Format for ANSWERING REVIEWERS

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Title: Efficacy and safety of telaprevir- and simeprevir-based triple therapies for older patients with chronic hepatitis C

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Dear Prof. Clara Balsano and Prof. Wan-Long Chuang,

Thank you for giving us the opportunity to submit a revised version of the above manuscript. We found the comments from both the editors and the reviewers to be very helpful. The manuscript has been improved according to the suggestions of the reviewers. The responses to the comments of the reviewers are as follows:

Reviewer No. 02860705: It would be interesting analyze also a group of patients younger than the age of two groups analyzed. It means that the age result to close between the two groups and with a younger group we will appreciate the real differences.

Response: Thank you for your valuable advice. We agree with your comment, but the present study enrolled only 2 patients 40 years of age or younger in both the TVR- and SMV group, respectively. Therefore, we believed that we could not analyze the differences between the two groups and a younger group.

Reviewer No. 01801217: Comments 1: Because there are few reports that analyzed

CXCL10 in a similar study, I think that you should describe CXCL10 in consideration

Response: Thank you for your advice. We added a description of previous studies on serum CXCL10 in patients treated with TVR-based triple therapy in the Discussion section and added 2 references. Although we re-analyzed our data on serum CXCL10, we could not confirm the utiligy of serum CXCL10 as a predictor of virological response and treatment efficacy in patients treated with TVR-based triple therapy.

Comments 2: The rate of relapse was higher in the SMV group than TVR group, although the rate of RVR was significantly higher in the SMV group than TVR group. I think that a description is necessary for consideration

Response: Thank you for your advice. We added a brief description of the higher rate of relapse in the Discussion section.

Reviewer No. 00012216: Comments 1: Interestingly, they obtain a high global sustained viral response with both combinations, despite the worse base-line situation of older cases (lower platelet count, lower creatinine level). This could be due to genetic features in the Japanese population or due to the liver fibrosis grade in this cohort. Therefore, it should be interesting to know the liver fibrosis grade in both groups of the study, but this information is neither sated in table 1 nor 2.

Response: Thank you for your advice. Because the number of patients who underwent liver biopsy was small, we had not described the liver fibrosis grades in tables 1 and 2. However, we added the liver fibrosis grades in tables 1 and 2 according to your valuable comment.

Comments 2: They should also state if they considered the type of treatment in the multivariate analysis since after reading the manuscript it looks like there is no difference between first and second generation protease inhibitors.

Response: Thank you for your advice. According to your comment, we first performed univariate analyses including the type of treatment (TVR vs. SMV) in all the enrolled patients, but we did not find any significance in the treatment type (odds ratio; 1.115, 95%CI: 0.415-3.192, P = 0.787). However, although the efficacy of TVR and SMV was

similar, we believed that the second-generation protease inhibitor SMV was better to use mainly because of the reduced induction of severe dermatologic and hematologic toxicities. We added a description of the results of the univariate analyses and our recommendation in the Discussion section.

Comments 3: Authors should also explain the criteria to modify telaprevir and simeprevir dose, since according to drug data sheet the drug dose should not be modified during treatment.

Response: Thank you for your advice. In the TVR group, the initial dose of TVR was determined by each attending physician based on each patient's baseline characteristics such as bodyweight. Moreover, the dose of TVR was also reduced by each attending physician based on each patient's adverse events such as anemia, malaise, and anorexia. In the SMV group, the dose of SMV was not modified. We found a mistake, as the number of cases involving dose reduction and discontinuation of SMV should have been 2 and 0 in table 2, respectively. Therefore, we revised table 2. Then, we added a description of the dose reduction of TVR in the Materials and Methods section.

Comments 4: The main concern about the manuscript is based on the future interest of the study, because direct acting anti-viral drug combinations will probably substitute interferon-based treatments.

Response: We completely agree with your comment. However, although the majority of patients with HCV infection are usually treated with IFN-free DAA combination regimens, PegIFN and RBV-based treatment may still have utility in a small number of patients who do not show a favorable effect after the treatment with IFN-free DAA therapies. Moreover, considering the effect of preventing HCC by eradication of HCV, long-term prevention of HCC has been shown only through the use of IFN-based therapies thus far. Therefore, we believe that the present study will provide useful information regarding antiviral treatment for older patients with CHC.

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

Sincerely yours,

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