Reviewer's report

Title: Treatment with Pirfenidone for two years decreases fibrosis, cytokine levels and enhances CB2 expression in patients with chronic hepatitis C: open-label clinical trial

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Reviewer: luigi adinolfi

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The authors performed this study with the aim to expand their previous pilot experience (from 12 to 24 months) on the treatment of advanced chronic HCV infection with Pirfenidone as anti-inflammatory/anti-fibrotic drug. In this trial they evaluated the change of some pro-inflammatory cytokines as well as the gene expression of cannabinoid receptor (CB1-2).

Overall the study should be of interest and of potential clinical significance, although this study add few information to the previous study. In addition, the design and the aim of the study are not very clear and the results deserve more considerations and explanations. On these bases the conclusion: “we propose the use of pirfenidone for liver cirrhosis in patients with CHC” is to strong and could be hazardous.

Specific point:
1. The background of the study is not well reported. The study was performed because the authors believed that necroinflammatory activity plays an important role in the progression of the disease. To facilitate the concept to the reader, I suggest to cite the recent publication reviewed this point (HCV and inflammation) (Zampino R. et al Word J Hepatol. 2013:5:528-540.)

2. The aim of the study should be better state; in other words, they want to expand their experience, to evaluate the safety, to evaluate the mechanisms, etc. The conclusion should be according to the aim and to the design of the study. It is important to keep in mind that there is a standard of care for CHC and that the virus clearance is necessary to cure the disease. This point is necessary to be discuss. The authors, perhaps want to deserve treatment with PDF in non responder to SOC; if so should be declared.

3. This is an open study. If the intention of the authors was to make a therapeutic trial why they did not perform a randomized trial, in which patients could be randomized according to age, sex and disease stage. Thus this study do not permit to give therapeutic conclusions and it should modify accordingly.

4. The enrolment of patients is not clear. What was the criteria of enrolment? All consecutive patients or there were other criteria.

5. The authors declare that they have enrolled only patients with advanced liver disease/cirrhosis. Figure 1 shows a mean score of 4.2, that means that a large proportion of patients did not have cirrhosis. The histological score of patients
must be clearly reported. Fig. 1 is confused what means HAI Fibrosis stage? Is necroinflammatory activity or fibrosis stage? The population studied must be better defined.

6. The most critical point, that must be cleared, is the six patients who were excluded from evaluation. The authors generically declare that “were non compliant or death”. The reason of non-compliance must be reported. More important, the cause of death as well as the eventually relation with treatment must be clearly reported.

7. It is not clear the data on cannabinoid receptors, the results should better discuss also in relation with the recent publication on the matter (Coppola N, et al.. Cannabinoid receptor 2-63 QQ varianti s associated with severe necroinflammation in chronic epatiti C. Clin Gastroenterol & Hepatol 2013; 2013 May 21. doi:pii: S1542-3565(13)00687-3. 10.1016/j.cgh.2013.05.008.)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

not to all