time points, and the need for drug optimization during maintenance therapy among 67 patients treated with VDZ (39 Crohn's disease [CD], and 28 ulcerative colitis [UC]). Associations between early VTLs and outcomes were assessed, with VTL cut-offs proposed using the area under the receiver operating curve (AUC). CD patients achieving W14 BioRES[CRP] had higher VTLs at W6 and W14. W54 BioRES[FC] responders and those not requiring drug optimization had higher W14 VTLs (11.2 *vs.* 3.8 μg/mL, *P*=0.036; 2.2 *vs.* 5.8 μg/mL, *P*=0.004). Proposed W14 VTL cut-offs were 5.3 μg/mL (AUC 0.859) for BioRES[FC] and 4.6 μg/mL (AUC 0.765) for drug optimization. In UC patients, higher early VTLs were noted in those achieving W14 corticosteroid-free clinical remission, W14 BioRES[FC], and W14 EH, but not consistently linked to W54 results. This real-life study suggests higher early VTLs correlated with better outcomes, with W14 VTLs potentially predicting long-term outcomes in CD patients. Future studies are needed to confirm these findings and guide VDZ therapy.

Keywords: vedolizumab; vedolizumab trough level; exposure-response relationship; inflammatory bowel disease

Introduction

Vedolizumab (VDZ) is a recombinant humanized immunoglobulin G1 monoclonal antibody to α4β7 integrin expressed on gut-specific lymphocytes, inhibiting adhesion of lymphocytes to mucosal addressin cell adhesion molecules-1 in gut endothelium[1,2]. In GEMINI trials, VDZ demonstrated both efficacy and safety in the treatment of both Crohn's disease (CD) and ulcerative colitis (UC)[3,4].

Since its advent as a therapy for inflammatory bowel disease (IBD), several studies have been conducted with the intention of using therapeutic drug monitoring (TDM) to optimize VDZ therapy. This involves correlating drug concentration and anti-drug antibodies with the achievement of therapeutic goals. In the post hoc analyses of GEMINI trials, patients with higher VDZ trough levels (VTLs) during induction therapy had higher rates of clinical response at week (W) 6, and higher rates of clinical remission at W52, both in UC and CD[3,4]. Aside from these, some observational studies have also demonstrated a good exposure-response relationship of VDZ during induction therapy[5-9].

Considering previous studies[3-9], assessing early VTLs appears to aid in therapeutic optimization by helping to determine whether a suboptimal response is due to inadequate exposure or primary non-responsiveness to VDZ. However, the utility of TDM for VDZ in clinical practice is still unclear with unproved causal-and-effect relationship. Further, the optimal VTL cut-off values for certain responses to guide therapeutic strategies are yet undetermined. Moreover, most exposure–response and pharmacokinetic data for VDZ have been derived from Western populations. Although population pharmacokinetic analyses suggest broadly similar VDZ pharmacokinetics between Asian and non-Asian patients[10,11], real-world exposure-response data from East Asian cohorts remain limited, warranting dedicated evaluation in this population. Therefore, we investigated the relationship of early VTLs with clinical, biochemical responses, and endoscopic healing (EH), together with the need for drug optimization during maintenance therapy among Korean patients with IBD.

Results

Baseline demographic data of patients

Table 1 presents the baseline patient demographic data. Patients with CD and UC had median ages at the first VDZ infusion of 35.0 (interquartile range [IQR], 29.0–43.0) and 47.5 (IQR, 35.8–50.3), respectively. The median disease duration was 13.6 (IQR, 9.5–17.2) years for CD and 3.6 (IQR, 2.6–6.7) years for UC. Male predominance was observed in both CD and UC patients, and only two (7.1%) patients with UC had a family history of IBD. Among the CD cohort, 33 (84.6%) had ileocolonic disease, 24 (61.5%) had penetrating disease, 21 (53.8%) had perianal disease, and five (12.8%) had a stoma. For UC, 20 (71.4%) patients had extensive colitis, and none had proctitis. All the patients had prior exposure to tumor necrosis factor (TNF) inhibitors. At the initiation of VDZ, 24 (61.5%) patients with CD and 11 (39.3%) patients with UC were on immunomodulators. Additionally, in contrast to 13 (46.4%) of the patients with UC, only three (7.7%) with CD received concomitant corticosteroids.

