

Format for ANSWERING REVIEWERS

October 27, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13536-review.doc).

Title: Lamivudine Resistance in Children with Chronic Hepatitis B

Author: Erhun Kasirga

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13536

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

1 Format has been updated according to the minireview.

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

(1) **Reviewed by 02447059**

1. The author should present a table listing the previous studies, type of treatment, duration of treatment, outcome whether seroconversion, relapse or breakthrough. This would be more informative to the reader than citing within the text.

A table listing the previous studies has been added to the article.

2. Introduction, page 1, line 6; the author mentioned that age allowance for IFN-alpha is children over 12 years. The author needs to revise such information.

It has been emphasized that "Interferon-alpha can be used in children older than 12 months of age, lamivudine starting at 3 years of age, adefovir and tenofovir in children aged 12 years and older, and entecavir starting from 16 years of age."

3. The author needs to analyze the factors that were associated with relapse or breakthrough in the previous study in order to offer an insight for future treatment decision, schedule and duration.

The factors that were associated with relapse or breakthrough in the previous studies in order to offer an insight for future treatment decision, schedule and duration were analyzed thoroughly.

4. Page, 2 line 22; is it compared with IFN or combined with IFN?

The objectives of this study are defined as assess and compare the long-term therapeutic response to lamivudine compared with interferon-alpha in children with chronic hepatitis B.

5. The author need to search clinical trials with recent antiviral drugs in children, especially those reporting the interim results. I would suggest "Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents with Chronic Hepatitis B" NCT00095121; and "Open Label Study of Pharmacokinetics and Safety of Dose of Adefovir Dipivoxil in Children and Adolescents With HBV" NCT00645294.

Two new studies which conducted with recent antiviral drugs were added to the review.

1. Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, Mondou E, Rousseau F, Sokal E. Safety, efficacy, and pharmacokinetics of adefovirdipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. *Hepatology* 2008; 47(6): 1863-1871. DOI: 10.1002/hep.22250.

2. Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, Mondou E, Rousseau F, Sokal E. Efficacy and safety of long-term adefovirdipivoxil therapy in children with chronic hepatitis B infection. *Pediatr Infect Dis J* 2012; 31(6): 578-582. DOI: 10.1097/INF.0b013e318255ffe7.

6. Page 3, Chan et al and Marrone et al, represented contrary results, the author need to analyze the possible causes of such conflicting results.

Possible causes of these conflicting results were analyzed in review.

7. The majority of references before year 2010 (12/38 references older than year 2004 and 17/38 references dated between year 2005-2009) only 9/38 references are 2010 and after. The review needs to be updated.

Twelve new references were added to the manuscript. The current distribution of references according to the years; 11/50 older than year 2004, 20/50 between year 2005-2009, 19/50 year 2010 and after. The review has been updated.

8. Minor concerns

1. The article format does not confers with the journal specifications

2. The manuscript need to be revised for proper English language and grammar.

The format of article has been optimized according to the journal specifications.

The manuscript has been revised thoroughly for proper English language and grammar.

(2)Reviewed by 00012513

The review of Erhun Kasirga is a topic of great interest, and shortly addressed, which is the antiviral treatment with lamivudine in children. The documentation is correct; however the review is basically a list of previous results that should be integrated in a final section that will summarize the data provided to facilitate their practical usefulness to readers.

This review should be useful to answer questions like.

If a child patient treatment with lamivudine what is the chance to fail the treatment and what must be the monitoring regimen that I should apply? What are the analytical and clinical parameters I should be determined for this track? If I observe a failure of treatment what can I do?

Responses or helps to solve all these questions are not easy to be find the current form of writing of this review. So I recommend a major revision.

In terms of response and resistance to LAM treatment, mildly elevated transaminase level is one of the most important parameters. Antiviral agents, other than lamivudine, have been used but to a limited extent in pediatric subjects. In the assessment of response to treatment of lamivudine, HBV-DNA and transaminase levels are important. If treatment with lamivudine is failed, addition of adefovir or switching to adefovir or entecavir therapies may be considered in older children. These issues were discussed in detail in the manuscript.

Other points to be resolved are:

1-What is the clinical significance of the minor presence of lamivudine resistance mutations before treatment?

The clinical significance of pre-existing YMDD mutants has been emphasized in the text. One new literature has been added to this section.

Lee SH, Kim HS, Byun IS, Jeong SW, Kim SG, Jang JY, Kim YS, Kim BS. Pre-existing YMDD mutants in treatment-naïve patients with chronic hepatitis B are not selected during lamivudine therapy. *J Med Virol* 2012; 84(2): 217-22. DOI: 10.1002/jmv.23191.

2-Develop more the section focused on vaccine escape mutations associated to lamivudine (page 5).

The section focused on vaccine escape mutations associated to lamivudine was developed. Two new literatures have been added to this section.

Yeh CT. Development of HBV S gene mutants in chronic hepatitis B patients receiving

nucleotide/nucleoside analogue therapy. Antivir Ther 2010; 15(3 Pt B): 471-475. DOI: 10.3851/IMP1552.

Sheldon J, Soriano V. Hepatitis B virus escape mutants induced by antiviral therapy. J Antimicrob Chemother 2008; 61(4): 766-8. DOI: 10.1093/jac/dkn014.

3 Add a summary table of the provided studies, including rates of resistance and virologic response

A summary table of the provided studies has been added to the manuscript (Table 1).

3 References and typesetting were corrected.

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'E. Kasirga', enclosed within a hand-drawn oval shape.

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