

## RESPONSES TO REVIEWERS AND EDITORS



May 12, 2015

**Title:** Management of entecavir-resistant chronic hepatitis B with adefovir-based combination therapies

**Author:** Hyoung Su Kim, Hyung Joon Yim, Myoung Kuk Jang, Ji Won Park, Sang Jun Suh, Yeon Seok Seo, Ji Hoon Kim, Bo Hyun Kim, Sang Jong Park, Sae Hwan Lee, Sang Gyune Kim, Young Seok Kim, Jung Il Lee, Jin-Woo Lee, In Hee Kim, Tae Yeob Kim, Jin-Wook Kim, Sook-Hyang Jeong, Young Kul Jung, Hana Park, Seong Gyu Hwang; on behalf of Antiviral Resistance Study Group.

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 16907

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16907-review.doc).

We are re-submitting our manuscript entitled "Management of entecavir-resistant chronic hepatitis B with adefovir-based combination therapies" for publication in *World Journal of Gastroenterology* as an original article. We appreciate the opportunity to revise and improve our manuscript and to resubmit to the journal. We also thank the reviewers for the comments.

The manuscript has been improved according to the suggestions of reviewers and editorial office as follows:

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer. The point by point responses and the revised sentences are described on the followings. **Revisions are high-lightened on the manuscript.**

### **Reviewer's Comment 1.**

Here Hyoung Su Kim et al report original data on long term efficacy of ADV-based combination therapies, i.e. ADV/ETV and ADV/LMV, on 50 CHB patients with genotypic

resistance to ETV. They find higher rates of virological response in patients treated with ADV/ETV vs ADV/LMV and they identify low baseline HBV DNA levels and IVR3 as independent predictive factor for VR. Its interest is limited to countries where TDF is not available or not reimbursed. Anyway the article is well-written and, even though the small sample size and the retrospective nature of the study shed some doubts on the reliability of results and conclusion, this study will be the largest one on this topic, hence worthy of attention and consideration. Results are comprehensive and conclusions are consistent with results. Furthermore limitations of the study are adequately acknowledged. My opinion is for acceptance without revisions.

**Response;** Thank you very much for the helpful comments.

## Reviewer's Comment 2.

The manuscript entitled Management of entecavir-resistant chronic hepatitis B with adefovir-based combination therapies by Hyoung Su Kim and co-workers can have a good clinical utility because in many countries indeed Tenofovir is either not available, either not reimbursed and finding other strategies in the situation of Entecavir resistance is highly important. Title: The main title marks the topic and the content of the study and the short titles successfully summarize subsequently debated issues. Abstract: The abstract synthesizes the structure of the article and it succeeds to briefly address the main topics of the study: the aims: long term efficacy ADV based combination therapies in Entecavir resistant CHB patients, the methods: the number of patients included in the study, and the number of patients that underwent each rescue therapy ADV/ETV respectively ADV/LMV. It also reviews the main results as the median levels of HBV DNA of the patients included in the study, the median duration of the treatment, the cumulative virologic response and a brief comparison between the two regimen of treatment. The abstract also emphasizes its importance by considering and alternative antiviral for the VHB DNA resistant to Entecavir, other than Tenofovir which has a reduced availability in many countries. In the introduction section authors may include another reference to support the statement that "As a result of sequential ETV monotherapy in LMV-resistant patients, resistance to ETV developed in a substantial number of patients currently.": Very recent data from the literature that showed that 15.62 % lamivudine-resistant patients treated with 1.0 mg day ETV are non-responders at 48 weeks, with Entecavir resistance. (Preda CM, Baicus C, Negreanu L, Tugui L, Olariu SV, Andrei A, Zambatu I, Diculescu MM. Effectiveness of entecavir treatment and predictive factors for virologic response. Rev Esp Enferm Dig. 2014 May;106(5):305-11. Methods: The methods rigorously describe the number and the selection criteria for the patients included in the study, the type and the duration of the therapies administered, the period of time and the number and the location of the medical centres that were enrolled in the study. The study refers itself as a retrospective cohort study, a 4 years evidence which is in concordance with the evaluation of the results. The methods also reveal the laboratory assay that were performed during the study and a very detailed explanation of the statistical analysis. Population of patients studied is relevant (50 patients with documented Entecavir resistance is a good sample size), methods of statistical analysis seem pertinent. The specificity and reliability of the study consists in the fact that the evaluation of the response to ADV in ETV resistant

VHB DNA was performed on selected patients, with documented ETV resistance and no other specific comorbidities that could interfere with the virological response. The novelty of the study is represented by the characterization of the virological response to the ADV therapy taking in consideration favorable predictive factors that were subsequently defined. The authors also noted that the study was approved by the Institutional Review Boards of each institution, and informed consent was obtained from each patient so the protocol conforms to the ethical guidelines. The study provides sufficiently detailed description also sustained by the data presented in the attached tables. Two minor changes in language should be done: Page 8: Title: Material and methods (instead of MATERIALS AND METHODS) Page 9: Authors should state that VBT is virological breakthrough. Results: The results are very interesting and well presented. Apart from the limitations that authors described, the study includes sufficient experimental evidence and data to draw firm scientific conclusion. The sample size and the graphical data can be considered adequate.

**Responses:** We appreciate your very detailed review. We have revised our manuscript according to your comments as follows.

- 1) We added the reference which you mentioned on page 7. (**Preda CM**, Baicus C, Negreanu L, Tugui L, Olariu SV, Andrei A, Zambatu I, Diculescu MM. Effectiveness of entecavir treatment and predictive factors for virologic response. *Rev Esp Enferm Dig* 2014; **106**: 305-311 [PMID: 25287232])
- 2) We made the minor corrections as you indicated.
  - Material and Methods; changed
  - Virological breakthrough (VBT); provided full description of VBT.

3 References were added, and the reference style and typesetting were corrected

4 An audio file of core tip has been enclosed.

5. English editing service certificated has been provided.

We requested English editing services to “Editage (www.editage.com)”, which is a world-leading English editing group, and received corrections on our manuscript.

6. Appropriate documents which editorial office requested were submitted.

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

Sincerely yours,

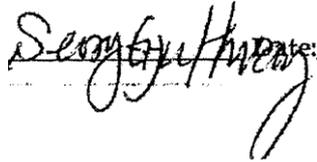
Hyung Joon Yim, MD, PhD



Department of Internal Medicine, Korea University Ansan Hospital, 123  
Jeokgeum-ro, Danwon-Gu, Ansan-Si, Gyeonggi-Do, 425-707, Republic of

Korea, Tel.: +82-31-412-6565, Fax: +82-31-412-5582, E-mail:  
gudwns21@medimail.co.kr

Seong Gyu Hwang, MD, PhD

A handwritten signature in black ink, appearing to read 'Seong Gyu Hwang', written over a horizontal line.

Department of Internal Medicine, CHA Bundang Medical Center, 59  
Yatap-ro, Bundang-gu, Seongnam 463-712, Republic of Korea, Tel.  
+82-31-780-5213, Fax. +82-2-780-5246, E-mail; sghwang@cha.ac.kr