Name of Journal: *World Journal of Gastroenterology*

Manuscript Type: MINIREVIEWS

Manuscript #80255-revised

Unveiling the biological role of sphingosine 1 phosphate (S1P) receptor modulators in inflammatory bowel diseases

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Responses to the comments made by the Reviewers

Dear Editor and Reviewers,

We thank you for the time and effort you have spent in thoroughly reviewing our manuscript. In the revised version, we have addressed all the points raised by the reviewers. In addition, the manuscript has been thoroughly revised for scientific context and language.

Reviewer 1:

This paper mini-reviewed recent literature on S1P in IBD pathogenesis and S1P targetted small-molecule drugs' therapeutic effects on IBD. Comments are below: 1. This is an important and novel piece of work. However, the English grammatical errors detract from the quality of the paper and makes it difficult to read. Please polish the English language furtherly. 2. The introduction, especially the immunological part, is tedious and obscure to follow, recommended adding an explicit schematic figure other than just Fig1.

We have added an explicit schematic Figure 1 to the text section "The role of T lymphocytes and cytokines in the inflamed IBD tissue".

Reviewer 2:

Specific Comments to Authors: The review is focused on discussion of effective therapeutic compounds against inflammatory bowel disease (IBD). The compounds target Sphingosine-1- phosphate (S1P) receptors and constitute a class of oral small-molecule drugs, which are currently in clinical development for IBD and have shown promising effects on disease amelioration. The review is interesting and addresses a novel topic. However, there are several issues to address.

1. Introduction does not reflect the current field of S1P receptor role in the regulation of gastrointestinal diseases. It is very general and does not provide a specific targets

or mention specific substances that will be discussed. For instance, authors did not describe the role of S1P in the regulation of diverse biological process (references should be provided/extended). Introduction also does not direct the reader to other large reviews that provide more detailed description and discussion of this filed. For instance, these review were not mentioned (https://pubmed.ncbi.nlm.nih.gov/32085881/ ; https://pubmed.ncbi.nlm.nih.gov/35158806/ ; https://pubmed.ncbi.nlm.nih.gov/31863815/).

We have updated the Introduction with the suggested recent reviews: "S1P is a highly bioactive molecule…..migration into the gut"(page 4, lines 22-29, page 5, lines 1-8) and mentioned the specific S1P modulators discussed: "Amiselimod (MT-1303)…… migration into the gut" and "S1P receptor modulators…… anti-inflammatory effects" (page 5, lines 5-8, lines 12-14).

2. Authors wrote in the Introduction " ... small-molecule drugs being" – which ones? It is reasonable to list those in clinical trials.

We have listed the S1P modulators in clinical trials in the Introduction: "Amiselimod (MT-1303) …..migration into the gut"(page 5, lines 5-8).

3. The first large subsection is focused in lymphocyte trafficking, however, it is not reflected in the Abstract properly. Authors did not indicate that they will be discussing the role of T cell subtypes, including Th17, Treg etc. Therefore, the abstract should be improved.

We have included data on the role of T cell subtypes in the Abstract: "T lymphocytes play an important role…...T helper cytokine levels was found" (page 3, lines 13-15).

4. Th1/Th17 was mentioned 32 times in the text, however it is not indicated as a keyword. Therefore, keyword list should be extended.

We have updated the keywords and added the term Th1/Th17 (page 3, line 22).

5. The authors also should cite the more recent reviews in the field. For instance, they cite Nielsen et al., 2017 (ref #63), although there are more recent paper in the field from 2020 (https://pubmed.ncbi.nlm.nih.gov/32085881/; https://pubmed.ncbi.nlm.nih.gov/31863815/) and 2022 https://pubmed.ncbi.nlm.nih.gov/35158806/

We have included data from the proposed most recent reviews in the text section "The biology of sphingosine-1-phosphate (S1P) metabolism and signaling in IBD":

"S1P signaling triggered by S1P…… of inflammation in IBD" (page 11, lines 10-18) and "The effect of SphK/S1P/S1PR signaling on linking…… inflammatory gastrointestinal cancers" (page 12, lines 3-24).

6. Authors could separate the Figure 1 into two figures. The second figure could provide a more comprehensive presentation of drugs targeting different S1P receptors. Figure 1 is confusing, it is unclear which drugs target S1P1, or S1P2 etc.

We have modified Figure 1 (it is now Figure 2) and added a new figure (Figure 3) that accurately illustrates the targeting of S1P receptors by specific S1P modulators.

7. Conclusions are too general and do not provide clear author-based support for any of the tested drugs. It does not provide a clear message – which S1P-binding drugs are more promising than others? The whole conclusion is too vacuous and should be re-written, indicating the exact names of the drugs that have higher chances to be used as an IBD treatment (if any).

We have changed the conclusion section and added new data: "The S1P receptor agonists etrasimod and ozanimod…… patients with multiple sclerosis" (page 20, lines 9-26)