

Format for ANSWERING REVIEWERS



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13385-edited.doc).

Title: Long-term antiviral efficacy of entecavir and liver histology improvement in Chinese patients with hepatitis B virus-related cirrhosis

Author: Yan Xu, Yonggui Zhang, Shaoyou Qin, Xu Wang, Wenqian Qi, Zhenhua Liu, Jian Jiao, Jiangbin Wang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13385

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

1 Format has been updated according to suggestions from the reviewers and editor, and the detailed revisions have been updated in the revised manuscript. Thanks!

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

- (1) Please provide language certificate letter by professional English language editing companies (Classification of manuscript language quality evaluation is B). For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies mentioned in 'The Revision Policies of BPG for Article'.

Reply: According to your suggestion, the manuscript has been completely checked and edited by a professional English language editing company ([the certificate of English editing has been presented here](#)). The detailed revisions have been highlighted in the revised manuscript. Thanks!

CERTIFICATE OF ENGLISH EDITING

This document certifies that the paper listed below has been edited to ensure that the language is clear and free of errors. The edit was performed by professional editors at Editage, a division of Cactus Communications. The intent of the author's message was not altered in any way during the editing process. The quality of the edit has been guaranteed, with the assumption that our suggested changes have been accepted and have not been further altered without the knowledge of our editors.

TITLE OF THE PAPER

Long-term antiviral efficacy of entecavir and liver histology improvement in Chinese patients with hepatitis B virus-related cirrhosis

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- (2) Please provide the author contributions. Authors must indicate their specific contributions to the published work. This information will be published as a footnote to the paper. See the format in the attachment file-revision policies. The format of this section should be like this: Author contributions: XXX (family name should be put first in full, followed by middle names and first name in abbreviation with first letter in capital) designed research; XXX performed research; XXX contributed new reagents or analytic tools; XXX analyzed data; XXX wrote the paper. An author may list more than one contribution, and more than one author may have contributed to the same aspect.

Reply: According to your suggestion, the relevant contents of Author contributions section have been added in the revised manuscript: “**Xu Y., Zhang Y.G., Wang J.B. designed research; Wang X., Liu Z.H. performed research; Zhang Y.G., Qi W.Q., Jiao J contributed new reagents or**

analytic tools; Xu Y., Qin S.Y. analyzed data; Xu Y., Zhang Y.G., wrote the paper. An author may list more than one contribution, and more than one author may have contributed to the same aspect." Thanks!

(3) Please provide the professional title of the corresponding author.

Reply: According to your suggestion, the relevant content has been added: "Yonggui Zhang, Attending physician".

(4) AIM should be no more than 20 words.

Reply: The current aim is only concludes 19 words: "To evaluate the clinical outcomes of 240-week treatment with entecavir (0.5 mg) in Chinese nucleoside-naïve patients with cirrhosis." Thanks!

(5) MATERIALS AND METHODS (no less than 140 words): You should present the materials and methods used for all of the data presented in the proceeding Results section of the abstract.

Reply: According to your suggestion, the relevant contents have been revised: "In this study, we enrolled 204 nucleoside-naïve patients with compensated (n = 96) and decompensated (n = 108) hepatitis B virus (HBV)-induced cirrhosis who attended the Department of Gastroenterology at the China-Japan Union Hospital (Jilin University, Changchun, China), treated with entecavir (0.5 mg) for 240 weeks. Liver biopsy samples obtained from 38 patients prior to treatment (baseline) and at week 240 were evaluated by different independent histopathologists. Efficacy assessments included the proportions of patients who achieved a HBV DNA level <500 copies/mL, the association of interleukin-28B genetic variation with antiviral therapy, clinical outcomes, and histological improvement. Changes in liver disease severity were analyzed, and liver histological evaluation was performed in 38 patients with paired biopsies. Statistical analysis was performed by using SPSS v13.0 (SPSS Inc., Chicago, Illinois, USA). The Student t test was used to compare the means of the continuous variables between the groups. The proportions of patients who achieved the end points were compared by using the chi-square test. All the tests were two-sided, and $P < 0.05$ was considered as statistically significant." Thanks!

(6) RESULTS (no less than 150 words): Observational and experimental results, including data, effects and outcomes, should be presented. You should present P values where appropriate. You must provide relevant data to illustrate how the statistical values were obtained, e.g. 6.92 ± 3.86 vs 3.61 ± 1.67 , $P < 0.001$. Articles not meeting this requirement will not be accepted.

