Review Article

Therapeutic drug monitoring of ustekinumab and vedolizumab in inflammatory bowel disease: worth the draw?

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Abstract: Biologic therapies have revolutionized the management of inflammatory bowel disease (IBD). Anti-tumor necrosis factor (anti-TNF) agents such as infliximab and adalimumab were the first approved class of biologics for the treatment of IBD. In utilizing anti-TNF agents, therapeutic drug monitoring (TDM) has emerged as an important tool for dose optimization and guiding decision-making in the setting of loss of response. Multiple studies have demonstrated an association between higher serum concentrations of anti-TNF agents and favorable outcomes including clinical, biochemical, and endoscopic remission for both ulcerative colitis and Crohn's disease (CD). Therefore, TDM is currently part of the standard of care in managing patients with IBD on anti-TNF agents and is recommended by multiple guidelines and consensus statements. More recently, there has been a significant expansion of available therapeutic agents with different mechanisms of action to treat IBD. These include anti-integrins such as vedolizumab (VDZ) and anti-interleukin (IL) such as ustekinumab (UST). VDZ and UST differ from anti-TNF agents in that they have a very low rate of immunogenicity. Therefore, data regarding TDM of anti-TNF agents are likely not applicable to these biologic agents. Currently, there is sparse evidence to guide the appropriate use of TDM with VDZ and UST in IBD. In this manuscript, we review the literature and summarize the most recent data on the utility of VDZ and UST TDM in IBD.

Keywords: Inflammatory bowel disease (IBD); Crohn's disease (CD); ulcerative colitis (UC); ustekinumab (UST); vedolizumab (VDZ)

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Introduction

Biologic therapies have revolutionized the management of inflammatory bowel disease (IBD). Anti-tumor necrosis factor (anti-TNF) agents were the first approved class of biologics for the treatment of IBD. In utilizing anti-TNF agents, therapeutic drug monitoring (TDM) has emerged as an important tool for dose optimization. TDM refers to measurement of drug concentration during a

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specified timepoint during the course of therapy. This is performed to maintain certain drug concentrations in patients' bloodstream in order to optimize the individual's dosage regimen (1). Such measurements provide valuable information for the treatment of IBD patients on anti-TNF therapy (2). In addition, TDM helps guide better decision making in the setting of secondary loss of response (SLR) to anti-TNF therapy as it will inform a more logical choice of a subsequent agent (3).

Reactive and proactive TDM are two different strategies that can be utilized to monitor biologic therapies in IBD. First, reactive TDM is defined as the monitoring of drug concentrations and anti-drug antibodies (ADA) when there is primary non-response (PNR) or SLR in those who are on a biologic agent. Proactive TDM refers to monitoring drug concentrations and ADA at a pre-defined timepoint to optimize the dose by targeting a certain drug concentration. Reactive TDM of anti-TNF agents has been shown to be more cost effective than empiric dose escalation (4,5). In addition, multiple studies have demonstrated an association between higher serum concentrations of anti-TNF agents and favorable outcomes including clinical, biochemical, and endoscopic remission for both ulcerative colitis (UC) and Crohn's disease (CD) (2,6). Proactive TDM with anti-TNF agents in IBD can potentially be beneficial by early dose optimization but high-quality clinical data regarding its effectiveness is uncertain. Although observational studies suggest a benefit of proactive TDM, a recent systematic review and metanalysis of randomized controlled trials found that proactive TDM with anti-TNF agents in IBD was not associated with clinical benefit compared to reactive TDM (7-9). Therefore, reactive TDM is currently standard of care in managing patients with IBD on anti-TNF agents and recommended by multiple guidelines and consensus statements while proactive TDM can be considered in certain clinical scenarios (10).

More recently, there has been a significant expansion of available therapeutic agents with different mechanisms of action to treat IBD (11). These include anti-integrins such as vedolizumab (VDZ) and anti-interleukin (IL) such as ustekinumab (UST). VDZ and UST differ from anti-TNF agents in that they have a very low rate of immunogenicity. Therefore, data regarding TDM of anti-TNF agents is likely not applicable to these biologic agents. Currently, there is sparse evidence to guide the appropriate use of TDM with VDZ and UST in IBD. In this manuscript, we review the literature and summarize the data on the utility VDZ and UST TDM of in IBD.

