Reviewer's report

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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Reviewer: HIROSHI KAJIYAMA

Reviewer's report:

Baba et al studied how IVCY affect ovary function in 45 year-old or younger female Japanese patients with SLE, and clarified clinical parameters, which is associated with amenorrhea after IVCY treatment by a single-center case-control retrospective study.

General comments

Although there are some limitations such as selection bias and insufficiency of subject number, the incidence for sustained amenorrhea by IVCY in Japanese patient was described by retrospective study. Authors also clarified that even low-dose IVCY caused transient amenorrhea, although it resumed in all 40 year-old or younger patients after IVCY, which might be interpreted as the one of the benefits in IVCY for Japanese patients younger than 40 with SLE. It was found in this study that 40 and older might be the risk factor for sustained amenorrhea. Complying with the review guideline by the editorial team, comments are categorized as follows:

Major Compulsory Revisions

1) Time between treatment and amenorrhea, duration of amenorrhea, and time to resumption of menses were raised in “Data Collection” part. However, the data were not presented anywhere. They are also important and helpful for physician and patients to plan the treatment, and especially, time to resumption would be one of the concerns for patients. Please consider describing these data.

>>> We added the data in the revised manuscript as suggested by the reviewer (page 12, line 11). We are afraid we do not have appropriate data about time between treatment and amenorrhea, and thus we eliminated this part from the revised manuscript.

- Authors properly revised the original manuscript as suggested.

Minor Essential Revisions

1) In Table 2 and 3, some parts show P value and OR comparing longitudinally and the other parts showed them comparing transversally, and that makes readers confusing. Please specify which data was subject to each univariate analysis in an appropriate way.

One of the examples are as follows:
In “Associations between amenorrhea and clinical parameters” part, P value, odds ratio and 95% CI (0.02, 3.5 (1.3-11.0) for the difference of amenorrhea incidence between the IVCY group and the steroid group described in the text are all same as what is described in the table 2 for amenorrhea incidence in the IVCY group. When readers see table 2, they might think that 0.02 and 3.5(1.3-11.0) are the data comparing 17/26 and 12/36 within the IVCY group.

Regarding the data comparing amenorrhea cases between subjects <40 and subjects 40 and older, it might be acceptable, since we could tell from the “raw” data – 17 and 9, described both in table 2 and 3.

>>> We modified the tables in the revised manuscript as suggested by the reviewer (Tables 3 and 4). We appreciate the reviewer’s suggestions, which have given more readability to our data.

- Authors properly revised the original manuscript as suggested.

2) In the third paragraph of “Discussion” part, we see the sentence “ The strongest risk factor for developing….”, and from the context, it could be known that the sentence is describing your study, but it might puzzle some readers. Some words or phrases might be added to this sentence to make readers understand that it describes your data, not data previously reported.

>>> We inserted the phrase “in the present study” in the sentence of the revised manuscript as suggested by the reviewer (page 15, line 18).

- Authors properly revised the original manuscript as suggested.

3) “in a retrospective study” might be changed to “in a single center retrospective study” in the beginning of the fifth paragraph of “Discussion” part.

>>> We inserted the phrase “single center” in the sentence of the revised manuscript as suggested by the reviewer (page 17, line 12).

- Authors properly revised the original manuscript as suggested.

4) “reported previously” might be added at the last of the sentence, “However, the size of our study population was comparable to similar studies” in the fifth paragraph of “Discussion” part.

>>> We inserted the phrase “reported previously” in the sentence of the revised manuscript as suggested by the reviewer (page 17, line 17).

- Authors properly revised the original manuscript as suggested.

Discretionary Revisions

1) If the incidence of pregnancy would be included in your database for this study, that would be more helpful for clinician to offer IVCY to patients with SLE. However, pregnancy itself is a risk factor for recurrence of lupus, and it might be difficult to find such cases.

>>> There is a patient who experienced pregnancies and delivers twice in the IVCY group. However, we feel it is difficult to discuss the effect of IVCY on
pregnancy because there are many other factors involved, as the reviewer suggested.
- Authors properly responded to the reviewer’s suggestion.

2) In “Discussion” part, comparison of your data and the previous data in high-dose IVCY is described, and this might be presented as Table 7, since this is also one of the most important parts, which makes your data valuable and appealing to the readers.

>>> This study was not designed to perform comparisons between low-dose and high-dose IVCY. Thus, we are afraid that it would cause other problems to present a table that shows direct and detailed comparisons. In addition, authors are encouraged to be concise in this journal. Because we already have 6 tables, we are afraid that it would be redundant to add another table describing other investigators’ data.
- Authors properly responded to the reviewer’s suggestion.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.