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Brief Report - Clinical

Higher Vedolizumab Clearance Associates with Poor Therapeutic Outcomes during Intravenous Vedolizumab Maintenance Therapy in Crohn's Disease

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Lay Summary

Vedolizumab clearance (CL) outperforms serum trough concentrations in predicting therapeutic outcomes in Crohn's disease. Higher CL was significantly associated with reduced remission rates, supporting CL as a pharmacokinetic marker for optimizing vedolizumab therapy.

Key words: Crohn's disease, Vedolizumab, Clearance

Introduction

The introduction of monoclonal antibodies has significantly improved disease outcomes in Crohn's disease (CD). The use of therapeutic drug monitoring (TDM) plays an important role in treatment optimization. Particularly with anti-tumor necrosis factor antibodies, TDM is widely used to enhance therapeutic efficacy and minimize immunogenicity. Over time, TDM strategies have evolved, and the importance of various pharmacokinetic (PK) parameters has been investigated. An exposure response relationship has been established for VDZ, and real-world study supports the notion the measuring drug concentrations might have value in the dosing optimization of therapy.[1] Yet, while concentrations at the interdose interval are helpful, their level of association with disease control is weak, and other PK metrics need to be evaluated. Among these, drug clearance (CL), reflecting the dynamics of drug elimination, has gained increasing recognition as a potential predictor of therapeutic response.[2] CL is calculated as the ratio of dose to the area under the serum concentration curve (AUC), providing an estimate of how rapidly the body eliminates the drug. Multiple studies have suggested that CL was a more reliable predictor of treatment outcomes than drug serum concentrations. For both infliximab and adalimumab, increased CL is associated with the development of antidrug antibodies against infliximab, leading to reduced serum concentrations and diminished therapeutic efficacy.[3,4] Lately, PK studies with interleukin-targeting therapies, such as ustekinumab (anti-interleukin-12/23), have also identified CL as a superior predictor of clinical and biochemical outcomes compared with serum drug concentrations.[5]

Vedolizumab (VDZ) is a gut-selective antibody targeting the α4β7 integrin that is widely used in the management of inflammatory bowel diseases. While previous studies have identified an association between serum VDZ concentrations and therapeutic response, this association appears to be weaker than what has been reported with other biologics.[6,7] The European Crohn's and Colitis Organization guidelines acknowledge the potential utility of TDM in VDZ therapy but do not provide strong recommendations due to limited supporting evidence.[8] One of the key unresolved questions for VDZ is whether CL is a better predictor of response than serum concentrations. To address this knowledge gap, our study aimed to evaluate the predictive value of serum VDZ trough concentrations vs CL in relation to endoscopic and clinical remission in patients with CD receiving intravenous VDZ maintenance therapy.

Methods

This was a post hoc analysis of a cohort of patients enrolled in LOVE-CD (Lowlands Vedolizumab in Crohn's disease study), a multinational prospective controlled trial.[9] For the purpose

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of the current analysis, only patients enrolled at Amsterdam University Medical Center were included. Blood samples were collected at trough during intravenous VDZ maintenance treatment starting at week 14, following induction treatment with 3 consecutive doses of 300 mg VDZ at weeks 0, 2, and 6. Nonresponders received an additional week 10 VDZ infusion. Blood samples were collected in serum separator tubes, allowed to clot, centrifuged and stored at −80 °C before being shipped to the clinical PK laboratory (Prometheus Laboratories). VDZ concentrations and antibodies to VDZ (ATVs) were measured using homogeneous mobility shift assay, which used size exclusion chromatography coupled with fluorometric detection. The lower and upper limits of quantification for VDZ concentrations were 1.6 µg/mL and 40.0 µg/mL, respectively. A sample was considered ATV positive if the result was >1.6 U/mL. Additionally, serum albumin was measured using immunoturbidimetry (Beckman Coulter).

VDZ PKs were estimated using Bayesian estimation methods via Monolix (Lixoft). The structural model and Bayesian priors were taken from the population PK model reported by Rosario et al[10] with a modification to account for the effects of ATVs on VDZ CL (Table 1). Specifically, the ATV status effect on VDZ CL was estimated using PK data from Prometheus Laboratories' clinical database, which included 8109 observations, of which 77 were ATV positive. The PK model used was a 2-compartment model with parallel linear and nonlinear CL, covariate effects of serum albumin and ATV status on the linear CL, and random effects on CL and the central volume of distribution. All the fixed and random effects of the population PK model were fixed to the estimates reported, and only the individual post-hoc estimates of CL and volume were determined. C-reactive protein (CRP) and weight were not used as covariates in this model. Samples with concentrations outside the assay's quantification range were treated as censored using the censoring approach defined in Monolix. For each sample, the conditional mode and conditional distribution of the individual parameter estimates (linear CL and volume) were determined and used for the statistical analyses with the therapeutic outcomes.