UST

UST is a fully human immunoglobulin G1 monoclonal antibody that binds to the p40 subunit resulting in attenuation of the immune cell activation properties of IL-12 and IL-23 (12). UST is administered as a weight based intravenous (IV) load dose followed by a fixed dose of 90 mg subcutaneously (SQ) every 8 weeks. The phase III UST program for the treatment of moderate-to-severe CD consisted of two 8-week induction trials (UNITI-1 and UNITI-2) and one 44-week maintenance trial (IM-UNITI) (13). UST resulted in higher rates of clinical response and remission at 8 weeks compared to placebo. By week 52, patients receiving UST were more likely to achieve primary and secondary outcomes when compared to placebo, including higher rates of clinical remission/response, steroids-free remission, and lower C-reactive protein levels (13). Similarly, in a phase 3 randomized trial (UNIFI) in patients with moderate-to-severe UC, UST at week 52 was superior to placebo in rates of clinical remission, maintenance of clinical response, endoscopic improvement, and steroids-free remission (14). In IBD, UST dose escalation to 90 mg SQ every 4 weeks have been reported to provide additional benefit in partial responders or in patients who developed a SLR (15).

The median half-life of UST is estimated at 21 days (16). Clearance of UST is affected by multiple factors including body weight, inflammatory burden (C-reactive protein, albumin), sex, race, and previous anti-TNF exposure (17). There are limited data on the role of UST trough concentration measurement in the management of IBD. Multiple studies have demonstrated a positive exposure-response relationship and are outlined below.

UST levels in CD: induction/post-induction phase

UST serum concentrations were measured during the pivotal UNITI trials for CD utilizing a drug tolerant enzyme-linked immunosorbent assay (ELISA) (13). In the UNITI-1 trial, the median UST concentrations at the end of induction (week 8) were 2.1 and 6.4 µg/mL for the 130 mg and 6 mg/kg dose groups, respectively (18). Similarly, in the UINITI-2 trial, the median UST concentrations at the end of induction (week 8) were 2.0 and 6.3 µg/mL for the 130 mg and 6 mg/kg dose groups, respectively (18). Receiver operating characteristic (ROC) analyses identified a UST serum concentration cutoff of 3.3 µg/mL to correlate with remission at week 8 with an

area under the curve (AUC) of 0.57 (P=0.001), sensitivity of 63% and specificity of 52%.

An open label prospective cohort study of 86 CD patients receiving UST revealed a higher median week 8 level of 7.2 µg/mL (3.4–10.5 µg/mL) compared to the UNITI trials (19). This study also showed that a UST level ≥4.2 µg/mL at week 8 was associated with a 50% decrease in fecal calprotectin (P=0.004) (19). Hanžel *et al.* investigated the association of postinduction UST levels measured via ELISA and outcomes in an observation cohort study of 41 patients with CD (20). The authors noted a significant association between week 2, week 4 and week 8 UST levels with biochemical remission (fecal calprotectin <100 mg/kg) at weeks 8, 16 and 24. In addition, peak levels of UST (measured 1 hour after the IV infusion) were associated with endoscopic remission (Simple Endoscopic Score for CD of ≤3) with an AUC of 0.72 [95% confidence interval (CI): 0.517–0.916] (20). A prospective, multicenter cohort from The Netherlands enrolled 90 CD patients who were treated with UST. The authors found that UST trough concentrations ≥5.9 µg/mL at week 8 were associated with significantly higher rates of biochemical remission at weeks 12 and 24 (21).

UST levels in CD: maintenance phase

Data regarding maintenance UST serum concentrations and association with outcomes have been conflicting. The earliest data regarding UST trough concentrations during maintenance in CD was from an anti-TNF refractory cohort of 62 patients who were treated UST 90 mg SQ load at weeks 0, 1, 2, followed by 90 mg SQ every 4–8 weeks (22). Week 26 UST concentrations were significantly higher at 4.7 µg/mL compared to 3.8 µg/mL (P=0.03) in patients who did and did not achieve endoscopic response, respectively (22). The AUC was 0.67 with a sensitivity of 67% and specificity of 70%. UST concentrations were not significantly different between patients who did and did not achieve clinical response and remission (22).

In the IM-UNITI maintenance trial (combining the every 8-week and every 12-week dosing groups), ROC analyses revealed a steady-state concentration cutoff between 0.8 to 1.4 µg/mL as the range associated with greater clinical remission (18). At week 24, UST level threshold of 0.82 µg/mL was associated with clinical remission with an AUC of 0.64 (P=0.003), sensitivity of 67% and specificity of 60%. At week 40, UST level threshold of 1.35 µg/mL was associated with clinical remission with an AUC of 0.66 (P=0.047), sensitivity of 82% and specificity of 47%.

