OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://brieflands.com/briefland/knowledgebase/category/tree.html#opr.html

Hepatitis Monthly
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Peer Review Report for "Hepatitis B Virus Infection Flare Induced Acute-on-chronic Liver Failure After COVID-19 Vaccination: A Case Report"

Author(s): Chih Yao Hu, Yi-Fan Tsou, Meng-Hsuan Chung, Niang-Cheng Lin, Cheng-Yen Chen, Pei-Chang Lee, Chin-Su Liu

Review Timeline:

Submit Date: 16 Apr 2022
Revised Date: 17 May 2022
Accepted Date: 17 May 2022

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0)

17 Apr 2022

Dear editor

The present study is a well-written case series on HBV reactivation following COVID-19 vaccination. The study is of high priority due to the ongoing pandemic and lack of sufficient evidence on vaccine complications in people with chronic liver disease. Here are some minor comments:

Case 1: It may be good to add more information about the previous HBV status in this patient, like the duration of disease, years of inactivation, HBV-related lab tests, or previous treatments.

Case 3: Please clarify the total duration of Tenofovir therapy. It is confusing because the patient has received chemotherapy from June 23, 2020 to Jan 27, 2021, which is 7 months. Besides, she has received Tenofovir from Jun 20, 2020 to Jul 26, 2021, which is 13

months. Based on these dates, she must have received Tenofovir for 6 months after chemotherapy completion. However, it has been stated that she received 5 more months of Tenofovir.

Also, please provide a reference for the guideline according to which the HBV treatment had been discontinued for this patient after 13 months. If this is controversial and there is a possibility that the treatment was discontinued too early, you can discuss this in the discussion.

Line 84: Please provide information regarding immunoassay for patient 3 and state the reason of testing refusal.

Discussion:

Having no existing reports on HBV flare after covid vaccination, authors can provide some information about the reported HBV (and maybe HCV) reactivation after covid diagnosis. Here are a few studies that I found and may be relevant:

1. Aldhaleei WA, Alnuaimi A, Bhagavathula AS. COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case From the United Arab Emirates. Cureus. 2020;12(6):e8645. Published 2020 Jun 15. doi:10.7759/cureus.8645

2. Lensen R et al., Hepatitis C Virus Reactivation Following COVID-19 Vaccination – A Case Report. 29 August 2021 Volume 2021 doi:10.2147/IMCRJ.S328482

3. Yavuz Yigit et al. Can COVID-19 Cause Flare-Ups of Acute Hepatitis B? An Atypical Presentation of COVID-19 with Acute Hepatitis B, Case Reports in Infectious Diseases, vol. 2021, Article ID 8818678, 5 pages, 2021. https://doi.org/10.1155/2021/8818678

4. Alqahtani SA, Buti M. COVID-19 and hepatitis B infection. Antivir Ther. 2020;25(8):389-397. doi: 10.3851/IMP3382. PMID: 33616549.

5. He T et al. Safety and antibody response to inactivated COVID-19 vaccine in patients with chronic hepatitis B virus infection. Liver Int. 2022 Feb 2. doi: 10.1111/liv.15173. Epub ahead of print. PMID: 35107848.

REFEREE: Reviewer | **Revision** (0) 6 May 2022

Dear associate editor
Regarding the manuscript, “HBV flare induced acute on chronic liver failure post COVID-19 vaccination: a need for prophylactic antiviral therapy?” I have only some minor comments

1- The case presentation section in the abstract section is too short. What has happened between vaccination and liver transplantation?
2- We do not know whether there is a cause-and-effect relationship between COVID-19 vaccination and hepatitis B virus (HBV) infection flare or not. So before writing a sentence

like “The mechanism of COVID-19 vaccine-induced HBV flare was not clear”, we must be sure of such a relationship first. Also, it is too soon to recommend or consider the prophylactic use of antiviral therapy based on a case report or case series paper. Therefore, I think that at least the tone of the conclusion must be more cautious and be changed.
3- Based on comment 2, the title of the project can be changed to reflect more caution in considering antiviral therapy.
4- Instead of the acronym of HBV, “hepatitis B virus” should be used in the title of the project.
5- There is also evidence regarding the safety profile of the COVID-19 vaccine (inactivated virus) among patients with chronic HBV infection that should be mentioned in the discussion section of the manuscript.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8591435/pdf/41423_2021_Article_795.pdf
Best
Reviewer

REFEREE: Associate Editor | **Revision** (0) 6 May 2022

Dear Editor in Chief
Thanks for assigning me as associate editor to handle the case-report manuscript NO.126460 entitled "HBV flare induced acute on chronic liver failure post COVID-19 vaccination: a need for prophylactic antiviral therapy?"
Although this is an interesting case presented in a good way, there are some concerns regarding the manuscript that should be addressed by the authors. See the attached peer-review comments for more details. Also, please mention the "case-report" phrase in the title, and choose your keywords from the PubMed MeSH database.

