

September 26, 2020

Dear Editor-in-chief,

Please find enclosed our edited manuscript in Word format for our Minireview No 58305. We thank the Reviewers for their constructive criticism. Their concerns and suggestions have been addressed thoroughly.

The manuscript has been improved according to the suggestions of the Reviewers, and every one of the points of the Reviewers has been addressed below in a point-by-point manner.

**Title:** "Hepatocellular carcinoma after direct-acting antiviral HCV therapy - a debate near the end"

**Authors:** Cristina Maria Muzica, Carol Stanciu, Laura Huiban, Ana Maria Singeap, Catalin Sfarti, Sebastian Zenovia, Camelia Cojocariu, Anca Trifan

**Name of Journal:** World Journal of Gastroenterology

## REVIEWER 1

### Comments

The authors review the most recent and relevant articles regarding the risk of HCC after DAA treatment and found a reduced incidence rate of both de novo and recurrent HCC after achieving SVR with DAA therapy, and considered that the debate regarding the impact of DAAs on HCC risk is drawing to an end. The quality and importance of this manuscript is good, and the conclusions appropriately summarize the data that this study provided. The author may appropriately enriches the research basis of HCV causing hepatocellular carcinoma.

*Answer: Thank you for the positive comments for our manuscript. We underlined that HCV-induced HCC is a gradual process affected by the duration of disease, and mediated by viral-induced factors and host-induced immunologic response. Please see page 4, first four phrases.*

## REVIEWER 2

### Comments

1. The last paragraph of the section of "THE RELATION BETWEEN HCC AND CHRONIC HCV INFECTION" does not seem to related to the subject of this part. It is

recommended to delete it and move the relevant content to the section of "RISK FACTORS FOR DE NOVO AND RECURRENT HCC".

*Answer: The last paragraph has been deleted and the relevant content has been moved to the section of "RISK FACTORS FOR DE NOVO AND RECURRENT HCC". Please see page 11, third paragraph.*

2. In the section of "HCC OCCURRENCE AFTER DAA THERAPY", the authors reviewed and cited a large number of articles, but the order is quite messy, and the interrelationships between the various studies are puzzling. It is recommended to classify articles according to the similarity of the studies, such as: research type (retrospective, prospective), conclusions (support, against), number of cases (single-center, multi-center), etc. Each category aggregate into separate paragraphs and add corresponding subtitles to describe separately. It would be convenient for readers to read and understand more clearly. In the section of "HCC RECURRENCE AFTER DAA THERAPY" and "RISK FACTORS FOR DE NOVO AND RECURRENT HCC", the above problems also exist. It is recommended to also aggregate each category into separate paragraphs with corresponding subtitles.

*Answer: The articles have been classified as suggested. Please see pages 7-13.*

3. For some reference, the results and conclusions cited by the authors are puzzling. Such as: Among patients with SVR to DAAs, the incidence rate of HCC was 6.9 per 1000 PY, while in individuals with SVR to IFN, the incidence rate of HCC was 1.8 per 1000 PY. The authors concluded that similarly to the interferon era, DAA-related SVR is associated with a 70% reduction in HCC risk [41]. Why is 6.9 similar to 1.9? The author seems to quote the results and conclusions directly from the abstract. It is recommended that authors quote more convincing content in the original manuscript.

*Answer: As suggested, we quote more convincing content in the original manuscript. Please see page 7, the last two phrases from section "Retrospective studies comparing outcomes after DAAs versus IFN-based therapy"*

4. Some references are too old. For example: the first reference. The latest article is "Global Cancer Statistics 2018 GLOBOCAN Estimates of Incidence and Mortality

Worldwide for 36 Cancers in 185 Countries". It is recommended to cite updated reference.

*Answer: We updated the reference as you suggested. Please see page 14, first reference.*

### **REVIEWER 3**

#### **Comments**

In the present review article, Muzica et al. discussed the relationship between DAA therapy for HCV infection and occurrence and recurrence of HCC. They concluded that DAA therapy suppress the risk of HCC after achieving SVR based on the recent results of retrospective and prospective studies. The authors compactly summarized the findings of recent researches; however, its impact is unsatisfactory after several meta-analyses and epidemiological studies in terms of this topic have already been published. 1. The recurrence of HCC can be stratified into (1) intra-hepatic metastasis of the original tumor and (2) multicentric carcinogenesis. If SVR is achieved by DAA therapy and progression of liver fibrosis is suppressed, multicentric carcinogenesis could be suppressed theoretically. However, tumor recurrence is frequently found after curative treatments for HCC. The authors are requested to refer to this issue based on the findings of the previous works.

*Answer: The recurrence of HCC has been stratified into intra-hepatic metastasis of the original tumor and multicentric carcinogenesis. Please see page 10, first paragraph.*

We are indeed thankful to the World Journal of Gastroenterology for providing us with valuable reviewers.

Sincerely yours,

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