Author’s response to reviews

Title: Interleukin-28B gene non-TT allele strongly predicts treatment failure for genotype 1 infected chronic hepatitis C patients with advanced fibrosis: a case control study

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Author’s response to reviews: see over
Dear Editors:

Thank you very much for your kind letter of January 12, 2015 and constructive comments on our manuscript. My colleagues and I greatly appreciate the suggestions offered by you and the reviewers, and the opportunity to improve our manuscript.
We have made the following point-by-point revisions with all changes in red color words according to the suggestions of you and reviewers:

Reviewer 1 has 3 points:

1. **Although this study is well conducted, the usefulness of PR and IL28B in the upcoming DAA era is less important.**
   
   **Ans:** We agree with the reviewer’s opinion. However, although the new DAAs could achieve high SVR12 rates, irrespective to IL28B genotyping and RVR, the extremely high cost of DAAs is another problem and many of the patients may not afford it. In addition, those advanced fibrotic HCV-infected patients has a 3.9% and 1.4-8% annual incidence rate of developing hepatic decompensation and HCC, and previous studies have demonstrated that they could benefit from the PR therapy when obtaining an SVR with decreased morbidity and mortality. Thus, PR therapy is still one of the choice for HCV-infected patients with advanced hepatic fibrosis.

2. **The major limitation of this study is the novelty and short treatment duration for G1 patients.**
   
   **Ans:** The limitation of present study is that the treatment duration in GT1 HCV-infected patients is 24 weeks. It is contradictory to the present treatment guideline on chronic HCV infection, especially those with pretreatment high viral load or low viral load without achieving RVR, the recommended treatment duration is 48 weeks. However, this treatment duration was stipulated in the reimbursement policy of the National Health Insurance in Taiwan at that time, but treatment duration is now determined by response guided therapy. (page 19, line 334-339)

3. **Authors should provide the distribution of viral loads in G1 patients**
   
   **Ans:** The distribution of viral loads in G1 patients is shown in page 12, lines 197-199 and lines 201-203.
Reviewer 2 has 5 points:

1. **The major concern of the present study is the treatment regimen was suboptimal that HCV-1 patients received peg-IFN/RBV therapy for only 24 weeks. As most of the studies implicated that patients with genotype 1 have to receive 48 weeks therapy in standard. For patients with RVR and low viral load may receive shortened course.**

   **Ans:** We agree with the reviewer’s opinion. The limitation of present study is that the treatment duration in GT1 HCV-infected patients is 24 weeks. However, this treatment duration was stipulated in the reimbursement policy of the National Health Insurance in Taiwan at that time, but treatment duration is now determined by response to therapy. (page 19, line 334-339)

2. **The pretreatment viral load deserves clearer description. To analyze the known important determinant RVR+viral load for the better response in the study is critical. Authors used 800,000 IU/ML as cutoff of the low and high viral load. It is also interesting to explore the cutoff of RNA level for predicting SVR in patients with or without advance fibrosis. What is the condition when RVR, IL 28B SNP and viral load are considered together**

   **Ans:**
   
   (1) The pretreatment viral load had been re-written in page 12, lines 197-199 and lines 201-203.

   (2) We try to use the 800,000 IU/ML and 400,000 IU/ML as the cutoff point for high and low viral load in HCV G1 infected patients. But, the SVR rates in patients with low and high viral load are not different when the cutoff point 400,000 IU/ML is chose (59.4% versus 39.7%; p = 0.07). The cutoff point seems better to be 800,000 IU/ML (LVL versus HVL, 59.4% : 39.7%; p = 0.02). However, in the multivariate analysis, the influence of low viral load on SVR rate seems to be attenuated by other factor.
(3) The influence of HCV RNA level over SVR in HCV G1 infected patients with and without advanced fibrosis is listed in the table.

<table>
<thead>
<tr>
<th>Advanced fibrosis</th>
<th>LVL cutoff</th>
<th>SVR(+) n/N(%)</th>
<th>SVR(-) n/N(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>400,000 IU/ML</td>
<td>2/6 (33.3)</td>
<td>5/19 (26.3)</td>
<td>0.739</td>
</tr>
<tr>
<td></td>
<td>800,000 IU/ML</td>
<td>4/6 (66.7)</td>
<td>6/19 (31.6)</td>
<td>0.126</td>
</tr>
<tr>
<td>No</td>
<td>400,000 IU/ML</td>
<td>17/40 (42.5)</td>
<td>8/35 (22.9)</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>800,000 IU/ML</td>
<td>22/40 (55.0)</td>
<td>12/35 (34.3)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

(4) Among the HCV genotype 1 infected advanced fibrotic patients with rs8099917 TT genotype and an RVR, the SVR rates of patients with HVL and LVL are 25% and 60%, respectively (p = 0.52). In contrast to those with the same parameters without advanced hepatic fibrosis, the SVR rates of patients with HVL and LVL are 60% and 91%, respectively (p = 0.42). Only one patient without rs8099917 TT genotype and an RVR achieved an SVR.

3. In the present study 44.4% of SVR rate was observed from HCV GT1-infected group A patients with an RVR. The viral load has to be taken into consideration firstly. By the way, the 44.4% SVR rate is lower than previous randomized control studies in Taiwan (76~89% for patients with GT1 and RVR). Authors may explain the possible reasons. How about the SVR rate from HCV GT1-infected group B patients with an RVR?

Ans: We agree with the reviewer’s opinion that previous reports from Taiwan have demonstrated a 76-89% SVR in HCV GT1 and RVR patients. However, if we take the hepatic fibrosis into account, one report from Taiwan has shown the SVR decreased to 30.8% in F3/F4 receiving 24 weeks PR therapy (reference). In contrast, present study has shown HCV GT1-infected advanced fibrotic patients with an RVR had a SVR rate of 44.4%. Hence, the SVR is reasonable and acceptable of present study. The SVR of HCV GT1-infected group B patients with an RVR is 75.6% and it had been listed in table 2.

4. Page 17 line 295: In this study, authors found that none of the patients with advanced fibrosis and rs8099917 non-TT genotype achieved an RVR, and all of them
failed to have an SVR after 24 week therapy. What are the roles of viral load and cEVR in these patients?

Ans: Of the three patients without an RVR, two patients had viral load below 800,000 IU/ML at baseline. One of the patients with LVL achieved cEVR. However, none of these achieved an SVR.

5. Page 13 line 227: lower HCV RNA should be “pretreatment lower HCV RNA level”

Ans: Thanks, we have modified the term accordingly (page 14, line 233)

Reference


Enclosed please find our revised manuscript with the changes/additions in red color words. I hope that it is now acceptable for publication in BMC Infectious Diseases. Thank you very much indeed for your kind attention, patience and help.

Looking forward to hearing from you at your earlier convenience.

Best Regards,

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