March 2020
Aarhus, Denmark

Dear Jin-Lei Wang, Science Editor

Thank you for the swift and positive handling of our review "Liver-related effects of chronic hepatitis C antiviral treatment" with the manuscript no. 53606.

We have uploaded the original figures in PowerPoint format in addition to the pdf figures to ensure that they are fully editable.

We look forward to the editorial decision.

Thank you in advance.

Yours sincerely,

Tea Lund Laursen, MD, PhD
Department of Hepatology and Gastroenterology
Aarhus University Hospital
Aarhus, Denmark
+45 7845 3813
tealaurs@rm.dk

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Aarhus, Denmark

Reviewer 1:

A very good review article.

Response: Thank you very much for this kind comment.

Abstract -Five years ago……..No, more than 5 (The first generation DAAs are since 2011)

Response: Thank you for noticing this. In the abstract, our intention was to note that it was 5 years ago since the all-oral regimens were introduced, but we agree that it is unclear and have changes the wording to: "More than five years ago…"(Abstract, line 1).

Hepatitis C -Hepatitis C virus (HCV) was isolated and named in 1989 [1], and in 2015, more than 70 million people ……no, 170 million people

Response: We agree that this may be unclear, and you are completely right that approximately 170 million people worldwide are infected with hepatitis C. The 170 million includes both acute and chronic infection, whereas the 70 million is an estimate of only chronically infected patients. To clarify, we have changed the wording in the revised manuscript (Introduction: Hepatitis C, page 4, lines 2-3).

Complications of CHC infection - Portal hypertension may be assessed by liver vein (catherization),……what is liver vein??? Plus spelling mistake (catheterization)

Response: The liver vein is the hepatic blood vessel assessed for hepatic pressure measurement during the catherisation procedure. Thank you for noticing the spelling mistake, we have corrected this (Assessment of liver disease severity: Complications of CHC infection, page 9, line 20).

Reviewer 2:

Thank you for your comments, which are both very interesting.

1. Can you briefly address the progress of current studies or its limitations on liver inflammation, fibrosis, and metabolic liver function secular changes after DAA treatment for CHC patients with advanced liver disease (i.e. METAVIR fibrosis stage 3 or higher before antiviral therapy)?

Response: It is difficult to address the progress of current studies other than our own studies. However, we are currently running studies further assessing especially the effects on fibrosis and metabolic liver functions after DAA in patients with cirrhosis. In general, such studies are often limited by the lack of histological verification of the disease severity

before treatment but especially after treatment. In addition, in the metabolic studies, a limitation is often the limited sample size. Metabolic studies are often logistically comprehensive and time-consuming, why sample size is often limited to make the study feasible. We have added these considerations in the revised manuscript (Future aspects, page 15, lines 15-19).

2. Explain the potential differences in liver function or fibrosis changes between patients who failed to IFN or DAA treatments because of the different action mechanisms of both drugs.

Response: Thank you for this very interesting comment. When evaluating patients who fail therapy the major difference between IFN regimes and DAA regimes pertains to the amount of available data. With the INF regimes many patients failed therapy and therefore a lot of data are available. It seems that patients who fail IFN therapy does not experience the beneficial effects of the treatment in regards to improvements in liver function or fibrosis. When it comes to DAA therapy, the data is much more limited as so few patients fail therapy, and so far, very little data on how these patients fair in regards to liver function and fibrosis are available. However, it seems like it is not the different mechanism of action of the drugs, but instead the clearance of the virus that primarily determines the changes after therapy. This is indicated in one study were liver inflammation ceases in responders to pegylated-INF + a first generation DAA or all-oral DAA therapy but not in the non-responders to pegylated-INF + a first generation DAA [1]. We have elaborated on this in the revised manuscript (Hepatic effects of antiviral treatment: Amelioration of inflammation, page 10, lines 18-19).

1 Lund Laursen T, Brockner Siggard C, Kazankov K, Damgaard Sandahl T, Moller HJ, Ong A, Douglas MW, George J, Tarp B, Hagelskjaer Kristensen L, Lund Laursen A, Hiramatsu A, Nakahara T, Chayama K, Gronbaek H. Rapid and persistent decline in soluble CD163 with successful direct-acting antiviral therapy and associations with chronic hepatitis C histology. *Scand J Gastroenterol* 2018: 1-8 [PMID: 29987961 DOI: 10.1080/00365521.2018.1481996]