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CLINICAL RESEARCH ARTICLE

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One-year follow-up of disease burden and medication changes in patients with myasthenia gravis: From the MG Patient Registry

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Abstract

Introduction/Aims: We studied the progression of myasthenia gravis (MG) disease burden and medication adjustment among MG Patient Registry participants.

Methods: Participants diagnosed with MG (age ≥18 years), registered between July 1, 2013 and July 31, 2018 and completing both 6- and 12-month follow-up surveys, were included in this investigation. Participants were grouped into high-burden (Myasthenia Gravis Activity of Daily Living scale [MG-ADL] score ≥6) and low-burden (MG-ADL <6) groups based on MG-ADL scores at enrollment. Demographics and disease history were compared between groups. MG-ADL score change and medication changes (escalation, no change, de-escalation) between enrollment and 12-month follow-up were compared between groups. Minimal symptom expression (MSE, MG-ADL <2) at 12 months was compared between groups. Logistic regression analysis was performed to study factors associated with MSE at 12 months.

Results: In total, 520 participants (56% female) were included in high-burden (n = 248) and low-burden (n = 272) groups. Those in the high-burden group were more likely to be younger, female, and have shorter disease duration. At 12 months, MSE was achieved in 6% of the high-burden group and newly achieved (42 of 201, 21%) or maintained (52 of 71, 73%) in the low-burden group. In the multivariable analysis, being in the high-burden group and use of pyridostigmine were associated with less likelihood of MSE, whereas MG-ADL score improvement (>2 or >20%) at 6 months significantly increased the likelihood of achieving MSE at 12 months ($P = .0004$).

Discussion: In both groups, but more so in the high-burden group, patients infrequently achieved MSE after 1 year of MG treatment. Baseline low disease burden,

Abbreviations: AChR, acetylcholine receptor; GEE, generalized estimating equation; GLS, generalized least squares; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGR, MG Patient Registry; MG-QOL15, 15-item MG Quality-of-Life scale; MG-QOL15R, revised 15-item MG Quality-of-Life scale; MSE, minimal symptom expression; QOL, quality of life; PLEx, plasma exchange; QMG, quantitative myasthenia gravis.

improvement at 6 months and no pyridostigmine use were associated with a higher likelihood of MSE at 12 months.

KEYWORDS
activities of daily living, disease severity, myasthenia gravis

1 | INTRODUCTION

Myasthenia gravis (MG) is commonly a lifelong disease, as complete stable remission (no symptoms, no medications) after onset is achieved in fewer than 10% of patients.[1] Current oral and intravenous treatment options have unique shortcomings, limiting their ability to aid patients in achieving minimal or no-symptom status.[2–6]

In a recent report, eculizumab was shown to be more effective in attaining minimal symptom expression (MSE) when measured as an MG Activities of Daily Living (MG-ADL) scale score of 0 or 1 in a comparison with placebo-treated patients at the end of a double-blind period.[7] Only 1.7% of the placebo-treated patients achieved MSE at the end of 26 weeks despite their other MG treatments, yet this may have been due to the severe and refractory disease of the participants in that trial. Studies from the MG Patient Registry (MGR)

TABLE 1 Demographics, disease history, and medication use comparisons for high- vs low-burden groups

