July 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11456-review.doc).

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

Authors: Kaartik Soota, Benedict Maliakkal

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 11456

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

(1) Abstract and Key Words have been added to the manuscript

(2) There is no mention on the section of methods as this is not an original research but proposition of a new hypothesis. Also, there is no specific data collection involved in this.

(3) Manuscript has been made more concise and with fewer references

(4) The official symbol for heme-oxygenase, HMOX1, has been incorporated into the manuscript

(5) CD 91 is expressed in many cells including hepatocytes. It has been shown it mediates hemopexin-heme internalization leading to heme uptake causing activation of HMOX1. This has been described in the article 'Identification of the receptor scavenging hemopexin-heme complexes' by Hvidberg et al. published in the journal Blood in 2005. (Blood. 2005; **106(7)**: 2572–2579)

(6) Activation of HMOX1 via hemolysis appears to be a plausible mechanism which explains ribavirin's synergy with IFN in Hepatitis C treatment but perhaps it not the only mechanism. A recent study by Lau et al. (Gastroenterology. 2013;**144(2)**:402-413) mentioned that non-responders to combination treatment have higher pretreatment level of IFN stimulated genes (ISGs) which leads to innate immune tolerance. We are proposing that RBV via induction of HMOX1 acts by decreasing the innate immune tolerance and improving efficacy of therapy.

(7) Appropriate references have been added and deleted at the places as suggested by the reviewers. We have deleted the sentence which mentions about the use of IMPDH inhibitors in chronic HCV infection to make the article more streamlined. However, in order to support what we mentioned earlier, we are providing references which are – [J. Hepatol. 2002 Dec; 37(6): 843–847] and [Liver Transplant. Off. Publ. Am. Assoc. Study Liver Dis. Int. Liver Transplant. Soc. 2003 Jan; 9(1): 57–61]. These references mention that mycophenolate does not have a significant biochemical or antiviral effect in patient with cHCV and inhibition of IMPDH does not seem to be the major mechanism in enhancing the synergistic effect of ribavirin with IFN in treatment of chronic hepatitis C.

(8) The term PBMCs now has peripheral blood mononuclear cells in parenthesis.

(9) In chronic life-long hemolytic disorders like Thalassemia, sickle cell anemia, several adaptive changes occur. These changes along with the decreased bone marrow reserve make the use of Ribavirin challenging. While large comparative trials are lacking, the response to Interferon alone is as good or slightly better in genotype 1 HCV patients with thalassemia. A recent large study showed over 60% SVR with IFN alpha and no benefit of RBV when combined with Interferon alpha in thalassemic patients who were below age 18 years, suggesting that additional hemolysis by RBV was not beneficial in younger patients who did not have the chronic adaptation/iron overload and liver fibrosis. [Ann. Hepatol. 2013 Aug; **12(4)**: 532–538].

(10) Article has been updated as a hypothesis paper now instead of a review article.

3 References and typesetting were corrected

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

Sincerely yours,

Kaartik Soota, MD
Dept. of Medicine
Unity Health System
1555, Long Pond Road
Rochester, NY- 14626
USA
E-mail: Kaartik_soota@urmc.rochester.edu