November 14, 2014
Su-Xin Gou,
Science Editor, Editorial Office
Baishideng Publishing Group Inc

Re: Resubmission of manuscript (Manuscript Number 13496) entitled "Prophylactic antiviral therapy in hepatitis B virus infection patients undergoing allogeneic hematopoietic stem cell transplantation

Dear Dr. Gou,

We would like to thank the reviewers for their thoughtful and careful critique of our manuscript. Please find attached a revised copy of the manuscript and a point-by-point response to the reviewers' comments.

We have slightly changed title to "Prophylactic antiviral therapy of allogeneic hematopoietic stem cell transplantation in HBV patients" in accordance with Editorial request. The Discussion section had been substantially revised and we have clarified that although the incidence of recurrence of HBV infection in HBsAg-negative/ HBcAb-positive patients is lower than that seen in HBsAg positive patients, recurrence can cause fulminant hepatitis which has a high mortality. The Consensus on the Management of Lymphoma Patients with HBV Infection in China (2013) recommends prophylactic antiviral therapy for patients with a high risk for recurrence of HBV infection (including those receiving Rituximab therapy or HSCT and those with concomitant hepatic cirrhosis).

We have also clarified that, based on our study, we could not conclude whether HBV reactivation in elderly patients (over 60 years old) can be also safely prevented with a threshold value of 10^3 IU/mL). We have included this as a limitation of this study.

We thank you for your time and consideration. We believe that the revised manuscript will be of interest to the readers of *World Journal of Gastroenterology* and look forward to a favorable response from you at your earliest.

Sincerely yours,

Wai-Yi Zou,
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Point-by-point response to reviewers' comments:

Reviewer 1

Manuscript Number	13496
Manuscript Title	Prophylactic antiviral therapy in hepatitis B virus infection patients undergoing allogeneic hematopoietic stem cell transplantation
Review Time	2014-09-11 18:06

Comments To Authors	Good work was carried out by you and your colleague. Good luck
Classification	◉ Grade A (Excellent) ○ Grade B (Very good) ○ Grade C (Good) ○ Grade D (Fair) ○ Grade E (Poor)
Language evaluation	◉ Grade A: priority publishing ○ Grade B: minor language polishing ○ Grade C: a great deal of language polishing ○ Grade D: rejected
Conclusion	◉ Accept ○ High priority for publication ○ Rejection ○ Minor revision ○ Major revision
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Confidential Comments To Editor

Comments To Authors

Reviewer 2

This paper investigated the efficacy of the prophylactic antiviral therapy in HBV-infected patients treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT). I consider the concept is important, but additional data should be provided to strengthen their conclusions.

The authors investigated the safety and efficacy of prophylactic antiviral treatment in HBV-infected patients who received allogeneic hematopoietic stem cell transplantation (allo-HSCT). Prevention of HBV reactivation is important in the management of HSCT, and antiviral therapy with nucleoside analogues (NAs) plays a key role in the clinical practice. In the present study, they defined the threshold of pre-transplantation HBV-DNA as 10^3 IU/mL and prospectively follow up the clinical courses of the patients. Although various threshold values of HBV-DNA level were proposed in the previous papers, the absolute standard has not been established. Therefore, the current study would provide a clinically useful data. However, I have some concerns to be clarified.

Major comments:
1) There are several kinds of NA available for the prophylactic antiviral treatment. In the present study, the patient were treated with entecavir (ETV), and they mentioned the accuracy of the threshold value of HBV-DNA (10^3 IU/mL) and treatment safety. In the lamivudine (LAM) treatment, LAM-resistant viruses can be easily induced. In addition, adefovir and tenofovir may influence the renal function of patients. They have to clearly mention the safety and efficacy was obtained from ETV treatment. The same concept should be applied throughout the paper.
Response: We thank the reviewer for this comment and agree that LAM treatment has been shown to induce LAM-resistant viruses and that treatment with adefovir and tenofovir have been shown to influence the

renal function of patients. We have expanded the Discussion section to emphasize our data which showed the safety and efficacy of ETV. Our data suggested that ETV is a safe and efficient alternative to lamivudine, adefovir and tenofovir for prophylactic HBV therapy prior to allo-HCST.

