CONFLICTS OF INTEREST

Dr. Raghav Govindarajan serves on the advisory board of Alexion Pharmaceuticals. Klaudia Kukulka reports no disclosures. Dr. Rohit Reddy Gummi reports no disclosures.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Correlation of Quantitative Myasthenia Gravis and Myasthenia Gravis Activities of Daily Living scales in the MGTX study

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Abstract

Introduction: Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Activities of Daily Living (MG-ADL) scales were compared using the data from the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) study.

Methods: Correlation between QMG and MG-ADL raw and change-from-baseline scores was calculated every 3 months for 60 months based on treatment groups and minimal manifestation status (MMS).

Results: QMG and MG-ADL change-from-baseline scores correlated significantly, with increasing strength of correlation over time, in both treatment groups. QMG and MG-ADL raw scores correlated significantly in both treatment groups, with increasing correlation only in the prednisone-alone group. Correlation between raw scores was weaker in patients who were in MMS, demonstrating a "floor effect" on the MG-ADL scale. Raw QMG scores could be modeled assuming a normal distribution, whereas raw MG-ADL scores could not be modeled this way.

Abbreviations: AChR, acetylcholine receptor; ANCOVA, analysis of covariance; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGTX, Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy; MMS, minimal manifestation status; PA, prednisone alone; QMG, quantitative myasthenia gravis; TPP, thymectomy plus prednisone.

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Discussion: The floor effect and skewed distribution of the MG-ADL measure should be taken into account in the design of myasthenia gravis clinical trials.

KEYWORDS
MG-ADL, MGTX, myasthenia gravis, outcome measure, QMG, trial design

1 | INTRODUCTION

The Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Activity of Daily Living (MG-ADL) scales are among the most commonly used outcome measures in clinical trials for the disease.[1–4] The QMG is a 13-item scale that includes physician assessment of ocular, cranial, respiratory, axial, and limb muscle function relevant to MG.[5,6] The use of QMG has been limited to clinical trials or research visits due to the need for trained personnel and equipment as well as time factors, requiring approximately 20 minutes to complete. The MG-ADL is an eight-item questionnaire asking patients to report on the extent to which they are impacted by common MG symptoms.[7] Administration of MG-ADL typically requires less than 3 minutes and intensive training is not necessary. Both scales have been validated and shown to have high interrater reliability and reproducibility, and to correlate with the clinician's impression of disease improvement.[6,8,9]

Which scale to use as a primary outcome in clinical trials has drawn significant interest among investigators, funding bodies, and regulators, as choosing a suboptimal primary outcome may lead to incorrect conclusions. Few studies have compared QMG and MG-ADL scores using clinical trial data.[10–12] Most recently, Howard et al analyzed the phase 2 and phase 3 eculizumab trial data and showed that QMG and MG-ADL scores correlated significantly, supporting the use of patient-reported MG-ADL scores for monitoring disease progression and assessing treatment effects.[11,12] However, the phase 3 REGAIN trial failed to demonstrate a statistically significant difference in change from baseline in MG-ADL scores between treatment and placebo arms when evaluated by worst-rank analysis of covariance (ANCOVA), although such a difference was found between QMG scores used as a secondary endpoint.[4]

In the randomized Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) study, QMG and MG-ADL scores were collected every 3 months for up to 60 months, providing another excellent opportunity to compare the scales.[2,3] In the present study we analyzed these measurements taken during the MGTX trial to investigate the correlation and distribution of QMG and MG-ADL scores with respect to treatment duration and group assignment.

2 | METHODS

MGTX was a multicenter, international, rater-blinded, randomized, 3-year clinical trial that was followed by a voluntary 2-year extension for patients with acetylcholine receptor (AChR) antibody–positive MG without thymoma. A total of 126 participants were enrolled and randomized: 66 to the thymectomy-plus-prednisone treatment (TPP) group and 60 to the prednisone-alone (PA) group. All participants in the trial received high-dose, alternate-day prednisone on a predefined titration and tapering schedule based on achievement of minimal manifestation status (MMS). Minimal manifestation status was defined as having "no symptoms or functional limitations from myasthenia gravis, but there may be some weakness on examination of some muscles."[2] The protocol prescribed thymectomy to be performed within 30 days for those randomized to the TPP group. Study-blind raters assessed the participants at baseline and from month 3 onward up to 60 months. The detailed protocol of the MGTX trial and results have been published elsewhere.[2,3]

