

Dear Dr .Ma,

We would like to thank the editor and the reviewers for their conscientious reviews, and insightful comments and suggestions to improve the manuscript. In the response below, we have resolved all issues in the manuscript based on the peer review report and make a point-to-point response to each of the issues raised in the peer review report, and highlighted the revised/added contents with yellow color in the revised manuscript. If somewhere of the revised manuscript is not appropriate, we will spare no effort to revise it again to meet the requirements of editor and reviewers.

I hope my paper could achieve the academic standards of your magazine and be published finally. Thank you very much.

Response to Editor and Reviewers Comments

Manuscript ID: 88715

Title: "**Potential therapeutic targets for nonalcoholic fatty liver disease: Glucagon-like peptide 1**"

Author(s): Yue-Hua Yin, Li-Xuan Sang, Bing Chang

Notes from the Editorial Office:

1 Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

2 RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision.

3 Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to

polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

4 Abbreviations conform to the basic rules

Response: Thank you very much for your careful reading of the manuscript, and thank you for your valuable comments for our manuscript. According to your comments, we made a point-to-point response.

We have repeatedly reviewed the literature to ensure that the abbreviations in the literature follow the basic rules, and have used RCA row keyword searches to ensure that references are selected correctly and selectively. In addition, we have added novel perspectives in an effort to contribute to the treatment of NASH. In order to ensure the correct use of language, we have asked professionals to make speech modifications.

Reviewer reports:

Reviewer #1:

Comments:

Specific Comments to Authors: I read with great interest the letter by Yin et al entitled "Popular potential treatments for non-alcoholic fatty liver disease". This letter will be improved by the addition of more details regarding the results of the trials and mechanism of action of drugs mentioned by the authors. Here are my comments: 1. Results from the combination treatments of semaglutide + cilofexor and semaglutide + firsocostat should be provided in more details. 2. Similarly, cotadutide and tirzepatide efficacy should be given in more details. 3. Which is the mechanism of action of cotadutide, tirzepatide, lanifibranor and aramchol?

Response: Yes, thank you very much for your careful reading of the manuscript, and thank you for your valuable comments for our manuscript. According to your comments, we made a

point-to-point response, we hope to be able to meet the requirements for publication, if you are not satisfied with the revised manuscript, we will make a second revision.

Major comments:

1 Results from the combination treatments of semaglutide + cilofexor and semaglutide + firsocostat should be provided in more details.

Response: Yes, we really appreciate your valuable advice. In a phase II trial of 108 patients with NASH, the combination showed greater improvements in hepatic steatosis, liver biochemistry, and non-invasive fibrosis measured by MRI-PDFF, despite similar weight loss (7-10%), compared to semaglutide monotherapy.

2. Similarly, cotadutide and tirzepatide efficacy should be given in more details.

Response: Yes, thank you for your helpful and valuable advice, We have added more details about the efficacy of cotadutide and tirzepatide in the letter.

3. Which is the mechanism of action of cotadutide, tirzepatide, lanifibranor and aramchol?

Response: Yes, we gratefully appreciate for your valuable suggestion, the mechanisms of action of cotadutide, tirzepatide, lanifibranor and aramchol have been added to our correspondence.

Reviewer #2:

Comments:

Specific Comments to Authors: The authors discuss the potential advantage of combination therapy in NAFLD/NASH, following the recent paper in WJG discussing the role of semaglutide. Considerations are not new. It remains to determine whether combination therapy with sema + colofexor, firsocostat and an abundance of new drugs is really able to improve the results. I have a lot of concern regarding the positive expectations reported in the letter; as far

as I know, cilofexor and firsocostat had been aborted by pipeline of respective companies, and for most combination treatments the results are not much better than with semaglutide alone (except for liver enzymes). I would greatly suggest to down-tune the enthusiasm. If sema works via weight loss, then we'll expect results in the long term, given the impressive results of new antiobesity drugs.

Major comments:

1 The authors discuss the potential advantage of combination therapy in NAFLD/NASH, following the recent paper in WJG discussing the role of semaglutide. Considerations are not new.

Response: Yes, thank you for your nice suggestion. After a recent literature review, the benefits of NASH in the treatment of semaglutide are not as great as expected, and it is inevitable to reduce the popularity of semaglutide.

Moreover, the use of mesa for the treatment of NASH has been studied for several years, and we have revised the name of the literature.

2 It remains to determine whether combination therapy with sema + colofexor, firsocostat and an abundance of new drugs is really able to improve the results. I have a lot of concern regarding the positive expectations reported in the letter; as far as I know, cilofexor and firsocostat had been aborted by pipeline of respective companies, and for most combination treatments the results are not much better than with semaglutide alone (except for liver enzymes). I would greatly suggest to down-tune the enthusiasm.

Response: Yes, thank you for your useful and valuable advice. We re-read the citations and other relevant literature, and it is true that cilofexor and firsocostat have a high incidence of side effects during the administration of cilofexor and firsocostat, and their production has been suspended. In our article, we mainly want to give examples of the benefits of combination medication, and semaglutide alleviates the associated side effects, so we didn't pay attention to thank you for the reminder.

3 If sema works via weight loss, then we'll expect results in the long term,

given the impressive results of new antiobesity drugs.

Response: Yes, thank you for your valuable comments. Although sema has shown potential in the treatment of NASH, the potential value of weight loss drugs and GLP-1 therapeutic targets in the treatment of NASH has to be recognized.

Reviewer #3:

Comments:

Specific Comments to Authors: The title of the manuscript is intriguing, yet not very precise. The abstract summarizes well the content of the manuscript, and the key words are selected appropriately. The manuscript is concise.

However, while briefly describing the current knowledge regarding the treatment options for NASH, the authors offer not much novelty nor different view of the problem. So, the Letter to the Editor does not add much to the field.

Major comments:

1 Specific Comments to Authors: The title of the manuscript is intriguing, yet not very precise.

Response: Yes, thank you for your valuable comments for our manuscript. We've changed it to a more appropriate title.

2 However, while briefly describing the current knowledge regarding the treatment options for NASH, the authors offer not much novelty nor different view of the problem. So, the Letter to the Editor does not add much to the field.

Response: We are sorry that our previous letter was not sufficient to fully express our point of view, and we have revised it in detail. In this regard, please give us another chance, and hope that the revised literature can be affirmed by you.