2017.12.6
Jin-Xin Kong M.D.,
Science editor
World Journal of Hepatology

Dear Professor Jin-Xin

Thank you for your email of Nov 27, 2017 regarding our manuscript, "Efficacy of Direct-Acting Antiviral Treatment for Chronic Hepatits C: a Single Hospital Experience " which was assigned the manuscript number: 36416.

I attach here our revised manuscript, as well as point-by-point responses to the reviewer's valuable comments.

We wish to express our appreciation to the reviewer for his or her comments, which have helped us significantly improve the paper.

Comment 1 (reviewer's code 03647881): In table 5, it showed that only Y93 RAS was associated with SVR. Due to the small sample size and the incomplete RASs acquisition, this conclusion may be risky and need more data to prove.
Response: We changed the conclusion in abstract (line 62-64) , and added the limitation (line 253-254).

Comment 2 (reviewer's code 03647881): During the relapse, there were 6 patients in the DCV/ASV group. Did these 6 patients achieve SVR12 or they took more time to get SVR and it might suggest difficulty in treating these patient who couldn't reach SVR12.
Response: "Relapse" defined as once viral disappearance and recurrence among follow-up period after prescription and "SVR12" means 12 weeks sustained virologic response after prescribing. So, those relapse 6 patients didn't achieve SVR12. The efficacy analysis usually discuss about the cases with SVR , relapse and on-treatment failure.

Comment 3 (reviewer's cord 00069423):

At the outset, it would be good to write out all the complex names of DAA'S followed by abbreviations that are repeated throughout the text.
Response: We added abbreviations (line 266-269).

In the Abstract:
Suggest reorganize the statement/description.
It would be easy for the readers to follow if it is written as shown below.
Total 177 patients. 135 with genotype 1 and 42 with genotype 2.
OF 135 pts with genotype 1, 16 received protease inhibitor+interferon +ribavirin and all achieved SVR. Of the 119 patients who received IFN free DAA (in different

combinations), 102 achieved SVR while 9 failed; 7/9 were on DCV/ASV and 2/9 on LDV/SOF.

Efficacy analysis was done only for 42 patients who received DCV/ASV. From this analysis, Y93 resistance-associated substitutions (RASs) were significantly correlated with SVR (? poor SVR or failure).

Question: How long is the follow up period after completion of 12 week treatment??
Response: We rewrite along with valuable suggestion. We added about primary endpoint in line52~53.

In the Introduction
Line 107-108: it is not clear the sentence……..predictors who fail to respond to DAA might be compromised by resistance-associated substitutions (RASs).
Q: Do you mean "The reason for patients' failure in responding to DAA might be related/or attributed to the presence or development of RASs?
Response: We want to say so and rewrite along with suggestion. Thank you.

Under the Results
Line 169-174:
It would be easier for the readers to follow if written the following way;
All 42patients with genotype-2 who received the treatment with SOF+Riba achieved SVR 12 weeks.
All 16 who received protease inhibitor + peg IFN+Riba (5 with telaprevir, 11 with Simeprevir),
achieved SVR 12.
Q: Was there no relapse, if so for how long, 12 months?
Response: We rewrite as suggested and added " no relapse until today" in line 165~168.

Line 169:
It would be easier to follow:
Of the 43 patients who were treated with DCV/ASV, one patient broke through and 6 relapsed.

Line 170,
Of the 66 patients on LDV/SOF, 2 relapsed and 2 patients had SAE; subarachnoid hemorrhage and cerebral hemorrhage. Although medication was stopped, SVR was achieved.
Response: We rewrite as suggested. (line169-173)

Q: How many weeks of LDV/SOF for each patient before the SAE (since they both achieved SVR)
Or how many months (weeks) after the SVR, did they develop SAE or relapse?

Did they take full 12 weeks medication? Did they have negative serum HCV RNA throughout?
Response: We added the description of 2 cases in line 172-173. DAA treatment was stopped at 8weeks and 6weeks respsctively.

Line 171.
Of the 10 patients who have been on OBV/PTV/r one was lost for follow up.
Response: We rewrite as suggested. (line 174-175)

Line 181-183, table 4,
Of the 9 failure patients, 7 were diagnosed as cirrhosis.
Q: Did they have cirrhosis before or after DAA treatment failure. And what happened to those cirrhosis patients? Same to 26 patients with history of HCC (table 1); Were the HCC related to HCV? Were the HCC cured before the treatment?
Comment: There are several recent reports describing the rapid recurrence of pre-existing or "cured" HCC related to HCV infection. The recurrence time interval is shorter with DAA treatment than with IFN therapy.
Q: What is your experience of these 26 patients whom you have treated (25/26 treated with DAA).
Response: They have cirrhosis before the start of DAA. We added this point in line182~183. We argued about relation among HCC recurrence and DAA treatment in line 190-192 and line 238-241.

Line 176-189
NS5A RASs were analyzed in 82 patients who received DCV/ASV
2 pts relapsed with WT Y93,
1 with Y93 hetero
3 relapsed with WT L131
6 pts failed SVR but no study for resistance.
Q: How about others? No relapse or no RASs?
Response: There is no relapse regardless of the presence or absence of RASs. We added this point in figure 1 legend.

Those who failed with DAA received second line therapy:
4 LDV/SOF+Riba: (they were on DCV/ASV before?) and 3 achieved SVR and **the remaining 1 pt?**
1 LDV/SOF, SVR
1 on DCV-TRIO (DCV/ASV/beclabuvir)
Response: We added about1 remaining case (relapsed with salvage LDV/SOF treatment) in line 187.

Comment 4 (reviewer's code 69837):

1- Abstract

In line 60-61, the authors stated ¨ Among genotype 1 with IFN-free DAA, 9 patients failed to achieve a sustained response (SVR)¨ and in conclusion they wrote that ¨ The SVR rate was 98% for genotype 1 and….¨. Please, clarify this point.

Response: We changed number of SVR and added about calculation method inline 58-59,62-63.

2- Materials and methods section

Line 132-133, the authors say ¨ Liver cirrhosis was diagnosed by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) or a liver biopsy¨. How many patients have been diagnosed by liver biopsy should be stated in this section

Response: We added about number of cases with pathology in line 155.

3- Results section

Line 172, the authors stated ¨Two patients had serious adverse events in the LDVSOF treatment…¨. It could be an important to know for how long HCV treatment was carried out by these patients before drugs withdrawal.

Response: We discribed this point in line 172-173.

4- Discussion section

In line 212 the authors wrote ¨SOFRBV has been approved for genotype 2 HCV…¨. Current guidelines recommendations regarding therapy for genotype 2 should also be discussed.

Response: We added about G2b OBV/PTV/r in line215-218.

5- In line 226-227 the authors stated ¨ Among these, cirrhotic change was common and 3 patients with a history of HCC were also reported ¨ . Please, clarify how many were cirrhotics patients and remove the inappropriate words ¨cirrhotic change ¨

Response: We rewrite as suggested. (line 230-231)

6- In line 232-234 the authors say ¨The physiological mechanism underlying the cerebrovascular adverse events is unclear¨

A comment on published data in literature regarding this adverse event should be added by authors. This is a very important point that emerges from this study due to the fact that authors have recommended to the readers to take in mind this issue in the conclusions section

Response:We added argument about this event in line236-242.

We feel that the revised manuscript is a suitable response to the comments, and has been significantly improved over the initial submission. We trust that it is now suitable for publication in the *World Journal of hepatology*.

Sincerely,
Rena Kaneko
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