November 9, 2017

Dear Dr. Ya-Juan Ma, Senior Editor, World Journal of Gastroenterology:

Please find enclosed the edited manuscript in Word format (file name: 36640-Revised Manuscript.docx).

Title: Retreatment of patients with treatment failure of direct-acting antivirals: focus on hepatitis C virus genotype 1b

Authors: Tatsuo Kanda, Kazushige Nirei, Naoki Matsumoto, Teruhisa Higuchi, Hitomi Nakamura, Hiroaki Yamagami, Shunichi Matsuoka, Mitsuhiko Moriyama

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 346640
The manuscript has been improved according to the suggestions of the reviewers:

1 The format has been updated.

2 The revisions have been implemented according to the suggestions of the reviewers:

(1) The comment from reviewer ***00032020***

Response to your Major comment: "In DAA treatment, SVR rate was inferior in patients with genotype 3, compared to patients with genotype 1 and 2. How about retreatment for patients with genotype?"

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised Table 3.

Response to your Minor comment: "Nonnucleoside inhibitors' had better replace to 'Non-nucleoside inhibitors"

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we revised our manuscript.

(2) The comment from reviewer ***00722050***

Response to your comment: "The review needs to be expanded in consideration of the fulminant liver failure associated with GT1b. In particular, Sergi C et al. reviewed this aspect in 1998 (please cite Journal of Hepatology 1998; 29: 861–871). Genotyping revealed type 1b in both cases. Of the two HCV RNA-positive cases with evidence of HBV infection, one case had a real coinfection showing simultaneous

detection of HBV DNA in serum and liver, while the other patient was a chronic HBV carrier, seropositive for HBsAg and anti-HBc IgG but negative for anti-HBc IgM and HBV DNA in liver tissue. Thus, the role of co-infection and the failure of DAAs need to be expanded."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised our manuscript as follows.

In CONCLUSION section, page 14, lines 3-12,

CONCLUSION

Sergi et al[47] reviewed that there was the association between HCV GT1b and fulminant liver failure, although HCV is a rare cause of fulminant hepatitis in Japan[48]. Of their two HCV RNA-positive cases with evidence of HBV infection, one case had a real coinfection showing simultaneous detection of HBV DNA in serum and liver, while the other patient was a chronic HBV carrier, seropositive for HBsAg and anti-HBc IgG but negative for anti-HBc IgM and HBV DNA in liver tissue[47]. It has been reported that hepatitis B reactivation during or after the treatment of DAA for chronic hepatitis C[49]. Similar SVR rates seem to be achieved with DAAs in HCV/HBV co-infected patients[50,51]. However, nucleos(t)ide analogues for HBV should be added to DAA therapy for HCV when serum HBV DNA levels are elevated[1].

There is no doubt that new,…..

(3) The comment from reviewer ***00030389***

Response to your Major comment #1: "In the section of "RETREATMENT OF PATIENTS INFECTED WITH HCV GT1B WITH FAILURE OF HCV NS5A INHIBITORS" and in the section of "HCV NS5B POLYMERASE INHIBITORS-RASs IN PATIENTS INFECTED WITH HCV GT1B", the same description from reference 39 appears in duplicated manner. It is easier to understand, if they can arrange these two sections to one section."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised our manuscript. However, as there are two topics, we left two sections intact

Response to your Major comment #2: "In the section of "RETREATMENT OF PATIENTS INFECTED WITH HCV GT1B WITH FAILURE OF PEGINTERFERON AND RIBAVIRIN PLUS HCV NS3/4A INHIBITORS", the description of AASLD guideline is lengthy and difficult to understand. Please describe more simple."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised our manuscript.

Response to your Major comment #3: "In the abstract, they say "It is important to avoid drugs that target the regions targeted by initial drugs", but they also say "it is possible that the next-generation new combinations of DAAs, such as sofosbuvir/velpatasvir/voxilaprevir for 12 weeks or glecaprevir/pibrentasvir for 12 weeks, seem to achieve SVR without considering these regimens". They did not explain this paradoxical description in the main text. They should explain this paradoxical description."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised our manuscript (please see page 10).

(4) The comment from reviewer ***02444760***

Response to your comment #1: "There are some redundancies in the text, such as 'For HCV GT1 and non-cirrhotic patients who were previously treated with peginterferon and ribavirin plus HCV NS3/4A protease inhibitors, a daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with or without ribavirin for 12 and 24 weeks led to SVR rates of 96.2% (50/52) or 100% (51/51) and 97.2% (35/36) or 100% (38/38), respectively[29]' (Page 9)."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised our manuscript.

Response to your comment #2: "It seems to be little information in the 'CONCLUSION'. Improvements with clinical instructions will be appreciated."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised 'CONCLUSION'.

Response to your comment #3: "The text may be somewhat complicated to the audiences. Plain, yet precise, expression is suggested, probably by the native speaker."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we asked the native speaker to edit our manuscript.

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised 'CONCLUSION section' of our manuscript.

Response to your comment #4: "Table 1 and 2 should be presented in the format of three-line table."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we revised Tables 1-3.

(5) The comment from reviewer ***02441096***

Response to your minor comment: "INTRODUCTION It provides nearly sufficient background regarding the studied topic, however, and in order to satisfy the reader, the authors need to emphasize the following: Viral proteins targeted by HCV DAAs in form of a diagram or even short description. Genotype coverage of each DAAs. Definition of SVR has to be included. Specifying ways of screening for (RASs); e.g. direct/ deep sequencing. Reviewing literature for mapping of naturally occurring HCV variants in different geographic areas in the context of current HCV therapy. The aim of the work has to be mentioned at the end of this section."

Thank you for your valuable suggestions. We agree with you. According to your suggestions, we extensively revised 'INTRODUCTION SECTION' of our manuscript.

Response to your minor comment: " Conclusion is satisfactory. 5. REFERENCES: • Relevant updated references are cited • Ref. No(4): title is missing • Ref. No (6) is that No (22): This has to be revised."

Thank you for your valuable suggestions. We agree with you. According to your

suggestions, we extensively revised ‘REFERENCES SECTION’ of our manuscript.