Journal of Crohn's and Colitis, 2017, 903–904
doi:10.1093/ecco-jcc/jjx033
Advance Access publication March 9, 2017
Editorial

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Blocking $\alpha_4\beta_7$ Integrin Through Vedolizumab: Necessary but not Sufficient?

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For over a decade, the biologics armamentarium for treating patients with inflammatory bowel diseases (IBD) was confined to anti-tumor necrosis factor (anti-TNF)-alpha monoclonal antibodies. The lack of therapeutic alternatives made it imperative to develop strategies to restore and maintain the response to these therapies. With the understanding that the actual drug exposure rather than the administered dose is related to the response, therapeutic drug monitoring (TDM) of anti-TNFs became an accepted practice.[1]

With a broad range of biologics in the late-stage drug development pipeline, the therapeutic options for treating patients with IBDs are expected to expand drastically in the next few years, making TNF just one of many therapeutic targets in clinical practice. The opportunity to choose between biologics with different mechanisms of action offers in the first place the potential for improved patient care, but it might also open the door for 'trial-and-error medicine'.

Vedolizumab is a humanized monoclonal antibody that specifically binds to the $\alpha_4\beta_7$-integrin on lymphocytes and thereby blocks its interaction with the mucosal addressin cell-adhesion molecule (MAdCAM)-1 on intestinal endothelial cells. Gastroenterologists now have the choice of preventing lymphocyte trafficking into the gut as well as that of blocking the anti-inflammatory cytokine TNF. The efficacy of vedolizumab in ulcerative colitis (UC) and Crohn's disease (CD) has been evaluated in three pivotal Phase 3 studies (GEMINI 1, GEMINI 2 and GEMINI 3). These studies have shown that there is room for therapeutic improvement, as the clinical response rates at Week 6 were only 47% in UC and 31% in CD, compared with a 26% placebo response in both UC and CD.[2–4]

Rosario et al. did an excellent job by thoroughly exploring the exposure–response relationship for vedolizumab induction therapy, using pooled data from the GEMINI studies.[5] They could confirm a positive relationship between vedolizumab trough concentrations and clinical outcome at Week 6 in patients with UC and CD, although the relationship was stronger in UC. Furthermore, they identified a higher baseline albumin concentration, a lower baseline C-reactive protein (CRP, CD only), a lower baseline fecal calprotectin (CD only) and no prior anti-TNF use as predictors of a higher probability of clinical remission at Week 6. Interestingly, prior anti-TNF use had the greatest impact on clinical outcome in both UC and CD.

Wyant et al. demonstrated that after binding to $\alpha_4\beta_7$, vedolizumab is internalized and the integrin is rapidly re-expressed after vedolizumab withdrawal.[6] Persistent blocking of lymphocyte trafficking therefore requires continuous, sufficiently high exposure to free vedolizumab molecules that are able to readily bind and block the newly expressed $\alpha_4\beta_7$ on the activated T-cells. The 'free' vedolizumab, which is also measured using the traditional TDM assays, waits for new $\alpha_4\beta_7$ to show up. In this perspective, vedolizumab trough concentrations can be considered as an indirect measure of $\alpha_4\beta_7$ expression, with lower vedolizumab trough concentrations reflecting a higher $\alpha_4\beta_7^+$ cell load (turnover). How this relates to disease severity and therapeutic response is at this stage unclear.

Causality in the exposure–response relationship as early as Week 6 might be due to a combined effect of disease severity on exposure and of exposure on response. Lower vedolizumab concentrations certainly reflect higher disease severity, often expressed in terms of low albumin or high CRP. Although the observed exposure–response relationship is more likely to reflect the influence of disease activity on vedolizumab exposure, this does not necessarily rule out the possibility that patients with lower vedolizumab exposure and higher disease activity might benefit from treatment intensification. However, to confirm this, a prospective study with dose optimization, or rather exposure optimization, is required. Furthermore, the potential for TDM in vedolizumab therapy is often questioned because GEMINI 1 and 2 report a >95% saturation of $\alpha_4\beta_7$ on $CD4^+CD45RO^+$ memory T-cells in the peripheral circulation.[2,3] On the one hand, it might be wondered whether other $\alpha_4\beta_7^+$ cell populations are involved in disease pathology. On the other hand, assuming indeed a complete target saturation from 1 μg/mL vedolizumab, $\alpha_4\beta_7$ saturation on

Abbreviations: TNF, tumor necrosis factor; CD, Crohn's disease; CRP, C-reactive protein; IBD, inflammatory bowel diseases; MAdCAM-1, mucosal addressin cell-adhesion molecule-1; TDM, therapeutic drug monitoring; UC, ulcerative colitis.

peripheral blood lymphocytes might be considered necessary but not sufficient for achieving optimal efficacy.[7]

The 'stronger' exposure–response relationship for clinical remission at Week 6 in patients with UC might be a reflection of differences in disease pathophysiology between CD and UC. For example, colonic dendritic cells are shown to have a more regulatory role than the ileal dendritic cells.[8] Furthermore, there are hints of a more important role for $\alpha_4\beta_7^+$ T-regs in UC, and cases of aggravated colitis under vedolizumab and etrolizumab have been reported.[9,10] At this point, it is still not clear whether patients with CD with an insufficient response to vedolizumab would benefit from a higher dose of vedolizumab or not. From the GEMINI trials, there is evidence that it takes more time for the inflammation in CD to resolve than it does in UC, making Week 6 generally a premature time-point for evaluating the response to induction therapy in patients with CD.

Rosario et al. reported that prior anti-TNF use, as an indicator of higher disease severity, had a great impact on clinical outcome in UC and CD, and that the effect was stronger in the latter.[5] A washout period of 60 days before start of vedolizumab in the GEMINI studies does, however, not exclude a pharmacokinetic and pharmacodynamic carry-over effect during vedolizumab induction therapy.[11]

As for the anti-TNFs, an exposure–response relationship has been observed for vedolizumab. At this point, the causality in this relationship is not clear. Blocking the gut-homing $\alpha_4\beta_7$-integrin on lymphocytes might be necessary but not sufficient to explain their mechanism of action. However, variability in disease severity might equally well explain lower vedolizumab trough concentrations at this early point in evaluating response, at least in patients with CD. Differences in efficacy between UC and CD and the impact of prior anti-TNF use on vedolizumab induction therapy have been observed but are not fully understood. Hopefully, this will boost the scientific community to elucidate the coordinated series of events that precede and follow leukocyte recruitment to the gut in patients with IBD. Only then can the high expectations for the novel target drugs be achieved.

Funding

This work was supported by the Fund for Scientific Research Flanders [grant numbers G.0617.12 and TBM T003716N].

Conflict of Interest

AG received financial support for research from Pfizer and MSD, speaker fees from Pfizer, Abbvie, Janssen Biologicals and MSD, and consultancy fees from UCB. ED has no conflicts of interest to declare.

Author Contributions

ED drafted the manuscript and AG critically revised the manuscript. Both authors read and approved the final manuscript.

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