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Therapeutic drug monitoring of vedolizumab in inflammatory bowel disease: current data and future directions

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Abstract: The introduction of vedolizumab, a lymphocyte adhesion inhibitor, has expanded the relatively limited therapeutic armamentarium available for Crohn's disease and ulcerative colitis. Despite its effectiveness, both primary nonresponse and secondary loss of response to vedolizumab do occur, as is observed with the use of anti-tumour necrosis factor (TNF) therapy. Further, in a proportion, onset of efficacy may be relatively slow. A large body of data support an exposure–response relationship with anti-TNF drug levels, which has led to therapeutic drug monitoring becoming incorporated into everyday clinical management. The influence of patient and disease factors on the pharmacokinetics of anti-TNF levels, including immunogenicity, has also been examined. The role of therapeutic drug monitoring with vedolizumab is less clear. This review summarizes the available evidence on the pharmacokinetics and pharmacodynamics of vedolizumab in inflammatory bowel disease and how drug levels, immunogenicity and other factors influence clinical outcomes. Vedolizumab clearance is increased with very high body weight and hypoalbuminaemia, but is not influenced by the addition of an immunomodulator. Immunogenicity is uncommon. $\alpha 4\beta 7$ receptor saturation occurs at low serum vedolizumab drug levels, and measuring it alone is insufficient to predict clinical outcomes. Using quartile analysis of vedolizumab drug levels, there appears to be a modest exposure–response relationship during induction. Drug levels at week 6 of approximately $>$20 μg/ml have been shown to be associated with improved clinical outcomes, including subsequent mucosal healing rates during maintenance and avoiding the need to dose escalate due to lack of response. There are currently insufficient data to support the routine use of therapeutic drug monitoring during maintenance therapy. Further studies to elucidate the role of therapeutic drug monitoring of vedolizumab are needed.

Keywords: Vedolizumab, therapeutic drug monitoring, drug levels, anti-drug antibodies, Crohn's disease, ulcerative colitis

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC), collectively referred to as the inflammatory bowel diseases (IBDs), are chronic relapsing-remitting inflammatory disorders of the gastrointestinal tract. The aetiology and pathogenesis remain poorly understood, but are felt to be due to a disordered immune response directed against unknown luminal antigens that comprise the gut microbiome in a genetically predisposed individual. IBD is associated with an increased risk of surgery,[1] impaired quality of life[2] and loss of productivity.[3] Modern medical management of IBD has evolved beyond the use of the modestly effective immunomodulators azathioprine, mercaptopurine and methotrexate to biologic therapies which target key proinflammatory cytokines (tumour necrosis factor in the case of infliximab, adalimumab and certolizumab pegol, and interleukin 12 and 23 for ustekinumab) or *via* novel mechanisms such as blocking lymphocyte tracking to the gut [for vedolizumab (VDZ)]. Despite these advances, a significant proportion of patients either fail to initially respond to these agents, or lose response with time.[4] Accordingly, there is an unmet need to optimize biologics in order to improve patient outcomes. Considering anti-TNF agents, robust

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data now support algorithms incorporating therapeutic drug monitoring (TDM; measuring drug levels and antidrug antibodies) which have been shown to deliver more clinically effective dosing.[5,6] Studies have also demonstrated that these approaches can be cost effective.[5] TDM has now become the standard of care when prescribing anti-TNF therapy in patients with IBD, in particular for managing primary or secondary loss of response; however it has taken the best part of a decade for its importance to be realized. Hence the focus of this review paper is to examine the role of TDM with VDZ.

