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ANSWERING REVIEWERS

September 23, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13150_revised.doc).

Title: Hepatitis C virus recurrence after liver transplantation: a 10-year evaluation

Author: Stefano Gitto, Luca Saverio Belli, Ranka Vukotic, Stefania Lorenzini, Aldo Airoldi, Arrigo Francesco Giuseppe Cicero, Marcello Vangeli, Lucia Brodosi, Arianna Martello Panno, Roberto Di Donato, Matteo Cescon, Gian Luca Grazi, Luciano De Carlis, Antonio Daniele Pinna, Mauro Bernardi, Pietro Andreone

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13150

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers:
(1) Gitto et al. analyzed HCV recurrence after liver transplantation with a 10-year evaluation. It seems important in this area. 1. In Discussion section, page 11, lines 17-18, Authors should delete "However, it is likely that in many countries.....in the next future".
As suggested, we deleted the requested part.

(2) Manuscript review-ESPS Manuscript NO: 13150 Gitto et al summarize the experience with HCV recurrence and therapy in patients transplanted for HCV related liver disease in 2 Italian centers. According to their data patients eligible for interferon and ribavirin based antiviral treatment with SVR show better survival than their counterparts without HCV clearance. However, a group of individuals defined as patients with mild recurrence have an even better 10-year survival rate without antiviral intervention. The paper is interesting and has a surprising result. To identify a transplanted patient group who will fare even better without treatment than those with SVR is an important finding and helps to sharpen the discussion about treatment resources with the advent of efficient but expensive DAAs. However the manuscript needs some more attention.
Which factors are associated with mild recurrence?
As reported in the text (page 9, line 14), patients with mild recurrence (followed by SVR group) showed

the lower donor age respect to others (see Table 3, p=0.001).

How and when can those patients be identified further?

As we reported at page 8, we define mild recurrence as the presence of "mild transaminase increase (alanine amino transferase <3x the upper normal limit) and mild fibrosis (Ishak stage <3) at the first post-LT liver biopsy performed within three years after LT". Being a retrospective study, we recorded data of biopsies performed in different time points. However, in our opinion, all transplanted patients have to be biopsied especially if transplanted for HCV. The ideal timing depends on many factors but we suggest that all patients with HCV recurrence have to be histologically framed within three years from the transplant. We added this assumption in the text (page 12, line 24-28).

Is there an algorithm that the authors could suggest with all the given limitations of this retrospective analysis?

We concluded the paper with the following assumption: "awaiting the consolidation of new interferon-free regimens, we suggest that in carefully selected patients with predictors of long-term favorable outcome, antiviral treatment might be delayed. Probably, the development of interferon-free regimens will completely change the approach to HCV in both pre- and post-LT settings". Indeed, in this complex and changing period, it results difficult to propose a detailed therapeutic algorithm.

One variable may be time since all patients who were too sick to be treated died within the first 12 months. When should antiviral therapy be started?

Until a few months ago, patients defined "too sick to treat" who cannot tolerate interferon-based therapy by definition, were never treated. With the oncoming of the new direct antivirals, the condition of the "too sick to treat" patients is changing. In this direction, we wrote at page 13, line 5 "Along with the availability of antiviral agents with low-toxicity profile, the limitations related to the patients' eligibility to the treatment are expected to be reassessed. Furthermore, according to recent compassionate programs derived results, the antiviral treatment will become more and more applicable in the so called 'too sick to be treated' population [18]. However, in those cases in whom a severe HCV recurrence is diagnosed, due to the latter's rapidly progressive nature, the treatment should be started as soon as possible".

The mean time between transplantation and initiation of antiviral therapy was later for the SVR group compared to the NR group. Which patients should be treated?

The time is statistically comparable as showed in Table 3 (p=n.s). In the "Introduction" we wrote about the clinical practice: "More recently, after the introduction of pegylated interferon, antiviral therapy was initiated at an earlier stage, when active hepatitis was found at first year liver biopsy [7]. Although widely accepted guidelines for antiviral therapy in LT setting do not exist [6], in every day practice, the vast majority of patients with HCV-recurrence experience at least one attempt of antiviral therapy. This purposeful approach is likely to become more and more adopted by a nowadays clinicians according to

the availability of shorter and better tolerated antiviral regimens."

