Author's response to reviews

Title: Association between low-dose pulsed intravenous cyclophosphamide therapy and amenorrhea in patients with systemic lupus erythematosus: A case-control study

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Author's response to reviews: see over
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Association between low-dose pulsed intravenous cyclophosphamide therapy and amenorrhea in patients with systemic lupus erythematosus: A case-control study

We have again revised our manuscript (1067683819515606) entitled, “Association between low-dose pulsed intravenous cyclophosphamide therapy and amenorrhea in patients with systemic lupus erythematosus: A case-control study” by Sayumi Baba et al.
We believe that we have suitably and substantially revised the content in accordance with the comments we received, as described below. The following are point-by-point listings of the changes that have been made in the revised version. The changed sections are highlighted in the revised manuscript.

Referee 2
The authors have adequately answered most of the comments. Nevertheless, the major drawbacks in this study are the small number of patients, especially in the age group over 40 years, the very low median cyclophosphamide dose and the very (unusually) high observed amenorrhea rates.

Major Compulsory Revisions
1. The authors added information on the amenorrhea rates observed in other age groups, eg. 32, 35 and 37 years of age. In the main document (Results, Associations between amenorrhea and clinical parameters, lines 7-8), they mention that there was no association between these age groups and the development of amenorrhea. Nevertheless, the statistical results for the age group of 35 years are marginally significant, as indicated by a p-value of 0.06, and for the age group of 37 years seem to be significant (p-value 0.04). Thus, there is an increasing risk for amenorrhea after the age of 35 years. The authors should emphasize this observation not only in the Results but in the Discussion, 3rd paragraph, as well.
>>> We inserted phrases in the revised manuscript that emphasize this observation as indicated by the reviewer (page 11, line 9; page 16, line 6).

2. The authors should delete the phrase “although we do not fully understand what occurred at around that age” in the Discussion at the end of the 3rd paragraph.
>>> We eliminated the phrase in the revised manuscript as indicated by the reviewer (page 16, line 10).
3. The statement that Japanese patients can be treated with weaker regimens because they tend to see rheumatologists early in their disease course is not reliable (Cover letter).

4. In the Discussion, 5th paragraph, the statement that it is not clear enough to conclude whether the incidence of amenorrhea in the present study is higher than usual is not true. In previous reports, both the rates of sustained amenorrhea (Boumpas 1993, 7 pulses: 12%# Mok 1998, <10 g: 4%# Huong 2002, 7 pulses: 18%# Park 2004, <5g: 0% and 5-10g: 8%# Appenzeller 2007, 5-9g: 0%# Laskari 2010, 5-7 pulses: 4%) and transient amenorrhea (Boumpas 1993, 7 pulses: 31%# Appenzeller 2007, 5-9g: 0%# Laskari 2010, 5-7 pulses: 14%) among patients receiving a low cyclophosphamide dosage were lower than in the present study. Moreover, the high amenorrhea rates in the study by Tham et al (2007) may be explained by the concomitant administration of cyclophosphamide and doxorubicin. It would be advisable to remove this paragraph from the main document.

>>> We removed this paragraph in the revised manuscript as indicated by the reviewer (page 17, line 3).