Clinical data supporting the role of vedolizumab in inflammatory bowel disease

VDZ is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that prevents lymphocyte migration to the intestine, thereby reducing inflammation.[7] VDZ binds to the α4β7 integrin expressed on gut-specific lymphocytes, in turn blocking their adhesion to mucosal addressin cell-adhesion molecules-1 (MAdCAM-1) in the gut vascular endothelium. It was approved for patients with moderate to severely active UC and CD intolerant or refractory to conventional therapy following the GEMINI phase III registration studies.[8–10] In these studies, eligible patients were adults with either UC or CD with active disease despite corticosteroids, immunomodulators or anti-TNF therapy. GEMINI 1 and 2 were similarly designed randomized, double-blind, placebo-controlled studies for UC and CD, respectively, and incorporated both induction and maintenance arms. In GEMINI 1, of 374 patients randomized to either VDZ or placebo, clinical response at week 6 was observed in 47.1% of the VDZ cohort, compared with 25.5% of placebo ($p < 0.001$). At week 52, clinical remission was achieved in 41.8% of patients treated with VDZ 8 weekly, compared with 44.8% of those treated with VDZ 4 weekly, and 15.9% of those receiving placebo ($p < 0.001$).[8] In GEMINI 2, among the 368 patients randomized to VDZ or placebo, clinical remission was achieved in 14.5% of patients assigned to VDZ compared with 6.8% of placebo ($p = 0.02$). CDAI-100 response was observed in 31.3% of the VDZ cohort *versus* 25.7% of placebo ($p = 0.23$). No significant differences in C-reactive protein (CRP) from baseline to week 6 were seen between the two treatment groups. At week 52 clinical remission was achieved in 39% receiving VDZ 8 weekly, 36.4% receiving VDZ 4 weekly, and in 21.6% receiving placebo ($p < 0.004$ for VDZ 8 weekly *versus* placebo and $p < 0.001$ for VDZ 4 weekly *versus* placebo).[9] In GEMINI 3 clinical remission at week 6 was achieved in 15.2% of patients receiving VDZ compared with 12.1% receiving placebo ($p = 0.43$). A secondary endpoint, clinical remission at week 10, was observed more frequently in patients receiving VDZ compared with placebo (26.6% *versus* 12.1%, $p < 0.001$).[10] A *post hoc* analysis of patients with UC who underwent paired endoscopies from the GEMINI studies found that a significant proportion with endoscopic healing also had histologic remission, although this effect was often delayed until week 52, consistent with the observation that VDZ can have a relatively slow onset of action.[11]

Real word experience with VDZ in IBD has been recently reported in a systematic review and pooled analysis of nine adult studies comprising 571 patients with UC and 994 patients with CD.[12] It is important to note that significant heterogeneity in study design, patient population and definition of response and remission were observed between studies. Data for response to induction at week 6 among patients with UC were reported from four studies totalling 288 patients. Clinical response was achieved in 43% [95% confidence interval (CI) 37–49%] and clinical remission in 25% (95% CI 12–45%). This increased to 50% and 30% of patients, respectively when considering a pooled later time of week 12, 14 or 22 in five studies enrolling 432 patients. Two real world studies which included 99 patients reported outcomes during maintenance (at week 52 or 54); clinical response and remission were achieved in 48 and 39%, respectively. Considering induction (at week 6) among five studies of 552 patients with CD, clinical response and remission were achieved by 54% (95% CI 41–66%) and 22% (95% CI 13–35%), respectively. Three studies of 347 patients with CD assessed outcomes during maintenance (week 52); clinical response and remission were observed in 45% (95% CI 28–64%) and 32% (95% CI 12–62%), respectively.

Pharmacokinetics–pharmacodynamics of VDZ

An extensive review of the pharmacokinetic–pharmacodynamic relationship of VDZ in IBD has been published by Rosario and colleagues.[7] Data from a phase I study among healthy volunteers administered a single VDZ dose at ranges of

Table 1. Factors affecting the pharmacokinetics of anti-tumour necrosis factor (TNF) therapy and vedolizumab (VDZ) in inflammatory bowel disease (modified from Steenholdt *et al.*[25]).

Variable	Influence on anti-TNF pharmacokinetics	Influence on VDZ pharmacokinetics
Sex	Increased clearance in men	No difference
Body mass index (BMI)	Increased clearance in those with high BMI	Increased clearance in those with increased weight (>120 kg)
Albumin	Low levels associated with increased clearance	Low levels associated with increased clearance
Inflammatory burden	More severe disease associated with increased clearance	More severe disease associated with increased clearance (ulcerative colitis only)
Immunogenicity (presence of antidrug antibodies)	Detectable antidrug antibodies increase clearance	Detectable antidrug antibodies increase clearance
Combination therapy with immunomodulators	Combination therapy associated with increased anti-TNF drug levels	No difference in combination therapy *versus* monotherapy
Mode of administration	Variable absorption with subcutaneously administered monoclonal antibodies	Further data needed (subcutaneous VDZ studies underway)
Genetic variation in Brambell receptor and Fc-y receptors	Variation in observed circulating drug levels	Not applicable given different mode of action

