ROUND 1

Responses to the Associate Editor's and Reviewers' Comments

5 July, 2021

Dear reviewers and editorial staff of *World Journal of Clinical Cases*

We would like to extend our sincere gratitude and appreciation for the thorough consideration and scrutiny of our manuscript, "**Biopsy-confirmed fenofibrate-induced severe jaundice: A case report and literature review**." The accurate comments of the reviewers have helped us better understand the critical issues of this paper. We have revised the manuscript according to the reviewers' suggestions. We hope that our revised version will be considered and accepted for publication in the *World Journal of Clinical Cases*. We acknowledge that the scientific and clinical quality of our manuscript was improved by the insightful comments of the reviewers and editors.

The changes within the revised manuscript were highlighted (underlined and in blue). Point-by-point responses to the reviewers' comments are provided below.

Reviewer #1 :

<GENERAL COMMENTS>

1) Reviewer's comment: The article needs review by a native English speaker.

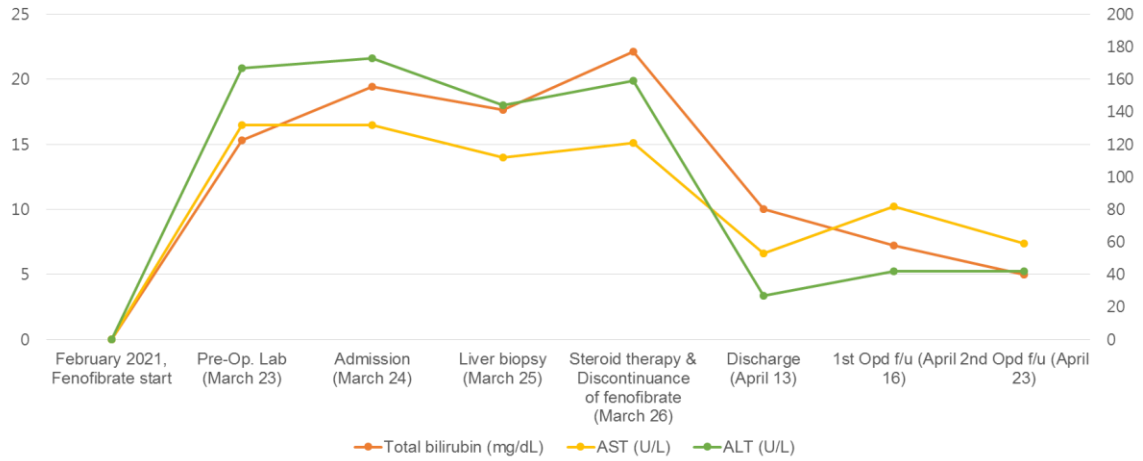
Author's response: We appreciate the reviewer's comment. The article was reviewed by a native English speaker and we have attached the English certification file.

2) Reviewer's comment: There is a need for more clinical details in the case summary. What was the maximum bilirubin level?

Author's response: We appreciate the reviewer's comment. The maximum bilirubin level of the patient was 22.13 mg/dL. We added this information to the main text and Figure 3.

"Over the course of several days after admission, the patient's serum bilirubin level rose up to a maximum of 22.13 mg/dL (Fig. 3).

Figure 3



3) Reviewer's comment: In the introduction ethanol is not mentioned as a cause of DILI as well.

Author's response: We appreciate the reviewer's comment. The content has been added to the Introduction section. Information on the patient's drinking history was also added as follows:

"DILI is usually caused by medications, herbal medications, ethanol, and dietary supplements."
"The patient was a non-drinker and non-smoker who quit smoking 10 years ago."

4) Reviewer's comment: It is not clear to me why liver tests were routinely performed prior

to an out patient visit.

Author's response: We appreciate the reviewer's comment. In February 2021, the patient was diagnosed with hyperlipidemia at a local hospital and was administered with fenofibric acid. After that, he was diagnosed with a ureter stone by accident and was recommended to undergo surgery at the local hospital. In Korea, routine blood tests are performed prior to surgery in clinical practice that requires general anesthesia. His jaundice was discovered incidentally on a preoperative blood test. The corrected content has been added to the ***History of present illness section*** as follows:

"In early February 2021, the patient was administered with 135 mg of fenofibric acid due to hyperlipidemia. In mid-February 2021, he was incidentally diagnosed with a ureter stone and was recommended to undergo surgery at the local hospital. In Korea, routine blood tests are performed prior to surgery in clinical practice that requires general anesthesia. The patient's jaundice was discovered incidentally through a preoperative blood test."

5) Reviewer's comment: It is not clear exactly when the patient developed jaundice.

Author's response: We appreciate the reviewer's comment. It is difficult to know the exact time when the patient developed jaundice, however the symptoms started two weeks before the laboratory test. Thus, we can assume that jaundice occurred in the first week of March, four weeks after the initiation of the drug. We added this information to the ***History of present illness section*** as follows.

