

May 5, 2015

Professor Yuan Qui  
Science editor  
*World Journal of Gastroenterology*

ESPS Manuscript NO: **17292**

Title: **Importance of virological response in the early stage of telaprevir-based triple therapy**

Authors: Satoshi Hiramine, Norihiro Furusyo, Eiichi Ogawa, Makoto Nakamuta, Eiji Kajiwara, Hideyuki Nomura, Kazufumi Dohmen, Kazuhiro Takahashi, Takeaki Satoh, Koichi Azuma, Akira Kawano, Toshimasa Koyanagi, Kazuhiro Kotoh, Shinji Shimoda, Jun Hayashi

Dear Professor Yuan,

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

We have revised the paper on the basis of the reviewers' comments. We appreciate that you and the reviewers have carefully read our paper and thank you for your helpful comments. The parts of the paper that have been revised are **highlighted in red**. We have also provided a point-by-point response to each of the comments. Although we have revised the abstract, the word counts meet the limits of *World Journal of Gastroenterology*.

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

Yours sincerely,

Satoshi Hiramine, MD.

Department of General Internal Medicine, Kyushu University Hospital,  
3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan, 812-8582.

**Telephone:** +81-92-6425909

**Fax:** +81-92-6425210

**e-mail:** hiramine@gim.med.kyushu-u.ac.jp

Response to Reviewer 1: We appreciate your careful reading and helpful comments on our paper. We hope that our responses are sufficient to address your concerns.

Comment #1: TVR is not any more the standard of care in patients with GT1 infection since many IFN-free DAA regimes are already approved both in Europe as well as in the US. I fully understand, that the study was conducted prior to the approval of DAA's; though it is imperative to discuss the current standard of care with IFN-free regimens as well as with the IFN-based treatment together with RBV and SMV. Furthermore the limitation of NS3-Inhibitors in patients with cirrhosis, in the post-transplant setting and in co-medication should be stated and discussed.

Response to #1: As the reviewer pointed out, TVR is no longer recommended in the guidelines of AASLD and the Japan Society of Hepatology and NS3/4A inhibitors should not be administered in some situations, as the reviewer mentioned. We added a discussion of these issues to the paragraph on the study limitation to clarify the limitations of TVR. ([Page 19, Line 13-](#)).

Comment #2: The authors do not comment or provide any data regarding the occurrence of resistance mutations within the NS3-region prior to therapy as well as in non-responders and relapsers (Sarrazin, Zeuzem Gastroenterology 2010).

Response to #2: As the reviewer pointed out, the occurrence of resistant mutations is an important issue in DAA therapy. Unfortunately, we did not determine the HCV mutations in this study. We added a new paragraph that discusses the limitations of

the study because of the lack of data on the resistant mutations of HCV. ([Page 21, Line 2-](#))

Comment #3: The multivariate analysis conducted by the authors does not include stage of fibrosis despite the highly significant association of stage of liver fibrosis to SVR shown in Table 1. Furthermore, i consider the involvement of both VR4 and VR6 within the multivariate analysis as problematic, since both parameters associate significantly to each other.

[Response to #3:](#) As the reviewer pointed out, stage of fibrosis was strongly associated to SVR in the Chi-square test. However, liver histology data was missing for 99 (39.1%) patients. (Page 14, Line 9-) Therefore, we thought that it was inappropriate to include the stage of fibrosis in the multiple logistic regression model.

As the reviewer also pointed out, it is problematic to involve both VR4 and VR6 within the multivariate analysis because both parameters were in strong association. In order to indicate the predominance of VR6 to other VRs, we calculated Kappa coefficients ([Table 2](#)). VR6 was the only VR with a moderate concordance with SVR. Thus, we included only VR6 in the multiple logistic regression model, and it remained an independent contributor ([Table 3](#)). However, the analysis stratified by age lost stability after VR4 was excluded and ferritin, serum gGT, and LDL-cholesterol were added as variables. Because of this, we deleted table 4 because it was a sub-analysis that was not related to the main argument of this paper.

