

Aarhus, Denmark
8 March 2018

Dear Editor,

Thank you for allowing us to submit a revised version of this manuscript. We found the comments from all three reviewers extremely valuable. The comments and suggestions allowed us to improve the manuscript in addition to correcting the errors and mistakes that the reviewers correctly made us aware of. Below, we reply to all comments point-to-point. In the revised manuscript, major revisions are highlighted with **yellow**. Further, the revised manuscript underwent professional language and style editing, and a language editing certificate is attached with the submission.

All authors approved the revised version of the manuscript. We hope that it may be found suitable for publication in its present form.

On behalf of all authors,

Yours sincerely

Christian Lodberg Hvas, MD, PhD, associate professor

Point-to-point responses to reviewer comments

Reviewer #1:

The authors report a severe case of a patient with primary bile acid diarrhoea, needing regular water and electrolyte replacement, and so meeting current definitions of intestinal failure. It is particularly interesting in that a new agent, the FXR agonist obeticholic acid, produced a good therapeutic response when other agents had been unsuccessful. This adds long-term data to the previous limited report on obeticholic acid in bile acid diarrhoea and suggests that further studies should be done. The paper will be improved with some further attention to details:

1. p4 Abstract Bile acid diarrhoea is also thought to be due to overproduction of bile acids -- this is particularly important in this case. Colestyramine is the INN spelling for this drug. "... possible novel treatment principle" is not quite right; the wording needs revision. This treatment has been used before and the principle established then (ref. 11). Similarly the last sentence this report should stress it shows "further proof".

R: The wording was changed to the suggested. The INN nomenclature was adapted throughout.

2. p5. Consider some rewording in the last sentence.

R: The last sentence was reworded.

3. p6 Introduction. Para. 1. Functional diarrhoea, as per Rome classification, should be included. Not all patients have the pain needed for IBS-D. Para. 3. Possibly expand on the response to conventional therapy with bile acid sequestrants. Para. 4. FGF19 is only a proposed cause for BAD. Normal levels of bile acids, not just "excess" can stimulate FGF19. Also needs consistency on use of "FGF19" rather than "FGF-19". Obeticholic acid has also been studied in NASH.

R: Functional diarrhoea was included in the list of potential causes. Further description of bile acid sequestrant failure was included. The paragraph describing FGF19 was revised and FGF19 used throughout. A reference to the use of obeticholic acid was included.

4. p7 Case report This needs some further attention. Use "lasting" in first sentence rather than "during". Note "SeHCAT" is the usual abbreviation. Also "taurine" not "thaurine". When was the SeHCAT performed? Consider where Table 1 and Table 2 are referenced in the text. The sequence of events is a little unclear with "At referral", "initial Examination", "at initial investigation" occurring in three separate paragraphs.

R: The suggested changes were implemented. Reference to the Tables was moved to the revised description of investigations and treatments performed after referral. In the revised manuscript, we described more clearly which examinations were performed before and after referral to our unit, respectively.

5. p8 Para. 2. It would be useful to state that the regular infusions meant she had "intestinal failure". Para. 3. Would it be possible to include simple statistics such as a Mann-Whitney U test on daily stool frequency, say for 7 days in week -1 and +2? Which NSAID was she given and for how long? The text should explain the annotations in Figure 1 of "Acute Diarrhoea" and "Running club".

R: Description of grade of intestinal failure and reference to the European consensus report were inserted. Comparison of before vs after obeticholic acid was performed using nonparametric statistics as suggested. The indications in Figure 1 were explained in further detail in the revised text.

6. p9 Para. 1. Specify if there were any changes in LFTs and Lipids. What was the Amylase value? Did she have an Ultrasound? Any gallstones? Para. 2. Discussion It would be useful to comment more on intestinal failure. The recent consensus definition including regular IV replacement would help (Pirone et al. Clin Nutr 2015; 34:171). Para. 4. Ref. 11. include "improvement of symptoms".

R: Details regarding bloods (liver function tests, lipids, amylase) and investigations were included in the revised manus. We agree that increased attention to the complication with intestinal failure would improve the text and incorporated this in the case report and the discussion.

7. p10 Para. 1. Please review first sentence "over" Para. 2. There are better references to the variability of FGF19 levels than the current ref. 18 in renal disease. See for instance Galman et al. J Intern Med 2011, 270; 580.

R: The sentence was revised, also in respect to the comment from reviewer 2 (see below). FGF19 variability was further discussed and the suggested reference inserted.

8. Table 1. There are a few misspellings "diarrhoea", "thaurine", "Neuroendocrine" "Chromogranine". Is this the sequence that was used to investigate causes?