QMG and MG-ADL scores based on treatment groups, MMS, and study visits were obtained from the study database. Raw QMG and MG-ADL scores represent total scores at each visit, whereas change-from-baseline (Δ) QMG and MG-ADL scores were calculated by subtracting baseline scores from scores at each visit. QMG and MG-ADL raw and Δ scores were plotted, and Pearson's correlation coefficients were calculated over time both by treatment group and by MMS at follow-up. The strength of correlation was determined based on the correlation coefficient (r): very high (0.9–1.0); high (0.7–0.9); moderate (0.5–0.7); low (0.3–0.5); or negligible (0.3–0.0).[13] These correlations were plotted, and analysis of covariance (ANCOVA) was used to evaluate the differences between treatment group or MMS and the trend in correlations over time. Utilizing the data of all patients with at least one follow-up observation, general linear models with autoregressive order 1 (AR1) covariance structure were employed to model the values of raw and Δ scores for each postbaseline measure using treatment group and time (linear function only) as independent variables. Such models estimate the average value of each measure as a function of treatment group and time. In addition, these models assume the values of raw and ΔQMG and MG-ADL for individuals are normally distributed around the group average at a given time. Such an assumption may be violated if the measures are severely skewed in one direction, which was evaluated by examining the distribution of model residuals.

3 | RESULTS

Of the 126 MGTX participants randomized, 123 were included in the analysis: 65 in the TPP group and 58 in the PA group. Mean follow-up

time was 45.2 months for the TPP group and 45.6 months for the PA group, with 118 patients having at least one follow-up visit with both measures obtained.

Raw QMG and MG-ADL scores correlated significantly in both treatment groups at all time-points, except for month 48 in the TPP group (r = 0.33, P = .0737). The strength of correlation was moderate to high in the PA group (range, 0.53–0.85) and low to high in the TPP group (range, 0.33–0.75). The strength of correlation increased over time only in the PA group (Figure 1, and Table S1 in the Supporting Information online).

ΔQMG and ΔMG-ADL likewise correlated significantly in both treatment groups at all time-points. The strength of correlation was generally moderate to high in both groups (range, 0.43–0.74). In contrast to the raw scores, the strength of correlation increased over time in both the PA and TPP groups (Figure 1 and Table S1).

When grouped by MMS at each visit, correlation coefficients for both QMG and MG-ADL raw and Δ scores were significantly lower in individuals with MMS than in those not with MMS (P < .0001 and P = .0059, respectively), with larger differences in correlation between raw scores (Figure 2 and Table S1). Participants with MMS were more frequent in the TPP group (60%–89%) than in the PA group (37%–58%) throughout the study period, with an increasing trend in both groups over time (Figure S1).

Model residuals of QMG raw and Δ scores deviate from zero in a fairly symmetric bell-shaped curve with a wide range of values (Figure 3A,B). The residuals for raw QMG scores are skewed, but the range of values is large enough and the shape symmetric enough that QMG raw and Δ scores could be modeled assuming normality without any practical change in type I error rate. In contrast, raw MG-ADL residuals (Figure 3C,E,F) are highly skewed and clustered below the mean, with more clustering in residuals when only visits from patients with MMS are modeled (Figure 3E) than for visits where MMS had not been achieved (Figure 3F). Conversely, ΔMG-ADL residuals follow a normal shape and could be assumed to follow an approximately normal distribution (Figure 3D).

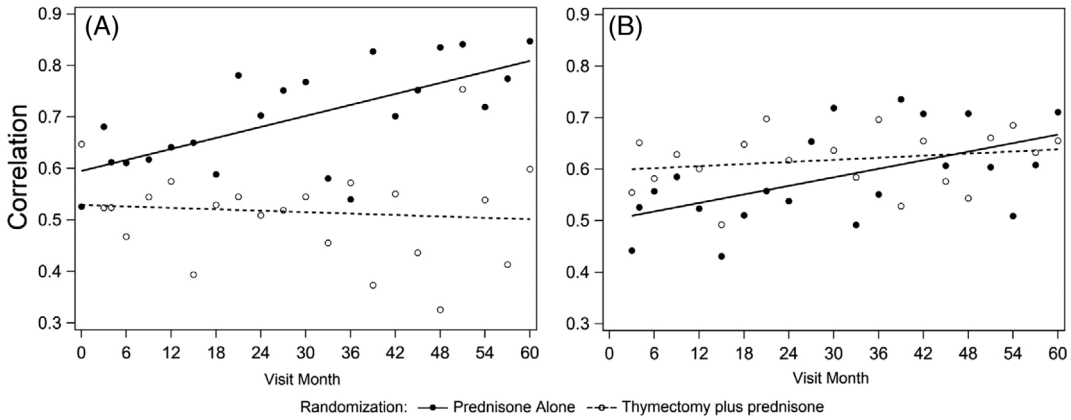

FIGURE 1 Observed correlation (dots) and ANCOVA-estimated correlation (lines) are shown by treatment group over time. The correlation between (A) QMG and MG-ADL scores increased for the prednisone-alone group only. The correlation between (B) ΔQMG and ΔMG-ADL scores increased in both treatment groups over time. ANCOVA, analysis of covariance; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis

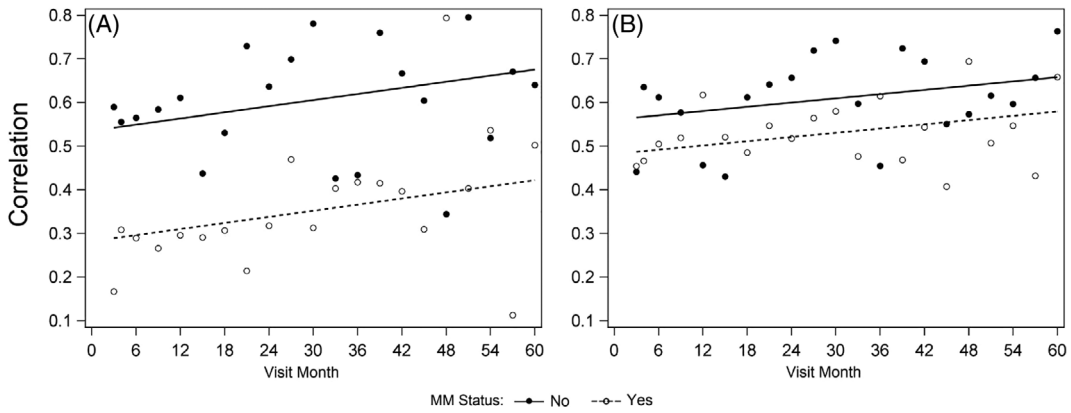

FIGURE 2 Observed correlation (dots) and ANCOVA-estimated correlation (lines) by MMS over time between (A) QMG and MG-ADL scores and (B) ΔQMG and ΔMG-ADL scores consistently showed lower correlation between the outcome measures in patients with MMS. ANCOVA, analysis of covariance; MG-ADL, Myasthenia Gravis Activities of Daily Living; MMS, minimal manifestation status; QMG, Quantitative Myasthenia Gravis