Overall outcome achievement rate in patients with CD and UC

Supplementary Tables 1 and 2 show the overall outcome achievement rates in patients with CD and UC. At W14, clinical remission (CREM) was achieved in 7 of 22 patients with CD (31.8%) and 6 of 26 patients with UC (23.1%), showing similar proportions between the two groups. However, by W54, the rate of clinical remission was lower in CD patients compared to UC patients. Regarding biochemical outcomes, the biochemical response based on C-reactive protein (BioRES[CRP]) at W14 was observed in 9 of 29 patients with CD (31.0%) and 7 of 16 patients with UC (43.8%), while the biochemical response based on fecal calprotectin (BioRES[FC]) was maintained in approximately 10% of patients. By W54, no patients achieved BioRES[CRP]. At W52, no patients with CD achieved EH; therefore, meaningful conclusions regarding endoscopic outcomes for CD could not be drawn. In contrast, EH was achieved in 10 of 28 patients with UC (35.7%) at W14 and in 10 of 20 patients (50.0%) at W52.

Relationship between early VTLs and clinical outcomes

In the analyses to reveal the relationship of early VTLs and clinical outcomes, 14 patients who were in clinically remitted status at baseline (12 with CD, and two with UC) and five CD patients with a stoma were excluded. **Supplementary Tables 3 and 4** present the median VTLs at W2, W6, and W14 in patients with CD and UC, categorized by clinical outcomes at W14 and W54. Outcomes include CREM, clinical response (CRES), corticosteroid-free clinical remission (CSF-CREM), and corticosteroid-free clinical response (CSF-CRES). A decreasing trend in median VTL values over time at W2, W6, and W14 was observed in both CD and UC patient groups as expected pharmacokinetics of VDZ, but the only significant difference was seen in W2 VTLs of UC patients who achieved CSF-CREM at W14. Serum VTL at W2 was significantly higher in UC patients who achieved CSF-CREM at W14 (5 responders) compared with non-responders (21 patients) (43.1 *vs.* 34.4 μg/mL, P=0.034) (**Figure 2A**). In the quartile analysis presented in **Supplementary Figure 1A**, the higher quartiles seemed to be numerically associated with a greater proportion of W14 CSF-CREM (P_{trend}=0.052). The cut-off value of W2 VTL to predict W14 CSF-CREM was 41.0 μg/mL, with an area under the receiver operating characteristic curve (AUC) of 0.810 (95% CI, 0.604–1.000) (**Table 2, Supplementary Figure 2A**).

Relationship between early VTLs and biochemical outcomes

In analyses assessing BioRES[FC] or BioRES[CRP], patients with a baseline CRP<0.6 mg/dL (n=9 in CD, n=12 in UC), or a FC<250 mg/kg (n=5 in CD, n=2 in UC) were excluded. Additionally, five CD patients with a stoma were also excluded from the analysis of BioRES[FC]. Among CD patients, higher serum VTLs at W6 and W14 were observed in those who achieved W14 BioRES[CRP], with particularly notable differences at 24.3 *vs.* 15.9 μg/mL (P=0.049) at W6 and 5.3 *vs.* 2.9 μg/mL (P=0.044) at W14 (**Supplementary Table 5, Figure 3A–B**). The quartile analysis demonstrated an increasing trend in the response rate of W14 BioRES[CRP] as VTLs at W6 and W14

increased, with P_{trend}=0.024 for both (**Supplementary Figure 3D**). The optimal VTL cut-offs for predicting W14 BioRES[CRP] were 19.1 μg/mL at W6 and 4.4 μg/mL at W14, with corresponding AUC values of 0.733 and 0.739, respectively (**Table 2, Supplementary Figure 3A–B)**. Additionally, serum VTL at W14 was significantly higher among those who achieved W54 BioRES[FC] (3 of 25 patients) compared to non-responders (11.2 *vs.* 3.8 μg/mL, *P*=0.036) (**Supplementary Table 5, Figure 3C)**. A greater proportion of patients tended to achieve a response in the higher quartiles of W14 VTLs, though without statistical significance (P_{trend}=0.055) (**Figure 4A**). The optimal VTL cut-off was determined to be 5.3 μg/mL, with an AUC of 0.859 (**Supplementary Figure 3C**).

Meanwhile, among UC patients, those who achieved W14 BioRES[FC] had higher serum VTLs at W2, W6, and W14 compared to non-responders, with notable differences of 43.1 *vs.* 32.0 μg/mL (*P*=0.016) at W2, 42.1 *vs.* 23.8 μg/mL (*P*=0.003) at W6, and 17.9 vs 5.6 μg/mL (*P*=0.007) at W14 (**Supplementary Table 6, Figure 2B–D**). The quartile analysis demonstrated an increasing trend in the response rate of W14 BioRES[FC] as VTLs at W2 and W6 increased, with P_{trend}=0.013 for W2 and P_{trend}=0.004 for W6, while VTLs at W14 showed an insignificant trend (P_{trend}=0.084) (**Supplementary Figure 1B**). The optimal VTL cut-offs at W2, W6, and W14 associated with W14 BioRES[FC] in UC patients were 41.0 μg/mL with an AUC of 0.815, 31.3 μg/mL with an AUC of 0.874, and 9.8 μg/mL with an AUC of 0.849, respectively (**Table 2, Supplementary Figure 2B–D**).

