Author's response to reviews

Title: Achieving sustained virologic response in hepatitis C: A review of the clinical, economic and quality of life benefits

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Author's response to reviews: see over
Achieving sustained virologic response in hepatitis C: a review of the clinical, economic and quality of life benefits

Firstly, we’d like to thank the reviewers for their time and critique of our manuscript. We hope we have managed to address their concerns adequately and improve the manuscript. However, if the reviewers feel that any sections need further clarity, detail or revision, we would be happy to make any changes required.

We have outlined our responses to the comments in blue text below and have made changes to the manuscript as detailed below.

Reviewers Report: Reviewer 1

Summary
The authors in this article aimed to make a review of the literature on the clinical, economic and benefits associated to SVR for patients with a genotype-1 chronic HCV infection. For this, the authors selected via PubMed, EMBASE, and the Cochrane libraries 62 articles from what 44 clinical studies, 16 quality of life studies, and 2 economic studies. The authors reported results of selected publications on SVR benefits on HCV complications. The authors concluded on the benefits of SVR versus non responders or untreated patients, in short- and long-terms. SVR reduces risks of HCC, liver-related mortality, risks of complications such as diabetes, costs, and increases quality of life.

This review makes a summary of the current literature on SVR benefits for patients infected by genotype 1 HCV. However I have several concerns; First why only genotype 1 HCV infected patients were considered?

There were several reasons for limiting the scope of the review to genotype 1 only. Firstly, we were conscious of the broad scope of the review in terms of endpoints included and therefore we aware that other limits to the scope of the review needed to be applied in order to keep the review within limits in terms of word count and number of references included. Therefore, we took the decision to apply several limits to the scope of the review including a minimum patient enrollment of 100 patients (although this limit was also applied to attempt to capture only relatively large scale studies with the power to detect small differences in endpoints and also exclude pilot studies in highly selected populations), limited the study to genotype 1, and excluded studies exclusively in HIV co-infected populations. Including studies from other genotypes and in HIV co-infected populations would necessarily have limited the depth of the discussion of results.

Additionally, several studies suggest that in some settings, the prevalence of genotypes 3 and 4 is disproportionately high among intravenous drug users\textsuperscript{12,34} and the evidence relating to whether rates of reinfection are higher among IDUs than non-IDUs is contradictory\textsuperscript{5,6,7,8} this is something that, if true, could influence outcomes following an initial SVR and is something that is beyond the scope of the current review. By excluding studies in non-genotype 1 patients, as well as IDU populations, engaging in controversy over this issue has been avoided.

Second, the strategy for literatures searches is not well defined. Was this in accordance with Cochrane collaboration guidelines. What keywords were used?
The literature review was performing in line with PRISMA guidance, search strategies were designed based on high level MeSH terms (e.g. Hepatitis C[MeSH] OR Hepacivirus[MeSH] for therapy area and costs and cost analysis[MeSH]) and supplemented with free text terms as there is no MeSH term for SVR. In the EMBASE database the “map term” term functionality was used to match MeSH terms used in the PubMed and Cochrane Library to their EMBASE equivalents. Wild cards were also used to capture variations in terminology (e.g. virologic and virological).

We have expanded the Methods section of the manuscript to incorporate this information. We would be happy to add a table of the complete search strings used in all three databases to either the article itself or in the form of an online Appendix, if the reviewer feels that this information is needed within the publication.

The quality of the studies reported were not at all considered; What does «validated quality of life instruments » mean ? Nothing is in general stated on the way the studies are conducted.

