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World Journal of Hematology
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Dear Professor Ma and Professor Jiang: January 27, 2014

Please find enclosed the edited revised manuscript in Word format (file name: WJH 7322-revised-Manuscript final form 2014-01-26.doc).

Title: Anti-CD20 Monoclonal Antibodies and Associated Viral Hepatitis in Hematological Diseases

Author: Shih-Hung Yang, Chiun Hsu, Ann-Lii Cheng, and Sung-Hsin Kuo

Name of Journal: World Journal of Hematology

ESPS Manuscript NO: 7322

Thank you very much for your favorable consideration of our paper for publication in “World Journal of Hematology”. We very much appreciate the comments of the reviewers and have improved our paper based on their suggestions. A point-by-point list of our responses and amendments is also attached.

We appreciate your tremendous patience and generous help in editing our manuscript.

Respectfully yours,

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Reviewer(s)' Comments:

Reviewer 1 (00502976)

1. *This review is interesting as it is well documented on the reported hepatitis following the use of the anti-CD20 monoclonal antibody rituximab for treating hematological malignancies. The manuscript needs minor language polishing.*

Authors' response:

We appreciate this comment. We had improved our article with copyediting service provided by a professional English language editing company suggested by editorial office (American Journal Experts: http://www.aje.com; attached file, certification).

Reviewer 2 (02453015)

1. *The review manuscript is comprehensive. I recommend adding a figure showing the relationship between anti-CD20 monoclonal antibodies and associated hepatitis, as well as potential ways to avoid or treat such complications.*

Author's response:

We appreciate this comment and, as suggested by the reviewer, have provided a new Figure 1 to demonstrate "Anti-CD20 monoclonal antibodies and dynamic immunity in HBV infection". The new Figure Legend of Figure 1 (Page 22) and Figure 1 are added.

Reviewer 3 (02462691)

1. *The review is really about viral hepatitis associated with the use of Anti-CD 20 antibodies, and therefore the title may need change. It was mentioned in*

table 1 that Ofatumumab did not have an associated hepatitis but a recent FDA alert seems to suggest a risk of HBV with this drug (Mitka M, JAMA 2013; 310:1664). Authors will need to update their literatures, and instead of "none", maybe it is better to reword as "none reported at the time of review", since an absence of hepatitis from phase I/II studies does not mean no association. Besides the start time and duration of HBV prophylaxis have not been adequately determined for chemotherapy that involves rituximab, even the choice of agents may not be well-defined, but literature (ref. 101) seems to favour entecavir over lamivudine due to a less breakthrough. I am not entirely sure how much rituximab is really causative of viral hepatitis since literatures seem to have biased against haematological malignancies/chemotherapy but not really autoimmune diseases. Furthermore, the newer Anti-CD 20 did not seem to have this problem (if this is true)? Are there any in-vitro or animal studies that suggest Anti-CD 20 alone induce viral hepatitis?

Authors' response:

We appreciate the comment and have revised the manuscript accordingly.

1. We change the title from "Anti-CD20 Monoclonal Antibodies and Associated Hepatitis in Hematological Diseases" to "Anti-CD20 Monoclonal Antibodies and Associated Viral Hepatitis in Hematological Diseases".

2. We provide the footnote "None, no associated hepatitis reported in hematological autoimmune disorders or malignancies at the time of review (excluding non-hematological diseases)" in Table 1. We also provide the information "HBV or drug-related associated hepatitis during treatment with new anti-CD20 mAbs" in Table 1. Actually, a case of HBV reactivation had

been reported in a patient with rheumatoid arthritis treated with ocrelizumab (Arthritis Rheum. 2012 Feb;64(2):360-70).

3. We have provided new information “The U.S. Food and Drug Administration announced that physicians should be alert to potential HBV reactivation caused by ofatumumab[114]. Liver toxicities had been reported with ofatumumab with or without chemotherapy in hematological malignancies. However, the data on HBV reactivation in these cases were lacking[45,50,115,116].” in Page 12 (Lines 4-8).

   We also update the reference (114-116) to describe the ofatumumab-related liver toxicity (Ref. 114. Mitka M, JAMA 2013; 310:1664*)*.

   In addition, as suggested by the reviewer, we provide “There were also scattered reports of anti-CD20 mAb-related liver function abnormalities in patients with hematological disorders. However, the etiology was most likely related to anti-CD20 mAb[45,50,51,55,69,115,116] ” in Page 18 (the last paragraph, Lines 22-25) to describe liver function abnormalities probably related to anti-CD20 mAbs.

4. To address the recommendation “Besides the start time and duration of HBV prophylaxis have not been adequately determined for chemotherapy that involves rituximab, even the choice of agents may not be well-defined, but literature (ref. 101) seems to favour entecavir over lamivudine due to a less breakthrough.” from the reviewer, we provide new information in **Page 13, Lines 2-18.** These information have been added the following:

   “Based on research findings, the optimal start time and duration of

HBV prophylaxis has not yet been determined[119-123]; however, initiating short-term antiviral therapy before starting anti-CD20 mAb treatment appears to be beneficial and safe. In a randomized trial involving HBsAg+ patients with NHL, the prophylactic use of lamivudine reduced considerably the occurrence of HBV reactivation and hepatitis flares[127]. In a meta-analysis, all-cause mortality, HBV reactivation, HBV-related mortality, and interruption of anti-CD20 mAb therapy were considerably reduced with lamivudine prophylaxis[128]. One major problem of lamivudine, telbivudine, and adefovir is that drug resistance and hepatitis flares increase with continuous use[125,129]; therefore, the use of entecavir and tenofovir was suggested for longer duration of prophylaxis[125]. In addition to HBsAg+ patients, HBV prophylaxis must be considered in patients with resolved HBV because the risk of reactivation remains (**Figure 1**)[106,130]. In a recent retrospective study of HBV reactivation by the Asia Lymphoma Study Group, the authors showed that patients receiving entecavir prophylaxis had a lesser incidence of HBV reactivation than those with lamivudine. Prospective studies to validate these findings are warranted (Page 13, Lines 2-18)."

5. As we know, there are numerous reports of animal lymphoma models to test the preclinical activity of anti-CD20 mAbs[180-182]. However, the safety data in liver toxicities of these animal models are very limited[180-182]. In addition, no animal or in vitro models of viral hepatitis-induced by anti-CD20 mAbs has been established. It would be very difficult to establish the animal model with viral hepatitis reactivated by anti-CD20 mAbs because most of

previous studies used tumor xenografts implanted into mice with severe combined *immunodeficiency* in their animal model. However, immune-mediated liver damage is important for anti-CD20 mAb-associated viral hepatitis. Most likely, this may work in evaluating the precise mechanism of hepatitis caused by the aforementioned viruses during and after anti-CD20 mAbs alone when using the immunocompetent animal model. These new information have been added to the new section "**Future in vivo or in vitro studies"** (Page 19, Lines 1-13). New references (180-182) are also added.