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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 11456

Title: RIBAVIRIN INDUCED HEMOLYSIS: A NOVEL MECHANISM OF ACTION AGAINST CHRONIC HCV INFECTION

Reviewer code: 00183339

Science editor: Su-Xin Gou

Date sent for review: 2014-05-22 13:36

Date reviewed: 2014-05-24 14:13

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The manuscript is well presented and of interest and it can contribute to increase the knowledge of this topic. However some minor issues need to be resolved. 1.Abstract and Key words should be added to the manuscript. 2.There is no section describing the methods used for locating, selecting, extracting and synthesizing data.



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Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 11456

Title: RIBAVIRIN INDUCED HEMOLYSIS: A NOVEL MECHANISM OF ACTION AGAINST CHRONIC HCV INFECTION

Reviewer code: 00070138

Science editor: Su-Xin Gou

Date sent for review: 2014-05-22 13:36

Date reviewed: 2014-05-24 19:13

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input checked="" type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

Reviewers' Comments to Author: The authors found that Ribavirin could synergize with direct acting agents against HCV (DAA) by improving the intracellular antioxidant and antiviral actions in the liver and improving the efficacy of endogenous IFN. The idea is new in this field and worthy to be published. However there is problem in this manuscript. Major 1. The manuscript should be written according to the format of journal and should be more concise. 2. Abstract and Key words should be added to the manuscript.



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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 11456

Title: RIBAVIRIN INDUCED HEMOLYSIS: A NOVEL MECHANISM OF ACTION AGAINST CHRONIC HCV INFECTION

Reviewer code: 00006993

Science editor: Su-Xin Gou

Date sent for review: 2014-05-22 13:36

Date reviewed: 2014-06-03 23:51

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Review of Manuscript for WJG Title: Ribavirin Induced Hemolysis: A Novel Mechanism of Action Against Chronic HCV Infection Overall, in the present manuscript, authors provided a summary on molecular mechanisms of ribavirin action against chronic hepatitis C. The topic is interesting to readers and important in the field. There are the following issues that need to be addressed by authors. Issues: 1. The main text is lacking an abstract, one of key elements. 2. The official symbol for heme oxygenase-1 is HMOX1. Please replace HO-1 with HMOX1 throughout the manuscript. 3. Figure 1 and its legend: "This activates HO-1 in hepatocytes (via CD91)". As authors know, hemolysis leads to increased accumulation of heme in liver, and it is well-demonstrated that heme directly induces HMOX1 expression. As such, the accuracy of the figure and its legend is questionable.

ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 11456

Title: RIBAVIRIN INDUCED HEMOLYSIS: A NOVEL MECHANISM OF ACTION AGAINST CHRONIC HCV INFECTION

Reviewer code: 02733636

Science editor: Su-Xin Gou

Date sent for review: 2014-05-22 13:36

Date reviewed: 2014-06-12 06:14

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Dear Editor, In this paper entitled "Ribavirin induced hemolysis: a novel mechanism of action against chronic HCV infection" the authors proposed an interesting hypothesis to explain the mechanism behind the role of ribavirin in treatment of chronic hepatitis C with combination regimens. The manuscript is well-written, perfectly organized and English language is good. However there are several issues to be elucidated. Major points: 1. An abstract is missing. 2. There are studies which provided evidence to explain the mechanism of ribavirin in the treatment of chronic hepatitis C. In a recent study, investigators showed in a cell culture model that ribavirin potentiates interferon action by inducing interferon-stimulated genes (Hepatology. 2011;53(1):32). In this model, heme oxygenase-1 activity is not needed to explain the synergistic effect of IFN+RBV combination. There are also several other evidences that provide explanation without a need for heme oxygenase-1 hypothesis. Therefore, the authors' conclusion to explain ribavirin action with only a single mechanism may be too strong. 3. Minor points: 1. "Unlike Ribavirin, potent IMPDH inhibitors like mycophenolic acid have not shown efficacy and synergy with Interferon in clinical trials." A reference is needed for this information. 2. "ITPA (Inosine triphosphatase) gene polymorphisms which decrease hemolysis appear to reduce clinically significant anemia and dose reduction of Ribavirin." A reference is needed for this information. 3. However, it has been shown that in many cHCV patients, IFN production by KCs lead to higher pre-treatment levels of ISGs in the PBMC and in the liver



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which is associated with reduced SVR rates. “Peripheral blood mononuclear cells” should be added to for the relevant abbreviation in parenthesis. 4. The authors mentioned about HCV patients with thalassemia. As we know, patients with thalassemia already have a chronic hemolytic status which eventually induces heme oxygenase-1 expression. If hemolysis is so and solely important for ribavirin action and treatment success as the paper suggests, why patients with thalassemia respond poorly to combination treatment? Could the investigators provide an explanation to clarify this discrepancy?



ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 11456

Title: RIBAVIRIN INDUCED HEMOLYSIS: A NOVEL MECHANISM OF ACTION AGAINST CHRONIC HCV INFECTION

Reviewer code: 00504455

Science editor: Su-Xin Gou

Date sent for review: 2014-05-22 13:36

Date reviewed: 2014-06-17 01:33

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Ribavirin induced hemolysis: a novel mechanism of action against chronic HCV infection

Throughout: The paper is too wordy and lacks structure and direction. Many sentences are too long. Other sentences are too short, and several HCV characteristics are introduced without the necessary context. There are several irrelevant sentences. A more direct writing style would help you get your point across. Throughout: Reference overload. Too many and inappropriate references. For instance, in the introduction, of the first 9 references, only number 9 (Lauer and Walker) and 1 reference about the newer direct-acting anti-HCV drugs would suffice. Reference 1 is not a reference. General: Lack of direction. In the cover letter the authors state that the article is a review. The title suggests that you are describing a new mechanism. It seems to me you are pitching a hypothesis about the effect of ribavirin in IFN-ribavirin combination treatment of chronic HCV infection. That is fine. But then label your paper as such. You patch a few hypotheses and published paper together to come up with a 'new' mechanism. That is interesting in itself. But then write a short, clear hypothesis paper and quote more references and give an overview of all the proposed and known mechanisms of action of ribavirin in interferon-ribavirin combination treatment for chronic HCV infection. I would like to encourage the authors to draft a shorter paper with more direction.