OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://brief.land/briefland/knowledgebase/category/tree.html#opr.html

Hepatitis Monthly
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Peer Review Report for "Telbivudine Plus Adefovir Versus Lamivudine Plus Adefovir for Lamivudine-Resistant Chronic Hepatitis B: TeSLA Randomized Trial"

Author(s): TaeHyung Kim, Minkoo Kim, Hyung Joon Yim, Sang Jun Suh, Young Kul Jung, Yeon Seok Seo, Soon Ho Um, Jung Il Lee, Sae Hwan Lee, Sang Gyun Kim, In Hee Kim, Hyoung Su Kim, Eun Young Cho, Tae Yeob Kim, Seong Gyu Hwang

Review Timeline:

Submit Date: 4 Dec 2021
Revised Date: 9 Jan 2022
Accepted Date: 10 Jan 2022

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) 15 Dec 2021

Dear AE,

This study reported a prospective multi-center study for comparison of drug combination for the specific situation, lamivudine-resistant chronic hepatitis B. Although the authors conducted interesting prospective study for a long time, I think there are several concerns to accept at this time.

Major

1. Most critical weakness of this study is that the authors investigated old drug. Most countries are available more potent drugs such as ETF, TDF, and recently TAF. Please more describe this limitation in the discussion session.

2. Summarizing safety result is required as table.

Minor
1. Please check typos. (line 49 ant etc.)
2. In line 201, is it correct “serum phosphorus > 2.4” not <2.4 ? Please indicate baseline phosphorous level in table 1.

Thanks

REFEREE: Reviewer | **Revision** (0) 26 Dec 2021

Dear associate editor of Hepatitis Monthly
I would like to thank you to provide me this opportunity for reviewing this manuscript entitled “Telbivudine Plus Adefovir Versus Lamivudine Plus Adefovir for
Lamivudine-Resistant Chronic Hepatitis B: TeSLA Randomized Trial” which has been submitted to the Hepatitis Monthly journal.
Summary of the project (named as TeSLA Randomized Trial)
In this prospective open-label pilot randomized multicenter study (ClinicalTrials.gov Identifier: NCT01804387), lamivudine-resistant
chronic hepatitis B (CHB) patients (n=43) were treated with lamivudine (LMV) and adefovir (ADV) [n=21] or telbivudine (L-dT) and ADV [n=22]. No significant intergroup differences have been reported regarding HBV DNA reduction after 52 weeks of antiviral treatment. None of the other secondary outcomes (HBV DNA
undetectability rates, mean HBV DNA level, or hepatitis B e antigen seroconversion rate at 13, 26, 39, and 52 weeks of treatment) have significant differences between study groups. Regarding safety concerns, mean level of CPK has been reported higher in the L-dT+ADV group compared to the LMV+ADV group.

My comments:
Regarding the methodology of this clinical trial, I checked all the related and necessary materials and they have been reported correctly. They are registration of this clinical trial, reporting exact criteria for inclusion and exclusion of patients, written informed consents, reporting funding sources, declaration of conflict of interest, method of randomization, Study flow diagram, defining outcomes, and statistical analysis. Also, I checked some of the analyses in the results section and found no problem.
In my opinion, the project can be accepted for publication in the Hepatitis Monthly Journal.
Best
Reviewer

REFEREE: Reviewer | **Revision** (0) 2 Jan 2022

Dear editor

This is a good study addressing one of the main concerns in countries where Tenofovir disoproxil fumarate is unavailable. Besides that current study improves our understanding of the effects of different regimens in patients suffering Lamivudine-resistant chronic hepatitis B.

According to CONSORT guideline for RCT reporting:
1. Title and abstract:
No comments to add

2. Introduction:
No comments to add

3. Methods:
Sample size: As the authors mentioned, the main weakness of the study was the limited and low sample size of the study, which is due to the nature of the pilot studies is applicable. However, according to protocol registration on clinicaltrials.gov (NCT01804387), the sample size was defined to be 60 participants. As stated by CONSORT FLOW DIAGRAM (figure 1), 59 patients were screened to enter the study, and finally, 43 patients participated. It was preferred to continue screening to reach the total number of participants to 60. I advise the authors to explain the sample size calculation and determination in the methods section.
Study termination: Authors did not mention the study termination conditions and criteria.

4. Results:
I advise the authors to explain the safety concerns and complications of both regimens.

5. Discussion:
No comments to add

Overall:
The article is well written and the design of the study is good. The results are adequately presented and the interpretation of results is applicable. The cited references are appropriate to study and up to date.

Decision:
Accept.

REFEREE: Associate Editor | **Revision** (0) 2 Jan 2022

Dear Editor in Chief
Thanks for assigning me as associate editor to handle the manuscript NO.121627 entitled "Telbivudine Plus Adefovir Versus Lamivudine Plus Adefovir for Lamivudine-Resistant Chronic Hepatitis B: TeSLA Randomized Trial".
I appreciate the authors' work to collect these data and to write its manuscript. Although the subject is not novel, the data are reportable. Also, the manuscript is well-written and could be published after a minor revision.
See the peer-review comments for further information.

