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Professor Ma

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Dear Professor Ma,

On behalf of all authors, I am deeply grateful to you and the reviewers for the expertise comments and suggestions on how to improve our manuscript entitled "Efficacy and Safety of Directly Acting Antivirals for the Treatment of Chinese Chronic Hepatitis C Patients in a Real-World setting." Based on the reviewers' comments, we revised our manuscript, all of the revisions were highlighted in the revised manuscript with track changes and cited in the response letter.

We revised the manuscript and responded to questions and comments point-by-point as follows:

COMMENTS TO AUTHORS (Reviewer's code: 00053556)

1. TITLE Reflect the major content of the article, however it is better to add the word combined Directly Acting Antivirals, as the combined therapy is the study topic.

Answer: Thanks for the reviewer's expertise suggestions, we have renamed the title as "Efficacy and Safety of combined Directly Acting Antivirals for the Treatment of Chinese Chronic Hepatitis C Patients in a Real-World setting" and revised the relevant terms in body text **(line 6, 39, 70, 87, 124, 249, 270, 275, 290, 300, 310, 313, 320).**

2. ABSTRACT It gives a clear delineation of the research background, Result section: “significantly higher than baseline levels” is better to be replaced by significantly increased than baseline levels. This has to be corrected. The aim and the conclusion were clearly identified. The conclusion provided by the authors was not convincing and has to be revised. This may be because of the small sample size.

Answer: According to the reviewer’s comments, we had replaced “significantly higher than baseline levels” with “significantly increased than baseline levels” **(line 62, 84, 261).** As the reviewer’s comments, small sample size resulted a reduced credibility of the conclusion, we will enlarge the sample size to further verify this finding in the following work. For this study, to ensure the convincing conclusion, we turned to statisticians in biostatistics department for help, and repeated measures analysis of variance was recommended to compare changes of clinical indices among different time points, this method gave the *P* value considering the sample size. Considering the complex comorbidity and drug combination in the real world, this finding will remind physicians of implementing close renal function monitoring in patients receiving combined DAAs treatment.

3. INTRODUCTION Provides insufficient background regarding the studied topic, advantages and disadvantages of DAAs were not fully elaborated; the authors has to emphasize the oral use, short duration and minimum toxicity of DAAs. Meanwhile, cost is still an obstacle in a lot of countries especially developing ones. Also the value of combined rather than monotherapy is better to be elucidated. It was mentioned that China has the greatest number of chronic hepatitis

C (CHC) cases worldwide. The common genotypes were missing and are better to be mentioned.

Answer: Thanks for the reviewer's expertise suggestions. We have supplemented the details regarding advantages and disadvantages of DAAs regarding the oral use **(line 97-99; Ref. 5)**, short duration **(line 99-102; Ref. 6)**, minimum toxicity **(line 104-106)**, combination therapy **(line 102-104; Ref. 7)** and cost **(line 110-114; Ref. 17)** and the common genotypes of HCV in China **(line 116-118; Ref. 19)**

4. MATERIALS AND METHODS: Full description is provided for this section. Sufficient experimental data were provided; however, the following remarks have to be considered: Patients: Total number of patients was missing in this section and has to be added. HCV genotypes: For the work to be reproducible, more details are better to be mentioned regarding amplification condition as well as PCR product purification and RFLP analyses.

Answer: Thanks for the reviewer's expertise suggestions, we have added the total number of patients excluded **(line 138-141)** and elaborated the process regarding amplification condition **(line 175-177)** as well as PCR product purification **(line 183, 184)** and RFLP analyses **(line 184, 185)**.

5. RESULTS: An overall theoretical analysis of the study results is well covered. ? Baseline characteristics of enrolled patients: P value is missing. ? Changes of clinical indices before and after DAAs treatment: It was mentioned that ALT and AST levels were significantly lower than baseline levels, although both within the range of normal accepted values. ? AEs during DAAs treatment: "The incidence of AEs during…….: It is the frequency rather than the incidence and

this has to be corrected. ? Table (3): It is frequency rather than incidence. This has to be corrected. AEs of values (fever, depression,...) have to deleted from the table. Their data have been already mentioned within the text.

Answer: Thanks for the reviewer's expertise comments. We supplemented an overall theoretical analysis of the study results in "Discussion" **(line 286-288, 292-294, 300, 301, 303-305, 308-315, 319, 320)** and added the results of interactive effects of DAAs regimens and time points on the changes of clinical indices **(Table 2, line 268-270)** and the missing *P* value in **Table 1** according to the reviewer's suggestions. ALT and AST levels at baseline were both over the range of normal values, and we incorrectly took the AST value at the end of treatment for the value at baseline (AST: 50.8 ± 33.1 vs 24.4 ± 10.4, P01<0.001; **24.4 ± 10.4** vs 22.4 ± 7.0, P02<0.001) and we had corrected it in the revised maunscript **(line 256).** We had replaced "the incidence of AEs" with "the frequency of AEs" **(line 65, 70, 127, 276, 287, 299)** and deleted the value of AEs (fever, depression, neutropenia, thrombocytopenia) from **Table 3** according the reviewer's expertise suggestion.

6. Discussion: The section is almost well organized; however, an overall theoretical analysis concerning the provided data is partially covered. More details are required concerning the evaluated results.

Answer: Thanks for the reviewer's expertise suggestions. We supplemented a comprehensive theoretical analysis concerning the provided data **(line 286-288, 292-294, 300, 301, 303-305, 308-315, 319, 320)**.

7. REFERENCES: Relevant and sufficient updated references were adequately cited. Ref. (12): The year is missing.

Answer: Thanks for the reviewer's comments, we have added "the missing year" in Ref. (12) **(line 429; ref. 13 in revised manuscript).**

COMMENTS TO AUTHORS (Reviewer's code: 02527569)

This study summarizes the real-world data when using DAAs against HCV. The data are concisely summarized and no major concerns exist. I have only one comment. In figure 2, the authors showed significant differences but it is hard to believe it because of the relatively large SD. Statistical methods should be re-considered carefully.

Answer: Thanks for the reviewer's affirmation and comment for our work. We used repeated measures analysis of variance to make comparison of clinical indices among different time points. To ensure the appropriate statistical method adopted, we turned to statisticians in Biostatistics Department of Peking University First Hospital before the beginning of the study, and teacher Zhu advised us to use repeated measures analysis of variance to carry on the comparison. We supplemented the biostatistics statement in the attachments. According to the reviewer's comments, we consulted teacher Zhu about this questions. She said repeated measures designs allowed a subject to serve as their own control, the standard deviation might have no significant effect on statistical significance of differences. Meanwhile, we reanalyzed the data to rule out the possibility of wrong operation and obtained the same results.

We hope that our revised manuscript will meet your expectations. Thank you again for your time and consideration.

Best regards

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