

Format for ANSWERING REVIEWERS



October 2, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Prevention of hepatocellular carcinoma by correction of metabolic abnormalities: Role of statins and metformin

Author: Javier Ampuero and Manuel Romero-Gomez

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13317

The manuscript has been improved according to the suggestions of reviewers.

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer: 1

Point 1: The figure 1 could be improved using regular squares instead of "hand-drawn" lines and putting in note the entire names of abbreviated factors.

Response: We agree. We have used regular squares instead of hand-drawn lines.

Reviewer: 2

Point 1: Whenever odd ratios (OR), relative risks (RR) or hazard ratios (HR) are shown they should be accompanied by their corresponding "p" value and/or 95% confidence interval. It would make easier the interpretation of data for the reader.

Response: We agree with the reviewer and have included "p" values to add information.

Point 2: As the authors have pointed out several studies reported a protective effect of metformin against HCC when compared with other anti-diabetics and insulin. However these studies are neither randomized, nor controlled, and most of them with a retrospective design. The risk of bias is extremely increased as diabetic patients taking metformin may not be comparable with those taking insulin or other oral anti-diabetics.

In addition the dosage and duration of metformin therapy is not controlled as a possible confounding factor in most studies. The heterogeneity of the studies, the lack of randomization and the increased risk of reporting bias prevent from any reliable conclusion when pooled analyses are performed. These limitations should be highlighted and further discussed in the text.

Response: We agree with the reviewer. It is needed further high-quality studies to reach stronger conclusions. Meanwhile, available data (from experimental studies and observational cohorts) suggest that metformin could play a quimiopreventive role in the prevention of HCC. We have edited this question in the manuscript.

Point 3: It would be helpful to add a table summarizing the studies evaluating metformin as a chemopreventive agent of HCC. The study design, number of patients included, doses and duration of metformin therapy, median follow-up and results may be included in the table.

Point 4: The English requires minor polishing.

Response: We have edited the manuscript to improve the grammar and style.

Reviewer: 3

Point 1: On the other hand, they report only one randomized controller trial regarding statins showing no impact of such drug on HCC incidence. What about metformin? I think that this part should be stressed: if no randomized controlled study using metformin was performed to date, a prospective randomized study should be strongly encouraged but meanwhile the indirect evidences of metformin usefulness should be taken into account.

Response: We have added a new comment about this aspect in the manuscript.

Point 2: Authors should approach the use of widespread use of insulin therapy by diabetologists (and concomitant metformin withdrawal) in cirrhotic patients, irrespective of their Child status. Insulin seems (Donadon, Liver Int 2010) to enhance HCC risk, metformin is very likely to reduce such risk. Why suspend a useful drug and introduce a potentially

harmful drug?

Response: This is a very interesting point. Probably, everybody should balance the risk and benefits of using oral antidiabetic drugs or insulin therapy. There are cases in which is required a strict control of glucemia (i.e. cardiovascular risk) and probably exogenous insulin is stronger than metformin. However, other situations could require less glucemic control and the benefits of metformin are higher than risks.

Point 3: The safety issue of metformin in well compensated cirrhotic patients is really a problem or (more probably) a legend? I think that this point deserves a more detailed analysis.

Response: Our group has a large experience in the use of metformin in liver diseases, including cirrhotic patients. We have presented a meta-analysis in which evaluated the safety profile of metformin and the conclusion was the increasing of the prevalence of diarrhea but did not serious adverse effects. We have included a new reference about metformin use in well compensated cirrhotic patients to prevent from hepatic encephalopathy.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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