

August 25, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 20990-Revised manuscript). According to the reviewer's comment, we changed the title in the revised version.

**Title:** Factors associated with the response to interferon-based antiviral therapies for chronic hepatitis C

**Authors:** Hirayuki Enomoto, Shuhei Nishiguchi

**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 20990

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer.

(1) Response to Reviewer 2273508's comments

This is a review about interferon treatment for chronic HCV infection. The content is quite complete and updated. However, for the role of anti-IFN- $\alpha$  neutralizing antibodies after IFN- $\alpha$  treatment, the authors have written a long paragraph to suggest that anti-IFN- $\alpha$  neutralizing antibodies may play a role in drug resistance to IFN- $\alpha$  treatment. This opinion appeared not well accepted so far. In the Table 2, the authors just list how many patients with the anti-IFN- $\alpha$  neutralizing antibodies were non-responsive to IFN- $\alpha$  treatment, or the % of non-responsive patients having this antibody. They did not show how many patients responsive to IFN- $\alpha$  treatment having the anti-IFN- $\alpha$  neutralizing antibody and the p value was significant or not. Since this is a review article, not a research original article, the authors should also mention the negative opinion about the role of anti-IFN- $\alpha$  neutralizing antibodies related to drug resistance to IFN- $\alpha$  treatment. They need to be more neutral in delivering the scientific comments and avoid personal bias.

*Responses:*

*Thank you for your valuable comments. According to your comment, we described the number of patients or the percentages of non-responsive patients with anti-interferon- $\alpha$  neutralizing antibodies and the p values in Table 2. In the revised version, we excluded control (non-treated) patients in the study cohort and changed the number of patients in some of the included references.*

*Although we were invited to write a review article in relation to our recent study (Matsuda F, et al., Anti-interferon- $\alpha$  neutralizing antibody is associated with nonresponse to pegylated interferon- $\alpha$  plus ribavirin in chronic hepatitis C, Journal of Viral Hepatitis, 2012, 19, 694–703), we also should have included the negative opinion of anti-interferon- $\alpha$  neutralizing antibody. In the revised version, we cited a new reference (No. 35) and described additional sentences in the text (Page 10: underlined) and in Table 2. In addition, we also mentioned that the role of anti-interferon- $\alpha$  neutralizing antibody had not been fully confirmed in the “Conclusions” section (Pages 12: underlined).*

## **(2) Response to Reviewer 3020350's comments.**

The authors discussed in this manuscript the viral and host factors associated with the response to pegylated and non-pegylated IFN- $\alpha$ -based therapies for chronic hepatitis C. Generally the paper is of interest and well-written with a few amendments necessary.

1. In the “Conclusions” part, in the first sentence “Because of its antitumor effects, IFN treatment is still important I HCV-infected patients, particularly in daysnese patients who are at a high risk of developing HCC”. What is the meaning of the word “daysnese” or if it is a mistake in word's spelling?

*Response:*

*The word “daysnese” should have been written as “Japanese.” We apologize for this oversight and have corrected the mistake in the revised manuscript. Thank you for your careful review.*

2. In the “References” part, the format of all references should be the same. But there are some references with different formats. For example, no. 7, 21, 22 etc.

*Response:*

*We unified the format of the references. We again thank you for your careful review.*

3. It may be more perfect if the authors can provide some clinical information regarding IFN- $\alpha$  treatment of chronic hepatitis C from other countries (such as USA, China and European country etc.) except Japanese documents. Because World Journal of Gastroenterology is an international journal.

*Response:*

*Thank you for your helpful comment. In the revised manuscript, we mentioned the current APASL guideline, as well as those of the AASLD and the EASL, in the first paragraph of the “Conclusions” section (Page 12: underlined).*

(3) Response to Reviewer 2922531's comments.

This article is a comprehensive and elaborate review of factors associated with the response to interferon-based therapies for chronic hepatitis C. Additionally, some recent findings regarding the role of anti-IFN- $\alpha$  neutralizing antibodies in the impact of IFN- $\alpha$  based therapy will also be described. This article is suitable for World Journal of Hepatology. I think some minor revision will improve the quality of this article.

Considering the content of this manuscript, I suggested that the title should be adjusted as "antivirus therapies" more than "interferon-based therapies".

*Response:*

*Thank you for your thoughtful suggestion. Since we did not describe IFN-free antiviral therapies in the present paper, we used "interferon-based antiviral therapies" in the title of our revised manuscript.*

In the abstract, too many words in the background or introduction of HCV and IFN. The structure should coincide with the manuscript. What are the main virus factor and the main host factor? What is the main conclusion of your recent study? In the end of "Viral factors associated with the response of HCV infection to IFN treatment" and "Host factors associated with the response to IFN treatment for HCV infection", a more detailed description of "the amino acid sequences in the core region and NS5A region" and "genotype of SNP" seems to make the article more deeper.

*Response:*

*Thank you for your valuable comments. We added sentences to describe the viral and host factors (Pages 7 and 8: underlined). Additionally, we rewrote the entire "Abstract" section.*

I think that a new part is better than present structure or the part of your study. "We studied a total of 129 patients who had received Peg-IFN- $\alpha$  plus RBV treatment....."

*Response:*

*Thank you for your comment. We generated a new section to describe our recent studies.*

In the part of conclusion, the structure should be rearranged. To clarify the virus factors, the host factors, mutations of HCV resulting in resistance to DAAs, the role of anti-IFN- $\alpha$  neutralizing antibodies, and your new results.

*Response:*

*Thank you for your helpful comments. We altered the structure of the "Conclusions" section to clarify the viral factors, host factors and our findings with regard to anti-IFN- $\alpha$  neutralizing antibodies.*

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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