0.2–10.0 mg/kg demonstrated that clearance is rapid and nonlinear at low serum concentrations (<10 μg/ml), however above this (at concentrations considered clinically relevant), clearance is linear.[13] Phase II studies of repeated doses of VDZ in patients with UC across dose ranges of 2–10 mg/kg demonstrated that pharmacokinetics was dose proportional.[14] In the GEMINI studies, VDZ concentrations at week 6 were similar in patients with CD and UC. In the maintenance arms of GEMINI 1 and 2 higher VDZ concentrations were observed at week 46 in patients treated with 4 weekly VDZ compared with 8 weekly VDZ (mean VDZ concentration 220 and 247 μg/ml *versus* 77 and 72 μg/ml, respectively).[8,9] A population-based model which included 2554 healthy volunteers and patients with UC and CD (from the phase I, II and III VDZ studies) aimed to further characterize the pharmacokinetics of VDZ and to identify clinically relevant determinants of clearance with several findings of interest.[14] The volume of distribution of VDZ was similar to that seen with other monoclonal antibodies. Half life was estimated to be 25.5 days. Clearance was similar between patients with UC or CD and not significantly different according to sex or age. Body weight did not affect clearance up to a weight of 120 kg, above which clearance did increase. In GEMINI 1, patients with higher Mayo endoscopic scores had lower VDZ serum concentrations compared with patients with lower scores. Levels of CRP and faecal calprotectin influenced clearance but this was not clinically significant. Hypoalbuminemia resulted in a clearance approximately 30% higher than that of a patient with normal albumin. Clearance was determined to be 12% higher in the presence of antibodies to VDZ, although interpretation is limited given the number of patients with persistent anti-VDZ antibodies in GEMINI 1 and 2 was small ($n = 9$). Modelling found no impact on VDZ clearance among patients treated with combination therapy compared with those treated with VDZ monotherapy. The relationship between patient and disease covariates and VDZ pharmacokinetics from the population-based modelling study is summarized in Table 1.

The pharmacokinetic–pharmacodynamic relationship of VDZ and its effect on α4β7 integrin

binding to peripheral blood memory T cells has been explored using flow cytometry binding interference assays. Near complete saturation of the α4β7 receptor with resulting inhibition of these assays was observed following administration of VDZ in single or multiple doses for as long as VDZ was measurable in serum.[14] MAdCAM-1-Fc binding returned to baseline levels when VDZ concentrations were no longer detectable. In the population pharmacokinetics–pharmacodynamics modelling study, complete receptor saturation was estimated to be reached at VDZ concentrations of 1 μg/ml.[14] However, data from GEMINI 1 and 2 demonstrate that patients require VDZ concentrations over 17 μg/ml at week 6 to reach response rates superior to placebo.[8,9] This discrepancy suggests that receptor saturation is necessary but not sufficient to predict efficacy.

Therapeutic drug monitoring of anti-TNF therapy in IBD

The introduction of anti-TNF therapy some 15 years ago revolutionized the modern management of IBD. Despite their proven efficacy, up to 30% of patients exhibit no primary nonresponse, and among responders subsequent secondary loss of response is observed in up to 30% after 12 months, and approximately 20% annually thereafter.[15–17] Improving the durability of response to anti-TNF therapy is therefore critical, given the relative lack of alternative efficacious treatment options and the high burden of cost involved. A large body of data supports a clear exposure–response relationship (ERR) with anti-TNF therapy, whereby minimum concentration thresholds of circulating drug are associated with improved clinical outcomes. Considering CD, infliximab drug concentrations over 3 μg/ml[18,19] and for adalimumab, concentrations over 4.95 μg/ml,[20] have been shown to best correlate with clinical remission in multiple cross-sectional studies. As treatment paradigms have evolved beyond clinical remission to target objective evidence of mucosal healing,[21] so too have higher drug thresholds been identified to neutralize systemic inflammation and heal the mucosa. In a cross-sectional study of 96 patients with CD, infliximab thresholds of 1.5, 3.4 and 5.7 μg/ml were associated with clinical remission, biochemical remission (normalization of CRP) and mucosal healing (using faecal calprotectin as a surrogate), respectively.[22] Similar target thresholds have been endorsed in recent international guidelines.[23,24] A range of patient-, disease- and drug-related variables, summarized in Table 1, have been identified which influence the pharmacokinetics of anti-TNF agents.