"Thus, we can assume that the patient developed jaundice during the first week of March, four weeks after the initiation of the drug."

6) Reviewer's comment: In the laboratory examination section no mention was made of factor

V levels, viral causes, ferritin or ceruloplasmin determinations. Nor were autoantibody results presented.

Author's response: We appreciate the reviewer's comment. All viral hepatitis markers were negative (hepatitis B virus surface antigen, immunoglobulin M antibody to hepatitis A, hepatitis C antibody, immunoglobulin M antibody to hepatitis E virus). Serum ferritin and ceruloplasmin were in the normal range at 128 ng/mL and 36.9 mg/dL, respectively. All of the following autoantibody results were negative; anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibodies type 1. Factor V laboratory test was not performed. We added this information to the main text as follows:

"All viral hepatitis markers (hepatitis B virus surface antigen, immunoglobulin M antibody to hepatitis A, hepatitis C antibody, immunoglobulin M antibody to hepatitis E virus) were negative. Serum ferritin and ceruloplasmin were in the normal range at 128 ng/mL and 36.9 mg/dL, respectively. All of the following autoantibody tests showed negative results: anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibodies type 1. Factor V laboratory test was not performed."

7) Reviewer's comment: No objective determination of DILI such as a RUCAM score was included

Author's response: We appreciate the reviewer's comment.

Suspected product:		Date:
Items for cholestatic or mixed liver injury	**Score**	**Result**
1. Time to onset from the beginning of the drug/herb		
• 5–90 days (rechallenge: 1–90 days)	+2	☐
• <5 or >90 days (rechallenge: >90 days)	+1	☐
Alternative: Time to onset from cessation of the drug/herb		
• ≤30 days (except for slowly metabolized chemicals: >30 days)	+1	☐
2. Course of ALP after cessation of the drug/herb		
Percentage difference between ALP peak and ULN	+2	☐
• Decrease ≥50% within 180 days	+1	☐
• Decrease <50% within 180 days	0	☐
• No information, persistence, increase, or continued drug/herb use		
3. Risk factors		
• Alcohol use current drinks/day: >2 for women, >3 for men)	+1	☐
• Alcohol use (current drinks/day: ≤2 for women, ≤3 for men)	0	☐
• Pregnancy	+1	☐
• Age ≥55 years	+1	☐
• Age <55 years	0	☐
4. Concomitant use of drug(s)/herb(s)		
• None or no information	0	☐
• Concomitant drug/herb with incompatible time to onset	0	☐
• Concomitant drug/herb with time to onset 5–90 days	-1	☐
• Concomitant drug/herb known as hepatotoxin and with time to onset 5–90 days	-2	☐
• Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	-3	☐
5. Search for alternative causes	Tick if negative	Tick if not done
Group I (7 causes)	☐	☐
• HAV: Anti-HAV-IgM	☐	☐
• HBV: HBsAg, anti-HBc-IgM, HBV-DNA	☐	☐
• HCV: Anti-HCV, HCV-RNA	☐	☐
• HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	☐	☐
• Hepatobiliary sonography/Doppler/CT/MRC	☐	☐
• Alcoholism (AST/ALT ≥2)	☐	☐
• Acute recent hypotension history (particularly if underlying heart disease)	☐	☐
Group II (5 causes)	☐	☐
• Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases	☐	☐
• Infection suggested by PCR and titer change for	☐	☐
◦ CMV (anti-CMV-IgM, anti-CMV-IgG)	☐	☐
◦ EBV (anti-EBV-IgM, anti-EBV-IgG)	☐	☐
◦ HSV (anti-HSV-IgM, anti-HSV-IgG)	☐	☐
◦ VZV (anti-VZV-IgM, anti-VZV-IgG)	☐	☐
Evaluation of group I and II	☐	☐
• All causes—groups I and II—reasonably ruled out	+2	☐
• The 7 causes of group I ruled out	+1	☐
• 6 or 5 causes of group I ruled out	0	☐
• Less than 5 causes of group I ruled out	-2	☐
• Alternative cause highly probable	-3	☐
6. Previous hepatotoxicity of the drug/herb		
• Reaction labelled in the product characteristics	+2	☐
• Reaction published but unlabeled	+1	☐
• Reaction unknown	0	☐
7. Response to unintentional re-exposure		
• Doubling of ALP with the drug/herb alone, provided ALP below 2 x ULN before re-exposure	+3	☐
• Doubling of ALP with the drugs(s)/herbs(s) already given at the time of first reaction	+1	☐
• Increase of ALP but less than ULN in the same conditions as for the first administration	-2	☐
• Other situations	0	☐
Total score		

*Adapted from a previous report (Danan and Teschke, 2016). The above items specifically refer to the cholestatic or mixed liver injury rather than to the hepatocellular injury (shown in **Table 2**).*

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CT, computed tomography; DILI, drug-induced liver injury; EBV, Epstein–Barr virus; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; MRC, magnetic resonance cholangiography; ULN, upper limit of the normal range; RUCAM, Roussel Uclaf Causality Assessment Method; VZV, varicella zoster virus. Total score and resulting causality grading: ≤0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; ≥9, highly probable.

