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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 53158

Title: Add-on pegylated interferon augments hepatitis B surface antigen clearance vs Continuous nucleos(t)ide analog monotherapy in Chinese patients with chronic hepatitis B and hepatitis B surface antigen ≤ 1500 IU/mL: An observational study

Reviewer's code: 03646555
Position: Peer Reviewer
Academic degree: BMed, FRACP, MBBS, MD
Professional title: Doctor
Reviewer's country: Australia
Author's country: China

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS

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[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[Y] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[Y] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[ ] Advanced
			[Y] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an impressive and useful study, but the manuscript needs massive improvement to be considered publishable. 1) The phrasing of the results in the abstract, in the second sentence onward, is very long and difficult to understand. Two variables (HBsAg clearance rate and seroconversion rate) are presented simultaneously in the add-on group at two separate different time points, and then this is repeated for the monotherapy group, then all of this is repeated in an intention-to-treat analysis. I propose that the abstract only present the figures for intention-to-treat analysis, omit the time point of week 48 (which was never a primary endpoint); and present the data for HbsAg clearance rate first between both groups, then the data for seroconversion rate between both groups. This maintains the overall message of the study without extraneous information that overfills the abstract. 2) In the abstract and throughout the manuscript (e.g. in the core tip, in the results), predictors of HbsAg clearance in the add-on group are mentioned such as age, baseline HBsAg concentration, HBsAg concentrations at weeks 12 and 24, and HBsAg changes from baseline to weeks 12 and 24. Frustratingly, however, it is not mentioned which direction of magnitude is predictive of HbsAg clearance for each of these predictors. Is it younger age? Or older age? Is it lower baseline HBsAg concentration or higher baseline HBsAg concentration? Is it HBsAg

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decline or elevation from baseline? This should be made explicit to the casual reader. 3) In the abstract, the percentage of patients in the add-on group with adverse events should be mentioned. 4) In the abstract conclusion, it should be mentioned that this study was only in HBeAg- patients. 5) In the section entitled "Study Design", it should be mentioned that HBsAg clearance at week 48 was also measured- I assume it was a secondary endpoint. 6) The statement "A patient was considered as a responder if HBsAg was cleared in 72 weeks" is redundant and should be deleted. The terminology "responder" is never again used by the researchers in the manuscript. 7) The statement "The statistical methods of this study were reviewed by Lei-Lei Pei from Institute of Public Health Xi'an Jiaotong University" is not appropriate. It is scientifically unprofessional to name assistants by their full names in the methods of a manuscript. Include this person instead in the thanks/acknowledgement section, or better yet include him/her in the author list as he/she made a significant contribution. 8) The description of ROC curves "which plot sensitivity by 1-specifity" should be omitted as ROC curves are commonly understood by readers. 9) The sentence "Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were used to predict the possibility of HBsAg clearance based on weeks 12 and 24 HBsAg change from the baseline" is completely wrong and must be deleted. The authors never present calculations of the positive predictive value or negative predictive value of any test. 10) The description of per protocol analysis "analyses were restricted to subjects who finished the scheduled treatment or follow-up" should be omitted, as this concept is commonly understood by readers. 11) The description of intention-to-treat analysis "all subjects who were enrolled in the study were included in the analysis" should be omitted, as this concept is commonly understood by readers. 12) Figure 2 is confusing as it presents multiple different outcomes in two different analyses. I propose it be split into two separate figures- one simply presenting data about HBsAg clearance, and the other presenting

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data about HBsAg seroconversion. 13) In the section titled "Primary endpoint", data is presented about HBsAg clearance rate at week 48. However this was not a primary endpoint. Only HBsAg clearance rate at week 72 was listed in the abstract and the methods section as a primary endpoint, further confusing the reader. 14) In the section entitled "HBsAg dynamics", serum HBsAg levels are expressed as medians, and the decline is presented as baseline values and values at weeks 48 and 72. However later in this section, HBsAg elevation is expressed as the mean of the quantitative elevation values. Thus there are two conflicting ways of presenting HBsAg dynamics, which is confusing. I suggest the authors standardise it throughout the manuscript. They should decide whether medians or means are more appropriate for HBsAg levels at baseline (depending on tests of the normality of the distribution of these values, e.g. the Shapiro-Wilk or Kolmogorov–Smirnov test) and present this accordingly. They should then present any HBsAg change as the median or mean of the quantitative elevation/decline values, whichever is more appropriate according to normality of distribution of these values. Then, the appropriate statistical testing for significance of the HBsAg change between add-on and monotherapy groups can be applied, and p-values herein should be stated. 15) Figure 3 is confusing as it presents multiple different outcomes. I propose it be split into two separate figures- one simply presenting data about HBsAg changes, and the other presenting data about ALT and AST changes. 16) In the paragraph beginning with "Furthermore, more patients in the add-on group had low levels of HBsAg at the end of follow-up than the monotherapy group", HBsAg levels are presented not as log10 values, but as absolute values (1000, 100 and 10). This is confusing. The authors should standardise their presentation of data to log10 values. 17) ADV sequential combination is not defined in the manuscript, and it is unclear to readers why these patients are specifically highlighted in the paragraph entitled "Efficacy of add-on peg-IFN α-2a to ongoing low-genetic barrier NA (ADV)", and why

