Author’s response to reviews

Title: Hepatitis B virus reactivation sustained by an HBsAg immune-escape mutant isolate in an anti-HBc positive patient during treatment with sofosbuvir and velpatasvir for HCV infection: a case report

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Version: 1 Date: 11 Jul 2019

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To Editorial Board Members

Journal of Medical Case Reports
Manuscript JMCR-D-18-00900

Article title: Hepatitis B virus reactivation sustained by an HBsAg immune-escape mutant isolate in an anti-HBc positive patient during treatment with sofosbuvir and velpatasvir for HCV infection: a case report

Authors: Luca Foroghi Biland; Ludovica Ferrari; Vincenzo Malagnino; Elisabetta Teti; Carlotta Cerva; Adele Gentile; Marianna Aragri; Romina Salpini; Valentina Svicher; Massimo Andreoni; Loredana Sarmati.

Corresponding Author: Prof. Loredana Sarmati

Dear Editors,

A revised version of the manuscript cited below is being re-submitted to your journal. The present version has been revised according to the suggestions of the reviewers. We have revised the manuscript accordingly and have highlighted all changed passages.

Attached below please kindly find our point-by-point responses to all the concerns highlighted all changed passages in the manuscript raised by the reviewers.
Reviewer reports:

Reviewer #1:

1. Do you believe the case report is authentic?
Yes/No

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.

Comments:

3. Does the Introduction explain the relevance of the case to the medical literature?
Yes/No

4. Does the article report the following information? Where information is missing, please specify.

a. The relevant patient information, including:
   - De-identified demographic information (age, gender, ethnicity)
   - Main symptoms of the patient
   - Medical, family and psychosocial history
   - Relevant past interventions and their outcomes

b. The relevant physical examination findings
c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at $T = 0$, follow up at $T = 1$ month.

d. Diagnostic assessments, including:
   - Diagnostic methods
   - Challenges (e.g., financial, language/cultural)
   - Reasoning and prognostic characteristics (e.g., staging), where applicable

e. Types and mechanism of intervention

f. A summary of the clinical course of all follow-up visits

Comments:

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments:

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

Yes/No

7. Is the Abstract representative of the case presented?

Comments:

8. Does the case represent a useful contribution to the medical literature?

Comments:
9. Additional comments for the author(s)?

The lack of emphasis on the social history of the patient or financial burden of treatment has always been a pressing concern. However, your case succeeds to a certain extent in terms of the academic merit it possesses by way of the important hypothesis that it intends to propose. Perhaps you could add a comment on the study on "Evaluation of Hepatitis B Reactivation Among 62,920 Veterans Treated With Oral Hepatitis C Antivirals" which states that though HBV re-activities are common, the occurrence of accompanying severe hepatitis is rare. I would also like to know whether the authors have taken any proactive steps to document the HBV DNA titres in future cases. Please add a note on indications for instituting anti viral treatment (against HBV) while on Directly acting antiviral agents for Hepatitis C as proposed in the AASLD guidelines first published in 2017. Add a note on any recent revisions to the guidelines.

Answer:

We would like to thank the reviewer for the useful and constructive comments on our case report.

Perhaps you could add a comment on the study on "Evaluation of Hepatitis B Reactivation Among 62,920 Veterans Treated With Oral Hepatitis C Antivirals" which states that though HBV re-activities are common, the occurrence of accompanying severe hepatitis is rare.

Answer:

We agree with the reviewer on the need to emphasize that hepatitis-related HBV reactivation in patients treated with DAAs is a rare event. Therefore, we added the citation of the study of Belperio PS et al. (reference no. 14) and modified the text accordingly:

Page 6, line 85-87:

“Though HBVr are not uncommon, the occurrence of accompanying hepatitis in patients with resolved HBV infection is a rare event [12,13,14] and only occasionally leads to clinically significant outcomes.”
I would also like to know whether the authors have taken any pro-ctive steps to document the HBV DNA titres in future cases

Answer:

We would like to thank this reviewer for the opportunity to illustrate our clinical practice in patients with resolved HBV infection who are in the process of being treated with DAAs for HCV infection. As we wrote in the discussion, in this group of patients we measure HBV DNA titers before the DAA treatment and, monthly, during the therapy. This approach enables us to identify early HBV reactivations and to find occult HBV infection with detectable viremia at baseline, that may be at increased risk of reactivation. We therefore added this comment:

Page 7, line 129-131:

“This approach could enable to identify early HBVr and to find a pre-existing detectable HBV viremia in the context of OBI, that may be at higher risk of reactivation.”

Please add a note on indications for instituting anti viral treatment (against HBV) while on Directly acting antiviral agents for Hepatitis C as proposed in the AASLD guidelines first published in 2017. Add a note on any recent revisions to the guidelines.