Exposure–response relationship with vedolizumab

Data are emerging supporting an ERR with VDZ, especially during induction therapy, in both CD and UC. Here we review data regarding serum VDZ levels and clinical outcomes, first from *post hoc* analyses of registration trials, and then observational series, some of which have only been published in abstract form to date. Immunogenicity data from these studies are then discussed. In interpreting the results of cross-sectional studies of TDM and VDZ it is important to note that these are reporting associations between drug levels and clinical outcomes, and as such, this does not necessarily imply causation. In this setting drug levels may be considered a biomarker of response; for example, higher drug levels are more likely to be found in responders with mucosal healing.

Vedolizumab drug levels and clinical outcomes

Post hoc *analyses of clinical trial data*

An ERR was demonstrated in the VDZ registration studies in both UC (GEMINI 1) and CD (GEMINI 2). Considering induction data from GEMINI 1, patients with UC and drug levels in the highest quartile (Q4, 33.6–65.6 μg/ml) *versus* the lowest quartile (Q1, 0–16.7 μg/ml) had higher rates of clinical response (74.1% *versus* 29.6%) and remission (37.0% *versus* 5.6%) at week 6. During 8-weekly maintenance therapy patients with drug levels in the highest quartile (Q4, 14.2–42.8 μg/ml) *versus* the lowest quartile (Q1, 0–6.0 μg/ml) had higher rates of clinical remission (80.0% *versus* 42.1%) at week 52.[8] In GEMINI 2 during induction therapy patients with CD and drug levels in the highest quartile (Q4, 33.8–142.0 μg/ml) *versus* the lowest quartile (Q1, 0–15.2 μg/ml) had higher rates of clinical response (48.0% *versus* 20.4%) and remission (22.0% *versus* 6.1%) at week 6. During 8-weekly maintenance therapy patients with drug levels in the highest quartile (Q4, 15.5–54.5 μg/ml) *versus* the lowest quartile (Q1, 0–7.5 μg/ml) had higher rates of clinical remission (84.2% *versus* 66.7%) at

week 52.[9] Neither comparative analysis to confirm whether differences in quartile were statistically significant, nor receiver operating characteristic (ROC) analyses to identify potential target threshold levels were included in the initial publications. Subsequently, a *post hoc* analysis of ERR for VDZ induction therapy was performed on a dataset from all three GEMINI studies, using quartile analysis of week 6 and week 10 VDZ levels, and included logistic regression to explore the impact of baseline patient and disease covariates. For patients with UC (GEMINI 1), median week 6 VDZ trough levels were higher in patients in remission than in those with active disease (34.7 *versus* 23.7 μg/ml), however the significance of this difference is not provided and some overlap in concentrations between the two subgroups was seen. By quartile analysis, using different cutoffs to the initial studies, induction levels greater than 17 μg/ml were associated with higher clinical remission rates than placebo and trough concentration increases from Q1 (⩽17.1 μg/ml) to Q4 (>35.7–140 μg/ml) increased remission rates by almost 31%. The ERR was more modest in CD (GEMINI 2 and 3). Although in GEMINI 2, week 6 VDZ trough levels were higher in remitters than nonremitters (26.8 *versus* 23.5 μg/ml), there was considerable overlap between both groups. Week 6 VDZ levels greater than 16.0 μg/ml (GEMINI 2) and 17.1 μg/ml (GEMINI 3) were associated with higher clinical remission rates than placebo, however trough concentration increases from the lowest to the highest quartiles increased response rates by only 14% (GEMINI 2) and 5% (GEMINI 3). In both UC and CD, of baseline covariates assessed by logistic regression, previous anti-TNF use had the highest impact on clinical outcomes; remission rates were 10% higher in anti-TNF naïve patients.[26]