Our revised Discussion section now includes:

(i) **Safety data:** Entecavir treatment was started at the time of chemotherapy initiation and was stopped at 1 year after discontinuation of immunosuppressive therapy. There was no significant difference in hematopoietic reconstitution, hematopoietic stem cell engraftment status and incidence of Graft-versus-host disease (GVHD) between the non-hepatitis B group (which received no Entecavir therapy) and the hepatitis B group, suggesting that Entecavir was safe for the transplantation of hematopoietic stem cells in HBV patients.

(ii) **Efficacy data:** There was no significant difference in the incidence of drug-induced liver injury, hepatic vein obstruction syndrome and liver involvement of GVHD between the non-hepatitis B group (which received no Entecavir therapy) and the hepatitis B group, suggesting the efficacy of Entecavir therapy for this group of patients.

(iii) Discussion of data showing that one patient in the HBV group was HBsAg-positive, and had HBV-DNA levels of 10^6 IU/mL at 5 months after discontinuation of immunosuppressive therapy. However, HBV-DNA was lower than <500 IU/mL in the rest of the patients.

(iv) an additional reference supporting our data to show ETV treatments are effective (Aoki et al., 2014).

2) Immunosuppressed status of the recipient could be one of major risks for HBV reactivation after HSCT. In the present study, they enrolled only the patients with their ages less than 60. Since elderly patients tend to have an immune-compromised status, I consider their data cannot be routinely applied to all patients. This paper is a prospective one, and they cannot add on the data of the aged patients. It would be interesting to describe whether HBV reactivation in elderly patients (over 60) can be also safely prevented with their proposed threshold value (10^3 IU/mL). Please evaluate and confirm the accuracy of the value based on the retrospective data in the clinical records of elderly patients. I would like to know whether HBV reactivation did not occur in patients with a lower HBV titer (less than the threshold value) irrespective of their ages.

Response: We thank the reviewer for this excellent question. However, based on our study, we could not conclude whether HBV reactivation in elderly patients (over 60 years old) can be also safely prevented with a threshold value of 10^3 IU/mL). We have included this as a limitation of this study.

We have also expanded our Discussion section to clarify that previous retrospective studies showed that HBV-DNA titer was a high risk factor for recurrence of HBV infection. However, although patients with low HBV-DNA titers were still shown to have a risk for recurrence of HBV infection, the specific threshold remains unknown. In our present study, patients with HBV-DNA titers of $<10^3$ IU/mL who were treated with prophylactic antiviral therapy did not develop recurrence of HBV infection. These data were consistent with another study showing that high viral load (HBV DNA$>10^5$ copies/mL) was an important risk factor for recurrence of HBV infection. We have also included a discussion of a previous study showing that in patients receiving chemotherapy, the incidence of recurrence of HBV infection was 37.8% in patients with detectable HBV DNA, and 10.9% in patients with undetectable HBV DNA . However, the exact threshold remains controversial. Three different studies proposed that the threshold of viral load dictating recurrence was 0.5×10^3 IU/mL, 1×10^3 IU/mL and 2×10^4 IU/mL, respectively. These data suggest that it would be advantageous to use antiviral therapy with nucleos(t)ide analogues to reduce the viral load before transplantation.

3) In patients with HBsAg(-)and HBcAb(+) and having an undetectable HBV level, I consider that the ETV treatment can be initiated after the confirmation of the HBV replication. With a careful monitoring, before their HBV titers increase to threshold value, the patients may be safely treated with ETV administration. Please discuss the indication of the ETV treatment in HBsAg(-) patients.

