Author’s response to reviews

Title: Vedolizumab Trough Level Monitoring In Inflammatory Bowel Disease: A State Of The Art Overview

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Version: 1 Date: 06 Mar 2019

Author’s response to reviews:

Response to the editor(s) of ‘BMC Medicine’ (BMED-D-19-00029)

Dear editor(s) of BMC Medicine,

We sincerely thank you for giving us the opportunity to submit a revised version of our original manuscript entitled "Vedolizumab Trough Level Monitoring In Inflammatory Bowel Disease Anno 2019: A State Of The Art Overview" by Pouillon et al. (BMED-D-19-00029), for consideration in BMC Medicine.

We thank you and the reviewers for the valuable comments that allowed us to improve the manuscript. As requested, we have changed the format of the article into a mini-review. All other changes are highlighted in red font. We also include a point-by-point response to the different remarks.

Sincerely,

Lieven Pouillon

REMARKS EDITORIAL BOARD

Comment 1: We agree with a comment made by reviewer Nos, and after discussion, we concluded your manuscript will be better classified as a Minireview, rather than a commentary. This is also in light of recent changes to our manuscript formatting. I have already changed the article type to Minireview in the system. When performing your revisions, I would be most grateful if the text could follow the Minireview format:
https://bmcmedicine.biomedcentral.com/submission-guidelines/preparing-your-manuscript/minireviews.

Answer 1: We thank you for this suggestion and fully agree. The format has been adapted accordingly.

Comment 2: Reviewer 1 Korzenik highlighted that a similar review by Ward et al was published in recent months:
www.researchgate.net/publication/325040992_Therapeutic_drug_monitoring_of_vedolizumab_in_inflammatory_bowel_disease_current_data_and_future_directions. Given the similar focus of this topic, we would suggest to highlight any novel and different aspects in your manuscript, to keep your submission as novel and impactful as possible.

Answer 2: We agree with this comment. Since the review of Ward et al has appeared, several new data have been published about the topic, e.g. Osterman et al performed a propensity-score-based case-matching analysis of data from GEMINI 1 (Aliment Pharmacol Ther 2019;49:408–18), Ungaro et al published the largest real-world cohort exploring the exposure-efficacy relationship of vedolizumab (J Crohn’s Colitis, epub ahead of print), and Pouillon et al linked histological healing and vedolizumab trough levels (J Crohn’s Colitis, epub ahead of print). Further more, more data add to the knowledge about the mechanisms underlying non-response or loss of response to vedolizumab (Gut 2019;68:25–39). All this new information is implemented in our article and lacks in the review of Ward et al. Further more, we include a concise overview of the available data in an easy-to-read table, and we give a SWOT analysis of the Promising features and potential drawbacks. To underline the novelty of our review in comparison to the one of Ward et al., we also adapted the title of the article.

REMARKS REVIEWER 1

Comment 1: The authors address an interesting and important question in their commentary, if therapeutic drug monitoring (TDM) is beneficial in the use of vedolizumab. The manuscript presents a well written overview of current knowledge on the topic including real world data from post hoc analyses and observational series to support their position that an exposure-efficacy relationship (EER) exists with vedolizumab.

Answer 1: We thank the reviewer for this encouraging comment.

Comment 2: Ward et al, recently published a review on the same topic.

Answer 2: We thank you for notifying this, and refer kindly to our answer to the same comment of the editorial board (cfr. supra).
Comment 3: The authors conclude that the available data confirm EER of vedolizumab. However, the current body of evidence is not close to being definitive and offers several reasons to be more skeptical of the benefit of trough monitoring with vedolizumab than the authors suggest. The pharmacokinetic profile of vedo differs in many respects from anti-TNF therapy, where TDM has been demonstrated to deliver more clinically effective dosing. Additionally, while antibody development may increase clearance of vedolizumab, available data suggests that antibody development is a less common event in anti-integrin therapy compared to anti-TNF. Trough level alone may be inadequate to predict clinical response and may not yield much benefit over clinical judgment to guide therapeutic decisions. Furthermore, results from cross sectional studies should be interpreted with caution due to heterogeneous study designs, including varying definitions of response and remission. As a result, it is difficult to confirm causation from associations between drug level and reported clinical outcomes. As arguments on both sides are speculative and supported by limited data, additional skepticism might strengthen the article to express the idea that we cannot extrapolate from the anti-TNF data to assume that there will be a clear role for TDM in using vedo. In anti-TNF TDM, the utility has been strengthened by clinical concerns in a patient with secondary loss of response and whether the subsequent medication would best be another in the same class or a medication with a different mechanism. As there is not yet another medication in the same class as vedo and antibody development appears much less, the same utility with vedo is attenuated and the utility of TDM may be more marginal. The authors touch on this but might discuss in more detail.

Answer 3: We fully agree and have adapted the article by implementing a critical review of the promising features and potential drawbacks of TDM for vedolizumab, including a SWOT analysis (figure 1).

Comment 4: The manuscript could also be improved if authors addressed the context of TDM in vedo. It is worth commenting on how to best incorporate TDM with vedolizumab (ie. primary versus secondary nonresponse or proactive versus reactive testing).

Answer 4: We thank the reviewer for this comment, and adapted this in the revised manuscript in the paragraph, entitled ‘Promising features and potential drawbacks’.

Comment 5: Authors could have commented on the differences in reported trough effect between UC and CD that were described in the GEMINI 2 and 3 trials, where the effect was more modest in CD.

Answer 5: We have now commented more on the differences (and similarities) between UC and CD patients throughout the available data, and this when describing the data from clinical trials as well as the data from real-world cohorts.

Comment 6: Lastly, although a minor issue, there are a couple typos as well as awkward phrases in the manuscript which can be improved upon.
Answer 6: We thank the reviewer for noticing this. Corrections were made where deemed necessary.

REMARKS REVIEWER 2

Comment 1: The review is adequate, the subject treated: knowledge about the levels of vedolizumab and its monitoring in inflammatory bowel disease is very well focused on the abstract and on the background.

Answer 1: We thank the reviewer for this encouraging comment.

Comment 2: In the line 51-52 (background) is more adequate, in my opinion review than commentary.

Answer 2: We have adapted the format of the article accordingly (mini-review instead of commentary).

Comment 3: In Current Knowledge: Line 10 the value is in expressed and $\infty$ and should be expressed in $\mu$. It seems a mistake.

Answer 3: This has been corrected.

Comment 4: Osterman MT, Rosario M, Lasch K et al. Aliment Pharmacol Ther. 2019 Jan 20. doi: 10.1111/apt.15113. [Epub ahead of print] Vedolizumab exposure levels and clinical outcomes in ulcerative colitis: determining the potential for dose optimisation. In these study a propensity-score-based case-matching analysis was performed using data from GEMINI 1 and an earlier large population pharmacokinetic study, with vedolizumab clearance or concentration as predictors of clinical remission and response, adjusted for age, weight, anti-tumour necrosis factor alpha therapy history, serum albumin and faecal calprotectin concentrations. Potential vedolizumab concentration targets at weeks 6, 14 and steady state were proposed. Association between early vedolizumab concentrations at weeks 2, 4 and 6 and clinical remission at weeks 14 and 52 was evaluated.

Answer 4: We thank the reviewer for this suggestion and have implemented the results of this article in the revised manuscript (reference 10).

Comment 5: At the end of the review, future prospects are set out in a very appropriate and concise manner.

Answer 5: We thank the reviewer for this comment.