OPEN PEER REVIEW

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As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

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Peer Review Report for "Treatment with Grazoprevir/Elbasvir in Post-kidney Transplant Patients with Hepatitis C Virus Genotype 4 Infection"

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Review Timeline:

Submit Date:	13 Feb 2021
Revised Date:	28 Apr 2021
Accepted Date:	11 May 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

20 Feb 2021

Dear editor,

1. Which evidence show this idea? “Renal transplant (RT) recipients have a high rate of hepatitis C virus (HCV) infection”

2. It was better to have a control group with standard treatment and the results were evaluated between the two groups

3. Although you said that the number of HCV infection after transplant is high, you only reported 9 cases of patients?!

4. For evaluate the safety and efficacy of a drug you need a large number of cases in study

Thanks

REFEREE: Associate Editor | **Revision** (0) 8 Apr 2021

Dear editor-in-chief,

The manuscript entitled “Treatment with Grazoprevir/Elbasvir in Post-Renal Transplant Patients with Hepatitis C Virus Genotype 4 Infection” has been reviewed by an expert reviewer and myself. There are some concerns about the methodology of the study, technical terminology used in the manuscript, and scientific writing skills. You can see more details in my comments below and also in the reviewer’s comment:

1- The manuscript needs a professional English editing. There are several spelling and grammatical errors throughout the text (e.g., page 4: over three hundred fifty thousand of them loss life due to HCV-related liver diseases.)

2- Introduction (page 4): “Hepatitis C virus (HCV) infection is prevalent in alarming levels, affecting more than 150 million people globally”. This estimate is not accurate. Please see: Blach S, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. The Lancet Gastroenterology & Hepatology. 2017;2(3):161-76.

3- Study design (page 6). The study design has been described as “prospective, single-arm, interventional cohort study” which is not correct. Cohort study is an observational study (in contract with “interventional”). This study can be described as a case-series.

4- Table 1: One of the inclusion criteria stated as “Based on creatinine clearance (CrCl), patients with stabke graft function after RT were categorized into two arms: <30 or ≥30 mL/min”. This sentence is not clear.

5- Intervention (page 6): Please explain what “St. John’s Wort” is.

6- Definitions and follow-up (page 7): The definitions of the study end points are confusing. For example, is SVR4 referring to week 4 of treatment or 4 weeks following treatment completion? Based on the reported results and also Figure 1, it seems that it refers to week 4 of treatment. If it is the case, it cannot be called as SVR (it is called HCV clearance). Similarly, if SVR12 refers to week 12 of treatment (end of treatment), it should be called “end of treatment response (ETR)”. SVR should be only used for negative HCV RNA following treatment completion. For example, if HCV RNA is negative 12 weeks after treatment completion (week 24 of the study from the baseline), it is called SVR12.

7- Definitions and follow-up (page 7): Please report the HCV RNA assay used, including the name of the kit and lower limit of quantification.

8- Baseline data (page 10): “one patient had fibrosis score 2-3 (11%), and three patients had fibrosis score 4 (33%)”. This is in contrast with inclusion criteria in Table 1 stating that only patients with no evidence of advanced fibrosis (only stage 0-1-2) have been eligible for inclusion.

9- Please report the median time from RT in the study population.

10- Virologic response (page 10): “At four weeks, two patients achieved SVR4, and there was a reduction in serum HCV RNA levels in all the patients who were tested”. Based on this sentence, it seems that SVR4 refers to week four of treatment. Then it is not correct to call it SVR. It could be called HCV clearance. Please revise “definitions and follow-up”, results, and Table 3, using the correct terminology.

Thanks

Seyed Moayed Alavian: EIC | **Revision** (0) 8 Apr 2021

Dear Authors,

Thank you for your submission. Please follow the peer-review comments and concerns and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Response to reviewers' comments on the manuscript entitled: Treatment with Grazoprevir/Elbasvir in Post-Renal Transplant Patients with Hepatitis C Virus Genotype 4 Infection

Reviewers' Comments:

Reviewer 1:
1. Which evidence show this idea? "Renal transplant (RT) recipients have a high rate of hepatitis C virus (HCV) infection"

Response: We would like to thank the reviewer for taking the time to review our manuscript and for helping us improve it.