An open label prospective cohort study of 86 CD patients found that a minimum UST concentration of 2.3 µg/mL at week 16 and 1.9 µg/mL at week 24 were associated with likelihood of endoscopic response at week 24 (19). Another study of 337 CD patients observed a positive association between maintenance UST trough concentrations and disease activity as defined by the Endoscopic Healing Index (EHI) (23). The EHI involves measurement of 13 protein markers in the serum and has been validated with endoscopy in patients with CD (24). UST concentration >3.75 µg/mL was able to accurately distinguish between active disease (EHI ≥50) and remission (EHI <20) with an AUC of 0.725 (23).

A recent prospective study enrolled 136 IBD patients (90% had CD) on maintenance UST (≥6 months) noted a significant association between higher UST trough levels and outcomes including: steroid-free remission [median: 6.4 µg/mL; interquartile range (IQR): 4.6–11.7] and endoscopic remission (median: 6.4 µg/mL; IQR: 5–15) (25). A prospective study of 56 CD patients demonstrated a correlation between tissue and serum UST levels (26). However, serum and not tissue UST concentrations was associated with biochemical response (>50% decrease in fecal calprotectin). In this study, serum UST concentration was not associated with clinical or endoscopic response (26). Similarly, a prospective study of 49 anti-TNF refractory patients with CD found no association between UST concentrations and clinical, biochemical and endoscopic response (27).

It is unclear if obtaining a UST serum concertation level significantly alters clinical decision making based on the above-mentioned data. In a multicenter, observational trial of 110 consecutive CD patients, obtaining UST concentration did not impact clinical decision making (P=0.16) but the addition of fecal calprotectin measurement did have a significant impact on clinical decision making (P=0.0006) (28).

UST levels in UC: induction, postinduction and maintenance

UST was U.S. Food and Drug Administration (FDA) approved for the treatment of moderate-to-severe UC in 2019 after the results of the pivotal phase III UNIFI trial. In the UNIFI trial, 961 patients were randomized to receive either UST 130 mg IV, UST 6 mg/kg IV or placebo (14).

Responders at 8 weeks were then randomized to receive UST 90 mg SQ at either 8- or 12-week intervals. Exposure-outcome relationship of UST in UC was evaluated via post hoc-analysis of the UNIFI trials (29). It was found that the steady state concentration of UST was reached after the second maintenance dose. UST serum concentrations were associated with clinical, biochemical, endoscopic, and histologic response. Immunomodulator combination therapy did not affect UST concentrations. ROC analysis revealed that a UST threshold level of 3.7 µg/mL at week 8 was associated with clinical response (AUC: 0.65; P<0.001). During maintenance, a threshold UST level of 1.3 µg/mL was associated with clinical remission (AUC: 0.64; P<0.001).

A prospective study of 42 UC patients being treated with UST found that patients who achieved histo-endoscopic improvement and histologic remission had significantly higher serum UST concentrations in comparison to patients who did achieve these outcomes (30). Week 8 UST serum concentration thresholds of 5.9 and 8.4 µg/mL were associated with clinical response and histo-endoscopic mucosal improvement at week 16, respectively (30).

Immunogenicity to UST

Post hoc analysis of UC patients receiving UST in the UNIFI trial showed that 5.7% (n=39) of patients developed ADA (29). In addition, 43.6% of these ADAs were transient (ADA disappeared on subsequent testing). More importantly, the presence of ADA in this cohort did not affect clinical outcomes (29). Similarly, a post-hoc analysis of the UNITI trials of UST treated CD patients revealed a very low rate of immunogenicity at 2.3% (n=27) (18). Only 17 of the 27 patients had neutralizing antibodies. No injection site reactions were noted in patients who developed UST ADA (18).

In summary, most of the data supports an exposure-outcome relationship with UST trough levels in CD and UC. The optimal UST trough concentration during post-induction and maintenance is variable and is based on the desired outcome and the timepoint in which the outcome is measured (*Table 1*). It is clear, however, that the rate of immunogenicity to UST is very low and adding an immunomodulator to UST does not affect pharmacokinetics of the agent. In contrast, it is unclear if dose optimization based on UST trough concentrations improves outcomes and prospective studies are needed to evaluate this question.

