Format for ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9666-Review.doc).

Title: A Delayed Hypersensitivity Reaction Resulting in a Maculopapular-Type Rash Due to Entecavir

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9666

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

point-by-point response to the reviewer's comment
Thank you for the thoughtful and expert review of our manuscript as well as for the valuable and insightful comments. We have responded to each of the Reviewer's comments as follows and have incorporated all the modifications suggestedby the Reviewers into the revised manuscript.
2 Revision has been made according to the suggestions of the reviewer

(1) How the authors confirm the type 4b hypersensitivity to ETV? The biopsy did not reflect unequivocally such assumption.

Response: Your question is very pointed for a speculation. We performed immunologic experiment to answer this question. We got the productive result. IL-4 cytokine was significantly higher than normal control at 18, 24 hours after the ETV treatment. Certain cytokines (IL-4, IL-5, IL-13), interact with eosinophils, which become the main cells involved.

Revision:

At the last part of Case, we described the experimental result. Figure 4 (cytokine release profile of PBMc) was added. But, other cytokines, such as IL-2, IL-6, IL-8 and TNF-alpha were statistically insignificantly elevated.

Our patient's skin lesions are classified as maculopapular exanthems. It is the most common type of drug-induced eruption, usually beginning 7 to 14 days after initiation of medication. Drug eruptions are involved in two types of hypersensitivity, type 1 and 4. Type 1 immnunologic reactions are usually immediate and present as acute urticaria. (Reference 7)

(2) The phenomena are described poor clarity. The rash appeared after a month of first round of ETV. But the patient continued under therapy for an additional one. What happened? The patient continued with ETV despite the rash during a month? The first appearance of rash is based on the patient reference without confirmation.

Response: I admit that I didn't show well organized big picture in terms of timeline in my first draft. In the first round, she finished 3 months of ETV medication. She didn't memorize the onset of skin eruption. She said that it was around 1 month from the starting point. But she didn't

notify me about the skin rash. She continued the medication for 3 months. The second round of ETV was in Oct, 2008. The period was just one week until cutaneous ADR occurred again. She experienced the same symptoms before in the first round. She thought that ETV might be culprit of skin rash and visited the Dermatology clinic in our hospital directly.

Revision: I rewrite the timeline to make the timeline clear in the case report. (line 6 from the bottom, page 5). Also, I indicated the sequential occurrence of events in Figure 3.

(3) Could this effect be related with hypersensitivity reaction type Ⅰ, as was reported by other? I would be relevant to evaluate the plasma level of specific IgE or at least, the total IgE when the skin rash is present.

Response: Cutaneous ADRs (adverse drug reaction) were classified into two types, type 1 and 4.
type 1: Acute urticaria is manifested by wheals and hives that appear as pruritic erythematous or pale-pink edematous patches. Anaphylaxis, also a type 1 hypersensitivity reaction, is a life-threatening condition that may follow a course with urticarial lesions plus systemic symptoms.
type 4: maculpapular exanthems are the most common type of drug-induced eruption, usually beginning 7 to 14 days after initiation of medication in nonsensitized patients. If a patient has been previously sensitized, the first signs of this CADR on the skin can appear earlier.
Authors think this case belonged to type 4. We didn't measure the specific IgE level around the skin rash, either total IgE level.

Cytokine release (IL-4) experimental data support the type 4 hypersensitivity. The maculopapular exanthema is more compatible for type 4 than type 1. Usual skin presentation for type 1 is generalized urticaria.
We had missed the opportunity to evaluate the plasma level of specific IgE or at least, the total IgE when the skin rash is present. It is a regret not to check the total IgE level at that time.

Revision: The levels of IL-4 were found to be significantly enhanced, indicating a classification of type Ⅳb delayed hypersensitivity (Fig. 4). I described the immunological experiment and showed the result at the end of the case part.

(4) Was the second round of ETV re-initiated 7 months after the first. In the description a period of two months were not mentioned (specifically the month 6 and 7) nor described what happened with the patient?

Response: I apologized that my description made the reader confused. I made a timeline table below. Please refer it.
Timeline of ETV medication

4th Feb-2008	Started ETV
3rd Mar-2008	Refilled 1 more month ETV
11st Apr-2008	Refilled 3 more month ETV
11st Jul-2008	She confessed not taking the medication, except first 1 month ETV out of total 3 months given. she refused the additional treatment. But, she went back with the next assignment.
10th Oct-2008	Re-initiated ETV treatment, but complained of skin rash 1week after treatment

Revision: Please refer the question number 2

(5) How the authors have discard the chance that the second rash could be associated with Garcinia Cambogia consumption?

Garcinia Cambogia leaf, plant extracts, is used to control body weight. The main content of

Garcinia cambogia was hydroxycitric acid. There was no previous case reports of skin eruption regarding to hydroxycitric acid administration when I searched the 95 literatures published until May 2014. Fatty liver has been known as mild side effect related to liver. But there was no report related to acute drug induced hepatotoxicity.

Revision: I described the indirect evidence of this weight loss supplement.(2nd paragraph in page 6) It is not permitted as a drug in Korean FDA. It is just a weight loss supplement.

Minor concerns

(1) define the lab procedures at least synthetically.(HBV viral load, transaminases, HBV qualitative DNA) How were preformed (commercial test)?

Response: we unified the HBV DNA unit into international unit with conversion rate. Various expression about HBV DNA and transaminase were changed into uniform expression as indicated.

How were perfomed (commercial test)?

HBV DNA levels were determined quantitatively by real time PCR (Roche Molecular Systems, Branchburg, NJ, USA). Genotypic resistance was investigated by RFMP analysis, as described previously by Lee et al (Green-Cross Medical Laboratories, Giheung, Korea)

Polish English writing:

AmEditor Med-Bio Editing helped me to proofread my manuscript. They will lock my document with special code.

I attached the certification from the company.

The x-axis in the figure should be defined with day-month-year. This will facilitate to follow the dynamics of the events.

Response: we corrected it as indicated

2nd reviewer: The HBVDNA unit should be turned to IU / ml from pg / ml

The unit was converted as indicated.

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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