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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 37708
Title: Obeticholic acid for severe bile acid diarrhoea with intestinal failure
Reviewer's code: 00036225
Reviewer's country: Austria
Science editor: Xue-Jiao Wang
Date sent for review: 2018-02-02
Date reviewed: 2018-02-09
Review time: 7 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

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

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problem in the small bowel) ? Bile acid malabsorption in quite unspecific in diarrheal diseases and 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 themseves state that this is the first report of primary bile acid diarrhoea of such severity. 2. The authors should provide the dose and duration of cholestyramine therapy 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). 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 woud be more appropriate to use „malabsorption" than „diarrhoea".

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 37708
Title: Obeticholic acid for severe bile acid diarrhoea with intestinal failure
Reviewer's code: 02567512
Reviewer's country: Denmark
Science editor: Xue-Jiao Wang
Date sent for review: 2018-02-17
Date reviewed: 2018-02-19
Review time: 2 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

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. The dose of obeticholic acid should be stated in the text and not only in the figure and discussion. Was an increased dose of obeticholic acid considered? If so, was there a dose-response? Is it taurine and not thaurine? The discussion of reasons this patient did not experience any side effects appears somewhat hypothetical and should either be deleted or a reference provided. Did control of the patients' epilepsia and plasma concentrations remain stable? FGF19

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values were measured and should be provided. Was changes in quality of life measured?

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 37708
Title: Obeticholic acid for severe bile acid diarrhoea with intestinal failure
Reviewer's code: 00009274
Reviewer's country: United Kingdom
Science editor: Xue-Jiao Wang
Date sent for review: 2018-02-17
Date reviewed: 2018-02-22
Review time: 5 Days

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

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: 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". p5. Consider some rewording in the last

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sentence. 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. 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. 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". 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". 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. Table 1. There are a few misspellings "diarhhoea", "thaurine", "Neuroendochrine" "Chromogranine". Is this the sequence that was used to investigate causes? Table 2. Obeticholic acid stimulates "ileal" FGF19 production and inhibits "hepatic" BA synthesis. 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?