Relationship between early VTLs and EH in UC

Regarding EH, two CD patients with endoscopic remission at baseline and four patients without baseline endoscopy were excluded. Although baseline endoscopic assessments were available for CD patients, no endoscopic evaluations were performed at W14 and no patients achieved EH at W52. Therefore, analyses exploring associations between VTLs and EH in CD were not feasible, and endoscopic findings in CD are presented descriptively only.

All UC patients were endoscopically active at baseline. Serum VTLs at W2 and W6 were significantly higher among patients with UC who achieved W14 EH (42.4 *vs.* 31.2 μg/mL, *P*=0.040 at

W2, and 41.6 *vs.* 28.7 μg/mL, *P*=0.035 at W6) (**Supplementary Table 7, Figure 2E–F**). As VTL quartiles at W2 increased, the response rate of W14 EH significantly increased (P_{trend}=0.034) (**Supplementary Figure 1C**). Although there was a numerical increase in the response rate of W14 EH with increasing VTL quartiles at W6, this trend was not statistically significant (P_{trend}=0.078). The predictive VTL cut-offs associated with W14 EH were 41.0 μg/mL with an AUC of 0.739 at W2 and 38.1 μg/mL with an AUC of 0.744 at W6 (**Table 2, Supplementary Figure 2E–F**). Regarding W52 EH, no significant differences in VTLs between responders and non-responders were observed during the induction period.

Relationship between early VTLs and drug optimization during maintenance therapy

During maintenance therapy, 18 (46.2%) patients with CD and 13 (46.4%) patients with UC required drug optimization (VDZ dose escalation). For patients with CD, serum VTLs at W14 were significantly lower in those who required drug optimization compared to those who did not (2.2 *vs.* 5.8 μg/mL, *P*=0.004) (**Supplementary Table 7, Figure 3D**). A decreasing trend in optimizing therapy during maintenance therapy was revealed when stratified by W14 VTL quartiles (P_{trend}=0.013) (**Figure 4B**). The optimal VTL cut-offs to predict drug optimization during maintenance therapy were 4.6 μg/mL at W14, with an AUC of 0.765 (**Table 2, Supplementary Figure 3D**).

Discussion

In our study, we investigated the relationship between early VTLs and various outcomes, such as clinical, biochemical, and endoscopic outcomes, and the need for drug optimization in patients with IBD. A particularly noteworthy finding in this study was the correlation between W14 VTLs and long-term outcomes in patients with CD, such as W54 BioRES[FC], and the need for drug optimization during maintenance therapy. This suggests that early assessment of VTLs may provide clinically valuable insights into long-term treatment trajectories, rather than serving as a definitive basis for treatment strategy.

Previously, both clinical trials and real-world studies have extensively investigated the association between serum VTLs and outcome achievement. A post hoc analysis of the GEMINI 1 and GEMINI 2 studies revealed higher serum VTLs at W6 in clinical remitters compared to non-remitters, with levels of 34.7 *vs.* 23.7 μg/mL among patients with UC, and 26.8 *vs.* 23.5 μg/mL among patients with CD, respectively[5]. Additionally, serum VTLs at W6 were associated with EH at W52, with a VTL cut-off of 18 μg/mL with an AUC of 0.74 (95% CI, 0.53–0.93)[6]. In contrast to such findings that highlighted the significance of W6 VTLs, our study demonstrated that, in patients with UC, only W2 VTLs showed a significant difference among those who achieved CSF-CREM at W14 (43.1 μg/mL *vs.* 34.4 μg/mL, *P*=0.034). No significant differences were observed in early VTLs when analyzed in other clinical outcomes. Dreesen et al.[7] reported that serum VTLs greater than 30.0 μg/mL at W2 were associated with improved outcomes at W14 in patients with IBD. Similarly, a recent study from the Middle East[12] found higher serum VTLs at W2 in responders compared to non-responders, though without statistical significance (23.3 μg/mL *vs.* 16.4 μg/mL, *P*=0.31). While the median VTL value observed in our study was notably higher than those reported in these real-life studies, our findings align with the idea that W2 VTL can serve as a predictor of short-term clinical outcomes. The relatively higher early VTLs observed in our cohort may be partly explained by differences in assay characteristics, as well as cohort-related factors such as a lower inflammatory burden and reduced VDZ clearance during early induction, particularly in patients with UC.