VDZ

VDZ is a gut selective humanized immunoglobulin G1 monoclonal antibody to α4β7 integrin, has been proven to be both safe and effective in the treatment of IBD for both UC and CD (32). VDZ is administered as a fixed 300 mg IV loading dose at weeks 0, 2 and 6 followed by the same dose (300 mg) IV every 8 weeks for maintenance. A subcutaneous form is available (outside the US) for maintenance at a dose of 108 mg every 2 weeks following IV induction. Terminal elimination half-life of VDZ is estimated at 25.5 days. Clearance of VDZ is affected by extreme low albumin and extreme high body mass index. In contrast, no significant effect on clearance of VDZ was noted with prior anti-TNF use or concomitant therapy (methotrexate, azathioprine, mercaptopurine, or aminosalicylates) (33).

The GEMINI 1 trial is a phase III, randomized, double-blind, placebo control trial that evaluated the efficacy of VDZ in induction and maintenance therapy in patients with moderate to severe UC and demonstrated effectiveness, including in patients with prior anti-TNF therapy failure. The trial also demonstrated an excellent safety profile and lower risk of infections with VDZ (34). The GEMINI 2 trial included patients with active CD that did not respond or had unacceptable side effects to glucocorticoids, immunomodulators, or anti-TNF agents. In this study, patients who received VDZ during induction were more likely to experience clinical remission when compared to placebo (14.5% *vs.* 6.8%; P=0.02). Patients who continued VDZ during maintenance had higher rates of clinical remission, steroids-free remission, and ≥100 points reduction in the Crohn's Disease Activity Index (CDAI) at week 52 compared to placebo (35). This effect was observed in patients who were randomized to receive VDZ every 4 weeks or every 8 weeks.

There is limited data on the role for TDM for VDZ in patients with IBD. Here we summarize the available literature investigating the role of TDM with VDZ in IBD.

VDZ levels in CD: induction/post-induction phase

The GEMINI 2 study was a phase III, randomized, parallel-group, double- blind, placebo-controlled study that included both induction and maintenance trials with participation of 829 patients with CD (368 induction cohort and 461 maintenance) from 285 medical centers. The study demonstrated that CD patients with higher VDZ trough concertation quartiles at week 6 had higher

Table 1 Ustekinumab exposure-outcome relationships in CD and UC

IBD type	Treatment phase	Week	Assay type	Trough level (μg/mL)	Outcome (timepoint)	Reference
CD	Induction	2	ELISA	24.7	Biochemical remission (week 8)	Hanžel (20)
CD	Induction	2	ELISA	24.7	Biochemical remission (week 16)	Hanžel (20)
CD	Induction	2	ELISA	27.2	Biochemical remission (week 24)	Hanžel (20)
CD	Induction	4	ELISA	15.0	Biochemical remission (week 8)	Hanžel (20)
CD	Induction	4	ELISA	15.0	Biochemical remission (week 16)	Hanžel (20)
CD	Induction	4	ELISA	15.0	Biochemical remission (week 24)	Hanžel (20)
CD	Induction	4	ELISA	23.7	Endoscopic remission (week 24)	Hanžel (20)
CD	Induction	4	ELISA	15.9	50% decrease fCal (week 8)	Verstockt (19)
CD	Post-induction	8	ELISA	7.2	Biochemical remission (week 8)	Verstockt (19)
CD	Post-induction	8	ELISA	6.8	Biochemical remission (week 8)	Hanžel (20)
CD	Post-induction	8	ELISA	5.9	Biochemical remission (week 12)	Straatmijer (21)
CD	Post-induction	8	ELISA	4.4	Biochemical remission (week 16)	Hanžel (20)
CD	Post-induction	8	ELISA	6.8	Biochemical remission (week 24)	Hanžel (20)
CD	Post-induction	8	ELISA	5.9	Biochemical remission (week 24)	Straatmijer (21)
CD	Post-induction	8	ELISA	2.0	Corticosteroid-free clinical and biochemical remission (week 16)	Soufflet (31)
CD	Post-induction	8	ECLIA	3.3	Clinical remission (week 8)	Adedokun (18)
CD	Post-induction	8	ELISA	11.1	Endoscopic remission (week 24)	Hanžel (20)
CD	Post-induction	8	ELISA	4.2	50% decrease fCal (week 8)	Verstockt (19)
CD	Maintenance	16	ELISA	1.4	Corticosteroid-free clinical and biochemical (week 16)	Soufflet (31)
CD	Maintenance	16	ELISA	3.1	Biochemical remission (week 24)	Verstockt (19)
CD	Maintenance	24	ECLIA	0.8	Clinical remission (week 24)	Adedokun (18)
CD	Maintenance	40	ECLIA	1.4	Clinical remission (week 44)	Adedokun (18)
UC	Post-induction	8	ECLIA	3.7	Clinical response (week 8)	Adedokun (29)
UC	Post-induction	8	ECLIA	3.5	Clinical remission (week 8)	Adedokun (29)
UC	Post-induction	8	ECLIA	3.5	Endoscopic improvement (week 8)	Adedokun (29)
UC	Post-induction	8	ECLIA	3.7	Histologic improvement (week 8)	Adedokun (29)
UC	Post-induction	8	ECLIA	3.7	Symptomatic remission (week 8)	Adedokun (29)
UC	Maintenance	NS	ECLIA	1.3	Clinical remission (week 44)	Adedokun (29)
UC	Maintenance	NS	ECLIA	1.2	Symptomatic remission (week 44)	Adedokun (29)
UC	Maintenance	NS	ECLIA	1.1	Endoscopic improvement (week 44)	Adedokun (29)
UC	Maintenance	NS	ECLIA	1.3	Histologic improvement (week 44)	Adedokun (29)