Variable	Total (N = 520)	High-burden (MG-ADL ≥6) (n = 248)	Low-burden (MG-ADL ≤5) (n = 272)	*P* value*	Missing (n)
Age (years)	59.1 (12.9)	57.2 (11.9)	60.8 (13.5)	.0015	0
Gender, F	292 (56.2%)	160 (64.5%)	132 (48.5%)	.0002	0
Race, white	468 (90.0%)	218 (87.9%)	250 (91.9%)	.2049	2
Disease duration (years) Disease duration (years), median (IQR)	4.6 (8.2) 1 (0-6)	4.0 (7.5) 1 (0-5)	5.2 (8.8) 2 (0-6)	.0245**	36
Age at symptom onset	49.6 (18.0)	46.2 (18.4)	52.7 (17.1)	<.0001	12
Onset at <50 years	216 (41.5%)	127 (51.2%)	89 (32.7%)	<.0001	12
MG-ADL	5.8 (3.9)	9.2 (2.8)	2.8 (1.7)	<.0001	1
MG-QOL15R	13.1 (7.7)	18.2 (6.1)	8.3 (5.7)	<.0001	3
AChR Ab^+	190 (36.5%)	83 (33.5%)	107 (39.3%)	.0025	NA
MuSK Ab^+	28 (5.4%)	17 (6.9%)	11 (4.0%)	.6055	NA
Thymectomy	136 (26.2%)	65 (26.2%)	71 (26.1%)	.9342	2
Thymic tumor	46 (8.9%)	22 (8.9%)	24 (8.8%)	.3332	4
ICU admission in the past	143 (27.5%)	74 (29.8%)	69 (25.4%)	.4541	5
Feeding tube in the past	51 (9.8%)	23 (9.3%)	28 (10.3%)	.7300	3
Pyridostigmine (current tx)	393 (75.6%)	212 (85.5%)	181 (66.5%)	<.0001	NA
Prednisone (current tx)	229 (44.0%)	105 (42.3%)	124 (45.6%)	.4559	NA
Steroid-sparing agent(s) (current tx)	230 (44.2%)	104 (41.9%)	126 (46.3%)	.3143	NA
Azathioprine (current tx)	82 (15.8%)	35 (14.1%)	47 (17.3%)	.3224	NA
Mycophenolate mofetil (current tx)	132 (25.4%)	60 (24.2%)	72 (26.5%)	.5512	NA
Other steroid-sparing agent(s) (current tx)	18 (3.5%)	11 (4.4%)	7 (2.6%)	.2460	NA
IVIg (current tx)	89 (17.1%)	63 (25.4%)	26 (9.6%)	<.0001	NA
PLEx (current tx)	19 (3.7%)	15 (6.1%)	4 (1.5%)	.0055	NA
Rituximab (current tx)	15 (2.9%)	15 (6.1%)	0%	<.0001	NA
Exacerbation in the past 6 months, yes	206 (39.6%)	125 (50.4%)	81 (29.8%)	<.0001	0

Note: Data expressed as mean (standard deviation) or as number (%), unless noted otherwise.
Abbreviations: Ab, antibody; AChR, acetylcholine receptor; F, female; ICU, intensive care unit; IQR, interquartile range; IVIg, intravenous immunoglobulin; MG-QOL15, 15-item MG Quality-of-Life scale; MuSK, muscle-specific kinase; NA, not applicable; PLEx, plasma exchange; tx, treatment.
**P* values based on two-sample *t* test (continuous) or chi-square test (categorical), unless noted otherwise.
***P* value based on Wilcoxon rank-sum test.

demonstrated that half of the participants had moderate to severe disease at enrollment, about half of whom met the criteria for refractory MG at some point during their disease.[8,9] It is unknown how frequently MSE, the newly defined minimal-symptom status, can be achieved in MG patients with varying disease severity outside of the clinical trial setting. In this study, we followed disease progression and medication changes among MGR participants over 1 year to determine how many achieve MSE and what factors may be associated with attain this favorable outcome.

2 | METHODS

The MGR is a patient-driven research project funded and supervised by the Myasthenia Gravis Foundation of America (MGFA) and managed by the coordinating center at the University of Alabama at Birmingham. Details of the MGR have been published elsewhere.[9,10] Enrollment and semiannual surveys collectively capture patient-reported outcome measures, including functional status and quality of life (QOL). In this study, basic demographic information, disease-related history, and outcome measures, all patient reported, were extracted from the enrollment and semiannual update surveys. Data are de-identified for research purposes. In addition to general approval from the MGR at the University of Alabama at Birmingham, research studies using MGR data, such as the current study, require approval by the University's institutional review board. Consent for participation is obtained virtually by each participant acknowledging completion of the survey.

The survey includes well-known assessment tools for MG. The MG Activities of Daily Living (MG-ADL) profile is a validated, simple, eight-question survey of MG symptoms, with higher score indicating more limitation in daily activities.[11] Participants were instructed to select the option that corresponds with his/her experience over the last 4 weeks with respect to each of the activities measured by the MG-ADL. The 15-item MG Quality-of-Life scale (MG-QOL15) is a