Regards
Associate editor

Seyed Moayed Alavian: EIC | **Revision** (**0**) 3 Jan 2022

Dear Authors,

Thank you for your submission. Please follow the peer-review comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

January 7, 2022

Dear Editors

Thank you for helpful comments on the manuscript titled “Telbivudine Plus Adefovir Versus Lamivudine Plus Adefovir for Lamivudine-Resistant Chronic Hepatitis B: TeSLA Randomized Trial” (Hepat Mon, manuscript ID: 121627).
We appreciate the opportunity provided to us to revise and improve our manuscript and to resubmit it to the journal. We have carefully revised the manuscript after considering the reviewers’ comments. We have also provided a point-by-point response with a specific list of changes and hope that our revised manuscript is now acceptable for publication.

Sincerely yours,

Point-by-point response to the reviewers’ comments

Reviewer 2

Major

1. Most critical weakness of this study is that the authors investigated old drug. Most countries are available more potent drugs such as ETF, TDF, and recently TAF. Please more describe this limitation in the discussion session.

- We agree with your comment and added the sentences.

  "The recommend antiviral agents, which had great efficacy and high genetic barrier such as ETV, TDF and tenofovir alafenamide, were widely available in most countries. This is another major limitation of the present study. However, LMV, ADV and L-dT has been still produced and prescribed to some patients with CHB."

2. Summarizing safety result is required as table.

- We agree with your comment and added Table 4.

Table 4. Changes in creatinine and creatine phosphokinase levels after 52 weeks of treatment.

	LMV+ADV	L-dT+ADV	P value
Change in Cr, mg/dL	0.013 ± 0.100	-0.006 ± 0.100	.55
Change in CPK, mg/dL	1.00 ± 38.69	119.39 ± 207.90	.03

Minor

1. Please check typos. (line 49 ant etc.)

- Thank you for pointing out my mistake. You mean

  "HBV DNA levels of LMV-
  resistant mutant viruses"

  We corrected as follows:

  "HBV DNA levels of LMV-resistant mutant viruses,"

2. In line 201, is it correct "serum phosphorus > 2.4" not <2.4 ? Please indicate baseline phosphorous level in table 1.

- You are right, and we corrected to "serum phosphorus < 2.4".
- In addition, we added baseline phosphorus level in Table 1.

Phosphorus (mg/dL)	3.37 ± 0.31	3.31 ± 0.32	3.42 ± 0.30	.24

We appreciate your valuable comments.

Reviewer 3

3. Methods:

Sample size: As the authors mentioned, the main weakness of the study was the limited and low sample size of the study, which is due to the nature of the pilot studies is applicable. However, according to protocol registration on clinicaltrials.gov (NCT01804387), the sample size was defined to be 60 participants. As stated by CONSORT FLOW DIAGRAM (figure 1), 59 patients were screened to enter the study, and finally, 43 patients participated. It was preferred to continue screening to reach the total number of participants to 60. I advise the authors to explain the sample size calculation and determination in the methods section.

- Thank you for the good comment. We agree with your opinion. Initially, we presented to Clinicaltirals.gov with 60 people considering the dropout rate of 30%, but as this study progressed, there was few dropout, so the registration was closed with 43 subjects.
- We added sentences in the supplementary material as follows:

  “The virological responses found through literature review were approximately 33% for LMV+ADV in LMV resistant and 75% for L-dT in treatment naïve chronic hepatitis B patients, respectively (1, 2). We presumed the virologic response rate of 75% for L-dT+ADV in LMV resistant patients as there was no previous data.

  We calculated the sample size using PASS 2008, setting alpha-error to 0.05 and power to 0.8, so that obtained 21 subjects to each group. Considering the dropout rate of 30%, 30 subjects were assigned to each group, and a total of 60 subjects were suggested to enroll. However, as the study progressed, there was few dropout, so the enrollment was closed with 43 subjects.”

4. Results:

I advise the authors to explain the safety concerns and complications of both regimens.

- Thank you for the good comment. We agree with you, and added sentences in the results section.

  “ADV combination therapy can cause renal injury and hypophosphatemia. In addition, LMV and L-dT can induce muscle injury and increase creatine phosphokinase.”

Thanks again for the expert review and constructive comments.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 9 Jan 2022

Dear Editor in Chief
Thanks for assigning me as associate editor to handle the revised version of manuscript NO.121627 entitled "Telbivudine Plus Adefovir Versus Lamivudine Plus Adefovir for Lamivudine-Resistant Chronic Hepatitis B: TeSLA Randomized Trial".
I appreciate the authors' work to revise their manuscript. This version of manuscript is suitable for being published in Hepatitis Monthly journal.
Regards
Associate Editor

REFEREE: EIC | **Revision** (1) 10 Jan 2022

Dear Authors,

I am delighted to inform you that your manuscript is accepted for publication in Hepatitis Monthly journal.

Regards
EIC