Format for ANSWERING REVIEWERS

February 28, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format
(file name: 150201_fulHepa_rTM_WJG_Rv).

Title: Anti-inflammatory effect of recombinant thrombomodulin for fulminant hepatic failure

Author: Kazutaka Kurokohchi, Osamu Imataki, and Fumiyoshi Kubo

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 15230

We thank the Reviewer for the helpful comments and suggestions.
The manuscript has been improved according to the Reviewer's suggestions, as follows:

1 Format has been updated.

2 Revision has been made according to the suggestions of the Reviewer:

To Reviewer 1 (reviewed by 01221925)

(1) Despite the potential role of thrombomodulin, the authors need to discuss and show more of a potential mechanism, as otherwise it is an observation only.

Response: We added our speculation and hypothesis based on the rational in vitro and in vivo mechanism reported previously. (page 9, lines 15 to page 10 line 7, in the Discussion)

(2) Addidtionally, have there been similar reports in the literature?

Response: To our knowledge so far on March 1, 2015, we were not able to find any similar report, likewise as our report, a treatment by rTM for acute hepatic failure. We only found the success treatment of lung fibrosis by rTM and it was slightly suggestive (BMJ Case Rep. 2014 Dec 17, online publication). Therefore, we believe this patient is first case report describing about a treatment by recombinant thrombomodulin for fulminant hepatic failure. We thank for your suggestion and made discuss about other inflammatory case treated with rTM referring this case report published in BMJ Case Rep (page 11, lines 7 to 8).

To Reviewer 2 (reviewed by 00729695)

(1) In this patient, steroid pulse therapy was performed with rTM administration. Steroid pulse therapy has very strong anti-inflammatory pharmacological effect. In the manuscript, author should comment the reasons why the improvement of fulminant hepatic failure was attributable only to rTM but not to steroid pulse therapy.

Response: Thank you for your comment. We speculate the anti-inflammatory effect was demonstrated specifically by rTM because that by corticosteroid is specific to lymphocyte. In our speculation, anti-inflammatory effect by rTM is via HMGB1 which is secreted mainly by monocytes. Nevertheless, corticosteroid cannot enough suppress activated monocytes. Glucocorticoids inhibit HMGB1-induced TNF-α production in downstream pathway from HMGB-1. Some other pathway from HMGB1 are assumed. This is a reason why corticosteroid pulse therapy could not attribute the improvement of hepatitis. This speculation was described in the text (page 9, lines 15 to page 10 line 7, in the Discussion). We hope that our revision meets your requirements.

(2) Author used rTM primary against DIC of this patient. More clinical description about DIC should be described, including the improvement of data concerning with DIC such as TAT, PIC, PAI-1, D-dimer and so on.

Response: Thank you for your suggestion. We added the more information about patient's coagulopathy, PT, APTT, fibrinogen, FDP and D-dimer (page 6, lines 14 to 15). Other coagulation parameters (TAT, OIC and PAI-1) you suggested had not been evaluated due to the weekend situation when the patient was admitted. However, patient's clinical data fit to the definition of DIC. We added these information in the text (page 6, lines 13 to 14, in the Case Presentation).

(3) It seems more valuable that histological data are available. Was autopsy performed in this patient? Is it possible that drug induced hepatitis was improved by steroid pulse therapy? To provide information, histological examination seems indispensable.

Response: Thank you for your advice. Unfortunately, we were not able to obtain a consent for autopsy. Therefore, drug-induced hepatitis is clinically probable diagnosis. Corticosteroid therapy is not a standard therapy for drug-induced hepatitis. But it is used for a relief of jaundice in fulminant hepatitis including drug-induced hepatitis in Japan, because some occasional cases had been reported to result in a successful treatment course. In this case, we observed dramatic recovery of hepatic function reflecting to the consequent recovery of PT level and confirmed the efficacy of rTM with the evaluation of cytokine milieu. As your suggestion, this report would be better if histological diagnosis were available. We added some information you suggested in the text (page 8, line 3) (page 7, lines 1 to 3). We hope that our revision satisfies your demand.

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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