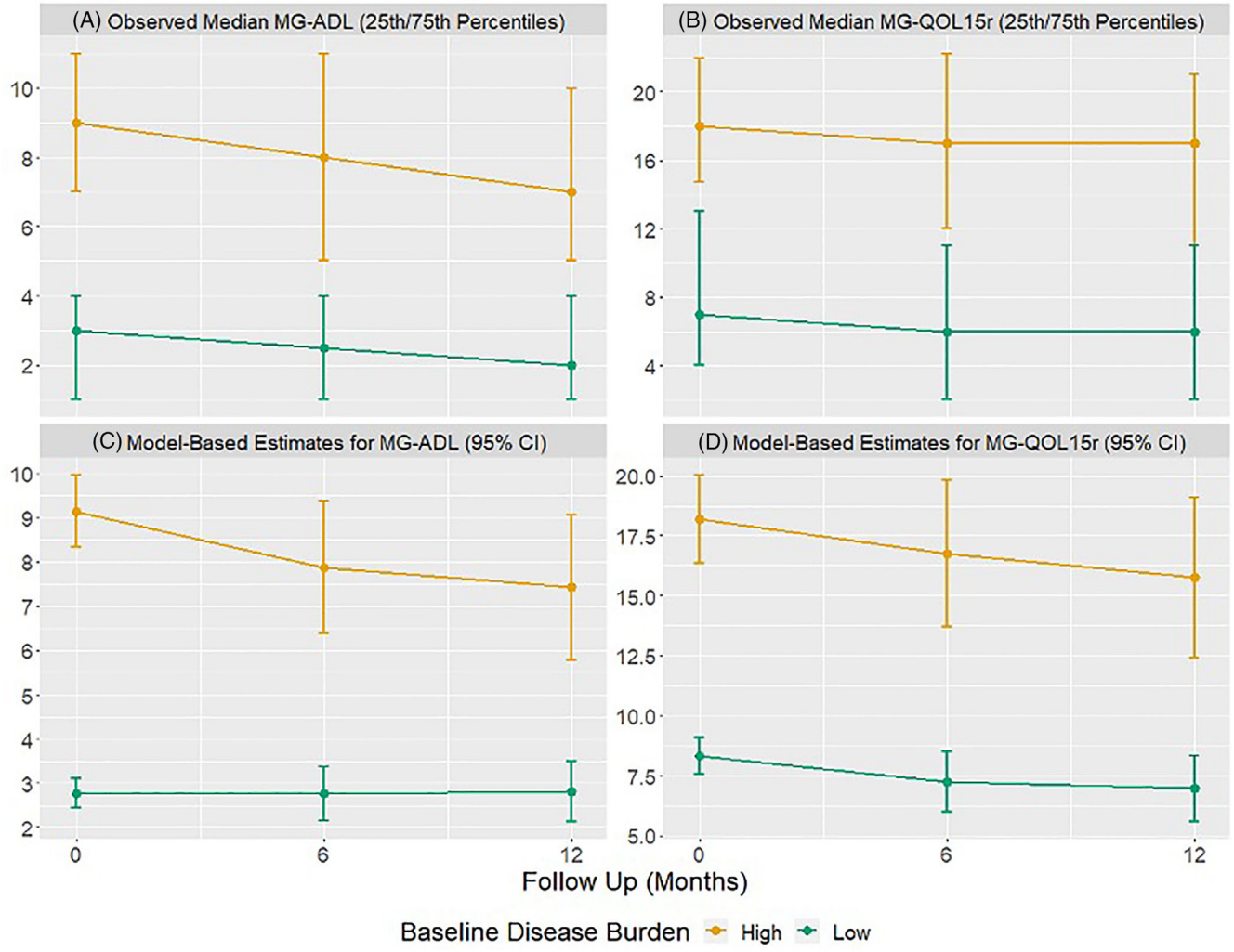

FIGURE 1 Change of MG-ADL and MG-QOL15R scores from baseline to 6- and 12-month follow-up between high- and low-burden groups. Median MG-ADL (A) and MG-QOL15R (B) scores trended down in both high- and low-burden groups. Estimated MG-ADL(C) and MG-QOL15R (D) trajectories demonstrate significant difference between groups, with steeper slope in the high-burden group. Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living scale; MG-QOL15R, revised 15-item MG Quality-of-Life scale.

