

Format for ANSWERING REVIEWERS

10th December 2014

Dear Editor,

Please find enclosed the original article which we were invited to revise for publication in the *World Journal of Hepatology* (WJH).



Title: A 100% SVR24 rate after a 48-week course of telaprevir-based triple therapy for HCV recurrence post liver transplant and predictors for outcome

Authors: Kerstin Herzer, Angela Papadopoulos-Köhn, Anne Achterfeld, Ali Canbay, Katja Piras-Straub, Andreas Paul, Andreas Walker, Jörg Timm, Guido Gerken

Name of Journal: World Journal of Hepatology

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Thank you for giving us the opportunity to resubmit our revised manuscript.

The authors want to thank the reviewers for their homogenously positive decision about the value of our paper and for their constructive remarks, which we are glad to address. All comments and suggestions have been answered in a detailed point-by-point response (see below) and the manuscript has been revised accordingly. We resubmit the revised manuscript with all changes highlighted in red and underlined. To appropriately address the reviewers concerns, we added one figure and two tables. We hope the manuscript is now considered to be suitable for publication in 'World Journal of Hepatology' and are looking forward to your response.

Please find a point-by-point response to the reviewers comments below:

Reviewer 1

The manuscript by Herzer et al described a cohort of 19 LT patients with recurrence of hepatitis C who received a telaprevir based triple therapy in a single institution. The study is somehow timely with the new direct antivirals already marketed in many countries. However the manuscript contains some relevant information which may add to the literature. There are several concerns, some of them important, to be addressed:

- 1- Although the title is striking, it does not mirror the actual results of the paper. The sustained virological response rates in the whole cohort (intention to treat analysis) were 58%, which may be higher than those reported in previous studies, but they are far from the 100% rates appearing in the title. Only after excluding those patients who received a shorter course of treatment a 100% SVR rates were obtained. This is a clear example of selection bias since some of the excluded patients met any stopping rule. Thus the title should be changed.

Answer: We meant to express in the title, that a SVR24 is highly probable if patients manage to complete the full course of treatment. We thank the reviewer for his remark that the current title might be misleading and changed the wording.

Changes in the text: page 1, line 1-2: 'Completion of a 48-week course of telaprevir-based triple therapy for HCV recurrence post liver transplant is a reliable predictor for SVR24'

- 2- The authors should clarify whether any data of the present manuscript has been previously published or submitted elsewhere. In methods the authors said that the demographic data of the patients may be found in table 1 and reference 9. Does this reference 9 contain any data included in the present manuscript? If it is so the manuscript should be unsubmitted to avoid duplication.

Answer: Reference 9 refers to an article discussing the current situation of postLT treatment of HCV recurrence postLT together with experiences from our center. The paper does not contain any data of the present manuscript and the present manuscript does not contain any data which have been previously published. To be less misleading, we disclaimed the reference in this position, as patients characteristics are completely described in table 1.

- 3- The authors should describe the median time between the liver transplantation and the treatment in the whole cohort.

Answer: The median time between LT and start of treatment is displayed in table 1, line 17: 'Time from LT to triple therapy [months] 22 [7-295]'. To be clearer, this data were included into the results section.

Changes to the test: page 9, lane 4: 'The median time between LT and treatment was 22 months (7-295).'

- 4- Explain the inclusion criteria. Which patients were eligible for telaprevir-based triple therapy? Were they selected by clinical, biochemical and/or histological parameters?

Answer: We thank the reviewer for this remark, certainly the inclusion criteria should be described, we included them into the manuscript.

Changes to the text: page 6, lane 17 : 'Patients were considered eligible for TVR-based triple therapy upon clinical and histological evidence of recurrence of HCV GT1 infection. Before PEG-IFN was administered, all patients underwent an allograft biopsy for evaluation of fibrosis stage according to the METAVIR system and for exclusion of graft rejection. Exclusion criteria for antiviral treatment were evidence of biopsy-proven acute rejection (BPAR) during the past 3 months or any

medical contraindication to treatment with PEG-IFN and RBV that would predict the occurrence of complications during IFN administration, such as platelet count lower than 100,000/ μ l or white blood cell (WBC) count lower than 2000/ μ l; clinical signs or laboratory values indicating decompensating liver function; renal insufficiency, with a glomerular filtration rate (GFR) lower than 60 ml/min; and anemia, with a hemoglobin level lower than 10 mg/dl at baseline. Whenever possible, treatment with mycophenolate mofetil and corticosteroids was discontinued before the initiation of antiviral treatment. '

- 5- There are some typos to be corrected in table 1 and in methods (page 7, first paragraph).

