POINT TO POINT REPLY TO THE COMMENTS OF REVIEWERES

Reviewer 1

Reviewer's comment 1

SVR at 12 could be shorter, even if significant; is it possible to look at SVR at 24?

Author's reply

We thank the reviewer for the useful comment.

We checked the achievement of SVR 24 in all patients studied.

Two of the SVR 12 patients experienced late relapse of chronic hepatitis C and additional two patients were lost to follow up. Then, the SVR24 resulted in 87.2% (342/392). We inserted the sentence "Because two of the SVR12 patients experienced late relapse of chronic hepatitis C and two additional patients were lost to follow-up, the final SVR24 resulted in 87.2%." to the RESULT section (page 14 line 17, revised version).

Reviewer's comment 2

Serum markers of liver fibrosis sholud ameliorate after treatment, contemporary to biochemical and virological markers; Authors should give data on this topic.

Author's reply

We thank the reviewer for the useful comment.

Unfortunately, we measured serum markers of liver fibrosis such as serum 7S fragment of type Ⅳ collagen in a limited cases depending on the institutions. Instead, we calculated the values of FIB4 index both at baseline and after SVR12 in all cases. As the reviewer pointed out, the values of FIB4 index significantly ($P<0.001$) decreased after SVR12.

So, we inserted the sentences "The eradication of HCV can ameliorate liver inflammation as well as liver fibrosis[18]. We calculated the values of FIB4 index both at baseline and after SVR12. We found that there was a significant decrease in the values of FIB4 index after SVR12 as compared with those at baseline (baseline: 4.1 versus SVR12: 3.8; $P < 0.001$)." in the DISCUSSION section(page 21 line 1, revised version). We cited the paper by

Tada et al (Tada T, Kumada T, Toyoda H, Mizuno K, Sone Y, Kataoka S, Hashinokuchi S. Improvement of liver stiffness in patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response. J Gastroenterol Hepatol 2017 [PMID: 28299813 DOI: 10.1111/jgh.13788])

Reviewer: 2

Reviewer's comment 1

1) there have been quite a few reports about the SVR12 rates of DCV+ASV. We hope that the author can provide SVR24, even SVR48, as much as possible. 12 weeks should not be the end of the clinical treatments.

Author's reply

We thank the reviewer for the useful comment.

In response the comment of reviewer 1, we checked the achievement of SVR 24 in all 392 SVR12 patients studied. Two of the SVR 12 patients experienced late relapse of chronic hepatitis C and additional two patients were lost to follow up. Then, the SVR24 resulted in 87.2% (342/392). We inserted the sentence "Since two of the SVR12 patients experienced late relapse of chronic hepatitis C and additional two patients were lost to follow up, the SVR24 resulted in 87.2% finally." to the RESULT (page 14 line 17, revised version)section. Because many patients did not reach 48 weeks after finishing the DCV/ASV therapy, we could not calculate SVR48.

Reviewer's comment 2

2) Daclatasvir (DCV) is a NS5A replication complex inhibitor, ASV is a NS3 protease inhibitor. RASs including NS5A:L31, and, NS3:D168, and Y93 were detected before and after treatment in author's study. But why only analyze the correlation between SVR12 and NS5A RASs. it's better to add the correlation analysis between SVR12 and NS3 RASs.

Author's reply

We thank the reviewer for the valuable comment.

It is ideal to check RASs as many as possible at baseline. However, it costs much and it is time-consuming. We did not check the RASs in NS3 for two reasons. One reason is that naturally occurring NS3 RASs are reported to be rare. Another reason is that the guideline for the treatment of hepatitis C edited by the Japan Society of Hepatology do not recommend to check NS3 RASs, but recommend to check NS5A RASs before starting DAC/ASV treatment. So, we examined the RASs in NS3 only in patients who failed in DCV/ASV treatment.

23 **Bartels DJ**, Sullivan JC, Zhang EZ, Tigges AM, Dorrian JL, De Meyer S, Takemoto D, Dondero E, Kwong AD, Picchio G, Kieffer TL. Hepatitis C virus variants with decreased sensitivity to direct-acting antivirals (DAAs) were rarely observed in DAA-naive patients prior to treatment. J Virol 2013; 87(3): 1544-1553 [PMID: 23152524 PMCID: 3554180 DOI: JVI.02294-12 [pii] 10.1128/JVI.02294-12]

Reviewer's comment 3

3) There are too many typographical errors to read in the word manuscript.

Author's reply

We thank the reviewer for the useful comment.

The English of this paper was checked by a native speaker.

We add the CERTIFICATE OF EDITING in a separate sheet.

We hope the response to the reviewer's comments are satisfactory and the revised manuscript is acceptable for publication.