47060-Answering Reviewers

Dear Dr. Ruo-Yu Ma

Science Editor
World Journal of Gastroenterology

We are pleased to re-submit our revised manuscript entitled, Autoimmune hepatitis and IgG4-related disease (Manuscript NO: 47060), to the World Journal of Gastroenterology as a review article. We appreciate the reviewers' comments and revised the original manuscript. In addition, we also revised the original manuscript and prepared additional files as suggested by the Science Editor. We have highlighted the changed portions as red color in this revision. Please see our responses to reviewers' concerns. We believe that our revised manuscript is suitable for publication in the World Journal of Gastroenterology.

Sincerely yours,

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Responses to the reviewers' comments

Reviewer #1

The authors should comment on the following questions:

1. *Can it be helpful to check HLA-Status to differentiate between IgG4-hepatitis and AIH ?*

Reply; We agree with this reviewer in that differences in HLA status might be helpful to differentiate between IgG4-associated AIH and classical AIH. In fact, HLA-DR3 and HLA-DR4 are associated with classical AIH. One study examined the positivity of HLA-DR 3 or 4 and reported that one of two patients

with IgG4-AIH was positive for HLA-DR4. We discussed the relationship between HLA status and IgG4-AIH/classical AIH in this revision (page 11).

2. *Are overlap-syndromes to PSC or PBC possible ?*

Reply; Canivet's study included two overlap syndromes; IgG4-AIH/PBC and IgG4-AIH/PSC. Thus, IgG4-AIH and PBC or PSC can occur concurrently. We added this information in the revision (page 9).

3. Does IgG4-hepatitis respond well to azathioprine ?

Reply; Azathiopurine (AZA) was administered to IgG4-AIH patients after the initial glucocorticoid treatment in three studies. They reported that the overall response rates to AZA at the maintenance phase were comparable between IgG4-AIH and classical AIH. We added this information in this revision (page 14).

Reviewer #2

IgG4-associated autoimmune hepatitis (IgG4-AIH) is a new disease entity characterized by the infiltration of IgG4-positive plasma cells in the liver. It is extremely rare and is not fully clear whether IgG4-AIH is a hepatic manifestation of IgG4-reated disease (IgG4-RD) or a subtype of autoimmune hepatitis (AIH). The authors in this review try to clarify clinical characteristics of IgG4-AIH by comparison with classical AIH and discuss whether IgG4-AIH should be considered as a subtype of AIH or as hepatic involvement of systemic IgG4-RD. It's really well organized and written.

Reply; We appreciate positive evaluation from this reviewer. In this revision, we carefully read the manuscript again and corrected typo-grammatical errors.

Reviewer #3

IgG4-RD is a field of considerable interest with a growing number of publications during the past years involving many organs and tissues, but the real impact in liver diseases is poorly

known. The authors have made an effort to update the most recent findings in this field. Unfortunately, diagnosis of IgG4- "autoimmune-like hepatitis" is uncommon and the few cases described in the literature are somehow contradictory, as stated in this review. It continues being difficult to distinguish IgG4-related liver disease from the classical autoimmune hepatitis (AIH).There are very few studies with very few cases and the interpretation of the results presented is not conclusive. It seems that IgG4-RD does not have a big impact in the liver, as extracted from the few publications in this field or it is an unexplored field. Despite the few published data, this review is an interesting update, based in 5 recent studies where the authors claimed to have identified a subclass of AIH, called IgG4-AIH, based on the presence of a higher number of IgG4-plasma cells in biopsy compared with classical AIH biopsies. It is well written and organized.

Reply; We appreciate positive evaluation from this reviewer. In this revision, we carefully read the manuscript again and corrected typo-grammatical errors.