Regards
AE

Seyed Moayed Alavian: EIC | **Revision** (0) 7 May 2022

Dear Authors,

Please follow the peer-review comments and submit a revision.

Regards
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Comment by the Associate Editor (indicated by **bold**)

1. **Please mention the "case-report" phrase in the title, and choose your keywords from the PubMed MeSH database.**

Response: Page 1, line 1~2 and Page 2, line 30
Thanks for your kindly reminder. We changed our title to "*Case report: Hepatitis B virus infection flare induced acute on chronic liver failure post COVID-19 vaccination: just a coincidence?*"
The keywords are also changed as follows: Hepatitis B; COVID-19; Vaccines; Liver failure, Acute; Transplantation

Comment by the Reviewer 1 (indicated by **bold**)

1. **The case presentation section in the abstract section is too short. What has happened between vaccination and liver transplantation?**

Response:
We revised the abstract to provide more information of the cases' clinical courses.

Page 1, line 13~21
The three patients' clinical conditions deteriorated during hospitalization. Patient 1 received Entecavir (Baraclude) 1 mg/day upon presentation but the serum bilirubin level and international normalized ratio (INR) kept increasing. He was comatose in one week and underwent urgent living donor liver transplantation. Patient 2 was on regular Entecavir (Baraclude) 0.5 mg/day and was increased to 1 mg/day upon admission. The serum bilirubin level and INR kept increasing and he developed grade 3 hepatic encephalopathy in 3 weeks. The patient then received urgent living donor liver transplantation. Patient 3 received Entecavir (Baraclude) 1 mg/day upon presentation. Her serum bilirubin and INR kept increasing and had altered in mental status in a week. She did not undergo liver transplantation for her old age.

2. **We do not know whether there is a cause-and-effect relationship between COVID-19 vaccination and hepatitis B virus (HBV) infection flare or not. So before writing a sentence like "The mechanism of COVID-19 vaccine-induced HBV flare was not clear", we must be sure of such a relationship first. Also, it is too soon to recommend or consider the prophylactic use of antiviral therapy based on a case report or case series paper. Therefore, I think that at least the tone of the conclusion must be more cautious and be changed.**

Response:
We revised the conclusions in our abstract and main text.

Abstract. Page 2, line 23~27
Whether there is a cause-and-effect relationship between COVID-19 vaccination and HBV infection flare or

not is still unclear. Furthermore, the mechanism of COVID-19 vaccine induced HBV reactivation is not established. More reports and studies were needed. However, during the pandemic of COVID-19, prophylactic antiviral therapy for HBV infection before COVID-19 vaccination deserves attention.

Discussion. Page 7, line 145~151
In summary, we presented three patients had acute on chronic liver failure suspected due to HBV reactivation post COVID-19 vaccination. Two of them received urgent living donor liver transplantation and one was not qualified for her old age (73 years old). The cause-and-effect relationship between COVID-19 vaccination and HBV infection flare was not established and the mechanism remained unknown. More reports and studies are needed. Even though, during the COVID-19 pandemic, prophylactic antiviral therapy for individuals with HBV infection prior to vaccination deserves attention.

3. **Based on comment 2, the title of the project can be changed to reflect more caution in considering antiviral therapy.**

Response:
We changed our title to "*Case report: Hepatitis B virus infection flare induced acute on chronic liver failure post COVID-19 vaccination: just a coincidence?*"

4. **Instead of the acronym of HBV, "hepatitis B virus" should be used in the title of the project.**

Response:
We changed our title to "*Case report: Hepatitis B virus infection flare induced acute on chronic liver failure post COVID-19 vaccination: just a coincidence?*"

5. **There is also evidence regarding the safety profile of the COVID-19 vaccine (inactivated virus) among patients with chronic HBV infection that should be mentioned in the discussion section of the manuscript.**

Response:
Thank you for your information. We added a paragraph regarding this in our discussion.