Additionally, in this study, it was observed that higher early VTLs were related to better biochemical outcomes at W54. Among CD patients, those who were responders for BioRES[FC] at W54 had a higher median VTL at W14 (11.2 μg/mL *vs.* 3.8 μg/mL, *P*=0.036) compared to non-responders. Ungaro et al. evaluated corticosteroid-free clinical and biochemical remission and found that remitters had significantly higher serum VTLs compared to non-remitters (12.7 *vs.* 10.1 μg/mL, *P*=0.002)[13]. When using a VTL cut-off of 11.5 μg/mL, those with higher VTLs showed a 2.4-fold better outcome achievement rate compared to those with lower values. Evaluating biochemical responses using CRP or FC is important as it provides a more robust and objective assessment of outcomes compared to more subjective criteria like Crohn's Disease Activity Index (CDAI). Notably, among the available laboratory markers, FC demonstrated the most consistent association with both early VTLs and long-term outcomes, supporting its role as a key adjunctive biomarker in clinical decision-making. Although a cautious interpretation is warranted due to the small sample size, this study is notable as it shows that VTLs at W14, the end of the induction period, can predict biochemical responses at W54.

As one of the long-term therapeutic goals suggested by STRIDE-II[14], the relationship between VTLs and endoscopic outcomes has been extensively investigated. In UC patients, responders who achieved EH at W14 had significantly higher VTLs at W2 compared to non-responders (31.7 μg/mL *vs.* 24.3 μg/mL, *P*=0.016), with a proposed VTL cut-off of 28.9 μg/mL and an AUC of 0.70[7]. In this study, UC patients who achieved EH at W14 had higher median VTLs at W2 and W6, measured at 42.4 μg/mL and 41.6 μg/mL, respectively. Although direct comparison is limited, numerically, it appears that patients achieving EH had higher median VTLs than those achieving clinical or biochemical outcomes. Given the inverse relationship between disease severity and VDZ clearance[7], and the fact that achieving EH indicates disease inactivity, the higher median VTLs observed in patients who achieved EH could be attributed to this relationship. Regarding EH at W52, a previous study[6] proposed a W6 VTL cut-off of 18 μg/mL to predict EH within one year. However, in the current study, while higher early VTLs were observed in UC patients, these findings did not reach

statistical significance. Further research with larger patient cohorts is warranted to determine cut-off values for predicting EH more accurately. However, due to the absence of EH events in CD—likely due to the modest sample size—the discussion of VTLs in relation to endoscopic outcomes is limited to UC.

Finally, in CD patients, low VTLs at W14 were associated with a higher probability of VDZ dose optimization during the maintenance period. Quartile analysis also revealed a trend where higher VTLs were linked to reduced rates of optimization. Importantly, the observed associations at W14—particularly in CD—may reflect not only pharmacokinetic exposure but also underlying disease severity and real-world clinical decision-making, including reimbursement-driven practice patterns, rather than a purely causal exposure–response relationship. This is further supported by the finding that, despite generally lower outcome achievement rates in CD compared to UC, the drug optimization rates between the two groups were similar (46.2% in CD and 46.4% in UC). Williet et al.[15] suggested a W6 VTL cut-off of 18.5 μg/mL (AUC 0.72) for patients requiring drug optimization within the first six months. In contrast, this study identified a W14 VTL cut-off of 4.6 μg/mL (AUC 0.765). Even considering the anticipated pharmacokinetic decline from W6 to W14, this remains a notably lower value. Therefore, the lower W14 cut-off identified in this study should be interpreted cautiously and regarded as exploratory rather than clinically prescriptive. This cut-off may be context-specific and influenced by real-world clinical practice patterns, particularly under strict national reimbursement policies in Korea, which tend to favor conservative continuation of therapy with close monitoring rather than early dose modification. Accordingly, the generalizability of these thresholds to other healthcare systems remains uncertain, and prospective interventional studies are needed to determine whether TDM-guided dose adjustments based on predefined VTL cut-offs can improve clinical outcomes.

Although higher early VTLs were associated with favorable outcomes and lower optimization rates, the clinical utility of VDZ TDM in managing secondary loss of response (LOR) remains uncertain. Dose optimization in patients with secondary LOR to VDZ has been shown to

recapture clinical remission in 28% of cases in a clinical trial[16] and 18% in a real-world study[17]. Given the low immunogenicity and near-complete α4β7 receptor saturation at low serum levels[18], further dose escalation may not confer additional benefit. Accordingly, our study primarily emphasizes the predictive rather than the interventional role of early VTL monitoring. From a practical standpoint, our findings suggest that low early VTLs—particularly at W14 in CD—should prompt closer clinical and biochemical monitoring and early consideration of treatment trajectory, rather than serving as an isolated criterion for immediate treatment discontinuation. In addition, our data do not support routine VDZ TDM for all patients; instead, a selective, context-dependent approach integrated with clinical assessment and objective biomarkers such as FC is recommended. Because this study was observational and focused on exposure–response associations, underlying biological mechanisms—such as disease-specific differences in intestinal inflammation, barrier function, or immune cell activation—that might explain the differential predictive value of early VTLs between CD and UC could not be explored, and causal relationships cannot be inferred.