The statement "Renal transplant (RT) recipients have a high rate of hepatitis C virus (HCV) infection" in the abstract is based on the view from the review by Pol et al. that states "Hepatitis C virus (HCV) infection is more prevalent and is associated with higher mortality in patients receiving dialysis and in kidney transplant recipients than in the general population" and the review by Ozer Etik et al. that states "In developed countries, the prevalence of anti-HCV seropositivity among patients on maintenance HD ranges between 5% and 60%. Patients on HD are at high risk for HCV, with frequency of infection several times higher than that in non-uremic patients" based on data from Selcuk et al. This point is also discussed in paragraph three of the introduction on page 3.

References

Pol S, Parlati L, Jadoul M. Hepatitis C virus and the kidney. Nat Rev Nephrol. 2019 Feb;15(2):73-86. doi: 10.1038/s41581-018-0081-8. PMID: 30455426.

Ozer Etik D, Ocal S, Boyacioglu AS. Hepatitis C infection in hemodialysis patients: A review. World J Hepatol. 2015 Apr 28;7(6):885-95. doi: 10.4254/wjh.v7.i6.885. PMID: 25937865; PMCID: PMC4411530.

Selcuk H, Kanbay M, Korkmaz M, Gur G, Akcay A, Arslan H, Ozdemir N, Yilmaz U, Boyacioglu S. Distribution of HCV genotypes in patients with end-stage renal disease according to type of dialysis treatment. Dig Dis Sci. 2006 Aug;51(8):1420-5. doi: 10.1007/s10620-005-9025-9. Epub 2006 Jul 26. PMID: 16868830.

2. It was better to have a control group with standard treatment and the results were evaluated between the two groups

Response: We agree that this would have been a more robust way of determining the effects of the treatment. However, as this study is small there would not have been enough patients in two groups for adequate comparisons between treatments. A larger study is needed in the future. We have now included this as a limitation of the study at the end of the discussion on page 14.

3. Although you said that the number of HCV infection after transplant is high, you only reported 9 cases of patients?!

Response: We agree that the study is small. Although King Faisal Specialist Hospital and Research Center is one of the largest transplant centers in Saudi Arabia, the number of RT is limited by the single center nature of the study. We have added this to the limitations of the study on page 14. Furthermore, the majority of HCV infected renal transplant patients including the majority of our patients were treated as part of the national HCV treatment program launched by the ministry of health prior to this study. This program has the advantage of easy accessibility in which treatment is offered with 24 hours under medical supervision for all transplant patients regardless of their geographic distribution within the country.

4. For evaluate the safety and efficacy of a drug you need a large number of cases in study

Response: We agree with this statement. As effectiveness is more often used in small studies, we have changed the use of the term safety and efficacy to effectiveness and occurrence of adverse events throughout the manuscript.

Associate Editor's Comments:

Associate Editor 1:
The manuscript entitled "Treatment with Grazoprevir/Elbasvir in Post-Renal Transplant Patients with Hepatitis C Virus Genotype 4 Infection" has been reviewed by an expert reviewer and myself. There are some concerns about the methodology of the study, technical terminology used in the manuscript, and scientific writing skills. You can see more details in my comments below and also in the reviewer's comment:

Response: Thank you for taking the time to consider our manuscript for publication in Hepatitis Monthly. We have followed your advice to improve the standard of the manuscript reporting. For details, please see our point-by-point responses below.

1- The manuscript needs a professional English editing. There are several spelling and grammatical errors throughout the text (e.g., page 4: over three hundred fifty thousand of them loss life due to HCV-related liver diseases.)

Response: We are sorry there were some spelling and grammatical errors throughout the manuscript. As you suggest the manuscript has now been edited by a professional English editor.

2- Introduction (page 4): "Hepatitis C virus (HCV) infection is prevalent in alarming levels, affecting more than 150 million people globally". This estimate is not accurate. Please see: Blach S, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. The Lancet Gastroenterology & Hepatology. 2017;2(3):161-76.

Response: We have corrected this statement, which was based on older data, according to the reference as follows: "Hepatitis C virus (HCV) infection is prevalent at alarming levels, affecting more than 70 million people globally." We have also cited the Blach et al. reference as reference 1.

