Letter for ANSWERING REVIEWERS

November 5, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6134-Edited.doc).

Title: The life cycle and pathogenesis of hepatitis D virus: a review

Author: Abbas Zaigham, Afzal Rafia

Name of Journal: World Journal of Hepatology

ESPS Manuscript NO: 6134-edited

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) To add: HDV replication can proceed in the absence of the helper virus, which is required only for virion assembly and export??

Page 8, 3rd paragraph

It is therefore evident that HBV plays no role in HDV replication and it can proceed even in the absence of the helper virus. It is required only for cell entry, virion assembly and export.

(2) The tentative receptor of HDV is now known, as suggested by a Chinese group (Yan H et al, eLife 2012;1:e00049); kindly add and comment??

Page 8, 1st paragraph

Recently, Yan et al have identified a putative receptor for the entry of HBV and HDV into the hepatocytes. The authors proposed that pre-S1 domain of L-HBsAg interact with sodium-taurocholate cotransporting polypeptide (NTCP), an integral transmembrane glycoprotein involved in enterohepatic circulation, to facilitate HDV infection.

(3) To add: original works in the chimpanzee animal model had suggested a direct cytopathic effect of HDV, especially in the acute infection setting?

Page 8, 1st paragraph of PATHOGENESIS

However, data from experimental chimpanzees has also suggested a direct cytopathic effect of HDV on hepatocytes particularly in acute hepatitis setting. It is postulated that in acute HDV infection, infected hepatocytes undergo degenerative changes characterized by shrunken eosinophilic cytoplasm and pyknotic nuclei as well as presence of minimal inflammatory cells in the liver parenchyma, consistent with cytopathic hepatocellular damage. These finding are also

evident from in vitro (cell culture system) and human studies. Small delta antigen expressed by infected hepatocytes is thought responsible for this direct cytopathic effect of HDV, while large delta antigen per se is non-cytotoxic and promotes persistence of HDV (chronicity) and makes hepatocytes susceptible to immune-mediated damage.

(4) The work carried out in the woodchuck animal model (including the vaccine experiments) is totally overlooked: please quote and comment accordingly?

Page 9, 1st paragraph

Experimental woodchuck models have proven very helpful in furthering our knowledge of HDV pathogenesis and the chronicity associated with HDV superinfection, owing to marked resemblance between the course of disease in woodchuck models and the outcome of HDV superinfection in humans. In addition, these models are also invaluable for testing the efficacy and protective role of new treatments for HDV including vaccine candidates. Studies on these experimental models have disclosed that both the protein immunization and DNA immunization for HDV are insignificant in protecting against HDV superinfection, highlighting the need of adopting different approaches to develop an HDV vaccine.

(5) To add: about the immune-mediated response during HDV acute and chronic infection, especially reporting the difference in co-infection and superinfection with HBV, showing the possible mechanism of liver injury.

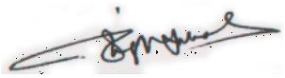
Page 9, 2nd paragraph

Variation in immune-mediated responses during acute and chronic HDV infection has been noticed, which may explain persistence and chronicity of HDV superinfection. Cytotoxic T lymphocytes are mainly responsible for clearing the virus by destroying HDV-infected cells. Delayed and insufficient immune response with ability of recognizing only limited viral epitopes has been implicated in failure to clear the infection coupled with establishment of chronic infection. Fulminant hepatic failure has been observed in 1% of HBV/HDV co-infected patients while in 5% of those superinfected with HDV. An exaggerated immune response particularly cell-medited one is proposed to be involved in causing massive hepatocyte necrosis and liver damage in fulminant hepatic failure.

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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