Format for ANSWERING REVIEWERS

July 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11818-edited.doc).

Title: Predictability of IL-28B-polymorphism on protease-inhibitor-based triple-therapy in chronic HCV-genotype-1 patients: a meta-analysis

Author: Nicolae-Catalin Mechie, Christian Röver, Silke Cameron, Ahmad Amanzada
Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 11818

The manuscript has been improved according to the suggestions of the reviewers:

1. We would like to thank you for your review and suggestions to improve our manuscript. We have taken them into consideration. We have highlighted with color the additional information. In the following we would like to comment on the reviewer's suggestions

Answer for the topics made from Reviewer 02458152

Abstract:

1. "The authors stated in the abstract that they searched PubMed, but in page#7, line#1 they did mention of Medline. Although PubMed and Medline do overlap the 2 databases are not in anyway the same. They should clarify the databases they searched"

   We thank the reviewer for this comment. We clarified our search in. (Page 4 line 1 and Page 8 , Para 3 , Line 1)
   "We searched in PubMed, Web of Knowledge, and the Cochrane Library databases"

2. "In the result section and elsewhere in the text, the authors made reference to 'odds' and odds ratio. Please, state which effect you used. If they mean odds ratio which I am sure is the case, they should state that."

   Again, we thank the reviewer. The "odds" represents the "chances" for an SVR, "odds ratio" (OR) is used when we compare the therapies, for example if we compare dual with triple therapy. We have included in the legend of Fig 2 and Fig 3 the equivalent of OR with the

explication "The differences between the shown estimates correspond to odds ratios". (Page25 , line 4, 5 and 8,9)

3. "Please delete the expression ' however it indicates a beneficial effect' in para#3, line#8-9 of the abstract"

Thank you for this suggestion. The expression in Page4 para3, line 8-9 was deleted.

Methods

1. "Pg#7, para#1, line#1: Instead of we have searched …….the authors should write we searched……"

Thank you for this suggestion. We corrected the sentence in (Page#8, para 1 line 2) accordingly.

2. "pg#7, para#1, line 2: please delete abstract and full length. What does full length mean here? if it's full text of the article please state that. I am not sure if the authors used results from abstracts. If that is the case, please state why you decide to use abstracts instead of full text."

Thank you for this important comment. We have searched full text and abstracts. Now we explain why we included also abstracts in this meta-analysis (page#8, para 1, line# 10-14).

3. "It is a bit confusing how the authors describe the search strategy. Please, clarify your search strategy. As it stands it is messy (please see The Meta-analysis of Observational Studies in Epidemiology consensus statement (MOOSE): Stroup DF et al. JAMA. 2000;283:2008–12). The authors should also provide an appendix describing in detail the search strategy."

4. "The criteria used to screen the studies were not clearly stated. Pls re-phrase you criteria (see the BMJ reference above)."

Thank the reviewer for the comments number 3 and 4. Below we summarize the items of the MOOSE study and state where they were included in our manuscript.

We rephrased our criteria and the following points correspond to the MOOSE table form the recommended journal:

- "Reporting of background":

All the MOOSE points are presented in our Introduction see (Page 6- 7)

- "Reporting the Search Strategy":

-" Qualification of the searchers"

see (Page #1, Para 3 Line #1-10)

-"Search strategy, Time Period, Databases and Key Words"

see (Page 8, Para 1 Line 2-10)

"Efforts to include all available studies, including contacts with the authors: "

see (Page 8,Para 1 Line10-15, and Para 3 Lines 2-4.)

-"Use of hand searching and software used: "

see (Page 8, Para 1, Line 15-17)

-"Method of addressing the abstracts "

see (Page 8 , Para 1 Line 10-13)

- "Method of addressing articles published in languages other than English"

see (Page 8, Para 2, Line 4)

- "Reporting of Methods": Assistant of relevance and statistical methods:

see (Page 9,Para 1, Line 1-10)

-"Reporting of results": Graphic:

see Fig 1, 2, 3 attached

-"Table giving descriptive information:"

see (Table 1 Page 26) was improved.

-Results of sensitivity /subgroup analysis:

see (Page 11)

- "Reporting of discussion": assessment of quality of studies

see(page 14, Para 4 Line 3-5)

-Alternative explanation:

see(Page 14, Para1 Line 1- 5, Para 2, Line 1-11)

-Generalization of the Conclusion:

see (Page 15, Para 1, Line 1-9)

-Conflict of Interest:

see (Page 16, Para 1,Line 1,2)

5. " I am wondering if the authors also search the reference lists of relevant articles. If they did they should state that. Else, they should state why they didn't."

Thanks the reviewer. We have integrated this suggestion in our manuscript. "For consistency we refrained from contacting the authors of the individual studies." (Page 8, Para 3,Line 3-4)

6. "Throughout the manuscripts the authors have been using reference and sometimes studies. I recommend they stick to 'studies' instead of 'reference.'"

