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## ESPS PEER-REVIEW REPORT

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

**ESPS manuscript NO:** 19579

**Title:** Antiviral therapy for chronic hepatitis B: How to combine nucleic acid analogs and interferon for a cure?

**Reviewer's code:** 02941955

**Reviewer's country:** Japan

**Science editor:** Jing Yu

**Date sent for review:** 2015-05-15 10:21

**Date reviewed:** 2015-05-15 17:47

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 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 checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" 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

Hagiwara S, et al. described the efficacy of combination therapy of IFN and nucleic acids analogues. The description was based on their previous publication. Although they summarize the recent data on this issue carefully, the manuscript has a fundamental lack of knowledge that may deepen the understanding of pathogenesis of CHB. The content is superficial. The authors should concern more deeply, in the aspect of such as immunology and virology to be accepted in the review criteria.



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## ESPS PEER-REVIEW REPORT

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

**ESPS manuscript NO:** 19579

**Title:** Antiviral therapy for chronic hepatitis B: How to combine nucleic acid analogs and interferon for a cure?

**Reviewer's code:** 00504882

**Reviewer's country:** United States

**Science editor:** Jing Yu

**Date sent for review:** 2015-05-15 10:21

**Date reviewed:** 2015-05-15 22:57

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 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"/> 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 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 type="checkbox"/> No	

### COMMENTS TO AUTHORS

Lamivudine (LAM) adefovir (ADV) and entecavir (ETV) are not nucleic acid analogs. These are nucleoside analogs. This should be corrected in the manuscript. These nucleoside analogs are activated upon phosphorylation to nucleoside triphosphate in the liver cells.



ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 19579
Title: Antiviral therapy for chronic hepatitis B: How to combine nucleic acid analogs and interferon for a cure?
Reviewer's code: 03020661
Reviewer's country: United States
Science editor: Jing Yu
Date sent for review: 2015-05-15 10:21
Date reviewed: 2015-05-29 03:18

Table with 4 columns: CLASSIFICATION, LANGUAGE EVALUATION, SCIENTIFIC MISCONDUCT, CONCLUSION. It contains checkboxes for various evaluation criteria like 'Grade A: Excellent', 'Duplicate publication', and 'Plagiarism'.

COMMENTS TO AUTHORS

The authors provide a concise review on combination therapy with nucleoside analogues and IFN-alpha. This subject is topical due to currently increasing interests in re-investigating combination therapy with IFN-alpha with new potent nucleoside analogues. The authors provide an overview and cite multiple studies for reference. I do have a few minor comments. Also, I did not check the numbers from each trial but I did check numbers for reference 19, Brouwer et.al. because I found it surprising there was 32% HBsAg negative after treatment. I could not find these numbers in the manuscript. Please clarify the paragraph (comment below) and I kindly request that you confirm any statistics/numbers included in the review. 1. In the first paragraph of the introduction the authors state that "interferon (IFN) induces cytotoxic T lymphocytes..." This may be the case for acute viral infections but there is substantial evidence that IFN-alpha therapy does not enhance the virus-specific T cell response in chronic HBV patients. a. References: i. Micco L, J Hepatol. 2013 Feb;58(2):225-33. ii. Penna A., J Hepatol. Elsevier; 2012;56(6):1239-46. iii. Tan AT, J Hepatol. 2013 Aug;60:54-61. 2. The manuscript by Tan et al (J Hepatol. 2013 Aug;60:54-61)



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also demonstrated that nuc therapy improved immune responsiveness to subsequent IFNalpha doses. Thus, suppressing viral replication may enhance the IFN-alpha effect. It would be worthwhile including is information. 3. Page 4, second paragraph. "Of 11 HBeAg-positive cases, four (36%) and eight (73%) showed HBeAg seroconversion" The numbers don't add up.  $4+8=12$  4. Page 4, last paragraph needs clarification. "HBsAg negative (18 vs. 32%, respectively,  $p=0.032$ ) and HBeAg seroconversion (11 vs. 26%, respectively,  $p=0.012$ ) rates" In the parentheses, the numbers are respective to what? Also, this confirm data. I did not find any evidence of 32% HBsAg negative patients in the paper and the numbers don't match for HBeAg loss.



ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 19579

Title: Antiviral therapy for chronic hepatitis B: How to combine nucleic acid analogs and interferon for a cure?

Reviewer's code: 02861124

Reviewer's country: Saudi Arabia

Science editor: Jing Yu

Date sent for review: 2015-05-15 10:21

Date reviewed: 2015-05-31 14:32

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 checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		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 mini-review entitled, "Antiviral therapy for chronic hepatitis B: How to combine nucleic acid analogs and interferon for a cure?" by Hagiwara et al. presents a very informative update on combinatorial chemotherapy in chronic hepatitis B cases. The manuscript is well conceived, structured and properly written. However, there are few language and grammatical errors that need to be corrected. I have highlighted my suggested corrections/modifications in the text (track change). Major: 1. P4/L9- Since viral genotype is discussed here, it is better to introduce all genotypes and there antiviral responses in the "introduction" section. 2. P5/L15- It would be better to define "HBeAg negative" cases and the viral pre-Core mutations associated with this. 3. Inclusion of a summarized flow-chart on combination/sequential therapy in HBsAg-positive and negative patients would be very valuable for readers.