

## **Answer to Editor and Reviewer's comments – Manuscript 12307**

We would like to thank the Editor and reviewers for their very accurate analysis and invaluable advices to improve our manuscript. Please find attached a point-to-point answer with a revised version of our manuscript, which takes carefully into account all the questions and comments of the Editor and reviewers.

### **Reviewer 1:**

#### **1.1. "The authors should add the Section of perspective for the future management of chronic hepatitis C in CKD patients".**

A: As suggested, we have added an additional section called "New perspectives for HCV therapy in CKD patients".

### **Reviewer 2:**

#### **2.1. "The prevalence of HCV infection in hemodialysis has a very wide range, according to the geographic area. Are there more representative data in a more recent bibliography? (6-7)."**

A: We agree with the reviewer regarding the wide prevalence range across regions. Although supportive data from the recent literature is scarce, we have managed to include a recent meta-analysis performed by Su Y et al. on the incidence of HCV infection in hemodialysis patients (Ref. 8, cited on page 4).

#### **2.2. "HCV infection attributable to transmission by the use of contaminated medication vials, authors should specify which medicines are involved. In the past, unfractionated heparin sodium was certainly the drug more involved, but more frequent use of low molecular weight heparin in single dose should have drastically reduced this option. Authors should develop more this topic."**

A: As suggested, a brief discussion about this topic was included (pages 4 and 5). Multi-dose saline vials, anesthetic vials and unfractionated heparin have been the most commonly implicated agents.

#### **2.3. "Is the clearance of HCV particles influenced by the type of dialysis treatment? It would be interesting to know if there are any studies on the clearance of HCV particles with different types of dialysis treatment (HDF, HDF On Line, AFB, PFD or in HFR)."**

A: It is not clear in the literature whether the type of dialysis would significantly affect the clearance of HCV particles. However, it has been suggested that HCV viral load is lower in CKD patients under chronic hemofiltration (Ishida H, Tanabe K, Tokumoto T, et al. *Artif Organs* 2004 Mar; 28(3) :316-8.). A brief discussion on the subject was included (page 9).

#### **2.4. "Patients in 4 stage KDOQI may remain with stable renal function for a long time, so waiting attitude does not risk impair liver function, increase cardiovascular risk and compromising future renal transplantation?"**

A: The waiting attitude for patients in CKD stage 4 is proposed only for those without significant liver fibrosis, considering the particularly low fibrosis progression rate and the expected low tolerability of these subjects. This concept was clarified in the text (page 8).

**2.5. “The authors do not develop fully the side effects of the therapies used for the treatment of HCV infection, both for the older therapies (IFN, PEG-IFN, ribavirin) that for the most recent (protease inhibitors and polymerase or cyclophillin inhibitors). Must be considered that the therapy is often discontinued because of adverse effects of these therapies (eg anemia, leukopenia, thrombocytopenia, Steven's Johnson). Should be developed further this topic.”**

A: We believe that a deeper discussion on the side effects of anti-HCV therapy would be out of the scope of the manuscript. However, as suggested, we included a brief summary on the matter on page 15.

### **Reviewer 3:**

**3.1. “The authors tried to make a review regarding HCV infection among patients with CKD. The subhead titles were “acute hepatitis”, “chronic hepatitis before KT”, and “chronic hepatitis after KT”, and to use these subhead titles seemed to be a novel way in describing summaries of HCV infection in patients with CKD. However, there are lots of reviews regarding HCV infection among patients with CKD and this review has a similarity to previous reviews. For example, Professor Fabrizi made a lot of reviews in this field and his reviews are very comprehensive and seem to be updated on a moment-to-moment basis. There were somewhat old-fashioned descriptions in this review compared to descriptions in Fabrizi’s reviews (ISRN Nephrology 2012, etc.), especially in descriptions in epidemiology. Descriptions in epidemiology should be updated on a moment-to-moment basis in this article.”**

A: We do recognize the significant contributions made by Professor Fabrizi regarding HCV infection in CKD patients, including several systematic reviews and meta-analysis about the impact of HCV infection and the therapeutic options available. However, we also believe that our review is rather comprehensive and includes relevant evidence on the subject that can impact on decision-making in the day-to-day clinical practice, from the hepatological point of view.

Regarding the descriptions in epidemiology, as discussed above, supportive data from the recent literature is really scarce. However, we have included a brief discussion on a recent meta-analysis on the incidence of HCV infection in hemodialysis patients (Ref. 8). In addition, we have included an updated meta-analysis by Fabrizi et al. evaluating the efficacy and safety of combination antiviral therapy (pegylated interferon plus ribavirin) of eleven trials in CKD patients on long-term dialysis with chronic hepatitis C.