

October 6, 2017

Prof. Clara Balsano,
Editor-in-Chief, World Journal of Hepatology

Re: Manuscript No. 35997 by Ozono et al.

Dear Prof. Clara Balsano,

Thank you for your letter and reviewer's comments regarding our manuscript. I am sending a revised version of our manuscript "Efficacy and Safety of Sofosbuvir and Ledipasvir in Japanese Patients Aged 75 Years or Over with Hepatitis C Genotype 1." by Ozono *et al.*, which I should like to submit for publication in *World Journal of Hepatology*.

Our point-by-point reply to the reviewer's comments is as follows.

Reviewer #1 (Reviewer's code: 00199582)

(COMMENT 1.) In the last line of page 1, authors should review if they really meant "Department of Gastroenterology and HEMATOLOGY" or if they meant "Hepatology".

(REPLY) Gastroenterology and "Hematology" is correct.

(COMMENT 2.) In page 5 (Abstract) and in page 12 (Results), authors should review the percentages of SVR, since it is not likely that SVR in the overall population could be higher than SVR in its subgroups (SVR in the overall population should probably be between the SVR values of the subgroups).

(REPLY) Exactly, SVR in overall population was wrong. 99.2% is accurate, and I corrected percentage of SVR in Abstract and RESULTS.

(COMMENT 3.) In page 12, authors should rewrite the last sentence of the 1st paragraph: baseline platelet count and glomerular filtration rate were lower and FIB4 was higher in the elderly.

(REPLY) We rewrote the sentence that were pointed out in RESULTS (1st paragraph).

(COMMENT 4.) In page 12, in the 2nd paragraph, authors should review the 5th sentence, since Table 2 does not evaluate the various parameters according to age group, but according to SVR.

(REPLY) Exactly, we have evaluated the SVR12 rate according to clinical and demographical factors, but not age group. Therefore, we deleted the “age” in the sentence in RESULTS (2nd paragraph)

(COMMENT 5.) Authors should inform which age group relapsers belonged to.

(REPLY) We added the informations in RESULTS (2nd paragraph)

(COMMENT 6.) In Results, authors should inform Child-Pugh classification of cirrhotic patients.

(REPLY) We added the information of Child-Pugh classification in RESULTS (1st paragraph).

(COMMENT 7.) In page 14, authors should discuss why their sample had only 32% of HCV patients over 75 years, while they state that people with HCV in Japan account for more than 50% of patients.

(REPLY) Elderly patients accounts for the majority of those with advanced cirrhosis (Child-Pugh class B or C), and patients with this condition were excluded from the present analysis. It is suggested that this is the reason for the relatively low proportion of elderly patients (≥ 75 years) compared with younger patients (< 75 years) in our study.

We added the above sentences in DISCUSSION.

(COMMENT 8.) In page 15, authors should consider changing the sentence “Elderly patients in the present study were more likely to develop advanced liver fibrosis...” to “Elderly patients in the present study were more likely to have advanced liver fibrosis...”.

(REPLY) We changed the sentence that were pointed out in DISCUSSION.

(COMMENT 9.) Authors should realign columns in all 3 tables.

(REPLY) We realigned columns in all 3 tables.

(COMMENT 10.) In the title of Table 2, “SVR12” should be spelled out.

(REPLY) We spelled out SVR12 in the title of Table 2.

(COMMENT 11.) In Table 3, authors should show adverse effects according to age-group.

(REPLY) We exhibited adverse effect according to age-group in Table 3.

Reviewer #2 (Reviewer's code: 02529596)

We thank the reviewer for his comment.

Reviewer #3 (Reviewer's code: 02540266)

(COMMENT 1.) The affiliation of author is department of gastroenterology and hematology or hepatology? I think hepatology is correct.

(REPLY) Gastroenterology and "Hematology" is correct.

(COMMENT 2.) Abbreviations should be explained as whole words, first. Key words should be presented as whole words not abbreviations.

(REPLY) We wrote whole words in key words.

(COMMENT 3.) The version 20 of SPSS is owned by IBM and should be cited appropriately.

(REPLY) We corrected the sentence in MATERIALS AND METHODS (3rd paragraph).

(COMMENT 4.) The duration of treatment is not defined. How many of patients received a 12 wks course of treatment and how many 24 wks?

(REPLY) All patients received a 12 week course of SOF/LDV treatment. We corrected the sentence in MATERIALS AND METHODS (1st paragraph).

(COMMENT 5.) The use of fibroscan for measurement of fibrosis should be mentioned in methods and Fib 4 indexed should be explained more before be used as an abbreviation NS5A RAV.

(REPLY) Because the majority of patients was not measured with fibroscan in this study, we don't mention fibroscan in this manuscript. Fib-4 index was explained in whole words in MATERIALS AND METHODS (2nd paragraph).

(COMMENT 6.) There is repetition of phrases in introduction and discussion.

(REPLY) We added and deleted the sentences in DISCUSSION so as not to repeat of phrases on introduction.

Reviewer #4 (Reviewer's code: 03317257)

(COMMENT 1.) you have to give same informations in your paper

1. The prevalence of hepatitis C in japan
2. The proportion of genotype 1 (a and b) in japan

(REPLY)

1. The prevalence of hepatitis C is estimated to be 0.9%.
2. In Japan the proportions of HCV genotype 1 are 70%, most of them was subgenotype 1b, and subgenotype 1a was reported to be ~1%.

We added these informations in INTRODUCTION.

(COMMENT 2.) Why did you not use ribavirin in association with SOF / LED in patients with cirrhosis for genotype 1 and in a Treatment-experienced patient ?

(REPLY) The combination of ribavirin to SOF/LDV therapy did not improve the SVR12 rate, but increase the number of AEs in the phase 3 clinical trial in Japan. Thus, the combination of ribavirin to SOF/LDV is not approved for treatment of chronic HCV infection including cirrhotic or treatment experienced patient in Japan, we did not use ribavirin.

We added the sentences in MATERIALS AND METHODS (1st paragraph).

Reference article is below.

Ref) Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect Dis.* 2015; 15: 645-53

(COMMENT 3.) How did you the evaluation of liver fibrosis ?(liver fibrosis ? liver stiffness ? only biomarkers ?)

(REPLY) We evaluated liver fibrosis by the imaging of cirrhosis including the presence of portosystemic shunt, splenomegaly, or esophageal/gastric varices and laboratory tests.

We added the sentences in MATERIALS AND METHODS (2nd paragraph).

(COMMENT 4.) Can you give more information about the patients with cerebral hemorrhage ? (evolution ?)

(REPLY) We added the informations as possible in RESULTS (3rd paragraph).

(COMMENT 5.) In discussion you repeat an important part of your introduction, you should discuss some major articles in your paper

(REPLY) We added the sentences in DISCUSSION using the articles which you presented, and deleted the sentences in DISCUSSION repeating on the INTRODUCTION. We added the articles Ref 14-16 and Ref 19.

We thank the reviewer for the helpful comments.

With kind regards,

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