

February 25, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16183-revised.doc).

Title: Antiphospholipid antibodies (APLA) are associated with Crohn's disease but they are not associated with disease phenotype or disease course in large prospective cohort study

Revised title: Prevalence, significance and predictive value of antiphospholipid antibodies (APLA) in Crohn's disease

Author: Nora Sipeki, Laszlo Davida, Eszter Palyu, Istvan Altorjay, Jolan Harsfalvi, Peter Antal Szalmas, Zoltan Szabo, Gabor Veres, Zakera Shums, Gary L. Norman, Peter L. Lakatos, Maria Papp

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16183

We are grateful to the reviewers for their positive opinion, useful recommendations and for suggesting our paper for publication. The manuscript has been improved according to the suggestions of reviewers and editor.

Answers to editor's comments:

1. We revised the title of our manuscript according to the editor's request.
2. We added missing postal codes.
3. We added author contributions.
4. We added additional support (IOIBD Grant).
5. We added information to the appropriate sections about ethics approval, clinical trial registration, informed consent, conflict-of-interest and data sharing.
6. We revised the abstract according to the editor's instructions. The length of "Aims" and "Conclusion" was reduced to the indicated word number. On the other hand the "Methods" and "Results" sections were extended to reach the preferred word counts in each part.
7. We added audio core tip in the appropriate format.
8. We added "Biostatistics statement" information to the "Materials and Methods" section affirming that the statistical review of the study was performed by a biomedical statistician.
9. We wrote the "Comments" section according to the editor's guidelines.
10. We rechecked the references and hereby confirm that all of the references are properly cited.
11. We revised the manuscript according to the reviewers' requests including language editing as well.

Answers to reviewer comments:

Reviewed by 00035859

"This article relooks at the role of anti phospholipid antibodies in IBD. In a cohort of 458 patients and reviews the earlier literature. This is well-designed and conducted study and gives clear conclusion that APLAs are not associated with disease phenotype including the thrombosis and do not need further study unless a newer aspect comes in future. The only negative point about this article is that it is long. It may be worth reducing the number of tables."

Thank you for your comments. Adjustments about the length of the article and the number of tables were made according to the reviewer's request. Supplementary Table 4 and regarding data

in the text ("Results" section, "APLA Markers and disease progression in CD" subsection) were eliminated since follow up of CD patients with complications (B2 or B3) at first sampling did not result in significant conclusions worth describing. For the same reasons data describing "Antiphospholipid antibodies (APLA), thrombophilia markers and clinical characteristics of total ulcerative colitis (UC) patient cohorts according to presence and type of thrombosis" in Table 6 part B was also deleted. Redundant and irrelevant information in Table 4 and 6 (e.g. rows of "Age at first sampling" and "Duration" and columns of "CD Total" and "CD Female Cohort Total") was decreased.

Answers to reviewer comments:

Reviewed by 00034489

"The authors show the analysis of antiphospholipid antibodies in patients with IBD using prospective cohort study and small systematic review. The manuscript has much information in APLA. However, there are several concerns with regards to the investigation. Please see below. Major comments 1) The authors detect significant differences in only a few antibodies among APLA between IBD and APLA. The manuscript is illegible manuscript because the authors load up on so many data in the manuscript. Authors should make choice of data to make easily comprehensible manuscript. Minor comments 1) There are so many abbreviations in the manuscript. Abbreviations should be decreased. 2) Table 1, 4 and 6 should be condensed. 3) The note of Table 3 is confused. 4) Figure 2 and 3 are unnecessary."

Thank you for your comments. Adjustments about the length of the article, the number of tables and figures were made according to the reviewer's request. 1) Unnecessary abbreviations were eliminated. 2) Supplementary Table 4 and Table 6 part B were deleted as well as related data in the text to reduce extensive information overload, thus making our manuscript easily comprehensible. Changes were made in Table 4 and 6 as well: redundant and irrelevant information (e.g. rows of "Age at first sampling" and "Duration" and columns of "CD Total" and "CD Female Cohort Total") was decreased to make tables more condensed without losing relevant information about study results. 3) We are grateful for your comment on Table 3's footnote. Some the symbols were switched by mistake; therefore corrections were made to clear this confusion. 4) Figure 2 and 3 were also deleted according to the reviewer's suggestions.

Answers to reviewer comments:

Reviewed by 02997185

"The manuscript by Sipeki et al described the association between Antiphospholipid antibodies (APLA) and Crohn's disease in a prospective cohort study. Several comments are given as follows. The presence of more different types of anti-phospholipid antibodies measured by different assays has higher tendency to develop thromboembolic events. Thus, to those patients with positivity of several different types of APLA should be grouped and analyzed individually to see if the co-existence of several APLA may have the higher tendency to develop thromboembolic events compared to those with only one type of APLA. The table presentation is hard to follow and should be effectively summarized and presented. Keep only the valuable messages in the table. Appropriateness of statistical analysis may need to be evaluated by an expert in the field. Abbreviations used in the text should be consistent. For example, HCONT in table 3 should be replaced by HC in table 1. English-editing is required to improve the quality of this report."

Thank you for your comments. Evaluation of multiple positivity for different APLAs was performed according to reviewer's suggestions; however co-existence of more than one type of APLAs was not associated with the development of thromboembolic events neither in CD, nor in UC patients. We added these new data into the text and supplementary rows to Table 6's appropriate part ("Positive Markers"). Statistical review of our manuscript was done by a biostatistician and a certificate is attached as required. Abbreviations were rechecked to be consistent in the text. English language editing was performed by a native English speaker. Certificate is attached as well.

Linguistic edits and other changes in the content of the text were highlighted **in red**.

Please find attached the “highlighted” version of the manuscript with the detailed changes that were made according to the reviewers’ comments.

We would like to thank you again for the helpful comments and for considering our paper. We do hope that the changes that have been made, have improved the quality of the manuscript also with regards to the presentation of the data.

All authors have fulfilled the criteria of authorship and seen and approved the final version of the revised manuscript and they have authorized the first author to grant on behalf of all authors to transfer exclusive copyright to World Journal of Gastroenterology in case of acceptance. We do hope that the new data presented could be of interest to the readers of the World Journal of Gastroenterology.

Sincerely yours,

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