

Format for ANSWERING REVIEWERS



January 3, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13661-review.doc).

Title: Current and future antiviral drug therapies of hepatitis B chronic infection

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Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO:13661

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

Response to Reviewer # 2861217,

Q1. Nevertheless, there are some mechanical mistakes in the text (mentioned with red) and so conceptual inaccuracies: ?

A1. Thank you for spotting these inaccuracies. I have corrected them and marked them in red.

Q2. Natural history of CHB infection. You mentioned that it consists four distinct phases: immune-tolerant, immune clearance, inactive residual and re-activation. It is preferable to take as the reliable source as EASL or APASL guideless. According to EASL the natural history of chronic HBV infection can be schematically divided into five phases (1) "immune tolerant phase", (2) "immune reactive HBeAg-positive phase", (3) "inactive HBV carrier state", (4) "HBeAg-negative CHB", (5) "HBsAg-negative phase", which are not necessarily sequential. In APASL the natural course of chronic HBV infection can be divided into (1) "immune tolerant phase", (2) "immune clearance phase", and (3) "residual or inactive phase". ?

A2. I corrected the phases of the natural course of chronic infection according to the guidelines of EASL. I also shortened this part of the review.

Q3. Eradication of the virus – complete eradication rarely occurs. Over time basic research has shown that even in patients positive for anti-HBs and anti-HBe, HBV DNA may persist lifelong in form of cccDNA (Hepatology – a clinical textbook. Mauss, Berg, Rockstoh, Sarrazin, Wedemeyer – 2014. – p. 40). ?

A3. I edited the concept of eradication of the virus after consulting the textbook of Hepatology.

Q4. NAs – It is not correct described only Entecavir as guanosine nucleoside analog. It is ought to be noticed all other NAs as a synthetic analogs of different nucleoside (f.e. telbivudine is a thymidine analog etc.). Besides, better to put entecavir before tenofovir and after telbivudine. ?

A4. I added the type of analogues to the other NAs and put entecavir before tenofovir.

Q5. Interferon-based therapy – later in future therapies strategies noticed Interferon cccDNA affecting mechanisms, but this information missed in paragraph "Interferon-based therapy". ?

A5. I mentioned the epigenetic manipulation of cccDNA by IFN- α in the Interferon-based therapy.
Q6. Current Antiviral Therapy – more correct title current antiviral drugs, because there is not any information about duration and monitoring of therapy, just a description of medications.
A6. Thank you for your suggestion, I agree and changed the title accordingly.
Finally I apologize for the spelling errors, and corrected the text as suggested.

Response to Reviewer # 92173

Q1. There are some minor typing errors throughout the text. Please correct.
A1. I apologize for the spelling errors, and corrected the text.
Q2. Introduction section, 2nd para. The citation for the HBV minichromosome is not correct (Bock et al Virus Genes 1994; 8:215-229; Newbold et al J Virol. 1995; 69:3350-3357; Bock et al J Mol Biol 2001; 307:183-196.
A2. I corrected the citation, thank you.
Q3. The chapter “natural history of CHB” is mainly textbook knowledge and can be shortened accordingly.
A3. I shortened this chapter accordingly.
Q4. Also the presented data in the chapter “natural history of CHB” should be updated according current guidelines of CHB (e.g. EASL guidelines)
A4. I updated the phases of the natural course of chronic infection according to the EASL guidelines.
Q5. Furthermore, after presenting such a comprehensive review the author may provide a schematic table summarizing in brief the presented therapeutic drug regimens. This would enhance the paper.
A5. I have added a table summarizing the potential therapeutic agents for the future treatment of HBV and their mechanism of action.

Response to Reviewer # 158184

Q. The manuscript needs to be shortened.
A. I reduced the manuscript by removing the characteristics of the stages of the natural course of the chronic infection.

Response to Reviewer # 1801241

Q. I think that you have performed a great review.

Response to Reviewer # 2861195

Q1. The manuscript needs considerable English language revision; at some points meaning is compromised. Some examples include: the use of the word “finitive”, the phrase “Both antiviral treatments are not capable to eliminate the virus and to efficiently control the infection”, “IFN therapy is of finitive duration and associates with low response rates...”, amongst others.
A2. I sincerely apologize for the spelling and grammar errors. I have corrected these in the text. The manuscript has been reviewed by a colleague and revised to improve readability.
Q2. The abstract warrants thorough revision, whereas the Core Tip is adequate.
A2. I revised and rewrote the abstract. The abstract has also been reviewed by a colleague.
Q3. The review is very extensive and the sections which, in my opinion, warrant further analysis and mention are actually those less developed within the text, including the new antiviral therapies.
A3. I reduced some sections and I am happy to perform a more in depth analysis of the new antiviral therapies if the reviewer insists.
Q4. The section on “Natural history of chronic HBV infection” does not mention the case of new onset

infection during adulthood, which is, unlike Asian countries where most infections are acquired during childhood, the case in the “Western world”. The definition of “occult hepatitis B infection” is not adequately explained.

A4. I removed this part of the review because it is not being further discussed in the development of future therapeutic regimens.

Q5. The manuscript could be enriched with several tables and/or figures which summarize the information given and are more attractive to readers.

A5. I have added a table summarizing the potential therapeutic agents for the future treatment of HBV and their mechanism of action.

Response to Reviewer # 2441405

Q1. This is a well written and comprehensive review. To understand the topics better, I will suggest author to add a few summery tables or diagrams illustrating HBV structures, drug targets, and mechanisms of therapeutic effect. For example, a cartoon for cccDNA of HBV will easily give readers a better idea about this structure and how the anti-cccDNA drug works. There is a similar review article published last year by Simon P. Fletcher, William E. Delaney IV (New Therapeutic Targets and Drugs for the Treatment of Chronic Hepatitis B. Semin Liver Dis 2013; 33(02): 130-137). To make this review unique, author may need add more updated information, such as new research on the drug discovery.

A1. Thank you for your suggestion I have added a table summarizing potential drugs in the treatment of chronic infection. Unfortunately, I do not have access to the review paper suggested, but if the reviewer insists I can send a request to the author to send it.

Yours sincerely,



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