disease-specific scale with higher score indicating worse QOL.[12] Participants were instructed to select the option that indicates how true each statement in the MG-QOL15 questionnaire has been for him/her (over the past few weeks). The MG-QOL15 was revised (MG-QOL-15R) in 2016 to improve clinometric properties and ease of use,[13] so the MG Registry survey adapted to use the MG-QOL15R from 2018 and forward. In this study, MG-QOL15 scale data were converted to MG-QOL15R as follows: 0 remained 0 ("not at all"); 1 and 2 became 1 ("a little bit" and "somewhat" became "somewhat"); and 3 and 4 became 2 ("quite a bit" and "very much" became "very much"). MSE in this study was defined by an MG-ADL total score of 0 or 1.[7] MSE was originally defined by Vissing et al by using either the MG-ADL total score of 0 to 1, or MG-QOL15 total score of 0 to 3.[7] In this study, only the MG-ADL criterion was used to define MSE because the MG-ADL baseline score was used to group participants and to define improvement over time, and also because a cut-off value for the MG-QOL15R scale was not defined in the original definition of MSE.[7] Nonetheless, we performed sensitivity analyses by using an MG-QOL15R cut-off value of less than 2 to define MSE, and observed that the association between variables and achieving this favorable outcome is consistent with MG-ADL–defined MSE (see Tables A1 and A2). Medication names were obtained and compared at each survey time-point (baseline vs 6 months and 6 months vs 12 months). Doses of medications were not collected in the registry. Treatment changes at 6- and 12-month follow-up were categorized as "escalation" if any new MG medication was added or existing MG medication was changed, "no-change" if there was no change in MG medication, and "de-escalation" if a previously reported MG medication was not reported.

2.1 | Inclusion and exclusion criteria

Participants were included if they were over 18 years of age; answered "Yes" to "Has your doctor diagnosed you with MG?"; resided in the United States; completed the enrollment survey between July 1, 2013 and July 31, 2018; and completed two consecutive follow-up surveys immediately after the enrollment survey.

TABLE 2 Change of disease severity and medication use for high- vs low-burden groups

	High-burden group (n = 248)			Low-burden group (n = 272)			
Follow-up (months)	**0**	**6**	**12**	**0**	**6**	**12 (vs baseline)**	***P* value***
MG-ADL decrease by ≥3 vs baseline		74 (30%)	86 (35%)		26 (10%)	26 (10%)	<.0001
MG-ADL decrease by ≥2 vs baseline		108 (44%)	114 (46%)		57 (21%)	61 (22%)	<.0001
MG-ADL decrease >20% vs baseline		95 (38%)	107 (43%)		98 (36%)	102 (38%)	.2589
Minimal symptom expression (MG-ADL <2)	0 (0%)	8 (3%)	14 (6%)	71 (26%)	89 (33%)	94 (35%)	<.0001
MG-ADL change							
Increased		68 (27%)	77 (31%)**		94 (35%)	97 (36%)**	.0003
No change		37 (15%)	56 (23%)**		70 (26%)	88 (32%)**	
Decrease		143 (58%)	114 (46%)**		108 (40%)	87 (32%)**	
Exacerbation	125 (50%)	122 (49%)	90 (36%)	81 (30%)	54 (20%)	52 (19%)	.0216*
Treatment change							
Escalation		137 (55%)	57 (23%)		86 (32%)	52 (19%)	<.0001*
No change		102 (41%)	117 (47%)		158 (58%)	163 (60%)	
De-escalation		9 (4%)	74 (30%)		28 (10%)	57 (21%)	
Prednisone, current	105 (42%)	151 (61%)	140 (56%)	124 (46%)	138 (51%)	124 (46%)	.0007*
Steroid-sparing agent(s), current	104 (42%)	140 (56%)	142 (57%)	126 (46%)	145 (53%)	146 (54%)	.5187
Azathioprine, current	35 (14%)	53 (21%)	48 (19%)	47 (17%)	60 (22%)	60 (22%)	.5948
Mycophenolate, current	60 (24%)	81 (33%)	81 (33%)	72 (27%)	81 (30%)	82 (30%)	.5903
IVIg, current	63 (25%)	110 (44%)	88 (35%)	26 (10%)	44 (16%)	49 (18%)	<.0001
Plasma exchange, current	15 (6%)	39 (16%)	29 (12%)	4 (1%)	12 (4%)	7 (3%)	<.0001
Rituximab, current	15 (6%)	18 (7%)	18 (7%)	0	7 (3%)	11 (4%)	<.0001[a]
Pyridostigmine, current	212 (85%)	223 (90%)	214 (86%)	180 (66%)	188 (69%)	182 (67%)	<.0001

Note: Data expressed as number (%).
Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale.
[a]Cochran-Mantel-Hantzel test due to 0 count(s).
*Significant interaction.
**Compared with 6-month follow-up.