Reply: According to your suggestion, the relevant contents have been revised: "At week 240, 87.5% of the patients with compensated cirrhosis and 92.6% of the patients with decompensated cirrhosis achieved a HBV DNA level <500 copies/mL. Three patients had genotypic entecavir resistance within the 240-week period. No significant association was observed between virological response and IL-28 genotype (CT, 88.2% vs. CC, 90.6%; $P = 0.751$). The proportion of patients with Child-Pugh

class A disease was significantly increased at week 240 (68%) from the baseline (47%; $P = 0.003$). The proportion of patients with Child-Pugh class B disease was significantly decreased at week 240 (25%) from the baseline (39%; $P = 0.02$). In the patients with paired liver biopsies, the mean reduction in Knodell necroinflammatory score from the baseline was 3.58 ± 1.03 points (7.11 ± 1.80 vs. 3.53 ± 1.35 , $P < 0.01$). The mean reductions in Ishak fibrosis score from the baseline was 1.26 ± 0.64 points (5.58 ± 0.50 vs. 4.32 ± 0.81 , $P < 0.01$).” Thanks!

- (7) (Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.)

Reply: According to your suggestion, the relevant contents have been revised: “Entecavir is a potent antiviral agent that has been shown to be effective and safe for the treatment of CHB. However, data on its clinical benefits in patients with cirrhosis, especially in long-term treatment, are limited. The aims of this prospective study were to evaluate the antiviral efficacy and clinical outcomes of entecavir treatment for 240 weeks in nucleoside-naïve Chinese patients with CHB, and compensated or decompensated cirrhosis.” Thanks!

- (8) Please provide all authors abbreviation names and manuscript title here. The abbreviation names should be the same as the copyright. World J Gastroenterol 2014; In press

Reply: According to your suggestion, all authors abbreviation names and manuscript title have been revised: “Xu Y, Zhang Y.G. *, Qin S.Y., Wang X, Qi W.Q., Liu Z.H., Jiao J, Wang J.B. Long-term antiviral efficacy of entecavir and liver histology improvement in Chinese patients with hepatitis B virus-related cirrhosis”. Thanks!

- (9) Please provide the “Highlighted contents” here, which is a necessary content. See the requirements as follows:

Reply: According to your suggestion, the relevant contents have been updated. Thanks!

Updated contents:

Background

To concisely and accurately summarize the related background of the article and to enable the readers to gain some basic knowledge relevant to the article, thus helping them better understand the significance of the article.

Research frontiers

To briefly introduce the hotspots or important areas in the research field related to the article.

Innovations and breakthroughs

To summarize and emphasize the differences, particularly the advances, achievements, innovations,

and breakthroughs, from the other related or similar articles so as to allow the readers to catch up with the major points of the article.

Applications

To summarize the actual application values, the implications for further application and modification, or the perspectives of future application of the article.

Terminology

To concisely and accurately describe, define or explain the specific, unique terms that are not familiar to majority of the readers but are essential for the readers to understand the article.

Peer review

To provide the comments from peer reviewers that most represent the characteristics, values, and significance of the article, and allow the readers to have an objective point of view toward the article.

- (10) Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. For those references that have not been indexed by PubMed, a printed copy of the first page of the full reference should be submitted. PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.**)

Reply: According to your suggestion, the reference section has been updated. The detailed revisions can be found in next comment. Thanks!

- (11) At least 30 references should be included, covering important publications cited in PubMed within the past 4 years. For seminal references, however, the publication date is not strictly limited.

Reply: According to your suggestion, the reference section has been updated to 35 references. Thanks!

Updated references:

- 1 **Dienstag JL.** Hepatitis B virus infection. *N Engl J Med* 2008;359:1486-1500. [DOI: 10.1056/NEJMra0801644]
- 2 **Fattovich G.** Natural history of hepatitis B. *J Hepatol* 2003;39(Suppl1):S50-S58. [PMID: 14708678]
- 3 **Fattovich G, Brollo L, Giustina G, Noventa F, Pontisso P, Alberti A, Realdi G, Ruol A.** Natural history and prognostic factors for chronic hepatitis type B. *Gut* 1991;32:294-298[PMID: 2013423]
- 4 **Liaw YF, Tai DI, Chu CM, Chen TJ.**The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *HEPATOLOGY* 1988;8:493-496. [PMID: 3371868]
- 5 **Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, Christensen E, Krogsgaard K, Degos F, Carneiro de Moura M.** Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. *HEPATOLOGY* 1995;21:77-82.[PMID: 7806171]

