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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 28607
Title: Future therapies for inherited cholestatic liver diseases
Reviewer's code: 00013491
Reviewer's country: China
Science editor: Ze-Mao Gong
Date sent for review: 2016-07-09 18:43
Date reviewed: 2016-08-25 21:09

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[ ] 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

Current therapeutic options for familial intrahepatic cholestasis, such as ursodeoxycholic acid and partial biliary diversion, are often insufficient to prevent progression of the disease. This review included information about current therapeutic regimen as well as the development of novel therapeutic strategies, focusing on surgical and pharmacological biliary diversion, hepatocyte transplantation and mutation-specific therapy. The authors cited all important, relevant and timely references in and summarized the advantages and limit of every current therapy. Moreover, the manuscript showed us the future therapeutic options, which were promising and interesting. I recommend that the content of the manuscript have value for publication and it helps the readers to understand the current and new symptomatic treatment options systematically.

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ESPS PEER-REVIEW REPORT

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Reviewer's country: Germany
Science editor: Ze-Mao Gong
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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

The paper "Future therapies for inherited cholestatic liver diseases" by van der Woerd deals with a topic of pediatric Hepatology. It describes treatment options of a group of inherited cholestatic diseases, which are due to transporter defects. It is a thorough review, which is nicely written. It is up to date. There are only minor things which should be addressed: 1. The title could be broadened to "Current and future therapies …." 2. Third page ("Familial intrahepatic cholestasis"): the second paragraph should be re-ordered. Different aspects of PFIC1, 2 or 3 should be described one after the other without a permanent change between these three subtypes of PFIC. 3. Page 4, second paragraph: "(TJP)" should be italic, since the gene is decribed. 4. Page 4, "Liver transplantation": A citation for the potential role of ATP8B1 in bile acid absorption could be given (e.g. van der Mark VA, et al. The lipid flippase heterodimer ATP8B1-CDC50A is essential for surface expression of the apical sodium-dependent bile acid transporter (SLC10A2/ASBT) in intestinal Caco-2 cells. Biochim Biophys Acta. 2014;1842:2378-86). 5. It would be nice to summarize the different surgical options (PEBD, PIBD, TBD and PIBD + BD-ligation) for the treatment of cholestasis in a figure. 6. Page 7, second to last row: "…, bearing the same mutation" – Do you mean patients with PBD and TBD, who have the same

mutations? 7. Page 8: The title of the second paragraph should be confined to PFIC1 patients ("Liver transplantation combined with biliary diversion in PFIC1 patients" and "… the long-term safety of total external drainage in this setting …."). In this section the paper Mali VP et al. Total internal biliary diversion during liver transplantation for type 1 progressive familial intrahepatic cholestasis: a novel approach. Pediatr Transplant. 2016 should be quoted. 8. Page 9, first paragraph: the sequence "BA – ileocyte – FXR-activation – FGF19-expression –hepatocyte – BA-synthesis" should be described more clearly. The sentence "FGF19 … forms a health risk" should be omitted for in favour of clarity. 9. Page 9/10: In the section about hepatocyte transplantation, the special difficulty in establishing a competent biliary drainage in organoids should be mentioned. 10. Page 12: not only ATP8B1 but also ABCB11 was investigated and should be mentioned (Byrne JA et al. Missense mutations and single nucleotide polymorphisms in ABCB11 impair bile salt export pump processing and function or disrupt pre-messenger RNA splicing. Hepatology. 2009;49:553-67.). A recent paper investigating splicing defects in vivo can also be mentioned: Dr?ge C et al. Exon-skipping and mRNA decay in human liver tissue: molecular consequences of pathogenic bile salt export pump mutations. Scientific Reports 2016;6:24827. 11. Page 14: there is also evidence that chaperons can improve surface expression not only of BSEP and FIC1 but also of MDR3, therefore it should be mentioned (e.g.: Gautherot J et al. Effects of cellular, chemical, and pharmacological chaperones on the rescue of a trafficking-defective mutant of the ATP-binding cassette transporter proteins ABCB1/ABCB4. J Biol Chem. 2012;287:5070. 12. There is some minor misspelling e.g. in citation 46 and 47.

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ESPS PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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		[Y] No	

COMMENTS TO AUTHORS

The review presents new therapies applied to patients with inherited cholestatic liver diseases. This review describes very completely the different types of current and future surgical treatments as well as new therapeutic options for these biliary diseases . The bibliography is more complete for the pathology PFIC1 than others PFICs. In this sense, some points have to be considered. -& Introduction Familial intrahepatic cholestasis, PFIC4 should be mentioned for TJP2 mutation. -& Non surgical therapies/ Medical therapy; The authors mentioned that "rifampicin treatment does not result in improvement of serum.....in only few patients". Could the authors add reference related to this result? Recently, it has been published a study on medical care of refractory cholestatic pruritus related to Alagille syndrome or PFICs Patients by serotonin reuptake inhibitor, this treatment could be a new opportunity for the treatment of pruritus in these PFIC pathologies. J Pediatr Gastroenterol Nutr. 2016 Aug 24. -& Surgical therapies; "PEDB is succesfull in improving pruritus and biochemical parameters of cholestasis". May the authors precise the biochemical parameters? Concerning surgical therapies, illustration of the different surgical therapies with diagrammatic representation could be provided. -& Total biliary diversion ; Do the total biliary diversion

presented as future therapy could be use to manage other PFIC than PFIC1 ,as 2 and 3 ? -& Mutation specific therapy; Recently, it has been published and proposed a functional classification of ABCB4 mutations according to their functional defect leading to PFIC3.This reference should be introduced and discussed. Hepatology. 2016 May;63(5):1620-31. & Molecular characterization; Authors discussed the absence of functional assay for ATP8B1. It has been published fluorescent assays to evaluate ATP8B1 activity by several group, Gastroenterology. 2009 Mar;136(3):1060-9. Hepatology 2001; 34: 768-775. Hepatology 2008; 47: 268-278. &Rescue of impaired protein trafficking; To complete all the work done on PFICs, there are several studies concerning the rescue of retained protein for ABCB4 (PLoS One. 2016 Feb 22;11(2); Hepatology. 2016 May;63(5):1620-31; J Biol Chem. 2012 Feb 10;287(7):5070-8) and for ABCB11 (J Hepatol. 2012 Sep;57(3):695-8.)