Discussion. Page 6, line 116~120
The safety of COVID-19 inactivated vaccine in patients with chronic HBV infection had been studied. The adverse effects were similar between patients with chronic HBV infection and healthy population (13). No serious side effects were observed even in patients with compensated liver cirrhosis and the immune response was better in patients receiving antiviral therapy for chronic HBV infection (14).

Comment by the Reviewer 2 (indicated by **bold**)

1. **Case 1: It may be good to add more information about the previous HBV status in this patient, like the duration of disease, years of inactivation, HBV-related lab tests, or previous treatments.**

Response:
We added more information about the HBV status in patient 1 during regular follow up. The patient was followed-up in a community hospital and transferred to our medical center due to acute on chronic liver failure. Therefore, we are sorry for the detailed HBV serology tests are not available.

Case presentation. Page 3, line 52~53
The patient had been followed up in a community hospital for inactive HBV infection for more than 10 years. The serum ALT level was within normal limits during follow-up.

2. **Case 3: Please clarify the total duration of Tenofovir therapy. It is confusing because the patient has received chemotherapy from June 23, 2020 to Jan 27, 2021, which is 7 months. Besides, she has received Tenofovir from Jun 20, 2020 to Jul 26, 2021, which is 13 months. Based on these dates, she must have received Tenofovir for 6 months after chemotherapy completion. However, it has been stated that she received 5 more months of Tenofovir.**

Response:
Thank you for pointing out the mistake. We had revised it.

Case presentation. Page 4, line 87~88
She received 6 more months Tenofovir alafenamide (Vemlidy) after completing chemotherapy with bendamustine plus rituximab treatment.

3. **Also, please provide a reference for the guideline according to which the HBV treatment had been discontinued for this patient after 13 months. If this is controversial and there is a possibility that the treatment was discontinued too early, you can discuss this in the discussion**

Response:
We added a paragraph regarding this in our discussion.

Discussion. Page 6, line 121~129
According to the AASLD 2018 guideline, patients with HBV infection receiving chemotherapy or immunosuppressive therapy should be administered antiviral therapy before and at least 6 to 12 months (at least 12 months for anti-CD20 therapy) after completing chemotherapy or immunosuppression (15). Tenofovir alafenamide (Vemlidy) was discontinued 6 months after completion of chemotherapy with bendamustine plus rituximab treatment with undetectable HBV viral load in patient 3. We discontinued Tenofovir alafenamide (Vemlidy) after 6 months but within 12 months after completing rituximab which could be criticized. However, the HBV viral load was undetectable at that time and the risk of reactivation of HBV infection should therefore be low.

4. **Line 84: Please provide information regarding immunoassay for patient 3 and state the reason of testing refusal.**

Response:
We added the information for patient 3. The test was not covered by public health insurance in Taiwan. The patient and her family refused to pay for the test.

Case presentation. Page 5, line 101
Patient 3 refused the test due to personal reason.

5. **Having no existing reports on HBV flare after covid vaccination, authors can provide some information about the reported HBV (and maybe HCV) reactivation after covid diagnosis.**

Response:
Thanks for the recommendation and information. We did research and added a paragraph discussing this in discussion.

Discussion. Page 6, line 130~136
COVID-19 related HBV reactivation had been reported (16-18). SARS-CoV-2 induced extreme inflammatory response is one of explanation and the immunosuppressive treatment for COVID-19 may also contribute to it. Furthermore, co-infection of SARS-CoV-2 and HBV poses risk of greater liver injury. Potential factors including direct liver injury by SARS-CoV-2, hepatotoxic antiviral drugs during COVID-19 therapy and immune-mediated inflammatory response post SARS-CoV-2 co-infection (18).
Hepatitis C virus (HCV) reactivation following mRNA-based Pfizer-BioNTech COVID-19 vaccine had been reported (19).

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 17 May 2022

Dear Editor in Chief
Thanks for assigning me as associate editor to handle the revised version of manuscript NO.126460 entitled "Case report: Hepatitis B virus infection flare induced acute on chronic liver failure post COVID-19 vaccination: just a coincidence?".
I appreciate the authors' work to revise their case-report. This version of manuscript is acceptable for being published in Hepatitis Monthly journal.

Regards
AE

Seyed Moayed Alavian: EIC | **Revision** (1) 17 May 2022

Dear Authors,

I am delighted to inform that your manuscript is accepted for publication.

Regards,
EIC