Dec 31, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7789-review.doc)

Title: An update on the hepatitis B virus infection

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Name of Journal: World Journal of Gastroenterology

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The manuscript has been improved according to the suggestions of reviewers:
Revision has been made according to the suggestions of the reviewer.

1.Please provide page and line numbers. This will greatly facilitate reviewing the manuscript.

Answer) We provided page and line numbers in this revision throughout the manuscript.

2.Abstract: These sentence are not clear: - "However, it is difficult to initiate comprehensive therapy for multi-drug resistance to NA because it lacks strong evidence to prove such issues." - "…because the initially its wrong treatment choice may induce long-term treatment failure."

Answer) Following comments provided by the reviewer, we clarified and revised the two sentences in the abstract as follows: "However, treatment of patients with drug resistance is still challenging, because only a few classes of anti-HBV drugs are available and cross-resistance between the drugs occurs." on page 2; "it is essential to choose a potent antiviral drug with a low risk of resistance for initial treatment of CHB to achieve sustained virological response." on page 2-3.

3.Introduction: "nucleos(t)ide analogues" I think that the non-expert reader would find help if the text reports which drugs are nucleoside or nucleotide analogues.

Answer) We clarified and categorized the NAs into nucleoside and nucleotide. The revised sentence is provided on page 5: "~ oral nucleos(t)ide analogues (NAs) such as nucleoside analogues including lamivudine (LAM), telbivudine (LdT), clevudine and entecavir (ETV) and nucleotide analogues including adefovir dipivoxil (ADV) and tenofovir dipivoxil fumarate (TDF)."

4."The main difference between immunomodulatory agents and NAs is that PEG-IFN has the advantage of a finite duration of use whereas the use of NA inhibitors is indefinite. The major drawback of PEG-IFN is its high frequency of adverse events. Long term NA use, on the other hand, poses the risk of drug resistance. They are, however, safe, effective and easily administered orally." The Authors should report also that the number of patients having a virological response after an IFN cycle of theraphy is lower compared with patients reaching

a viral replication suppression with new NAs. However IFN therapy has higher rates of HBe seroconversion and HBsAg loss than NAs.
In order to achieve more curative antiviral effects, new therapeutic approaches, such as combination therapies using an antiviral and an immunomodulating agent or multiple antiviral agents used together, have been tried to address this problem, but evidence demonstrating that combination therapy is superior to monotherapy still is lacking [8,9].

Answer) As per the reviewer's request, we rearranged and added some sentences on page 5. We added the sentence "the number of patients having a virological response after an IFN cycle of therapy is lower compared with patients reaching a viral replication suppression with new NAs." on page 5. We would think, however, within the contents of description, the sentence "In order to achieve more curative antiviral effects, new therapeutic approaches, such as combination therapies using an antiviral and an immunomodulating agent or multiple antiviral agents used together, have been tried to address this problem, but evidence demonstrating that combination therapy is superior to monotherapy still is lacking [8,9]." would better placed following the sentence "LAM, the first approved .. LAM therapy [6,7]". Accordingly, it was not moved and placed as it was on page 6.

5. The development of new antiviral agent or optimized therapeutic approaches that can achieve long-term control of viral replication with fewer adverse effects is therefore necessary. New NAs with very low/absent resistance profile are already available. Could the development of drugs eradicating the virus, not only suppressing its replication, be another target? Please comment.

Answer) We appreciate the reviewer's constructive comment. The sentence appears to be unintentionally confusing. Therefore, we would like to make a revision to the sentence within a context. The following revision " In the long run, the development .. on the management of CHB." is added on page 6.

6. Results/discussion: What do the authors mean for "DC"? Please provide the word in extenso

Answer) We changed "DC" into the full description "dendritic cell" throughout the manuscript.

7. The chapter on immunopathogenesis is very detailed and a resuming figure may help the reader (see below).

Answer) We added the Figure summarizing immunopathogenesis by HBV.

8. Page 7, Pegylated Interferon: "low degree of compliance due to injection-related problems". Please could the Authors go more in detail and provide reference.

Answer) We provided the detailed information on the sentence (on page 12) with the following reference: Lau GK, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352**: 2682-2695.

9. The Authors should distinct the treatment with IFN or NAs in patients with HBeAg + or ? and providing indications on duration/stopping rules.

Answer) As the reviewer requested, we inserted the following sentence that summarizes the distinct duration and stopping rules between PEG-IFN and NAs on page 5: "Treatment strategies with (PEG-)IFN or a NA are intended to achieve a sustained off-treatment virological response. A 48-week course of PEG-IFN is mostly recommended for HBeAg-positive CHB patients with the best chance of HBeAg seroconversion. It can also be opted for HBeAg-negative CHB patients. Unlikely NAs, PEG-IFN potentially offers a chance of sustained off-treatment response after a finite duration of therapy in HBeAg-negative patients. For HBeAg-positive CHB patients, NA therapy can be stopped after additional 12 months following HBeAg seroconversion, whereas the long-term use of NA is needed due to high rate of off-therapy relapse for HBeAg-negative patients, in whom the ideal end point is HBsAg loss.".

10. Page 14, third line: "There are several factors…" change to "There are three"

Answer) As per the reviewer indicated, we changed "There are several factors…" to "There are three" on page 18.

11. Conclusions: Page 19: "However, the emergence of HBV mutants strains leads to long-term treatment failure."The risk is very low/absent with ETV and TDV. Please comment.

Answer) We would like to insert the sentence "The risk is very low or absent with ETV and TDV." following "However, the emergence of HBV mutants strains can lead to long-term treatment failure." on page 24.

12. Last page: This sentence is not clear: "…the initially its wrong treatment choice…"

Answer) In line with the above response to the comment, we revised the sentence on page 25: " ~ it is essential to choose a potent antiviral drug with a low risk of resistance for initial treatment of CHB to achieve sustained virological response".

13. Last page: "Furthermore, for patients with HBV mutant strains, combination therapy of NA with high genetic barrier might be more effective than sequential therapy of NA with low genetic barrier." According to previous statements is better to say "…is more effective.."

Answer) We changed the statement as the reviewer mentioned on page 25 (making a revision to the wording into "...is more effective..".

14. References: Please provide references here: Immunopathogenesis chapter page 3 “Type 1 IFNs produced by infected cells also play an important role in the inhibition of viral replication early on but does not provide long-term protective immunity against viruses”;

Answer) We added the reference.

15. Page 5 “The other factors influencing HBV-specific tolerance include immunoregulatory effects of CD4+ CD25+ Foxp3+regulatory T cells (Tregs) and the dysfunction of DC.” I would suggest to cite this study: Pol S, Lampertico P. First-line treatment of chronic hepatitis B with entecavir or tenofovir in 'real-life' settings: from clini~

Answer) In this revision, we cited the study that the reviewer mentioned

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

Sincerely yours,

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