Ya-Juan Ma, Science Editor
World Journal of Gastroenterology

Date: 27th March, 2016

Subject: Resubmission of manuscript 35187

Dear Editor,

Thank you for the opportunity to resubmit our manuscript, entitled "*Auto Immune hepatits, epidemiology, clinical aspects and treatment*" by van Gerven *et al*.

We thank the reviewers and Editor for their comments, which enabled us to improve the manuscript. Below, we provided a point-by-point reply to each of the reviewers' comments. With this thorough revision we hope that the manuscript will become acceptable for publication in the *World Journal of Gastroenterology.*

Sincerely yours,

Nicole van Gerven,
Chris Mulder

COMMENTS TO AUTHORS

Reviewer 1:

Autoimmune hepatitis (AIH) is an immune meditated progressive inflammatory liver disease that predominantly affects middle-aged females. In this manuscript, the authors reviewed and discussed the latest trends in epidemiology, clinical course, diagnostics, complications and treatment of AIH. This is a comprehensive review on clinical aspects of autoimmune hepatitis, including epidemiology, clinical course, diagnostics, complications and treatment. The manuscript was well prepared. Although there remain significant areas of unmet etiological and clinical needs, e.g. pathogenesis, optimal therapy, duration of treatment and treatment alternatives in those patients unresponsive to standard treatment, this review provided useful information for the clinicians to diagnose and manage the AIH.

Response: We thank the reviewer for the careful review of our manuscript.

COMMENTS TO AUTHORS

Reviewer 2:

This paper reviewed the epidemiology, clinical aspects and treatment of auto immune hepatitis. The manuscript is well presented and of interest and can contribute to increase the knowledge of this topic.

Respons: We thank the reviewer for the careful review of our manuscript.

COMMENTS TO AUTHORS

Reviewer 3:

The manuscript "An update of auto immune hepatitis: epidemiology, clinical aspects and treatment: a systematic review" is a comprehensive review of the current state of the epidemiology, pathogenesis, diagnosis, treatment and prognosis of the autoimmune hepatitis. Although it is a complete and well-written review, there are some errors to be amended to improve its quality. I have only few minor comments.

Minor comments:

Reviewer: Abstract. In the aim section, use autoimmune hepatitis instead AIH, this abbreviation has not been described previously.

Respons: we would like to thank the reviewer for bringing this to our attention. This has been corrected.

Reviewer: Page 6, first paragraph, line 2; add the abbreviation Treg after "regulatory T cells". Page 6, first paragraph it is stated that "That impaired immunoregulation could partially account for the pathogenesis of AIH is suggested by studies showing that a numerical Treg impairment affects both children and adults with AIH(15-17)." What is the meaning of the numerical Treg impairment? Does it referring to an enhancement or decrease of the Treg?

Respons: The abbreviation is added.

Imbalance between effector and regulatory mechanisms results in the breakdown of immune tolerance and consequent development of autoimmune disease. Numerical and functional defects of regulatory T cells (Tregs)—a subset central to the maintenance of immune homeostasis—play a permissive role enabling autoimmune responses to occur and persist. Patients with autoimmune hepatitis (AIH), have numerically and functionally defective T-regs. This defect relates to the stage of liver disease, being more evident at disease presentation than during treatment induced remission, where a partial restoration is observed. The study from Peiseler et al showed that he Treg frequency was significantly higher in those AIH patients with active disease than in those who were in a state of remission, suggesting that the Treg frequency may increase with the degree of inflammation. Indeed, analysis of FOXP3+ Treg in liver histology revealed that the intrahepatic Treg frequency was higher in AIH patients than in NASH patients and correlated with the inflammatory activity of the liver.

This is now added on page 5.

Reviewer:
Page 9. The abbreviations ALP, GGT and IBD have not been defined. The anti-smooth-muscle antibodies are abbreviated as SMA (page 4) or as ASMA (page 9). Please unify the abbreviation for the anti-smooth-muscle antibodies in the manuscript.
Respons: we would like to thank the reviewer for bringing this to our attention. This has been corrected.