3- Study design (page 6). The study design has been described as "prospective, single-arm, interventional cohort study" which is not correct. Cohort study is an observational study (in contract with "interventional"). This study can be described as a case-series.

Response: We agree that this study is correctly described as a case series and we have changed this throughout the manuscript.

4- Table 1: One of the inclusion criteria stated as "Based on creatinine clearance (CrCl), patients with stabke graft function after RT were categorized into two arms: <30 or ≥30 mL/min". This sentence is not clear.

Response: We are sorry about this mistake it should have read "Based on creatinine clearance (CrCL) patients with stable graft function after RT were categorized into two arms <30 or ≥30 mL/min". This has now been changed.

5- Intervention (page 6): Please explain what "St. John's Wort" is.

Response: St John's Wort is a herbal remedy for depression, widely available over the counter. We have changed the following in the intervention paragraph on page 6 to describe this: "Drugs, which could severely or moderately induce cytochrome P450 (CYP) 3A4 and P-

glycoprotein (P-gp), such as phenobarbital, nafcillin, phenytoin, rifampin, carbamazepine, and St. John's Wort (Hypericum perforatum, a herbal remedy), were stopped during the study period due to their known contraindications with certain DAA therapies.

"

6- Definitions and follow-up (page 7): The definitions of the study end points are confusing. For example, is SVR4 referring to week 4 of treatment or 4 weeks following treatment completion? Based on the reported results and also Figure 1, it seems that it refers to week 4 of treatment. If it is the case, it cannot be called as SVR (it is called HCV clearance). Similarly, if SVR12 refers to week 12 of treatment (end of treatment), it should be called "end of treatment response (ETR)". SVR should be only used for negative HCV RNA following treatment completion. For example, if HCV RNA is negative 12 weeks after treatment completion (week 24 of the study from the baseline), it is called SVR12.

Response: We are sorry about the confusion; you are correct in your assumption so the section on page 7 has now been changed as follows: Effectiveness was defined at various time intervals during the trial period. The specific endpoints were HCV RNA less than the lower limit of quantitation (HCV RNA < LLOQ) at weeks 4/8 and 12 of treatment, defined as HCV clearance and end of treatment response (ETR), respectively and 12 weeks follow-up after treatment (SVR12).

We have; therefore, updated the results section, the abstract, and table 3 to reflect these changes in definitions.

7- Definitions and follow-up (page 7): Please report the HCV RNA assay used, including the name of the kit and lower limit of quantification.

Response:

HCV detection and quantitation is performed using Abbott RealTime M2000 rt instrument. The assay utilizes two distinct sets of primers and probes. The first set targets a conserved region of the 5' untranslated region of the HCV genome, the second set is specific for an internal control (IC) that is processed with each sample to control for sample recovery and inhibition. The Abbott RealTime HCV assay provides detection limit (Analytical Measurement Range) from 30 to 100,000,000 IU/ml. This was added in the text.

8- Baseline data (page 10): "one patient had fibrosis score 2-3 (11%), and three patients had fibrosis score 4 (33%)". This is in contrast with inclusion criteria in Table 1 stating that only patients with no evidence of advanced fibrosis (only stage 0-1-2) have been eligible for inclusion.

Response:

That was the initial plan however we decided to include all stages of fibrosis and this specific inclusion criterion was removed from table 1

9- Please report the median time from RT in the study population.

Response:

The median time from RT to treatment in our study population was 72 months this was added in the text.

10- Virologic response (page 10): "At four weeks, two patients achieved SVR4, and there was a reduction in serum HCV RNA levels in all the patients who were tested". Based on this sentence, it seems that SVR4 refers to week four of treatment. Then it is not correct to call it SVR. It could be called HCV clearance. Please revise "definitions and follow-up", results, and Table 3, using the correct terminology.

Response: We are sorry for this mistake and we have changed the description in the results and Table 3 to HCV clearance.

EIC Decision:

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 11 May 2021

Dear EIC,

The authors have addressed the reviewers' comment properly and made required revisions.

Regards

Seyed Moayed Alavian: EIC | **Revision** (1) 11 May 2021

Dear Authors,

Thank you for submitting the revision. I am delighted to inform that your manuscript is accepted for publication in Hepatitis Monthly.

Regards,
EIC