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Larissa 03-09-2013

Professor M. Kudo, MD, PhD
Editor-in -chief, *World Journal of Hepatology*

Dear Professor Kudo,

Thank you very much for your e-mail message concerning our manuscript by Rigopoulou et al your Ref. ESPS Ms No: 4918 entitled "**Primary biliary cirrhosis in HBV and HCV patients: clinical characteristics and outcome**" that is kindly been accepted for publication after minor revisions in *World Journal of Hepatology*.

Today we submit our revised manuscript following your instructions with all changes precisely indicated in the text; deletions are also obvious. This work has not been published nor is under consideration elsewhere and I clearly state that all co-authors have seen and agreed with the contents of the manuscript. In addition, all authors have substantially contributed to this work and they have not any financial, consultant or institutional conflict of interest.

We are very grateful to you and the assessors for the helpful and thoughtful recommendations and for your willingness to consider a revised manuscript. We believe that we addressed all of them satisfactorily. All of us feel that our paper has now been significantly improved.

Title: Primary biliary cirrhosis in HBV and HCV patients: clinical characteristics and outcome

Authors: Eirini I. Rigopoulou, Kalliopi Zachou, Nikolaos K Gatselis, Georgia Papadamou, George K Koukoulis, George N Dalekos

Name of journal: World Journal of Hepatology

ESPS Manuscript NO: 4918

Editor comments:

Format has been updated as a "brief article". Corrections and quires made by the editor and typesetting were accepted and addressed accordingly (please see new revised

edited article). Finally, several reconstructions and corrections of grammatical errors in the whole new text have been done by a native speaker of English.

Reviewer #1:

1. *"This is an interesting article on the association between primary biliary cirrhosis and viral hepatitis Major points: The series is significant for a rare disease, and several relevant questions are raised, such as potential impact of B and C virus on clinical course"*.

Reply: Table 1 shows the demographic, clinical, laboratory and histological characteristics of 17 HBV or HCV patients with concurrent PBC. It could be ideal if we can compare these data with HCV and HBV patients without PBC, to see if there are any differences between the groups. Therefore, in order to satisfy the reviewer, we have now added 98 and 303 randomly selected patients from our records with HCV and HBV (please see new Table 1, page 6, 1st paragraph and page 13, lines 1-3). However, it should be stated clearly that this data serves for general information only and not for a statistical comparison (unfortunately you cannot compare characteristics of 9 HBV and 8 HCV patients with high numbers of HBV or HCV patients; please see also page 6, 1st paragraph) since there could be type I and II statistical errors. For these reasons, no statistical comparison was done among these groups.

2. *"Follow up period: It should be mentioned in the text and abstract, not just in the Table"*.

Reply: We have followed your recommendation (please see new abstract and page 8).

3. *"Table 1: Statistical analysis should be provided whenever possible"*.

Reply: According to your recommendation we have now provided in the new Table 1 statistical comparisons where appropriate (actually only between PBC+HBV and PBC+HCV groups).

4. *"It is not essential, however if the authors could calculate demographic and clinical variables for their patients with HBV and HCV without PBC, it would help to arrange an additional Table, or include in Table 1, highlighting statistical differences. That would enrich the article and provide insights regarding natural history of PBC"*.

Reply: Please refer to my response No. 1 to you.

5. *"Minor points: Some sentences need to be restructured, such as... Antiviral treatment with nucleos(t)ide analogues received all 4 patients..."*.

Reply: Your suggestions have been taken into account throughout the revised text.

Reviewer #2:

1. *"This is an interesting retrospective analysis of 17 patients with PBC who had in addition infections by HBV or HCV. The study cohort was derived from 1493 patients with HBV infections and 526 patients with HCV infections. The details are well described, the conclusion asks for better evaluations of patients with HBV or HCV infections regarding concomitant PBC. I have only few suggestions. Minor points: 1. In the abstract, you mention twice $P=0.05$. Is this <0.05 and thereby significantly different or not? Please clarify in the text here and later on."*

Reply: Thank you for your comments. We have now corrected this mistake (<0.05) throughout text (please see the new revised version).

2. *"The conclusion in the abstract should mention that cholestasis is an important sign to further search for PBC"*.

Reply: According to your suggestion the conclusion of the abstract has now been changed.

3. "Under Materials and Methods, para 2, line 5 from bottom: alaninaminotransferase should read alanine aminotransferase".

Reply: The suggested change has now been done.

4. "Under your section 3.4, please clarify the questions concerning p values and significance".

Reply: Please refer to my response No.1 to you.

5. "Discussion, your first para is very long, please make 2-3 paras".

Reply: We have followed your recommendation and the discussion section has now been changed accordingly.

Reviewer #3:

1. "Compared the HBV or HCV patients without PBC, whether or not the patient with viral hepatitis and PBC had different outcomes?".

Reply: Please refer to my response No.1 to Reviewer #1.

2. "How the effect of UDCA for these patients? Whether or not the patients had different response of treatment?".

Reply: Please refer to my response No.1 to Reviewer #1 and new revised Table 1.

3. "Do factors of viral or antiviral therapy especially IFNs-based therapy possibly lead the bad outcome for the patients HCV concurrent PBC? According to the guideline of APASL, EASL and AASLD, it is contraindication or caution to treat the chronic hepatitis C by using interferon based therapy".

Reply: I absolutely agree with you and we have already commented on this issue in the previous but also in the revised manuscript (please see our last two sentences of the discussion section in our previous version of the manuscript). However, the rarity of this viral and PBC coincidence precludes the possibility to draw general conclusions. I also agree that all liver international authorities underline the caution to treat HCV patients with autoimmune phenomena (e.g. anti-LKM1 positive HCV patients) but clearly no contraindication is stated on this (only close follow-up). Therefore, a small new sentence has now been added to strengthen further the need of close follow-up on this occasion (please see the last sentence on page 13).

4. "This manuscript didn't describe what statistical software they used in statistical methods. The Table 1 and Table 2 didn't give the exact value of the chi-square values or T".

Reply: I absolutely agree with you and we have already commented on this issue in the previous

Once again, I would like to thank you and the referees for your helpful suggestions and for giving us the opportunity to submit our accepted revised manuscript for publication in the *World Journal of Hepatology*.

Best wishes

Sincerely yours,



George N. Dalekos, MD, PhD

Professor of Medicine
Head, Department of Medicine and
Research Lab of Internal Medicine