Deciphering the vedolizumab dosing conundrum in IBD: when less is more

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Already in the 1990s, the integrin α4β7, expressed on innate and adaptive immune cells, has been implicated in the control of lymphocyte recruitment to the intestinal mucosa.[1] Pharmacological blockade of α4β7 with a monoclonal antibody, later termed vedolizumab, protected against spontaneous chronic colitis in the cotton-top tamarin model.[2] Almost two decades later, phase III clinical trials in patients with IBDs proved vedolizumab efficacious for induction and maintenance of remission in UC[3] as well as Crohn's disease (CD),[4] which led to the drug approval by the European Medicines Agency in 2014. Only recently, the VARSITY trial indicated superiority of vedolizumab compared with adalimumab in UC with respect to clinical remission and endoscopic improvement,[5 6] while at the same time displaying a favourable safety profile[7] and the potential to predict treatment response (in CD) by a clinical scoring system.[8] Notably, the initial reasoning for this therapeutic concept appeared rather clear; however, we are only beginning to appreciate its mechanisms of action. For example, characterisation of the mucosal and systemic immune cell compartment before and during vedolizumab treatment of 18 patients with IBD did reveal neither alterations in the abundance nor the receptor repertoire of mucosal T cells. Unexpectedly, vedolizumab rather resulted in profound effects on the innate immune system.[9] A second study corroborated this notion by demonstrating that vedolizumab affected mucosal homing of non-classical monocytes,[10] indicating that the immunomodulatory actions of vedolizumab are more diverse than previously anticipated. These findings were paralleled by the observation that vedolizumab efficacy is counterintuitively affected by dosing, in that higher trough concentrations appear to confer an unfavourable clinical response.[11 12] More specifically, these studies reported worse clinical outcomes in the highest dosage group (when compared with medium dosing), challenging the concept of intensified dosing due to a linear dose–response relation reported for other biologics in IBD, for example, anti-tumour necrosis factor-α (TNF-α)[13] or anti-interleukin (IL)-12/IL-23 antibody therapy.[14] Collectively, these studies emphasised the need for a better mechanistic understanding of vedolizumab efficacy in human IBD. The study by Becker *et al*[15] in *Gut* deciphered aspects of this vedolizumab dosing conundrum.

The authors studied potential mechanisms by which this non-linear exposure efficiency of vedolizumab might be explained. They took advantage of fluorescently labelled vedolizumab, which was applied to bind and quantify peripheral human T-cell subsets from patients with IBD in vitro. By doing so, the authors noted that the concentration of vedolizumab influenced its binding to specific T-cell populations. Most notably, at 10 µg/mL, vedolizumab (reflecting the trough concentration with the most favourable clinical response in a phase II trial) targeted mostly effector T cells (T_{eff}) and less so regulatory T cells (T_{reg}), while 50 µg/mL equally labelled both populations. In line, 10 µg/mL vedolizumab preferentially impaired adhesion and transmigration of T_{eff} when compared with T_{reg} (though with small effect size) in in vitro assays. As such, functional blockade of α4β7 with vedolizumab requires higher concentration for T_{regs} when compared with T_{eff}. This is notable because T_{regs} serve widely documented anti-inflammatory functions that allow to maintain gut homeostasis.[16] In subsequent experiments, these data were confirmed in vivo in a humanised mouse model, demonstrating that 10 µg/mL vedolizumab preferentially blocked mucosal homing of T_{eff} when compared with T_{reg} in the mouse colon. To better understand this effect, free α4β7 binding sites were determined in the presence of ascending vedolizumab concentration in vitro and in T cells isolated from peripheral blood mononuclear cells of vedolizumab-treated patients. These experiments suggested that 10 µg/mL vedolizumab results in higher residual availability of α4β7 on T_{reg} than on T_{eff}. To identify the $\alpha4\beta7^+$ T-cell population that is not targeted by vedolizumab, the authors performed flow cytometry sorting and single-cell sequencing of peripheral $\alpha4\beta7^+$ T cells (coexpressing $CD4^+CD45RO^+$) that were fluorescently labelled with vedolizumab$^+$ or were unlabeled (vedolizumab$^-$). These studies revealed a specific T_{reg} subpopulation expressing $\beta1^+PI16^+$ which was poorly targeted by vedolizumab at 10 µg/mL. Functional experiments on these purified $\beta1^+PI16^+$ T_{reg} cells confirmed reduced in vitro and in vivo binding to vedolizumab. Single-cell transcriptional profiling of $\beta1^+PI16^+$ T_{reg} in the mucosa of vedolizumab-treated patients with IBD indeed demonstrated a pronounced regulatory phenotype. Vedolizumab trough concentration in patients with IBD indirectly correlated with free α4β7 binding sites in peripheral human T cells, which, however, was not observed for $\beta1^+PI16^+$ T_{reg} cells, suggesting that the reported 'vedolizumab resistance' of this subpopulation is also found in patients with IBD. Finally, a post hoc analysis of the phase III trials in CD suggested that the optimal trough concentrations associated with clinical remission (at week 6) was in the range of 40–55 µg/mL, while higher (or lower) trough concentrations were associated with poor outcome. Collectively, this study provides an explanation for the non-linear dose–response conundrum of vedolizumab, which inhibits residual homing of anti-inflammatory $\beta1PI16^+$ T_{reg} at higher concentrations in IBD (figure 1). Whether these insights help to establish an ideal therapeutic window for vedolizumab in IBD warrants prospective controlled clinical trials.

