

ANSWERS TO ESPS PEER-REVIEW REPORT

Name of Journal: World Journal of Gastroenterology

ESPS manuscript NO: 22388

Title: De novo autoimmune hepatitis in liver transplant: state-of-the-art review

Manuscript #: 22388 The authors provide a comprehensive review about the current knowledge of de novo autoimmune hepatitis, a complication of the liver transplant whose pathogenic mechanisms are not completely understood. The manuscript is well written and addresses all the known issues about this disease. It is a very complex process and there are probably more than one pathway leading to its development. Specific comments to the manuscript

1. Association of HLA type and development of de novo autoimmune hepatitis has not been properly addressed in this review. HLA DRB1*0301 and/or DRB1*0401 are susceptibility alleles for AIH and, in general, for autoimmune diseases but their relevance in de novo AIH has not been demonstrated. Most of the citations do not reflect what they say in this context.

The Reviewer's suggestion has been greatly appreciated and, along with this, more addressing sentences regarding HLA type impact on post-transplant de novo AIH have been added. In particular:

- Page 5: Reference 9 (Kerkar, 1998) The frequencies of DRB1*03 and *04 observed among patients with de novo AIH are similar to those in the control group.

This has been specified correspondingly to the respective citation.

-Page 7 The authors say "it is generally accepted that this entity (de novo AIH) shares very similar if not identical mechanisms with classical AIH, including viral antigens and a predisposing genetic milieu (56)". Reference 56 (Guido, 2011) refers to a paper by Czaja (Liver Transplant, 2002) in which these HLA class II alleles are only implicated in classical AIH but not in de novo AIH.

The statement has been softened and contextualized.

-Page 8 "This process probably occurs even more easily in genetically predisposed subjects, i.e., those with HLA DR3 or DR4 phenotypes... (2, 8, 56) Reference 2 (Selzner, 2011) these alleles are only associated with AIH. Reference 8 (Liberal, 2012) is a review that cites publications by Kerkar (already discussed), Heneghan, 2001 that did not find "statistically significant differences in prevalence of DRB1*0301 or DRB1*0401 between patients with graft dysfunction mimicking AIH and control patients".

Given its exceedingly broad meaning, the sentence has been removed.

-The importance of HLA alleles in de novo AIH has been

overestimated. This message should be softened. My suggestion to the authors is that either they remove some of these sentences or replace them with more precise original citations.

As suggested, the concerns on HLA alleles importance in de novo AIH have been rearranged both by the removal of inadequate statements and by a more appropriate referencing to the literature.

2. Minor issues:

-In page 3 (Core tip) when they say autoantibodies, it would be more correct to say either just antibodies or auto- and alloantibodies (atypical LKM/GSTT1 are alloantibodies).

The suggested correction has been brought.

-In page 5 one report is missing among those that describe de novo AIH in adults. It is the first report to substantiate the importance of the GSTT1 system in de novo AIH in a large cohort of patients (Aguilera et al, Liver Transplantation 2004)

The citation has been added to the pathogenesis insight dedicated to the researches of Dr Aguilera and Colleagues.

Finally, the Manuscript has been modified according to Editor's suggestions and tracked changes.

The revisions are highlighted through the revised Manuscript copy.

The Authors