ANSWERING REVIEWERS

January 4, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7144-review.doc) and my IELTS diploma.

Title: Management of Autoimmune Hepatitis: focus on pharmacologic treatments beyond corticosteroids.

Author: Marta Casal Moura, Rodrigo Liberal, Andreia Albuquerque, Filipe Vilas-Boas Silva, Hélder Cardoso, Ana Maria Horta e Vale, Guilherme Macedo

Name of Journal: *World Journal of Hepatology*

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The manuscript has been improved according to the suggestions of reviewers.

1 Format has been updated according to the writing requirements for mini-reviews and editor suggestions.

a) The abstract was converted an informative, unstructured abstracts of no less than 200;
b) The format of first title sections – bold Book Antiqua 13 (like **Introduction**); the subsections in bold Book Antiqua 12 (like **Standard pharmacologic treatment**); the sub-subsections as a…., b. ….., in bold Book Antiqua (like **a. Mycophenolate mofetil (MMF)**) and then the sub-sub-sections in regular Book Antiqua 12 as a.1. …. a.2. … (like b.1 Cyclosporine A (CyA)).
c) The format of the numbers related to references were changed to superscript.
d) Page numbers were included.

2 Revision has been made according to the suggestions of the reviewer

First reviewer (nº 01836203):

a) Original articles were added as references along the article and the others already referred were cited as references in more appropriate places in the text (page 13). The reference numbers added were number 31, 36, 45, 47 and 48.
b) Reference to 6MP as an active metabolite of azathioprine (page 11).
c) Costs: "Newer agents are much more expensive than the standard treatment irrespectively of the generic use (as recently available generic mycophenolate mofetil may attenuate this problem) and this may be a limitation to the accessibility to these treatments." (page 14). The lower costs attributed to standard therapy may be obviate by generic appearance as in the casa of mycophenolate mofetil. Of course that for other therapies, this issue remains impossible to overcome.
d) Table was modified according some suggestions of the reviewer. Outcomes were included. Follow-up time and number of patients of the most relevant studies were included.
e) It's rather controversial include budesonide in this mini-review although I thing you're right at least histoically speaking. So I've included a reference on page 12 to budesonide as an alternative corticosteroid regimen.

f) Not very good data about prevalence or incidence of arthralgia presence in autoimmune hepatitis. "AIH can be associated with a variety of extrahepatic immune-mediated symptoms and diseases, which affect about 25% of patients, being arthralgia the most frequent". (page 6).
g) Of course the sentence wasn't clear, about the presence of cirrhosis and mortality – it's its presence at diagnosis - "The presence of cirrhosis at diagnosis is associated with a mortality rate of 58% within 5 years". (page 7).
h) Reference to factors that influence the prognosis "In addition, the prognosis of disease is influenced by age (young patients having an increased risk), presence of cirrhosis, treatment response (as opposed to activity) and relapses." (page 6).
i) About relapsing, references about remission and relapse rates were updated and Dutch Group study on relapsing was included. "Retrospective analysis indicates that loss of remission or relapse occurs in virtually all patients with AIH in long-term remission when immunosuppressive therapy is discontinued". (page 10)
j) The definitions of difficult-to-treat patients were revised in all the text.
k) About histological remission, I absolutely agree with the comment and I've changed the text to an explicit reference to histological remission based on the comment. "Histological remission should be differentiated from biochemical remission (complete normalization of aminotransferase levels including IgG). Treatment should definitely be considered in any patient with proven AIH, histological activity and a more than marginal elevation of aminotransferase levels, not only in patients with levels greater 5xULN." (page 10).
l) Abbreviations were corrected.
m) Emphasis was given to the combination therapy being the regimen of choice in standard pharmacologic therapy as monotherapy is preferably avoided. "Combination therapy, the treatment of choice, with low-dose prednisolone (30 mg/day) with 1 mg/kg azathioprine permits to reduce steroid related side-effects in the induction phase[11]. While a flat dose of 50 mg is used for azathioprine in the US, a higher dose of 1–2 mg/kg bodyweight is often used in Europe[2]. Alternatively, monotherapy may be used, with 60 mg of steroid with reduction by 10 mg/week to maintenance of 20 mg for at least 6 months, and further reduction until lowest dose in 2.5 mg decrements." (page 11).
n) Considered the comment about starting with high doses of prednisolone since response rates are higher. "Maybe the initial prednisolone dose in combination therapy should be considered since the percentage of response is higher. Both are equally effective in the induction of remission, although combination therapy is generally preferred because it frequently allows for the reduction of the prednisone dose to below 10 mg and thereby reduces the unwanted steroid-associated side effects[6]." (page 11).

Second reviewer (nº 02462024):

a) Budesonide wasn't included in this minireview initially because it's a steroid. This question was rather controversial between the authors but I personally agree that historically speaking and regarding the posible indications of this regimen it should be mentioned. So I've included a reference to budesonide (page 12).
b) Utility of AZA metabolite measurement reference was absent as it was allopurinol use. It was really a flaw. On page 11 and 12 I explain the role of both as pharmocologic treatment adjuvants.
c) Relapsing and remission rates were revised according to the comments. (page 10)

Third reviewer (nº 02447151):

a) Genetic/population background – although many differences are seen in Asian populations regarding presentation, outcome and treatment response, the best documented genetic factors distinguish European and North American and also the prospective good data present were obtained in non Asian populations. So it's difficult to approach the real differences in Asians as we don't have very good data on that.
b) Ursodeoxycholic reference included as reference number 73 (page 21).

c) Mistakes in the references were corrected.
d) Correction of phase I Rituximab study citation referring to number 66 (page 18).
e) Misspelling pointed were corrected.

3 References and typesetting were corrected according to the suggestions of the editor and reviewers.

a) PubMed citation numbers for the reference list, e.g. PMID and DOI, were included. All references have PMID but DOI was included when posible because in some of the references it wasn't retrieved by http://www.crossref.org/SimpleTextQuery/. It happen in 17 references. The references numbers are: 22, 27, 31, 36, 39, 44, 45, 46, 48, 49, 58, 62, 63, 66, 68, 69, 71.
b) Mistakes on the references highlighted by reviewer nº 02447151 were corrected.
c) All the references were reviewed in order to find some spelling or form mistakes.

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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