- 6 **Realdi G**, Fattovich G, Hadziyannis S, Schalm SW, Almasio P, Sanchez-Tapias J, Christensen E, Giustina G, Noventa F. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. *J Hepatol* 1994;21:656-666. [PMID: 7814813]
- 7 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65-73.[PMID: 16391218]
- 8 **Iloeje UH**, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006;130:678-686.[PMID: 16530509]
- 9 **Mommeja-Marin H**, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *HEPATOLOGY* 2003;37:1309-1319.[PMID: 12774009]
- 10 **Chen CJ**, Yang HI, Iloeje UH. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *HEPATOLOGY* 2009;49(Suppl):S72-S84.[DOI: 10.1002/hep.22884]
- 11 **Gigi E**, Sykia A, Sinakos E, Koumerkeridis G, Raptopoulou-Gigi M, Bellou A, Mougiou D, Orfanou E, Vrettou E. Virologic response and resistance to lamivudine in patients with chronic hepatitis B: a ten-year retrospective analysis. *Hippokratia* 2012; **16**: 342-346. [PMID: 23935314]
- 12 **Chung GE**, Lee JH, Kim YJ. Does antiviral therapy reduce complications of cirrhosis? *World J Gastroenterol* 2014; **20**: 7306-7311. [DOI:10.3748/wjg.v20.i23.7306]
- 13 **Nishida T**, Kobashi H, Fujioka S, Fujio K, Takaguchi K, Ikeda H, Kawaguchi M, Ando M, Araki Y, Higashi T, Shoji B, Takaki A, Iwasaki Y, Sakaguchi K, Shiratori Y, Yamamoto K. A prospective and comparative cohort study on efficacy and drug resistance during long-term lamivudine treatment for various stages of chronic hepatitis B and cirrhosis. *J Gastroenterol Hepatol* 2008; **23**: 794-803. [DOI:10.1111/j.1440-1746.2007.05240.x]
- 14 **Lai CL**, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, DeHertogh D, Wilber R, Zink RC, Cross A, Colonno R, Fernandes L. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006;354:1011-1020.[PMID: 16525138]
- 15 **Yao G**, Chen C, Lu W, Ren H, Tan D, Wang Y, Xu D, Jiang Z, Liu J, Xu D, Macdonald L. Efficacy and safety of entecavir compared to lamivudine in nucleoside-naïve patients with chronic hepatitis B: a randomized double-blind trial in China. *Hepatol Int* 2007; **1**: 365-372. [DOI:10.1007/s12072-007-9009-2]
- 16 **Yao G**, Chen C, Lu W, Ren H, Tan D, Wang Y, Xu D, Liu J, Xu D, Llamoso C. Virologic, serologic, and biochemical outcomes through 2 years of treatment with entecavir and lamivudine in nucleoside-naïve Chinese patients with chronic hepatitis B: a randomized, multicenter study. *Hepatol Int* 2008;2:486-493.[DOI: 10.1007/s12072-008-9088-8]
- 17 **Wang J**. Clinical utility of entecavir for chronic hepatitis B in Chinese patients. *Drug Des Devel Ther* 2013; **8**: 13-24. [DOI:10.2147/DDDT.S41423]
- 18 **Schiff E**, Simsek H, Lee WM, Chao YC, Sette H Jr, Janssen HL, Han SH, Goodman Z, Yang J, Brett-Smith H, Tamez R. Efficacy and safety of entecavir in patients with chronic hepatitis B and advanced hepatic fibrosis or cirrhosis. *Am J Gastroenterol* 2008; **103**: 2776-2783. [DOI:10.1111/j.1572-0241.2008.02086.x]
- 19 **Shim JH**, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2010; **52**: 176-182. [PMID:20006394]
- 20 **Schiff ER**, Lee SS, Chao YC, Kew Yoon S, Bessone F, Wu SS, Kryczka W, Lurie Y, Gadano A, Kitis G, Beebe S, Xu D, Tang H, Iloeje U. Long-Term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic

hepatitis B. *Clin Gastroenterol Hepatol* 2011; **9**: 274-276. [DOI:10.1016/j.cgh.2010.11.040]

