

Response to reviewers and editors

First of all, we wish to thank both reviewers and editors for their constructive and helpful advice. We reviewed and modified our article carefully according to the comments of the expert consultants.

Response to the Reviewers #1:

Comment: I read the manuscript written by Xue Y and others with great interest. In my honest opinion, the topic is interesting and the retrospectively studies novel enough to attract the readers' attention. Nevertheless, the authors should clarify some points and improve the discussion citing relevant and novel key articles about the topic. I have just some minor comments. 1. Please replace figures with higher resolution images. 2. English language needs correction.

Response: Thank you for your suggestion. We have invited a professional English language editing specialist to help us to improve the English language of our manuscript. We also provided figures with higher resolution images as you suggested.

Response to the Reviewers #2:

Comment: NAs are primary therapeutic agents for HBV infection, they significantly improved outcomes in patients with CHB. Current guidelines recommend that patients with HBeAg seroconversion discontinue NAs after relatively long-term consolidation therapy. A considerable proportion of patients fail to achieve HBeAg seroconversion after the long-term loss of HBeAg, even if HBsAg loss occurs.

Therefore, it remains unclear whether NAs can be discontinued in this subset of

patients. Some patients in the authors previous cohort discontinued NAs after achieving HBeAg loss for long periods because of personal decisions and were not included in the previous analyses, while some maintained SVR. Therefore, the purpose of this present study was to determine the outcomes and related factors in patients with HBeAg-positive CHB with HBeAg loss (without HBeAb) after NAs cessation. The current study included patients who discontinued NAs after achieving HBeAg loss (without HBeAb) for long periods since 2001. And they concluded that these patients may be able to discontinue NAs therapy after long-term consolidation. Their analysis helped in therapy for HBeAg-positive patients with CHB. The methods of data analysis are very clear, and the results are presented well. The manuscript is written clearly and it's in acceptable form without any major changes.

Response: Thank you for your kind advice. We have improved the English language and updated our manuscript. The revision has been highlighted.

Response to the Reviewers #3:

Comment: In the manuscript “Exploration of Nucleos(t)ide analogues cessation in chronic hepatitis B patients with HBeAg loss”, the authors tried to investigate the outcomes and factors associated with HBeAg-positive CHB patients with HBeAg loss (without HBeAb) after cessation of NAs. They performed an observational cohort of patients discontinued NAs therapy and underwent regular follow-up. They conclude that HBeAg-positive CHB patients with HBeAg loss may be able to discontinue NAs therapy after long-term consolidation. HBsAg at cessation <100 IU/ml predicts SVR after NAs cessation. Careful monitoring, especially in the early stages after cessation,

should be adopted to ensure favorable outcomes. The topic of this work is interesting. The authors conclude discontinuing NAs therapy should aim to outcomes and related factors in patients with HBeAg-positive CHB with HBeAg loss (without HBeAb). I suggest the authors give more details on the relationship between HBeAg loss and discontinuing NAs therapy in both their retrospective study and literature review.

Response: Thank you for your suggestion. We have reviewed literatures and revised the “Introduction” part to further clarify the functions of HBeAg and relationship between HBeAg loss and discontinuing NAs therapy. New references were cited. The modified part has been highlighted.

New references:

(1) Ref.8: Milich DR. Is the function of the HBeAg really unknown? Human vaccines & immunotherapeutics 2019;15(9):2187-2191 [PMID: 31063442 DOI: 10.1080/21645515.2019.1607132]

This reference described the immunomodulatory functions of HBeAg, including “downregulation of TLR2 expression”; “downregulation of NF- κ B activation and promotion of viral replication; downregulation of IL-18-mediated signaling of IFN γ expression; interaction with RIPK2 to regulate IL-6 expression; interaction with IL-1 receptor accessory protein to trigger IL-1 responses”. We summarized the above functions and revised the “Introduction” part. The previous Ref.8 was deleted.

(2) Ref.13: Sohn HR, Min BY, Song JC, Seong MH, Lee SS, Jang ES, Shin CM, Park YS, Hwang JH, Jeong SH, Kim N, Lee DH, Kim JW. Off-treatment virologic relapse and outcomes of re-treatment in chronic hepatitis B patients who achieved complete viral suppression with oral nucleos(t)ide analogs. BMC Infectious Diseases 2014; 14: 439 [PMID: 25125320 DOI: 10.1186/1471-2334-14-439]

This study also included CHB patients with HBeAg loss and the off-treatment virologic responses remained poor. It was not explicitly designed for this subpopulation; the sample size was small, and the consolidation periods were short. To our knowledge, our study might be the first study which was explicitly designed for nucleos(t)ide analogues cessation in CHB patients with HBeAg loss. The above reference was also added in the revised “Introduction” part.

Response to Science editor:

Comments: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text; and (11) Authors should always cite references that are relevant to their study. And authors should not cite their own unrelated published articles. Please check and remove any references not relevant to this study.

Response: Thanks for your great effort for our manuscript and your advice. We have uploaded the approved grant application forms or funding agency copy, the original pictures, and the “Article Highlights” section (at the end of the main text and highlighted). We have checked the 5 self-citations (Ref. 5, 13, 14, 15, 22), although reference 14 (Liu ZR *et al*) described relapse features of CHB patients discontinuing

NAs, it was deleted because of its substitutability by ref. 5 (Liu F *et al*) and 13 (Wang L *et al*) in this situation.

Response to Company editor-in-chief:

Comments: The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company.

Response: Thanks for your great effort for our manuscript and your advice. We have invited a professional English language editing specialist to improve the English language quality of our manuscript. The revision has been highlighted. The English Language Certificate issued by a professional English language editing company was also uploaded.