Therapeutic outcomes included endoscopic remission (total Simple Endoscopic Score for Crohn's Disease score <3; centrally read) measured at 1 year after starting VDZ treatment, and clinical (Crohn's Disease Activity Index <150 points) and biochemical remission (CRP <3 mg/L)) at each maintenance cycle. Statistical analyses included receiver-operating characteristic (ROC) curves, AUC (comparison using the DeLong method), and logistic regression with therapeutic outcomes as the dependent variable and PK parameters as independent variables.

Results

For this analysis, 50 patients (24 females, median age 31 years [interquartile range [IQR], 25-47 years]) were evaluated. At enrollment, median weight, Crohn's Disease Activity Index, serum albumin, CRP, and Simple Endoscopic Score for Crohn's Disease were 70 kg (IQR, 61-89 kg), 248 points (IQR, 232-293 points), 4.3 g/dL (IQR, 4.1-4.5 g/dL), 4.0 mg/L (IQR, 2.4-6.1 mg/L), and 10 points (IQR, 6-16 points), respectively, with 8% (n = 4 of 50) patients receiving concomitant immunosuppressants. At 1 year, endoscopic data were available for 39 patients, 17 (44%) of whom were in endoscopic remission. Across all 50 patients, 38% (n = 120 of 312) of cycles (median 6 per patient) showed clinical and biochemical remission.

Median trough concentrations and CL were 16.0 µg/mL (IQR, 9.5-23.8 µg/mL; 47% with VDZ >15 µg/mL) and 0.154 L/day (IQR, 0.125-0.190 L/day; 51% with CL >0.156 L/day), respectively. ATVs were found in 8 (2.5%) of 323 specimens, and median serum albumin was 4.1 g/dL (IQR, 3.9-4.3 g/dL).

ROC analysis yielded higher AUC for CL (AUC, 0.824; 95% CI, 0.683-0.964) than for trough concentrations (AUC, 0.606; 95% CI, 0.421-0.790; difference = 0.218; 95% CI, 0.074-0.362; $P = 0.003$) in distinguishing endoscopic remission from active endoscopic disease. Similar results were observed with the clinical and biochemical remission outcome (AUC [concentration], 0.530; 95% CI, 0.466-0.595 compared with AUC [CL], 0.646; 95% CI, 0.584-0.709; difference: 0.116; 95% CI, 0.063-0.169; $P < .001$).

Interestingly, logistic regression revealed that trough concentrations were not significantly associated with endoscopic outcome (odds ratio, 1.0; 95% CI, 0.6-1.3) and clinical and biochemical remission outcome (odds ratio, 2.4; 95% CI, 0.6-8.9) ($P > .28$) (Figure 1 and Table 1). In contrast, higher CL (>0.156 L/day) was associated with 9.0-fold (95% CI, 1.7-44.0) and 2.1-fold (95% CI, 1.3-3.4) lower likelihood of endoscopic and clinical and biochemical remission, respectively ($P < .01$ for both comparisons) (Table 1). Positive and negative predictive value (with 50% pretest) for endoscopic remission with CL below 0.156 L/day was 82% (+32%) and 66% (+16%).

Table 1. Performances characteristics of lower VDZ serum concentrations and higher CL with therapeutic outcomes.

	Absence of endoscopic remission		Absence of clinical and biochemical remission	
	VDZ <15 µg/mL	CL >0.156 L/day	VDZ <15 µg/mL	CL >0.156 L/day
Sensitivity, %	47	54	50	53
Specificity, %	53	88	71	66
Positive LR (95% CI)	1.02 (0.80-1.30)	4.64 (1.44-17.27)	1.70 (0.78-4.01)	1.54 (1.17-2.06)
Negative LR (95% CI)	0.99 (0.80-1.22)	0.51 (0.30-0.81)	0.71 (0.41-1.21)	0.72 (0.59-0.88)
Odds ratio (95% CI)	1.0 (0.6-1.3)	**9.0 (1.7-44.0)**[a]	2.4 (0.6-8.9)	**2.1 (1.3-3.4)**[a]
PPV (50% pretest), %	50 (+0)	82 (+32)	63 (+13)	61 (+11)
NPV (50% pretest), %	50 (+0)	66 (+16)	58 (+8)	58 (+8)

Endoscopic remission corresponds to SES-CD lower than 3 points. Clinical & biochemical remission corresponds to CDAI below 150 points with C-reactive protein below 3 mg/L.
Abbreviations: CDAI, Crohn's Disease Activity Index; CI, confidence interval; CL, clearance; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SES-CD, Simple Endoscopic Score for Crohn's Disease; VDZ, vedolizumab.
[a] $P < .05$.

