

Dear Editor,

Thanks for the kind and thoughtful suggestions from the review of our manuscript entitled "Hepatitis B virus reactivation in rheumatoid arthritis".

We have carefully considered the editor and reviewer's comments. According to the suggestions, the manuscript has been fully revised. Please find below our point-by-point responses to the comments. The revisions in the manuscript was highlighted in yellow for easy identification.

Sincerely,

Dong Zhao

Center for Endocrine Metabolism and Immune Diseases, Beijing Luhe Hospital,
Capital Medical University, 101149, Beijing, China

Tel: +86-10-69543901-6901, E-mail: zhaodong@ccmu.edu.cn

Point-by-point responses

Response to the Science editor:

1. The authors should address the possible role of abatacept in this context, as has been suggested by the reviewer.

R: Thank you very much for your suggestion. We have added this part to the article. (line:267-286)

2. In the section of the manuscript entitled "prevention and management of HBV reactivation in RA", there is no information regarding the management of reactivation; the section is written entirely about prevention. In the same section, the authors could provide further information on the ideal time interval between initiation of antiviral treatment and the beginning of immunosuppressive treatment.

R: Thank you very much for your suggestion. We have added this part to the article. (line:380-390)

Company editor-in-chief:

1. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

R: Thank you very much for your suggestion. We have prepared the figures and tables as required.

Reviewer 1:

1. The relatively high prevalence of both hepatitis B infection and various forms of rheumatoid arthritis in some parts of the world will result in the coexistent diagnoses of both diseases in a substantial number of patients. The exact frequency of this association will vary according to the prevalence and incidence of each disease in each country.

R: Thank you very much for your suggestion. The prevalence of HBV infection and RA prevalence in different countries are different. The exact frequency of

the association between these two diseases will vary according to the prevalence and incidence rate of each disease in each country. We have added the basic knowledge in the introduction. (line:96-105)

2. Methotrexate has been in clinical use for more than 50 years and only a small number of cases have been described in the literature where HBV-reactivation (HBVr) was attributable to this agent when used alone. Based on these findings there is little uncertainty that it causes reactivated hepatitis B in less than 1% of cases.

R: Thank you very much for your suggestion. There are still few studies on methotrexate and HBV reactivation. Based on current research, it is generally believed that methotrexate has a relatively low risk of HBV reactivation and has a certain safety. About this part, we researched the literature and made some modifications. (line:180-192)

3. Moderate doses of glucocorticoids given for 3 or more months have been shown to be associated with an increases risk of HBVr in HBsAg-positive patients. There is a high level of confidence that the true risk of HBVr with chronic systemic corticoid therapy is anticipated to be lower in HBsAg-negative, anti-HBc-positive patients. However, paucity of data, a precise estimate cannot be provided.

R: I couldn't agree with you more. The reactivation rate of HBV can be influenced by different doses of corticoid, different courses of treatment and different HBV infection status. High dose, long course of treatment, HBsAg-positive are easy to cause HBV reactivation, while low dose, short course of treatment and HBsAg-negative, anti-HBC-positive are not easy to relapse. About this part of the content, we have made a further explanation in the article. (line:222-226)

4. Abatacept blocks co-stimulation of T lymphocytes and is currently used in advanced cases of rheumatoid arthritis. Abatacept would be associated with reactivation rate

that is greater than 1% but less than 10%, but due to the paucity of data there is little confidence in this estimate.

R: Thank you very much for your suggestion. We have added this part to the article. (line:267-286)

5. *When compared to HBsAg-positive patients, individuals who are HBsAg-negative, anti-HBc-positive appear to have a lower risk of HBVr when exposed to moderate risk immune suppressive drugs such as TNF alpha inhibitors; however, due to the paucity of data, a precise estimate of baseline risk was not possible. The existing data support that the risk may be partly attributable to the concomitant use of other immune suppressive drugs which are in the low risk category. By contrast, when high risk agents such as rituximab are used in anti-HBc-positive patients, high rates of reactivation in excess of 10% occur and antiviral prophylaxis can be anticipated to result in similar absolute risk reduction as described for HBsAg-positive patients.*

R: Thank you for your reminding. We have modified it in the article.(line:235-249)(line:359-375 or figure2)

Reviewer 2:

Dear authors, thank you for your review. I have no more comment.

R: Thank you very much.