November 11, 2015

To:

Editorial Board of World Journal of Gastroenterology

ESPS manuscript NO: 23034

Title: Atypical onset of bicalutamide-induced liver injury

We would like to express our appreciation to the reviewers and editor for their time and effort in reviewing our manuscript. Your suggestions were valuable to help us strengthen our work.

Reviewer(s)' Comments to Author:

1. Reviewer's code: 00181421

COMMENTS TO AUTHORS
Agree to publish

2. **Reviewer's code:** 00070847

COMMENTS TO AUTHORS
Interesting case study with valuable insights for the monitoring of liver enzymes in patients being treated with bicalutamide. Please insert labels for the y axes in Figure 2 prior to final publication.

RESPONSE: Thank you for pointing this out. We have inserted the labels for the y-axes in Figure 2.

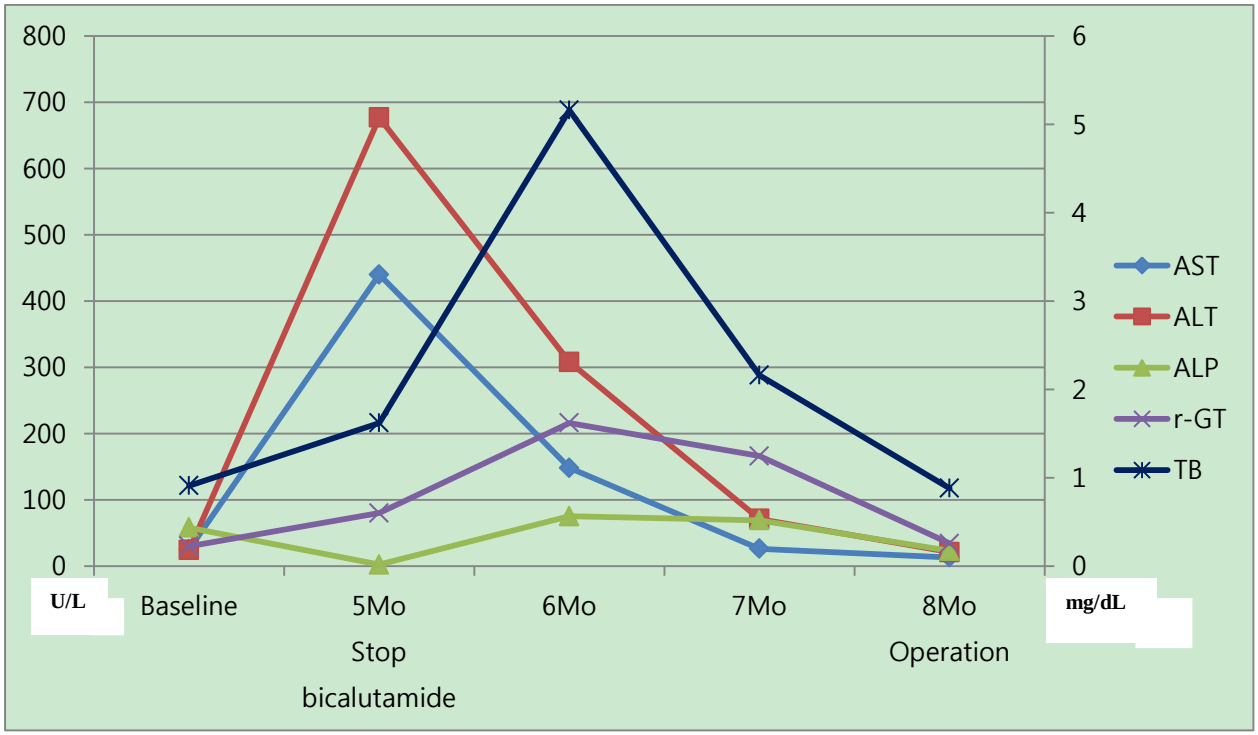

Figure 2 Courses of the laboratory findings from baseline (treatment initiation) to 8 months later. The right axis (0–6) shows the values of TB (mg/dL). The left axis shows the values for AST, ALT, ALP, and r-GT (U/L).
(ALP – alkaline phosphatase, ALT – alanine aminotransferase, AST – aspartate aminotransferase, TB – total bilirubin, r-GT – gamma-glutamyl transpeptidase, Mo – months)

3. **Reviewer's code:** 00502973

COMMENTS TO AUTHORS

In the current submission, Yun et al reported a case with bicalutamide-induced liver injury. This is a rare case and deserves publication. The English is acceptable. Minor concerns existed and should be addressed. 1. Did the author detect the HEV serum marker of this patient? HEV infection is also an important etiology of liver impairment. 2. In Conclusion, The first 2 sentences have been stated earlier, and should be deleted. 3. The legend of Figure 1 stated "Liver biopsy showed acute

intrahepatic cholestasis (red arrow) in zone 3 and sinusoidal dilation with moderate lobular inflammation (blue arrow)". However, I can see neither the red arrow nor the blue arrow in Figure 1. 4. Figure 2: What did the numbers on the right or left vertical axises mean? As there are 5 parameters in this figure, I suggest that the vertical axis may use number to indicate folds of ULN (Upper Limit of Normal).

