Author’s response to reviews

Title: Safety and efficacy of direct-acting antivirals for chronic hepatitis C in patients with chronic kidney disease

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Reviewer reports:

M Jadoul (Reviewer 1): Iliescu et al have studied, in a prospective observational study, the safety and efficacy of one direct-acting antiviral agent (DAA) regimen (PROD) for chronic hepatitis C in patients with chronic kidney disease.

Their results are largely confirmatory of those published in several smaller-sized studies but still may deserve publication, after appropriate major revision along the suggestions below.

General comments

1. The most important concern is related to the selection of the study participants. We are told that this is a prospective observational study but the reader should know whether these were all consecutive patients with CKD and chronic hepatitis C seen at the outpatient liver clinic at this hospital in Bucharest, etc… Were some patients that were referred not treated? This information is key to understand whether there is a referral or treatment bias and to what extent the study results may be generalized to CKD patients in general. For instance, can the authors clarify whether all HD patients with chronic hepatitis C HD some units were referred or is there some selection bias too (frequent in such observational studies)?

We conducted an observational prospective study on a number of 232 patients, infected with HCV genotype 1b, who received interferon-free treatment with paritaprevir/ombitasvir/ritonavir and dasabuvir, for 12 weeks. The subjects were admitted to our clinic between May 2017 and December 2018 and presented different forms of renal disease, including: CKD of various causes, renal transplantation and undergoing hemodialysis. During this period of time, there were only 4 patients referred to our clinic who were considered ineligible for the initiation of antiviral therapy - due to the presence of different types of malignancies that required specific oncological
treatment. All HD patients with chronic hepatitis C that were referred to our clinic received antiviral treatment and were included in the study.

2. The manuscript is much too long and should be markedly shortened. In addition, the added value of the detailed description of the results in the various subpopulations is unclear. Can some grouping spare some space?

We understand that the length of our manuscript might seem overwhelming. We chose to describe each of these subpopulations separately, since they all have their specific baseline characteristics and we would find it hard and confusing to group some of them together. For example, we cannot group cryoglobulinemic patients with another category, since our goal was to emphasize the HCV causality/association with cryoglobulinemia. Patients undergoing hemodialysis and kidney transplant recipients also represent distinct categories that we believe should be treated separately, due to their particularities. We believe that describing these populations separately represents precisely the novelty of our study and we sincerely hope to have the chance to bring it into the field, especially since we have addressed all the others comments.

We hope that adding more figures to the manuscript will bring more clarification.

3. The authors mention the use of Fibromax as the test to assess the extent of liver fibrosis. Has Fibromax been validated in CKD and especially in end-stage kidney disease patients? Please provide a reference and clarify.

As stated by the Technical Recommendations for FibroTest and FibroMax assays (last reviewed in March 2018), the interpretation of these tests has been validated in renal transplant patients. In patients with renal insufficiency or on dialysis, FibroTest had an acceptable diagnostic value.

In our study, the degree of fibrosis was assessed by both Fibromax and Fibroscan, before initiating the treatment. The results of the tests were concordant: 139 patients with F2 fibrosis stage, 74 patients with F3 and 19 patients with F4 (cirrhosis). Due to the liver disease and to potential complications, no patient underwent liver biopsy.


4. The abstract should stress that whereas some of the previous studies were RCT data, this is a real-world study with the advantages of that approach.

Thank you for this observation. We have included this brief mention in our abstract.

5. The paper should absolutely include key references that are missing, such as the main results with other DAA regimens in late CKD/dialysis: the C-surfer by Roth et al Lancet
We definitely understand the importance of these studies. We have included these references into our paperwork.

6. The authors mention in the introduction that approximately 180 million people are currently affected by HCV globally. This reference is outdated and should be adapted according to the most recent figures: Polaris Observatory HCV Collaborators: Global prevalence and genotype distribution of hepatitis C virus infection in 2017: a modelling study. Lancet Gastroenterol Hepatol 2017.

We have modified this information.