R: Spelling errors were corrected. The chronology of investigations is difficult to illustrate because several investigations were performed more than once, and some results changed over time. We revised the Table so that it reflects the priority during a pragmatic clinical approach.

9. Table 2. Obeticholic acid stimulates "ileal" FGF19 production and inhibits "hepatic" BA synthesis.

R: Description of mode of action was included in the Table.

10. Figure 1. In the Figure legend, omit "Development of". Also on the Figure would it help to have a vertical line when Obeticholic acid was started?

R: The legend was revised. We kept the indication of treatment changes using arrows.

Reviewer #2

This paper describes an interesting and particularly resistant case of bile acid diarrhoea. The patient had a long history and underwent a thorough diagnostic workout. The paper provides a complete and coherent message and suggests

an alternative treatment with a rationale given reference to recent progress in the understanding of BAD pathogenesis. This is true even if it cannot be the complete story given the fact that the patient during treatment had a persistent and abnormally high bowel frequency including nightly defecation. I have only a few comments.

1. The dose of obeticholic acid should be stated in the text and not only in the figure and discussion.

R: The dose of obeticholic acid was inserted in the case report.

2. Was an increased dose of obeticholic acid considered? If so, was there a dose-response?

R: We did not increase the dose which would have been interesting, though.

3. Is it taurine and not thaurine?

R: Yes, corrected to taurine throughout.

4. The discussion of reasons this patient did not experience any side effects appears somewhat hypothetical and should either be deleted or a reference provided.

R: The hypothetical part of this paragraph was deleted.

5. Did control of the patients' epilepsy and plasma concentrations remain stable?

R: Plasma values were measured (and increased, in fact), and a brief comment was inserted in the revised case report.

6. FGF19 values were measured and should be provided.

R: FGF19 values were described and discussed in the revised manus.

7. Was changes in quality of life measured?

R: Yes, by EQ5LD. Development in QoL scoring was described in the revised manus.

Reviewer #3

This is a well written and interesting report of a young women with Crohn's disease and multifactorial severe diarrhea. The diarrhea improved (but did not subside) on treatment with obeticholic acid. Comments:

1. The authors claim the patient has primary bile acid malabsorption. I do not think this diagnosis can be established based on the provided data. –
 - a. The patient has Crohn's disease. The diagnosis of primary bile acid malabsorption requires absence of other intestinal disease (Camilleri M. Gut and Liver, Vol. 9, No. 3, May 2015, pp. 332-339, cited by the authors themselves ,Ref 3 of the manuscript). Further, bile acid metabolism can be deranged in colonic Crohn's disease and in the absence of inflammation of the ileum (recently reviewed: Vitek L. Inflamm Bowel Dis 2015;21:476–483).
 - b. Other possible causes of this severe diarrhea have not been ruled out. E.g. Were small bowel biopsies obtained? Could the patient have celiac disease or some other small bowel disease (the high stool volume of 5 L suggests a problem in the small bowel) ? Bile acid malabsorption is quite unspecific in diarrheal diseases and can be a manifestation of an underlying intestinal motility or absorptive defect rather than the primary cause of diarrhea (Schiller LR et al. Gastroenterology 1987;92:151-60). Further, obeticholic acid may be effective also in secondary bile acid diarrhea (ref. 11 of the manuscript).
 - c. The symptoms are highly atypical for bile-acid diarrhea. The authors themselves state that this is the first report of primary bile acid diarrhoea of such severity.

R: This is a relevant comment. We acknowledge that the patient may be classified as having type 1 BAD because she has Crohn's disease, but because active inflammation was ruled out and treatments targeting BAD were most effective, we considered the condition primary BAD. We included the study by Nolan and coworkers who found that FGF19 is low in Crohn's disease and diarrhea, independently of resection and activity, although both are associated with even lower values. We therefore think that the mechanism may apply to both type 1 and type 2 BAD. We revised the introduction to comply with this, we incorporated the suggested references, and we revised the discussion. Small bowel investigations were described in further detail and the discussion of intestinal failure made more specific. We included celiac disease and autoimmune enteropathy as potential causes for chronic secretory diarrhoea listed in Table 1.

2. The authors should provide the dose and duration of cholestyramine therapy.

R: This was inserted.

3. Abstract: The authors write „Diarrhoea recurred shortly after cessation of obeticholic acid.“ It would be more appropriate to write „worsened“ (or something similar) because diarrhea was still present on obeticholic acid (7 stools/day).

R: Agree, this was revised to the suggested.

4. Discussion: The authors write: „Because the seHCAT retention rate was 0% on day 7, severe bile acid diarrhoea was present.“ This sentence does not sound logical to me. It would be more appropriate to use „malabsorption“ than „diarrhoea“.

R: Agree, this was revised.