ANSWERING REVIEWERS

June 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10905-review.doc).

Title: Boceprevir Is Highly Effective In Treatment-Experienced HCV-Positive Genotype-1 Menopausal Women

Author: Bernabucci V, Ciancio A, Petta S, Karampatou A, Turco L, Strona S, Critelli R, Todesca P, Cerami C, Sagnelli C, Rizzetto M, Cammà C, Villa E.

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made as follows according to the suggestions of the reviewers

Reviewed by 02860784

Major points: The study is limited by population number and restricted to a single cohort. It would be interesting to include an additional geographically distinct cohort of menopausal women to strengthen the results.

Reviewer is right underlying that the number of retreated is not large: the study was prospectively done when Boceprevir was not available through the NHS. Therefore, being an experimental study, the number of patients to be treated was decided after calculating the number of retreatments necessary in order to have a demonstrated superiority of the novel treatment over standard dual therapy.

Regarding the second observation (i.e. additional geographically distinct cohort of menopausal women to strengthen the results), *we are able to give more details on this issue. Indeed, the cohort was composed for a 60% of women from Northern Italy (Turin and Modena centers) while 40% was from Southern Italy (Palermo and Naples center). The final SVR rate was not different between women from different geographical origin. This detail has been added to results (page 9, lines 30-31; page 10 lines 1-2; page 10 lines 15-17).*

Minor points: The end of the first paragraph references that the SVR rates of menopausal women are resistant to retreatment, referencing “personal data”. A proper reference should be given for this finding, or the primary data should be presented, it is not acceptable that such findings should be assumed as personal data or from anectodal experience.

We agree with Reviewer #02860784 that either a proper reference or the actual data should be given. As we have not published these data yet, we have modified the sentence describing these data (Introduction (page 5, lines 24-30) giving more details on SVR after retreatment with standard dual

antiviral therapy in menopausal women.

Reviewed by 02860818

Self citation is good but should not be the only argument when establishing the idea of a study. The fact that after menopause HCV infection becomes more aggressive is not subject of consensus yet.
*We agree that there are not many studies yet on this subjects; however few papers were available before we published our paper on Gastroenterology in 2011, and few others appeared thereafter. Apart from the study by Poynard et al (Ann Hepatol. 2003) at least two other papers agree with our findings. The first was the one by Codes et al (Gut 2007) that stated "*Severity of fibrosis was associated with a longer duration of infection (>15 years), a higher body mass index, advanced steatosis and the menopause. Menopausal women receiving HRT presented with a lower stage fibrosis. These results reinforce the hypothesis of a protective role of oestrogens in the progression of fibrosis*". The other is a big cooperative, prospective cohort study Italian study enrolling 670 patients (303 females) (Di Marco et al., JVH 2013, 20, 790–800) that confirmed both the inverse relationship between menopause and higher severity of disease and lack of SVR.*
These references were added to the paper.

Please add inflammation data from liver biopsy in support of this.
The details of inflammatory activity occurring in menopausal woemn have been described in detail in the study reported in Reference 3. In this paper, we have described the course of inflammatory activity and of resulting fibrosis in the 4 reproductive ages (fertile, premenopausal, early and late menopausal) of Hep C women (paired with men of similar age). Women have stable and low inflammation until menopause when this rapidly increases with subsequent increase in fibrosis entity. The histologic details of the present cohort are given in Table 1.

Reviewed by 02860618

Veronica Bernabucci and co-workers studied the efficacy and safety of Boceprevir plus PEG-Interferon Alpha/Ribavirin (IFN/RBV) in 56 menopausal women affected by Hepatitis C genotype 1 with a previous failure of standard IFN/RBV therapy. They observed that the triple therapy increased the sustained virological response (SVR) with few adverse events. I have some main concerns that do not come in favour of the acceptance of this manuscript: 1. the Authors cite their previous work stating that menopausal women affected with chronic hepatitis C are "extremely" resistant to IFN/RBV (Villa E, Gastroenterology, 2011). However, this study shows that menopausal women achieved SVR less frequently than women of reproductive age but as frequently as men. Moreover, the study demonstrates that SVR is reduced in early menopause (< 5 years) only. However, the present study generally considers the enrolled patients as menopausal women, without any stratification based on the length of menopause. According to the previous study, this group could be considered similarly to men.
*We do appreciate the careful reading of the Gastro paper by Reviewer #02860618; it is true that the period at higher risk of worsening both liver condition and SVR is that corresponding to early menopause. Afterward, SVR rate is similar to that of men of comparable age, which is not exceedingly good in general and much worse than that of women in fertile age in particular. It should be underlined that the cohort treated with Boceprevir was composed, of course, entirely of genotype 1 women. In these women, as stated in the same paper (*Restricting analysis to genotype 1–infected women, logistic regression analysis identified only menopause as an independent predictive factor for SVR failure (OR, 2.908; 95% CI, 1.544 –5.478, P=.001) (Table 4, bottom).

Substituting “duration of estrogen deprivation” for “menopause” in the multivariate model revealed that the OR of SVR failure decreased in parallel with increasing time from the menopausal event: less than 5 years, 3.933 (95% CI, 1.274 –12.142; P=.017); 5–10 years, 2.300 (95% CI, 0.982–5.386; P =.055..... in G1, when replacing length of estrogen deprivation as a categorical variable with the linear variable, the latest remained significantly associated with lower SVR rate (OR, 1.088; 95% CI, 1.006 –1.177) *the relationship with menopause is stronger and extended, the OR of failing SVR for a menopausal length between 5 and 10 years being 2.3 and the association with menopause length as a linear variable being 1.088). If the data are re-analyzed according to Reviewer #02860618 observation, i.e. excluding the 9 women with menopause duration higher than 10 years, the SVR percentage does not change (44.7 and 44.4% respectively). This percentage, although satisfactory, is certainly lower than that obtained in registration studies of retreatment with Boceprevir (e.g. Bacon et al., NEJM, 2011) confirming our assumption of a difficult-to-treat population.*

2. the Authors state that menopausal women are resistant to re-treatment. This point is very important, since it could justify a single-arm study; nevertheless, they cite personal unpublished data. I suggest either to publish these data or to perform a randomized study comparing the re-treatment versus the triple therapy.
These data are derived from a database of more than 2000 Hepatitis C patients (unpublished) and from a smaller database of a study in which we tested the association of HRT to dual antiviral therapy (submitted for publication). The results from these studies indicate that the SVR rate after retreatment of menopausal women with the same drug combination of the previous therapeutic cycle, ranges from 10 to 20%, especially, as in the case of 60% of the women enrolled in this study, more than one previous therapeutic failure was present in the history of the patients. These details have been added to Introduction (Introduction (page 5, lines 24-30). Furthermore, we have added references in the Discussion which report SVR rate after retreatment with standard PEG IFN/R therapy vs. PEG IFN/R+BOC (e.g. Flamm et al, CGH 2013) which supports the fact that retreated patients without RVR have negligible SVR rates.

Minor points:
1. several results in the text are different from those in the tables; : *mended*
2. “experienced” should be replaced by “treatment-experienced”; *corrected*
3. English spelling and grammar need to be extensively revised by a native speaker*: Manuscript has been revised by NPGLE Language Editing Service (see certificate)*

3 References and typesetting were corrected

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

Sincerely yours,

Prof. Erica Villa

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