The University of Michigan group obtained data on 472 patients with CD from the VDZ registration trials and performed random forest machine learning algorithm modelling on first testing and then validation cohorts to try and identify early predictors of week 52 corticosteroid-free remission. Baseline data and variables through to week 6, including VDZ trough levels, were used to construct the study models. Using baseline data only, the accuracy of the model to predict week 52 steroid-free remission, as assessed by the area under the ROC curve, was only modest (AuROC 0.65, 95% CI 0.53–0.77). However, the AuROC increased to 0.75 (95% CI 0.64–0.86) when data through to week 6 were included, and of all variables tested, week 6 serum VDZ levels were one of the five strongest predictors of remission in the model. Hopefully future iterations of the model will increase its clinical validity as only 35.8% of patients predicted to be in corticosteroid-free biologic remission at week 52 by the model achieved this endpoint, compared with 6.7% of patients who were predicted to fail to achieve remission.[27]

In another *post hoc* analysis of GEMINI 1, published only in abstract form to date, early VDZ trough concentrations at weeks 2, 4 and 6 were correlated with clinical remission rates at week 14. Patients in clinical remission at week 14 had numerically higher median VDZ at weeks 2, 4 and 6 than those with active disease, although again there was considerable overlap between the groups. When stratified into quartiles by trough concentration only, higher trough levels at week 6 were associated with higher remission rates at week 14 but no ROC analysis to identify a potential target threshold level was performed.[28]

Prospective, cross-sectional and retrospective observational series

A multicentre French prospective observational study of 47 patients with disease that failed to respond to two anti-TNFs (31 CD, 16 UC) and commencing VDZ investigated whether serum trough levels during induction could predict the need for subsequent dose escalation within 6 months. All patients received induction corticosteroids in the first 4–6 weeks and were on VDZ monotherapy. Patients not in clinical remission at week 6 were escalated to 4-weekly VDZ therapy. Dose escalation was required in 30 of 47 patients (23 CD and 7 UC) and all patients responded. Comparing patients who required dose escalation with those who did not, week 2 VDZ levels were identical in the two groups (33.0 *versus* 33.0 μg/ml, $p = 0.31$). However, by week 6 VDZ levels were numerically lower in patients requiring dose escalation (23.5 *versus* 42.5 μg/ml, $p = 0.15$). No differences in drug levels were seen between patients with CD and those with UC. By ROC analysis, all patients with a week 2 VDZ level less than 24.5 μg/ml required subsequent dose escalation within 6 months, although the accuracy of this analysis was only moderate (AuROC 0.63, 95% CI 40.6–83.9). A better predictor of the need for dose escalation within 6 months was a week 6 VDZ level of

less than 18.5 μg/ml (positive predictive value 100%, negative predictive value 46.2%, AuROC 0.72, 95% CI 0.48–0.96). These results suggest that levels taken at week 6 are the best predictor of the need for subsequent 4-weekly VDZ therapy.[29] The same group explored the relationship between VDZ trough levels collected prospectively at weeks 2, 6 and 14 and subsequent rates of mucosal healing during maintenance treatment at week 52 among 82 patients with IBD. Only trough levels at week 6 differentiated patients with and without mucosal healing (26.8 *versus* 15.1 μg/ml, $p = 0.035$). In this study, a VDZ cutoff level of 18 μg/ml at week 6 correlated with mucosal healing (positive predictive value 88.2%, negative predictive value 66.7%, AuROC 0.74, 95% CI 0.53–0.94).[30] The potential importance of the week 6 time point was confirmed in another prospective observational study of 106 patients (67 CD, 39 UC) treated with VDZ at two Israeli centres and followed for a median of 30 weeks. In addition to VDZ levels, α4β7 receptor saturation was measured by flow cytometry analyses of CD3+ CD45RO+ memory T cells isolated from both peripheral blood and intestinal biopsies in a subset of patients. Clinical remission was seen in 48/106 patients (45%) by week 6 and 50/106 patients (48%) by week 14. During induction therapy, median week 6 VDZ levels were higher in patients achieving remission than those with active disease (40.2 *versus* 29.7 μg/ml, $p = 0.05$); these results are similar to the aforementioned French study. On quartile analysis of week 6 VDZ levels, a dose response was demonstrated in response rates between quartiles 2 and 3 ($p = 0.02$) and 2 and 4 ($p = 0.006$). VDZ drug levels were not associated with remission at any other time points during induction. On multivariate analysis of baseline variables, only baseline serum albumin correlated with VDZ levels at weeks 6 and 14. During maintenance therapy VDZ levels were higher in patients who normalized CRP levels compared with those who did not (21.8 *versus* 11.9 μg/ml, $p = 0.0006$). On flow cytometry analysis, α4β7 receptor saturation was near complete at weeks 2 and 14 and during maintenance therapy and occupancy was unrelated to response to VDZ or to drug levels at week 14. The percentage of positive α4β7 T cells prior to therapy did not predict response. Similar findings were seen in both peripheral blood and intestinal biopsies.[31] Conversely, published only in abstract form, others have observed a positive association between pretreatment α4β7 expression on multiple peripheral blood lymphocyte subsets and response to VDZ, and further, during maintenance, both higher VDZ serum trough levels and high α4β7 reception saturation correlated with response to therapy.[32] These findings suggest that receptor saturation may be a relevant biomarker to predict response to VDZ, however other potential mechanisms of action of the drug need to be explored.

