April 28, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17562-review.doc).

Title: Impact of partial reimbursement on hepatitis B antiviral utilization and adherence

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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 reviewers

Response to reviewer No 11164.

Proper counseling, selection of appropriate therapeutic regimens and compliance of patients with treatment maneuvers are critical to have optimum outcome of any management strategy of patients with chronic hepatitis B, although a completely cure from this pathological lesion is not expected at this point. Usually anti-viral drugs are required for prolonged period to manage these patients and to delay the emergence of complications. However, due to cost and nature of health care delivery system of most countries, the majority bulk of patients are usually unable to carry out treatment for requisite time. The numbers of patients with chronic hepatitis B in China are surprisingly high and seem to be more than total population of many countries of the world. The medical delivery system of China is highly heterogeneous and going to take a complex shape with advancement of time. The health insurance system is also of different forms in different parts of China. Within these state of confusion about health care support for its people, some parts of China have started to receive partial re-imbursement for hepatitis B treatment. The study presented here has tried to elucidate the implication of partial reimbursement of hepatitis B antiviral treatment on utilization and adherence to treatment. Two groups of patients have been compared to assess this effect. Generally speaking, these types of studies are highly warranted not only in China but also from other parts of the world to design antiviral treatment for chronic hepatitis B. However, the present study should be critically analyzed to assess its suitability as a scientific publication.

Comments 1.
The study has shown that introduction of reimbursement in Peking has made some alteration in the strategy of antiviral treatment in CHB patients. In one hand, there has been an increased utilization rate of antiviral in all sorts of patients after introduction of partial reimbursement. Also, insured patients had higher persistence rate of drug than paid out of pocket patient. When I went this manuscript, it seems to me the manuscript needs some alteration. The authors may omit general description about HBV and antiviral drug. Rather, they should provide information about medical insurance and health care delivery system of Peking and other part of china. More information is required about patients with medical insurance (PMI) and patients with paid out of pocket (PPO).

What about the cost of drugs? What is the average income of these people? What is the cost of PMI? Are the PPO patients needed to pay entire cost? What is the extent of partial reimbursement? These points are more important in this article than the general description of HBV and its treatment.

Response: Thanks for this constructive comments. We have added the detailed information for the cost of drugs, the average income of these patients and the extent of partial reimbursement in "Introduction" section , paragraph 3. The details are in the followings:

In China, both generic and branded drugs are currently available for antivirals and annual cost differs greatly across modalities. The branded drugs cost more than the generics. Annual cost ranges from $600 to $900 for LAM, $600 to $1000 for ADV, $ 1500 to $2000 for ETV, and $1400 for the only branded Ldt approved in China. The conventional IFN costs as much as $1500-$2500 annually while the Pegylation of IFN-α costs $7000-$8000.In Beijing, no reimbursement for all anti-HBV agents had been implemented before July 1, 2011 and all expenses were covered by the patients. Patients bear out of pockets no matter they were with or without medical insurance, which may have led to a poor adherence of antiviral therapy. Currently, all antiviral agents including IFN and NAs are on the list of National Reimbursement Catalogs of Drugs for Basic Medical Insurance and partial reimbursement has been implemented since July 1, 2011 in Beijing. Patients with medical insurance could receive a 75-85% reimbursement of the cost between a deductible of $300 and a ceiling of $3300. While for those without medical insurance, they still need to bear out of pockets themselves. It was estimated that the disposable personal income in Beijing was $5,353 in 2012. So, annual cost for CHB patients with antivirals was great burdens for patients and their families.

Comments 2.
There are significant rationale facts that must be solved. The authors mentioned that approval was obtained from 3 medical institutions of Peking. Subsequently, they mentioned that the authors took informed consent from hospital authority for data collection. This is hard to understand. To my knowledge, there is no scope to take any informed consent after there is an IRB. In addition, there is no authority in hospital that can give informed consent for any study except that has been shown in IRB.

Response: Sorry for our confused description. In fact, this study was approved by the Ethical Review Committee of Beijing You'an Hospital of Capital Medical University and Institute of Basic Medical Sciences Chinese Academy of Medical Sciences. And for the informed consent, given that the study poses no more than the minimal risk, and it would not be practicable to contact all the 30451 CHB patients in the two cohorts. A waiver of the informed consent was allowed by the Ethical Review Committee for the first part of study, involving secondary analysis of data of the two cohorts for a total of 30451 CHB patients. Deidentification was done to assure confidentiality of the study data.

Comments 3.
Also, no informed consent was taken form patients as data form electronic data base was used. This is a matter that to be addressed according to Chinese regulation. However, questioner was sent to 212patients who were randomly selected for this study. Also, telephonic discussion was made about personal information. Informed consent and written consent are probably needed to be taken from these patients. Please clarify these points.

Response: Really a good comments. In fact, an informed consent, written or oral was obtained from the participants dependent on questionnaire survey by face-to-face interview or telephone interview for the validation study part.

Comments 4.
The involvement of Bristol-Myers Squibb Company should be properly clarified.

Response: Although partly funding we received was from a commercial source "Bristol-Myers Squibb Company", which is the manufacturer of BARACLUDE (entecavir), one of the antiviral agents studied in our study for research grants, we have not signed an agreement with Bristol-Myers Squibb Company of the research reported in the contribution that prevents us from publishing both positive and negative results or that forbids us from publishing this research without the prior approval of the sponsor.

Response to reviewer No 1567591.

