ANSWERING REVIEWERS

July 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: HCV Treatment Roadmap V9 – ESPS manuscript no 12032).

Title: CHRONIC HEPATITIS C GENOTYPE 1 TREATMENT ROADMAP FOR RESOURCE CONSTRAINED SETTINGS

Author: Seng Gee Lim
Name of Journal: *World Journal of Gastroenterology*
ESPS Manuscript NO: 12032

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

1 The inconsistencies in the text and figures (1B and 2A) have been checked and corrected.

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

(1) In the Introduction (page 4), an additional sentence was added: Resource constrained countries are defined as those countries where the latest therapies sofosbuvir and simeprevir and not currently available nor likely in the near future, and where pegylated interferon and ribavirin (PR) ± boceprevir, are are still the standard of care.

(2) In the results section, subheading "Importance of TW4 HCVRNA as a predictor of SVR" an additional three sentences were added: With regards to predictors of SVR, [14] multivariate analysis showed that the strongest predictor of SVR in Caucasians and Black patients given boceprevir triple therapy was ≥1 log reduction in HCV RNA, even stronger that the IL28B cc genotype. In the largest Asian study of peginterferon and ribavirin, [15], multivariate analysis again showed that week 4 undetectable HCV RNA was a stronger predictor of SVR than IL28B cc genotype. Consequently while IL28B genotype is still an important predictor, it may not be crucial in the decision to start therapy since week 4 HCV RNA is the stronger predictor.

A detailed reply to each reviewer is listed below:

Sincerely yours,

Seng Gee Lim, MBBS, MD, FRCP (London), FRACP, FAMS

Department of Gastroenterology and Hepatology

National University Hospital, 5 Lower Kent Ridge Road

Singapore (119074)

Tel: (65) 67724369; Fax: (65) 67724361

Email: mdclimsg@nus.edu.sg

Reviewer 02943058

The work is very interesting, although don't indicate the importance of the CC/TT IL28B determination clearly, don't forget that many countries to lead its treatments based mainly in the use of the INF/RBV alone, without DAA, and in this cases the knowledge of IL28B genotype is primordial. To revise the figure 1B and 2A, and the text where are cited, some percentages don't matched. To revise some repeated words and with missing letters. I suggest this job for publication, later to make these changes.

Response to reviewer

Thank you for you positive comments. The reviewer has raised an important point with regards to the use of IL28B genotype. Poordad et al, Gastroenterology 2012;143:608–618, showed by multivariate analysis that the strongest predictor of SVR in Caucasians and Black patients given triple therapy was ≥1 log reduction in HCV RNA, even stronger that the IL28B cc genotype. In the largest Asian study of peginterferon and ribavirin, (Liu et al, Antiviral Therapy 2012;17:477-85), multivariate analysis again showed that week 4 undetectable HCV RNA was a stronger predictor of SVR than IL28B cc genotype. Consequently the roadmap was designed with this in mind. However, the role of IL28 cannot be ignored, as this is still an important predictor. There are however, two important considerations. The first is that 70-80% of Asians are carrying IL28B cc genotype hence 8 of 10 persons will be positive for IL28B cc genotype, making this test almost always positive and somewhat redundant. Moreover, regardless of the result of this test, almost always the patient will be offered peginterferon and ribavirin to evaluate week 4 response, making IL28B less useful as a decision tool whether to start therapy or to change therapy. However, to acknowledge this matter, I have added in a paragraph to clarify this matter.

The inconsistencies in the text and figures (1B and 2A) have been checked and corrected.

Reviewer 02943043

Outlining a treatment roadmap for resource constrained settings is a important initiative. However, the lack of a definition for what is considered a "resource constrained" setting is the major flaw of this study. Roadmaps outline treatment algorithms which include the use of regular quantitative HCV RNA measurements and DAAs. Are these available in truly resource constrained settings? A clear definition of what is considered a resource constrained setting and the actual resources available in these locations is required. There is limited data on the use of IFNL3 genotyping prior to therapy in order to guide treatment selection. There is no data on African patients which comprise a large population from "resource constrained" regions. They have poorer treatment outcomes. There is no clear indication on the exclusion / inclusion criteria of RCTs selected for the study or a summary of the actual studies used for the analysis.

Response to reviewer

I thank the reviewer for his valuable comments. The definition of “resource constrained” setting was deliberately left vague but was meant to convey the message that these countries or regions do have have the latest treatment such as third wave DAAs, sofosbuvir and simeprevir or daclatasvir (just approved in Japan). Consequently without the latest therapies, physicians have to rely on the “standard of care” which in many countries is still peginterferon and ribavirin, and in some countries, boceprevir (rarely telaprevir). The manuscript addresses this matter, giving readers the SVR outcome of using pegylated interferon or ribavirin and where available boceprevir triple therapy. Hence is relevant to such countries where the latest therapies are not available. To clarify this point, an additional sentence has been added in the introduction.

