14th of December 2012

Dear Editor,

Please find enclosed the edited manuscript entitled "Factors associated with early virological response to peginterferon-α-2a/ribavirin in chronic hepatitis C".

Authors: Javier García-Samaniego, Miriam Romero, Rafael Granados, Remedios Alemán, Miguel Jorge Juan, Dolores Suárez, Ramón Pérez, Gregorio Castellano, Carlos González-Portela.

Manuscript No: 96

We thank the reviewers for their detailed and useful review of our manuscript. We appreciate the positive feedback as well as the constructive suggestions to further improvement of our manuscript, and we are glad to have the chance to properly complete the content of our manuscript.

The manuscript has been improved according to the suggestions of the reviewers and the scientific editor as follows:

1. Format has been updated

2. We have carefully revised the original manuscript and have modified it according to the suggestions of the reviewers (major points 1-6). Detailed responses to all comments requested by the reviewers are provided below.

1. We agree with the reviewer that some explanation to justify the high EVR in Spain CHC patients must be provided in the manuscript. As we have recorded in the original manuscript, we believe that the excellent treatment compliance is the main factor explaining the high EVR seen in our series given that adherence to the prescribed treatment seems to be crucial during the first 12 weeks, and significant reductions and interruptions in either drug seem to dramatically reduce the chance of responding to therapy. However, we have now completed the explanation to justify the high EVR in the Discussion section (page 14, first paragraph) as follows: "The good treatment compliance is one of the factors explaining the high rate of EVR seen in our study. Treatment modifications and motivation of patients may have had a great impact on adherence to treatment. Therefore, the low dose reductions required for both drugs could have encouraged patients to complete the prescribed course of treatment. Additionally, determination of EVR provides patients and physicians with an early goal and motivates them to adhere to treatment recommendations. Moreover, it is noteworthy that patients were treated by hepatologists belonging to specialized units with wide experience in the care of CHC patients".

   On the subject of the other major comment, as we state in the Discussion section, the lack of IL28B genotype determination represents an important limitation of the current study as it has been described as a relevant predictive factor of treatment response. However, the impact of IL28B polymorphism on treatment response was described just after our study had finished. As the reviewers suggest, it would be interesting to analyze a significant proportion (>20%) of the large study cohort in order to explore a possible relationship of human IL28B polymorphisms with the astonishing high EVR in Spanish CHC patients. Indeed, we have planned to complete this study in the future by the

assessment of IL28B polymorphisms in a notable proportion of our series.

2. According to the reviewers suggestion, all comments and conclusions regarding the association of EVR with ferritin levels have been removed from the manuscript given that this relation is clearly irrelevant (OR=0.999). Accordingly, the paragraph addressing this issue on page 12 of the Discussion has been deleted and the lack of utility of this clinical factor has been commented instead as follows: "Although the multivariate analysis identified high levels of ferritin as an indepent predictor of EVR, this association is clearly irrelevant (OR=0,999). Therefore, ferritin level lacks of clinical validity as a predictive factor of EVR in this setting."

3. We agree with the reviewers that he paragraph "With regard to gender, it is notable that men comprised 70% of the wide patient sample included in our study" must be removed provided that this proportion of men is not infrequent. Therefore, we have now deleted this statement, and the remaining paragraph commenting on CHC men/women proportion regarding treatment has been summarized and potential causes of the unbalance men/women has been commented on page 12, 3rd paragraph. As we have stated in the manuscript, our findings show that the proportion of women with CHC treated with peginterferon plus ribavirin in routine practice in Spain is much lower in comparison to the proportion of men, in the absence of demographic variables justifying this difference, or known barriers to access to treatment for women. However, we can speculate that the lower fibrosis severity as well as the higher rate of normal ALT levels in women with CHC could explain the relative low proportion of female patients treated in our series.

4. As the reviewer states, it would be interesting that additional data about adverse events (particularly anemia) were provided given the large study cohort and the wide covering of this population. However, the purpose of this study was not the safety of the combination of peginterferon and ribavirine, and adverse events were not therefore collected for this analysis. Moreover, given the cross-sectional nature of this study it would have not been possible to obtain toxicity data from most of medical records. Nevertheless, we consider that we could complete this study in the future by determining ITPA polymorphisms in relation to anemia risk and the possible reduction of ribavirine dose.

5. We agree with the reviewer that the information regarding the relevancy of optimization of the dual therapy with regard to the higher cost of the new DAAs should be commented, and we are glad to have the chance to properly complete the content of our manuscript. Therefore, as suggested by the reviewer, we have now addressed this issue in the Discussion section, page 14, 2nd paragraph.

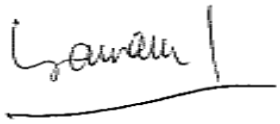
6. According to the reviewer valuable comment, we have removed the sentence stating that HCV-RNA levels were measured by using Amplicor Monitor HCV v2.0 from Roche Disgnostics. We have now clarified this matter in the revision version as follows: "HCV-RNA levels were measured using quantitative polymerase chain reaction (PCR) assays, mostly Amplicor HCV Monitor (Roche, Kenilworth NJ, USA). Although other commercial tests were used in some centers, a lower limit of detection of 50 IU/mL was considered in all participating hospitals."

3. References have been properly edited. PubMed citation numbers and DOI citation have been added to the reference list and all authors have been listed.

4. "Comments" section has been included.

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Sincerely yours,



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