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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 49644

Title: Lumacaftor/ivacaftor therapy is associated with reduced hepatic steatosis in cystic fibrosis patients

Reviewer's code: 03257773
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's country: Norway
Author's country: United States

Reviewer chosen by: Ruo-Yu Ma
Reviewer accepted review: 2019-09-05 10:39
Reviewer performed review: 2019-09-05 12:49
Review time: 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

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This is a presentation of a very interesting study. The extra-pulmonal manifestations of cystic fibrosis has received little attention, though there is a high (and probably increasing) impact of these manifestations in patients. The manuscript is in a generally well written language. The main hypothesis is that fatty liver disease in CF is assosiated with CF associated diabetes mellitus. Patients are recruited from database, and characterized genotypically, through simple clinical and clinical chemical tests and state of art imaging modality for determining fatty liver. Patients are divided in two main groups: The ones receiving CFTR modulators, and the ones not. There is stated no reason for this difference in treatment between the two groups. The main finding is that no significant association is demonstrated between fatty liver disease and development of diabetes mellitus. An incidental finding is that patients receiving modulator treatment have less fatty liver. This finding is the most described finding in the manuscript, and also reflected in title. There are some major concerns that should be addressed: 1. The modulator and non-modulator groups are genotypically different. The modulator group are all homozygous for F508del. In the non-modulator group, 9 out of 11 are heterozygous for F508del, only one homozygous, and one has no F508del mutation at all. Hence the difference in genotypes between the two groups may confound the result, rather than modulator. I think this at least should be discussed as a possible limitation / confounder more than is done. The one patient with F508del/F508del with high fat-level cannot be a guarantist for this effect. 2. I think the conclusions on no association between CFRD and fatty liver is presented too firm. This finding may be a type 2 error result. The patients are heterogeneous with regards to age and genotype and the number is small. As development of CFRD is multifactorial (loss of beta cells and increased insulin resistance), a non-significant result (that even is borderline) does not rule out such an association.

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INITIAL REVIEW OF THE MANUSCRIPT

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[ ] Plagiarism

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 49644

Title: Lumacaftor/ivacaftor therapy is associated with reduced hepatic steatosis in cystic fibrosis patients

Reviewer's code: 00631989
Position: Editorial Board
Academic degree: BSc

Professional title: Professor, Associate Professor, Research Associate

Reviewer's country: Italy

Author's country: United States

Reviewer chosen by: Artificial Intelligence Technique

Reviewer accepted review: 2019-09-09 11:27

Reviewer performed review: 2019-09-24 14:01

Review time: 15 Days and 2 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

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This study deals with hepatic steatosis in cystic fibrosis (CF) patients. The Authors demonstrated that CF related diabetes was not associated with hepatic steatosis as was originally hypothesized. However, they found that Lumacaftor/Ivacaftor therapy is associated with reduced hepatic steatosis in CF. The methods used are appropriate. The results and the abstract are clear and focused. Tables and figure are appropriate. The conclusions appear sustained by results. The subject is appropriate for the journal. The scientific content fits the standard for publication. The major flaw of this research is the limited number of individuals studied. However, the findings introduce a reasonably level of novelty ad are of interest for CF community. I think the manuscript is acceptable after minor revisions. Please find below two lists of items, accordingly with criteria checklist proposed by the World Journal of Hepatology. The first list includes items I think do not need revision. The second list includes my suggestions for minor revisions. The number corresponds to item numbering of WJH. Items that do not need revision. 1) The title reflect the main subject/hypothesis of the manuscript. 6) The research objectives are achieved by the experiments used in this study. Although the case series is small, the manuscript represents a significant contribute to a CF clinical aspect little explored. 7) The manuscript interprets the findings adequately and appropriately, highlighting the key points concisely, clearly and logically. The findings and their applicability/relevance to the literature are stated in a clear and definite manner. The discussion is accurate and discusses the paper's scientific significance and/or relevance to clinical practice sufficiently. 9) The Authors certified that the statistical analysis was performed by a biomedical statistician. 12) The manuscript is well, concisely and coherently organized and presented. The style, language and grammar are accurate and appropriate. 13) The Authors uploaded the STROBE Statement – case control study. Item that need minor revisions. 2) The abstract summarizes and reflects the work described in the manuscript. However, the study of

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the effect of Lumacaftor/Ivacftor therapy is not listed within the aims. I suggest to add it as an additional point. On the other hand, one aim reported in the abstract would be to "identify predictors of hepatic steatosis in cystic fibrosis" but in the text this concept is not well focused. If the Authors intend to highlight predictors of hepatic steatosis, this should be better described in Results and Discussion. Otherwise, the point should be eliminated from the abstract. 3) The key words reflect the focus of the manuscript. However, I suggest to add a keyword about the therapy and, possibly, about its effect on hepatic steatosis. 4) The manuscript adequately describes the background, present status and significance of the study. However: a) it does not mention the genetics of CF. I suggest to add a short paragraph about CF genetics, mutational search in the CFTR gene and its influence on personalized therapy of CF in Introduction and to quote the following papers: Quotation 1: Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet. 2015 Jan;16(1):45-56. doi: 10.1038/nrg3849 Quotation 2: Targeted sequencing reveals complex, phenotype-correlated genotypes in cystic fibrosis. BMC Med Genomics. 2018 Feb 13;11(Suppl 1):13. doi: 10.1186/s12920-018-0328-z Quotation 3: A New Targeted CFTR Mutation Panel Based on Next-Generation Sequencing Technology. Journal of Molecular Diagnostics. 2017 19(5), 788-800. doi: 10.1016/j.jmoldx.2017.06.002 Quotation 4: The impact on genetic testing of mutational patterns of CFTR gene in different clinical macrocategories of cystic fibrosis. Journal of Molecular Diagnostics 2016, 18(4):554-565, doi: 10.1016/j.jmoldx.2016.02.007. b) The abbreviations have to be checked (also in the abstract). Some terms are not abbreviated the first time they appears and, on the contrary, terms already abbreviated are used in full. c) The sentence which refers to hepatic steatosis as "… a benign finding" (Introduction, page 6) should be better explained. d) In Materials and Methods, Patients characteristics (page 7), the sentence "… with genetically confirmed cystic fibrosis …" is unclear. The Authors should affirm that the diagnosis of CF has been

