

Response to reviewer's comments - Manuscript No. 6500



January 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Response to reviewer comments-Manuscript No 6500.docx).

Title: Management of antiviral drug resistance in chronic hepatitis B

Author: Ki Bae Bang, Hong Joo Kim

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6500

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 reviewer

(1) Reviewer 1

This review is an update on the management of HBV resistant variants arising during therapy. In that regard, the table 1 can be view as a guide for selecting the best regimens base on HBV rt-polymerase amino acid sequences. Although there is several review on this topic published every year, this one is short, concise and up-to-date. Therefore I support its publication in WJG.

Major comments:

-The figures 1 and 2 are already available on the website «Wikipedia» under HBV. I guess the authors of this review are also the authors of the text on HBV in Wikipedia. If not they should clarified this or change the figures.

→ We deleted the figures 1 and 2 because the schematic organization of HBV genome (figure 1) and replication cycle of HBV (figure 2) were well known to the readers of this review article and we speculated that it will be just repetition to provide this well-known figures.

-The figure 2 could be improved. Indeed, the symbols for the HBV polymerase and HBsAg are too similar in size and color. The mRNA is barely visible. The cccDNA should be labelled in the nucleus as (cccDNA) and not at the bottom of the figure with a big arrow. The discrepancy between red and blue arrows should be explained.

→ We deleted the figure 2.

-There is no comment on drug toxicity for the different combinations.

→ We described the drug toxicity for the different combinations and marked those with red font.

Minor comments:

-First line: { nucleos(t)ide } remove the second «t».

→ We removed the second «t».

-Line 27: «rt» in rt-polymerase should be described.

→ We change the rt-polymerase to reverse transcription (rt)-polymerase.

-Page 5, last line: ...and in patients **are** resistant to both...

→ We deleted “are”

-Figure 1 is not on focus.

→ Figure 1 was deleted from our manuscript.

(2) Reviewer 2

The paper “Management of antiviral drug resistance in chronic hepatitis B” is well written and provides an accurate and complete analysis of this important topic. The figures are of high quality and the table is well organized. Minor change: page 5, line 35: add who after the word patients

→ We added the word as you recommended.

(3) Reviewer 3

Its a very comprehensive paper about resistance to drugs in chronic HBV. There are not referencies to IFn and may be the title has to be change refering only to oral drugs....

It s the only suggestion about the acceptance of the paper.

→ IFN do not show drug resistance, hence we speculate that the change of title to “Management of oral antiviral drug resistance in chronic hepatitis B” may not be needed.

(4) Reviewer 4

This is well-written, comprehensive and informative review on “management of antiviral resistance in chronic hepatitis B”. Newer information on currently developing agents was provided in this draft. I have several minor comments to improve the quality of the manuscript.

Specific comments] 1. The authors reviewed systematically and described most of studies related with antiviral resistance in chronic hepatitis B. However, what the readers need is the summary of data which can be applied to real clinical practice. I would recommend the authors to compare the currently available practice guidelines for management of antiviral resistant-CHB in relation to data described in this manuscript. This should be presented as table or figure. 2.

→ We added relevant contents under the subheading of “Recommendations of guidelines for rescue therapy in patients with antiviral drug resistance” and Table 2, and marked them with red font.

The part of “background to the development of antiviral drug resistance” is long and redundant. This part should be shortened and figure 1 is not necessary → We shortened the relevant contents and deleted the figure 1.

3. Table or figure to summarize the antiviral efficacy of various rescue therapies (ADV monotherapy, ETV monotherapy, LAM+ADV, LDT+ADV, ETV+ADV) need to be shown. In this regards, the following important articles are missing and should be described in references: 1. Lee JM et al. Long-term adefovir dipivoxil monotherapy for up to 5 years in lamivudine-resistant chronic hepatitis B. *Antivir Ther.* 2010;15(2):235-41.; 1. Park H et al. Efficacy of switching to telbivudine plus adefovir in suboptimal responders to lamivudine plus adefovir. *World J Gastroenterology* 2013 Nov 21; 19(43):7671-7679.

the antiviral efficacy of various rescue therapies (ADV monotherapy, ETV monotherapy, LAM+ADV, LDT+ADV, ETV+ADV) in subheading of Summary of antiviral drug efficacies in rescue settings and Table 3 and marked those with red font. Also, we add the references you have indicated.

4. HBV genotype in relation to antiviral response can be referred in the article of Kim BK et al. *Antiviral Therapy* 2011;16(8):1169-86.

→ The contents relevant to HBV genotype in relation to rescue antiviral responses were described in last and first paragraph of page 273 and marked those with red font. The reference of Kim BK et al. *Antiviral Therapy* 2011;16(8):1169-86 was cited in reference 27 and marked with red font.

5. Table 1: If the content of this table is adopted from other articles, it should be described in the context and beneath the table. 6. The word spacing is wrong in some sentence and thus this need attention.

→ We described the source of this table in the context and beneath the table and marked those with red font.

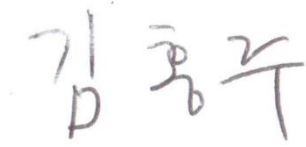
6. The word spacing is wrong in some sentence and thus this need attention.

→ We corrected the word spacing (1.5) through the entire manuscript.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in dark ink, consisting of the Korean characters '김홍주' (Kim Hong-joo) written in a cursive, fluid style.

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