

May 11th, 2021

Dear Dr. Ke-Qin Hu,

Editor in chief

World Journal of Hepatology

We are sending via web-based submission the revised version of the manuscript N° 64738: "Hepatitis C Virus Failure to Treatment: Clinical Utility of Testing Resistance Associated Substitutions" by Ridruejo et al. We would like to thank the reviewer and editors for their comments and suggestions, which were helpful to improve our review. We hope that the revised manuscript will be suitable for publication.

Thank you in advance for your consideration.

Yours sincerely,

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Referee(s)' Comments to Author:

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to the issues raised in the peer review report. Authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and make point-by-point responses to the issues raised in the peer-review report(s), which are listed below:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The clinical relevance of resistance-associated substitution (RAS) in the era of direct acting antivirals (DAA) for the treatment of hepatitis C is not known. In one hand the efficacy of DAA is very high and independent of baseline RAS, in the other hand in difficult to treat patients (as scarce genotypes, cirrhotic patients or previously treated patients) RAS could be helpful for building the best treatment. Data are scarce; meanwhile this review could be useful for clinicians to make decisions. Limitations: The writing is a bit confusing, It sometimes reach unclear or contradictory conclusions.

The clinical relevance of resistance-associated substitution (RAS) in the era of direct acting antivirals (DAA) for the treatment of hepatitis C is not known.

In one hand the efficacy of DAA is very high and independent of baseline RAS, in the other hand in difficult to treat patients (as scarce genotypes, cirrhotic patients or previously treated patients) RAS could be helpful for building the best treatment. Data are scarce; meanwhile this review could be useful for clinicians to make decisions.

The paper is an exhaustive review of the data we have so far, this is the main strength of the study; however, I think it could be improved before publication.

MAJOR SUGGESTION

- The organization of the paper should be improved. I would advance RAS determination. I think in this order the paper is more clear:

1. Abstract
2. Introduction
3. RAS determination
4. Clinical utility (Naïve/retreatment)
5. Conclusion

Author's reply: The text was modified following the reviewer's suggestion.

MINOR SUGGESTION

1. Abstract. "For this reason only a small percentage of treated patients will not benefit from DAA therapy" I don't understand what you want to say. Than only few patients don't obtain SVR? I don't understand the relation with RAS.

Author's reply: Following the suggestion of the reviewer, the sentence was removed from the abstract, as it was dispensable.

2. Clinical utility

I suggest making two different sections with its titles: naïve patients, pretreated patients.

Author's reply: Manuscript was change following the reviewer's suggestion.

3. The paragraph SOF/VEL should be revised. SOF/VEL is not recommended in Genotype-3 with cirrhosis in EASL and AASLD guidelines. But authors also question the efficacy of GLE/PIB because of a metanalysis that is not yet published and it is no clear how many GT3 patients are included in the studies.

Author's reply: This point has been clarified in the text.

In the latest AASLD update, for infections caused by genotypes 1 to 6, the recommender therapeutic scheme is Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food during 8 weeks.

For Genotype 1, 2, 4, 5, or 6, the recommendation is Sofosbuvir (400 mg) / velpatasvir (100 mg) during 12 weeks.

NOTE: Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, see HCV guidance for treatment recommendations.

EASL guidelines do not make any differences between genotypes.

The cited meta-analysis has been listed in the review reference list as follows:

48.- Zhang Y, Jiang X, Zhao Y, Xu Y. Effect of baseline resistance-associated substitutions on the efficiency of glecaprevir/pibrentasvir in chronic hepatitis C subjects: A meta-analysis. J Viral Hepat. 2021; 28(1):177-185. [PMID: 32961624 DOI: 10.1111/jvh.13409].

Guidelines recommend the use of GLE/PIB, in Gt_3 patients without previous resistance. Please clarify these data. Even more in the next paragraph, authors recommend RAS testing of HCV-3 patients (all of them) while guidelines recommend this strategy only in GT-3 cirrhotic patients.

Author's reply: This has been clarified in the text.

4. The results of POLARIS 4 are not clear. Overall SVR 98% (178/182) vs 90% (136/151) in retreated with SOF/VEL (retreated or pretreated?). Overall, included patients pre-treated and not-pretreated or only not pretreated?

Do the authors recommend perform RAS before SOF/VEL/VOX? The authors said that real live studies supported high SVR.

Author's reply: Polaris 4 population has been clarified. RAS before SOF/VEL/VOX is not recommended and this was included in the text.

5. CONCLUSIONS

I will focus on the indication of RAS in naïve and pretreated patients. The authors repeat what have just said in pretreated patients.

Author's reply: This has been clarified in the text.

LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Author's reply: Following the reviewer's consideration, a thorough revision of the manuscript was carried out. The grammar was revised, and some sentences were rephrased to improve the text's readability. In addition, the manuscript was sent for grammar revision to Silvina Heisecke who works in the CEMIC-CONICET Scientific Text Writing and Editing Service belonging to CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas, National Council of Scientific and Technical Research)

EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

Science editor:

1 Scientific quality: The manuscript describes a minireview of the hepatitis c virus failure to treatment. The topic is within the scope of the WJH.

(1) Classification: Grade C;

(2) Summary of the Peer-Review Report: This review could be useful for clinicians to make decisions. The questions raised by the reviewers should be answered;

(3) Format: There is 1 table and 1 figure;

(4) References: A total of 64 references are cited, including 30 references published in the last 3 years;

(5) Self-cited references: There are 9 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated.

Author's reply: The manuscript was modified following the editorial requirements and three self-citations were removed in order to decrease the self-citation rate below 10%.

(6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

2 Language evaluation: Classification: Grade B.

3 Academic norms and rules: No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not been previously published in the WJH.

5 Issues raised:

(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and

Author's reply: Following the suggestion, the figure was provided using PowerPoint to ensure that the editor can reprocess all graphs or arrows or text portions.

(2) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If

the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Author's reply: Figure 1 was originally created by the authors for this manuscript and was not re-used or published elsewhere.

6 Recommendation: Conditional acceptance.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.