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: 4 May 2011

Reviewer: Matthew Meriggioli

Reviewer’s report:

Major Compulsory Revisions
None

Minor essential revisions:
1. It is never expressly stated in the “methods” at what time point the primary outcome was to be assessed – I presume this is 24 months - this should be stated explicitly under "Methods”.
2. It is also not expressly stated when the clinical assessments were performed in relation to pyridostigmine dosing, which would obviously have an effect on QMG score.
3. Obviously the therapeutic effect of prednisone cannot be assessed in isolation from the potential effects of the study drugs, and the steroid dose required to maintain a therapeutic effect differs in disease of varying severity. The vast majority of patients in both groups were “responders” based on an improvement of at least 3.5 QMG points, but given that this improvement was seen within 6 months in over 80% of patients, it is possibly steroid effect. This should be noted in the discussion section.

Discretionary Revisions/Comments
The study design was a 24 month parallel group study designed to mimic the study of Palace and colleagues. An obvious problem is that the PI and patients were unblinded. In addition, the study medications were administered by prescription, with limited ability to verify doses actually taken – which is crucial since mean prednisone dose was the primary outcome measure. As there were patients who could not afford AZA, the randomization process was compromised. Also, given that mean prednisone dose was the primary outcome, it is troubling that it appears that patients were initially enrolled on different baseline doses, with some patients even entering the study as prednisone-naïve (with a ‘standard’ protocol for prednisone initiation, that was different for hospitalized patients).

The methods do not indicate that baseline steroid doses were adjusted to a certain baseline “standard” prior to enrollment in patients already on prednisone. Although the mean prednisone dose at baseline did not differ significantly between the study groups, this design is not ideal, but I suspect was initiated to encourage enrollment and mimic the real-life situation.
As suggested in the “discussion” section, time to achievement of sustained minimal manifestations state might have been a more appropriate primary outcome in this particular study given the limitations.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

**PATENTS HELD:**