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their mean HBsAg decline is highlighted. I would suggest deleting this paragraph for brevity. 18) It is unclear what "virological breakthrough" is defined as. Furthermore, the phrase "(No.69 and No.91)" to describe two patients with breakthrough is meaningless to the reader and should be deleted. 19) It is unclear why a discussion of one patient who developed HCC is significant enough to warrant its own paragraph. It is not relevant to this overall study. I strongly suggest, for brevity, both virological breakthrough and HCC development are instead briefly included in the analysis of adverse outcomes/adverse events, rather than taking up their own unnecessarily long paragraphs. 20) In the paragraph entitled "Baseline HBsAg level and age for HBsAg clearance at week 72", baseline characteristics include "NA". It is not defined what NA means in this context. Does it mean the type of nucleot(s)ide analogue used? Furthermore, the presentation of univariate analysis and multivariate analysis is poorly done. Firstly, the authors should list which variables were assessed in univariate analysis. Ideally, this should be presented with the odds ratios in a table with appropriate p values. Then, those variables that were significant or approaching significance (P <0.10) should be combined in a multivariable logistic regression analysis with the odds ratios and p values presented in the same table, in a different column. 21) Furthermore, the authors have failed to define which units are being used for each of these variables in univariate and multivariate analysis. Is the unit of age months or years? Is the unit of baseline HBsAg level 1 log10 IU/mL, 0.1 log 10 IU/mL, or 1 IU/mL? Without these units, the odds ratios are impossible to interpret. 22) the term "cut point" should be "cut-off point", and the cut-off points should be "33 years" and "2.25 log10 IU/mL", without the "<" symbol. 23) In the paragraph entitled "ALT elevation, HBsAg levels and changes of HBsAg for HBsAg clearance at week 72", the presentation of univariate analysis and multivariate analysis is again poorly done. They should follow the same advice as per my point 20 above. I am most interested to know if these

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univariate and multivariate analyses have also included the same baseline demographic variables and HBsAg levels as in the previous analyses referred to in point 20. If they have not, I believe they must be. These on-treatment dynamic changes of ALT and HBsAg may actually be confounded by baseline variables. 24) Furthermore, the units in this second univariate analysis and multivariate analysis are not defined, just like in my point 22 above. Most importantly, what are the units of HBsAg change at week 12 and 24? Without these units, the odds ratios are impossible to interpret. 25) It is unclear why the paragraph entitled "The effect of HBsAg levels at weeks 12 and 24 and the changes of HBsAg from baseline to weeks 12 and 24" is a separate paragraph. It should be combined with the paragraph above as it is describing the ROC curves of those variables. Similarly, it is unclear why the paragraph entitled "The effect of early ALT elevation for HBsAg clearance" is a separate paragraph. It should be combined with the paragraph above. 26) In the paragraph entitled "Safety", p values should be presented for the difference in adverse events. 27) In the discussion, the sentence "Several reasons including higher baseline HBsAg titer and poor compliance to full treatment in that study could well explained the discrepancy between our and Marc Bourlière's results" is unprofessional. Full names of previously uncited authors are not to be used in scientific writing. Furthermore, the quantitative differences in compliance between the current study and Bourliere et al's study should be made clear. 28) The statement "Therefore, we believe that extension of the time with peg-IFN α-2a therapy may further improve HBsAg clearance in patients with HBsAg <100 IU/ml at week 72" is not backed up by any reasoning and should be omitted. There is no data in this study, where IFN durations were fixed, suggesting that longer IFN treatment results in greater HBsAg clearance. 29) The statement "The patients in the treatment group were not randomized. This may lead to bias that potentially impact the follow-up results" is unclear. What exact types of bias are the authors referring to? After all, demographic and

