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Yuan Qi
Science Editor, Editorial Office
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Dear Prof. Yuan Qi
I, along with my coauthors, would like to return back our revised manuscript entitled "Interferon-free treatments in patients with hepatitis C genotype 1–4 infections in a real-world setting".

Right after, we address each of the points raised by the reviewers in italics. These modifications have been done and highlighted in the updated version of the manuscript.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Reviewer 03647931

This real-world prospective multi-center study was conducted at 9 centers in Spain on a fair number of patients, the study is well designed and the paper is well written, however, I have some comments.

1- The term rapid virologic response (RVR), was extensively used during the Interferon era, the duration of therapy was 48 weeks for most genotypes, in this study, the duration of therapy ranged from 8-12 weeks, the use of this term in the era of DAAs is questionable, the authors can alternatively use the term undetectable HCV RNA at week 4.

We have followed the advise and we have substituted the term "rapid virologic response" by "undetectable HCV RNA at week 4".

2- Exclusion of patients co-infected with HBV should be added at page 8.

It has been added in the text.

3- Was HCC an exclusion criterion?

No, it is not. It has been added in the text.

4- Did patients with a significant thrombocytopenia undergo an upper GI endoscopy?.

We agree that it would be interesting to know this information but it was not included in the registered variables of the study so we do not have this data.

5- Please explain why 2 patients required blood transfusion and none required erythropoietin.

Due to this study was a real world setting one, the use of blood transfusion or erythropoietin in case of anaemia was entirely at the discretion of the treating physician.

6- This phrase at page 21 should be changed from "in a cohort of patients with all genotypes" into " in a cohort of patients with genotypes 1-4".

This phrase has been modified.

7- Table 1 is too big

Table 1 has been shortened.

8- Why the regimen Simperprevir and Daclatasvir was used in 7 patients although it was not mentioned in guidelines?

Indeed, we agree with the reviewer's comment. These patients have not been excluded because the study is a real-world one and we have not taken part in the decisions of treatment because the decision to treat and the choice of treatment was entirely at the discretion of the treating physician. We have modified page 9 (Patients and methods) to explain that in some cases the selected treatment was not included in the guidelines.

Reviewer 01560031

The paper is interesting, however some problems remain to be clarified.

1. The authors should describe the SVR rate in HCV genotype 1, separating genotype 1a and genotype 1b, respectively.

This data is shown in Supplementary Material (tables 3 and 4), including confidence interval 95%. We have also included it in the body of the manuscript (page 12).

2. The authors should describe the occurrence rate of mutation and the kind of mutation, when SVR isn't attained in genotype 1, 3 and 4.

As we commented on the Discussion (page 21), we do not have this data. When the cases were collected, it was really infrequent to do the basal mutation analysis "in real-world setting".

3. The authors should describe side effects such as edema when using OBV/PTV/r/DSV.

The adverse events (AEs) that appeared with a frequency over 3% are described in Table 3. The most frequents AEs are shown in pages 13 and 14. We did not comment the mild AEs occurred in all patients because the list would be too extensive. In particular, none of the patients treated with OBV/PTV/r/DSV presented edema.

4. The authors should describe the change of AFP value and platelets before and after DAA therapy, and describe the difference between SVR and non SVR cases.

We do not know AFP value at baseline or after the end of treatment for every patient because EASL Recommendations on Treatment of Hepatitis C 2015 and 2016 did not recommend to determine this value systematically prior to starting therapy in hepatitis C patients.

We agree with the reviewer that the change of platelets count before and after DAA therapy is very interesting but it is not one of the objectives of this article and it would be the reason for an additional study.

5. Although the authors analyzed the factors regarding non SVR case generally, the authors should collect the factors and analyze regarding non SVR cases and describe that respectively.

In our opinion, the factors regarding non SVR have been described and thoroughly analyzed in Results (page 13) and in Supplementary Material (tables 3 and 4). These results are discussed in page 16.

Reviewer 02439938

The manuscript is well presented and interesting. This is very helpfully understanding the efficacy and safety of DAA treatment for HCV patients in real world settings. And also SVR patients need to be follow up at least 24 weeks. However, some mistyping needs to be solved, such as table1 "AAD" should be "DAA".

These mistakes have been corrected in table 1.

Reviewer 02937519

Ramos H. et al. analyzes the chronic infected genotype 1, 2, 3 and 4 HCV hepatitis treatment and all the possible combinations with direct antiviral agents which are nowadays available in Spain. However, this study has several crucial limitations and problems. (Major comments) A main point of this thesis is incomprehensible. What would the authors like to call from this result? In this paper, the authors analyzed the therapeutic effect and adverse events of various DAAs together, but it's different in the therapeutic effect depending on genotype and also different in side effects. Only of the therapeutic effect and a side effect, as it results clearly, for, no new knowledge was obtained. It should be analyzed according to combination of DAAs at least.

The therapeutic effect according to combination of DAAs was analyzed in table 2 and Supplementary Material (table 3 and 4), including a confidence interval 95%.

In effect, adverse events had not been analyzed for every combination of treatment to avoid extend the article in excess. We decided to describe in detail the globally most frequent adverse events, specially serious adverse events and liver decompensation (body of the manuscript and table 3), to give a general vision of the safety of these treatments in a real-world setting. The adverse events in every group of treatment were varied and they occur in few patients, so to provide all this data would mean to show an extensive table or text, that would not add any new information.

In addition, the basis which set "Clinical trial inclusion criteria" should be described.
Patients were randomly classified in each group following the criteria described in Patients and methods (page 15). We have modified the first sentence of the Methods in this sense. The reason for this sub-analysis and its possible usefulness are described in the Discussion (page 20).

(Minor comments) 1. What are "VHC" at Introduction, "HVC" at Patient selection and Clinical effectiveness, and "fibrosis measurement performed by TE" at Inclusion criteria?
The errors have been corrected. The phrase "fibrosis measurement performed by TE", have been substituted by "liver stiffness measurement was performed using transient elastography (FibroScan, Echosens, Paris France)".

2. In Abstract (Result), what does mean "96.2% patients in the CT-met group vs 91.9% patients (94.6%) in the CT-unmet group"?
This error has also been corrected and the phrase has been modified.