

## Letter in Response to REVIEWERS

April 30, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 17396-review.doc).

**Title:** Effectiveness and safety of first-generation protease inhibitors in clinical practice: HCV patients with advanced fibrosis

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript No.:** 17396

The manuscript has been revised in accordance with the reviewers' suggestions:

1 The format has been revised;

2 The following changes have been made, in accordance with the reviewers' suggestions:

(1) Reviewer 02462085:

*"Nevertheless, the revised version of the manuscript has to provide full information on how the propensity score was calculated (i.e. which confounders/covariates have been chosen)"*

This observation has been addressed in the revised manuscript and the additional information on how the propensity score was calculated has been included. In nonrandomized studies, treatment selection is often influenced by subject characteristics. Thus, in our case, the baseline characteristics of the subjects may differ depending on the treatment used. Therefore, one must account for systematic differences in baseline characteristics between different treatments when estimating the effect of treatment on outcomes. For this reason, we used methods based on the propensity score to reduce or eliminate confounding effects when using observational data (Circulation. 2007; 115:2340-2343, Multivariate Behavioral Research, 46:399-424, 2011). Thus, in a set of subjects, all of whom have the same propensity score, the distribution of the observed baseline covariates will be the same between the two treatment groups. To adjust the regression, we incorporated a large set of background covariates to estimate the propensity score and then used a subset of these covariates (previous response, IL28B, fibrosis, treatment, logarithm GGT and logarithm viral load) and the propensity score in the regression adjustment.

*"The criteria for "failure to respond during the 4-week lead-in period" should be given in the revised version of the manuscript"*

This comment has been addressed in the revised manuscript. The criteria for “failure to respond during the 4-week lead-in period” has been replaced by “excluding patients who had a decrease of less than 1log10 IU per millilitre in the HCV RNA level during the 4-week lead-in period and had not received any dose of BOC or TVR”

*“In particular, an effort should be made to clarify the cause of death in the four patients who died of a “nonspecific cause” and this information has to be added to the revised version of the manuscript”*

These observations have been addressed in the revised manuscript and the requested additional information on the cause of death, for all patients, has been included.

The following causes of death were recorded: two patients, cardiovascular problems; one patient, lung neoplasm unrelated to treatment; two patients, severe infection (pneumonia and salmonellosis respectively); one patient with non-F4 stage, hepatic decompensation; four patients with very advanced liver cirrhosis, multi-organ failure caused by severe anaemia, hepatic decompensation, hepatic encephalopathy, infection and digestive haemorrhage; one patient, unknown cause unrelated to treatment.

*“The references have to be checked”*

In the revised manuscript, all references have been checked and cited according to the format of the journal.

*“Minor issues: Abstract; results: The sentence:” The analysis by groups showed that only the TN patients treated with TVR by ITT .....” should be deleted. Instead, information on drop outs for safety reasons should be added. The paragraph on “RNA-HCV follow up” is somewhat unclear and should partially be revised (e.g. “following local practice” seems to contradict the information given shortly above)”.*

These observations have been addressed in the revised manuscript.

(2)Reviewer by 02542077:

*“Comment: 1-Tables are not clear, could be changed”*

This comment has been addressed in the revised manuscript. We have made some changes to clarify the tables.

(3)Reviewer 03252209:

*“1. The efficacy and safety of boceprevir and telaprevir was well validated in previous studies. Limited new evidence was provided in this study.”*

We agree that many validation studies have been made of the efficacy and safety of BOC and TVR. The novel aspect of our study is the large cohort of patients treated in Spain with triple antiviral therapy against HCV, with the first-generation protease inhibitors boceprevir and telaprevir. This large cohort includes 56% of patients with cirrhosis. Because of the high financial cost of treatment, one of the recommendations of the Ministry of Health and of the Autonomous Communities (regional governments) was to primarily treat patients with advanced stages of fibrosis (stage F3-F4). We believe that knowledge of our results could be useful to the medical community, especially in countries where access to new direct antiviral agents may be restricted or impossible.

*“2. The fibrosis severity was determined by FibroScan which would lead to inaccuracy. Were any other measures of fibrosis severity used and what number of patients did not have a validated FibroScan result? Was there an*

*analysis of the FibroScan result rather than the fibrosis stage?"*

Our study is a record of patients with chronic hepatitis C who were treated with triple antiviral therapy with first generation protease inhibitors, at 38 Spanish hospitals. The data collected on fibrosis include the FibroScan value in kPa, and also the liver biopsy. Of the 1057 patients in our study, 99 patients received no FibroScan or liver biopsy and therefore were eliminated from the analysis of fibrosis. For most patients, Fibroscan was used, applying the following values to determine the degree of fibrosis: <7.5 kPa, mild or no fibrosis (F0-F1);  $\geq 7.5$  kPa and <9.5 kPa, significant fibrosis (F2);  $\geq 9.5$  and <12.5 kPa, severe fibrosis (F3);  $\geq 12.5$  kPa, liver cirrhosis (F4).

*"3. More detailed information will be needed about the patient inclusion/exclusion criteria and treatment protocol. Did both BOC and TVR groups have a lead in period with Peg/rib?"*

The treatment protocol was applied following the standards recommended by the Ministry of Health and by the Autonomous Communities. However, in actual clinical practice and in particular circumstances, these recommendations may be modified. The following criteria for inclusion/exclusion were applied:

Inclusion criteria: Patients infected with HCV genotype 1 who have either never been treated or have been previously treated; indication for treatment with boceprevir or telaprevir, as directed by the Ministry and by each Autonomous Community, i.e. Metavir fibrosis score of F3 or F4 or, in certain cases, F0, F1 or F2, and who have signed the Informed Consent form and who have attended their scheduled medical consultations.

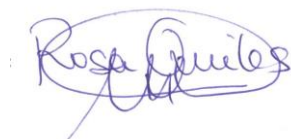
Exclusion criteria: Simultaneous participation in another research study, non-availability to follow up, contraindications for triple therapy, coinfection with HBV and/or HIV, advanced liver cirrhosis and liver transplantation.

Regarding the lead-in phase, per protocol is indicated for treatment with boceprevir. As mentioned above, in actual clinical practice, some patients received a lead-in phase in their treatment with telaprevir, as directed by their physician.

3 The references and typesetting have been corrected

Thank you again for evaluating our manuscript and we hope it is now considered suitable for publication in *World Journal of Gastroenterology*.

Yours sincerely,

A handwritten signature in blue ink, reading "Rosa Quiles". The signature is stylized with a large, looped 'Q' and a long horizontal stroke at the end.

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