

Dec 9, 2014

Professor Su-Xin Gou
Science Editor
World Journal of Gastroenterology

ESPS Manuscript NO: **13660**

Revised Title: **Impact of direct acting antiviral-based triple therapy on the serum alpha-fetoprotein level**

Dear Professor Su-Xin Gou:

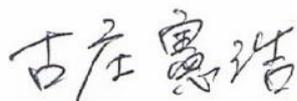
Please find attached our revised paper, which we would like to resubmit for publication in *World Journal of Gastroenterology* as Clinical Research Paper.

We have thoroughly revised the paper on the basis of the referees' comments. We thank them for careful reading of our paper and for their constructive criticism. The parts of the paper that have been revised are **highlighted in red**. In addition, we have provided a point-by-point response to each of the comments.

This paper has not been published or presented elsewhere in part or in its entirety and is not under consideration by another journal. The study design was approved by the Kyushu University Hospital Ethics Committee and written informed consent was obtained from each participant prior to the examination. All authors have approved the revised manuscript and agree with resubmission to *World Journal of Gastroenterology*.

We would be grateful if our paper could be reviewed to assess its suitability for publication in *World Journal of Gastroenterology*.

Yours sincerely,



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Response to Reviewers:

We thank the Editor and reviewers for your careful and excellent critique of our manuscript. We hope that our responses are adequate to meet your concerns.

Comments to author 1.

#2861031. The manuscript authored by Takayama et al is an interesting study, which aims to investigate the effect of telaprevir-based triple therapy on the serum AFP level. The present study addresses a novel question that has been poorly explored. The author stated at the discussion that this is the first study addressing this issue; however, they have to add and discuss the following reference: Shimada N, Tsubota A, Atsukawa M, Abe H, Ika M, Kato K, Sato Y, Kondo C, Sakamoto C, Tanaka Y, Aizawa Y. α -Fetoprotein is a surrogate marker for predicting treatment failure in telaprevir-based triple combination therapy for genotype 1b chronic hepatitis C Japanese patients with the IL28B minor genotype. J Med Virol. 2014 Mar;86(3):461-72

Response to #2861031

Thank you for your valuable comment. According to your comment, we have added the above reference and have made the recommended change as follows.

Page 15, Line 15 to Line 24

IL28B (rs8099917) non-TT genotype is widely known to be related to reduced rates of successful treatment in both telaprevir-based triple therapy and dual therapy of PEG-IFN α and RBV [5, 8, 32]. Moreover, recent study suggests that high levels of baseline AFP are a surrogate marker for predicting treatment failure in telaprevir-based triple therapy for patients with the IL28B non-TT genotype [33]. To apply this to our study, the SVR rate of IL28B non-TT genotype patients undergoing telaprevir-based triple therapy was significantly lower in the high baseline AFP level group (i.e. ≥ 10 ng/mL) than in the low baseline AFP level group (46.2% vs. 80.8%, $P=0.027$). These findings suggest that a high baseline AFP level may be a useful surrogate marker for predicting treatment failure in other DAA-based triple therapy regimens for patients with IL28B non-TT genotype.

Comments to author 2.

#2518868. This manuscript needs to discuss strongly. The discussion and comparison with previous studies are slightly poor.

Response to #2518868

We appreciate for your advice. According to your comment, we have totally revised the description as follows.

Page 12, Line 23 to Page 13, Line 3

The distribution of HCC, which varies geographically, is related to the prevalence of hepatotropic virus. The burden of the disease is highest in Eastern Asia, sub-Saharan Africa, and Melanesia where hepatitis B infection is endemic. Meanwhile, in Japan, the United States, and Europe, HCV infection is prevalent, and subsequently, is the major risk factor for acquiring HCC in these regions. One of the most commonly used surveillance tests for HCC is measurement of the AFP level.

Page 15, Line 15 to Line 24

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Page 16, Line 1 to Line 8

Serum AFP levels together with iconography and pathology detection are commonly used clinically in the early diagnosis of HCC. Recent developments in molecular biology have led to the identification of new tumor markers (heat shock protein 70, AFP-L3, fucosylated GP73, α -1-fucosidase, squamous cell carcinoma antigen, glypican-3, transforming growth factor- β 1, and endothelial growth factor), including proteantigens, cytokines, enzymes and isoenzymes, as well as related genes that can be used in the treatment and prognosis of liver cancer [34]. Additional studies are likely to show these novel markers to be improved by antiviral treatment.

Comments to author 3.

#2841615. The results of this study was only convinced that direct acting antiviral agent-based triple therapy could reduce the serum AFP level, so it was better to discuss the possibility of suppressing hepatocellular carcinoma of direct acting antiviral agent-based triple therapy in discussion section rather than in conclusions of the Abstract.

Response to #2841615

We appreciate for your advice. According to your comment, we have focused on the AFP changes in Abstract and have changed it as follows.

In Abstract:

“**AIM:** To investigate the impact of telaprevir-based triple therapy on the serum alpha-fetoprotein (AFP) level of chronic hepatitis C patients.”

“**RESULTS:** Among patients with a high baseline AFP level (≥ 10 ng/mL), the decline of the AFP level was significantly higher in the triple therapy than in the dual therapy group (15.9 ng/mL vs. 1.6 ng/mL, $P=0.037$).”

“**CONCLUSION:** Regardless of virological response, telaprevir-based triple therapy reduced the serum AFP level.”

Jan 15, 2015

Ya-Juan Ma, Science Editor,
Editorial Office
World Journal of Gastroenterology

ESPS Manuscript NO: 13660

Title: Impact of direct acting antiviral-based triple therapy on the serum alpha-fetoprotein level

Dear Dr. Ya-Juan Ma;

We here send you our revised original manuscript.

According to your comments, we have mentioned co-infection with HIV and HBV in Materials and Methods section. They are shown in red and underlined words.

Also, we have deleted 264 words in Discussion section.

Please find attached our revised paper, which we would like to resubmit for publication in *World Journal of Gastroenterology* as an Original article.

Thank you for your kindness.

Yours sincerely,

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