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Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 29204

Manuscript Type: Editorial

Point-by-point responses to reviewers' comment

Sept 28, 2016

Dear Dr. Ma,

Please find attached the edited manuscript in Word format (file name: 29204_revised.doc).

Title: Drug-Induced Liver Injury: Towards Early Prediction and Risk Stratification

Authors: Emanuel Raschi, Fabrizio De Ponti

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 29204

Revision has been made according to the suggestions of the reviewers. A point-by-point outline of responses is provided below. References and typesetting were corrected.

Reviewer # 00069855.

This manuscript reviewed recent publications on Drug-Induced Liver Injury (DILI) from Medline and try to stratify the risks of drugs that can induce liver injuries or damages. DILI is very common in clinical practice, so the contents of this manuscript meet the mission of World Journal of Hepatology, and also are concerned by not only physicians but also patients. The writing of this manuscript is fluent, the conclusion is reasonable, and no ethic issues is concerned on a review article. However, the contents of this manuscript seems as if short, and the main concerted issues of DILI did not well addressed. I am recommending you to publish this manuscript if the authors can add the content of main kinds of medicines that induce liver damage as well as their pharmacological mechanisms.

We agree with the reviewer that a brief discussion of drugs most frequently reported to cause DILI is an important piece of clinical information. We add a specific paragraph on this issue entitled "The contribution of drugs in DILI occurrence". As regards the underlying mechanism, with few exceptions (e.g., paracetamol), it must be acknowledged that DILI is by definition idiosyncratic, thus making mechanistic basis still uncertain. We briefly mentioned this aspect in the revised version.

Reviewer # 00032726.

This article reviewed the researches of Drug-Induced Liver Injury (DILI) published in recently

years. The authors thought that there is an urgent unmet clinical need to develop tools for risk assessment and stratification in clinical practice and, in parallel, to improve prediction of pre-clinical models to support regulatory steps and facilitate early detection of liver-specific adverse drug events. In the end of this article, the authors suggested that existing consortia should pursue a joint effort along this innovative pathway aiming to develop algorithms capable not only of discriminating hepatotoxic from non-hepatotoxic compounds, but also to differentiate the risk among agents belonging to the same therapeutic class. This article provided very important information to develop a comprehensive DILI risk score and fulfill clinicians' and patients' expectations about "primum non nocere". This paper should be shared and discussed widely with clinicians. In conclusion, this is very interesting paper and should be instructive.

We thank the reviewer for these comments.

Reviewer # 03576081.

In the manuscript entitled "Drug-Induced Liver Injury: Towards Early Prediction and Risk Stratification", the authors summarized recent progress in DILI research especially DILI risk annotation. The manuscript is concisely and well written and information provided is useful.

We thank the reviewer for these comments.

Minor comments:

1. (Page 4, lines 10-16) The association of the two sentences ("The proportion among …studies in 2015." and "This, however, …..with elevated transaminases.") is difficult to understand. Although most of publications are pre-clinical investigations, but why has this generates concern among clinicians. *We agree with the reviewer on the possible misunderstanding. We have modified the sentence.*

2. (Page 4, line 7 from the bottom) What type of "registries" does the author assume? I cannot understand what the author claim in the fourth paragraph of Introduction. *Our intention was to compare benefits and limitations of using population-based studies and registry data for DILI evaluation. We have specified this issue.*

3. (Page 7, lines 9-11) In the discussion on DILI biomarkers, more information should be added. From these sentences, it is difficult to understand why keratin-18 provides mechanistic insight into DILI. *The text was extensively revised by detailing the evidence underlying the use of biomarkers in the different settings.*

4. (Page 8, line 6 and last line) "Bjornsson" should be corrected to "Björnsson". *Done.*

5. (Page 9, lines 8-10) The sentence "However, among DOACs, …post-marketing data have reported rivaroxaban to be most likely associated with DILI. " needs a reference. *We added a recent review article on this issue, also by providing a practical recommendation for clinician to monitoring liver enzymes.*

6. (Page 9, lines 13 and 22) "Moyeties" should be corrected to "moieties". *Done.*

7. (Page 10, line 3 from the bottom) There is a grammatical error in the sentence "…, because of their provide a stable source for hepatocytes… ". *The sentence was corrected.*

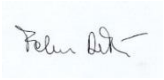
Reviewer # 00069262.

Congratulations is an excellent document.

We thank the reviewer for this positive comment.

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

Sincerely yours,



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