The remaining observational studies of VDZ TDM have been published only as abstracts to date. First induction, and then maintenance, studies are now briefly reviewed. In a prospective cohort of 45 patients (21 CD, 24 UC) commencing VDZ, of patients achieving remission at 22 weeks, VDZ trough levels were significantly higher at weeks 2 (25.0 *versus* 21.8 μg/ml, $p = 0.009$) and 6 (26.1 *versus* 12.7 μg/ml, $p < 0.001$) and numerically higher at week 14 (15.5 *versus* 8.5 μg/ml, $p = 0.08$). VDZ levels were slightly higher in patients on combination therapy, only reaching significance at week 2. On logistic regression the strongest predictors for week 22 remission were baseline serum albumin and week 2 and 6 VDZ levels.[33]

Another referral centre induction study assessed the relationship between VDZ levels and response, including mucosal healing rates, up to week 22 in 75 patients (46 CD, 29 UC), 70 of whom had previously received anti-TNF therapy. Of patients undergoing endoscopic assessment, mucosal healing was achieved in 18% (5/28) of patients with CD and 66% (19/29) of patients with UC. Patients with UC and mucosal healing had significantly higher VDZ trough levels at weeks 2, 6, 14 and 22 compared with patients without mucosal healing. Patients with CD and mucosal healing had significantly higher VDZ levels at weeks 6 and 10 compared with patients without mucosal healing. Thirty patients still had detectable anti-TNF concentrations at their first VDZ infusion. Interestingly, patients with CD and recent anti-TNF exposure had lower trough VDZ levels at all time points compared with patients with no recent anti-TNF exposure (e.g. week 6: 16.8 *versus* 28.5 μg/ml, $p = 0.006$; and week 22: 6.8 *versus* 15.5 μg/ml, $p = 0.005$). Patients with recent anti-TNF exposure had numerically, but not significantly, lower response rates to VDZ.[34] In a single-centre prospective cohort of 51 patients (27 CD, 23 UC, 1 IBD unclassified) followed for 6 months after commencing VDZ, an association between VDZ trough levels and biological

response was seen. Patients with CD who normalized their CRP (<5 mg/l) had significantly higher VDZ levels than patients with elevated CRP levels (34.9 *versus* 21.7 μg/ml, $p = 0.002$). Patients with UC and haemoglobin levels greater than 12 g/dl had significantly higher VDZ levels compared with patients with lower haemoglobin levels (35.4 *versus* 15.6 μg/ml, $p < 0.0005$).[34]

