ANSWERING REVIEWERS

November 2, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13135-edited.doc).

Title: Protracted anaphylaxis developed after peginterferon alfa-2a administration

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

2 Revisions have been made according to the suggestions of the reviewers and are highlighted in yellow in the text. We thank the reviewers for the complimentary remarks and many insightful and constructive comments. A point-by-point response to the Reviewers is as follows:

Reviewer1 (00058353)

-It's a very interesant case report. May be the long acting action of pegylated IFN has something to do in the protracted anaphylactit reaction.

Response: No changes required.

Reviewer2 (00035760)

- The authors describe a very unusual case of delayed anaphylaxis to peg interferon. It truly would have been exciting had a re-challenge been administered demonstrating the same symptoms. However, I'm curious why the authors performed a skin test in this gentleman prior to administering the medication. Is this a routine in the authors' practice? Why?

Response: For this case, we did not perform a re-challenge test because of the danger of recurrence of serious anaphylaxis. At our facility, it is a routine procedure to perform a skin test before administering interferon because the manufacturers' product enclosure sheets for this drug circulated throughout Japan recommends conducting a skin test before administering it.

Reviewer3 (01648266)

Major comments

1) In abstract, there is no conclusion and/or the authors message withdrawn from the case report.

Response: In line with your suggestion, I revised the abstract.(Page 2, Line 13-15)

2) It is well known that antihypertensive medication use is associated with severe anaphylaxis (Lee S, J Allergy Clin Immunol 2013). Therefore, amlodipine and irbesartan might exacerbate and prolonged peginterferon-induced anaphylaxis. Please discuss the possibility of the involvement of the antihypertensive medication in the protracted anaphylaxis.

Response: We cited the report that you suggested and added a discussion on the relationship between anaphylaxis and antihypertensive medication for this case.(Page 7, Line 9-17)

3) The clinical course of anaphylaxis is written in detail in the text, whereas Figure indicates only blood pressure and heart rate. The figure is not indispensable. If the clinical course were shown in a figure, the description in the text should have been concise. The gastrointestinal and respiratory symptoms and skin manifestation should have been schematically illustrated in the figure.

Response: We considered revising the figure; however, we finally decided to delete it based on your comment because we believe that it would be difficult to represent in detail the parameters for digestive tract symptoms and skin symptoms, which are difficult to quantify.

4) The description of two cases of anaphylaxis developing after interferon administration in the discussion is too long and redundant. Please summarize the cases.

Response: In line with your suggestion, we revised some of the content regarding past reports. We believe that information regarding symptoms and treatment regimens in past reports would be significant for readers when they encounter similar cases in the future owing to the low number of case reports and literature reviews of interferon-induced anaphylaxis. Thus, we were not able to reduce the word count considerably and we believe that allocating a certain amount of words to this section is unavoidable because differences between our case and those in past reports with regards to course and drug administration frequency until onset were characteristic and we wanted to emphasize this point. We would be very grateful for your understanding regarding these circumstances.(Page 6, Line 15-23)

5) Page 15, Line 7, generally, the negative result of DLST(Drug Lymphocyte Stimulation Test) does not support the notion that non-IgE-mediated mechanism was involved in the patient ㄱ s anaphylaxis.

Response: In line with your suggestion, we have deleted this from our report.(Page 5, Line 27-30)

Minor comments

1) Please check all reference numbers. Some of them are wrong (e.g. [7])

Response: In line with your suggestion, we have checked all reference numbers. Thank you very much for your careful review.

2) Page 15, Line 1, the explanation of non-IgE-mediated anaphylactoid is needless. -

Response: We have revised this section in accordance with your suggestion. (Page 5, Line 25-27)

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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