



To BPG Editorial Office

Journal title: World Journal of Hepatology

Manuscript NO: 56743

Title: "HBsAg and HBcrAg kinetics after the addition of pegylated interferon to nucleos(t)ids analogues in HBeAg-negative chronic hepatitis B patients"

We would like to thank the BPG Editorial Office and the reviewers for their comments and for giving us the opportunity to resubmit a revised version of our manuscript. This has been revised according to the reviewers' comments and appropriate changes have been made.

A point-by-point response to reviewers' comments is included in the next pages.

We hope that you find the revised version of the manuscript suitable for publication in World Journal of Hepatology.

Yours sincerely,

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Point-by-point response to reviewers' comments:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The manuscript which entitled "HBsAg and HBcrAg kinetics after the addition of pegylated interferon to nucleos(t)ids analogues in HBeAg-negative chronic hepatitis B patients" has been thoroughly reviewed. Although it is an important and qualified article, some major concerns identified in this manuscript are given below.

- 1) In abstract section the dose of PEG-IFN should be added.

We would like to thank the reviewer for the effort in revising our manuscript. According to his/her recommendation, we have added the dose of PEG-IFN in the abstract section of the reviewed manuscript.

- 2) Exclusion and inclusion criteria should be clearly expressed. If transplanted patients were included in this study, this should be clearly stated as this may affect the results of this study.

We would like to thank the reviewer for bringing this to our attention. Liver transplantation was an exclusion criteria and we have included this exclusion criteria in the new version of the manuscript. Moreover, despite kidney transplanted patients were allowed, none of them achieved to fulfill the inclusion criteria. Therefore, no transplanted patients were included. We have added this information in the results section of the revised manuscript.

- 3) Because of high risk of neuropathy, the combination of PEG-IFN with telbivudine is contraindicated. Accordingly, it should be explained why PEG-IFN was initiated in a patient who took telbivudine in this study.

We would like to thank the reviewer for giving us the opportunity to further clarify this important observation. The warning regarding the risk of neuropathy in patients treated with telbivudine and PEG-IFN was published in December 11th, 2014 on Medicines and Healthcare products Regulatory Agency (<https://www.gov.uk/drug-safety-update/telbivudine-and-pegylated-interferon-risk-of-peripheral-neuropathy>) based on the results of Marcellin et al. (Marcellin P. et al. *J Hepatol.* 2015;62(1):41-47). This study, that was published in

January 2015, showed a risk of 14% (7/50) to develop neuropathy after combining Telbivudine plus Pegylated Interon-alfa-2a. Our patient treated with Telbivudine was included in the study in August 2014. After treatment initiation, the patient remained without signs of neuropathy and showed a great decline in HBsAg levels. Therefore, authors decided to continue antiviral treatment with a close monitoring according to the Regulatory Agency recommendations (<https://www.gov.uk/drug-safety-update/telbivudine-and-pegylated-interferon-risk-of-peripheral-neuropathy>).

- 4) There are some misspellings in the manuscript. - Regression (page 2 and 7) should be corrected as regression - Peg-NA (page 2) should be corrected as Peg-IFN-NA Average age and distribution should be specified in Tables 1 and 2.

We thank the reviewer to identify the misspelling in the manuscript. Following this kind recommendation, we have made the changes on the reviewed version of the manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The number of patients in the study were very low. The work would be more valuable if the number of patients are more in the study.

We thank the reviewer for his/her revision and we agree with his/her comment. As noted in discussion section, our study had several limitations and the number of patients was low for different reasons. First, the acceptance of the add-on strategy was low and only 40% of eligible patients with a previous (well-tolerated) NA therapy accepted the addition of Peg-IFN due to its potential toxicity. Second, the frequent adverse events of Peg-IFN (22% of discontinuations) caused a low number of patients completing 48 weeks. And third, patients of both treatment strategies were individually matched for age and treatment duration to make the cohort comparable. Despite these limitations, our results have demonstrated that the addition of Peg-IFN to NAs decreased HBsAg levels further and faster compared to NA monotherapy.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The study of Broquetas et al. evaluated the effect of Peg-IFN addition on HBsAg loss in HBV patients undergoing NAs therapy. The study is clear and easy to follow; however, there are some aspects that need to be ameliorated.

Specific comments:

- 1) Abstract: Add the dose of Peg-IFN Change “regresion” with “regression”

We are very grateful with the reviewer for the comprehensive and fair review of our manuscript. We have included the dose of PEG-IFN and the correct word of “regression” in the abstract section of the reviewed manuscript.

- 2) Methods: At the end of page 5, you mention that patients with any malignancy and transplant (should be “transplanted”) patients were eligible for NAs monotherapy. These patients, in particular the immunosuppressed ones are not comparable with other patients without such comorbidities. Did you include in your NAs group these patients?

We thank the reviewer and we agree with his/her comment. Liver transplantation was an exclusion criteria and we have clarified it in that reviewed manuscript section. Despite kidney transplanted patients were allowed in our study, none of them achieved to fulfill the inclusion criteria. Therefore, no transplanted patients were included. Moreover, the only two patients (in the control group) who used immunosuppression had rheumatoid arthritis and they were receiving low-doses of corticosteroids (prednisone 2.5 to 5 mg/day). We have added this information in the reviewed version of the study.

- 3) Results: You excluded from your analysis some patients to obtain a better matching of the two groups. To my opinion this is a reductive statistical approach. It would have been more correct to use all your patients and then perform a multivariate analysis using as outcome HBsAg loss and including as variables the type of therapy, and the length of NAs therapy as well as the age of patients (both significantly different in the two groups).

We would like to thank the reviewer for giving us the opportunity to further clarify this important observation. As we described in the results section and table 1, 65 patients were included: 36 (55.4%) accepted to add Peg-IFN and 29 (44.6%) continued with their NA. However, patients in Peg-IFN-NA group

compared to NA group were younger (age 45 vs. 53, $p=0.01$) and had a shorter previous NA treatment duration (259 vs. 393 weeks, $p=0.01$)(Table1). Due to these significant baseline differences and according to previous published studies showing a decrease of HBsAg levels after 4 years of NA therapy (Papatheodoridis G et al. J Hepatol. 2014;60(1):62-68. doi:10.1016/j.jhep.2013.08.023) and a higher probability to HBsAg clearance in aged populations (Tsai PS et al. Liver Int. 2011;31(7):971-979. doi:10.1111/j.1478-3231.2010.02363.x) our patients were individually matched for age and treatment duration. We have included a better explanation and the references in the discussion section of this reviewed version of the manuscript for a better understanding.

- 4) Discussion: The first part contains some repetitions regarding the results, and therefore should be shortened. Add to references 28 and 29 a new reference (doi: 10.3748/wjg.v20.i25.1).

According to the reviewer recommendation we have shortened the first part of the discussion section to avoid repetition about the results. However, we have not been able to find the reference suggested by the reviewer despite we have performed an exhaustive search in PubMed. So, the authors think that there could be an error in this reference.

- 5) Figure 1: Eliminate the two boxes with “?” Table 1: In the first column, you report “Age (years)” but in the second column you report the mean age and the range in parenthesis. Even if it is perceptible that the number in parenthesis represent the range, this should be reported in the bottom of the table. This is for age, liver enzymes and NA treatment duration. Table 2: See comments on table 1.

We would like to thank the reviewer for their exhaustive review and we have made the changes in figure 1 and tables 1 and 2 according to his/her comments.