Reviewer’s report

Title: A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in newly diagnosed generalized myasthenia gravis

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Reviewer: Kimiaki Utsugisawa

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Heckmann and colleagues report steroid-sparing effects of safety dose MTX in comparison with those of conventional dose AZA among de novo generalized MG patients by assessing prednisone requirements to maintain MMS in a prednisone-tapering regimentation. Although there was no difference in steroid-sparing effects between the AZA- and MTX-groups at the final observation (at 24M), MTX-group showed an earlier effect within one year into the study. Considering a paucity of MTX trials for MG and the need for inexpensive MG therapies in developing countries, I feel that the subjects handled in this article are very important.

As for the primary outcome (the prednisone requirement), the results are well described and sound. However, unnecessary data handling for other estimation items and the use of undefined and inconsistent nomenclature made the paper redundant and scattered. The current paper, a small sized study, should be more concise.

The reviewer would encourage and suggest the following points to improve clearer understanding of this manuscript.

#1 Major points

1. If the authors estimated patients with MG-ADL=0 as MMS, a description ‘Firstly, we used the improvement in Quantified MG Score (QMGS) compared to baseline aiming for minimal manifestation status (MMS)...’ is inconsistent. (Methods section, the second paragraph). In fact, there is no reason that MMS should be provided in severity scores. The improvement in QMGS is better to be included in secondary outcomes, and Table 2 and 3 should be integrated into one table. Actual QMGS point should be given in the table.

2. Frequency and explanation of adverse events should be more concisely described.

3. Data handling and presentation using the Kaplan-Meier method appear to be somewhat interesting but are very confusing in this paper, because items analyzed were apart from main outcome measurements. And your intended meanings of ‘sustained remission’ and ‘first study failure’ are unclear. The term ‘remission’ should not be used without definition. The Y-axis in Figure 3 should indicates frequency or ratio but not time. I strongly suggest omitting Figure 3 and related descriptions.
# Minor points

1. ‘Quantified’ MG Score (QMGS) should be read as ‘quantitative’ MG score throughout the text.

2. ‘Seropositive or -negative’ should be read as ‘AChR-Ab-positive or -negative’.
   (throughout the text and Table 1).

3. Original plan for a multicenter trial is unnecessary to be mentioned and should be omitted (Methods section, the first paragraph; Results section, the first paragraph).

4. Differences between minimum MG symptoms and MMS should be commented. (page 4, line 5 from bottom; page 6, the last sentence); otherwise are both the same?

5. I cannot catch authors’ meaning for a sentence ‘Thymoma(-associated) MG subjects were stabilized as per standard care and surgery scheduled at the earliest possible time.’ (Subject section, the second paragraph)

6. Did the authors try and see if the requirement for cholinesterase inhibitors was changed during the course or if dose of cholinesterase inhibitors affected evaluation of severity such as QMGS and MMS?

7. The reviewer accept a modification of QMGS concerning hand grip, but descriptions for explanation ‘...and thus adjusted the normal values for the grip dynamometer from 50- to that of 70-years as per manufacturer(page 8, line 5)’ is not clear.

8. A description ‘...worsening during the first year as defined by more than 20% loss in the baseline QMGS (page 9, lines 7-8)’ is not clear.

9. ‘An additional 7 subjects’ is better to be ‘The residual 7 subjects’ (page 9, the last line).

10. The term ‘prednisone-naïve’ would not be good.

11. It is unclear how did ‘sustained MMS’ differ from ‘MMS’ (page 8, line 5 from bottom; page 11, the first line).

12. ‘hospitalization (± IVIg or P/E)’ would not be good.

13. ‘Unrelated events’ in table 3 is better to be replaced by ‘Myocardial infarction’ and explanations in the text (page 11 the third paragraph) to be shortened.

14. Your expressions regarding ‘either’ and ‘neither’ are incorrect.

15. Meaning of ‘for a month’ underlined in ‘Two patients omitted prednisone for a month at month-2 (AZA) and month-5 (MTX) and another in the MTX-group omitted all drugs at month-11.’ is unclear (page 12, lines 6-7). And such minor results are better to be omitted.

16. A sentence ‘Our results concur showing that....’(page 12, lines 6-4 from bottom) is better to be omitted.

17. ‘...periods, both of which are expected if the protocol-guided prednisone reduction was followed.’ is unclear (page 13, the first line).
18. ‘measured by the minimum QMGS improvement [15].’ is unclear (page 13, line 3).

19. “symptom remission rate” is unclear (page 13, lines 5-6).

20. I feel the last paragraph in page 13 regarding folate supplementation is better to be omitted.

21. As for the first paragraph regarding limitations of the paper, sentences from ‘The failed effort…’ to ‘…therefore not a confounder in this study.’ all are better to be omitted. And if MuSK-Ab-positivity was not systematically examined, that should be commented as a limitation of this paper, and thereafter, be continued to descriptions for your MuSK-Ab-positive case. Sentences from ‘We have shown that MTX is …’ to the last of this paragraph are also better to be omitted. And the remaining sentences should be integrated with the next paragraph ‘Other limitations…’.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.