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performed accordingly to guidelines and quote: Quotation 5: Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017;181S:S4-S15 e1, doi: 10.1016/j.jpeds.2016.09.064. e) All the clinical and biochemical characteristics described in Table S2 and statistically significant should be described and commented, even in separate paragraphs; on the contrary, in Results the Authors included only two paragraphs about "Hepatic steatosis" and "Diabetes" almost neglecting the other statistically significant aspects. f) the sentence "… standard deviation …" (Discussion, page 10) is unclear; I think it is better to reformulate it. 5) The Methods section should be expanded to include the description of the methods used for each variable/data reported in Results section and in Figure and Tables (also supplemental). For example, it is not sufficient to affirm that: - " Pancreatic insufficiency was defined by a need for pancreatic enzyme replacement." (page 7). Was fecal elastase dosage performed? By which method? - "Only subjects with two class 1-3 mutations were included in the final analysis.". (page 7) Which was the mutational search method used, allowing the genetic findings reported in Table S1? - How was assessed the glucose dosage, glucose tolerance and diabetes? - How was assessed the HbA1C, Alk Phos, Total bilirubin, AST, ALT, GGT, Triglyceride (so, all data reported in Table 2 and Table S2)? Indeed, the only method referred is the MRI proton density but also the other laboratory methods should be synthetically reported or, at very least, paper(s) for method(s) should be quoted. 8) The figures, diagrams and tables are sufficient, good quality and appropriately illustrative of the paper contents. They do not require labeling with arrows, asterisks, etc., nor better legends. However: a) table S2 is a key table of the manuscript. I suggest to move it from supplementary to main body b) also Table S1 (along with Table 1) should be cited in "Participant characteristics" c) in table S1 the legacy name of "1898 1G>A" is "1898+1G>A", with "+" and the legacy name of "1717

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1G>A" is "1717-1G>A" with "-". 10) The manuscript meets the requirements of use of SI units. However: a) sometimes micromole is written as "umol" (with "u"). For example in Table 2 (legend) and Table S2 (footnote), but please check throughout the manuscript. The "u" should be changed to the greek letter "m" (micro) b) the name of each CFTR mutation should be reported in HGVS 19.01 nomenclature, both nucleotidic and proteic, as well as in legacy name. For example, for F508del as follows: c.1521_1523delCTT p.Phe508del (HGVS 19.01 name), F508del (legacy name). The HGVS name of each mutation can be easily found in the CFTR2 database and could be added to the Table S1 and within the text. c) the term "mutation" is obsolete. It is generally recognized that it is better to use "pathogenic variant" (instead of "mutation") and "non-pathogenic variant" (instead of "polymorphism"); also "CF-causing variant" or "non CF-causing variant" may be used. If there is no indication about the ability of a variant to cause CF, just "variant" can be used. 11) The manuscript cites appropriately the latest, important and authoritative references in the introduction and discussion sections. The Author do not over-, self-, omit or incorrectly cite. The 5 papers reported in point 4 could be usefully added to quotations in the Introduction. 14) The Authors uploaded the authorization to publish of their ethical committee. However, the expiration date for the study was 09/12/2017. I think the Authors should submit to the Journal an explanation for this.

INITIAL REVIEW OF THE MANUSCRIPT

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 49644

Title: Lumacaftor/ivacaftor therapy is associated with reduced hepatic steatosis in cystic fibrosis patients

Reviewer's code: 00002080
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's country: Ireland

Author's country: United States

Reviewer chosen by: Artificial Intelligence Technique

Reviewer accepted review: 2019-09-09 09:47

Reviewer performed review: 2019-09-25 05:54

Review time: 15 Days and 20 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection	Peer-Review: [Y] Anonymous [ ] Onymous Peer-reviewer's expertise on the topic of the manuscript: [Y] Advanced [ ] General [ ] No expertise Conflicts-of-Interest: [ ] Yes [Y] No

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This is a a carefully performed research study and is clearly written which seeks to address an important question in the era of new modulator therapies. Unfortunately the study design is not adequate to address the aims of the study as there is no baseline MRI to demonstrate the level of hepatic steatosis prior to commencement of Orkambi. While MRI is not standard practice this is understandable, however prior liver ultrasound data, even with the limitations of ultrasound would be helpful to the reader in determining if participants had any evidence of hepatic statosis prior to commencing modulator therapy. In addition this study also has many other study design issues which are very difficult to overcome but do bias the results including a very high proportion of males, (80%) those who are older have CFRD and coincidently are likely to take Orkambi.

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