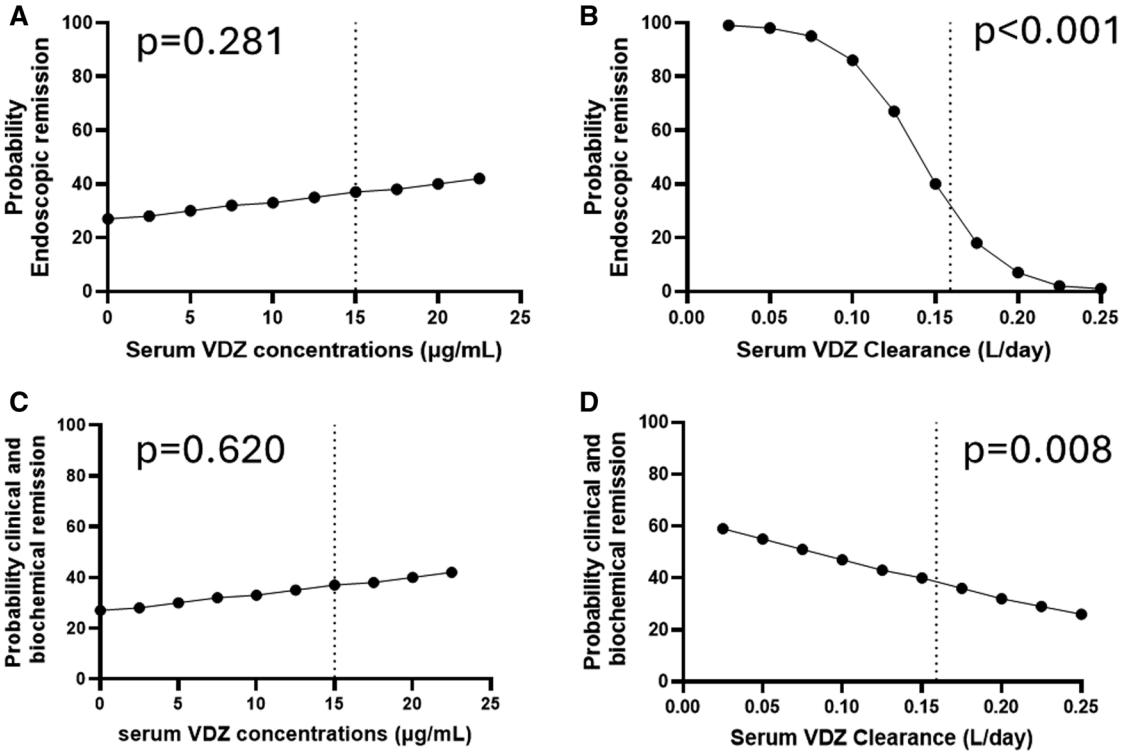

Figure 1. Logistic regression of therapeutic outcomes with (A, C) concentrations and (B, D) clearance. VDZ, vedolizumab.

Discussion

Here, we demonstrate that VDZ CL is a superior PK predictor of therapeutic outcomes compared with serum trough concentrations in patients with CD receiving maintenance therapy with intravenous VDZ. Specifically, we show that higher CL is associated with a significantly lower likelihood of achieving both endoscopic and clinical and biochemical remission, whereas serum trough concentrations were not independently associated with these outcomes. Our findings are consistent with previous research with other biologics, such as infliximab and adalimumab, and more recently ustekinumab, in which CL has been identified as a reliable predictor of treatment response.[3–5] CL is not only influenced by drug-specific properties, but also by patient-intrinsic and disease-related factors, such as serum albumin levels, systemic inflammation, and immunogenicity. These features make CL a more comprehensive marker of drug disposition than static trough levels alone, particularly in complex, inflammatory conditions, such as inflammatory bowel diseases.

Our results show that VDZ trough concentrations have a limited association with clinical and endoscopic outcomes, whereas CL exhibited a clear exposure–response relationship. This underscores the limitations of relying solely on serum drug concentrations for TDM and highlights the potential of CL to serve as a clinically useful, individualized parameter for optimizing VDZ therapy. In our study, patients presenting with CL >0.156 L/day were 9.0-fold more likely to lack endoscopic remission compared with those with CL <0.156 L/day. It follows that routine clinical monitoring of CL in patients using VDZ therapy might help identify those with higher CL and who might benefit from dose intensification, proactively or reactively during treatment, or those who would need to switch treatment.

