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July17, 2014

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Dear Dr. Ya-Juan Ma,

Please find enclosed the edited manuscript in Word format (file name: 11598-review.doc).

Title: Resistant mutants induced by adefovir dipivoxil (ADV) in HBV isolates

Author: Su-Wen Jiang, Li-Peng Yao, Ai-Rong Hu, Yao-Ren Hu, Shi-Xiang Chen, Tao Xiong, Guo-Sheng Gao, Xiao-Yue Liang, Shi-Xiong Ding, Peng-Jian Weng

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 11598

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

Reviewer 1:

(1)Response to comment: In Study design and patients section, how many patients received ADV mutant study? This may show the incidence of ADV drug resistance mutant.

Response: Thanks for the reviewer's comments. We have made the corrections which are marked in red in the paper: "The study included 281 ADV monotherapy patients treated at Ningbo No. 2 Hospital between June 2008 and August 2010, 79 of these patients had ADV-resistant HBV mutants."

(2)Response to comment: The duration of treatment when ADV resistant mutant appeared was not mention. This variable should be included in Table 2 (single mutant or multiple mutants) as well as Table 3 (rtA181T and non- rtA181T).

Response: We have added the duration of treatment in Tables 2 and 3. It revealed that the duration of treatment with ADV in the single mutant group was shorter than that in the multi-mutants group.

(3)Response to comment: The discussion should be focus at the finding of this study. In general, the discussions were quite redundant. The first paragraph of discussion was not derived from data in this study that can be removed completely.

Response: We have removed the first paragraph of the discussion completely. Thanks for the reviewer's comments.

(4) Response to comment: Studies have found that an rtA181T and rtN236T mutation /substitution could generate cross-resistance against tenofovir disoproxil fumarate (TDF). The cited references did not support this statement.

Response: We have removed the No.37 reference and added the No.2 reference.

(5) Response to comment: There is a higher prevalence of non-rtA181T in HBeAg positive patients (uni-variate analysis p=0.023). The mechanism and the significant of this finding were not discussed. If this finding remained significant in multi-variate analysis, a brief discussion will be needed.

Response: We have added a brief discussion: "HBV genes that encode the polymerase and envelope proteins of HBV overlap, studies have found that an rtA181T mutation could affect HBV replication and protein secretion [31], so there was a higher prevalence of non-rtA181T in HBeAg positive patients. But it needs further basic research into HBV replication and pathogenic mechanisms."

(6) Response to comment: The investigators suggested ADV monotherapy should not be used for patients with genotype C. Based on the data of this series, should we avoid ADV monotherapy to all patients when other drug with high resistance to mutant is available?

Response: Yes! In the end of the Discussion we state: "First-line antiviral treatment and customized medication based on the clinical characteristics of patients is important to avoid subsequent improper drug use and the need for salvage treatment." The first-line antiviral drugs are TDF and ETV.

(7) Response to comment: In the conclusion of the abstract, the author mentioned some of the mutant may be present before treatment. This sentence should be removed. No pre-treatment data in this study can be found.

Response: We have removed the sentence of "some of the mutant may be present before treatment."

Reviewer2:

(1) Response to comment: In Introduction, page 2, lines 10-11, Does "….for HBV-related liver disease, as well as monotherapy subsequent to treatment with other NUCs for which the virus developed resistance" mean "for patients with HBV-related liver disease, as well as monotherapy to patients with NUCs-resistant HBV."??

Response: Yes! Thanks for the reviewer's comments. We have made the corrections which are marked in red in the paper: "In China, ADV is routinely applied in initial monotherapy for patients with HBV-related liver disease, as well as monotherapy to patients with NUC-resistant HBV."

(2) Response to comment: In Introduction, page 2, last line, Do you mean "chronic HBV infection"?

Response: We have removed the sentence of "chronic HBV infection" and modified as "NUCs".

(3) Response to comment: In Methods section, How long study patients take ADV? How was doses? How the renal function? Authors should mention HBV genotype and HBeAg-status in the study population. How the methods for HBV genotype and HBeAg??

Response: i These ADV-resistant patients had been given only ADV monotherapy, for 2.7 to 4.5

years, with a median duration of 3.4 years. **ii** We have added "ADV monotherapy (10 mg, oral and once daily) ". **iii** We have added "During the course of ADV treatment, the serum creatinine and creatinine clearance rate of all patients were normal." **iv** We have added "Forty-five cases were e-antigen negative and 34 cases were e-antigen positive. There were 16 cases with genotype B and 63 cases with genotype C." **v** HBV serologic markers were analyzed with an Abbott AxSYM System immune assay analyzer (USA). HBV genotyping was performed by an ABI 3130xl sequencing instrument (USA).

3 References and typesetting were corrected

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

Sincerely yours,

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