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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 25785
Title: Delayed resolution of liver stiffness in PNPLA3 variant I148M after alcohol detoxification
Reviewer's code: 01429800
Reviewer's country: Italy
Science editor: Ya-Juan Ma
Date sent for review: 2016-03-23 11:20
Date reviewed: 2016-06-09 00:50

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] 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
[Y] 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
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Rausch et al. analized the influence of PNPLA3 genotype in heavy drinkers on serum markers and liver stiffness (LS) during all stages of alcoholic liver disease (steatosis, steatohepatitis, fibrosis) prior and after alcohol detoxification. This is a study of great interest that can help the researchers in evolving in this field. However, some minor points could be addressed. The methods are incomplete and it needs to be implemented. It is not clear the study design and the inclusion and the exclusion criteria. How much time has passed after alcohol withdrawal? Please discuss limitations of the study, taking into account sources of potential imprecision.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
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Title: Delayed resolution of liver stiffness in PNPLA3 variant I148M after alcohol detoxification
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Reviewer's country: Netherlands
Science editor: Ya-Juan Ma
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] 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
[Y] 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
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Summary: in this study, liver stiffness by fibroscan and serum markers were prospectively studied in Caucasian heavy drinkers (n=521) with all stages of alcoholic liver disease. The patatatin like phospholipase A3 variant (a well known variant correlated with various aspects of liver disease) rs738409 variant (CG and GG) was primarily associated with hepatocellular damage but not with steatosis. The OR to develop cirrhosis was 1.295 (95% CI 0.787-2.131) for CG+GG carriers. Similarly, liver stiffness was significantly elevated in these genotypes and primarily associated with fibrosis stage, ballooning, steatohepatitis but not with steatosis. After alcohol withdrawal, LS decreased to a lesser extent in GG carriers due to prolonged resolution of inflammation. Comments: 1. Introduction: "However, twin studies,the enhanced sensitivity of female drinkers and the fact that only a minority ofpatients progress to cirrhosis despite heavy drinking clearly suggest a genetic predisposition". The enhanced sensitivity of female drinkers could also relate tot other (non-genetic) facturs such as different gastric alcohol dehydrogenase, higher body fat, changes in alcohol absorption with menstrual cycle. 2. Methods: "Other causes of liver diseases were ruled out

serologically by screening for AMA, ANA, HCV and HBV." How many cases were excluded? Were these tests performed in all patients? 3. Were all eligible patients attending the clinic consecutively included? 4. 80 patients had liver biopsy. Which criteria determined the decision to perform this procedure? Probably this bias can explain significant part of the results and discrepancy between biopsy and Fibroscan. 5. Mean biopsy length was 15.6 mm. This could lead to significant underestimation of biopsy length. This limitation should be mentioned in the discussion (see ref. Bedossa, Hepatology 2003). 6. Methods: fibroscan was performed with M probe. How many patients were unsuccessfully measured? Was X-L probe available? 7. 80 patients apparently had fibroscan as well as liver biopsy. What was the time period between both investigations? What was the correlation of results with 2 methods in the same patients? 8. Fig 2: detailed info shoud be presented on the time periods elapsed between repeated fibroscan measurements resp repeated ast measurements in the patients of the various PNLPLA3 subgroups.

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E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

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

COMMENTS TO AUTHORS

The authors analyzed the correlation between PNPLA3 rs738409 genotypes (CC, GC and GG) and the liver stiffness (LS) measured by transient elastography, and the clinic-pathological findings of liver biopsy in heavy drinkers. They also compared the resolution of LS and liver inflammation between different genotypes after the patients stop drinking. They concluded "In heavy drinkers, PNPLA3 GG primarily correlates with liver damage but not steatosis resulting in a delayed inflammation-associated resolution of LS. Consequently, sustained LS elevation could be a major risk factor in PNPLA3 GG carriers". 1. In the results, the authors stated "Mean LS was lowest in CC carriers (13.1 kPa) as compared to CG and GG carriers (both 17.6 kPa)". But in table 2, mean LS if CC, CG and GG carriers were 13.1 kPa, 17.6 kPa and 17.2 kPa repectively. The authors did not show any statistical difference between CC and GG group. The authors need to make the statement clear and precise. 2. In the results, the authors stated "After alcohol withdrawal, LS significantly decreased in CG-carriers from 17.6 to 12.7 kPa but not significantly in CC carriers. Moreover, LS decreased to a lesser extent in GG carriers from 17.6 to 14.5 kPa due to prolonged resolution of inflammation". But

in fig. 2A, the LS decrease in GG group was not statistically significant. The statement is not adequate. 3. In both the results and discussion the authors speculated that LS decreased to a lesser extent in GG carriers was due to "prolonged resolution of inflammation", but they did not explain why LS did not significantly decreased in CC carriers, whose transaminase level significantly reduced after stop alcohol drinking. 4. In the conclusion, the authors stated "In heavy drinkers, PNPLA3 GG primarily correlates with liver damage but not steatosis". However, this may not be true for all heavy drinkers. Other factors more than PNPLA3 genotype may cause liver damage in heavy drinkers. This statement is only true in particular group of patient. The definition of this particular group should be well defined. 5. In the conclusion, the authors stated "sustained LS elevation could be a major risk factor in PNPLA3 GG carriers". Dose they mean "GG carrier is a major risk factor for sustained elevated LS value". 6. In the materials and methods, the authors included 521 alcoholic liver disease patients in the study. Subgroup analysis were performed according to the method of evaluation (non-invasive e.g. transient elastography, n=503 and histological, n=80). It means 62 patients received both examinations. The correlation between the evaluation results may be performed in these 62 patients. The comparison made between the whole cohorts is complex and may be misleading. 7. In the results, line 10, the authors stated "CC carriers represented 42.1% of the F0 cohort but 35.5% of the F4 cohort". They did not describe by which evaluation method were the results obtained. 8. GC carriers and GG carriers are sometimes discussed together, and sometimes separately. The analysis makes the result complex and not easy to understand. The authors did not explain why they had to perform the analysis in this way. 9. In the results, the authors stated "In summary, GG-associated liver damage results in a reversible, inflammation-associated increase of liver stiffness. In addition, GG carriers show a slower resolution of liver damage and LS after withdrawal from alcohol". This statement is not exactly true according to figure 2B, which did not showed significant resolution of LS in GG group. 10. The results showed LS is highly associated with fibrosis stage, but the genotype distribution of F4 cirrhosis evaluated with fibroscan and histology are different. The authors did not explain the difference clear enough. 11. The conclusion is not fully supported by the results. The statement should be revised.