

February 15, 2014

Editor

World Journal of Gastroenterology

Re: ESPS Manuscript NO: 7389

Dear Editor:

El-Shamy and I are most grateful to you and the reviewers for the helpful comments and suggestions on the original version of our manuscripts (NO: 7389). The manuscript has been revised according to the reviewers' suggestions, as described below.

Reviewer #1:

To the major concern:

1. A new section discussing the correlation between sequence heterogeneity in E2 and NS3 and IFN resistance has been added in the revised manuscript (Page 13, line 409 to Page 14, line 446).

To the minor concerns:

1. The phrase "recent update" has been changed to "updated information" (Page 4, line 87).
2. The word "sever" has been corrected to "severe" (Page 6, line 177).
3. The words "taht" and "PKRBD" have been corrected to "that" and "PKR-BD", respectively (Page 10, line 303).
4. The word "obtained" has been deleted (Page 13, line 402).
5. The legend to Figure has been changed to "Average of SVR rates were calculated based on SVR rates achieved in clinical studies cited in references for genotype 1 (GT1), GT2, GT3, GT4, GT5 and GT6." (Page 37, lines 1168-1171).

Reviewer #2:

1. Following the Reviewer's suggestion, the sentence has been changed to "In particular, among the HCV proteins, core and nonstructural proteins (NS) 5A have been extensively studied for their correlation with responses to IFN-based treatment." (Page 2, line 36).
2. The word "ca." has been changed to "about" (Page 3, line 51).
3. According to the current consensus, there are three structural (core, E1, E2) and seven non-structural (p7, NS2 to NS5B) proteins. A recent reference article (no. 11) has been cited (Page 3, line 70).
4. "HCV genotype 1" has been used throughout the revised manuscript. For subtypes, abbreviated forms, e.g., HCV-1a, -1b, etc. have been used.
5. Two reference articles, "Ray et al., *J Virol* 1996" and "Moriya et al., *Nat Med* 1998", have been added as references nos. 48 and 49, respectively, in the revised manuscript (Page 20, line 632 to Page 21, line 638).
6. The phrase has been changed to "Gln70/His70 and/or Met91 (non-wild core) are" in the revised manuscript (Page 6, line 179).

7. The word "sever" has been corrected to "severe" (Page 6, line 177).
8. Two reference articles, "Alestig et al., *BMC Infect Dis* 2011" and "Polyak et al., *Hepatology* 1999", have been added as references no. 76 and 89, respectively, in the revised manuscript (Page 24, lines 759-762; Page 26, lines 815-818).
9. The reference article "Tanji et al., *J Virol* 1995" has been added as reference no. 88 in the revised manuscript (Page 26, lines 813-814).
10. The treatment durations for different HCV genotypes have been described in the legend to Figure 1 in the revised manuscript (Page 37, lines 1171-1174).

Reviewer #3:

Major points:

1. The reference sequences of the ISDR and IRRDR for each HCV subtype have been shown in Figures 3 and 4. Also, criteria for IFN-responsive and -resistant groups of the ISDR and IRRDR have been described in the revised manuscript (Page 9, lines 258-261; Page 11, lines 325-328).
2. The methodology used to analyze the ISDR and IRRDR heterogeneity has been described in the revised manuscript (Page 9, lines 250-256; lines 272 -277; Page 10, lines 313-314).
3. Our recent data about the correlation between NS3 polymorphism and HCC development in the revised manuscript (Page 14; lines 434-446).

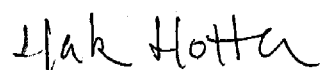
Minor points:

1. The reference article, "El-Serag et al., *Gastroenterology* 2012" and "Thomas, *Nat Med* 2013", have been added as reference nos. 9 and 10, respectively, in the revised manuscript (Page 16, line 497 to Page 17, line 504).
2. Reference nos. 90 and 91 have been added in the revised manuscript (Page 9, line 249).

The revised portions have been highlighted in red.

We hope that the manuscript is now suitable for publication in *World Journal of Gastroenterology*.

Sincerely yours,



Hak Hotta, M.D., Ph.D.

Professor

Division of Microbiology

Kobe University Graduate School of Medicine

Fax: +81-78-382-5519

e-mail: hotta@kobe-u.ac.jp