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; ELISA, enzyme-linked immunosorbent assay; fCal, fecal calprotectin; ECLIA, electrochemiluminescent immunoassay; NS, not specified.

rates of clinical remission at the end of 6 weeks of induction therapy. The highest quartile of VDZ trough concentrations (33.8–142 µg/mL) had a rate of clinical remission rate of 22% compared to 6% in the lowest quartile (<15.2 µg/mL) (35). In GEMINI 3 study with a focus on moderate to severe CD, patients with VDZ levels >32.5–128 µg/mL at week 6 and >35.4–173 µg/mL at week 10 had the highest rates of clinical remission (25% and 51% respectively) (36,37).

A prospective open-label study of 110 patients with active CD on VDZ revealed that serum concentration of 25.5 µg/mL at week 6 was associated with endoscopic remission at week 26 (59% specificity; 82% sensitivity; P=0.006). In this study, VDZ trough concentration cutoffs of 30.5 and 19.5 µg/mL at weeks 2 and 6 respectively were associated with endoscopic response at week 26 (38). Another observational, retrospective study of 113 CD patients on VDZ found that VDZ trough levels >35.2 µg/mL at week 2 were associated with biological remission at week 6 [58% specificity; 88% sensitivity; area under the receiver operating characteristic curve (AUROC) 0.71; P=0.026] (39).

VDZ levels in CD: maintenance phase

The GEMINI 2 trial investigated the association of VDZ trough concentrations measured at week 46 with week 52 outcomes. In the group of CD patients receiving VDZ every 8 weeks the rate of clinical remission was about 20% higher in the second quartile group (VDZ trough concentrations ≥7.5 µg/mL) compared to the first quartile group (VDZ trough concentrations <7.5 µg/mL) (35).

Löwenberg *et al.* demonstrated in a prospective open-label study of 110 patients with active CD on VDZ that VDZ serum concentration of 9.9 µg/mL at week 22 was associated with endoscopic remission at week 26 (54% specificity; 91% sensitivity; AUC: 0.74; P=0.0002). In addition, a VDZ trough concentration cutoff of 10.5 µg/mL at week 22 was associated with endoscopic response at week 26 (59% specificity; 79% sensitivity; AUC: 0.69; P=0.003) (38). Dreesen *et al.* reported in a retrospective analysis of 113 VDZ-treated CD patients and found that VDZ trough levels >13.6 µg/mL at week 22 was associated with mucosal healing at week 22 (71% specificity; 69% sensitivity; AUROC: 0.70; P=0.018) (39).

In a systematic review and meta-analysis of 4 studies of CD patients on VDZ (n=181 with endoscopic outcomes), trough concentration of VDZ during maintenance was numerically but not significantly higher in those who achieved endoscopic remission when compared to those who did not (median concentration of 14.4 *vs.* 10.9 µg/mL, respectively with mean difference of 3.6 µg/mL; 95% CI: 1.4 to 8.6, P=0.16). The authors conducted another meta-analysis including 2 of the 4 CD studies (n=167 with clinical outcomes), and found that patients who achieved clinical remission had similar trough concentrations during maintenance compared to those who did not (median concentration of 12.3 *vs.* 12.5 µg/mL, respectively with mean difference of 2 µg/mL; 95% CI: –5 to 4.5, P=0.11) (40).