Participants who did not complete the MG-ADL at enrollment were excluded from the main analysis. Participants were grouped into those with high disease burden ("high burden," MG-ADL score ≥6) and low disease burden ("low-burden," MG-ADL score ≤5) based on their enrollment MG-ADL score.[14,15] Demographics, disease history, and medication use at enrollment were compared between the two groups. Use of MG medication that was current at any time-point between enrollment and 12-month follow-up was compared between males and females at least 45 years old vs females less than 45 years old to evaluate differences in medication based on gender and child-bearing potential.

2.2 | Statistical analysis

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) and figures were generated with the ggplot2 package in R version 3.6.3. (R Foundation for Statistical Computing, Vienna, Austria). Hypothesis tests for between-group comparisons were conducted using two-sample *t* tests for continuous variables and the chi-square test for categorical variables unless assumptions were violated, in which case we conducted tests using the Wilcoxon rank-sum test and the Freeman and Halton extension of the Fisher exact test for continuous and categorical variables, respectively. All models that include multiple time-points treat follow-up time as discrete to avoid questionable assumptions of linearity with only three time-points. Binary outcomes were modeled with logistic regression and, when necessary, generalized estimating equations (GEEs) were used to account for repeated measurements; unstructured working correlation and empirical standard errors were used for hypothesis tests. Ordinal variables with repeated measurements were modeled with GEEs using the alternating logistic regression method with exchangeable working correlation, and empirical standard errors were used for hypothesis tests.[16] Interactions between baseline disease burden and follow-up time were initially included in the models; when not significant at the 0.05 level, the interactions were removed, and models were refitted. Trends over time for MG-ADL and MG-QOL15R were modeled with generalized least squares (GLS), assuming an interaction between baseline disease burden and follow-up; Akaike information criterion was used to select the optimal covariance structure, which was Toeplitz in both cases. MSE at 12-month follow-up was modeled with uni- and multivariable logistic regression, and variables were included in the multivariable logistic regression according to predetermined clinical relevance or collinearity concerns rather than *P*-value thresholds. $P < .05$ was used for statistical significance without adjustments for multiple comparisons because of the exploratory nature of our study.