Is there a positive selection for patients benefitting most?
No, we have no evidence of a positive selection.

Given the availability of DAAs patients in group E will likely be future candidates for antiviral treatment. What kind of comorbidities etc were contraindications for antiviral treatment?
Among the causes of death of the group E, we reported the presence of neoplasms (6/20) and infections (3/20) (see Table 4). Indeed, we can assume that, as expected in transplanted patients, these two are the main non-liver related cause of ineligibility. Moreover, the few number of deaths and the relevant inhomogeneity of this subgroup makes the analysis of the comorbidities not feasible. However, we do agree that the analysis of the role of comorbidities in the treatment eligibility might be very interesting, ideally in a dedicated study.

Did the MELD score differ?
Since in this study we aimed at evaluating a 10-year survival and, considering that in the clinical practice MELD score is used as a short-term predictor of survival in cirrhotic patients awaiting for liver transplant while its utility in the post-transplant setting was not validated, we did not record the MELD score of patients.

Did the patients need hemodialysis?
Four patients all from "too sick to treat" group, have necessitated hemodialysis immediately after transplantation.

Were they more likely to have low platelets?
We did not record the platelet count.

The grouping needs to be refined. The 10-year survival is presented as a Kaplan Meyer curve. The authors should also provide information on the mean (median) survival time of the different groups.
The retrospective design of the subanalysis concerning the not-treated patients definitely shows some limits. However, the three most relevant groups seem to be: SVR, NR and not-treated with mild recurrence. As suggested, the definition of these three groups in the text was revised and the requested data about survival time were added (Page 8, line 28 - Page 9, line 2).

Is there more information about the donor organs besides age like steatosis, if they met extended criteria etc?
In our study, we recorded only partial data about donor and in particular the donor age which is, according to the literature, one of the most relevant prognostic factor in transplanted patients.

If patients with cyclosporin were more likely to achieve SVR, what was the ratio in the mild disease group?

Patients achieving SVR were more frequently in cyclosporine compared to non-responders but without a statistical significance (we added this specification in the text, page 9, line 19). Regarding the mild disease group, as in the other group, the cyclosporine was the most used drug. Nevertheless, since this group is formed by patients not treated with antiviral therapy, the possible role of cyclosporine as a predictor of virological response was not assessable in this context.

Did more of these patients receive tacrolimus?

As showed in Table 3, in all groups cyclosporine was the most used drug. In particular, the distribution of immunosuppressants was not significantly different among groups (p=n.s.).

Figures Need attention. They are way too small to be easily read.

We modified the figures as suggested.

(3) The present study is a retrospective analysis of a cohort of patients transplanted with hepatitis C, some of which received pegylated interferon and ribavirin. The main finding of the study was that there was no difference in overall survival in treated patients compared with untreated patients, but that SVR patients had a survival rate higher than non-responders.

Whilst the latter is expected the authors should discuss the reasons for the finding that untreated patients have similar survival to treated patients presumably this is due to patients with milder disease not receiving therapy.

We added a part with the requested observations (page 11, line 8-14). Moreover, we positioned forward the citation number 23, Belli et al. (we changed the numbering in the reference section).

The manuscript would be enhanced with some further baseline detail of patients in each cohort- some detail of the degree of liver disease, and graft histology would enhance the paper.

We added data about survival time of each group (Page 8, line 28 – Page 9, line 2). We added data also about necessity of dosage reduction in treated patients (Page 8, line 1-4). Concerning the degree of liver disease we reported that, by definition, patients with mild recurrence showed an Ishak stage <3. Regarding the other groups, not all were biopsied within three years. Indeed, the comparison of data appeared not feasible. However, NR (as showed in Table 4) showed the highest number of death for HCV recurrence (48.57%) and indeed we can assume that had the more advanced histology. We have no data regarding the graft histology but only about donor age as reported.

3 References and typesetting were corrected

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Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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