- 21 Chinese Society for Infectious Diseases, Chinese Society for Hepatology, Chinese Medical Association. Guideline on prevention and treatment of chronic hepatitis B in China (2005). *Chin Med J (Engl)* 2007; **120**:2159-2173
- 22 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: management of chronic hepatitis B. *J Hepatol* 2009; **50**: 227-242. [DOI:10.1016/j.jhep.2008.10.001]
- 23 **Liaw YF**. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263-283. [DOI:10.1007/s12072-008-9080-3]
- 24 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662. [DOI:10.1002/hep.23190]
- 25 **Park H**, Park JY, Kim SU, Kim do Y, Han KH, Chon CY, Ahn SH. Efficacy of switching to telbivudine plus adefovir in suboptimal responders to lamivudine plus adefovir. *World J Gastroenterol* 2013; **19**: 7671-7679. [DOI:10.3748/wjg.v19.i43.7671]
- 26 **Kim JK**, Ma DW, Lee KS, Paik YH. Assessment of hepatic fibrosis regression by transient elastography in patients with chronic hepatitis B treated with oral antiviral agents. *J Korean Med Sci* 2014; **29**: 570-575. [DOI:10.3346/jkms.2014.29.4.570]
- 27 **Ridruejo E**. Treatment of chronic hepatitis B in clinical practice with entecavir or tenofovir. *World J Gastroenterol* 2014; **20**: 7169-7180. [DOI:10.3748/wjg.v20.i23.7169]
- 28 **Ke W**, Liu L, Zhang C, Ye X, Gao Y, Zhou S, Yang Y. Comparison of efficacy and safety of tenofovir and entecavir in chronic hepatitis B virus infection: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e98865. [DOI: 10.1371/journal.pone.0098865]
- 29 **Raymond PD**, Harold D, Thomas R.O. Interferon-lambda and therapy for chronic hepatitis C virus infection. *Trends Immunol* 2011; **32**:443-450[DOI: 10.1016/j.it.2011.07.002]
- 30 **Yu ML**, Huang CF, Huang JF, Chang NC, Yang JF, Lin ZY, Chen SC, Hsieh MY, Wang LY, Chang WY, Li YN, Wu MS, Dai CY, Juo SH, Chuang WL. Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. *Hepatology* 2011; **53**:7-13. [DOI: 10.1002/hep.23976].
- 31 **Pagliaccetti NE**, Robek MD. Interferon-lambda in the immune response to hepatitis B virus and hepatitis C virus. *J Interferon Cytokine Res.* 2010; **30**:585-590. [DOI: 10.1089/jir.2010.0060].
- 32 **Li W**, Jiang Y, Jin Q, Shi X, Jin J, Gao Y, Pan Y, Zhang H, Jiang J, Niu J. Expression and gene polymorphisms of interleukin 28B and hepatitis B virus infection in a Chinese Han population. *Liver Int.* 2011; **31**:1118-26. [DOI: 10.1111/j.1478-3231.2011.02507.x.].
- 33 **Fabris C**, Falletti E, Cussigh A, Bitetto D, Fontanini E, Bignulin S, Cmet S, Fornasiere E, Fumolo E, Fangazio S, Cerutti A, Minisini R, Pirisi M, Toniutto P. IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: role in the course of chronic viral hepatitis and the development of HCC. *J Hepatol.* 2011; **54**:716-22. [DOI: 10.1016/j.jhep.2010.07.019].
- 34 **Martin MP**, Qi Y, Goedert JJ, Hussain SK, Kirk GD, Hoots WK, Buchbinder S, Carrington M, Thio CL. IL28B polymorphism does not determine outcomes of hepatitis B virus or HIV infection. *J Infect Dis.* 2010; **202**:1749-53. [DOI:10.1086/657146].
- 35 **Sonneveld MJ**, Wong VW, Woltman AM, Wong GL, Cakaloglu Y, Zeuzem S, Buster EH, Uitterlinden AG, Hansen BE, Chan HL, Janssen HL. Polymorphisms near IL28B and serologic response to peginterferon in HBeAg-positive patients with chronic hepatitis B. *Gastroenterology.* 2012; **142**:513-520.[DOI: 10.1053/j.gastro.2011.11.025].

- (1) The graphs supplied should be **decomposable** (each part of your figure could be moved so as to easily edited). You can send it as excel, word or powerpoint format so that I can edit them easily.

Reply: The original data have been provided as supplementary file. Thanks!

- (2) The graphs supplied should be **decomposable** (each part of your figure could be moved so as to easily edited). You can send it as excel, word or powerpoint format so that I can edit them easily. If it isn't decomposable please provide figures no smaller than 85 mm in height and 126 mm in width, and at a **resolution of 300 dpi** as **TIFF** format.

Reply: The original data have been provided as supplementary file or the figures have been updated. Thanks!

3 References and typesetting were corrected

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