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ESPS PEER-REVIEW REPORT

Reviewer's code: 02861175

1. COMMENTS TO AUTHORS

over all this study is good, it's important knowledge for clinicians before treating HVC patients. There are some comments: 1. What is the clinical reason of using 8 week DAAs tx? please explain in the introduction 2.why you choose HCV RNA 8.000.000 as cut off in bi-variate and uni-variate analyses? please explain it? if you want to determine the cut of point, AUROC analyses is the available cut off. 3. Explanation of figure 1 as the subject selection must be placed in study population.

Response: Thank you very much for your constructive comments and suggestions.

1. We added the following sentence to Introduction 4th paragraph: 'We contemplated that the shorter duration of treatment could provide the lower cost of the treatment, the higher patient compliance and adherence as long as the shorter therapy can provide the comparable outcomes".

2. It was not 8,000,000 IU/mL. It was 800,000 IU/mL. All patients had HCV RNA less than 6 million IU/mL. The reason for choosing/analyzing 800,000 IU/mL was that it was traditionally used for "high" and "low" viral load pre-DAAs and post-DAAs era. Earlier trials had used this cutoff value for their subanalyses on >800,000 and <800,000 IU/mL. (Ion-1 trial)

Ref:

a) Afdhal N, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med*. 2014 May 15;370(20): 1889-98. [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]
b) Cavalcante LN et al. Predictive factors associated with hepatitis C antiviral therapy response. World J Hepatol. 2015 Jun 28;7(12):1617-31. [PMID: 26140082 DOI: 10.4254/wjh.v7.i12.1617]

We took the reviewer's advice and re-ran our analyses – AUROC. We found that HCV RNA level plays a role with AUROC 0.734 (CI: 0.66-0.82]. We found a cutoff value of HCV RNA 2.2 million IU/mL with sensitivity of 73% and specificity of 64%. We used 2.2 million IU/mL as a cutoff and re-ran the univariate and multivariate binary logistic regression models on SVR impact. We found that patients with HCV-RNA less than 2.2 million IU/mL were more likely to achieve SVR compared to those with more than 2.2 million IU/mL [OR: 0.22, CI: 0.1-0.49, p<0.001].This finding is a new highlight of our study. Traditional cutoff values have been suggested as 400,000 IU/mL, then 800,000

IU/mL and 6 million IU/mL.
3. We added the explanation of Figure 1 - inclusion/exclusion criteria in Study Population section of the manuscript.

COMMENTS TO AUTHORS

(1) The overall structure of the manuscript needs to be completed (abstract, keywords). (2) The authors (in the "Study population" section) refer that according to the protocol constructed, the close monitoring of patients during treatment was documented by laboratory testing every 2 weeks. It is strange to me and I need a comment on this, taking account that this is a real life study and in every day clinical practice lab tests are suggested to be performed on wk2, wk4, eot and svr12. (3) Patients who missed doses were excluded. Which was the criterion exactly for this (how many doses?). (4) Which was the method for HCV RNA test and what was the cut-offs? (5) Which were the criteria for the clinical judgment of the presence/absence of cirrhosis. (6) Page 8, 1st sentence "value of HCV-RNA level for SVR is currently available data": It is not comprehensible, need to be reconstructed. (7) The authors should discuss and provide their explanations for the differences of their results with other studies. (8) According to which classification the fibrosis score was classified to stage "0", "1", "3", "3-4", "4". (9) Tables should be reconstructed according to journal guidelines (i.e. row 4 in Table 2). (10) P-values for non-significant differences should be added in Table 2. (11) Figure 2: There is a discordance with factors and number of bars. (12) Kowdley et al recently published in Hepatology 2016 data indicating the effectiveness of an 8-week duration of treatment with LDV/SOF. (13) Similarly, Lai et al published their results in Drugs 2017, showing that 8-weeks courses of LDV/SOF are comparable to 12-week courses in real world use among selected patients supported by a multidisciplinary team.

Response: Thank you for your constructive comments.

1. We have completed the overall structure of the manuscripts according to WJG's guidelines.

2. We agree that checking blood tests every 2 week might be unnecessary and overwhelming. However, this approach did bring up patient's compliance and adherence. Kaiser Permanente physicians (Southern California Permanente Medical Group) work for Kaiser Health Plans and this protocol was set up according to the internal guidelines. We did perform EOT, SVR12, SVR24 and SVR at 1 year.

3. The exclusion criteria for "patients who missed doses "was more than 7 days (cumulative or consecutive). We have added this information to exclusion criteria under Study Population section.

4. The method for HCV RNA testing was "Quantification y Real-Time Reverse Transcription-PCR". All patients in the cohort had HCV RNA less than 6 million IU/mL.

5. The criteria for the clinical judgement for non-cirrhotic state:
A) abdominal sonography: hepatic morphology, spleen size

B) Platelet count

Some physicians calculated and documented APRI index score but we did not find this documentation in all patients. Hence, we did not include this data in our assessment. All clinicians used their judgement by looking at hepatic morphology and spleen size on abdominal sonography and platelet count.
Platelet count: 150-200x10^9/L, abdominal sonography findings were added in to account for consideration.
Platelet count < 150x10^9/L -> all patients underwent one of the fibrosis tests such as VCTE, FIBROSPECT or liver biopsy.

6. The sentence has been reconstructed. It was a typo.

8. Our pathologists used Metavir scoring system for liver biopsy fibrosis staging.

COMMENTS TO AUTHORS

Good work... Study Highlights ? Validation of clinical outcome with high overall SVR24 96% in selected subset of patients with HCV infection and good safety profile in a large real-world cohort NOT SVR 24 ....SVR 12 must be... in table ≥800.000 and ≤800.000 ???..800.000< and ≥800.000 Figure 2 so complicated??

Response: Thank you for your constructive comments.

1. We have deleted SVR 24 in the highlights section. That was a typo. In discussion, we mentioned that 59% had SVR24 data. We tried to state that 59% of patient had 96% overall SVR in 24 weeks follow up. If we look at now, all patients probably had SVR24-48. However, it might appear confusion. We completely deleted SVR24 from the manuscript.

2. Table has been reconstructed. Now, our cutoff is HCV RNA 2.2 million IU/mL after AUROC analysis. We paid special attention to the character ≥ and <.

3. The reason for figure 2 being so complicated was we wanted to sum up all SVR data among

divided subgroups and we wanted to save journal's space. We agree that Figure 2 appeared busy. We reconstructed 1 graph and also multiple small graphs in PPT for the editors to choose appropriately for the journal space.