ANSWERING REVIEWERS

December 15th, 2014

Dear Editor,

Title: Predictive factors associated with hepatitis C antiviral therapy response

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We thank the editor and reviewers for all comments. We have accepted the suggestions and have revised the article carefully. Responses to peer reviewer comments are as follows point by point.

We have reviewed the manuscript using cross-reference as recommended; however, some key-words could not be deleted or modified to avoid overlapping.

Please find attached the edited manuscript in Word format (file name: 13651-review 15 dec 2014.doc).

Answers:

#Reviewer 1: Interesting review I. It needs some language corrections

Re: We appreciated your comment. The language has been improved.

#Reviewer 2:
The present manuscript by L. Nascimento and A. Castro is an informative review summarizing the predictive factors of SVR after antiviral therapy in HCV patients. The authors provided a detailed description of these predictive factors according to the different antiviral protocols available. This is a very relevant issue and I feel that the most relevant information is already included in the manuscript. However there are some aspects deserving further discussion:

1- Given the large amount of features related to reduced SVR rates after antiviral therapies... Would the authors recommend to avoid antiviral treatment under certain unfavourable conditions? For instance triple therapy may not be used in patients with advanced cirrhosis with portal hypertension. This information may be added to the final section of the manuscript.
Re: We thank you for this comment. This information was added in the manuscript as suggested.

2- The liver transplantation is a complex scenario for antiviral therapies but their role for the patient within waiting list or with severe HCV recurrence is central. Please comment.
Re: Treatment of HCV infection in the transplant settings is indicated in two different situations: patients waiting for liver transplantation to prevent HCV infection of the graft (considering compensated and decompensated liver disease; with and without hepatocellular carcinoma); and patients with recurrent hepatitis C after LT in order to stop damage. These scenarios are really complex and important. We added a new topic in review about this subject.

3- The efficacy of the antiviral agents in the randomized controlled trials is far from the actual clinical impact in daily practice, as nicely shown with the

CUPIC series. The importance of well designed observational studies is critical. Please comment.

Re: We agree with the reviewer that Cupic study is a good example about differences between "real life" and randomized controlled trials. We have added a comment in the text highlighting this point.

Unfortunately, phase 3 studies of first-generation DAA showed a few selection biases; however, we did not explore those aspects in this review because this was not our main goal.

4- The increased cost of the new antivirals is another reason to improve the selection of candidates to receive the therapy. The grade of liver fibrosis is the most powerful predictor of SVR (even more than IL28 polimorphism status in my opinion). In many countries the use of the new antivirals is restricted to patients with advanced liver disease. A recent metaanalysis published in Hepatology by Tsochatzis et al may add relevant information to the present manuscript regarding the cost-effectiveness of the new antivirals.

Re: Thank you for your comment. The increased cost of new antivirals is an important point particularly in developing countries, where these new therapy strategies will not be available for everyone and where in many places they will not be available soon. HCV-genotype and liver fibrosis are the most important variables considering the strategies of therapy; however in some developing countries, where dual PR therapy may still be one of the offered therapeutic regimens, IL28B might be considered. First-wave DAA is yet used in developing countries, and liver fibrosis is the best predictor of response; however, IL28B could be used in both cases: 1- as a predictor of shortened therapy with boceprevir or telaprevir; 2- in addition to other favorable response predictors including no advanced liver fibrosis C/C IL28B patients might be considered to dual therapy in some developing countries due to economic issues.

The metaanalysis published in Hepatology by Tsochatzis is very impacting, but the results are only applicable to developed countries. We have added the data in the paper. We thank you for the suggestion.

4- As a minor remark the manuscript may benefit from further English proofing.

Re: We thank you for this comment. Of note, the manuscript had been revised by AJE. Anyway, the language has been further improved.