May 16, 2022

Professor Lian-Sheng Ma
Company Editor-in-Chief
World Journal of Gastroenterology

Re: Manuscript Number: 77278 titled "Real-World Retrospective Nationwide Cohort Study of Hepatitis B Virological Response and Improvement in Liver Stiffness Measurement in 465 Chronic Hepatitis B (CHB) Patients on Nucleos(t)ide Analogue (NA)Therapy"

Dear Professors,
We have revised the paper to address minor edits. Our responses are highlighted in bold font.

Sincerely,

Alnoor Ramj, MD, FRCPC
Clinical Associate Professor of Medicine
Gastroenterology and Hepatology
Division of Gastroenterology
University of British Columbia

Carla S. Coffin, MD, MSc, FRCPC
Professor of Medicine
Cumming School of Medicine
University of Calgary

cscoffin@ucalgary.ca

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision
Specific Comments to Authors: In this retrospective, multi-centre cohort study of 465 CHB patients utilizing the Canadian Hepatitis B Network cohort data, the results highlighted the effectiveness of both antiviral drugs in inducing fibrosis regression in a diverse HBV patient cohort. Although, there was

some limitation in this real-world study, it really represented the large North American study conducted to date on long-term follow-up with NA therapy utilizing non-invasive fibrosis assessment method.

Thank you

Several points need to be revised.

1. In the part 1 of results, serum HBV DNA level and ALT levels were similar in both group showed in table 1, these parameters were very important in assessing the therapeutic effect, therefore these findings should be emphasized in words.

Thank you. We have emphasized in the results section that TDF and LAM showed significant therapeutic benefits in achieving a virological and biochemical response (lines 171-173).

2. A greater proportion of persons in the TDF group had advanced fibrosis (>stage F3/4) at baseline compared to LAM due to the local standard clinical practice. These patients were more likely to be HBeAg positive. What's the relationship between advanced fibrosis and HBeAg positive ?

Thank you. This was an unexpected finding. Based on the study data this finding is interesting but cannot determine an association per se. The authors recognize that in the natural history of chronic hepatitis B, persons who develop pre-core mutant with reactivation of HBeAg negative disease are often at higher risk for more advanced fibrosis. As you have also noted, a higher proportion of persons were able to access TDF based on having extensive fibrosis based on previous public drug reimbursement policy in one of the jurisdictions. Otherwise LAM was used as first line therapy, and TDF coverage if patient failed LAM (i.e., developed antiviral resistance).

3. In the part 2 of the results, follow-up evaluation and outcomes need to be separated according to different parameters.

Thank you for your suggestion. We have re-organized the result section/s with regards to the different paramaters evaluated.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)
Specific Comments to Authors: In November 2021 I reviewed this manuscript that had a different number at that time (manuscript number 73367). The Authors have satisfactorily addressed the reviewer's concern. I don't have any additional comment.

Thank you.