We limited the quality of life aspect of the review to studies that used validated quality of life instruments, such as the EQ-5D and SF-36 where data can be mapped to provide utility values as this provides a robust method of comparing quality of life within and between studies. We found that several studies identified in the literature searches assessed quality of life as a secondary or exploratory endpoint and provided little in terms quantitative analysis, with some studies that emphasized clinical outcomes limiting the reporting of quality of life outcomes to a short qualitative discussion. Additionally, a small number of studies used questionnaires or scales that had been designed specifically for that study and lacked documented evidence of validation processes including assessment of internal consistency, test-retest reliability, measurement error and construct validity. For such studies it was difficult to discuss these within a broader context so the decision was taken to include only those presenting quantitative findings and utility values. We also wanted to avoid studies where crude quality of life assessments that may have been subject to key limitations such as response shift were used as a discussion of the caveats of individual studies would have been beyond the scope of our review.

We did not perform a formal assessment of the quality of each of the included studies. Part of the rationale for not doing this was that it would have necessitated the use of several different checklists, for example the Drummond checklist for the health economic studies, the Jadad scale (or other) scale for clinical studies etc. In hindsight, this is a key limitation of the review and we’ve added a statement to acknowledge this to the Discussion section.

Minor comments

- The layout of the document is not pleasant

We’ve attempted to modify the layout by adding more sub-headings and paragraph breaks. We think that some formatting changes may have occurred due to hyperlinks not working or different versions of Word being used. We’ve worked through the document to identify all the formatting issues mentioned and believe we have fixed these.

- Tables are very hard to read; a more friendly presentation of these tables would be interesting.

We have updated the formatting of the tables; we hope this makes them easier to read, but we’d be happy to make any more revisions necessary as we understand that there is a lot of content “squeezed” into the summary tables.
- The process for identifying eligible studies could be summarized in a Table
  We have added a table detailing inclusion and exclusion criteria for the review.

- There are problems with page numbering
  We have corrected this in the word document, and will check that there are no conversion/upload problems.

- Line 54: problems with references, please update the “order” of your references
  We have fixed the reference numbering issue here.

**Level of interest:** An article of importance in its field
**Quality of written English:** Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.
**Declaration of competing interests:**
I declare that I have no competing interests

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**Reviewers Report: Reviewer 2**

**Reviewer’s report:**

Major Compulsory Revisions: none

Minor Essential Revisions:
Although the editor will improve the presentation of the manuscript, I would like to emphasize that it is not good:
1/ the first 16 pages are in landscape orientation
   The formatting of the document has been fixed, only Tables 2–6 are now in landscape orientation.

2/ some pages are suddenly interrupted in the middle of a line with a jump of pages
   We believe that this issue was caused by a problem with the cross-referencing of tables and believe that this has now been fixed.

3/ all the pages are numbered “39”
   We have fixed and updated the page numbering issue.

4/ unsuitable formatting for references: e.g. replacing 5, 6, 7, 8 by 5-8
   We have updated the formatting of the references in line with the reviewer’s request.

-Methods, 1st paragraph: the authors should justify why they have chosen a minimum enrollment of 100 patients for studies to be included, why 100? How many studies have been excluded because of this limit?
A minimum enrollment of 100 patients was chosen to select for relatively large scale studies with the power to detect relatively small differences in outcomes. This minimum size was also selected to exclude small scale pilot studies in highly selective populations exclusively comprised patients with thalassemia or on hemodialysis, for example that would have had an impact on the generalizability of any conclusions. This information has been added to the methods section.
- Figure 1: spelling mistake “moninfection” to be replaced by “monoinfection”
This has been corrected.

-Discussion: the authors should discuss the lack of data on the impact of SVR on the long-term quality of life. We do not know whether these benefits are maintained over the long term. Some “patients” report a feeling of abandonment, up to a depressive state, because no longer monitored regularly as before.
We have added text to the discussion section to address the lack of long-term follow-up in quality of life studies.

Discretionary Revisions:
-Tables: what is the logic of chronology? The studies are not sorted alphabetically or by year of publication, or by country or by type of study ... Authors should order them by country, I think, to facilitate comparison.
We have updated the tables in line with the reviewer’s suggestion to sort firstly by country, and then alphabetically within each country.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I have received research grants from Roche, Janssen and Schering-Plough/Merck, and consultancy honoraria from Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Schering-Plough/Merck and Glaxo Smith Kline