Thank you to the reviewer. We changed to "studies" instead of references throughout the manuscript.

7. "In the inclusion criteria, the authors stated ' no English reference'. It's not clear to me what they mean"

Thanks the reviewer. We have rephrased: "Only articles in English were included." (Page 8, Para 2 Line 4)

8. “Revise the sentence ‘2 authors independently made the data extraction’ on pge#7,para#3, line#1”

Thanks the reviewer, this sentence was revised “The studies were reviewed independently by two authors (NCM and AA)”. (Page 8, Para 3, Line 1)

9. “pg#7, para#3, line#2-3: Move ‘the statistical analysis was performed by CR (It wasn’t necessary to state the person who did the analysis here) to the next paragraph.”

Thank you to the reviewer, this sentence was moved to the next paragraph (Page 9 , Para 1, Line 1)

10. “Figure 1 is messy. It is poorly presented. It doesn’t match with the eligibility criteria in the text. I strongly recommend modification of this figure to conform to standard practice”

Thank the reviewer for this important comment. We have modified Fig 1 according to the standard practice. (See Fig 1 attached)

Results.

1. “The entire sentence from para#1, line#1-7 is inaccurate. Please modify figure and revise the sentence accordingly.”

   Thanks again to the reviewer for this important comment. This paragraph was rewritten. (Page10, Para 1,)

2. “line#6 should read…..This meta-analysis was based on 10 studies. ‘Not based on the remaining references’”

   Thank you for your suggestion; we have rephrased the sentence. (Page 10, Para 2 Line 1)

3. “I am not sure why the authors decided to number the references in the tables. Again I was expecting to see more information about eligible studies in Table I: The information in the Table and in the text is scanty. The authors should consider revising the table”

   Thanks again the reviewer for this comment. In Table 1 we included the data from the 10 studies included in our meta-analysis. IL-28B SNP, SVR and pretreatment Type (INF naïve or experienced) are shown. The other details of the studies, like time of therapy, RVR etc. were not analysed in our Meta-analysis as they are not included in our endpoints. In the meeting abstracts, which were included in our study, only this data was available.

4. “The column containing relevant papers should be labelled reference.”

   Thank the reviewer; we have labeled the column in Table 1 as “reference” (page 26)

5. "The sentence beginning with…. Regarding SMP and FLP our search should be revised (para#1, line#14-15)"

   Thank the reviewer; the sentence was revised "For SMP and FLP only one study could be included for each of them" (Page 10, Para 2, Line 8).

6. "para#2: I am not sure if the point estimates reported by the authors were odds or odds ratio. I suspect the latter. The authors have used in some cases odds and in other cases odds ratio. They should be consistent."

   Thank you for this important comment. We discussed with our statistician. The "odds" represents the "chances" for an SVR, "odds ratio" (OR) was used when we compared the therapies, for example when we compared dual with triple therapy. We have included in the legend of Fig 2 and Fig 3 the equivalent of OR with the following explanation "The differences between the shown estimates correspond to odds ratios" (Page 25)

Discussions:

1. "The authors did mention only one limitation in their study. I suggest they add more discussion on this."
   Again, thanks to the reviewer. We added more discussion regarding the limits of our study. (Page 14, Para 5, Line 5-8. Page 15, Para 1 Line 1-2)

Answer for the topics made from Reviewer 02860745

1. **Unclear database:**

   Thank you for this important comment**.** We clarified our search in (Page 8 line 1) and Fig 1 was revised accordingly.

   "We searched in PubMed, Web of Knowledge and the Cochrane Library databases"

2. **"The hole paper mentions odds is that correct or do you mean odds ratio:"**
   Thank you for this important comment. We discussed with our statistician. The "odds" represents the "chances" for an SVR, "odds ratio" (OR) was used when we compared the therapies, for example when we compared dual with triple therapy. We have included in the legend of Fig 2 and Fig 3 the equivalent of OR with the following explanation "The differences between the shown estimates correspond to odds ratios "(Page 25)

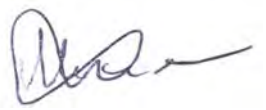
3. Figure 2 and 3, indicate of beneficial effect, information on axis.

   We thank the reviewer for this suggestion.
   Figure 2 and 3 represent the "odds" which are the "chances" or events for an SVR (odds=p/(1-p), where p represents the probability. The Odds ratios (OR) correspond to the

differences between the shown estimates. The beneficial effect is represented by the difference between the odds for CC vs nonCC genotype patients. A protease inhibitor has a more potent beneficial effect on CC-genotype patients if the difference is greater. We have introduced in the legend of Figure 2 and 3 the explanation "A greater difference of odds between the both IL-28B-genotype corresponds to a more beneficial effect." (Page 25)

We would be looking forward to the publication of our manuscript in World Journal of Hepatology.

Sincerely yours,
Nicolae Catalin Mechie



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