Reviewer's report

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

Version: 1 Date: 04 Dec 2017

Reviewer: Yee Hui Yeo

Reviewer's report:
The authors have made significant improvement this time. Replies and edits are attached:
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.
Reply: It is good to add the patient’s medical history. It would be better to say "the patient denied a past history of significant comorbidities including…" instead of "the patient didn’t has other disease history".

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.
Reply: sounds reasonable now

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.
Reply: It is good to add the patient's ALT and bil data. It would be better to write "Total bilirubin and indirect bilirubin levels were normal" or "Total bilirubin and indirect bilirubin levels were within normal limits" instead of "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.
Reply: Sounds reasonable, would be better if you could say "to rule out liver cancer" instead of "To differentiate liver cancer".

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.
   Reply: Sounds reasonable.

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.
   Reply: please use "warm skin" instead of "higher skin temperature".

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.
Reply: sounds reasonable now.

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.
Reply: sounds reasonable to refer to the incidence of severe adverse events in previous clinical trials. In clinical trials, however, the inclusion/exclusion criteria is stricter. Therefore, it is important to have this case report to demonstrate the real-world findings.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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Not relevant to this manuscript

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