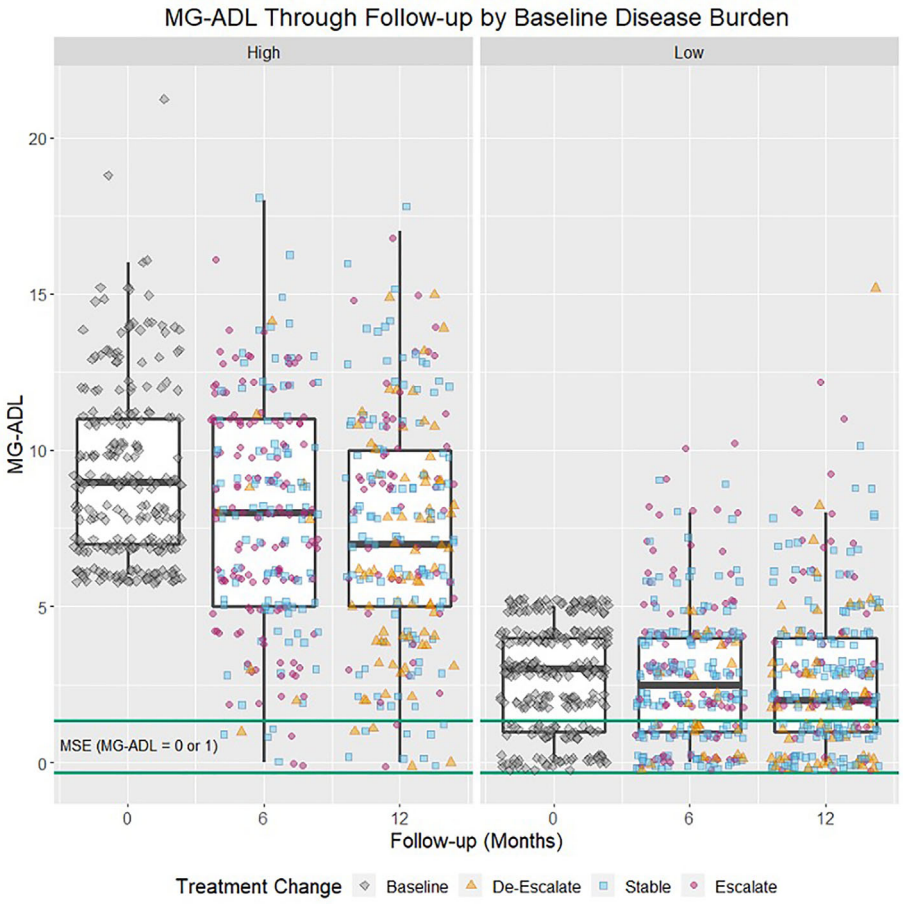

FIGURE 2 Distribution of scoring on Myasthenia Gravis Activities of Daily Living scale and corresponding medication change through follow-up by baseline disease burden.

3 | RESULTS

Overall, 2528 participants completed enrollment surveys. Of these, 520 met the inclusion and exclusion criteria and were included in the analysis. Participants were significantly older, more frequently male and white, and had a shorter duration of disease and lower disease burden, compared with the excluded participants (n = 2008).

There were 248 participants in the high-burden group and 272 participants in the low-burden group. Those in the high-burden group were more likely to be female, younger at time of reporting, younger at symptom onset, more likely to have had symptom onset prior to age 50 years, and had shorter disease duration [Correction added on 29 July 2022, after first online publication: In the preceding sentence, "after 50 years of age" was changed to "prior to age 50 years".]. Positive acetylcholine receptor (AChR) antibody was reported more frequently in the low-burden group. Exacerbation in the past 6 months, current use of pyridostigmine, intravenous immunoglobulin (IVIg), plasma exchange (PLEx), and rituximab were more frequently reported in the high-burden group (Table 1).

The observed median MG-ADL and MG-QOL15R scores declined (disease severity improved) at 6- and 12-month follow-up compared with baseline in both the high- and low-burden groups. The declining trend in the high-burden group was more prominent compared with the low-burden group, as evidenced by the significant interaction between time and disease group (MG-ADL: $P < .0001$; MG-QOL15R: $P = .0469$). This difference is displayed in the plot for estimated MG-ADL from the fitted GLS model (Figure 1).

Declines in the MG-ADL scores of at least 3 points or at least 2 points at 6- and 12-month follow-up were more frequent in high-burden group. The frequency of decline in MG-ADL of more than 20% at

TABLE 3 Multivariable logistic regression results for minimal symptom expression (MG-ADL score <2), N = 472

Variable	OR	95% CI	*P* value
Sex: male vs female	1.173	0.642-2.142	.6039
Disease duration	1.007	0.969-1.047	.7149
Age (symptom onset, years)	1.018	0.995-1.041	.1200
High burden vs low burden	0.154	0.076-0.309	<.0001
MG-ADL improved vs not (6 months)	2.755	1.576-4.817	.0004
AChR antibody			
Positive vs other	1.371	0.788-2.387	.2641
Thymectomy			
Positive vs other	1.415	0.591-3.390	.4356
Thymoma			
Positive vs other	1.591	0.562-4.509	.3820
Prednisone			
All 3 visits vs none	1.221	0.559-2.668	.2201
1-2 visits vs none	1.737	0.925-3.261	
Azathioprine			
All 3 visits vs none	0.592	0.212-1.648	.4536
1-2 visits vs none	0.694	0.306-1.573	
Mycophenolate mofetil			
All 3 visits vs none	10.668	0.277-1.612	.4001
1-2 visits vs none	0.645	0.313-1.331	
IVIg			
All 3 visits vs none	0.739	0.299-1.824	.0861
1-2 visits vs none	0.237	0.065-0.864	
Pyridostigmine			
All 3 visits vs none	0.393	0.164-0.942	.0002
1-2 visits vs none	0.225	0.112-0.453	
Treatment escalation (6 months)			
De-escalate vs none	2.051	0.750-5.610	.2318
Escalate vs none	0.808	0.367-1.779	
Treatment escalation (12 months)			
De-escalate vs none	1.475	0.706-3.080	.0844
Escalate vs none	0.493	0.194-1.256	

Abbreviations: AChR, acetylcholine receptor; CI, confidence interval; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living scale; OR, odds ratio.

