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.[4] Pharmacological blockade of α4β7 with a monoclonal antibody, later termed vedolizumab, protected against spontaneous chronic colitis in the cotton-top tamarin model.[5] Almost two decades later, phase III clinical trials in patients with IBDs proved vedolizumab efficacious for induction and maintenance of remission in UC[6] as well as Crohn’s disease (CD),[7] 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 for T-cell subset 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 (Teff) and less so regulatory T cells (Treg), while 50 µg/mL equally labelled both populations. In line, 10 µg/mL vedolizumab preferentially impaired adhesion and transmigration of Treg when compared with Teff (though with small effect size) in in vitro assays. As such, functional blockade of α4β7 with vedolizumab requires higher concentration for Treg than on Teff. To identify the α4β7+ T-cell population that is not targeted by vedolizumab, the authors performed flow cytometry sorting and single-cell sequencing of peripheral α4β7+ T cells (coexpressing CD4+CD45RO+) that were fluorescently labelled with vedolizumab or were unlabelled (vedolizumab-). These studies revealed a specific Treg T-cell population expressing β1+IL16+ which was poorly targeted by vedolizumab at 10 µg/mL. Functional experiments on these purified β1+IL16+ Treg cells confirmed reduced in vitro and in vivo binding to vedolizumab. Single-cell transcriptional profiling of β1+IL16+ Treg in the mucosa of vedolizumab-treated patients with IBD indeed demonstrated a pronounced regulatory phenotype. Vedolizumab trough concentration in patients with IBD indi rectly correlated with free α4β7 binding sites in peripheral human T cells, which, however, was not observed for β1+IL16+ Treg 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 β1+IL16+ Treg 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.[8] 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 defined in prospective clinical trials, comparing intravenous with subcutaneous vedolizumab application.[9] 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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Commentary

Gut: first published as 10.1136/gutjnl-2021-325893 on 8 September 2021. Downloaded from http://gut.bmj.com/ on September 19, 2021 by guest. Protected by copyright.
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.

Contributors TA and BS jointly discussed, structured and wrote the commentary.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests BS has served as consultant for Abbvie, Arena, BMS, Boehringer, Celgene, Falk, Galapagos, Janssen, Lilly, Pfizer, Prometheus and Takeda, and received speaker’s fees from Abbvie, CED Service GmbH, Falk, Ferring, Janssen, Novartis, Pfizer and Takeda (payments were made to the institution).

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Adolph TE, Siegmund B. Gut Epub ahead of print; [please include Day Month Year]. doi:10.1136/gutjnl-2021-325892

Received 22 August 2021
Accepted 31 August 2021

http://dx.doi.org/10.1136/gutjnl-2021-324868.R1
Gut 2021:0–1–2.

doi:10.1136/gutjnl-2021-325893

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