A key strength of this study is the well-characterized prospective patient cohort from LOVE-CD, a prospective controlled trial investigating the efficacy of early vs late use of VDZ. This was supported by robust, longitudinal PK assessments and comprehensive therapeutic outcome evaluations, including objective centrally read endoscopies. Additionally, our Bayesian PK modeling approach allowed for precise estimation of individual CL values, enhancing the reliability of our findings. However, the relatively small sample size limits our ability to conduct detailed subgroup analyses that could offer further insights into specific patient subgroups such as those with immunogenicity to VDZ (which was low in this study) or low albumin. We also acknowledge that our study was a post hoc analysis from data generated at a single center and that the interpretation of the data might be subjected to selection bias. Additional validation will be required to confirm these findings. Nonetheless, even for VDZ, a promising TDM solution appears to be within reach: CL emerges as a novel and clinically meaningful parameter that could significantly enhance personalized dosing strategies with VDZ, as part of model informed precision-guided tools available through dashboards or within the clinical laboratory, all scalable approaches for the implementation of CL in clinical practice.

In conclusion, we demonstrate that VDZ CL is associated with most relevant therapeutic outcomes in CD, outperforming VDZ trough concentration measurements. A CL-based approach may enable more timely and individualized dosing adjustments, potentially improving treatment outcomes in CD patients receiving VDZ therapy. Further prospective studies are needed to integrate a CL-driven, TDM-based treatment approach into clinical practice and to explore its impact on long-term disease control.

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Author Contributions

All authors contributed to the design of the study, the interpretation of the data, and approved the final manuscript. All results were discussed collectively by the LOVE-CD steering group and associated researchers, none of whom received personal financial compensation for their contributions.

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Conflicts of Interest

S.I.A. and E.C. declare no conflicts of interest. G.D. has received research grants from AbbVie, Alimentiv, BMS, Eli Lilly, Pfizer, Takeda, and Celltrion; consulting fees from AbbVie, Agomab, Alimentiv, AstraZeneca, Celltrion, Eli Lilly, GlaxoSmithKline, Pfizer, Johnson and Johnson, Merck, Sanofi, SorrisoPharma, and Spyre; and speaker fees from AbbVie, Eli Lilly, Pfizer, Takeda; Data monitoring board: Galapagos, AstraZeneca, and Seres Health. F.B. has received grant/research support from AbbVie, Amgen, Janssen, and Takeda; served as a speaker for AbbVie, Celltrion, Ferring Holding SA, Janssen, Merck Sharp & Dohme, Pfizer, and Takeda; and received honoraria from AbbVie, Amgen, Arena, Celltrion, Ferring Holding SA, Fresenius Kabi AG, Galapagos, Janssen, Merck Sharp & Dohme, Pfizer, and Takeda. P.B. has received financial support for research from AbbVie and EG; lecture fees from AbbVie, AMC ICP, Amgen, Bristol Myers Squibb, Celltrion, Dr. Falk Benelux, EG, Galapagos, Globalport, Lilly, Medtalks, Materia Prima, Pentax, and Springer Media; and served on the advisory board for AbbVie, Bristol Meyers Squibb, CIRC, Galapagos, Janssen, Lilly, Pentax, PSI-CRO, Roche, Takeda, and Tetrameros. F.H. has served on advisory boards or as speaker for AbbVie, CCRN, Janssen, MSD, Takeda, Pfizer, Celltrion, Teva, Sandoz, Amgen, and Pendopharm; and received independent research funding from Celltrion, Janssen, AbbVie, Pfizer, and Takeda. T.M. has received speaker honoraria from MSD, AbbVie, Egis, Goodwill Pharma, Takeda, Pfizer, Janssen, Sandoz, MundiPharma, Phytotec, Roche, Fresenius, Bristol-Myers Squibb, Lilly, and Teva. M.L. has received consultancy/lecture fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Galapagos, Janssen-Cilag, Johnson & Johnson, Medtronic, Pfizer, Takeda, and Tillotts; and received grant support from Alfasigma, NFU transformation deal, ZonMW, and TKI. S.V. has received grants from AbbVie, J&J, Pfizer, Takeda, and Galapagos; has received consulting and/or speaking fees from: AbbVie, Abivax, AbolerIS Pharma, AgomAb, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Avaxia, BMS, Boehringer Ingelheim, Celgene, CVasThera, Cytoki Pharma, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, GSK, Hospira, Imidomics, Janssen, J&J, Lilly, Materia Prima, MiroBio, Morphic, MrMHealth, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillotts Pharma AG, and Zealand Pharma. J.C.P. has served as a consultant for Prometheus. T.D. is employed by Prometheus.

Data Availability

Data are available upon reasonable request to the corresponding author.

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