To the best of our knowledge, this study is the first to analyze real-world data on early VTLs and their association with outcome achievement in VDZ treatment among East Asian patients with IBD, based on prospectively collected data. In Korea, unique reimbursement policies for VDZ therapy mandate clinical response evaluation after three to four (CD) or three (UC) IV infusions, typically leading to an assessment at W14. Additionally, interval shortening from the standard 8-week schedule to a 4-week schedule is only permitted after W14. Although an additional 300 mg IV infusion at W10 was approved for CD patients after November 2020, most patients had already initiated treatment before then, and consequently, none underwent drug optimization prior to W14. Accordingly, drug optimization in this study was operationally defined solely as interval shortening, and other potential strategies (e.g., dose escalation or combination therapy) were not evaluated. Under these strict policies, we were able to evaluate the relationship between VTLs at W2, W6, and W14 and the need for further VDZ dose optimization. This scheme also simplified the categorization of patients requiring dose optimization after W14. Meanwhile, the relationship between VTL and BioRES[FC] was evaluated

for the first time in this study. Biochemical parameters such as CRP and FC are considered more objective measures than clinical parameters like CDAI or pMS, and FC also demonstrates a strong correlation with intestinal inflammation[19], which is thought to aid in deciding the direction of treatment.

We acknowledge several limitations in our study. The primary limitations arise from its single-center design and relatively small sample size. To better reflect real-world practice, patients in remission at baseline were excluded, which inevitably reduced the sample size and may have biased the cohort toward patients with more active or refractory disease. Therefore, our findings should be interpreted as reflecting the effectiveness of VDZ in a clinically relevant population requiring therapeutic escalation, rather than across the full disease spectrum. Missing laboratory, endoscopic, and trough level data at later follow-up may have further reduced statistical power; however, the missing data did not differ significantly according to treatment response, suggesting limited outcome-dependent bias. Second, VTLs at W54 included data from patients receiving IV VDZ at both 8-week and 4-week intervals, with dose optimization performed at the discretion of the clinicians under restrictive reimbursement policies. As a result, VTLs at W54 may partly reflect prior dose optimization rather than standardized trough exposure, potentially influencing the observed VTL distributions and exposure-response associations. This heterogeneity limits the external applicability of the proposed VTL cut-off values. Nevertheless, this variability reflects real-world clinical practice and illustrates how TDM and dose optimization are implemented under routine care conditions rather than within a controlled trial setting. Thirdly, anti-VDZ antibody concentrations were not measured, limiting our ability to distinguish among inadequate exposure, inflammation-related increased clearance, and potential anti-VDZ antibody–mediated elimination as causes of lower VTLs. However, many studies, including the pivotal GEMINI I and II trials[3,4], have reported rates of immunogenicity below 5% with drug-sensitive assays. Even with drug-tolerant assays, anti-VDZ antibodies appeared transient and had no impact on outcomes. Previous study reported anti-VDZ antibody positivity rate of 1.6% during induction therapy[13], and in one study, 17% were positive during induction therapy, but

only 3% remained positive during maintenance therapy[18]. Therefore, their impact on our study results is likely minimal. Finally, as all participants had prior exposure to TNF inhibitors, our findings may not be applicable to biologic-naïve patients with IBD. Smoking status did not significantly differ between CD and UC in our cohort, which contrasts with findings from Western populations. This discrepancy may reflect regional or ethnic differences, as well as the limited sample size. Therefore, larger multicenter studies—including biologic-naïve patients and more ethnically diverse populations—are needed to validate our findings and enhance their external generalizability. Moreover, multiple statistical comparisons were conducted across various outcomes and time points without formal adjustments for multiplicity, thereby increasing the likelihood of chance findings. The number of evaluable patients for individual outcome analyses was limited (typically 20–30 patients), precluding reliable multivariable adjustment for potential confounders such as age, disease duration, and concomitant medications due to a substantial risk of model overfitting. Furthermore, the ROC-derived VTL cut-off values lacked internal validation (e.g., bootstrapping) and should therefore be considered exploratory and hypothesis-generating rather than definitive thresholds for clinical decision-making.