Optimisation of immunosuppressive therapy in IBD is highly desirable due to poor long-term efficacy.[17] As such, optimised dosing and therapy stratification of available therapeutics is a high priority. Remarkably, vedolizumab challenges the rather simple concept of dose intensification typically observed for anti-TNF-α antibodies or ustekinumab. Thus, the optimal therapeutic window for vedolizumab should be refined in prospective clinical trials, comparing intravenous with subcutaneous vedolizumab application.[18] This appears particularly important because experimental data and clinical post hoc analysis of patients with CD from the GEMINI trials indicated a different range of this therapeutic window. Likewise, the mechanism of a vedolizumab-resistant state of specific T-cell subsets is currently unresolved, which could pave

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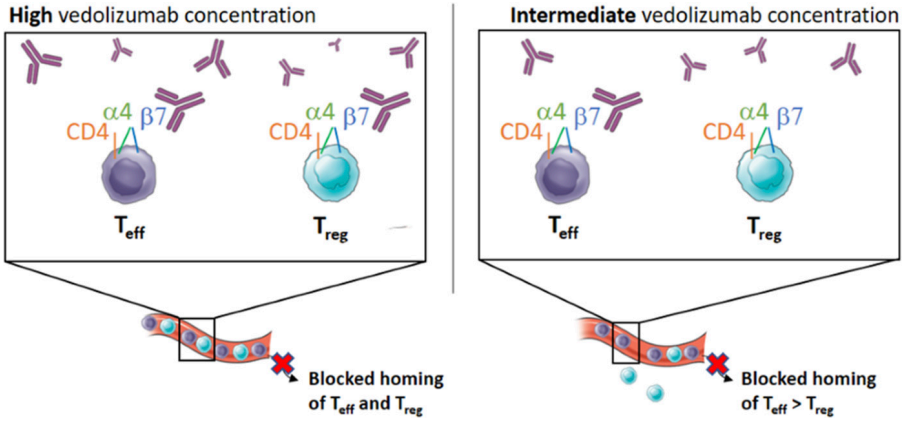

Figure 1 Vedolizumab concentration differentially affects α4β7 binding and homing efficacy of specific T-cell subsets in IBD. In the setting of a high vedolizumab serum concentration, α4β7 on T_{eff} and regulatory anti-inflammatory$\beta1^+PI16^+$ T cells (T_{reg}) is equally blocked and prevents gut homing. In the setting of intermediate vedolizumab serum concentration, T_{eff} cell gut homing is prevented to a larger extend as compared with anti-inflammatory $\beta1^+PI16^+$ T_{reg} cells, which are poorly targeted by vedolizumab. This may explain why higher vedolizumab doses do not correspond with better clinical outcome, suggesting a tight therapeutic window for optimal efficacy. Notably, the optimal serum concentration of vedolizumab in IBD for clinical practice remains to be determined, similar to the mechanism for 'vedolizumab resistance' of $\beta1^+PI16^+$ T_{reg} cells. T_{eff}, effector T cell; T_{reg}, regulatory T cell.

the way for boosting vedolizumab efficacy in IBD in the future. Thus, this study opens up new clinical perspectives and research questions. For example, does the reported observation hold true for patients with CD and UC alike, and is there a comparable window of opportunity in these disease entities? Moreover, considering alternative mechanisms of vedolizumab efficacy (on innate immunity),[9 10] does dosing differentially affect homing of specific innate immune cell populations?

Collectively, this work beautifully exemplifies that we need to scratch deeper into gut immunology to appreciate the effects of targeted therapy on distinct immune populations in IBD. Understanding these mechanisms will be rewarding as this may also help to select patients for designated immunosuppressive therapy, to step into the era of individualised medicine.

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