RESPONSE

1) Did the author detect the HEV serum marker of this patient?

-> We agree with the reviewer that it is important to detect the HEV serum marker. Actually, we did perform tests to detect the presence of the HEV serum marker in this patient, but the result was negative.

-> The case report section (Paragraph 1, Sentence 13) now reads, "…undetectable. The results for hepatitis E immunoglobulin M and G were also negative. On the…"

2) In Conclusion, The first 2 sentences have been stated earlier, and should be deleted.

-> We agree with the reviewer and have deleted the first two sentences of the conclusion.

-> The conclusion now reads, "This case emphasizes that liver function measurements should be monitored from baseline for at least the first 6 months of therapy, and then periodically during the entire period of treatment with bicalutamide."

3) The legend of Figure 1 stated "Liver biopsy showed acute intrahepatic cholestasis (red arrow) in zone 3 and sinusoidal dilation with moderate lobular inflammation (blue arrow)". However, I can see neither the red arrow nor the blue arrow in Figure 1.

-> We agree with the reviewer, and we inserted the red and blue arrows.

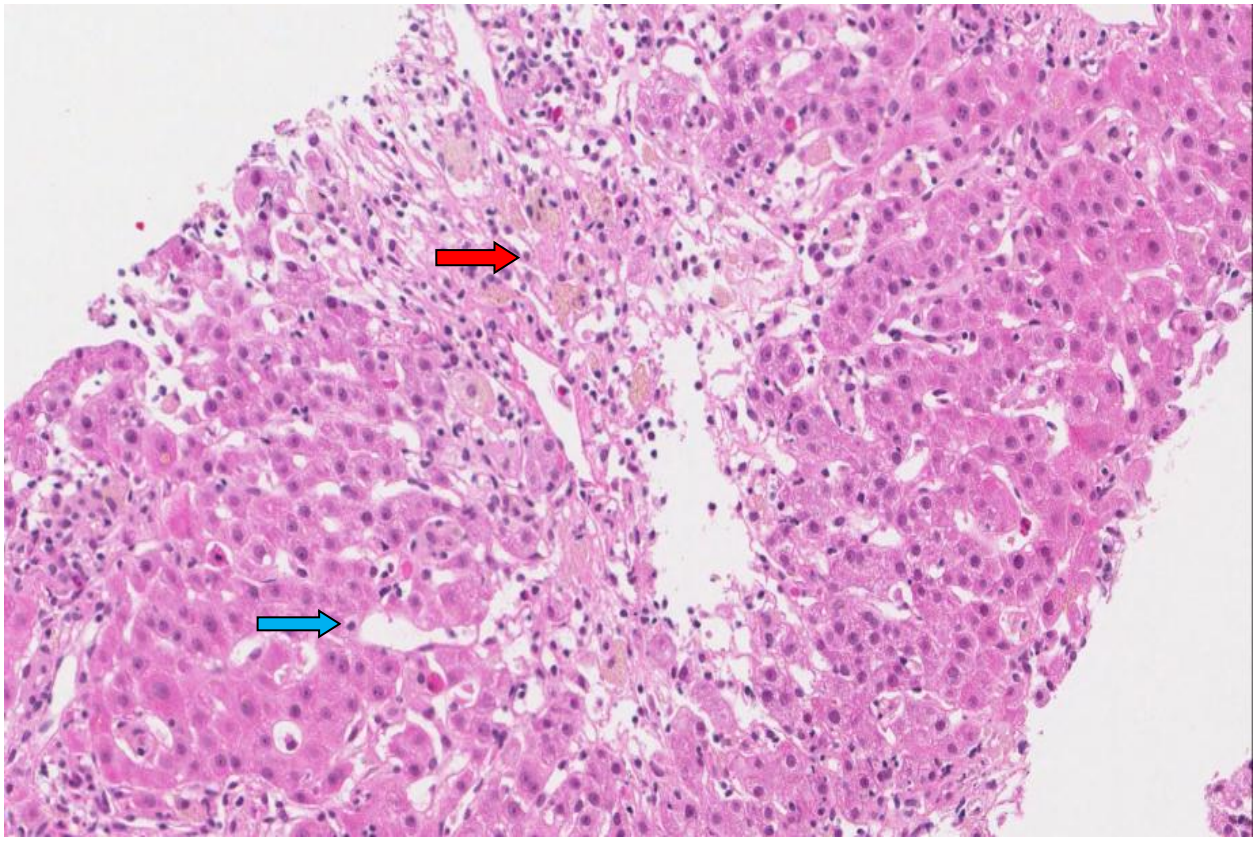

Figure 1 Liver biopsy showed acute intrahepatic cholestasis (red arrow) in zone 3 and sinusoidal dilation with moderate lobular inflammation (blue arrow) (hematoxylin and eosin, ×200)

4) Figure 2: What did the numbers on the right or left vertical axises mean? As there are 5 parameters in this figure, I suggest that the vertical axis may use number to indicate folds of ULN (Upper Limit of Normal).

-> Thank you for pointing this out; in accordance with your and the previous reviewer's suggestion, we have added labels for the vertical axes. The revised figure is shown above.

-> In this patient, we believe that it is hard to interpret the figure when we use numbers to indicate the folds of the ULN. Thank you for your suggestion, but we would not prefer using number to indicate the folds of the ULN.

4. Reviewer's code: 01869153

COMMENTS TO AUTHORS

MS# ESPS 23034 Title: Atypical onset of bicalutamide-induced injury This study is a case report that a 62 year-old Korean man with prostate cancer was administered with bicalutamide as a neoadjuvant chemotherapy and he experienced delayed liver injury but not shortly after the chemotherapy initiation. This case report firstly presents bicalutamide-induced liver injury via immune-independent manner in a Korean patient. This manuscript may be acceptable in the journal as a case report.

5. Reviewer's code: 00037846

COMMENTS TO AUTHORS

