# ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13941-review.doc).

**Title:** Risk of HBV reactivation in rheumatoid arthritis patients undergoing biologic treatment: extending perspective from old to newer drugs

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**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 13941

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

1. Omatuzumab and other recently developed biotherapies are not included in this paper because it regards molecules commonly prescribed in clinical practice, not only in experimental trials. This distinction is relevant because data coming from clinical trials are insufficient to describe the real-life risk of infective side-effects. That's also the reason why I didn't consider approved molecules for RA treatment such as anakinra: because I didn't find any observational report in scientific literature.
2. As suggested, I eliminated unnecessary informations concerning HBV natural history and HBV vaccination.
3. Rheumatological conditions associated with HBV vaccination often develop through different forms of arthritis. In patients treated with bDMARDs for RA the possible overlap with a vaccine-related form of arthritis could confound the evaluation of RA disease activity after treatment start. This is one of the reasons why often rheumatologist don't think about vaccinating patients before immunosuppression. Even if the paragraph about HBV vaccination is long, these considerations might be important in order to give appropriate recommendations about HBV vaccination, that shouldn' be administered in all patients without a proper risk-benefit evaluation.

4. Regarding anti-HBs titer >100 IU/L, I fully agree that this threshold has not been sufficiently supported by other observational data (***Lunel-Fabiani F***, *Masson C, Ducancelle A. Systemic diseases and biotherapies: Understanding, evaluating, and preventing the risk of hepatitis B reactivation. Joint Bone Spine 2014; In press [PMID: 24561021 DOI:10.1016/j.jbspin.2014.01.015]*), so as suggested I decided to cut it off from the discussion.

5. I checked all of the minor revisions. I believe that the sentence 'delay from treatment initiation to HBV reactivation diagnosis' is not formally wrong but certainly ambiguous. I changed into

'delay from immunosuppressive therapy initiation to HBV reactivation diagnosis'. I think that the tables will be soon edited with the editor's final layout.

6. Regarding occult HBV infection (OBI), I fully agree that definitions should be more appropriate and precise. I gave a clear definition in the first occurrence in the text (introduction), along with expert opinion (***Raimondo G***, *Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, Craxì A, Donato F, Ferrari C, Gaeta GB, Gerlich WH, Levrero M, Locarnini S, Michalak T, Mondelli MU, Pawlotsky JM, Pollicino T, Prati D, Puoti M, Samuel D, Shouval D, Smedile A, Squadrito G, Trépo C, Villa E, Will H, Zanetti AR, Zoulim F. Statements from the Taormina expert meeting on occult hepatitis B virus infection. J Hepatol 2008;* ***49*** *Suppl 4: 652–657 [PMID: 18715666 DOI: 10.1016/j.jhep.2008.07.014]*): 'HBsAg negative individuals presenting liver HBV-DNA with detectable or undetectable serum HBV-DNA'. Liver HBV-DNA test is certainly uncommon unless in research field, but I believe that the experts' definition had to be cited, because OBI is a concept recently developed in the field of immunosuppressive therapy, that is precisely the topic of this paper. Later in the text, I give a more precise definition which I don't believe to be contradictory: 'detectable liver HBV-DNA with serum undetectable or <200 IU/mL HBV-DNA in HBsAg- individuals'. In other parts of the text, I abandoned that definition referring only to CHB patients vs patients with *resolved* HBV infection. In the latter group, only a distinction between HBV-DNA positive or negative patients is made.
7. I have simplified the final recommendations to provide a clearer message. I kept separated the paragraphs concerning HBsAg+ and HBsAg-/anti-HBc+ patients. For the latter, I tried to distinguish the case for different drugs and risk factors, underlining that for newer bDMARDs only suggestions and not strict recommendations can be made.
8. In addition, I have added other unpublished data coming from our rheumatology clinic that you can find the last sentence of the 'abatacept' paragraph.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*.

Sincerely yours,

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