Comment #4: Further known non-invasive predictors of SVR such as ferritin (Lange et al. Hepatology 2012), serum gGT (Weich et al. J. Gastroenterol 2011), and cholesterol (Sarrazin et al Gastroenterology 2011) are not considered in the current study.

Response to #4: According to the reviewer's comment, we added ferritin, serum gGT, and LDL-cholesterol as variables and re-analyzed the data. Ferritin and serum gGT were not associated with SVR. LDL-cholesterol was associated with SVR in univariate analysis, however, it did not remain an independent contributor to SVR in multivariate analysis (Tables 1 & 3). Your comment has greatly improved our results, and we very much appreciate your helpful advice.

Comment #5: The authors should state that PEG-IFN/RBV+TVR is only considered for GT1 patients in regions of the world, where new approved DAA's (SMV, LDV, SOF, DCV) are not available.

Response to #5: According to the reviewer's comment, we added the sentence to discuss this issue. (Page 20, Line 3-).

Comment #6: From my point of view the conclusion of the study, that VR6 would be more beneficial than VR4 is controversial to many studies conducted so far with a high number of included patients as well as with all the published guidelines (EASL and AASLD) regarding the individualization of IFN-based treatment regimes. I suggest to the authors to reevaluate the main conclusion drawn from their current study.

Response to #6: As the reviewer pointed out, it is controversial to the published guidelines of both EASL and AASLD that checking VR6 will be more beneficial than VR4. The EASL guidelines recommend HCV RNA testing at weeks 4, 12, and 24 for virological response-guided TVR-based triple therapy. The AASLD guidelines also recommend the assessment of HCV viral load at week 4 to determine initial response to therapy and adherence. However, other time points, weeks 1, 2, 3, 6, and 10 are not mentioned in these guidelines. RVR and EVR were probably chosen because they have been considered conventional markers since the era of PegIFN- $\alpha$ /RBV therapy and because the efficacy of other time points in DAA containing therapy had not yet been fully investigated. The AASLD guideline also state, "There are minimal data on how to use HCV RNA level during treatment to determine when to stop treatment for futility." To our knowledge, this is the first study that investigated VR at frequent time points in the early stage of DAA therapy, and we believe that our study is sufficiently reliable to show the possibility that the most efficient time point for checking VR in DAA therapy might be different than the conventional RVR and EVR. According to your comment, we added sentences to the discussion ([Page 17, Line 10-](#)), and revised the conclusion. ([Page 21, Line 12-](#)). We hope this is sufficient to meet your concerns.

Response to Reviewer 2: We are much obliged for your helpful comments on our paper and hope that our responses are sufficient to address your concerns.

Comment: Hiramine et al. in the article “importance of virological response in the early stage of teleprevir-based triple therapy” describe in detail the factors which can be used for the prediction of therapeutic outcome. The limitation of the study is as mentioned by the authors too that all the results are only for HCV genotype 1 Japanese patients. IL28b polymorphism are now a known factor influencing the treatment response, author has taken this as a predictive factor too. But the polymorphism at IL28b rs8099917 is studied while another very important polymorphism rs12979860 which is well documented to influence the therapeutic outcome is not studied, it would be great if authors have studied that too on these patients. Overall the study is well-designed and well written, if accepted it will definitely help in early detection of therapeutic response in patients taking triple therapy.

Response to the comment: As the reviewer pointed out, rs12979860 was reported to be more strongly associated with the outcome of treatment against HCV than rs8099917, especially in Caucasian and African populations. However, it has also been reported that rs8099917 and rs12979860 represent 98.6% of the Japanese population. Therefore, we only determined rs8099917 in this study. According to the reviewer's comment, we added a discussion to allay the readers' possible concerns about this issue. (Page 11, Line 18-)