

Format for ANSWERING REVIEWERS



Jun 24, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 18645-Revised manuscript.doc).

Title: Is the use of IL28B genotype justified in the era of interferon-free treatments for hepatitis C?

Author: Tatsuo Kanda, Shingo Nakamoto, Osamu Yokosuka

Name of Journal: *World Journal of Virology*

ESPS Manuscript NO: 18645

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) The comment from reviewer 00504271

Response to your comment: "The manuscript by Kanda et al. describes the interleukin-28B (IL28B) genotype distribution in Japanese HCV patients and no relationship between this locus and the new interferon-free HCV therapy. As described in the manuscript, IL28B genotyping is used for prediction of interferon sensitivity of HCV patients. In the regimen of HCV treatment, interferon is being replaced with that without interferon because of less population of interferon-sensitive patients and because of its strong side effects. It is nice timing to be published."

Thank you for your encouraging comments.

(2) The comment from reviewer 00009937

Response to your comment: "To the authors The title may better reflect what is stated in the review if there is a reference of the use of IL28 for eg "is the use of IL28 genotype justified in the era of free interferon treatments for hepatitis C"?"

Thank you for your encouraging comments. According to your suggestion, we fixed the Title.

Response to your comment: "In the abstract, last sentence, you would use availability instead of invention. In conclusion the same sugerence-"

Thank you for your encouraging comments. According to your suggestion, we revised our manuscript.

Response to your comment: "In Core Tips: IL28 is associated to the response to IFN, not to IFN plus ribavirin. In the third row of NTERLEUKIN -28B (IL28B) GENOTYPES the same observation about plus ribavirin."

Thank you for your encouraging comments. According to your suggestion, we revised our manuscript.

(3) The comment from reviewer 02521807

Response to your comment: "The manuscript is interesting but needs to be extended to general readers who potentially do not have background in general terms that authors could offer as well known. In example it will be useful to explain certain terms such as SVR, general concepts on different IL28 genotypes."

Thank you for your encouraging comments. According to your suggestion, we revised our manuscript as follows.

In Introduction section, page 4, lines 8-9,

.....death^[15]; and (4) improved quality of life^[15]. A sustained virologic response (SVR), **which is defined as HCV RNA negativity 24 weeks after completion of antiviral therapy**, could have beneficial effects in HCV-infected patients. In the era of direct-acting antivirals (DAA) against HCV, regimens including interferon remain important treatments for HCV eradication^[5,16-33], although interferon-free regimens should be available worldwide soon^[34]. In this review, we focused the distribution of IL28B status in Japanese patients currently infected with HCV, and their treatment.

In INTERLEUKIN-28B (IL28B) GENOTYPES section, page4, lines 21-22,

..... drug response^[37,39]. **IL28B major or minor genotype, respectively, could predict better or poor response to interferon therapy in patients infected with HCV**. An association between.....

Response to your comment: "In order to illustrate, the authors wrote: Page 4: "The IL28B minor genotype plays a crucial role in interferon resistance. The host genetic polymorphism may be useful for predicting drug response. An association between inosine triphosphatase (ITPA) genetic variants and treatment-induced anemia has been reported in HCV-infected patients treated with peginterferon plus ribavirin. A genetic polymorphism of interferon-lambda-4 has also been associated with the treatment response to interferon-including regimens for chronic hepatitis C infection." These several central concepts are consigned without any connection between them, diffculting their comprehension by readers."

Thank you for your encouraging comments. According to your suggestion, we revised our manuscript as follows.

In INTERLEUKIN-28B (IL28B) GENOTYPES section, page4, lines 21-page 5, line 1,

....response^[37,39]. **IL28B major or minor genotype, respectively, could predict better or poor response to interferon therapy in patients infected with HCV**. An association between inosine triphosphatase (ITPA) genetic variants and treatment-induced anemia has been reported in HCV-infected patients treated with peginterferon plus ribavirin^[40-42]. **ITPA major genotype could predict profound anemia induced by peginterferon plus ribavirin treatment in HCV-infected**

patients. A genetic polymorphism of interferon-lambda-4 has also been associated with the treatment response to interferon-including regimens for chronic hepatitis C infection^[43-45]. Similar to IL28B genotypes, interferon-lambda-4 major or minor genotype, respectively, could predict better or poor response to interferon therapy in HCV-infected patients.

Response to your comment: "A similar scenario is observed for the topic titled "Mechanism of the association between the IL28B genotype and treatment response"."

Thank you for your encouraging comments. According to your suggestion, we revised our manuscript as follows.

In Mechanism of the association between the IL28B genotype and treatment response section, page5, lines 23-25,

.....mRNA and binding of HCV-induced microRNAs during infection^[57]. At the present, we do not know the precise mechanisms between IL28B variants and treatment response to interferon. Additional studies investigating these mechanisms are needed.....

Response to your comment: "When described the CURRENT DISTRIBUTION OF IL28B GENOTYPES IN JAPANESE PATIENTS INFECTED WITH HCV, the authors should add other representations or figures (besides figure 1a-1c) accompanied by statistical analysis of results that they found. The authors mentioned genotype 2 (page 8, at the top) but previously they generically express "genotype non-1". It is mandatory to take an unique criteria in order to be clear. As commented above, in the conclusions the authors mentioned several DAA not previously explained. Consdiering the different targets in the viral replication cycle, it should be explained previously more clearly."

Thank you for your encouraging comments. According to your suggestion, we revised our manuscript as follows.

In page 7, line 2 from the bottom-last line,

.....ineligible. The distribution of IL28B genotypes is not significantly different between HCV genotype 1 and non-1 ($p= 0.947$; Figure 1B and 1C).

In page 8, line 1-last line,

Thus, the patients infected with HCV genotypes 1 and non-1, who had IL28B minor genotypes in 40.6% (58/143) and 34.1%(14/41), respectively, should be treated.

.....In Japan, interferon-free 24-week regimens of **asunaprevir, a HCV NS3/4A inhibitor, and daclatasvir, a HCV NS5A inhibitor**, can now be used for HCV genotype 1b-infected patients who are interferon-intolerant or ineligible, or previous-treatment null-responders^[68-70]. In the near future, interferon-free 12-week regimens of sofosbuvir plus ribavirin for HCV genotype 2-infected patients will be available^[71]. Interferon-free 12-week regimens of **sofosbuvir, a HCV NS5B nucleoside polymerase inhibitor, and ledipasvir, a HCV NS5A inhibitor**, for HCV genotype 1-infected patients will also be available^[72]. The response to the treatment with interferon-free regimens appears to have no association with IL28B genotypes. In conclusion, although some HCV-infected individuals have IL28B favorable alleles, importance of IL28B will be reduced with **availability** of oral interferon free regimen.

3 References and typesetting were corrected

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

Sincerely yours,



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