Answer:

We thank the reviewer for this suggestion. We cited in bibliography the AASLD guidelines and added the following sentences accordingly:

Page 6, line 95-100:

“According to the AASLD-IDSA Recommendations [16], HBsAg-positive patients meeting criteria for treatment of active HBV infection should be started on therapy at the same time or before that HCV DAA therapy is initiated, whereas patients with low or undetectable HBV DNA titres can either receive prophylactic treatment for or be monitored at regular intervals. Conversely, the same Guidelines do not provide clear recommendations for the monitoring of HBV DNA among patients with resolved HBV infection.”
Reviewer #2:

1. Do you believe the case report is authentic?
   Yes

2. Do you have any ethical concerns? Please consider if local Institutional Review Board approval or ethical approval was obtained (if appropriate) and if the patient (or their parent or guardian in the case of children under 18) gave written, informed consent to publish this case and any accompanying images. A statement to this effect should appear in the manuscript.
   Comments: no

3. Does the Introduction explain the relevance of the case to the medical literature?
   Yes

4. Does the article report the following information? Where information is missing, please specify.
   a. The relevant patient information, including:
      - De-identified demographic information (age, gender, ethnicity)
      - Main symptoms of the patient
      - Medical, family and psychosocial history
      - Relevant past interventions and their outcomes

   b. The relevant physical examination findings

   c. Important dates and times in this case (if appropriate, organized as a timeline via a figure or table); if specific dates could lead to patient identification, consider including time relevant to initial presentation, i.e. initial presentation at T = 0, follow up at T = 1 month.
d. Diagnostic assessments, including:
   - Diagnostic methods
   - Challenges (e.g., financial, language/cultural)
   - Reasoning and prognostic characteristics (e.g., staging), where applicable

e. Types and mechanism of intervention

f. A summary of the clinical course of all follow-up visits

Comments:

5. Is the interpretation (discussion and conclusion) well balanced and supported by the case presented?

Comments: yes

6. Is the anonymity of the patient protected? Please consider any identifying information in images such as facial features or nametags, whether the patient is named etc. If not, please detail below.

Yes

7. Is the Abstract representative of the case presented?

Comments: yes

8. Does the case represent a useful contribution to the medical literature?

Comments: yes
9. Additional comments for the author(s)?

1. Please add the HBV surface antibody, surface antigen, E antibody, E antigen, and core antibody (anti-HBc) results corresponding to the day of collection in the figure.

Answer:

We thank the reviewer for this useful observation. We have modified the figure and the figure legend according to the indications of the reviewer: (see Figure 1)

“Figure legend

Figure 1. Virological and biochemical parameters trend during and after DAA treatment. HBV surface antibody (anti-HBs), HBV surface antigen (HBsAg), HBV e antibody (anti-HBe), HBV e antigen (HBeAg), and HBV core antibody (anti-HBc) results are presented corresponding to the time point of collection.”

2. Please include the anti viral therapy received by the patient described in reference no 11 (Fusco et al) in the discussion.

Answer:

We apologize for not mentioning the therapy received by the patient described in the case of Fusco et al. We have added this data in the discussion:

Page 7, line 119:

“Fusco et al. [20] described a reactivation of vaccine-escape HBV mutants during anti-HCV treatment with ledipasvir/sofosbuvir (90/400 mg) for 12 weeks.”
3. please mention the indication for performing HBV DNA levels in this patient while the recommendations say that HBsAg-negative/HBcAb-positive patients should be monitored with ALT alone until SVR12, and should be tested with HBsAg ± HBV DNA only if ALT increases or fails to normalize on therapy.

Answer:

We agree with the reviewer on the necessity to justify the choice of detecting HBV at week 4 after starting of DAA treatment in a patient without ALT increase. We decided to perform HBV DNA levels at that time point because of the European Medical Agency warning on the risk of early reactivation in patient with overt or occult HBV infection (warning letter EMA/795452/2016, 2 December 2016). Furthermore, as already reported in the discussion (page 6, line 66-68), the increase of transaminases related to HBV reappearance is a rare event, and it usually occurs after the viremic flare. We have added these sentences to motivate our decision in the discussion:

Page 6, line 100-105:

“Despite the lack of indications from the current guidelines, we have decided to search for HBV DNA at week 4 because of the European Medical Agency warning on the risk of early reactivation in patients with overt or occult HBV infection (warning letter EMA/795452/2016, 2 December 2016). Furthermore, as reported above, the increase of transaminases related to HBV reappearance is not so frequent, hence only monitoring the level of transaminases could not be sufficient.”

We hope that our revised paper will be published in Journal of Medical Case Reports, and we look forward to hearing from you. I thank you and send my best regards.

Sincerely,

Loredana Sarmati, MD
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