A single-centre cross-sectional study assessed associations between VDZ levels and clinical outcomes during maintenance therapy in 180 patients (90 CD, 90 UC). Overall median VDZ level was 10.9 μg/ml, and although levels tended to be higher in clinical remission, this was not significant. Patients with biologic remission (CRP <5 mg/L) had significantly higher VDZ levels (11.7 *versus* 10.0 μg/ml, $p = 0.02$); this was significant only in CD. On quartile analysis patients with VDZ levels greater than the lowest quartile (>7 μg/ml) were significantly more likely to be in remission [odds ratio (OR) 2.5, 95% CI 1.2–5.1], albeit with a modest AuROC of 0.61.[35] Another cross-sectional study of 56 patients (41 CD, 15 UC) explored the correlation between VDZ levels and rates of deep remission during maintenance therapy, stringently defined as clinical, biochemical and endoscopic remission. Forty-three percent of patients had disease in deep remission, although this was only steroid free in 16%. VDZ levels were significantly higher in patients with deep remission and steroid-free remission compared with patients not achieving these outcomes (12.9 *versus* 9.4 μg/ml, $p = 0.008$; and 15 *versus* 9.5 μg/ml, $p = 0.02$), respectively. On quartile analysis patients with VDZ levels above the lowest quartile (⩾5.1 μg/ml) were more likely to be in deep remission (OR 6.6, 95% CI 1.55–45.8, $p = 0.009$). On ROC analysis a VDZ cutoff level of 5.1 μg/ml during maintenance therapy best predicted deep remission (AuROC: 0.713, $p = 0.03$).[36]

Immunogenicity: anti-vedolizumab antibodies

As with any biologic therapy, immunogenicity, in the form of anti-vedolizumab antibodies (AVAs), occurs with VDZ, although the prevalence, permanence and clinical effects of these antibodies is significantly lower than those observed with anti-TNF agents. Using a drug-sensitive assay the rates of AVAs from the registration studies were as follows: GEMINI 1 (3.7% AVA positive, 1% persistently positive, defined as detectable AVAs on at least two successive occasions), GEMINI 2 (4.1% AVA positive, 0.4% persistently positive) and GEMINI 3 (1.0% AVA positive, 0.0% persistently positive). These rates were reduced by approximately 1% in patients on concurrent immunomodulators.[8–10] From the maintenance arms of GEMINI 1 and 2, nine patients had persistently positive AVAs and none of these patients achieved clinical remission at week 52. Only three patients (5%) with persistently positive AVAs experienced infusion reactions.[7] Most abstracts from observational studies report rates of AVAs of less than 5% with drug-sensitive assays, with rates being higher when a drug-tolerant assay is used.[33,34,36] Immunogenicity data from full manuscripts are now briefly reviewed. In the French observational cohort already described, no patients developed AVAs using a drug-sensitive assay.[29] The Israeli cohort employed a drug-tolerant assay and found an AVA prevalence of 17% during induction therapy, however the presence of AVAs did not influence clinical outcomes (AVA positive in 14.3% of responders *versus* 20% of nonresponders, $p = 0.63$). During maintenance therapy the prevalence had decreased to 3%, suggesting that AVAs are often transient.[31] This potential for transient immunogenicity to VDZ was also demonstrated in a study from Leuven where, using a drug-tolerant assay, 4 of 179 (2.2%) vedolizumab-treated patients developed AVAs, all of which were present after the first infusion, but all of which were transient, disappearing before week 40. There was no correlation between AVAs and VDZ trough levels (Pearson's $r = 0.10$, $p = 0.76$, $n = 12$), and patients who were AVA positive did not require dose optimization.[37]

Conclusions and future direction

Data pertaining to the role of TDM with VDZ are clearly not as robust as those seen with anti-TNF therapy. The relative lack of an ERR is presumably attributable to the differing mode of action between the two classes of therapy. There is a signal emerging, especially during induction, that clinical outcomes do vary between VDZ concentrations at the extremes of the measurable range, as assessed by quartiles. Objectively, a week 6 VDZ threshold of over 20 μg/ml appears to be associated with improved clinical outcomes. Data to date have demonstrated that this ERR is stronger for UC than for CD. The lack of a similar

association during maintenance therapy may be due to a paucity of studies designed to specifically address this question. Further, it is possible that unlike with anti-TNFs, serum trough levels alone may be inadequate to predict clinical response with adhesion molecule inhibitors. Similarly, receptor saturation alone appears insufficient to predict response. Therefore, new biomarkers which more accurately reflect this pharmacokinetic–pharmacodynamic relationship are needed. In addition, different methodology such as measurement of area under the curve or peak concentration of VDZ, rather than sampling at trough, may be of relevance. Finally, complex personalized algorithms which incorporate patient and disease factors, may be necessary to guide management decisions.[38] Further studies utilizing therapeutic drug monitoring of VDZ in both CD and UC which prospectively examine the ERR in both reactive and proactive settings are needed.

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