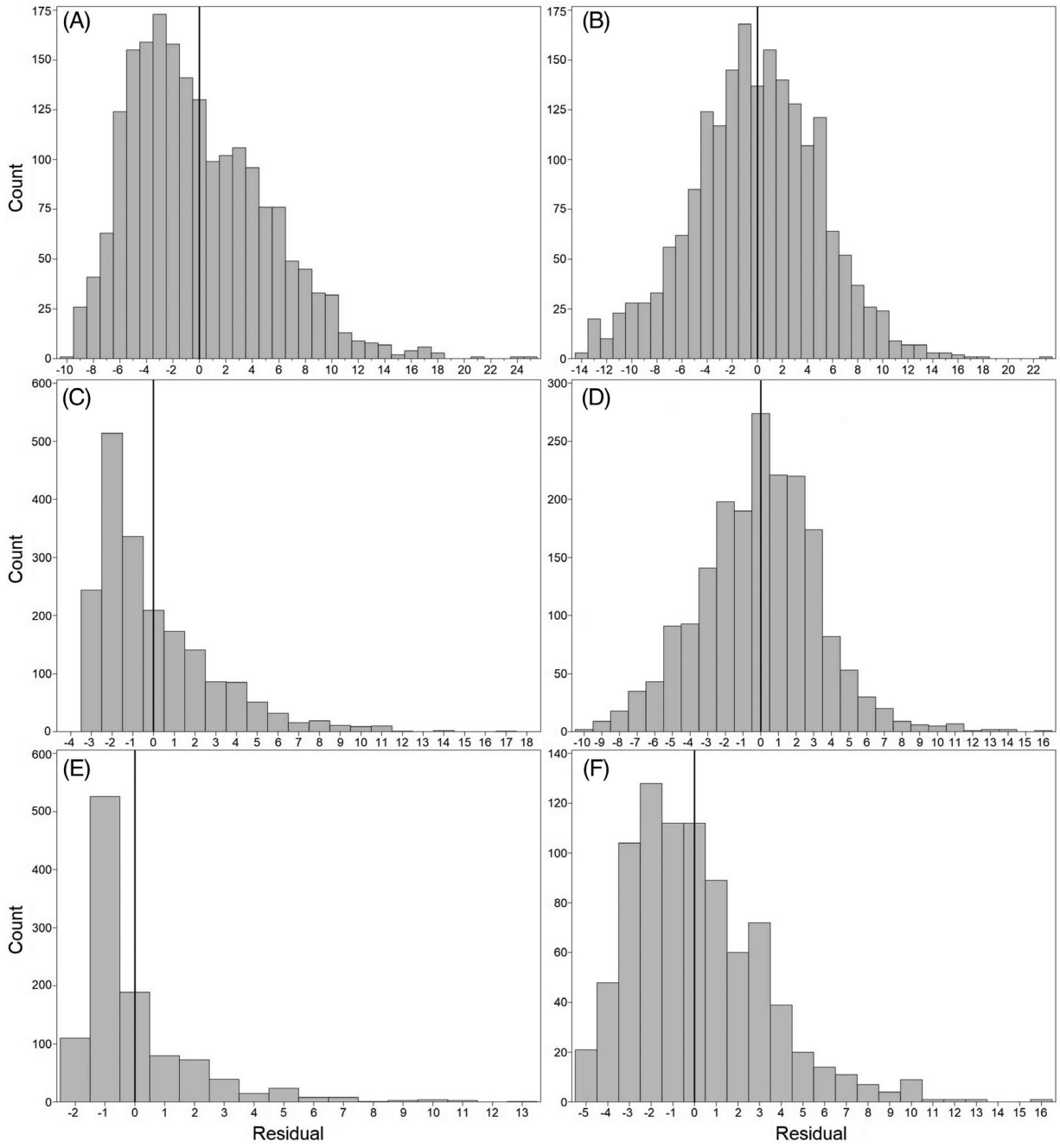

FIGURE 3 Distribution of GLM model residuals, or distribution of the difference between observed and model-estimated scores. Although QMG (A), ΔQMG (B), and ΔMG-ADL(D) residuals all appeared to follow a roughly normal distribution centered around zero, the MG-ADL(C) residuals were highly skewed, indicating substantial departure from normality. This skewness was more apparent in residuals when only MMS visits are modeled (E) than when only non-MMS visits are modeled (F). GLM, generalized linear model; MMS, minimal manifestation status; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis

4 | DISCUSSION

In this study we have demonstrated that both QMG and MG-ADL raw and Δ scores correlated moderately to strongly throughout the 60-month study period of the MGTX study. In particular, the strength of the correlation of ΔQMG and ΔMG-ADL scores was similar between treatment groups and increased over time. On the other hand, the strength of correlation between raw scores increased over time in the PA group but not in the TPP group. We hypothesize that this phenomenon was due to a "floor effect" in the MG-ADL score. Floor effect refers to the MG-ADL reaching the lowest possible score while QMG score continues to improve, resulting in a clustered distribution of MG-ADL scores (Figure S2). Our hypothesis is supported by the findings that: (a) correlation

coefficients were consistently lower in the MMS group with very low MG-ADL scores; and (b) frequencies of patients in MMS were higher in the TPP group throughout the study period.

The assumption of normality appeared adequate for QMG, ΔQMG, and ΔMG-ADL scores but not for raw MG-ADL scores, particularly in patients with MMS. Assuming normality facilitates statistical analysis in two major ways. First, many statistical techniques, such as analysis of variance, linear regression, and their extensions to repeated measures, require this assumption. Unlike many alternative methods of analyses, these techniques are simple to implement and often accompanied by techniques to assess the quality of results (eg, R^2 values).[14] Second, the distribution of an outcome measure determines how the sample size required for a trial should be calculated, and methods relying on the assumption of normality are often better developed and easier to implement. Thus, change scores or raw QMG scores may be more easily modeled than raw MG-ADL scores, and the floor effect and skewness of this measure should be considered if raw scores are to be utilized.

In conclusion, we have demonstrated a floor effect and skewed distribution of the MG-ADL raw scores that may affect the exchangeability of these two measures, and these should be considered when designing future studies.

CONFLICT OF INTEREST

T.M. receives funding from the Myasthenia Gravis Foundation of America (MGFA) for maintenance of the MG Registry. I.A. receives funding from the MGFA for maintenance of the MG Registry, and has received funding from the Transverse Myelitis Association. I.L. receives funding from the MGFA for maintenance of the MG Registry. G.C. has served on data and safety monitoring boards for AMO Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Galmed Pharmaceuticals, Horizon Pharmaceuticals, Hisun Pharmaceuticals, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva Pharmaceuticals, the NHLBI (protocol review committee), and the NICHD (OPRU oversight committee), and has served on consulting or advisory boards for Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Klein-Buendel, Medimmune, Medday, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion Pharmaceuticals, Roche, Somahlution, and TG Therapeutics. G.C. is employed by the University of Alabama at Birmingham and is president of Pythagoras, Inc, a private consulting company in Birmingham, AL. G.I.W. has served on consultant/advisory boards for Grifols, Takeda, ArgenX, and Momenta, and has been on the speaker's bureau for Grifols and Alexion. H.J.K. is principal investigator for the Rare Disease Clinical Research Network dedicated to Myasthenia Gravis MGNet (U54 NS115054); has served as a consultant for Alnylam Pharmaceuticals, Ra Pharmaceuticals, and UCB Pharmaceuticals; and is CEO and CMO of ARC Biotechnology, LLC (based on US Patent 8,961,9810. P.W.D. and R.F.-F. are employees of Ra Pharmaceuticals.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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