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Dear Prof. Ma,

Please consider for publication in World Journal of Gastroenterology our review article entitled **“Antiviral therapy for chronic hepatitis B: combination of nucleoside analogs and interferon”** by Nishida et al. This is an invited review, for which I got an invitation on Nov. 21, 2014 with **number ID: 19579**. We would like to bring to your notice that we have changed the title from **“Antiviral therapy for chronic hepatitis B: How to combine nucleic acid analogs and interferon for a cure?”** to **“Antiviral therapy for chronic hepatitis B: combination of nucleoside analogs and interferon”**.

The goal of chronic hepatitis B treatment has advanced from HBV-DNA negativity and ALT stabilization to HBs antigen (HBsAg) negativity. Various combination therapies with nucleoside analogs and IFN formulations have been reported. Their therapeutic effects are enhanced using agents with different pharmaceutical properties, although the outcomes are not necessarily

satisfactory. Combination therapies with IFN and nucleoside analogs and so-called sequential therapies with nucleoside analog administration followed by IFN therapy have been routinely employed. Combination therapy with ETV and PEG-IFN showed antiviral effects in 71% of patients, a more satisfactory result than that of combination therapy with lamivudine. This is partially explained by the use of entecavir with more potent antiviral effects than lamivudine. In addition, only patients who developed ALT flare-up on intervention were registered, and HBsAg levels before the treatment were relatively low. Thus, the appropriate selection of patients, as well as therapy, is critical.

We think this review article could be informative for understanding the combination of nucleoside analogs and interferon in HBV treatment.

We would like to thank all the reviewers for their comments and would like to confirm **that we have addressed all these comments below, and introduced revisions in the manuscript accordingly.** We have also included the following documents in our submission:

- 1 19579-Revised manuscript
- 2 19579-Answering reviewers
- 3 19579-Copyright assignment
- 4 19579-Audio core tip
- 5 19579-Conflict-of-interest statement
- 6 19579-Google Scholar
- 7 19579-CrossCheck
- 8 19579-Language certificate.

We hope that now our manuscript will be acceptable. We look forward to hearing further on the review process and acceptability of our manuscript in World Journal of Gastroenterology.

Sincerely,

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Response to the Editors and Reviewers comments:

Antiviral therapy for chronic hepatitis B: combination of nucleoside analogs and interferon.

We appreciate reviewers' interest in our work, and the helpful suggestions, criticisms and thoughts. Each reviewer also raised specific concerns. We learned each comment carefully, and hereby address all these concerns as below.

1. **Reviewer's comment (00504882):**

Lamivudine (LAM) adefovir (ADV) and entecavir (ETV) are not nucleic acid analogs.

These are nucleoside analogs. This should be corrected in the manuscript. These

nucleoside analogs are activated upon phosphorylation to nucleoside triphosphate in

the liver cells.

Response:

As you suggested, they were revised to nucleoside analogs.

2. **Reviewer's comment (02941955):**

Hagiwara S, et al. described the efficacy of combination therapy of IFN and nucleic acids analogues. The description was based on their previous publication. Although they summarize the recent data on this issue carefully, the manuscript has a fundamental lack of knowledge that may deepen the understanding of pathogenesis of CHB. The content is superficial. The authors should concern more deeply, in the aspect of such as immunology and virology to be accepted in the review criteria.

Response:

A paragraph was inserted in the text to describe the immune response and therapeutic effects in detail.

3. **Reviewer's comment (02941955):**

The authors provide a concise review on combination therapy with nucleoside analogues and IFN-alpha. This subject is topical due to currently increasing interests in re-investigating combination therapy with IFN-alpha with new potent nucleoside analogues. The authors provide an overview and cite multiple studies for reference. I do have a few minor comments. Also, I did not check the numbers from each trial but I did check numbers for reference 19, Brouwer et.al. because I found it surprising there was 32% HBsAg negative after treatment. I could not find these numbers in the

manuscript. Please clarify the paragraph (comment below) and I kindly request that you confirm any statistics/numbers included in the review.

Query 1:

In the first paragraph of the introduction the authors state that “interferon (IFN) induces cytotoxic T lymphocytes...” This may be the case for acute viral infections but there is substantial evidence that IFN-alpha therapy does not enhance the virus-specific T cell response in chronic HBV patients. a. References: i. Micco L, J Hepatol. 2013 Feb;58(2):225–33. ii. Penna A., J Hepatol. Elsevier; 2012;56(6):1239–46. iii. Tan AT, J Hepatol. 2013 Aug;60:54–61.

Response:

CTL was revised to NK cells.

A paragraph was inserted in the text to describe the immune response and therapeutic effects in detail.

Query 2:

The manuscript by Tan et al (J Hepatol. 2013 Aug;60:54–61) also demonstrated that nuc therapy improved immune responsiveness to subsequent IFNalpha doses. Thus, suppressing viral replication may enhance the IFN-alpha effect. It would be worthwhile including is information.

Response:

A paragraph was inserted in the text to specify the immune response and therapeutic effects.

Query 3

Page 4, second paragraph. "Of 11 HBeAg-positive cases, four (36%) and eight (73%) showed HBeAg seroconversion" The numbers don't add up. $4+8=12$

Response:

The numbers are correct.

Query 4

Page 4, last paragraph needs clarification. "HBsAg negative (18 vs. 32%, respectively, $p=0.032$) and HBeAg seroconversion (11 vs. 26%, respectively, $p=0.012$) rates" In the parentheses, the numbers are respective to what? Also, this confirm data. I did not find any evidence of 32% HBsAg negative patients in the paper and the numbers don't match for HBeAg loss.:

Response:

This was revised to HBeAg loss with HBV DNA <200 IU/mL.

4. **Reviewer's comment (02861124):**

The mini-review entitled, "Antiviral therapy for chronic hepatitis B: How to combine nucleic acid analogs and interferon for a cure?" by Hagiwara et al. presents a very informative update on combinatorial chemotherapy in chronic hepatitis B cases. The

manuscript is well conceived, structured and properly written. However, there are few language and grammatical errors that need to be corrected. I have highlighted my suggested corrections/modifications in the text (track change).

Query 1:

P4/L9- Since viral genotype is discussed here, it is better to introduce all genotypes and there antiviral responses in the “introduction” section.

Response:

I specified it in Introduction.

Query 2:

P5/L15- It would be better to define “HBeAg negative” cases and the viral pre-Core mutations associated with this.

Response:

The article that I quoted did not have mention about pre-Core mutations.

Query 3:

Inclusion of a summarized flow-chart on combination/sequential therapy in HBsAg-positive and negative patients would be very valuable for readers.

Response:

I am sorry, but I do not analyze it about having HBs antigen or not.