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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 12346

Title: The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine

Reviewer code: 00506450

Science editor: Su-Xin Gou

Date sent for review: 2014-07-03 19:24

Date reviewed: 2014-07-14 21:39

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The data suggested that naturally occurring YMDD mutation is detectable in a majority of CHB patients without anti-viral therapy. Incidence of YMDD mutation may be correlated with HBeAg and HBV DNA level. This study aimed to determine the natural prevalence of variants of tyrosine-methionine-aspartic acid-aspartic acidmotif in patients with chronic hepatitis B, and to evaluate the efficacy of lamivudine therapy in HBV patients with natural YMDD mutation. This is an interesting paper with reasonable hypothesis, logical work and nice illustration.



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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 12346

Title: The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine

Reviewer code: 02861377

Science editor: Su-Xin Gou

Date sent for review: 2014-07-03 19:24

Date reviewed: 2014-07-25 21:06

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input checked="" type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair		BPG Search:	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E: Poor	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This is an original article about the natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine. The comments are listed below: Firstly, the quality of writing is poor. I definitely advise the authors to get their manuscript corrected by a scientific editing service. Secondly, the reference part is missing in the maintext and the figures is not professional. . Finally, the data is not presented in a clear and concise way that it is very hard to understand the intent of the author in discussion part.

ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 12346

Title: The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine

Reviewer code: 01221188

Science editor: Su-Xin Gou

Date sent for review: 2014-07-03 19:24

Date reviewed: 2014-07-28 16:03

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Tan et al evaluated the frequency of spontaneous YMDD mutation in patients with chronic hepatitis B who have no history of treatment with lamivudine. Although the references were not attached, this paper is very interesting. The sample size is large. The method is good. However, there are several mistakes. Moreover, there are many misspellings. The authors should revise this carefully. Final version should be checked by a native English speaker.

- 1) There is no reference in the text. I cannot find any references.
- 2) Is Table 1 correct? It seems that Table 1 is Table 2.
- 3) There are a lot of misspellings.
- 4) In the abstract, the conclusion is wrong. YMDD mutation was not detected in not a majority of CHB patients but approximately 20% of CHB patients.
- 5) There are two kinds of HBV DNA units in this paper (LGE in Table 1 and 2, and copies/mL in the text and Table 3). Therefore, it seems that two methods were applied for the measurement of HBV DNA. However, only one method is described in this paper. The authors should explain this.
- 6) In page 6, the authors should reconfirm the patients number in mutation data of 1042 CHB cases.
- 7) What is the definition of virological breakthrough hepatitis?
- 8) In page 7, 11, 12, and 13, what is X2?
- 9) Table 3 is not necessary. The all results of univariate analysis and multivariate analysis including no-significant data should be shown in Table 2.



ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 12346

Title: The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine

Reviewer code: 00504365

Science editor: Su-Xin Gou

Date sent for review: 2014-07-03 19:24

Date reviewed: 2014-07-28 19:30

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input checked="" type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This work aims to study the prevalence of YMDD-motif mutants in the HBV polymerase in CHB patients and its relationship to the clinical course of the disease. This could be an interesting original work but, unfortunately, I believe there are a number of important concerns. First, I would advice the authors to deeply revise and edit the text since it contains language mistakes that often make it hard to understand the meaning of several paragraphs. Second, there are no references attached. This also points to some negligence and disregard. I will give also a couple of specific examples of confusion and contradictions: The authors detected YMDD mutations in about 20% of the patients and not in the majority of them. It is not clear at all what is meant by virological breakthrough. In conclusion, although this study could provide some interesting information and the number of studied patients is undoubtedly high, I cannot support its publication in the present form.

ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 12346

Title: The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine

Reviewer code: 02860590

Science editor: Su-Xin Gou

Date sent for review: 2014-07-03 19:24

Date reviewed: 2014-08-01 21:22

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Article - The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine My specific queries and comments are below: ? Please, get a native English speaker to check the English used in the paper. Various sentences should be reviewed due to grammatical error. Title: The title is so long. Can the authors please provide a title more centred on the objective of the article? Abstract: The conclusion achieved in the abstract is different from the conclusion of the manuscript. Furthermore, the text should be reviewed due to grammatical error. Introduction: The introduction is under-elaborated. There is limited information regarding a theoretical framework that grounds the research. Additionally, long-term treatment with lamivudine is associated with an increasing rate of antiviral drug resistance reaching approximately 70% after 5 years in patients with HBeAg-positive infection. Therefore, in many guidelines lamivudine is not considered a first-line agent in the treatment of chronic HBV anymore. Please, the authors should discuss this issue. Materials and methods: The data analysis section is under-elaborated. There is limited discussion regarding the clinical implications of the findings. The exclusion criteria is so limited. Did the authors verify other aetiologies of liver disease? Page 5, line 34, Please, clarification should be provided for the statistical analysis. Results: The text should be reviewed due to grammatical error. Discussion:. The text should be reviewed due to grammatical error. References: The references are not included in the manuscript. ? Accept but needs revision



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(major and minor, profound revision).

ESPS PEER REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 12346

Title: The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine

Reviewer code: 02733636

Science editor: Su-Xin Gou

Date sent for review: 2014-07-03 19:24

Date reviewed: 2014-08-08 01:33

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> Existing	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E: Poor		<input type="checkbox"/> Existing	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Dear Editor, In this manuscript entitled "The natural prevalence of YMDD-motif mutants in chronic hepatitis B patients and its influence the clinical course of lamivudine" authors investigated the prevalence of naturally occurring YMDD mutations in patients with chronic hepatitis B and evaluated the efficacy of lamivudine treatment in this setting. The authors found that HBeAg status and HBVDNA levels are predictive of naturally occurring YMDD mutations. Their results about the efficacy of lamivudine in patient with YMDD mutations showed that emergence of resistance, virological and biochemical breakthrough were more prevalent in YMDD (+) patients which is not surprise. That's why the current guidelines suggest against lamivudine therapy in patients with chronic hepatitis B. In conclusion, I think this paper is not suitable for publication. 1. English language and the quality of writing have many flaws. Even the title is wrong. 2. The reference list is missing. 3. It was mentioned that the second sample obtained from patients was stored at -80C and was later used for the assessment of resistance mutations and HBVDNA levels. Then how could it be possible to have information about the resistance profiles and HBVDNA levels of the matched (selected) 40+40 cases before starting lamivudine treatment. 4. The demographic data and clinical features of the study group are not summarized in Table 1. 5. The conclusion at the end of discussion is wrong. For example, YMDD mutation was not detected in a majority of CHB patients. 6. The authors should provide resistance mutations as L80V/I, V173L, L180M and M204V/I instead



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of resistance loci as YMDD, YVDD, YIDD.