ANSWERING REVIEWERS

October 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13863-review.doc).

Title: Hepatitis C and Kidney Disease- An Overview and Approach to Management

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Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13863

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) Reviewer 00503243 commented:
"This is a relevant manuscript on an important issue. The manuscript is very good and updated both for nephrologists and hepatologists. The authors should clarify better some point to gain further quality to their manuscript. …"

a) In the introduction: 16.5 % of seropositive patients is true worldwide or are there differences among countries?
- The figure was true for a population-based study in Taiwan and there are differences among countries. Thus we have revised the statement to: "The prevalence of HCV positive among hemodialysis patients can vary from <5% to as high as 60% from different region in the world[3, 4]. The link between HCV infection and kidney disease is well recognized[5, 6]. In a large population-based study in Taiwan, the prevalence of CKD among those who are seropositive for hepatitis C was 16.5% and chronic hepatitis C infection was found to be an independent risk factor for development of CKD[5, 7].

b) under the heading hepatitis C resulting in kidney disease, please explain better why HCV is an independent risk factor for developing ESRD
- We have added this paragraph under the same heading: "This study also reported that HCV infection is an independent risk factor for developing ESRD[12]. The risk for CKD is higher in HCV patients with other co-morbidities such as diabetes, hyperlipidemia, cirrhosis, male gender, age < 50 years, and those on more than 6 years follow-up for HCV[10].

Several factors may contribute to the development of ESRD in HCV infected patients. HCV may trigger a cascade of immune reactions that subsequently attack the kidneys and result in glomerulonephritis. HCV was also found to be associated with insulin resistance and dyslipidemia[13], thus, indirectly increasing the risk of renal disease."

c) the mechanisms of cryoglobulinemia should be better explained . Indeed, cryo is a globulin anti globulin, that is to say an autoantibody.

- Under the heading 'Hepatitis C resulting in kidney disease', we have added this statement to the manuscript: "Cryoglobulins are immunoglobulins which become insoluble at below body temperature and dissolve when rewarmed. In individuals with HCV infection, these cryoglobulins are immune complexes formed by monoclonal immunoglobulin M (usually IgM Rheumatoid factor), polyclonal immunoglobulin G and HCV RNA which are deposited in the small and medium-sized vessels of the skin, kidneys and peripheral nerves. The deposition of these immune complexes in the mesangium of the kidneys trigger glomerulonephritis."

d) under the heading hepatitis C and renal transplantation in the cited studies lack comparison with patients remained on waiting list

- We have added 4 more references/studies in comparing to patients remained on waiting list versus Hep C patients who received renal transplant: "A prospective study showed that despite significant decrease in patient and renal graft survival post renal transplant in HCV positive recipients compared to their HCV negative counterparts, the survival of HCV positive ESRD is still better with renal transplant rather than remaining on maintenance hemodialysis[41]. Kidneys from anti-HCV positive donors have been used to transplant HCV infected renal recipients[42]. This approach will help to shorten the waiting time for HCV RNA positive renal transplant candidates[43, 44]. In addition to the benefit of shorter waiting time, the use of kidneys from HCV positive donors had also been shown to improve the overall survival compared to staying on the waiting list (adjusted hazard ratio for death 0.76, 95% CI 0.60, 0.96)[45]. However, transmission from infected donor may produce super-infection from a different HCV genotype[46]."

e) In the study of Hsu the uninfected group is a control one? In such case why the patient number is so different than the other two groups?

- Hsu et al. has divided to 3 groups; 1,411 patients (treated patients), 1,411 (untreated patients) and 5,644 (uninfected group). Hsu et al. has calculated in their methodology where the propensity score was estimated by logistic regression. Each untreated patients was matched with one treated patient, while the uninfected cohort was matched 4:1 with their treated counterpart. To avoid confusion among readers, we have taken out the numbers.

f) Is there interference between new drugs, principally the DAAs and calcineurin inhibitors?

- To date, there are limited evidence on the interaction of DAAs and calcineurin inhibitors. However, we have added available data on interference between these drugs. We added this paragraph into the revised manuscript under the heading 'Treatment For Chronic Hepatitis C In Post-Kidney Transplant Patients': "There are limited data on the use of the new DAAs together with the calcineurin inhibitors like cyclosporins and tacrolimus in HCV infected post renal transplant recipients. Prescribing information from Boceprevir and Telaprevir showed significant increase in plasma concentration of cyclosporin, sirolimus or tacrolimus thus the plasma concentration level of these drugs should be monitored closely[76, 131]. The AASLD/IDSA guideline does not recommend the co-administration of simeprevir and cyclosporine[132] based on a pharmacokinetic study of simeprevir, daclatasvir and ribavirin in recurrent hepatitis C patients after orthotopic liver transplant, where the simeprevir plasma concentration was found to be raised by 6-fold in the presence of cyclosporine[133]. According to the AASLD/IDSA guidelines, no dose adjustment is required for combination therapy of sofosbuvir and simeprevir when co-administered with tacrolimus based on studies in liver transplant patients."

(2) Reviewer 00503339 commented:

"A truly important subject with an encyclopedic list of suggested actions for treating internists, hepatologists, and nephrologists. What is distressing are the large number of life or death issues for which experimental proof of therapy has not been developed. Nevertheless, after reading your paper, this Nephrologist is motivated to test for and manage the formerly large number of patients - especially those undergoing hemodialysis - who will probably benefit from the suggested therapies."

- Thank you. No changes made based on this comment.

(3) Reviewer 00503014 commented:

"The review article had been written. Beside language minor polishing, I did not have any comments for the draft."

- Thank you. Minor language polishing was done.

3 References and typesetting were corrected

4 Crosscheck document reviewed and revised to minimized similarities.

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

Sincerely yours,

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