Author’s response to reviews

Title: Case report: lactic acidosis and rhabdomyolysis during telbivudine and tenofovir treatment for chronic hepatitis B

Authors:
Yue Ying (10300300055@fudan.edu.cn)
Yue-Kai Hu (huyuekai@fudan.edu.cn)
Jia-Lin Jin (jinjialin@fudan.edu.cn)
Ji-Ming Zhang (jmzhang@fudan.edu.cn)
Wen-Hong Zhang (zhangwenhong@fudan.edu.cn)
Yu-Xian Huang (yxhuang@fudan.edu.cn)

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Author’s response to reviews:

Dear editor,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate you and reviewers very much for your positive and constructive comments and suggestions on our manuscript entitled “Case report: lactic acidosis and rhabdomyolysis during telbivudine and tenofovir treatment for chronic hepatitis B” (BMGE-D-17-00374). We have studied your comments carefully and have made correction which we hope meet with your approval.

For editor’s comments:

1. We are sorry that we neglected the report regarding an HIV patient who developed Fanconi syndrome and rhabdomyolysis two months after the initiation of tenofovir during antiretroviral treatment. We have read this paper before, but we forgot to cite it for some reason. Now we have already cited this report in page 10, row 12-13. Thank you for your
pointing out this report to give another evidence of the association of tenofovir and muscle-related adverse events.

2. As you kindly suggested, we carefully reviewed the patient`s history and added the medication history of the patient in page 5, row 16-17. He didn`t take any other concomitant drugs except telbivudine and tenofovir. And without the evidence of infection and history of injury, we think that rhabdomyolysis (RM) was most likely caused by telbivudine and tenofovir.

3. We followed this suggestion and provided details about GFR levels in page 6, row 15-17. As you pointed out, cirrhosis can cause impairment of renal function. We reviewed his laboratory results. The patient`s renal function was normal during the whole period from taking tenofovir to recover from RM.

4. As you kindly pointed out, Fanconi syndrome is characterized by hypophosphatemia due to phosphaturia, renal glucosuria, aminoaciduria, tubular proteinuria, and proximal renal tubular acidosis. There were many reports about tenofovir might induce Fanconi syndrome. The patient we reported do occur metabolic acidosis, but as we revised in page 5, row 10, he took tenofovir for only one month. Besides, his electrolytes and urine pH were normal. As a result, we didn`t consider the diagnosis of Fanconi syndrome. Thank you for mentioning this important differential diagnosis.

For reviewer Yee Hui Yeo`s comments,

1. We agreed that we should have mentioned the patient`s medical history. The patient hadn`t other comorbidities like diabetes and chronic kidney disease. We added the information about the medical history in page 5, row 15-16.

2. We were sorry for not presenting important drug history of the patient. He didn`t take concurrent drugs or Chinese herbs or nutritional supplements except telbivudine and tenofovir. The information about drug history was added in page 5, row 16-17.
3. We considered necessary to present the results of other liver function test in page 4, row 21-22. His aspartate transaminase was 129U/L. Total bilirubin and indirect bilirubin were normal.

4. Thank you for pointing out that the indication of MRI was not clear. The patient had a history of cirrhosis, MRI was aimed to rule out liver cancer. We justified the indication of MRI in page 4, row 22 and page 5, row 1.

5. We considered it’s right to give more information about the therapy for his acidosis before admission. The patient received sodium bicarbonate as the revision showed in page 5, row 4-5.

6. We appreciated the suggestion about giving more details like urine color and output to establish the diagnosis of RM. His urine color was black and urine output was about 200ml per day. The electrolytes test was normal, while uric acid was 1.019mmol/L. His follow-up arterial blood gas analysis returned to normal, showing pH between 7.40 and 7.45. We added the information in page 5, row 7-8, 10 and page 6, row 11-12.

7. We agreed that we should have given more details to rule out other cause of RM, like infection, injury and other concurrent drugs. To rule out infection, we added the information about normal white blood cell count and percentage of neutrophils in page 5, row 6-7. Physical examination about no redness and higher skin temperature on lower extremities can also help differentiate infection of muscle, which presented in page 5, row 14-15. To rule out injury and concurrent drugs, the information was added in page 5, row 16-17. The description of differential diagnosis was added in page 6, row 6-7.

8. We agreed to make it clear about the changing strategy of antiviral treatment. The explanation and discussion was added in page 10, row 3-14. At first, we converted antiviral therapy to entecavir because its lower reporting portion of muscle-related adverse drug reaction. As entecavir and telbivudine shared cross-resistance in some HBV variants, it was recommended that tenofovir should be the rescue strategy when telbivudine resistance occurred according to EASL guidelines in 2017. On the other side, tenofovir disoproxil fumarate was recommended as first-line monotherapy against hepatitis B with a high barrier to resistance. So far, tenofovir was only reported a side effect of rhabdomyolysis during antiretroviral
treatment in HIV patients, which combined with other concurrent antiretroviral drugs. In a clinical trial studying the safety of tenofovir monotherapy for 5 years (Marcellin, P., et al., Kinetics of hepatitis B surface antigen loss in patients with HBeAg-positive chronic hepatitis B treated with tenofovir disoproxil fumarate. J Hepatol, 2014. 61(6): 1228-37.), the researchers reported no fatal adverse reaction like LA or RM. So, we thought tenofovir monotherapy was safe. When the patients` condition was steady, we used tenofovir under close monitoring.

9. We did as suggest, moving the clues to clinical presentation part in page 6, row 3-4.

10. We agreed that it was very important to compare the severe adverse events of trials that have investigated the safety of Telbivudine + Tenofovir combination therapy in chronic hepatitis B patients. Additional discussion is presented in page 10, row 14-20. There were no muscle-related severe adverse events reported during at most 1 year`s follow-up. For the patient we reported, he took telbivudine for two years and suffered myalgia immediately after addition of tenofovir, so we conjure that tenofovir sometimes may still have a synergistic effect on the development of myopathy after much longer medication time, especially in patients with cirrhosis.

For reviewer Etem Alhan, thank you for your encouragement to our manuscript. We will do our best to improve further.

We enclosed our revised version, which all changes are marked as yellow color, for your kind consideration. We hope that the revised manuscript is now suitable for publication.

Looking forward to hearing from you. Thank you and best regards.

Yours sincerely,

Ying Yue
Corresponding author:

Name: Huang Yu-xian

Address: Huashan Hospital Fudan University, Department of Infectious disease, 12 Middle Wulumuqi Rd, Building 5, Room 504, Shanghai, CN 200040

Phone: +8602152887954

E-mail address: yxhuang@fudan.edu.cn