

Paris, 01/11/2018

Name of journal: World Journal of Hepatology

Manuscript NO: 37412

Title: Hepatitis C Virus: morphogenesis, infection and therapy

Dear Editor,

Sorry for the mistake. We provide 37412-Revised-Manuscript-revision with word.

First of all, we are grateful to the reviewers for their helpful remarks that allow improving the manuscript. Please find below our comments and point by point response to the Reviewers.

Reviewer's code: 02462252

Thank you for your positive comments. The language was polished by the native English Speaker.

Reviewer's code: 018008

This review covers many aspects of hepatitis c, delving deep into pathogenetic mechanisms of the infection. Unfortunately, the review offers little in regards to novel medical knowledge and is submitted in a period that hepatitis c treatment is already reaching its peak, with current therapies achieving >95% SVR rates and research for new pharmacological regimens being put in a hold due to the efficacy of our current pharmacologic options.

Answer. That is not a review on HCV therapy and virus therapy is only a part of it. It is not clear what kind of “*novel medical knowledge*” is expected in a broad review on HCV. Better understanding of the virus molecular biology and biochemistry allows obtaining solid background for advance in treatment. By the way, it can provide with a better vision of the problem and can induce new ideas, which at the end can result in a new pharmaceutical and medical knowledge. In fact, fundamental studies on viral proteins largely stimulated appearance of DAAs.

We agree that the standard of care for hepatitis C is changing rapidly. Sofosbuvir, daclatasvir and the sofosbuvir/ledipasvir combination are part of the preferred regimens in the WHO guidelines, and can achieve cure rates above 95%. These medicines are much more effective,

safer and better-tolerated than the older therapies. Therapy with DAAs can cure most of the persons with HCV infection, while this treatment is rather short (usually 12 weeks). WHO is currently updating its treatment guidelines to include pangenotypic DAA regimens and simplified laboratory monitoring. Nevertheless, resistance to DAAs was postulated, so the problem is not solved completely. Not to forget, that prophylactic anti-HCV vaccine is still not available. Thus, more fundamental research is required and that is one of the most important part we have tried to present in the manuscript. To justify that the problem is not completely solved we included five papers that focused on emerging viral resistance to DAA:

307. Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H. *Hepatology*, Clinical textbook, 8th Edition **2017**, Medizin Fokus Verlag, Hamburg, Germany
[www.hepatologytextbook.com/download/hepatology2017.pdf]

308. Schneider MD, Sarrazin C. Antiviral therapy of hepatitis C in 2014: do we need resistance testing? *Antiviral research* 2014; 105: 64-71 [DOI:10.1016/j.antiviral.2014.02.011]

309. Wyles DL, Gutierrez JA. Importance of HCV genotype 1 subtypes for drug resistance and response to therapy. *J Viral Hepat* **2014**; 21: 229-40 [DOI: 10.1111/jvh.12230]

310. Tornai I. Significance of hepatitis C virus baseline polymorphism during the antiviral therapy. *Orv Hetil* **2015**; 156: 849-54 [DOI: 10.1556/650.2015.30180]

311. Sun D, Dai M, Shen S, Li C, Yan X. Analysis of naturally occurring resistance associated variants to NS3/4A protein inhibitors, NS5A protein inhibitors and NS5B polymerase inhibitors in patients with chronic hepatitis C. *Gene Expression* 2017 GE-000551 Provisionally Accepted November 6, **2017** for publication [DOI 10.3727/105221617X15100607143377]

The language was polished by the native English speaker.

Reviewer's code: 00069855

For better description, I would suggest to make changes in some sub-titles: 1. change "overviews on epidemiology of HCV" as "Introduction"; 2. change "Physiopathology of HCV Infection" as "Clinical manifestation of HCV Infection". Also, the whole part of "Molecular Biology of HCV" is better to put before "HCV Transmission Routes".

Answer. We have followed the suggestion and made the changes in subtitles, as recommended:

1. Heading "Overviews on epidemiology of HCV" is now given as "Introduction"

2. Heading “Physiopathology of HCV Infection” is now given as “Clinical manifestation of HCV Infection”.

3. Finally, the part “Molecular Biology of HCV” is placed before the “HCV Transmission Routes”.

Please feel free to contact us for any remark. Thank you.

Happy New Year 2018!

Best regards,

Vladimir A Morozov PhD, DrSc,

Sylvie Lagaye PhD, DrSc.