



UNIVERSITY OF THESSALY
MEDICAL SCHOOL
DEPARTMENT OF MEDICINE AND
RESEARCH LAB OF INTERNAL MEDICINE



DIRECTOR: Professor George N. Dalekos
e-mail: dalekos@med.uth.gr

Larissa, October 30, 2014

Dear Editor of WJG,

Thank you very much for your e-mail message dated September 17, 2014 concerning our invited review article by Gatselis et al, your Ref. ESPS Ms No: 13256, entitled **"Autoimmune hepatitis, one disease with many faces: Etiopathogenetic, clinico-laboratory and histological characteristics"** that is kindly accepted for publication after minor revisions in *World Journal of Gastroenterology*.

Today we submit our revised manuscript in Word format (**file name: Marked_Revision_13256_Edited.doc_review_WJG**) following your instructions (including revisions for cross checking) with all changes precisely indicated in the text; deletions are also obvious.

We also upload the **"BPG Copyright Assignment_13256"**, the current file **"Answering Reviewers_ESPS_Ms No 13256"**, and a clean version of the revision (**Clean_Revision_13256_Edited.doc_review_WJG**).

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. We believe that we addressed all of them satisfactorily. All of us feel that our paper has now been significantly improved.

Title: Individualization of chronic hepatitis C treatment according to the host characteristics

Author: Nikolaos K Gatselis, Kalliopi Zachou, George K Koukoulis, George N Dalekos

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13256

Science Editor's comments:

- We have now revised our manuscript thoroughly according to the Science Editor comments (e-mail dated September 22, 2014) in order to avoid a significant amount of overlapping text

(please see new edited article).

Reviewer #1:

"This is an excellent review article dealing with comprehensive and updated information of AIH. I find no obvious fault within the contents, literature organization, or signed references. Overall, this is a high quality manuscript that has implications for the theoretical basis and clinical development of AIH. My comments here are concerned solely with that the figures legends are not detailed enough and clear labeling. For example: -All figures legends did not describe experimental procedures. - Figure 3: Please use the asterisk or arrowhead to indicate the apoptotic bodies (Fig.3A), plasmacytosis (Fig.3B), emperipolesis and hepatocellular rosette formation (Fig.3C). Once these questions are addressed, the article should be published".

Reply: We would like to thank the reviewer for his kind words concerning our review. According to the reviewer's comments we have now added detail information in figure legends and also labeling (please see new legends and arrows).

Reviewer #2:

Autoimmune hepatitis (AIH) is a chronic immune-mediated liver disorder and has a global occurrence. Currently, the diagnosis of AIH has proved to be difficult. This manuscript reviews current information about the etiopathogenetic, clinicolaboratory and histological characteristics of AIH, which were presented in more details than previous reviews. It also points out the current challenges of AIH diagnosis and then provides a future perspective. The objectives were clear and relevant. Generally speaking, the presentation and organization of the manuscript is good, and this is a topic of interest to the researchers in the related areas. However, several points need clarifying and certain statements require further correction. Based on the above, this manuscript could be considered "minor revision".

- 1. "The difficulty in AIH diagnosis by current criteria was particularly mentioned in the manuscript and the importance of specific diagnostic markers or tests was consequently emphasized. However, the current standard criteria for the diagnosis of AIH are not specifically provided in the manuscript. Thus, it is more logical to give the current standard criteria conducted by IAIHG in the manuscript, at least in a simplified form".*

Reply: We have followed the suggestion made by the reviewer and the simplified criteria for AIH diagnosis have now been included (please see new Table 3).

- 2. "In the section of "2.1. Genetics of AIH", the typical "susceptibility" genes of AIH were elaborately presented. However, there are also some other reports of susceptibility to AIH, such as the polymorphisms in genes located outside the MHC, tumour necrosis factor-alpha gene promoter and etc. It is suggested to briefly describe these uncommon factors in this section either, to provide more comprehensive understanding".*

Reply: We agree with the reviewer recommendation and these issues have been added in brief with the appropriate references in the last sentence of section 2.1.

- 3. "In the section of "2.2. Molecular mimicry in AIH": although there is abundant evidence for molecular mimicry, especially following HCV infection, a universal trigger for AIH has not yet been established. Therefore, some other mechanisms that may contribute to AIH development should also be briefly described at the end of this section".*

Reply: We would like to thank the reviewer for this valid comment. Yes, of course there are some other mechanisms apart from molecular mimicry and this has now been clearly stated in brief at the end of section 2.2. (p.10, 1st par. of the clean version).

- 4. "In the first paragraph of "3.1 Clinical features of AIH", the development of the naming of AIH was detailedly described. This part is redundant in the section of "Clinical phenotypes of the disease" and should be deleted or move to the introduction".*

Reply: According to the reviewer's suggestion we deleted this paragraph.

5. *"In the section of "3.1. Clinical features of AIH": how about adding the description of natural history of AIH in this section?"*.

Reply: We have followed the suggestion and a brief description of the natural history of AIH with the appropriate reference has now been added (see last paragraph of section 3.1).

6. *"The subtypes of AIH were used prior to the declaration of the classification of AIH (section 4), such as "...susceptibility to AIH-type 1" and "...susceptibility to AIH-type 2" mentioned in "2.1.Genetics of AIH". Readers may be curious about the number of subtypes of AIH and the differences among them when first meet the term like AIH-1 or AIH-2. Thus, it is recommended to briefly describe the classification of AIH at first in the introduction"*.

Reply: According to your recommendation we briefly describe the classification of AIH firstly in the introduction (please see p.6 of the clean version).

7. *"In the section of "4.2.Detection of autoantibodies in AIH-2", IIF appearance on tissue substrates of the anti-LKM1 autoantibodies, which is the diagnostic of AIH-2, was illustrated in figures. Why IIF figures of ANA and/or SMA were not given in "4.1.Detection of autoantibodies in AIH-1" section, since both of them contribute to the autoantibody profiles of AIH-1 that are distinct from AIH-2? If there are reasons, give it"*.

Reply: This was done for space frame and also because the pattern of ANA and SMA is very common in clinical practice whereas, anti-LKM pattern is quite peculiar and interesting as sometimes routine labs ignore it or mistakenly they give this result as AMA. By the way, if you insist there is no problem to incorporate these patterns too.

8. *"In the first paragraph of "4.2. Detection of autoantibodies in AIH-2, line 6" & "Legend to the figure 2": anti-LKM1 versus "Antimitochondrial antibodies", keep them uniform"*.

Reply: We have changed these expressions according to your suggestion.

9. *"In the fourth paragraph of "5.Liver histology in AIH", line 6: "Two distinctive patterns of massive hepatic necrosis" should change to "There are two distinctive patterns of massive hepatic necrosis"*.

Reply: We have changed it accordingly.

10. *"In the sixth paragraph of "6.Conclusions" section, line 1: the necessity of liver biopsy was only emphasized in the term of AIH diagnosis. In general, the utility of liver biopsy in disease severity evaluation of AIH should also be mentioned"*.

Reply: We completely agree with the reviewer and this statement has now been added.

11. *"In the "Legends to the figures " section: change "Fig. 4"*.

Reply: We have changed it accordingly.

In addition, a native speaker of English has done some further reconstructions of English language in the whole new text.

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

Sincerely yours,



