Journal of Crohn's and Colitis, 2020, 1183–1184
doi:10.1093/ecco-jcc/jjaa069
Editorial

Editorial

Invited Editorial: Targeting Alpha 4 Beta 7, More Trafficking Inhibition Than We Thought?

Bram Verstockt[a,b] and Gianluca Matteoli[b]

[a]University Hospitals Leuven Department of Gastroenterology and Hepatology, KU Leuven, Leuven, Belgium [b]KU Leuven Department of Chronic Diseases, Metabolism and Ageing, Translational Research Center for Gastrointestinal Disorders [TARGID], Leuven, Belgium

Corresponding author: Bram Verstockt, MD, PhD, Department of Gastroenterology and Hepatology, University Hospitals Leuven, Herestraat 49 3000 Leuven, Belgium. Tel.: 0032 [0]16 34 42 18; Email: bram.verstockt@uzleuven.be

The discovery of the gut-selective lymphocyte homing receptors, such as the heterodimers alpha 4 and beta 7 integrins [47] and their ligand, mucosal addressin cellular adhesion molecule-1 [MAdCAM-1], offered the hope of an effective new targeted therapy for inflammatory bowel disease [IBD].[1] This brought the development of the anti-α4β7 integrin antibody vedolizumab, successfully used in clinic and confirming the importance of lymphocyte trafficking to the inflamed mucosa in IBD pathophysiology.

Hence, targeting α4β7-positive lymphocytes and thus blocking gut-selective lymphocyte trafficking, vedolizumab's mode of action was generally considered a straightforward therapeutic approach to IBD. However, Zeissig *et al.* already highlighted the unanticipated impact of vedolizumab on the innate, rather than the adaptive, immune system.[2] Similarly, the Erlangen group reported the influence of vedolizumab on non-classical monocytes, which might result in a reduction of wound healing macrophages.[3] Furthermore, Uzzan and colleagues demonstrated that vedolizumab therapy importantly reduced naïve B cells in intestinal mucosa of HIV-infected IBD patients,[4] preventing subsequent priming by dendritic cells which are surveying the mucosal barrier for invading pathogens. Similarly, Zeissig *et al.* also pointed towards a potential influence on the B cell compartment, as B cell receptor signalling was downregulated upon vedolizumab exposure.[2] Using deconvolution methods, we also observed a significant baseline difference in naïve B cells between vedolizumab responders ands non-responders.[5]

In the current issue of *JCC*, Coletta *et al.* further unravelled the consequences of vedolizumab exposure on the composition of the adaptive immune system, with a specific focus on the T cell compartment in particular.[6] In their exploratory study, they demonstrated a significant reduction in lamina propria memory Th17 [CXCR3- CCR6+] and α4β7+ CD4 T cells upon vedolizumab exposure. In contrast, circulating α4β7+ Th1/Th17 [CXCR3+ CCR6+] cells significantly increased during vedolizumab exposure. Although not observed by others,[2] the current findings suggest a spill-over of circulating pro-inflammatory T cells in the blood, no longer being able to migrate towards the intestinal wall upon vedolizumab exposure.

Coletta *et al.* also questioned whether baseline immunological characteristics, either in tissue or in blood, could be used as predictive markers for treatment response.[6] Indeed, prioritising drugs based on the molecular/immunological fingerprint of an individual is one of the key unmet needs in IBD care.[7] Very little is known on potential predictors for vedolizumab response, with conflicting data even on whether baseline expression of α4β7 on circulating T cells can be used to predict vedolizumab response.[8,9] The authors in the current study report on distinct proteomic panels that might separate vedolizumab responders from non-responders, though validation in large independent cohorts is absolutely warranted before implementation in daily clinical practice. Instead of the targeted approach studying a few potential markers, biomarker discovery projects should ideally consider an unbiased protein-wide approach, including machine learning and system biology analyses, to identify the best surrogate predictive markers. This, however, requires big cohorts to overcome statistical challenges, including power, and could be achieved by closer collaborations between multiple academic centres and/or industry, as currently aimed at by the COLLIBRI consortium [Collaborative IBD Biomarker Research Initiative].

Nevertheless, the detailed immunophenotyping preceding vedolizumab exposure in the current study provides interesting insights into how vedolizumab responders differ from non-responders. Interestingly, associations with clinical and endoscopic outcomes turned out differently, once more highlighting the discrepancy between symptoms and mucosal inflammation, especially in Crohn's disease. Clinical responders had higher baseline circulating memory Th1 [CXCR3+ CCR6-] and Th1/Th17 [CXCR3+ CCR6+] cells, although the subpopulation of α4β7+ Th1/Th17 [CXCR3+ CCR6+] cells at baseline was significantly lower in responders. Furthermore, reduced baseline proportions of lamina propria Th17 [CXCR3- CCR6+] and Th1/Th17 [CXCR3+ CCR6+] cells were linked to endoscopic response. In line with this, cellular deconvolution techniques on bulk transcriptomic mucosal biopsies also suggested a lower proportion of baseline effector CD4+ T cells in endoscopic responders.[5] Hence, one could question whether these observed mucosal findings

are not just a reflection of a reduced pro-inflammatory environment in vedolizumab responders, in line with what was previously observed with anti-tumour necrosis factor [TNF] agents.[10] In order to get a better understanding of how drugs differ in their mode of action and how they shape the immune system, future studies should compare different modes of action in parallel, in order to highlight overlapping and distinct profiles linked to treatment response.[11] Many of the currently reported signals linked to individual therapies might rather reflect disease refractoriness, instead of a true drug-specific signature.