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baseline characteristics between treatment groups were not statistically different. 30) Table 4 should include p values. 31) Table 2 uses the term "cut point" instead of "cut-off point" 32) Fibro Scan is not the technical term for a test. Authors should use the term "transient elastography" instead, and state in the methods that the Fibroscan technology was used (FibroScan; EchoSens, Paris, France) . 33) Transient elastography/Fibroscan values in Table 1 need a unit (I assume kPA). 34) In Tables 2 and 3, units for every measurement must be given, and the direction of HBsAg change (elevation or decline) must be made clear, rather than just using the term "HBsAg change". 35) The authors have presented very provocative 'cut-off points' on ROC curves for variables predicting the primary outcome. However in their discussion, they should discuss the implications of these cut-off points. Do they, at present, believe that add-on therapy should be denied to patients who have unfavourable characteristics based on one of these cut-off points (e.g. a 34 year old person)? Or on several of these cut-off points (e.g. a 34 year old person with HBsAg 2.26 log10 at baseline)? Or do the authors propose, as future research, combining these characteristics into a mathematically modelled and weighted scoring system which can be retrospectively and prospectively validated?

INITIAL REVIEW OF THE MANUSCRIPT

Google Search:

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Reviewer's code: 02522427
Position: Editorial Board
Academic degree: MBChB, MD
Professional title: Professor
Reviewer's country: Saudi Arabia
Author's country: China
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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS

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[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept (High priority)	Peer-Review:
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Accept (General priority)	[Y] Anonymous
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[Y] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[ ] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

The study is aimed to evaluate the effect of add on PEG INF alpha to stable chronic oral antiviral therapy using HBsAg levels as a predictor for a response. Major comments: The study is well planned and well written. Mainor comments: it is well known that the response to first-line anti-HBV treatment Entecavir and Adefovir is much better compared to second-line treatment like adefovir. So did the patient looked to the difference in the response between patients who were on ETV and TDF versus those who were on ADV in the group that had add on peg INF. Another point since all those patients were assessed for hepatic fibrosis using transient elastography (fibroscan) did the author found any difference in response to treatment in the two groups across the different stages of fibrosis. In some parts of the discussion section, the authors seem repeating the result rather than discussing their findings. With regards to the development of HCC longer follow-up might be needed to evaluate the effect of peg INF add on therapy in reducing the risk of HCC. This can be addressed in the discussion section. Additionally, the authors can use their findings to add recommendations at the end of the discussion section.

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Title: Add-on pegylated interferon augments hepatitis B surface antigen clearance vs Continuous nucleos(t)ide analog monotherapy in Chinese patients with chronic hepatitis B and hepatitis B surface antigen ≤ 1500 IU/mL: An observational study

Reviewer's code: 02540672
Position: Peer Reviewer
Academic degree: FEBG, FRCP, MBBS, MRCP, PhD
Professional title: Doctor, Senior Lecturer
Reviewer's country: United Kingdom
Author's country: China

Manuscript submission date: 2019-12-09
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Reviewer accepted review: 2019-12-09 18:13
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[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Minor revision	[ ] Onymous
[ ] Grade D: Fair	[ ] Grade D: Rejection	[Y] Major revision	Peer-reviewer's expertise on the topic of the manuscript:
[ ] Grade E: Do not publish		[ ] Rejection	[Y] Advanced
			[ ] General
			[ ] No expertise
			Conflicts-of-Interest:
			[ ] Yes
			[Y] No

SPECIFIC COMMENTS TO AUTHORS

Dr Wu and co-authors have studied the effect on HbsAg loss of add-on peg ifn in patients the CBD and low level HbsAg already on nucleos(t)ides in an observational study. This research question has already been addressed in Dr Bourliere's 2017 RCT which did not identify a significant improvement in HbsAg loss in a less restricted sample with CHB. As this remains an important clinical unmet need and as Dr Wu's study is sufficiently different to Dr Bourliere's study, this concept deserves to be further explored. Points to be addressed: 1. Please explain in more the limitation of a non-randomised study when answering a research question 2. 1537 patients were screened and 1342 were excluded because of their DNA and HBsAg levels etc. This suggests that this highly selected group is very hard to find in clinical practice - please comment on this. 3. The baseline fibrosis stage seems to be lower in Dr Wu's study than Dr Bourliere's study and this may explain the results - please discuss this. 4. Dr Bourliere's study did not include any data on HBV genotype and this was considered a weakness. Can Dr Wu describe the genotype mix in his study? 5. The core tip is very poorly written and this should be revised. 6. The second paragraph in the introduction does not make sense and is not clear- please revise this. 7. The word 'debated' is not used in the correct sense in the core tip and discussion 8. I think Dr Wu's data and Dr

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Bourliere's study data are more similar than the authors suggest - please add a paragraph in the discussion about this.

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[ ] The same title

[ ] Duplicate publication

[ ] Plagiarism

[Y] No

BPG Search:

[ ] The same title

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[ ] Plagiarism

[Y] No