The authors describe a case of bicalutamide hepatotoxicity. Overall, the report is interesting as it reports a case where liver toxicity occurred after several months of treatment. Several comments for improvement of the manuscript need to be considered: 1. In the introduction, the authors refer to 3 previous case reports of bicalutamide hepatotoxicity. These reports should be cited in the introduction. 2. Discussion: the references 4-6 cited as support for the statements in the first paragraph do not appear appropriate as they only involve a single compound (flutamide), which may not be representative for idiosyncratic drug hepatotoxicity. More general reviews on this topic should be cited. 3. In the discussion, the authors mention again the 3 previous case reports and even mention the dosing regimen and outcome but only cite 1 of the reports. All three reports need to be cited. 4. The authors concluded based on the time of onset of liver dysfunction that the previous cases were immune-mediated but their own case was not. This conclusion appears not justified for the previous reports if it is only based on the time when the liver injury started. Furthermore, the liver biopsy of the authors' patient shows some inflammatory infiltrates. Thus, it appears premature to exclude an immune-mediated mechanism. The discussion needs to be more based on the known facts

1) In the introduction, the authors refer to 3 previous case reports of bicalutamide hepatotoxicity. These reports should be cited in the introduction.
-> We agree with the reviewer that it is important to cite the 3 previous case reports of bicalutamide hepatotoxicity. However, actually, there were 4 previous case reports of bicalutamide hepatotoxicity, as follows.

① Beza C, Sánchez Ruiz J, Peracaula Espino FJ, Villanego Beltrán MI: Drug-related hepatotoxicity and hepatic failure following combined androgen blockade. Clin Transl Oncol, 2008; 10(9): 591–92

② Dawson L, Chow E, Morton G: Fulminant hepatic failure associated with bicalutamide. Urology, 1997; 49: 283–84 [PMID: 9037299 DOI: 10.1016/S0090-4295(96)00355-X]

③ O'Bryant CL, Flaig TW, Utz KJ: Bicalutamide-associated fulminant hepatotoxicity. Pharmacotherapy, 2008; 28(8): 1071–75 [PMID: 18657023 DOI: 10.1592/phco.28.8.1071]

④ Hussain S, Haidar A, Bloom RE, Zayouna N, Piper MH, Jafri S-MR. Bicalutamide-induced hepatotoxicity: A rare adverse effect. The American journal of case reports 2014; 15: 266

Accordingly, we have cited these 4 reports in the introduction.

2) Discussion: the references 4-6 cited as support for the statements in the first paragraph do not appear appropriate as they only involve a single compound (flutamide), which may not be representative for idiosyncratic drug hepatotoxicity. More general reviews on this topic should be cited.