Answer: We thank the reviewer for the attentive remark, edited the manuscript carefully and did the corrections.

- 6- In the statistical methods used, the authors said that a p value <0.05 was considered significant, and two lines below they said that p values ≤ 0.05 was considered significant. Please clarify and eliminate one of these statements. If the contrasts were two-tailed please add this information.

Answer: The passage was corrected accordingly.

- 7- In page 10 the authors said that none of the patients had histological signs of cirrhosis, but the fibroscan values reported were high (the maximum value was 46 KPa).

Answer: the reviewer is certainly right that description of patient characteristics is misleading, some of the patients had F4/ cirrhosis but none of them were decompensated. Signs of decompensation were exclusion criteria for the treatment. We corrected the passage accordingly

Changes to the text: page 6, line 24: '...; clinical signs or laboratory values indicating decompensating liver function;... And page 9, line 5: 'None of the patients had clinical signs of decompensation.'

- 8- The figure 1 is difficult to read. There are two different diagrams in the same figure. Please consider eliminating one of them.

Answer: We apologize to not fully understand the point of the reviewer. Figure 1

intends to display improvement of liver function, in order to be as clear as possible we chose the same type of diagram for all parameters. What does the reviewer refer to as 'different diagrams'?

- 9- There is a citation quoted several times along the manuscript but it does not appear among the references (Papadopoulos-Köhn, Transplantation, in press). If the manuscript is already accepted for publication, please quote it properly among the references. Similarly in page 17, first paragraph, the authors based one of their statements in a "manuscript submitted". *If this paper has not been published or at least accepted for publication, it should not be quoted.*

Answer: The paper is published and now properly cited.

- 10- The limitations of the study, including the reduced sample size, the retrospective design and the lack of control for possible confounding factors (by multivariate analysis) should be highlighted in the discussion.

Answer: The discussion has been supplemented accordingly. In addition, we want to refer to page 16, line 14 where we state: 'Although the cohort size is not sufficient to adequately address this question, this reveals a clear trend towards lower SVR rates in patients infected with genotype 1a.'

Changes to the text: page 16, line 18: 'However, conclusions have to be drawn with cautiousness as the sample size is reduced due to a limited number of patients who is eligible for this treatment, analysis has been performed retrospectively and controls are missing for possible confounding factors.'

- 11- Some of the conclusions made by the authors are not supported by their results. In their first conclusion the authors said that telaprevir based triple therapy is superior to dual therapy in LT patients with HCV recurrence. This comment should be either eliminated or significantly softened since the present study did not perform any randomized comparison between both approaches. Later in the same paragraph the authors said that RVR, low baseline bilirubin and GT1b were independent predictors of beneficial course and outcome of telaprevir based triple therapy. However there is no multivariate analysis (nor enough sample size to attempt it) to control for possible confounding factors and therefore the identified predictors were not "independent".

Answer: We are sorry for the misleading expressions and changed the text accordingly.

Changes to the text: page 16, line 13: 'Taken together, our results confirm that TVR-based triple therapy represents a considerable alternative for LT patients with HCV reinfection in terms of effectiveness.' And page 16, line 17: '... also a low

bilirubin at baseline and GT1b are related to a beneficial course and outcome of TVR-based triple therapy.’ And page 3, line 15: ‘...Bilirubin level at baseline is also related to SVR ($p < 0,030$). None of the patients had to discontinue treatment due to side effects. Conclusions: RVR, GT and bilirubin are clearly related to achievement of SVR.’

12-Please describe the non-standard abbreviations used along the manuscript to be included in the title page.

Answer: A list of abbreviations in alphabetic order is included on page 2, as required in the ‘instructions for authors’.

Reviewer 2

authors evaluated telaprevir-ribavirin-PEG IFN treatment in post-transplant HCV infection. overall sir were 58%. RVR, genotype and bilirubin were determinants of SVR and there were no severe adverse effects. my minor comments: *result section should be shortened. * table 3 should be omitted and NS3 should be added to table4 * figure 1 is unnecessary so should be omitted.

Answer: We thank the reviewer for his assessment and considered carefully to somehow shorten the results. However, it is the intention of the report to give a thorough description of our observations and estimations in order to share our experiences with the community, in particular in those parts of the world where the second generation DAAs are not yet available.

Therefore, we hope the reviewer agrees with us that a more detailed analysis and report of our data may be of interest and value for those colleagues who intend to work with TVR-based triple therapy.

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