The study from Qiu and colleague's described the impact of partial reimbursement of CHB treatment on adherence in Beijing, China. The study showed that partial reimbursement, implemented in 2011, improved adherence as well as influenced the choice of NAs selected by the patients which should improve the overall outcome. On the positive side, large retrospective cohorts were followed just prior and after partial reimbursement implantation. However the results from this study confirm what could have been suggested intuitively.

Comments 1.
Although this study appears as a well design analysis, the reader would gain from having more information on the cost of treatment in China compared to income status. A comparison of IFN and NAs cost as well as a comparison between the cost of NAs.

Response: Thanks for this constructive comments. We have added the detailed information for the cost of drugs, and the average income of these patients in "Introduction" section , paragraph 3. The details are in the followings:

In China, both generic and branded drugs are currently available for antivirals and annual cost differs greatly across modalities. The branded drugs cost more than the generics. Annual cost ranges from $600 to $900 for LAM, $600 to $1000 for ADV, $ 1500 to $2000 for ETV, and $1400 for the only branded Ldt approved in China. The conventional IFN costs as much as $1500-$2500 annually while the Pegylation of IFN-α costs $7000-$8000.It was estimated that the disposable personal income in Beijing was $5,353 in 2012. So, annual cost for CHB patients with antivirals was great burdens for patients and their families.

Comments 2.
A better description of partial reimbursement? (is it 10% or 80%?). Is the reimbursement equal for every one? If not, is there a correlation between the level of reimbursement and adherence? What exactly is PMI in China? Indeed, the conclusion of the author is based on the assumption that partial reimbursement might reduce the economic burden. However, the reader does not have a real feeling of the economic burden on the Beijing population before reimbursement and on how much is reimbursed. A better description of the partial reimbursement will also help to evaluate the moderate improvement of the MPR observe on PPO (only 2%).

Response: Thanks for this constructive comments. We have added the detailed information for the cost of drugs, the average income of these patients and the extent of partial reimbursement in "Introduction" section , paragraph 3. The details are in the followings:

In Beijing, no reimbursement for all anti-HBV agents had been implemented before July 1, 2011 and

all expenses were covered by the patients. Patients bear out of pockets no matter they were with or without medical insurance, which may have led to a poor adherence of antiviral therapy. Currently, all antiviral agents including IFN and NAs are on the list of National Reimbursement Catalogs of Drugs for Basic Medical Insurance and partial reimbursement has been implemented since July 1, 2011 in Beijing. Patients with medical insurance could receive a 75-85% reimbursement of the cost between a deductible of $300 and a ceiling of $3300. While for those without medical insurance, they still need to bear out of pockets themselves. It was estimated that the disposable personal income in Beijing was $5,353 in 2012. So, annual cost for CHB patients with antivirals was great burdens for patients and their families.

Comments 3.
Page 15, line 10: PPI instead of PPO.

Response: We are very sorry for the incorrect writing and the mistake has been revised.

Comments 4.
Figure 2: instead of 4 symbols, could the symbol for before and after reimbursement be the same respectively?

Response: Thanks for the reviewer's suggestion and the symbol has been changed the same.

Response to reviewer No 1429800.

This study for the first time analyzed the impact of medication reimbursement on adherence to Hepatitis B antiviral treatment in Beijing, China, where chronic hepatitis B infection is endemic.

Comments 1.
The study is interesting, and improved description of features of PMI and PPO might be suitable.

Response: Thanks for your constructive comments. The description of PMI and PPO, especially the effect of reimbursement on their affordability is very important. So, we have added detailed information in the introduction part, paragraph 3. The details are in the followings:

In Beijing, no reimbursement for all anti-HBV agents had been implemented before July 1, 2011 and all expenses were covered by the patients. Patients bear out of pockets no matter they were with or without medical insurance, which may have led to a poor adherence of antiviral therapy. Currently, all antiviral agents including IFN and NAs are on the list of National Reimbursement Catalogs of Drugs for Basic Medical Insurance and partial reimbursement has been implemented since July 1, 2011 in Beijing. Patients with medical insurance could receive a 75-85% reimbursement of the cost between a deductible of $300 and a ceiling of $3300. While for those without medical insurance, they still need to bear out of pockets themselves.

Also, detailed description about the features of PMI and PPO have been added in the results part, paragraph 2. Details are in the followings:

Further analysis of cohort 1 showed that PMI was older than PPO (42.9±13.1 vs. 35.6±11.2, $P<0.0001$) and had less male patients (65.7 vs. 67.7, $P=0.0126$). The proportion of PMI with severity disease status was also higher than PPO (29.9% vs. 25.3%, $P<0.0001$). Similar tendency was observed between PMI and PPO in cohort 2 (data not shown).

As the characteristics were significantly different between PMI and PPO either before or after reimubursment, we also adopted multiple logistic regression analysis to explore the impact of reimbursement on antiviral utilization for PMI and PPO after adjusting the baseline characteristic. The details have been shown in the results part, paragraph 4:

As the characteristics were differently distributed between PMI and PPO either before or after reimbursement, multiple logistic regression was adopted to adjust the above covariates. Our results showed that the reimbursement can significantly improve the antiviral utilization for PMI than PPO even after adjusting the covariates, with the interaction odds ratio of 2.194 (95%CI: 1.979-2.432, P <0.0001) (data not shown).

3 References and typesetting were corrected

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

Sincerely yours,

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