

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 23933

**Title:** Elevated serum IL-38 level at baseline predicts virological response in telbivudine-treated patients with chronic hepatitis B

**Reviewer's code:** 00030389

**Reviewer's country:** Japan

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2015-12-28 10:49

**Date reviewed:** 2015-12-29 18:09

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

## COMMENTS TO AUTHORS

The authors investigated serum IL-38 level and its clinical role in predicting virological response to telbivudine (LdT) in patients with chronic hepatitis B. They found that higher serum IL-38 levels before treatment indicate a greater probability of VR to LdT treatment and that elevated serum IL-38 levels in untreated patients with CHB reflect ongoing liver injury. This is an interesting paper. I have a few comments. Major comment #1. There are papers indicating that cytokines inhibit HBV replication. Their discussion should refer those papers such as below. Galun E, Nahor O, Eid A, Jurim O, Rose-John S, Blum HE, Nussbaum O, Ilan E, Daudi N, Shouval D, Reisner Y, Dagan S: Human interleukin-6 facilitates hepatitis b virus infection in vitro and in vivo. Virology 2000;270:299-309. Bouezzedine F, Fardel O, Gripon P: Interleukin 6 inhibits hbv entry through ntcp down regulation. Virology 2015;481:34-42. Kuo TM, Hu CP, Chen YL, Hong MH, Jeng KS, Liang CC, Chen ML, Chang C: Hbv replication is significantly reduced by il-6. J Biomed Sci 2009;16:41-49. Zhao XM, Gao YF, Zhou Q, Pan FM, Li X: Relationship between interleukin-6 polymorphism and susceptibility to chronic hepatitis b virus infection. World J Gastroenterol 2013;19:6888-6893. Minor



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comments #1. Page 9, line 9. What is PR? #2. Table 3. The serum IL-38 level which determined low or high should be indicated.

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**Title:** Elevated serum IL-38 level at baseline predicts virological response in telbivudine-treated patients with chronic hepatitis B

**Reviewer's code:** 02943023

**Reviewer's country:** South Korea

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2015-12-28 10:49

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	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 checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

This manuscript demonstrated that higher pretreatment serum IL-38 levels are associated with a greater probability of VR to LdT treatment. Authors suggested that elevated serum IL-28 levels reflect ongoing liver injury, which is an indicator of endogenous clearance of HBV infection. These findings are interesting because of it might provide a novel predictors for good response to antiviral therapy. However, there is still need to be revised in several points. Comments. 1. As authors suggested, if serum IL-28 levels could predict a vigorous endogenous HBV clearance and better response to LdT therapy, it would be better to show treatment outcomes at week 52 including the markers for serological response (HBsAg levels or reduction, HBeAg less or seroconversion), biochemical response (serum ALT normalization) as well as virological response (HBV DNA reduction or undetectability). 2. What is the reference for dividing serum IL-38 level into high and low by cut-off level 250 pg/ml? 3. Analyze the factors including serum IL-38 levels for virological response at week 52 by multivariate logistic regression model. 4. Because of higher genetic barrier and lower antiviral resistance, the first recommend oral NAs for CHB treatment are entecavir or tenofovir. But, in this



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study, patients were treated with telbivudine. Please comments about the background for this point.

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**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 23933

**Title:** Elevated serum IL-38 level at baseline predicts virological response in telbivudine-treated patients with chronic hepatitis B

**Reviewer's code:** 02860897

**Reviewer's country:** Japan

**Science editor:** Ze-Mao Gong

**Date sent for review:** 2015-12-28 10:49

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
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## COMMENTS TO AUTHORS

Many of our clinical experiences suggest that replication of HBV is affected by host immune response. Nucleotide analogues are not so potent to eradicate HBV; therefore the potency of HBV is also affected by host immunity. It has been reported that several cytokines have some effect on HBV replication. In this paper authors describe newly discovered IL-38 has crucial effect on anti-viral treatment. Relationship between IL-38 and HBV replication is vague in this report. Authors described here the relationship AMONG IL-38, IL-6 and IL-12. Please clarify the role of IL-38 in cytokine cascade and host immunity that is related to HBV replication.