26 September, 2016
Name of journal: World Journal of Hepatology
ESPS manuscript NO: 29412

Dear Editor,

The revised manuscript entitled "On-treatment quantitative HBeAg predicted response to nucleos(t)ide analogues in chronic hepatitis B" has been submitted. We appreciate the valuable comments and corrections from editors and reviewers, and our point-by-point responses to the reviewers' comments are detailed below. The corresponding corrections are highlighted in red in the revised manuscript.

Reviewers Comments

1. Nowadays, we can choose several types of NAs. Why did you choose the combination of lamivudine and adefovir. LAM has a profile of low genetic barrier and ADF has suboptimal antiviral effect.

Response: This study was started in 2011 when lamivudine (LAM) and adefovir (ADV) were widely used in China since the price of entecavir (ETV) was high and tenofovir (TDF) was not approved for treatment of chronic hepatitis B (CHB) in China. This is one of the limitations of this study since LAM and ADV are no longer the first-line antiviral drugs nowadays, and we have added this limitation to Discussion. In addition, nucleos(t)ide analogues (NAs) have a similar antiviral mechanism, and HBeAg seroconversion rates in CHB patients are comparable between ETV (or TDF) therapy and an optimized therapy with LAM and ADV. Hence, we propose that the combination parameter of HBeAg level and its declined value at 24-week might be used as a reference parameter to predict the efficacy of ETV or TDF treatment.

2. I understand your statement that HBeAg level and its decline are useful reference marker to predict 96-week therapy. By any kind of basis did you set these endpoints?

Response: In our study, on-treatment virological response and HBeAg seroconversion were set as the main endpoints. These were based on the Chinese Guideline of Prevention and Treatment for CHB, which recommended that sustained or maintained virological remission was a more realistic endpoint because few patients can achieve HBsAg loss by the currently available NAs. Thus we set maintained virological response (serum HBV DNA ≤ 300 copies/mL) and HBeAg seroconversion as the endpoints.

3. After 96-week treatment, how many patients did you cease the treatment. Let us know the outcome of the cessation of the treatment.

Response: The treatment has been continued for all patients after week 96. We just analyzed the data of the patients at 96-week treatment, and the data were not available from the patients after 96 weeks. We have added the additional description in Patients and Methods.

4. Add adverse events during the treatment.

Response: In our study, we have recorded adverse events in the Case Report Form (CRF). However, no drug related adverse events were found in CHB patients during the 96-week antiviral therapy.

We would like to express our sincere thanks to the editors and reviewers for the constructive comments. Hopefully the manuscript has been improved satisfactorily and will be accepted for publication in **World Journal of Hepatology**.

Sincerely yours,

Xueen Liu
Associate Professor
Department of Microbiology and Infectious Disease Center
School of Basic Medical Sciences
Peking University Health Science Center

Hui Zhuang, M.D.
Professor
Department of Microbiology and Infectious Disease Center
School of Basic Medical Sciences
Peking University Health Science Center