

Format for ANSWERING REVIEWERS

September 5, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 19306-Review.doc).

Title: Era of direct acting antivirals in chronic hepatitis C - Who will benefit?

Author: James Fung

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 19306

Thank you for the following comments from the editor and reviewers. I have revised the manuscript accordingly.

Review 1: Minor revision

The author summarized the using of direct acting antivirals (DAA) drugs for the treatment of chronic hepatitis C (CHC) infection, especially the limitation of the availability and the high cost. This review provided a development strategy for the clinical treatment of CHC patients using DAA drugs. However, there are still some minor revisions as follows: 1) It is suggested to complement a table or figure to summarize the using of DAA drugs in different patients. 2) Paragraphs of text lack of references, please add them. 3) Some abbreviations are not consistent, such as DAA. The full name is "directing antiviral" in abstract, whereas "direct acting antivirals" in text, please revise.

1. Thank you for your comments and suggestions. We have now added a figure to illustrate the current treatment paradigm in the era of DAAs and referenced it in page 6 & 7 under the heading "Who will benefit" and also under the heading "Conclusion" in page 12.
2. We have now added the missing references
3. The typo in the abstract has been corrected

Review 2: Minor revision

General considerations: In the way it is written, this review appeared to me closer to an editorial, which may explain the lack of references in the text, but does not justify the fact that it is necessary to cite the source of the information provided. Thus, it becomes imperative to add references whenever necessary, which provides credibility to the review of the text information. Special considerations: Abstract: lacked the term "acting" in "directing antiviral (DAA)." Text: the subtitle "Patients with established cirrhosis", the 5th

line, I suggest changing "compensation" for "decompensation". Summary: As the manuscript already has the abstract, I suggest the author place this subtitle as Conclusions.

Thank you for the comments and suggestions.

1. We have added in the missing references
2. The typo in the abstract has been corrected
3. The typo on the 5th line has been amended
4. The subheading has been changed as suggested

Review 3: Minor revision

The article is very interesting and useful for clinicians. It would be good to mention the disadvantages of prior therapies against hepatitis C virus and possible adverse effects of new combinations of direct acting antivirals. The author can also mention the challenges that may arise in the future regarding the new therapies, as the emergence of drug resistance or naturally occurring polymorphism in HCV sequences which can compromise HCV treatment response. DAA must have the same explanation in abstract and article.

Thank you for the comments and suggestions

1. There is a short segment under "Evolution of Antiviral Therapy for CHC" which describes the disadvantages of using interferon-based therapies – on page 4.
2. This is an excellent point, and although beyond the scope of this review, there is a short section now added under "Is the therapy cost-effective?" on page 11 highlighting the potential problems of drug resistance, as more patients will be treated in the future.
3. The typo in the abstract has been corrected

Review 4: Major revision

In this review, Dr. Fung described the benefit of DAA to patients with chronic HCV infection, the review is valuable for clinicians. I have following comments to this report. Major comments: 1) the author had not detailed the history of INF-based therapy, in that era, the effect of IFN-based treatment is largely dependent on the viral genotypes. 2) The author had not detailed the side effects of INF-based treatment and DAA therapy, so, the reader could not understand what favorable side effects are. Minor comments 1) The abstract is too simple to know the questions you raised and the answer you given. 2) Citations are inefficiency and imprecise. 3) Abbreviations are not consistent, in abstract DAA is "direct antiviral agents (DAA)", while, in paper body, DAA is "direct-acting antiviral (DAA) agents". 4) You claimed that "An estimated 170 million people worldwide are chronically infected with the hepatitis C virus (HCV), affecting 2-3 percent of the world population, and constituting a major health burden globally.[1]", be sure to figure out whether "170 million people are chronically infected with HCV" or they are HCV antibody positive, actually, the HCV infection rate is not that high as WHO estimated. Could you find the original literature for "An estimated 170 million people worldwide are

chronically infected with the hepatitis C virus (HCV), affecting 2-3 percent of the world population, and constituting a major health burden globally”?

Thank you for your comments and suggestions

1. There is a short description regarding the genotypes and its importance in treatment duration and SVR under “Evolution of Antiviral Therapy for CHC” – which will suffice for the purpose of this review. Further discussion on genotypes will be beyond the scope of this review.
 2. There is a short description regarding the disadvantages of interferon-based therapy under the heading “Evolution of Antiviral Therapy for CHC” – which will suffice for this review which primarily addresses who might benefit from the new DAAs in the first instance. Further description is also given under the heading of “Patients ineligible for IFN therapy” on page 7.
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1. The abstract has been revised as suggested
 2. The references have been amended and revised as suggested
 3. The typo in the abstract has been corrected as suggested.
 4. The estimate figure of 170 million is widely quoted and accepted, and represents those with chronic infection. The updated references actually shows a possible higher prevalence of >185 million. The references have been updated as suggested. Hopefully with DAAs this figure will fall eventually.