

January 25, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: DAA manuscript_15655 Revision 1272015.doc).

Title: Impact of all Oral Anti-HCV Therapy: A Meta-analysis

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Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 15655

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers:

Reviewer 1 Comments and our response

Thank you for your insightful review and comments

1. It is hard to discuss oral therapies without quoting and discussing the Abbvie 3D regime (will be FDA approved within the next days), Sof/ledipasvir (FDA approved) and the Hallmark study (drugs available in Japan).

Ans- We have included only FDA approved regimens to date, and have not included non-FDA approved regimens as mentioned in inclusion and exclusion criteria.

Therefore, as mentioned by the reviewer, although Abbvie 3D has filed for FDA approval but was not approved as of the manuscript submission date of Dec 2 2014. But we have included Abbvie's Viekira Pak (ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets) in final revised submission as this drug got approved on Dec 19 2014.

Sof/Ledipasvir (FDA approved) has been included in the analysis; please refer to study Lawitz (reference number 16), Afdal (35), Kowdley (36).

Hallmark Study was excluded as it contains Asunavir, which is not FDA approved.

2. The cost-efficiency calculation is at best valid for the USA and is worthless for other countries

Ans- We agree with the reviewer that the cost-efficiency calculations reflect \$ amount and cost in US. It might not reflect cost in other countries as the cost of medication is different amongst individual countries and there is no international standard available to regulate them and are governed by drug companies. Our analysis thus, provides relative cost-effectiveness in US. This has now been addressed in the limitations section of the review.

3. All the phase 3 studies have a major selection bias and may not be applicable for "real world" patients, see the problems in the CUPIC study.

Ans- Reviewer mentions an inherited selection bias in all phase 3 trials. Ours is a meta-analysis of the available studies and by the inherent nature of a meta-analysis, this becomes a limitation of our review and is unavoidable. This also has now been addressed in the discussion as a limitation.

4. The problem of treating cirrhotic patients is not dealt with in sufficient detail

Ans- We agree with the reviewers, the cirrhotic patients were not dealt with in details in the included trials. We will include these in Limitation section in the manuscript.

5. The selection of studies is hard to understand - the authors quote the Sprint 1 study but not PROVE 1 and PROVE 2. Why was the ILLUMINATE study not chosen? Just to mention a few.....

Ans- We did include PROVE 1, PROVE 2 as well as ILLUMINATE trial, please refer to McHutchison 2009 (reference number 33), Hezode 2009 (32) and Sherman 2011 (26) respectively in our study.

Reviewer 2.

Thank you for your insightful review and kind comments

Reviewer 3.

Thank you for your insightful review and comments

1: Outcome measures: SVR is internationally defined as negative HCV RNA for 24 weeks; 12 weeks should not be mentioned.

Ans: Incorporated, Thank you for the correction.

2: Discussion and summary: In view of the extremely rapid development of approval of new DAAs a table with the current licensed substances would be helpful. At least in the end of the report the new treatment option with Paritaprevir/Ritonavir/Ombitasvir/Ribavirin (Abbvie) should be mentioned, because its approval is expected in these days. This then can also be added to the summary. Furthermore it would be useful to add that there are some more fixed combinations awaited to be licensed in 2015 (e.g. Daclatasvir, Asunaprevir, Beclabuvir or Grazoprevir with Elbasvir)

Ans: We agree with the reviewer and have added this information under a new section: "Limitations and Recent developments" and added a new Table 3 titled "Various Direct Acting Antivirals: Approved and investigational"

Currently FDA Approved DAA	Under Development but currently Non-FDA approved
Telaprevir; Boceprevir; Ledipasvir; Sofosbuvir; Simeprevir; Sof/Ledipasvir (Harvoni) Ombitasvir/ Paritaprevir/Ritonavir with Dasabuvir (Viekira Pak)	Daclatasvir, Asunaprevir, Beclabuvir Faldaprevir Mericitabine Tegobuvir Grazoprevir with Elbasvir

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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