-> We appreciate your thorough review. We have added a new reference and changed a few sentences. Therefore, the first paragraph of the Discussion now reads, "Numerous patterns of liver injury can occur secondary to various drugs, including hepatitis, cholestasis, and mixed pattern injuries. Such drug-induced liver injury is generally divided into intrinsic and idiosyncratic reactions based on the dose dependency and predictability. Intrinsic hepatotoxicity is dose dependent and can subsequently be predicted once a specific threshold amount has been consumed. Conversely, idiosyncratic hepatotoxicity is dose independent and is subsequently unpredictable [2, 7-10]."

Added reference: Stephens C, Andrade RJ, Lucena MI. Mechanisms of drug-induced liver injury. *Current opinion in allergy and clinical immunology* 2014; **14**(4): 286-292

4) The authors concluded based on the time of onset of liver dysfunction that the previous cases were immune-mediated but their own case was not. This conclusion appears not justified for the previous reports if it is only based on the time when the liver injury started. Furthermore, the liver biopsy of the authors' patient shows some inflammatory infiltrates. Thus, it appears premature to exclude an immune-mediated mechanism. The discussion needs to be more based on the known facts for these cases.

-> We appreciated your thorough review. I have changed the last paragraph of the discussion. It now reads, "These previous reports suggest that the possible mechanism of bicalutamide-induced liver injury include an idiosyncratic reaction and direct hepatotoxicity. Initially, our patient was first treated in the urology department where he received 100 mg bicalutamide daily. He developed liver injury after daily bicalutamide use for 19 weeks, but slowly showed improved liver function 12 weeks after ceasing medication use. The higher daily dose (100 mg), compared to that administered to patients described in the previous case reports (50 mg), may be associated with a dose-response effect. On the other hand, the delayed liver injury may indicate an idiosyncratic reaction, because of the unpredictable latency. Irrespective of the mechanism, clinically significant and

potentially life-threatening liver injury can result from the use of bicalutamide. Therefore, prompt recognition and discontinuation of bicalutamide is necessary to avoid serious complications such as fulminant hepatitis. Liver function tests should be regularly conducted during and after bicalutamide administration."

3) In the discussion, the authors mention again the 3 previous case reports and even mention the dosing regimen and outcome but only cite 1 of the reports. All three reports need to be cited.

-> As mentioned in our previous comment, we agree that it is important to cite the 3 previous case reports of bicalutamide hepatotoxicity; however, because there were actually 4 previous case reports of bicalutamide hepatotoxicity, we have now included 4. The references have been given above.

5) Figure 1: The red and blue arrows mentioned in the legend are not present in the figure.

-> We agree with the reviewer, and we have inserted the red and blue arrows.

6. **Reviewer's code:** 00050424

COMMENTS TO AUTHORS

The authors describe a rare case of bicalutamide-induced hepatotoxicity. As the authors discuss bicalutamide-induced hepatotoxicity is a well reported side effect and develops after a few days but in their case hepatic injury occurred 5 months after treatment initiation. However they do not present ALT, AST, and bilirubin levels during treatment. They report only basal and fifth month's levels. Probably the patient had elevated liver enzymes during treatment and this might be not a delayed liver injury but a delayed diagnosis of prolonged liver injury.

RESPONSE: Unfortunately, the patient did not undergo follow-up for the liver enzymes for 5 months after treatment initiation. Therefore, this is a limitation in this

report.

In fact, regrettably, this patient was referred to our department from the urology department 5 months after treatment initiation. The follow-up of liver enzymes is usually performed after bicalutamide treatment initiation, although this seems to have been neglected, possibly because of the rareness of bicalutamide hepatotoxicity as a side effect. Moreover, this patient had no symptoms similar to those observed in the 4 previous case reports.

In conclusion, we suggest that the follow-up of liver enzymes is needed after bicalutamide treatment. Follow-up for examination of laboratory parameters should be done within a week after bicalutamide treatment initiation. After that, the examinations should be conducted at weekly or monthly intervals.

-> The conclusion now reads, "Actually, the patient described herein was referred to our department from the urology department 5 months after bicalutamide treatment initiation. The exact time at which bicalutamide-induced liver injury occurred may be unclear, because liver enzyme measurements were not followed at the urology department. This case emphasizes that liver function measurements should be monitored from baseline for at least the first 6 months of therapy, and then periodically during the entire period of treatment with bicalutamide."

We again appreciate the time that the reviewers and the editor have spent in bringing these points to our attention. We believe that the manuscript is now much improved, and we hope that the responses are adequate. We also appreciate your consideration for publishing this manuscript in World Journal of Gastroenterology.

Sincerely,

Gee Young Yun