



# Integrin Calculus: The Predictive Power of Vedolizumab Concentrations in IBD Therapy

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Although biological therapies, including the monoclonal antibody directed against the  $\alpha_4\beta_7$  integrin, vedolizumab, have revolutionized the treatment of patients with inflammatory bowel disease (IBD), response and remission to this therapy are not universal. Up to 30% of patients with Crohn's disease (CD) and ulcerative colitis (UC) do not respond at all, and up to 70% of initial responders only partially respond, with many patients losing response over time. Many of these undesired therapeutic outcomes can be explained by undetectable or low drug concentrations due to antibody formation or an increased non-immune drug clearance rate. Numerous studies suggest that higher serum biological drug concentrations are associated with a greater rate of favorable therapeutic outcomes [1]. Nonetheless, most of these studies relate to therapies directed against tumor necrosis factor (TNF), whereas exposure–outcome relationship studies remain limited for vedolizumab. Consequently, the time to assess drug concentrations and the related therapeutic drug window for vedolizumab remains undefined.

In this issue of *Digestive Diseases and Sciences*, Yarur et al. [2] recently added to knowledge regarding therapeutic drug monitoring (TDM) of vedolizumab. They performed a nicely designed single-center prospective cohort study that reported that serum vedolizumab concentrations obtained shortly after therapy initiation correlated with long-term steroid-free endoscopic remission. This study of 55 patients with IBD (CD,  $n = 25$ , and UC,  $n = 30$ ) and with active endoscopic disease in whom vedolizumab therapy was initiated demonstrated that patients achieving steroid-free endoscopic remission by week 52 of therapy had statistically significant higher serum vedolizumab concentrations at weeks 2 and 6.

Additionally, they identified that vedolizumab concentration thresholds  $\geq 23.2 \mu\text{g/ml}$  at week 2 and  $\geq 19.8 \mu\text{g/ml}$  at week 6 were independently associated with endoscopic (odds ratio [OR] 8.8; 95% confidence interval [CI] 2.6–29.7;  $p < 0.001$ ) and clinical (OR 6.8 [95% CI 1.2–4],  $p = 0.033$ ) remission at week 52. Furthermore, they demonstrated a positive correlation between serum vedolizumab concentrations and serum albumin and an inverse correlation with C-reactive protein (CRP), fecal calprotectin, and body mass. Finally, immunogenicity was very low as only 3/55 (5.5%) patients had detectable antibodies to vedolizumab through the 52 weeks of follow-up using a drug-tolerant homogeneous mobility shift assay.

These results are in line with previous studies, showing that higher vedolizumab concentrations, during both induction and maintenance treatments, are typically associated with superior therapeutic outcomes in patients with IBD (Table 1) [2–8]. The identification of clinically relevant vedolizumab thresholds is important as this would be the first step for applying both reactive and proactive TDM-based therapeutic algorithms. These algorithms for reactive TDM have been proven useful and cost-effective for clarifying the etiology and managing the loss of response to anti-TNF therapy, whereas proactive TDM is associated with superior clinical outcomes when compared to standard of care (empiric dose escalation and/or reactive TDM) for both infliximab and adalimumab.

This prospective, though rather small, study highlights the significance of TDM for optimizing vedolizumab therapy for IBD therapy during the early induction phase in order to achieve superior long-term outcomes. Similar to anti-TNF therapies, this study showed that TDM is likely even more clinically important for patients with a greater inflammatory burden, such as patients with high CRP and low albumin. Nevertheless, as the authors also stated, interventional studies testing higher drug doses during induction in order to improve therapeutic outcomes are needed. Before proactive TDM of vedolizumab can be widely implemented

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**Table 1** Association of serum vedolizumab concentration thresholds with therapeutic outcomes in inflammatory bowel disease

IBD type	Study type	Time point	Threshold ( $\mu\text{g/ml}$ )	Therapeutic outcome	TDM assay	References
CD	Retrospective	Induction (w2)	> 35.2	Biological remission (w6)	ELISA	[3]
UC	Retrospective	Induction (w2)	> 28.9	Clinical response (w14)	ELISA	[3]
UC	Retrospective	Induction (w2)	> 23.7	Mucosal healing (w14)	ELISA	[3]
CD/UC	Prospective	Induction (w2)	< 24.5	Drug optimization (within w24)	ELISA	[4]
CD/UC	Prospective	Induction (w2)	$\geq$ 23.2	Endoscopic remission (w52)	HMSA	[2]
UC	Retrospective	Induction (w6)	> 20.8	Clinical response (w14)	ELISA	[3]
UC	Post hoc analysis of RCT <sup>a</sup>	Induction (w6)	> 37.1	Clinical remission (w14)	ELISA	[5]
CD/UC	Prospective	Induction (w6)	< 18.5	Need for extended therapy	ELISA	[4]
CD/UC	Prospective	Induction (w6)	> 27.5	Sustained clinical response	ELISA	[4]
CD/UC	Prospective	Induction (w6)	> 18	Mucosal healing (within w54)	ELISA	[6]
CD/UC	Retrospective	Induction (w6)	> 28	Sustained response	ELISA	[7]
CD/UC	Prospective	Induction (w6)	$\geq$ 19.8	Clinical remission (w52)	HMSA	[2]
UC	Retrospective	Post-induction (w14)	> 12.6	Clinical response (w14)	ELISA	[3]
UC	Retrospective	Post-induction (w14)	> 17	Mucosal healing (w14)	ELISA	[3]
UC	Post hoc analysis of RCT <sup>a</sup>	Post-induction (w14)	> 18.4	Clinical remission (w14)	ELISA	[5]
CD	Retrospective	Maintenance (w22)	> 13.6	Mucosal healing (w22)	ELISA	[3]
CD	Retrospective	Maintenance (w22)	> 12	Biological remission (w22)	ELISA	[3]
UC	Retrospective	Maintenance	> 25	Histological healing	ELISA	[8]
UC	Post hoc analysis of RCT <sup>a</sup>	Maintenance	> 12.7	Clinical remission (w52)	ELISA	[5]

ELISA enzyme-linked immunosorbent assay, HMSA homogeneous mobility shift assay, w week, CD Crohn's disease, UC ulcerative colitis, RCT randomized controlled trial, Ref reference

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in “real-life” clinical practice, several goals need to be achieved, including determining the optimal concentration range and therapeutic window to target, obtaining more data regarding specific IBD phenotypes that respond most favorably, defining the types of TDM assays used, and conducting prospective studies on the implementation of proactive TDM.

### Compliance with ethical standards

**Conflict of interest** KP has nothing to disclose; ASC received a consultancy fee from Janssen, Abbvie, Takeda, Pfizer, Samsung, Arena, Bacainn, EMD Serono, Arsanis, Grifols, and Prometheus and research support from Inform Diagnostics.

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