In conclusion, our real-world study suggests that higher early VTLs are associated with increased rates of favorable outcomes at both W14 and W54. Notably, long-term outcomes—such as BioRES[FC] at W54 and the need for drug optimization during maintenance therapy—were associated with W14 VTLs in patients with CD. Current study demonstrates an association between early VTLs and subsequent clinical outcomes; however, it remains uncertain whether the identified VTL cut-off values can directly guide dose adjustments. Nevertheless, monitoring early VTLs may provide clinically valuable insights into future treatment trajectories, particularly regarding biochemical responses and therapeutic optimization for patients with IBD receiving VDZ. To confirm and better define the clinical utility of TDM and VTL cut-offs for optimizing VDZ therapy, future well-designed interventional studies are warranted.

Methods

Patient eligibility and study flow

This prospective observational study follows the CONSORT (Consolidated Standards of Reporting Trials) flowchart to illustrate participant flow, detailing patient evaluations at each outcome stage (**Figure 1**). A total of 72 patients with IBD who initiated VDZ therapy from August 2017 through March 2020 at Asan Medical Center, a tertiary referral center in Korea, and who agreed to participate in the prospective VDZ registry were eligible for this study. Eligibility criteria included patients with IBD aged >18 years who received scheduled VDZ therapy during the study period. Patients with IBD type unclassified or drug switching to another class of drug before W14 were excluded. Among the 72 patients, five were excluded: four who discontinued VDZ before W14 and one who had intermittent VDZ infusions during maintenance therapy. The remaining 67 patients (39 with CD and 28 with UC) were included in the final analysis.

VDZ treatment

Patients with IBD received induction therapy with intravenous (IV) VDZ infusions of 300 mg at W0, W2, and W6. Those who showed clinical response to VDZ induction therapy received IV infusions of VDZ (300 mg every 8 weeks) as maintenance therapy from W14. At the discretion of clinicians, patients with an inadequate response to VDZ could receive optimized treatment with a 300 mg dose every 4 weeks from W18.

VTL measurement

Serum VTLs were checked via VDZ enzyme-linked immunosorbent assay (ELISA) mAb-based assay (IG-AB116, ImmunoGuide®, AybayTech Biotechnology Ltd.) before infusion at W2, W6, W14, and W54 among the patients who maintained VDZ therapy. Serum VTL for each respective week was determined as the average of two measurements. This immunoassay was based on drug-specific mAbs (catcher Ab, ImmunoGuide® clone IG-19F3). The reported analytical sensitivity is 5

ng/mL and the upper detection limit is 6000 ng/mL. All the samples were analysed by a single researcher (AR Yoon) in an affiliated research laboratory of the study center.

Data collection

Patient demographics, clinical characteristics, and laboratory results, including serum albumin (g/dL), serum CRP (mg/dL), and FC (mg/kg), were collected from the electronic medical records. IBD-related data included date of initial IBD diagnosis, family history of IBD, previous and concomitant medication history, baseline disease activity (CDAI for CD, partial Mayo score [pMS] for UC), and endoscopic disease activity. For patients with CD, disease location/behavior (L1–L3, B1–B3, perianal disease modifier) based on the Montreal classification[20], CD-related bowel resection history, and stoma presence were recorded. For patients with UC, disease extent (E1–E3) based on the Montreal classification[20] was documented. This study was conducted in accordance with the Declaration of Helsinki and its later amendments. The study protocol was approved by the Ethics Committee of Asan Medical Center (IRB No. 2017-0792), and written informed consent was obtained from all participants.

Outcome definition

We investigated the relationship of serum VTLs and clinical, biochemical, and endoscopic outcomes, and the need for drug optimization during maintenance therapy. Serum VTLs at W2, W6, and W14 were compared among groups to assess differences between those who achieved the effectiveness outcomes and those who underwent drug optimization.

Clinical activity at W14 and W54 was assessed using CDAI and pMS for patients with CD and UC, respectively. For patients with CD, CREM was defined as CDAI ≤150 points[21], and CRES was defined as a reduction in CDAI of ≥100 points from baseline[21]. For patients with UC, CREM was defined as a pMS of ≤2 points with no individual subscore >1 point, and CRES was defined as a reduction from baseline in pMS of ≥3 points and ≥30% along with either a reduction in rectal

bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of ≤1 point[21]. CSF-CREM and CSF-CRES were evaluated only in patients with baseline concomitant use of corticosteroids and defined as the same as CREM and CRES without concomitant corticosteroid use.

BioRES[CRP] and BioRES[FC] were assessed at W14 and W54. BioRES was defined as a decrease in CRP or FC below the predefined cutoffs among patients with biochemical activity at baseline, defined as CRP ≥0.6 mg/dL[22] or FC ≥250 mg/kg[23], consistent with established thresholds.

