Reviewer's report

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

Version: 1 Date: 11 May 2011

Reviewer: Henry J Kaminski

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MAJOR COMPULSORY REVISIONS.

The study presented is to provide a direct comparison of methotrexate and azathioprine in treatment of MG. It is an important comparative effectiveness study. Such studies are important for the field of MG. I have several comments.

1) As written the entrance criteria are equivocally stated. The Methods describe subjects as all having the MGFA classes greater than 1 and duration of symptoms greater than 4 years, but was that specified by defined entrance criteria or what was defined at the end of the study. Was disease less than 4 years a requirement for entrance?

2) The primary endpoint is not clear. It is stated as “average prednisone dose to maintain MMS” but at one time. End of study? There appears not to have been an exact expectation set prior to start of the study. How much of difference was expected to be clinically meaningful? OR was the expectation of no difference and then a conclusion made that methotrexate is superior because of lower costs. How was the original sample size of 60 estimated and what is the impact of not reaching the target?

3) There are 2 issues that appear to potentially bias the study. 1) Only patients refusing thymectomy were entered into the study. There may be non-random influences on patient characteristics. 2) Some patients could not be entered into an azathioprine group because of inability obtain the medication and therefore entered into methotrexate treatment. It is not know what potential bias could have occurred because of this situation. The investigators should discuss this point.

4) It appears the PI evaluated patients and escalated dose of prednisone. It is not clear how decisions to adjust prednisone dose were made in conjunction with blinded evaluators.

5) The trial did not achieve recruitment goals and it is critical for the investigators to provide a focused assessment of how compromised recruitment influenced study results. Also, it would benefit the field to learn why recruitment was poor. Only 1 of 4 centers recruited any patients!

6) The Results section should be condensed significantly to emphasize the largely negative study, except for minor differences found during months 10 and 12.

7) The Discussion on page 14 describes “newly diagnosed” but inclusion criteria
state a 4 year disease duration, which I would not consider newly diagnosed.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.