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Dear Editor and Reviewers,

We would like to thank the editor and the reviewers for their conscientious reviews, and insightful comments and suggestions to improve the manuscript. In the response below, we have addressed all the concerns raised by the editor and the reviewers in the revised manuscript. We hope the editor and the reviewers will find that our revised manuscript has improved and is suitable for publication. Due to the limited period, our reply may be not perfect. If complement the experiment is needed, we will finish it as soon as possible. All changes have been marked in red.

I hope my paper could achieve the academic standards of your magazine and be published finally. Thank you very much.

Yours Sincerely,
Bing Chang

Response to Reviewers Comments

Manuscript NO.: 63780, Minireviews

Novel mechanism of hepatobiliary system damage and IgG4 elevation caused by clonorchis sinensis infection

Xin-He Zhang, Die Huang, Yi-Ling Li, and Bing Chang.

Editor comments:

(1) The “Author Contributions” section is missing. Please provide the author contributions;

Response: Sorry, we have added in *Authorship*. Bing Chang designed the study; Xin-He Zhang, Die Huang wrote the original draft; Xin-He Zhang, Yi-Ling Li, and Bing Chang reviewed and edited; All authors read, revised and approved the final manuscript.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: Sorry, we will provide the original picture using PowerPoint.

(3) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. *World J Gastroenterol* 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable; and

Response: These pictures have not been published in any magazines. They are from our patients whose IgG4 was elevated due to *Clonorchis sinensis* infection. We have obtained the consent of patients and published the pictures.

(4) The column should be minireviews.

Response: Sorry, we will modify the column.

Reviewer reports:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1. In this paper, the authors describe the new mechanism of IgG4 elevation caused by *Clonorchiasis sinensis* infection in the form of review. The hypothesis is bold and the idea is novel. If confirmed, it will provide new ideas and new methods for clinical diagnosis and treatment. 2. This article reviews the epidemiology, clinical manifestations, serology, imaging, pathogenesis and control measures in detail. 3. In general, this paper focuses more on the epidemiology, clinical manifestations and the routine diagnosis methods of *Clonorchiasis sinensis* infection, while the relevant mechanisms related to the increase of IgG4 are not elaborated in detail, especially the correlation between cytokines and IgG4 is not clearly explained, and the

relevant basic research needs to be improved. 4. It is suggested to add the basic research content on the association between cytokines and IgG4, as well as the correlation content between the severity of Clonorchiasis sinensis infection and IgG4 changes. If the valuable interval can be determined, this will provide a strong basis for the application of the research.

Response:

- 1) Thank you for the evaluation. We explored the relationship between Clonorchis sinensis infection and elevated IgG4 through a novel and fully treated case. Hope our review can provide new clinical ideas.
- 2) Thank you for reading our article carefully. We review the epidemiology, clinical manifestations, serology, imaging, pathogenesis, control measures and related mechanism.
- 3) Yes, the correlation between cytokines and IgG4 have been discussed. We have added the content on discussion. This part of the content is marked as blue. The content is as follows:

T cells and their cytokines play an important role in the increase of IgG4 and the conversion of IgG4 classes[60]. Th1 cells produce IL-2 and TNF- α to induce inflammatory response, and Th2 cells produce IL-4, IL-5 and IL-13 to counteract the microbicidal effect mediated by Th1. In terms of IgG4-RD, the major disease with elevated IgG4, many studies have found the deviation from Th1 / Th2 balance to Th2 and Th2 contributes to the pathogenesis of IgG4-RD. This is closely related to the cytokines produced by Th2. IL-4 and IL-10 are considered to be the main inducers of IgG4-type switching in naive B lymphocytes[61]. It has been proved that the class switch to IgG4 is caused by co-stimulation with IL-4 and IL-10. In addition to T helper lymphocytes, IL-4 is also derived from eosinophils, basophils, and mast cells. In eosinophils and mast cells, IL-4 exists in the form of particle-related peptides, which can be released quickly in allergic inflammatory reactions. IL-4 stimulates MHC class II molecules, B7, CD40, surface IgM and low-affinity IgE receptor expressed by B cells, thus promoting the antigen presentation ability of B cells. IL-4 induces the isotype conversion of immunoglobulin from IgM to IgE. Through cell experiments, it was found that IL-4 can significantly increase the content of IgG and IgG4 in IgG4-RD. The level of IL-4 was directly proportional to the value of IgG4[62]. IL 10 is an important regulator of immune response, which directly affects APC by down-regulating the expression of MHC class II and costimulatory molecules on the surface of macrophages and monocytes. IL-10 reduces the conversion to IgE induced by IL-4, and increases the conversion to IgG4[63]. IL-13 are also responsible for the production of IgG4 and IgE by B cells, which drive the deposition of extracellular matrix through activated fibroblasts. At present, the specific mechanism of the relationship between cytokines and IgG4-RD is not clear, probably because the inflammatory environment constructed by cytokines is a key step in the pathogenesis of IgG4-RD.

Reference:

60. Kubo S, Nakayamada S, Tanaka Y. Immunophenotype involved in IgG4-related disease. MOD RHEUMATOL.2019;29(2):226-30[PMID:30334637.DOI:10.1080/14397595.2018.1537962]
61. Della-Torre E, Lanzillotta M, Doglioni C. Immunology of IgG4-related disease. CLIN EXP IMMUNOL.2015;181(2):191-206[PMID:25865251.DOI:10.1111/cei.12641]
62. Akiyama M, Yasuoka H, Yoshimoto K, Takeuchi T. Interleukin-4 contributes to the shift of

balance of IgG subclasses toward IgG4 in IgG4-related disease.

63. Moriyama M, Nakamura S. Th1/Th2 Immune Balance and Other T Helper Subsets in IgG4-Related Disease. *Curr Top Microbiol*

4). Yes. The clinical mechanism needs to be confirmed by basic experimental theories. Therefore, we searched for keywords (clonorchis sinensis, IgG4, mice, rats, rabbits) in PUBMED and EMBASE and other databases. No relevant animal models have been seen yet. Therefore, our team is actively planning and plans to complete the model of C57BL6 male mice infected by Clonorchis sinensis with IgG4 increased within one year. We will explore the relevant mechanism, whether cytokines are involved in this process and the relationship between the severity of Clonorchis sinensis infection and IgG4 indicators. However, due to the complexity and uncertainty of the experiment, it could not be completed within the specified time for the time being. And we will show our further results in our magazine.

Yours Sincerely,

Bing Chang