Interestingly, Coletta *et al.* identified CXCR3 expression on total memory CD4+ T cells [and not on the α4β7+ subset] as a potential unknown and indirect target of vedolizumab therapy. Indeed, peripheral α4β7 saturation can be achieved with very little drug, resulting in near-complete α4β7 occupancy at Week 2 already, regardless of response status or drug levels.[12] Hence, alternative mechanisms of vedolizumab's mode of action should be further investigated, given the clear dose-response relationship observed in randomised trials as in real-life cohorts,[13] which cannot be explained by α4β7 occupancy at all. Whether whole-blood *CXCR3* expression could be used as a predictive marker for vedolizumab should therefore be further investigated.

Overall, the current study shed new lights on how vedolizumab may resolve mucosal inflammation in IBD. Besides its recently established influence on the innate immune system,[2,3] vedolizumab also affects subpopulations of the adaptive immune system, not just through its direct interaction with α4β7 but potentially also through several unknown indirect mechanisms, including the proposed CXCR3 pathway. Further functional experiments are absolutely required to further understand its detailed mode of action, which can subsequently be used in the development of vedolizumab-specific predictive biomarkers.

Funding

GM: laboratory is supported by an FWO grant [G.0D83.17N], a grant from the International Organization for the Study of Inflammatory Bowel Diseases [IOIBD], a grant from the European Crohn´s and Colitis Organisation [ECCO], and grants from the KU Leuven Internal Funds [C12/15/016 and C14/17/097].

Conflict of Interest

BV: research grant, Pfizer; consultancy, Janssen and Sandoz; peaker's fee, Abbvie, Ferring Pharmaceuticals, Janssen, R-biopharm, and Takeda. GM received financial support for research from DSM Nutritional Products, Karyopharm Therapeutics, and Janssen.

Acknowledgments

BV and GM wrote the manuscript. Both authors agreed with the final version of the manuscript submitted.

References

1. Berlin C, Berg EL, Briskin MJ, *et al.* Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell* 1993;**74**:185–95.
2. Zeissig S, Rosati E, Dowds CM, *et al.* Vedolizumab is associated with changes in innate rather than adaptive immunity in patients with inflammatory bowel disease. *Gut* 2019;**68**:25–39.
3. Schleier L, Wiendl M, Heidbreder K, *et al.* Non-classical monocyte homing to the gut via α4β7 integrin mediates macrophage-dependent intestinal wound healing. *Gut* 2020;**69**:252–63.
4. Uzzan M, Tokuyama M, Rosenstein AK, *et al.* Anti-alpha4beta7 therapy targets lymphoid aggregates in the gastrointestinal tract of HIV-1-infected individuals. *Sci Transl Med* 2018, Oct 3. doi: 10.1126/scitranslmed.aau4711.
5. Verstockt B, Verstockt S, Veny M, *et al.* Expression levels of 4 genes in colon tissue might be used to predict which patients will enter endoscopic remission after vedolizumab therapy for inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019, Aug 22. doi: 10.1016/j.cgh.2019.08.030. [Epub ahead of print.]
6. Coletta M, Paroni M, Alvisi M, *et al.* Immunological variables associated with clinical and endoscopic response to vedolizumab in patients with inflammatory bowel diseases. *J Crohn Colitis* 2020;14(9):1190–1201.
7. Noor NM, Verstockt B, Parkes M, Lee JC. Personalised medicine in Crohn's disease. *Lancet Gastroenterol Hepatol* 2020;**5**:80–92.
8. Boden EK, Shows DM, Chiorean MV, Lord JD. Identification of candidate biomarkers associated with response to vedolizumab in inflammatory bowel disease. *Dig Dis Sci* 2018;**63**:2419–29.
9. Rath T, Billmeier U, Ferrazzi F, *et al.* Effects of anti-integrin treatment with vedolizumab on immune pathways and cytokines in inflammatory bowel diseases. *Front Immunol* 2018;**9**:1700.
10. Verstockt B, Verstockt S, Creyns B, *et al.* Mucosal IL13ra2 expression predicts nonresponse to anti-tnf therapy in Crohn's disease. *Aliment Pharmacol Ther* 2019;**49**:57281.
11. Arijs I, De Hertogh G, Lemmens B, *et al.* Effect of vedolizumab [anti-α4β7-integrin] therapy on histological healing and mucosal gene expression in patients with UC. *Gut* 2018;**67**:43–52.
12. Ungar B, Kopylov U, Yavzori M, *et al.* Association of vedolizumab level, anti-drug antibodies, and α4β7 occupancy with response in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2018;**16**:697–705.e7.
13. Pouillon L, Vermeire S, Bossuyt P. Vedolizumab trough level monitoring in inflammatory bowel disease: a state-of-the-art overview. *BMC Med* 2019;**17**:89.