12 months was comparable between the two groups. MSE (MG-ADL score <2) at 12 months, regardless of MSE status at baseline or newly achieved MSE at 12 months for subjects who had not achieved MSE at baseline, were both less frequent in the high-burden group compared with the low-burden group (6% vs 35% and 6% vs 21%, respectively, both $P < .0001$). MSE was maintained at 12 months in 73% of participants who had MSE at baseline, all of whom were in the low-burden group. Exacerbations were reported more frequently in the high-burden group at all time-points (Table 2).

The majority of participants in the high-burden group had escalation of treatment at 6 months (55%), which decreased to 23% at 12 months. The majority of participants in the low-burden group had no change in medication at both 6 and 12 months. Current treatment with pyridostigmine, IVIg, PLEx, and rituximab were more frequent in the high-burden group at all time-points (Table 2). When distribution of MG-ADL score was plotted with treatment change, escalation of treatment was more concentrated in the high-burden group at 6 months, whereas no change was concentrated in the low-burden group at both 6- and 12-month follow-up, illustrating similar findings (Figure 2).

In the multivariable logistic regression analysis, low baseline disease burden and improvement of MG-ADL score at 6 months were associated with a higher likelihood of achieving MSE, whereas any use of pyridostigmine was associated with lower likelihood of achieving minimal symptom expression when adjusting for other variables (Table 3). Results of the univariable logistic regression analysis are presented in Table A1.

Reported use of prednisone was less frequent in women age 45 years and older compared with women younger than 45 years and men, but only the difference between men and women over 45 years of age was statistically significant. Similarly, reported use of mycophenolate mofetil was less frequent in women both under and over age 45 and when compared with men, but only the difference between men and women 45 years old and older was statistically significant (see Table A3).

4 | DISCUSSION

In this study, modest improvement was noted in both the high- and low-burden groups, as represented by the decline in MG-ADL score over time. Significant improvement, as represented by an MG-ADL decrease of more than 2 points, was more common in the high-burden group at both 6 and 12 months. However, when a decrease in MG-ADL of more than 20% was used as a cut-off (as has been done in other disease models, such as multiple sclerosis[17]), frequencies of those with significant improvement were similar between groups. Participants in the low-burden group are already at or close to lowest possible MG-ADL score, and further improvement by 2 or 3 points may be more difficult or impossible. One study demonstrated a floor effect of MG-ADL at the lowest possible score while continued improvement was seen on an alternate scale such as the Quantitative Myasthenia Gravis (QMG) instrument.[18] It needs to be confirmed whether a 20% reduction in MG-ADL score represents clinically relevant improvement.

Participants in the high-burden group rarely achieved MSE (MG-ADL of 0 or 1) at 12 months, despite greater medication use and escalation of treatment. In the low-burden group, 26% were already in MSE at baseline, which increased to 35% at 12 months. These results indicate that achieving MSE after 12 months of treatment is uncommon, regardless of disease severity at baseline, and in line with an earlier report from the eculizumab trial.[7] Based on multivariable analysis, low-burden group and decrease in MG-ADL by more than 2 points at 6 months were associated with achieving MSE at 12 months, each increasing the odds by 6.49- and 2.76-fold, respectively. Any use of pyridostigmine was associated with a lower likelihood of achieving MSE. This result should be interpreted with caution as pyridostigmine use is clearly driven by the severity of MG symptoms. Nonetheless, this observation suggests that pyridostigmine may not be effective enough to achieve symptom remission over a 1-year period. Prednisone, azathioprine, and mycophenolate mofetil were also not significantly associated with achieving MSE at 12 months. Many participants with high disease burden (high MG-ADL scores) did not change their medications, or de-escalated them. Although the rationale for these individual decisions is unknown, it may be due to the limited treatment options available at the time of the survey or barriers to escalating treatments (side effects, need for infusions, cost, insurance coverage). Although the general goal in MG treatment should be achieving MSE, participants seem to make compromises given individual circumstances.

Previous studies have shown that women with MG more frequently have generalized disease,[19,20] more severe fatigue,[21,22] depression, and worse QOL than men with MG.[10,23] Women have also reported more frequent adverse effects of prednisone, which may limit their use of this treatment.[24,25] Furthermore, mycophenolate mofetil has a teratogenic effect, which limits its use in women of childbearing age. Our findings also show that prednisone and mycophenolate mofetil are used less frequently in older women.