Endoscopic response was assessed at W14 for UC patients, and W52 for both UC and CD patients. EH was defined as no visible ulcers for patients with CD[24], and Mayo endoscopic subscore ≤1 point for patients with UC[25].

Drug optimization was defined as the reduction of IV VDZ dosing interval to 300 mg every 4 weeks from 300 mg every 8 weeks.

Patients in remission for any effectiveness outcomes at baseline (W0) were excluded from each outcome assessment. In patients with a stoma, clinical outcomes and BioRES[FC] were not assessed; instead, BioRES[CRP], EH, and the need for drug optimization were evaluated. Patients who stopped VDZ because of primary or secondary LOR, or who received bowel resection were considered as having failed to achieve any outcomes. Effectiveness analyses were performed using available-case analyses without imputation. Cases with missing data at a given time point were excluded from the corresponding outcome evaluation. Missing laboratory, endoscopic, and trough level measurements primarily reflected real-world clinical practice and variability in follow-up schedules.

Statistical analyses

Categorial variables were expressed as numbers and percentages and analyzed using Fisher's exact or $\chi 2$ test. Continuous variables were stated as medians and IQRs. The Mann-Whitney U test was performed to compare VTLs between groups that achieved each effectiveness outcome and those that did not. Trends in outcome achievement status at W14 or W54 (W52 for EH) stratified by VTL

quartiles at W2, W6, and W14 were explored using the exact Cochran-Armitage trend test. The performance of serum VTLs to predict outcome achievement was assessed through receiver operating characteristic curve analyses and estimated by AUC. The optimal cut-off value of VTL for predicting outcomes and the need for drug optimization was determined using the Youden index. All P-values were two-sided, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using R (version 4.3.1; R Core Team, Vienna, Austria).

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Competing interest

BDY reports consulting fees from AbbVie Korea, BMS Pharmaceutical Korea Ltd., Celltrion, Chong Kun Dang Pharm, CJ Red BIO, Curacle, Daewoong Pharm, Dong-A ST, Ferring Korea, Hanmi Pharmaceutical, Imscout, IQVIA, Johnson & Johnson, Johnson & Johnson Korea, Jeil Pharmaceutical Co., Kangstem Biotech, Korea Otsuka Pharm, Korea United Pharm, Lilly Korea, Medtronic Korea, NanoEntek, ORGANOIDSCIENCES Ltd., Pfizer Korea, Samsung Bioepis, Takeda, Takeda Korea and Yuhan; speaker fees from AbbVie Korea, BMS Pharmaceutical Korea Ltd., Celltrion, Cornerstones Health, Curacle, Daewoong Pharm, Eisai Korea, Ferring Korea, IQVIA, Johnson & Johnson Korea, Pfizer Korea, Samsung Bioepis, and Takeda Korea; and research support from Celltrion and Pfizer Korea. None of these is relevant to this article. The other authors declare no competing interest.

Data availability statement

The data underlying this article are available from the corresponding author upon reasonable request.

Figure legends

Figure 1. The CONSORT flowchart

Participant flow of this study is illustrated in the CONSORT (Consolidated Standards of Reporting Trials) flowchart. BioRES[CRP], biochemical response based on C-reactive protein; BioRES[FC], biochemical response based on fecal calprotectin; CD, Crohn's disease; CREM, clinical remission; CRES, clinical response; CSF-CREM, corticosteroid-free clinical remission; CSF-CRES, corticosteroid-free clinical response; EH, endoscopic healing; UC, ulcerative colitis; VDZ, vedolizumab; VTL, vedolizumab trough level; W, weeks

Figure 2. Boxplots of VTLs at W2, W6, and W14 according to outcome achievement among UC patients.

Box plot illustrating the VTLs of responders and non-responders according to achievement of (A) W14 CSF-CREM at W2, (B–D) W14 BioRES[FC] at W2, W6, and W14, and (E–F) W14 EH at W2 and W6. BioRES, biochemical response; CSF-CREM, corticosteroid-free clinical remission; EH, endoscopic healing; FC, fecal calprotectin; UC, ulcerative colitis; VTL, vedolizumab trough level; W, weeks

Figure 3. Boxplots of VTLs at W2, W6, and W14 according to outcome achievement among CD patients.

Box plots illustrating the VTLs of responders and non-responders according to achievement of (A) W14 BioRES[CRP] at W6, (B) W14 BioRES[CRP] at W14, (C) W54 BioRES[FC] at W14. (D) Box

plot comparing the VTLs of the patients in the context of drug optimization during maintenance therapy.

BioRES, biochemical response; CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; VTL, vedolizumab trough level; W, weeks

Figure 4. Long-term outcome achievement rates, stratified by W14 VTL quartiles.