- Time to onset from the beginning of the drug/herb: 5-90days >> +2
- Course of ALP after cessation of the drug/herb: decrease > 50% within 180 days >> +2
- Risk factors: Age > 55years >> +1
- Concomitant use of drug/herb: none >> 0

- Search for alternative causes: The 7 causes of group 1 ruled out >> +1
- Previous hepatotoxicity of the drug/herb: Reaction unknown
- Response to unintentional re-exposure: Other situations >> 0

Therefore, the patient's RUCAM score was 6.

The content has been added to the Final Diagnosis section as follows:

"The Roussel Uclaf Causality Assessment Method (RUCAM) score was 6 (time to onset from the beginning of the drug/herb: 2 points; course of ALP after cessation of the drug/herb: 2 points; risk factors such as age: 1 point; search for alternative causes: 1 point) which indicates that fenofibrate is the probable cause of DILI."

8) Reviewer's comment: In the review of the 11 cases in the NIH Hepatox site there is a high number with an elevated BMI and this is not so in the patient presented. In the discussion it would be useful to discuss further the effect of obesity- it may be bias since triglycerides are likely to be elevated in patients with the metabolic syndrome

Author's response: We appreciate the editor's comment, and we fully agree with the reviewer's opinion. Hyperlipidemia is one of the metabolic syndrome items, and hyperlipidemia patients are often accompanied by obesity. In fact, in most of the previous case reports of fibrate-induced jaundice, most of the patients were obese with a BMI of 25 mg/m^2 or higher. However, it is not yet known whether high BMI is a simple bias or a real risk factor. Further research is needed to determine whether the two factors have a simple association or a temporal causal relationship. In our case as well, the patient's BMI was 24, demonstrating that fibrate-induced jaundice can sufficiently occur even in patients with low BMI. We added this information to the Discussion section as follows:

"High BMI is frequently reported in patients with fibrate-induced liver injury. Hyperlipidemia is one of the metabolic syndrome items, and such patients are often accompanied by obesity. In fact, in most of the previous case reports of fibrate induced jaundice, the majority of patients were obese with a BMI of 25 mg/m^2 or higher. However, it is not yet known whether high BMI

is a simple bias or a real risk factor. Further research is needed to determine whether the two factors have a simple association or a temporal causal relationship. In our case as well, the patient's BMI was 24, demonstrating that fibrate-induced jaundice can sufficiently occur even in patients with low BMI."

ROUND 2

Responses to the Associate Editor's and Reviewers' Comments

20 July, 2021

Dear reviewers and editorial staff of *World Journal of Clinical Cases*

We extend our sincere gratitude for your thorough consideration and scrutiny of our manuscript, "**Biopsy-confirmed fenofibrate-induced severe jaundice: Case report and literature review**". The accurate comments of the reviewers have helped us better understand the critical issues of this paper. We have revised the manuscript according to the reviewers' suggestions. We hope that our revised manuscript will be considered and accepted for publication in the *World Journal of Clinical Cases*. We acknowledge that the scientific and clinical quality of our manuscript was improved by the scrutinizing efforts of the reviewers and editors.

The changes within the revised manuscript were highlighted (underlined and in blue). Point-by-point responses to the reviewers' comments are provided below.

Reviewer #1 :

<GENERAL COMMENTS>

1) Reviewer's comment: The authors have responded to the comments and the manuscript is fine except for a few language issues. In order to save time I have taken the liberty of suggesting the changes required.

Author's response: We appreciate the reviewer's comment. We changed the manuscript as the reviewer's suggestion. Below are the corrected sentences.

"In early February 2021, the patient was treated with 135 mg of fenofibric acid due to hyperlipidemia. In mid-February 2021, he was incidentally diagnosed with a ureteric stone and was recommended to

undergo surgery at a local hospital."

"The patient was a non-drinker and former smoker who quit smoking 10 years ago. He was diagnosed with hypertension 5 years ago and was administered with a daily dosage of amlodipine 5 mg and valsartan 160 mg."

"All of the following autoantibody tests showed negative results: anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibodies type 1. Factor V levels were not determined."

"After the biopsy, the patient was treated empirically for DILI with prednisolone 40 mg daily for one week. The dose of prednisolone was subsequently rapidly reduced."

"One underwent liver transplantation at 8 months and the other eventually died of renal failure at 26 months."