VDZ levels in UC: induction/post-induction phase

In GEMINI 1, UC patients who were in the higher VDZ trough concentration quartile of 33.3 to 65.6 µg/mL (4th quartile) at the end of induction (week 6) had higher rates of clinical response (74.1%) and clinical remission (37%) when compared to patients in the lower trough quartiles. In this same population, induction trough levels <17 µg/mL were associated with remission rates similar to placebo (34,37).

Few real-world studies reported on TDM in UC patients receiving VDZ. A prospective study analyzed 39 UC patients on VDZ and found that a trough level >32.7 µg/mL at week 2 was significantly associated with clinical remission at week 6 (61.1% specificity; 90% sensitivity; AUROC: 0.73; P=0.01; odds ratio of 8, P=0.019) (41). A recent multicenter, multinational retrospective study included 695 IBD patients on VDZ (304 UC and 391 CD) demonstrated that higher VDZ trough concentrations at earlier time points were associated with achieving clinical remission at later time points. A trough level ≥31 µg/mL at week 6 was associated with clinical remission at week 14. In addition, a VDZ level ≥32 µg/mL at week 6, ≥36.5 µg/mL at week 10, and ≥13.6 µg/mL at week 22 were all associated with clinical remission at week 52 (42).

A retrospective cohort study including 66 VDZ-treated UC patients from Belgium found a positive exposure-response correlation when certain VDZ trough levels were reached during therapy. VDZ trough concentration levels >23.7 µg/mL at week 2 predicated mucosal healing at week 14 (86% specificity; 50% sensitivity; AUROC: 0.70; P=0.016). VDZ trough levels >20.8 µg/mL at week 6 predicted clinical response at week 14 (75% specificity; 69% sensitivity; AUROC: 0.72; P=0.008) (39). Similarly, another retrospective study reported VDZ trough cutoff values of 23.9 and 21.6 µg/mL at week 6 as being

associated with clinical and biologic remission by week 14, respectively (43).

VDZ levels in UC: maintenance phase

In the pivotal GEMINI 1 trial, week 52 clinical remission rates were analyzed based on VDZ trough level quartiles measured at week 46. UC patients who continued maintenance VDZ every 8 weeks in the second VDZ trough level quartile (VDZ trough levels 6–9.8 µg/mL) had a clinical remission rate of 78.9% compared to 42.1% in patients in the first VDZ trough level quartile (VDZ trough level <6 µg/mL) (34).

In a cross-sectional, multicenter study involving 116 UC patients on maintenance VDZ, a trough concentration cutoff of 10.1 µg/mL was associated with higher rates of corticosteroid-free clinical and biochemical remission (specificity 45.3% and sensitivity 88.9%). This study, however, included both pediatric and adult patients with a median age of 33 years and IQR of 22–55 years (44).

In a systematic review and meta-analysis of 5 studies of UC patients on VDZ (n=179 with endoscopic outcomes), trough concentrations of VDZ during maintenance were significantly higher in those who achieved endoscopic remission when compared to those who did not (median concentration of 13 *vs.* 9.7 µg/mL, respectively with mean difference of 5.1 µg/mL; 95% CI: 2.2 to 7.9, P<0.01). The authors further conducted another meta-analysis including 4 of the 5 UC studies (n=216 with clinical outcomes), and found that patients who achieved clinical remission had higher VDZ trough concentrations during maintenance compared to those who did not (median concentration of 14.3 *vs.* 10.5 µg/mL, respectively with mean difference of 5.1 µg/mL; 95% CI: 2.8 to 7.4, P<0.01) (40).

VDZ TDM for dose optimization

There are limited data on the optimal trough level cutoffs that predict response to VDZ dose intensification. In a retrospective study of 5 centers in the US, 192 IBD patients on VDZ (87 had CD, 94 UC and 11 had IBD-unclassified) were included of which 58 of them underwent dose escalation. The optimal VDZ trough level cutoff for dose escalation was found to be 7.4 µg/mL. In a multivariate logistic regression analysis, patients with a week 8 VDZ trough concentration below 7.4 had 3.7 times higher odds to achieve clinical remission after dose escalation (95% CI: 1.1 to 13; P=0.04) (45).

An observational prospective study included 47 IBD patients (31 CD and 16 UC) who were started on VDZ after non-response to 2 anti-TNF agents. VDZ trough levels of <18.5 µg/mL at week 6 were associated with the need for dose optimization within the first 6 months (100% positive predictive value, 46.2% negative predictive value with area under ROC of 0.72). When dose optimization was required at week 10, all patients who had trough levels of <19 µg/mL at week 6 achieved clinical remissions 4 weeks after optimization (46).