With regards to IL28B genotyping, Poordad et al, Gastroenterology 2012;143:608–618, showed by

multivariate analysis that the strongest predictor of SVR in Caucasians and Black patients given triple therapy was ≥1 log reduction in HCV RNA, even stronger that the IL28B cc genotype. In the largest Asian study of peginterferon and ribavirin, (Liu et al, Antiviral Therapy 2012;17:477-85), multivariate analysis again showed that week 4 undetectable HCV RNA was a stronger predictor of SVR that IL28B cc genotype. Consequently the roadmap was designed with this in mind. However, the role of IL28 cannot be ignored, as this is still an important predictor. However, regardless of the result of this test, almost always the patient will be offered peginterferon and ribavirin to evaluate week 4 response, making IL28B less useful as a decision tool whether to start therapy or to change therapy. However, to acknowledge this finding, I have added in a paragraph to clarify this matter.

No African data have been included as there are no African RCTs using peginterferon and ribavirin or boceprevir. However, this ethnic group is well represented in most HCV studies as African-Americans and this has been adequately covered in the current manuscript.

With regards to inclusion criteria for RCTs, almost all systematic reviews of therapy chose RCTs as key inclusion criteria, as I have done in this study. After inclusion, studies are manually viewed to determine if indeed they are true RCTs. If they were not true RCTs – no randomisation, or no randomisation concealment, then this may fall under the category of quasi-randomised study. RCTs in a systematic review also undergo quality weightage and data pooling but since this manuscript is not a systematic review, such measures were not undertaken. The reason why the current manuscript was not performed as a systematic review was because there was more than one "PICO" question being addressed, as the objective of this manuscript is quite different to that of a systematic review. Typically a systematic review only addresses one "PICO" question. In the current manuscript each decision point generated a separate "PICO" question, eg "what is the best treatment if HCV RNA was negative at treatment week 4", followed by "what is the best treatment if HCV RNA was positive at treatment week 4". Hence, a list of selected publications could not be generated, but a list is referenced for each of the "PICO" questions as described in the manuscript.

Reviewer 02937519

Dr. Lim SG described the road map for antiviral therapy to HCV genotype 1 patients. This study is review article. As the author pointed out, direct acting antivirals (DAAs) present substantial advance in efficacy with better tolerability, though they are very expensive. Although telaprevir and boceprevir are not already recommended in AASLD and this study does not have new information, the road map is required in a poor country. 1. As the treatment period tended to be longer in treatment without DAAs than with DAAs, there were patients who discontinued the treatment. In addition, the frequency of adverse events in treatment with telaprevir and boceprevir were very high. Therefore, the author should describe about the adverse events and adherence. 2. For new generation of DAAs, the devices which do not make tolerance variation in HCV are required. I think the author has to comment about tolerance variation in HCV. 3. The 4-week PR read-in was very important for the road map. It is a demerit that a treatment period becomes four weeks long. How does the author consider this demerit?

Response to reviewer

I would like to thank the reviewer for his valuable comments.

Reply to comment 1

With regards to adverse events and tolerance, I fully agree with the reviewer that this was not discussed in the manuscript. The reason is that the review offers guidance/roadmap with regards to efficacy only and

inclusion of adverse events and non-compliance would add significant complexity to the roadmap. Clearly, adverse events that are not tolerable lead to treatment interruption, and this as well as non-compliance lead to poor response at week 4, 8 or 12. These are factored into the roadmap as such poor responses ultimately result in treatment failure or lower SVR rates. A full discussion of adverse events and non-compliance would be beyond the objectives of the manuscript and indeed would be a paper in itself. Such reviews have been adequetely covered by others.

Reply to comment 2

A discussion about factors that affect tolerability to therapy in the new generation of DAAs is important but not the primary objective of the manuscript. It is generally accepted that older age and more advanced cirrhosis makes tolerability lower, however, on a patient by patient basis it is almost impossible to predict as some older patients have virtually no adverse events while some younger ones have poor tolerability. As discussed in the previous section, poor tolerability regardless of the cause leads to treatment interruption or non-compliance thus resulting in poor responses at week 4, 8 or 12 and thus lower SVR rates.

Reply to comment 3

I believe the reviewer is referring to the duration of lead-in and whether a longer lead-in would affect the results. Unfortunately there is no data on this subject, whether a longer lead-in would be more beneficial. My personal belief is that regardless of the duration of lead-in the HCV RNA at the end of the lead in period is probably more important, but I do not have any data to support this contention.