Author's response to reviews

Title: Cost-effectiveness of adding rituximab to splenectomy and romiplostim for treating steroid-resistant idiopathic thrombocytopenic purpura in adult

Authors:

Kayoko Kikuchi (kayokok@a6.keio.jp)
Yoshitaka Miyakawa (miyakawa@saitama-med.ac.jp)
Shunya Ikeda (shunya@iuhw.ac.jp)
Yuji Sato (yjsato@a3.keio.jp)
Toru Takebayashi (ttakebayashi@a3.keio.jp)

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Author's response to reviews: see over
November 14, 2014

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Title: Cost effectiveness of adding rituximab to splenectomy and romiplostim for treating steroid-resistant idiopathic thrombocytopenic purpura in adult.

Dear Dr. Morrey,

Thank you for your email of October 27, 2014, regarding our manuscript, “Cost effectiveness of adding rituximab to splenectomy and romiplostim for treating steroid-resistant idiopathic thrombocytopenic purpura in adult”, and the valuable comments of the three reviewers. In the following pages are our point-by-point responses to each of the comments of the reviewers. Please find attached a revised version of our manuscript which was revised according to reviewer’s comments and edited by a native-English speaker according to editorial request.

We feel that the revised manuscript is a suitable response to the comments, and is significantly improved over the initial submission. This would certainly be the final version for publication in the BMC Health Services Research.

Thank you in advance for your kind consideration of this paper.

Sincerely yours,

Kayoko Kikuchi
Center for Clinical Research, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan
TEL: +81-3-6804-6716
FAX: +81-3-6804-6631
<Response to reviewer: Philippe Boierling>
I appreciate your attention and cooperation.

<Response to reviewer: Helmut Ostermann>
I appreciate your attention and cooperation.

<Response to reviewer: Anneke Brand>
We wish to express our appreciation to you for your insightful comments on our paper. The comments have helped us significantly improve the paper. Our responses to your comments are as the following.

Comment: Q1 Page 5, although 60% of patients show a sufficient platelet increment, the median response duration is limited and after 5 years 20-25% have sufficient platelet cts.(ref 7). The authors proposed the following change: “it was reported that the platelet count exceeded 50x10E9/L in 62.5% of the patients, while relapses are also reported”. I remarked that after 5 yrs only 20-25% have relapsed. In my perception their adjustment is an understatement.

Response: In accordance with the reviewer’s comment, we have changed the following text from (p7, line 104):

“In a systematic review of the curative effect of rituximab targeting approximately 300 ITP patients, it was reported that the platelet count exceeded 50×10^9/L in 62.5% of patients, while relapses are also reported [7]."

To

“In a systematic review of the curative effect of rituximab targeting approximately 300 patients with ITP, it was reported that the platelet count exceeded 50 × 10^9/L in 62.5% of patients [7]. The median response duration is limited; after 5 years, 20%–25% of patients have sufficient platelet counts [7]."
Comment: Q2-Q8: answers OK

Response: We are grateful for your cooperation.

Comment: Q9: although the answer is covering the question, it remains crucial how many patients responding to Ri and for how long (thus avoiding TPO-RA) are required to be cost-effective.

Response:
We appreciate the reviewer’s comment on this point. The analysis was conducted assuming that the efficacy of rituximab was 71.6% and relapse rate was 0.88%/4weeks. As a result, adding the treatment option of rituximab is less costly and more effective than sequence1 (SP-romiplostim). Assuming that the mortality rate was 2.1-fold higher than that in healthy individuals, which is half of the mortality rate of the base analysis, we conducted the sensitivity analyses to assess the impact of the mortality rate. The mortality rate did not have great influence on the base case analysis.

The result of sensitivity analysis is as follows:

<table>
<thead>
<tr>
<th>Treatment order</th>
<th>Deaths*</th>
<th>Cost-effectiveness ratio †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base analysis‡</td>
<td>Sensitivity analysis§</td>
</tr>
<tr>
<td>Sp- TPO-RA</td>
<td>87.02</td>
<td>79.86</td>
</tr>
<tr>
<td>Sp- TPO-RA- Ri</td>
<td>85.44</td>
<td>79.67</td>
</tr>
<tr>
<td>Sp- Ri- TPO-RA</td>
<td>85.65</td>
<td>79.69</td>
</tr>
</tbody>
</table>

* The number of patients among 10,000 people.
† Two-year expected cost (USD) / period of PL ≥ 30×10⁹/L (years).
‡ We assumed that the mortality rate of ITP patients with a platelet count < 30 × 10⁹/L is 4.2-fold higher than that in healthy individuals.
§ We assumed that the mortality rate of ITP patients with a platelet count < 30 × 10⁹/L is 2.1-fold higher than that in healthy individuals.

In accordance with the reviewer’s comment, we have added the following to the Discussion (p19, line 341):

New text
It is possible that the mortality rate, even if the platelet count is <30 × 10⁹/L, is no longer
4.2-fold higher than that of the healthy population because the referred mortality rate was determined prior to the availability of rituximab and romiplostim. Therefore, assuming that the mortality rate was 2.1-fold higher than that in healthy individuals, which is half of the mortality rate of the base analysis, we conducted the sensitivity analyses to assess the impact of the mortality rate. The mortality rate did not have great influence on the base case analysis.

Comment: Q9 through Q20: are adequately addressed.

Response: We are grateful for your cooperation.

Comment: In the text (in contrast to tables) the punctuation in amounts of USD is lacking.

Response:
Regarding the punctuation marks in the amount of USD, we checked out again in the text, but we think they are inserted on suitable positions like tables and we couldn't find out the parts you mentioned. So could you point out specifically where we should correct?

Thank you again for your comments on our paper. I trust that the revised manuscript is suitable for publication.