There have been recent data suggesting a limited role of TDM with VDZ TDM in guiding dose optimization. In a multicenter open-label prospective study, Outtier *et al.* reported on 59 IBD patients on VDZ (28 CD and 31 UC) who had loss of response and underwent VDZ dose escalation from every 8-week to every 4-week dosing interval. Dose escalation in this cohort resulted in higher trough levels and regain of clinical and biological response, but baseline VDZ trough levels in this study did not predict successful outcome after dose escalation (47).

The ENTEPRET trial was an open-label, phase 4 randomized controlled trial that investigated the role of VDZ dose optimization in patients with UC who were non-responders at week 6 and had high drug clearance at week 5 (defined as VDZ concentration <50 µg/mL). The study enrolled 108 non-responders; 55 were randomized to the VDZ dose optimization group based on week 5 VDZ trough concentrations while 53 patients continued standard VDZ induction and maintenance dosing. In the dose optimization group, patients with a week 5 VDZ level of 30–50 µg/mL received 600 mg of IV VDZ on week 6 then 300 mg IV every 4 weeks, while patients with a VDZ concentration of <30 µg/mL received IV VDZ 600 mg on week 6 then every 600 mg IV every 4 weeks. The VDZ standard dose and dose optimization groups had similar rates of endoscopic mucosal healing and durable clinical response at week 30 (48). These results suggest that dose optimization based on VDZ drug levels following PNR to VDZ during induction who have high clearance is unlikely to be beneficial.

Similarly, a multicenter observational study included a total of 161 IBD patients (129 of them underwent VDZ dose intensification) investigated the role of VDZ TDM in predicting response to dose intensification. The pre-intensification VDZ trough levels were comparable or higher among those who achieved post-intensification clinical and endoscopic remission when compared to those who did not (49). This highlights the limited role of TDM

with VDZ to guide dose optimization.

Immunogenicity to VDZ

Immunogenicity to VDZ have been persistently reported to be low. In the pivotal GEMINI trials, 3.7–4.1% of patients had at least 1 sample with positive antibodies at any time while only 0.4–1% being persistently positive with 2 or more consecutive samples (34,35). Multiple observational studies also reported similar rates of VDZ antibodies between 0–4% (38,46). The presence of antibodies does not appear to affect outcomes and the majority of antibodies were transient and eventually disappeared on repeat testing (38).

In summary, as noted with TDM with UST, multiple studies have demonstrated a positive exposure-response relationship with VDZ concentrations in IBD. An ideal cutoff level for VDZ concentration is variable and depends on the timepoint in which TDM is obtained, the type of assay and desired outcome (*Table 2*). Unlike the case with UST, there are multiple studies now with VDZ that highlight the limited role of pre-dose intensification VDZ trough levels in predicting response. Therefore, VDZ levels should be interpreted with caution and in the context of objective inflammation markers and previous response history when dose VDZ intensification is considered.

Heterogeneity of TDM assays

The majority of studies cited in this review used an ELISA assay, however, a few utilized electrochemiluminescence immunoassays (ECLIA) or homogeneous mobility shift assays (HMSA). This heterogeneity should be taken into consideration when interpreting concentration cut-offs from different studies.

Few studies compared serum drug concentrations between different commercial assays. Verdon *et al.* studied 1 HMSA (assay A) and 2 ELISA (assays B and C) UST assays in a total of 60 samples from 40 CD patients; all assays showed linear quantitative correlation with a good agreement in concentrations between the ELISA tests [interclass correlation coefficient (ICC): 0.958; 95% CI: 0.928 to 0.975]. However, agreement was poor between the HMSA and each ELISA test with near twofold increased difference in the absolute drug concentrations between both assays (ICC: 0.671 between assays A and C, 95% CI: –0.165 to 0.878; ICC: 0.649 between A and B, 95% CI: –0.208 to 0.874) (50). Another study compared the ECLIA assay used in the pivotal trials for UST with a commercially available ELISA assay and found strong agreement between both assays (51).

Similar comparisons were conducted for anti-TNF assays; one group evaluated 45 infliximab and 30 adalimumab samples comparing between ELISA and HMSA assays. Findings included good correlation, but agreement was weak for both infliximab (ICC: 0.356; 95% CI: 0.069 to 0.720; P<0.001) and adalimumab trough levels (ICC: 0.395; 95% CI: –0.073 to 0.759; P<0.001) (52).