Response: We thank the reviewer for raising this question. We have now expanded our Discussion section to include a detailed rationale for ETV treatment in HBsAg-negative patients. HBV is known to remain stably in the nucleus of affected hepatocytes in the form of covalently closed circular DNA (cccDNA). In HBsAg negative / HBcAb positive patients with normal immune function, HBV-specific CD8+T cells in the peripheral blood may

attack the affected cells via the Fas or perforin pathways and inhibit viral replication via release of IFN-r and TNF-a. However, after allo-HSCT, low levels of autogenous IgG may cause recurrence of HBV infection and increased HBsAg levels, resulting in increased incidence of HBV recurrence and high mortality rates.

Although the incidence of recurrence of HBV infection in these patients is lower than that seen in HBsAg positive patients, recurrence can cause fulminant hepatitis which has a high mortality. Rituximab therapy and hematopoietic stem cell transplantation are risk factors of HBV recurrence. Previous studies have shown that the incidence of recurrence of HBV infection is 10-20%. A retrospective study reported that the incidence of recurrence of HBV infection was 9.0%, 21.7% and 42.9% at 1, 2 and 4 years, respectively. The Consensus on the Management of Lymphoma Patients with HBV Infection in China (2013) recommends monitoring of hepatitis B immune markers and HBV DNA for patients with good compliance, and initiation of antiviral therapy when HBV DNA becomes positive. For patients with poor compliance, prophylactic anti-viral therapy is recommended before chemotherapy. Prophylactic antiviral therapy is also recommended for patients with a high risk for recurrence of HBV infection (including those receiving Rituximab therapy or HSCT and those with concomitant hepatic cirrhosis)

Minor comments:

1) In the Results section, they used various significant digits (such as 37.14%, 40%, and 48.7%...etc). Please show their data appropriately.
Response: The Results section has been revised to ensure consistency in presentation of data.

2) Please unify the terminology of two different descriptions (“anti-viral” and “antiviral”).
Response: The terminology has been unified to “antiviral”.

3) Methods: (Patients) HbsAg ⇢ HBsAg, HbcAb ⇢ HBcAb
Response: This correction has been made.

4) If possible, they should include the genotypes of HBV in Table 1.

Response: HBV genotypes were not determined in this study, and we have now included this as a limitation of the study.

Classification	○ Grade A (Excellent)	
	○ Grade B (Very good)	
	◉ Grade C (Good)	
	○ Grade D (Fair)	
	○ Grade E (Poor)	
Language evaluation	○ Grade A: priority publishing	
	◉ Grade B: minor language polishing	
	○ Grade C: a great deal of language polishing	
	○ Grade D: rejected	
Conclusion	○ Accept	
	○ High priority for publication	
	○ Rejection	
	○ Minor revision	
	◉ Major revision	

Reviewer 3

Comments To Authors	About 15% of the patients who are HBsAg-negative/antiHBc-positive would have HBV reactivation after chemotherapy or allo-HSCT. However in this study all of the patients received nucleoside analogs, about 80% of these patients would not need nucleoside analogs. It is ethical concerns.
Classification	○ Grade A (Excellent) ○ Grade B (Very good) ○ Grade C (Good) ○ Grade D (Fair) ◉ Grade E (Poor)
Language evaluation	○ Grade A: priority publishing ○ Grade B: minor language polishing ○ Grade C: a great deal of language polishing ◉ Grade D: rejected
Conclusion	○ Accept ○ High priority for publication ◉ Rejection

	Minor revision
	Major revision

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Confidential Comments To Editor

Response: We would like to clarify that this study was approved by the Ethics Committee of our hospital.
We do agree with the reviewer that the incidence of recurrence of HBV infection is low in HBsAg-negative/anti-HBc-positive patients. However, we have now emphasized in our Discussion section that HBV recurrence in this population of patients can result in severe liver injury or even fulminant hepatitis, and this may impact immunosuppressive therapy after transplantation, thereby influencing the prognosis of these patients. Furthermore, the Consensus on the Management of Lymphoma Patients with HBV Infection in China (2013) recommends prophylactic antiviral therapy for patients with a high risk for recurrence of HBV infection (including those receiving Rituximab therapy or HSCT and those with concomitant hepatic cirrhosis)

In this context, it is also important to note that the use of antiviral therapy has been shown to have no negative influence on the outcome of hematopoietic stem cell transplantation.