Bar plots showing the proportion of (A) W54 BioRES[FC] and (B) drug optimization during maintenance therapy across W14 VTL quartiles. BioRES, biochemical response; CD, Crohn's disease; FC, fecal calprotectin; Q, quartile; VTL, vedolizumab trough level; W, weeks

Tables

Table 1. Baseline demographic data of the patients

	Crohn's disease (n=39)	Ulcerative colitis (n=28)
Age at VDZ initiation, median (IQR), years	35.0 (29.0–43.0)	47.5 (35.8–50.3)
Disease duration, median (IQR), years	13.6 (9.5–17.2)	3.6 (2.6–6.7)
Male, n (%)	26 (66.7)	16 (57.1)
BMI, median (IQR), kg/m^2	19.6 (17.2–23.0)	21.1 (19.5–24.2)
Family history of IBD, n (%)	0 (0.0)	2 (7.1)
Smoking history, n (%)		
Never smoker	33 (84.6)	20 (71.4)
Ex-smoker	4 (10.3)	7 (25.0)
Current smoker	2 (5.1)	1 (3.6)
Patients with an ostomy, n (%)	5 (12.8)	0 (0.0)
IBD phenotype[a], n (%)		
Disease location		
Ileal (L1)	5 (12.8)	
Colonic (L2)	1 (2.6)	
Ileocolonic (L3)	33 (84.6)	
Disease behavior		
Non-stricturing/non-penetrating (B1)	5 (12.8)	
Stricturing (B2)	10 (25.6)	
Penetrating (B3)	24 (61.5)	
Perianal disease modifier	21 (53.8)	
Disease extent		
Left-sided colitis (E2)		8 (28.6)
Extensive colitis (E3)		20 (71.4)
Previous exposure to TNF inhibitors, n (%)	39 (100.0)	28 (100.0)
Concomitant CS, n (%)	3 (7.7)	13 (46.4)
Concomitant IMMs, n (%)	24 (61.5)	11 (39.3)
Disease activity at VDZ initiation		
Crohn's disease activity index, median (IQR)	173.5 (124.5–217.8)	
Partial Mayo score, median (IQR)		6.0 (5.0–7.0)
Baseline albumin, median (IQR) (g/dL)	3.3 (3.1–3.8)	3.6 (3.2–3.9)
Baseline C-reactive protein, median (IQR) (mg/dL)	1.2 (0.6–2.4)	0.8 (0.1–1.2)
Baseline fecal calprotectin[b], median (IQR) (mg/kg)	694.0 (525.0–1230.0)	1543.5 (689.8–4657.5)

BMI, body mass index; CS, corticosteroids; IBD, inflammatory bowel disease; IMM, immunomodulator; IQR, interquartile range; IST, immunosuppressive therapy; SD, standard deviation; TNF, tumor necrosis factor; VDZ, vedolizumab; W, week

[a]Disease location, behavior, and extent were based on the Montreal classification.
[b]Baseline fecal calprotectin values from two patients with Crohn's disease were missing.

Table 2. Area under the receiver operating curve for vedolizumab trough level cut-offs associated with effectiveness outcomes

Outcomes	Week	Cut-off VTL, μg/mL	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CSF-CREM at W14 in UC	2	41.0	0.810 (0.604–1.000)	80.0	81.0	50.0	94.4
BioRES[CRP] at W14 in CD	6	19.1	0.733 (0.539–0.928)	88.9	70.0	57.1	93.3
	14	4.4	0.739 (0.530–0.948)	77.8	75.0	58.3	88.2
BioRES[FC] at W54 in CD	14	5.3	0.859 (0.730–0.988)	100.0	80.8	54.5	100.0
BioRES[FC] at W14 in UC	2	41.0	0.815 (0.636–0.994)	71.4	82.4	62.5	87.5
	6	31.3	0.874 (0.733–1.000)	100.0	70.6	58.3	100.0
	14	9.8	0.849 (0.692–1.000)	100.0	70.6	58.3	100.0
EH at W14 in UC	2	41.0	0.739 (0.527–0.951)	70.0	83.3	70.0	83.3
	6	38.1	0.744 (0.540–0.949)	70.0	77.8	63.6	82.4
Drug optimization in CD	14	4.6	0.765 (0.613–0.917)	83.3	66.7	68.2	83.3

AUC, area under the receiver operating curve; BioRES[CRP], biochemical response based on C-reactive protein; BioRES[FC], biochemical response based on fecal calprotectin; CD, Crohn's disease; CI, confidence interval; CSF-CREM, corticosteroid-free clinical remission; EH, endoscopic healing; NPV, negative predictive value; PPV, positive predictive value; UC, ulcerative colitis; VTL, vedolizumab trough level; W, week