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January 25, 2017

Dear Jing Yu:

Thank you very much for your e-mail dated 19-Dec-2016, concerning our paper (#ID 31434) entitled, “**Hepatitis B Virus Infection and Alcohol Consumption**” We have revised the manuscript extensively according to the reviewers’ comments and would like to submit the revised manuscript. Below are our point-by-point responses to the reviewers’ comments.

#### **Responses to Reviewer 1**

The authors should bring more details about the relationship between the protective immune response vs the harmful autoimmune response in HBV infection in the context of alcohol intervention.

>We thank the reviewer for pointing the important issue. As HBV is not directly cytopathic (**page 6, line 14**), the liver injuries in chronic HBV infection are mediated by excess host immune response. To our knowledge, however, the relationship between the protective versus harmful immune response in HBV infection remains to be fully defined in the context of alcohol intervention. We added the discussion in the revised manuscript as follows: ‘A weakened immune response may result in not only persistent HBV infection, but also immune-tolerant state. On the contrary, excess immune response can cause hepatitis exacerbations. The relationship ... (**page 8, lines 12-16**).’

#### **Responses to Reviewer 2**

The mechanisms described on Fig. 1 are OK, but too general for this type of review. Please also add number of citation on page 5 concerning the sentence: "...deposition of the majority of excess extracellular matrix (predominantly collagen types I and III...)".

>We thank the reviewer’s comment. We added the ‘*ECM deposition (ex. collagen types I and III)*’ to the **Figure 1**.

### **Responses to Reviewer 3**

1. The heading 'Basic Background' is vague. As this section addresses potential mechanisms of alcohol- and HBV-related liver disease progression and experimental studies of the impact of alcohol on HBV replication, transcription and immune responses, a more appropriate title for this section might be 'Potential Mechanisms of Alcohol- and HBV-related Liver Disease' or similar. Alternatively, ...

>As the reviewer kindly suggested, we divided the '*Basic background*' section (**starting at page 5**) into two parts with the first one dealing with '*Mechanisms of alcohol- and HBV-induced liver damage*' and the second one dealing with '*Interplay between alcohol and HBV in liver disease progression*', and then broke the second large part into three paragraphs.

2. In some instances the findings of previous studies are 'listed' without relating the findings to one another or discussion of the strengths/weaknesses of the study...

>We agree. We added '*similarly*' (**page 7, line 14; page 11, line 9**), '*in contrast*' (**page 9, line 10**), or '*consistent with clinical observations*' (**page 7, line 19**) where appropriate, so that readers can understand that these studies were related to each other.

3. The concluding summary sentences at the ends of the 'Light-to-moderate alcohol...' and 'Heavy alcohol consumption...' sections are helpful.

>As the reviewer recommended, we added the short summary at the end of the '*Alcohol consumption and outcome of antiviral treatment*' section (**page 13, lines 19-22**). The summary sentence has also been put at the beginning of the '*Interplay between alcohol and HBV in liver disease progression*' section (**page 7, lines 2-5**).

4. In the 'Genetic Factors' section, the discussion of genetic polymorphisms that are associated with HBV-related liver disease should be expanded.

>We added the sentences regarding 1) SNPs near *HLA-DPA1* and *HLA-DPBI* genes (**page 14, lines 21-23**), 2) SNPs near *INST10* gene (**page 14, line 23-page 15, line 5**), and 3) SNPs near *IL28B* gene (**page 15, lines 6-10**). In addition, we have summarized the 'Genetic polymorphisms associated with HBV infection' in a new Table 4.

5. The referencing style for these tables should be brought into line with one another.

>We brought the referencing style for the **tables 1-3** into line with one another.

6. In the 'Conclusions' and 'Core tip' sections it is stated strongly that alcohol abuse can impair the response to interferon-alpha therapy.

>As the reviewer stated, there is no compelling evidence that alcohol abuse can impair the response to interferon- $\alpha$  therapy in chronic hepatitis B patients. We therefore toned down our conclusion on this topic in the 'Conclusion and perspectives' (**page 16**) and 'Core tip' (**page 3**) sections.

7. The Figure 1 figure legend is very brief and should be expanded upon.

>We agree. We made the **figure legend** more detailed.

Yours sincerely,

**Masaru Enomoto, M.D.**