Given these findings, it is important for clinicians to familiarize themselves with the assays they are utilizing on a regular basis before making management decisions as absolute concentrations may vary among different commercial assays.

Conclusions

TDM has consistently been shown to be beneficial with the use of anti-TNF biologics in IBD. TDM with anti-TNF agents has been demonstrated to be cost effective and significantly informs management in primary and secondary non-responders. There has been accumulating data on the value of TDM with VDZ and UST. The data suggests a clear exposure-response relationship with VDZ and UST in IBD. For example, patients with favorable outcomes such as clinical and endoscopic remission tend to have higher VDZ and UST drug concentrations compared to those who do not achieve these outcomes. The data, however, is limited by variable time-points in which TDM was performed and the utilization of different assays. There is also limited data on the utility of VDZ and UST drug concentrations in guiding dose optimization/intensification. In the case of VDZ, preliminary data suggests a limited value of VDZ drug concentration in guiding dose optimization. Therefore, interpretation of VDZ and UST drug concentrations should be taken in the context of the inflammatory burden and initial response rather than pure drug concentration value. Based on the reviewed data, the utility of TDM with VDZ and UST in IBD is limited. For one, the rate of immunogenicity is low with these agents. Although there's clear exposure-response relationship, dose escalation based on VDZ and UST levels are not supported by the current data. Empiric dose escalation without TDM can be considered in patients with IBD who are partially responding to VDZ and UST. Further large, prospective studies are needed to investigate the benefit of TDM with VDZ and UST to pave the way in creating a standardized approach with well-defined concentrations cutoffs.

Table 2 Vedolizumab exposure-outcome relationships in CD and UC

IBD type	Treatment phase	Week	Assay type	Trough level (μg/mL)	Outcome (timepoint)	Reference
CD	Induction	2	ELISA	35.2	Biological remission (week 6)	Dreesen (39)
CD	Induction	2	ELISA	30.5	Endoscopic response (week 26)	Löwenberg (38)
CD	Induction	6	ELISA	19.9	Biological remission (6 months)	Verstockt (43)
CD	Induction	6	ELISA	23.4	Biological remission (week 6)	Dreesen (39)
CD	Induction	6	ELISA	13.8	Endoscopic remission (6 months)	Verstockt (43)
CD	Induction	6	ELISA	25.5	Endoscopic remission (week 26)	Löwenberg (38)
CD	Induction	6	ELISA	19.5	Endoscopic response (week 26)	Löwenberg (38)
CD	Post-induction	14	ELISA	25.2	Biological remission (6 months)	Verstockt (43)
CD	Post-induction	14	ELISA	21.2	Clinical remission (6 months)	Verstockt (43)
CD	Post-induction	14	ELISA	30.1	Endoscopic remission (6 months)	Verstockt (43)
CD	Maintenance	NS	HMSA	6.8	Corticosteroid-free clinical and biochemical remission	Ungaro (44)
CD	Maintenance	Within 1 month from endoscopic assessment	ELISA	12.1	Biological remission (6 months)	Verstockt (43)
CD	Maintenance	Within 1 month from endoscopic assessment	ELISA	10.1	Endoscopic remission (6 months)	Verstockt (43)
CD	Maintenance	22	ELISA	12.0	Biological remission (week 22)	Dreesen (39)
CD	Maintenance	22	ELISA	9.9	Endoscopic remission (week 26)	Löwenberg (38)
CD	Maintenance	22	ELISA	10.5	Endoscopic response (week 26)	Löwenberg (38)
CD	Maintenance	22	ELISA	13.6	Mucosal healing (week 22)	Dreesen (39)
UC	Induction	2	ELISA	32.7	Clinical remission (week 6)	Ungar (41)
UC	Induction	2	ELISA	23.7	Mucosal healing (week 14)	Dreesen (39)
UC	Induction	6	ELISA	23.9	Clinical remission (week 14)	Verstockt (43)
UC	Induction	6	ELISA	20.8	Clinical response (week 14)	Dreesen (39)
UC	Post-induction	14	ELISA	6.8	Biological remission (week 14)	Verstockt (43)
UC	Post-induction	14	ELISA	10.1	Clinical remission (week 14)	Verstockt (43)
UC	Post-induction	14	ELISA	17.0	Mucosal healing (week 14)	Dreesen (39)
UC	Maintenance	NS	HMSA	10.1	Corticosteroid-free clinical and biochemical remission	Ungaro (44)

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; ELISA, enzyme-linked immunosorbent assay; NS, not specified; HMSA, homogeneous mobility shift assay.

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Footnote

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