January 10, 2015

Dear Editor-in-Chief,

The attached manuscript, "Combination therapy with daclatasvir and asunaprevir for dialysis patients infected with HCV," by Ken Sato et al, has been revised for publication in the World Journal of Clinical Cases. The corrections are shown in red. The format was changed according to the authors' instructions for the World Journal of Clinical Cases. The revised manuscript was edited by American Journal Experts. We have responded point-by-point to the reviewer's comments, as follows.

Please find enclosed the edited manuscript in Word format (file name: 23291-manuscript.doc).

Title: *Combination therapy with daclatasvir and asunaprevir for dialysis patients infected with HCV*

Author: *Ken Sato, Yuichi Yamazaki, Tatsuya Ohyama, Takeshi Kobayashi, Norio Horiguchi, Satoru Kakizaki, Motoyasu Kusano, and Masanobu Yamada*

Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 23291

Reviewed by 01562153

Comments To Authors

In this manuscript, the author reported the treatment of daclatasvir and asunaprevir in 4 cases of chronic hepatitis C patients with hemodialysis. The authors found that one patient had viral breakthrough and the 3 others had sustained virologic response, and that only one patient was admitted for heart failure and the combination therapy was well tolerated in the other 3 patients. This is a retrospective observational study on the combination therapy of daclatasvir and asunaprevir in 4 cases of chronic hepatitis C patients with

hemodialysis, the originality of this manuscript is not high. However, this article can provide some useful information for the clinicians for managing chronic hepatitis C patients with end stage renal disease. Comments 1. The Section of Case Report is too redundant. This part should be condensed. 2. The authors should provide the severity of liver disease of these patients, e.g. severity of fibrosis. 3. The authors should not treat the patient No.1, because they had found the existence of resistance associated virus (RAV) before treatment. The authors should not treat the patient just because the patient had a strong desire to receive treatment. 4. Some spelling errors should be corrected, e.g. sustained virologic response (not sustained virological response), resistance associated virus (not resistance associated viral resistance), etc.

First, this is a "prospective case report" on the combination therapy of daclatasvir and asunaprevir in 4 cases of chronic hepatitis C patients on hemodialysis. Until now, there have been no original articles or case reports regarding treatment with daclatasvir and asunaprevir in cases of chronic hepatitis C patients on hemodialysis in Japan. Thus, we believe that the originality of our case report is warranted.

Comments 1. The Section of Case Report is too redundant. This part should be condensed.

The Section of the case report was corrected and condensed.

2. The authors should provide the severity of liver disease of these patients, e.g. severity of fibrosis.

Considering the risk of liver biopsy for dialysis patients, it was not performed less than a year before treatment. Regarding case 1, the liver biopsy was performed approximately 10 years ago, and the histology showed fibrous portal expansion without bridging fibrosis. In fact, the patient had slight anemia due to bleeding detected by CT, three hours after liver biopsy. At that time, the platelet count was already at several tens of thousands. The patient had thrombocytopenia for unknown reasons. Thus, the severity of liver disease in all cases was judged as chronic hepatitis based on other laboratory data and imaging. We added the description in the text.

3. The authors should not treat the patient No.1, because they had found the

existence of resistance associated virus (RAV) before treatment. The authors should not treat the patient just because the patient had a strong desire to receive treatment.

We can understand the reviewer's opinion. The Japan Society of Hepatology (JSH) guidelines for the management of hepatitis C virus infection (version 3) at the time recommended the following: 1) simeprevir/peginterferon/ribavirin or daclatasvir/asunaprevir for partial responders to IFN-based therapy or 2) continuing without treatment and considering waiting for a promising future drug based on RAV. The most recent guidelines from the Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis published by the Ministry of Health, Labor and Welfare recommends the combination therapy of daclatasvir and asunaprevir or simeprevir/peginterferon/ribavirin for partial-responders to IFN-based therapy. In this case, the Y93H mutation was slightly positive, and the D168E mutation was positive. As ribavirin could not be used, the combination therapy of daclatasvir and asunaprevir or waiting for a promising future drug were alternative treatment options for case 1. Similar to the reviewer's opinion, we had the option of waiting for a promising future drug. The patient in case 1 had no liver atrophy but did display splenomegaly. We took into consideration that her liver showed at least hepatic fibrosis but not cirrhosis. Thus, waiting for a promising future drug without treatment may increase the risk of hepatocellular carcinoma, and we did not predict a period of HCC development. However, at the same time, we fully explained the risk of RAV and waiting for a promising future drug. Nevertheless, the patient had a strong desire to receive treatment. We showed remorse for the treatment failure in the "Discussion" section. This information should be useful for dialysis patients who will receive combination therapy in the future.

4. Some spelling errors should be corrected, e.g. sustained virologic response (not sustained virological response), resistance associated virus (not resistance associated viral resistance), etc.

We changed "sustained virological response" to "sustained virologic response". The abbreviation for RAV is "resistance-associated variants "due to the AASLD guidelines. Please see www.hcvguidelines.org. Thus, we corrected "resistance associated viral resistance "to "resistance-associated variants".

Reviewed by 00071472

Combination therapy with daclatasvir and asunaprevir for dialysis patients infected with HCV

Authors

Comments: The authors reported combination therapy with daclatasvir and asunaprevir for four dilaysis patients infected with HCV genotype 1b. Except for one patient which was discontinued after viral breakthrough, this combination therapy was quite effective, however long term observation and monitoring of patients should be done. Overall, this combination therapy was well tolerated in patients. This case report will be useful as a base for further investigate the effectiveness of the combination therapy of daclatasvir and asunaprevir in dialysis patients. However, extensive study should be done in order to establish guideline for application of direct-acting antiviral agents (DAAs) in dialysis patients infected with HCV. Although there is no guidance for application of DAAs in dialysis patients, it is much better if the authors explain the reasons why they discontinued this combination therapy in case 1.

The most recent guidelines from the Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis published by the Ministry of Health, Labor and Welfare recommends consideration for the discontinuation of antiviral therapy in the case of viral breakthrough referring to the reappearance of HCV RNA while still on therapy in patients who had >1 log10 increase in HCV RNA above the nadir. The maintenance of combination therapy for the patient who had viral breakthrough may promote multiple drug resistance. Thus, we discontinued the combination therapy after the definite diagnosis of viral breakthrough in case 1. We added this content in the text.

Best regards,

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