7. The authors should stress in the conclusion of the abstract that the SVR rate is 100%. The reader might thus wonder why they conclude that interferon-free regimens in such patients need further investigation!

We added the suggested information in the abstract. However, we would like to emphasis on the fact that we conducted our study on a cohort of 232 patients that were only observed until reaching SVR and not afterwards. We consider that additional observation of this population is required for a longer period of time, in order to assess efficacy, tolerability and long-term adverse effects of these drugs and to clarify their impact on the natural history of the renal disease.

8. The authors analyze the results in the HCV-infected population presenting cryoglobulinemia but it isn't clear from the lengthy paper how cryoglobulinemia was defined. Based on the presence of cryoglobulin in blood or was it based on clinical diagnosis? Please clarify.

Cryoglobulinemia was defined based on the presence of cryoglobulin in the blood of the patients. As mentioned in the article, 50 patients (representing 89.28%) presented clinical manifestations of cryoglobulinemia.

9. The authors mention on the second page of the results that the use of DAAs was associated with a reduction of proteinuria. It should be clarified whether other drugs were given concomitantly or started such as ACE-inhibitors or angiotensin receptor blockers.

The patients included in this study received no other drugs concomitantly.

Specific comments
1. Results: regarding HCV infection population undergoing hemodialysis. The authors mention that 27 were males. Useless to mention that 21 were women if total = 48.

2. In the section of HCV infection with CKD due to diabetic or hypertensive nephropathy "a jeun" should be "fasting" in English.

3. Similarly, in the last section of the methods, "anamnesis" should be "history".

4. In the section about kidney transplant recipients, tacrolimus "doses" should be "dosages", and 2 "mg/week" instead of 2 "ng/week".

5. ref 41 should be updated.

6. Table 1: all figures should be rounded, limiting the number of decimals.

Thank you for your observations. We have addressed these issues, as instructed.

Marie Essig (Reviewer 2): Iliescu et al reported their real life prospective survey of 232 patients, infected with HCV genotype 1b, with impaired kidney function, who were treated by the association of paritaprevir / ombitasvir / ritonavir and dasabuvir.

The study seems to have been well conducted. The number of patients included in the study is relatively high. However, the paper gives no new information on the tolerance of this treatment in patients with CKD. In fact, several publications have already described the use of these treatments in CKD patients.

Major comments:

* The background section did not explain the questions remaining in the use of paritaprevir / ombitasvir / ritonavir and dasabuvir in CKD patients and thus the place of the study.

In the background section, we emphasized the fact that hepatitis C virus has well-known liver, kidney, and cardiovascular consequences in patients with chronic kidney disease, including those undergoing dialysis as well as in kidney transplant recipients. Therefore, finding the best therapeutic regimen for each category of patients has always represented a major challenge. The DAAs regimen based on paritaprevir/ombitasvir/ritonavir and dasabuvir (which was the chosen option for the patients included in our study) had already shown promising results with very good tolerance. Even if our results have confirmed those published in smaller-sized studies, we consider that our paper deserves publication since it follows a relatively high number of subjects, with real-world evidence.

* In the methods section, there is no clear definition of the objectives of the study.
The main objective of this study was to evaluate the effectiveness and safety of HCV treatment in CKD population – which we have mentioned in the methods section, as advised.

* In the result section,

- the patient's mode of HCV infection and the infection duration must be detailed in the baseline characteristics of the population (it is currently indicated only for transplanted patients).

The information was added for each category of patients, as advised.

- The results are quite boring to read and their presentation could have been improved by using more tables or figures to describe the evolution of biological parameters.

- In the present form, it is not possible to have a global view of the clinical or biological adverse effects of the treatment.

We added more figures, corresponding to the Results topic of the paper. We understand that the length of our manuscript might seem overwhelming, but we can ensure you that a lot of effort and hard work was put into the making of this article. We believe that the whole content of our paper is worth reading.

Minor comment

P11, L1: I suppose that the dose of Tacrolimus is 2 mg/week rather than 2 ng/week.

We corrected this typing error.