

## RESPONSE LETTER

NAME OF JOURNAL: World Journal of Gastroenterology

Manuscript Number: 49851

### **Dear Editors and Reviewers:**

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Tenofovir is a more suitable treatment than entecavir for chronic hepatitis B patients carrying the naturally occurring rtM204I mutations" (manuscript number 49851). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research.

We have carefully revised the manuscript based on your suggestions, and the revised manuscript is attached. The revised portions are marked in red with track changes. The guidelines and requirements from the editors have been checked or provided throughout the manuscript. We hope this paper in its current revision is acceptable for the publication in "World Journal of Gastroenterology".

We deeply appreciate your further consideration of our manuscript and look forward to hearing from you.

Thank you and best regards.

**Below please find the responses to all comments.**

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**Reviewer 1 (03269732)**

**Specific comments to authors :**

In this paper, a new LNA-RT-PCR method was used to investigate prevalence of the naturally-occurring rtM204I mutations in treatment-naïve CHB genotype C2 patients and their influence on antiviral therapy. This study confirmed that rtM204I-mutations were more frequent in patients with liver-fibrosis. Tenofovir is more suitable than entecavir for CHB-patients infected with naturally-occurring rtM204I-mutations. The article is not innovative and has a statistical error. Recommendations are listed in the commentary to the article.

(Answer) We very appreciate reviewer's kind suggestions, As reviewer suggested, the statistical error has been corrected, and the manuscript has been revised according to reviewer's recommendations.

**Reviewer 2 (01221188)**

**Specific comments to authors :**

Choe. *et al* evaluated the association between rtM204I variants and clinical characteristics. This study shows that rtM204I variants are associated with the progression of liver fibrosis and the poor response of NA treatment.

Minor revisions:

1) The authors should describe the hypothesis of the reason why rtM204 I variants are associated with liver fibrosis and NA treatment failure.

(Answer) We thank the Reviewer for these important comments. Although the mechanism is unclear, the possible reason for the significant association between naturally occurring rtM204I variants and liver fibrosis might be related to HBV genotype C. Because, naturally occurring mutations, such as variant in the pre-S region of HBV, are associated with liver cirrhosis, in chronic hepatitis B patients, especially those infected with genotype C. Therefore, we suggested that progression

of fibrosis or cirrhosis might be related to spontaneous occurrence of rtM204I mutations de novo, as well as infection with naturally occurring pre-S variants, in treatment-naïve patients infected with HBV genotype C2 strains. We mentioned these sentences on the “Discussion” section of the revised manuscript, as the reviewer’s comments.

2) The patient number of individual group should be described in Table 7.

(Answer) We thank the Reviewer for this comment. We add the patient number of individual group in Table 7 in the revised manuscript.

3) The names of drugs with the low genetic barrier should be written in Table 7.

(Answer) We thank the Reviewer for this comment. We add the name of drugs with low genetic barriers in Table 7 of the revised manuscript.

4) The details of NA treatment should briefly be described in the text.

(Answer) We thank the Reviewer for this comment. We briefly described the details of NA treatment on the “Result” section (subtitle: baseline characteristics of enrolled 403 CHB patients) of the revised manuscripts).

### **Reviewer 3 (02540510)**

#### **Specific comments to authors:**

The study is interesting and novel. The data has been presented well and merits publication.

(Answer) Thank you very much for the thorough review and the positive comments, which encourage us a lot for the better research in the further.

**Reviewer 4 (03486791)**

**Specific comments to authors:**

Spontaneous rtM204I mutations can exist in NAs-naïve patients with CHB genotype C infection. In this study, the authors aimed to investigate prevalence of the naturally-occurring rtM204I mutations in treatment-naïve CHB genotype C2 patients and their influence on antiviral therapy. 410 individuals were included in the study. They found that seventeen samples (4.1%) were identified as carrying rtM204I variants. They have concluded that the newly-developed LNA-RT-PCR method could detect naturally-occurring rtM204I-mutations with high-sensitivity and mutations were more frequent in patients with liver-fibrosis. Tenofovir is more suitable than entecavir for CHB-patients infected with naturally-occurring rtM204I-mutations. I think this is a good study, and the manuscript is well written; also the tables are all appropriate.

(Answer) We thank the reviewer for the excellent summary of our research and the positive comments

**Editors**

Response:

1. We have changed the abbreviations in the "Title" to their full name.
2. We revised the "Short running title" not to exceed 6 words.
3. We provided the author- affiliations including address and postcode.
4. We have modified the content of author contributions accordingly.
5. We have submitted an audio core tip whose format is mp3 on the system.
6. We have added article highlights accordingly.
7. For References, we have modified the format of them accordingly.
8. We have modified the title of Table 1, Table 2, and Table 3, accordingly.

9. We have revised the notes in the “Tables” accordingly.

10. We explained all the abbreviations in the Table.

11. We provided the decomposable Figures, and organized them into PPT file.