

January 16, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: [6733-review.docx](#)).

Title: Practical Approach In Hepatitis B e Antigen-Negative Individuals To Identify Treatment Candidates

Author: Ahmad Najib Azmi, Soek-Siam Tan, Rosmawati Mohamed

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: [6733](#)

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

1 Format has been updated

2 Revision has been made according to the suggestions of the 1st reviewer 00011088

(1) "If the authors propose a new classification outlining the crucial issue of a possible underlying fibrosis or cirrhosis in inactive carriers, they should give us more convincing data on the real role of LSM, a staging technique not universally accepted apart for HCV patients."

Respond: We have included more data on the role of LSM, including a recent meta-analysis which showed that good correlation of LSM using transient elastography with fibrosis stage in CHB patients. Refer to page 10, paragraph 5, section "Assessment Of Chronic Hepatitis B Patients Who Are HBeAg-Negative".

(2) "Regarding the nucleos(t)ide treatment it should be emphasized that the majority of patients will have an indefinite treatment."

Respond: We have added this statement to page 18, 1st paragraph in "Stopping therapy in HBeAg-Negative Disease" section.

(3) "It would be nice to report the data on virologic endpoints (including resistance) as well as on clinical (decompensation rate and HCC cumulative probability in patients with advanced fibrosis/cirrhosis) and histological endpoints of long term (five-six years) treatment with entecavir and tenofovir."

Respond: We have added the data on virologic endpoints, data on histological endpoints of long term treatment with entecavir and tenofovir in page 17, 1st paragraph, section "Oral Nucleos(t)ides Analogues (NA) in Chronic HBeAg-Negative disease.

(4) "When a rule is proposed (for example when to stop NA treatment) it should be better to report the difference (if any) among the international guidelines (asian, european and american ones) and this should be applied for all the statements throughout the whole review."

Respond: We have updated the differences/similarities among the international guidelines and made a table for this information (Refer 'Table' section, page 31)

(5) "Authors should mention qHBsAg in the management (stopping rules) of IFN and Peg-IFN treatment."

Respond: We have added the role of qHBsAg in stopping treatment of IFN and Peg-IFN to page 19, last paragraph section "Stopping therapy in HBeAg-Negative Disease".

3 Revision has also been made according to the suggestions of the Science Editor.

(1) "Overall it is an accurate review and English is acceptable, but it is not much shorter or more readable than the same section in the guidelines themselves and it is unclear if the audience is general physicians, some specialty training or what. Furthermore it is only an incremental update of a similar review that your own journal published in 2011 Liedo et al, Mar 28th, p 1563-8. It is true that the submitted manuscript references some 2012 papers including updated AP society but the argument that this updated review is fundamentally better or state of the art has fundamentally changed needs to be strengthened".

Respond: Our target audience are clinicians involved in the management of chronic Hepatitis B (stated in abstract). We have included a few more recent articles including a recent meta-analysis which showed that substantial proportion of HBeAg-negative patients with slight increases in level of ALT have significant fibrosis and in addition another recent article which questioned the accuracy of international guidelines for identifying significant fibrosis in HBeAg-negative patients based on ALT and HBV DNA. We have also added in the last paragraph in the introduction that this review "summarizes international guidelines on the management of HBeAg-negative individuals and includes recent data on the use of non-invasive tools such as HBsAg quantification and transient elastography in order to assist clinicians to identify those who warrant treatment." (Page 5, 3rd paragraph, section 'Introduction')

There has been no recent review specifically addressing the management of HBeAg-negative individuals. The article by Liedo et al, Mar 28th, p 1563-8, is on the "Management of occult hepatitis B virus infection"

(2) Make a Figure summarizing all 3 guidelines

Respond: We made a table to summarize the treatment difference/similarities for HBeAg-negative disease. The included table comparing the 3 guidelines and emphasize on the role of liver biopsy or non-invasive tools such as HBsAg quantification and transient elastography in addition to ALT and HBV DNA to identify treatment candidates. (Page 32, Table section)

(3) "Page 14 there is a statement that genotypic analysis should guide antiviral selection if breakthrough occurs, but here is a place where too little detail knowledge is given, and in fact a basic understanding of the fact that resistance to L nucleosides, (lamivudine, telbivudine, emtricitabine) confers complete resistance to all other L NAs and

compromises entecavir response necessitating a higher dose while generally there is no cross resistance to tenofovir would be clinically useful knowledge sometimes obviating the need for expensive genetic analysis."

Respond: We have included the statements in page 17, 2nd paragraph at section "Oral Nucleos(t)ides Analogues (NA) in Chronic HBeAg-Negative disease".

(4) "Page 4 paragraph 3 is too long and obscures the simple point measurement of ALT is often insufficient to rule out disease. It needs to be shortened."

Respond: We noticed the paragraph was mixed up with other point. We have split the paragraph, as the second part is not just referring to ALT (Refer to page 9, section "Assessment Of Chronic Hepatitis B Patients Who Are HBeAg-Negative" and "Who Needs Treatment?" on page 15, 2nd last paragraph)

(5) "It should be acknowledged that Hep B Ag quantification, and elastography is unavailable in many parts of the world, including the US."

Respond: We have added this statement to page 10, paragraph 5, section "Assessment Of Chronic Hepatitis B Patients Who Are HBeAg-Negative" and to last paragraph section "Role of HBsAg Quantification In The Assessment of Patients With Negative HBeAg".

3 References and typesetting were corrected.

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

Sincerely yours,



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