Peer Review File

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Reviewer A

This is a well-written and well-designed study with valuable, interesting results that contribute to understanding the resistance to MG immunosupressant treatment. Please find below the reviewer's comments:

Comment 1: The authors state in the discussion session (p. 12, line 4) that "Previous studies have found that HSP90AA1 is closely associated with resistance to therapy by inhibiting apoptosis and inducing autophagy (22)". However, reference 22 is about mechanisms of resistance to osteosarcoma therapy. In the case of cancers, autophagy can play a prosurvival role, which would lead to therapy resistance. How does autophagy lead to MG therapy resistance?

Reply 1: We appreciate the reviewer's valuable comments. The relationship between autophagy and therapy resistance in MG remains unclear and has been elucidated in the revised discussion (see Page 12, lines 4-5).

Comment 2: HSP90AA1 rs7160651 might be related to glucocorticoid resistance, for which another mechanism has been proposed in the discussion section in reference (8). It concerns HSP90 overexpression and accumulation in the nucleus, hindering GC-GR complext interaction with the DNA. This mechanism should be briefly described in the discussion session.

Reply 2: We thank the reviewer for this important comment. The mechanism above has been described in the revised discussion (see Page 12, lines 9-12).

Comment 3: In page 6, line 11, please replace "retrospectively" with "retrospective".

Reply 3: This error has been corrected (see Page 6, line 10).

Comment 4: In the statistical analysis section, the authors state that no multiple testing correction was applied due to the exploratory character of the study. Many of the significant p values of the analysis are close to p = 0.05 and the tests would therefore lose significance if multiple testing correction was applied. Therefore, this should also be added as a limitation of the study.

Reply 4: Thank you for the suggestion. We have pointed out this limitation in the revised manuscript (see Page 14, line 7).

Comment 5: Please provide the number/ID of the ethical approval.

Reply 5: Thank you for the comment. The approval ID has been provided in the revised manuscript (see Page 6, line 14).

Reviewer B

This is a well-done study using the generally recommended outcome measures defined the MG Foundation of America. Using these instruments the group identified likely polymorphisms that determine refractory myasthenia gravis patients. Most critically HSP90AA1 and CYP3A5 were associated with refractory MG. The association with drug metabolism provides a logical state to influence response to treatment.

One generic challenge for the field is that there is no accepted definition of refractory MG, which makes identification of genetic associations even more impressive.

As a discovery study, I think the authors go a step to far in recommendation potential for screening for these polymorphisms to guide therapy.

Reply: We appreciate the reviewer's kindly comment. Our follow-up studies are currently planned and in progress to screen for these polymorphisms to guide therapy.