

Dear Professor Lian-Sheng Ma,
Editor-in-Chief of World Journal of Gastroenterology

We kindly thank the reviewers' and editorial comments that we believe have improved our manuscript. Here is a response to the issues raised.

Best regards,

Diogo Libânio, MD
Rui Tato Marinho, MD PhD

Reviewed by 03674603

Only after your last letter, i have found previous letters in my spam. As for myself- i am not hepatologist, dealing with hepatic patients. Though, hepatic encephalopathy and portal hypertension development are in the area of our interests. The authors of editorial mamuscript ?Impact of hepatitis C oral therapy in portal hypertension? raised an important question on the determination of a point of no return (PNR) in the process of patients treatment, when further viral elimination along the process of SVR, can not prevent portal hypertension progression and liver decompensation. Apparently, this is hot topic, which is actively discussed by different groups, who start to apply new treatment options of HCV (i.e. DAAs). The authors very briefly outlined the importance of further determination of possible markers of PNR. To my nonprofessional opinion this may be hard challenging task,- how to select some biochemical markers, changes of which may be related to metabolic and signaling alterations in liver residentnal cells and endothelial cells, and resulting in observed liver architecture disturbances. All in all, as the question addressed to scientists , who are dealing with the problem, this manuscript (NO: 32770) may be recommended for publication in the World Journal of Gastroenterology.

Answer: We thank the reviewer for the comments. We agree that markers of the point of no return are lacking and would be useful to select the patients who benefit from continued surveillance after HCV treatment. However, available studies did not found markers of this point of no return. We addressed this issue on the manuscript and we make a suggestion at the end of the manuscript to include markers of extracellular matrix and hepatic stellate cell remodeling (e.g. hyaluronic acid or alpha-2 macroglobulin) in further studies. "Evaluation of molecular markers of extracellular matrix and hepatic stellate cell remodeling such as hyaluronic acid or alpha-2 macroglobulin may also have an investigational interest to assess if they can be a surrogate marker of the point of no return."

Reviewed by 03429673

This manuscript draws our attention to an interesting and important topic that worth further investigation by better designed clinical studies with more standard methods for outcome measures and longer duration of follow-up. The effective DAA agents with higher SVR and better tolerance have expanded therapeutic options to more patients with varying degree of disease stages and changed the natural course of hepatitis C-related complications including portal hypertension. The favorable SVR

rates have translated into improved clinical outcomes including hepatitis C-related mortality. It is highly relevant to further study the association between SVR and liver fibrosis regression which plays a significant role in the development of portal hypertension in this new era of hepatitis C treatment with all oral agents. The manuscript has mentioned a list of clinical findings suggestive of the positive impact of SVR obtained with hepatitis C treatment, especially the recent studies with new DAA agents, on portal hypertension. However, those clinical studies provide limited evidence due to the nature of suboptimal study design and conduction, and lack of standard methods to evaluate progression of fibrosis as well as portal hypertension. It would be better if the manuscript would also address some of the challenges that we may face and possible solutions/alternatives in order to further explore this renewed interest. For example, reasonable inclusion/exclusion criteria for heterogeneous study population with different fibrosis stages, scientifically sound and ethically acceptable study designs, sufficient sample size to ensure the power for detection of differences, adequate duration of follow-up for clinical outcomes, appropriate data collection and statistical analysis to determine potential clinical predictors of improvement of fibrosis and portal hypertension, the pros and cons of methods in the evaluation of fibrosis, and the strengths and limitations of methods in the assessment of portal hypertension. Rather than simply raising the awareness, this strategy would be more useful to provide a realistic whole picture and lead the readers to the next step.

Answer: We thank reviewers' comments that we believe to have improved our manuscript. We added a new paragraph about the issues raised (below). However, we believe that extensive discussion of the pros and cons of the different methods for the evaluation of fibrosis and of the different methods of portal hypertension assessment are difficult to integrate in a short editorial article, and so we briefly discussed these issues along the manuscript.

"The available evidence is mainly based on retrospective studies with heterogeneous populations and endpoints definitions. As randomized controlled trials with active treatment and control groups are not ethically acceptable at this time point, the best studies to answer these unsolved questions are prospective studies with well-defined inclusion and exclusion criteria, well-defined clinically significant endpoints and with long follow-up. We suggest that further studies include patients along the spectrum of hepatitis C infection (from asymptomatic with minimal liver damage to cirrhotic patients) with stratification according to the stage of liver disease (ideally evaluated by non-invasive methods validated in HCV infection such as elastography since liver sequential liver biopsy are difficult to obtain in clinical practice). Additionally, the evaluated endpoints should be clinically significant and well defined (e.g. *de novo* varices, variceal enlargement from small to large varices, *de novo* hyperesplenism) and follow-up should be longer than 5 years to assess the true impact of HCV treatment according to the stage of liver damage. Data collection should include an adequate characterization of disease stage at the beginning and at the end of follow-up (including aminotransferases, platelet count, ultrasound findings, liver stiffness, presence of ascites, varices and encephalopathy). These studies should then assess the

treatment effects according to the stage of liver disease and should compare patients who achieve SVR with patients in whom these endpoint is not achieved.”

This manuscript could also benefit from linguistic consultation.

The language of the manuscript was revised by a native English speaker.