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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 24851
Title: HBsAg clearance in inactive HBsAg carriers treated by peginterferon alfa-2a
Reviewer's code: 00007116
Reviewer's country: South Korea
Science editor: Yuan Qi
Date sent for review: 2016-02-12 19:36
Date reviewed: 2016-02-25 16:32

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Title: HBsAg clearance in inactive HBsAg carriers treated by peginterferon alfa-2a The paper submitted by Li et al. examined the effect of peginterferon alfa-2a in inactive HBsAg carriers with serum HBsAg level <100 IU/ml. The authors found that HBsAg clearance was achieved in 13 out of 20 patients (65%) after 72 weeks of peginterferon alfa-2a therapy, while no patients in control group experienced HBsAg clearance. Although it has demonstrated a clear link between peginterferon therapy and HBsAg loss, the benefit of treatment for inactive carriers is still questionable in the real clinical practice. The following comments are the reasons why I think so. (Major comments) 1. The result of this paper is substantial value as HBsAg clearance is suggested as optimal endpoint of antiviral therapy. However, antiviral therapy is not recommended for inactive carriers, since the inactive HBV carrier status confers a favorable long-term outcome with a very low risk of cirrhosis or HCC in the majority of patients. So far, there has been lack of evidence whether interferon-induced HBsAg loss in inactive carriers is beneficial in the real clinical practice or not. In addition, I think the possibility of spontaneous HBsAg clearance should have been taken into account. According to Tseng et al (Hepatology 2012; 55:68-76), HBsAg levels<10 IU/mL at baseline is the strongest predictor

of HBsAg loss. But, half of the subjects included in this study already had HBsAg<10 IU/mL and undetectable HBV DNA. It is recommended for authors to comment on these facts in the discussion section. 2. The comparison of clinical characteristics between patients with HBsAg loss and patients without HBsAg loss is recommended in the results section. (Specific comments) A specific correction on its use of English language can improve this manuscript. Abstract In the results section, "HBsAg levels decreased from 25.72±25.58 IU/ml at baseline to 17.11±21.62 IU/ml at week 96 (p=0.108)" is unclear. Specific description of which patients' group it refers is needed. Introduction This manuscript defined inactive carriers as patients who are HBsAg positive, HBeAg-negative, anti HBe-positive with undetectable HBV DNA level and normal ALT levels. Others may be okay, but, in case of HBV DNA, the practice guidelines include not only undetectable HBV DNA but also low HBV DNA (<2,000 IU/mL). Methods 1. The definition of normal ALT is missing (<40/mL for all patients? 19 IU/mL for females and <30 IU/mL for males?). 2. Based on what reference was the treatment duration set as 72 weeks? 3. Please define the 'clinical evidence cirrhosis' in the exclusion criteria. 4. Please describe the information about the HBV genotypes of the subjects. 5. Please define 'hepatitis reactivation'. Results In patients with HBsAg loss, what was the mean/median time of achieving HBsAg loss after the initiation of treatment? Discussion As a retrospective study, it carries the limit that every retrospective study does. It is recommended to comment about the limitation of this study in the discussion section. Table Since the manuscript can give enough information on the patient selection criteria in the methods section, Table 1 seems unnecessary. Please describe it in the method section in more detail. Reference The international guidelines are recently updated (Reference 1 and 3). But it has not been applied to this manuscript. Please check them and update the citations.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 24851
Title: HBsAg clearance in inactive HBsAg carriers treated by peginterferon alfa-2a
Reviewer's code: 03538290
Reviewer's country: Russia
Science editor: Yuan Qi
Date sent for review: 2016-02-12 19:36
Date reviewed: 2016-02-16 04:22

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The manuscript entitled "HBsAg clearance in inactive HBsAg carriers treated by peginterferon alfa-2a" discusses a possible application of an interferon therapy in inactive HBsAg carriers with a very low HBsAg level. The authors report that in their study the HBsAg disappeared in 65% of treated patients. This result seems to be very good, taking into account that usually HBsAg clearance is rarely observed. However, it seems to me that a treatment by peginterferon alfa-2a 180 μg/week for such a long period as 72 weeks is not justified for inactive HBsAg carriers. For such patients the risks of complication development outweigh the possible benefits. As a practical doctor I know that it is very difficult for patients to receive this therapy for a long time. Therefore I can not recommend this manuscript for publication.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 24851
Title: HBsAg clearance in inactive HBsAg carriers treated by peginterferon alfa-2a
Reviewer's code: 03473435
Reviewer's country: United States
Science editor: Yuan Qi
Date sent for review: 2016-02-12 19:36
Date reviewed: 2016-02-26 14:34

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[ ] Duplicate publication	
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		[Y] No	

COMMENTS TO AUTHORS

In this manuscript by Li et al. entitled "HBsAg clearance in inactive HBsAg carriers treated by peginterferon alfa-2a," the authors evaluated the effectiveness of 72 weeks of peginterferon alfa-2a in inducing HBsAg loss and seroconversion in a subset of treatment-na?ve, chronic HBV inactive carriers with completely suppressed HBV DNA and low HBsAg (<100 IU/ml) at baseline. The authors retrospectively evaluated 20 patients treated with 72 weeks of peginterferon-alfa-2a and followed off treatment for 24 weeks (for a total observational time of 96 weeks) and compared outcome and safety measures to 40 untreated control chronic HBV patients matched for age, sex, baseline HBsAg and HBV DNA levels. Pertinent findings included a high HBsAg loss and anti-HBs seroconversion rates in the treatment arm compared to the control arm, where HBsAg loss was not observed. The followings are comments and questions: 1. As this study is really focused on a subpopulation of CHB inactive carriers with virally suppressed HBV DNA and HBsAg < 100 IU/ml who are treatment-naive, this needs to be made clear throughout the abstract and manuscript. The findings cannot be generalizable to all CHB inactive carriers, only to this subpopulation. 2. As response to peginterferon-alfa-2a is HBV genotype-dependent, this needs to be addressed in the

manuscript. If patient data are not available (given prolonged history of undetectable viral load), then additional epidemiologic HBV genotype breakdown of the surrounding region would still be useful. 3. It would be useful to elaborate further on the clinical course of the treatment patients and expand on the Result Section. What was the timing of HBsAg loss for these treatment patients? Was it on-therapy or during the follow-up period? At what week did HBsAg loss occur? Was there HBsAg loss and sero-revision observed? What were the baseline anti-HBs levels (as some patients will have detectable anti-HBs levels but < 10IU/ml)? Did anti-HBs relate to clinical outcome? What was the age and gender breakdown of those who achieved HBsAg loss and did these parameters have a bearing on the outcome? 4. Please expand on the safety data. Immunomodulator therapy is associated with increased risk of ALT flares both on and off-treatment. ALT flares, particularly when immune-induced, are associated with good clinical outcome. What was observed on and off-treatment and how did these findings impact clinical outcomes? 5. Please use local lab conversion factor to convert HBV DNA to IU/ml. Please provide upper limit of normal for ALT used in this manuscript.