A major limitation of this study is the short follow-up time of 1 year, which was chosen so we could maximize the number of eligible participants. Despite this, many participants were still excluded as they did not complete two consecutive follow-up surveys after baseline. The frequency of achieving MSE may increase with time because of the benefits of immunosuppressive agents such as azathioprine and mycophenolate, in general, over longer time periods. Furthermore, the dose of each medication was not collected, which limits interpretation of the results. All information obtained in the MGR, including the diagnosis of MG, is self-reported and without physician confirmation, which may raise some concerns regarding the validity of such information. In a recent study from an online patient registry of MG and Lambert-Eaton myasthenic syndrome, documented antibody status was confirmed in 79% of MG patients and the distributions of AChR, muscle-specific kinase, and seronegative patients were similar those seen in previous reports.[26] In a similar registry of multiple sclerosis in which participants self-reported their diagnosis, the diagnosis was confirmed in 98.7% of validation study participants.[27] Considering the similarity between these registries and the MGR, the MGR participants may sufficiently represent the general MG population, but further validation studies are needed for confirmation.

This study has provided information on the trajectory of disease severity and medication use change over 1 year in a large MG

population of mainly white and more often slightly older male adults residing in the United States, with varying disease severity. Overall, the population showed gradual improvement in disease severity and more than 30% of the participants demonstrated significant improvement during the 1-year period. However, achieving MSE was quite rare, especially in those with high baseline disease burden and without significant improvement after 6 months. Future therapeutic developments should focus on this unmet need.

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The authors appreciate the support from the Myasthenia Gravis Foundation of America in establishing and maintaining the MG Patient Registry.

CONFLICT OF INTEREST

I.L. receives research support from the Myasthenia Gravis Foundation of America for the MG Registry, served on a medical advisory board for Alexion and received honorarium. I.A. receives research grants from the University of Alabama at Birmingham through the Myasthenia Gravis Foundation of America (MGFA), Ra Pharmaceuticals through MGFA, Alexion through MGFA, Argenx through MGFA, Catalyst through MGFA, and Verona Pharmaceutical. T.M. receives research funding from the MGFA. P.W.D. is an employee of UCB Pharma and holds stock/stock options in UCB Pharma. G.C. is employed by the University of Alabama at Birmingham and is president of Pythagoras, Inc, a private consulting company located in Birmingham, AL. G.C. serves on the Data and Safety Monitoring Boards: AstraZeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Mapi Pharmaceuticals, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata, Teva, VielaBio, NHLBI (protocol review committee), NICHD (OPRU oversight committee). G.C. serves on the Consulting or Advisory Boards: Antisense Therapeutics, Biodelivery Sciences International, Biogen, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Klein-Buendel, Medimmune/Viela Bio, Medday, Merck/Serono, Neurogenesis LTD, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences, Recursion/Cerexis Pharmaceuticals, Regeneron, Reckover Pharmaceuticals, Roche, SAB Blotherapeutics, and TG Therapeutics.

DATA AVAILABILITY STATEMENT

Data will be available upon request to qualified researchers after review of the request by the study team.

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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TABLE A1 Univariable logistic regression results for minimal symptom expression (N = 472) by MG-ADL score <2, MG-QOL15R score <2, and either of those criteria (sensitivity analysis)

	MG-ADL <2 or MG-QOL15R <2				MG-ADL <2				MG-QOL15R <2			
Variable	**OR**	**LCL**	**UCL**	***P* value**	**OR**	**LCL**	**UCL**	***P* value**	**OR**	**LCL**	**UCL**	***P* value**
Age (enrollment; in years)	1.02	1.01	1.04	0.004859	1.02	1.01	1.04	0.01	1.02	1	1.05	0.0391
Sex: male vs female	1.6	1.06	2.39	0.023679	1.64	1.07	2.52	0.0221	1.16	0.69	1.94	0.5814
Race: white vs nonwhite	1.01	0.51	2.01	0.968945	1.06	0.51	2.2	0.8707	0.89	0.38	2.07	0.7877
Disease duration	1.02	1	1.05	0.063386	1.01	0.99	1.04	0.2442	1.05	1.02	1.07	0.0006
Age (symptom onset, in years)	1.02	1	1.03	0.009069	1.02	1	1.03	0.0086	1	0.99	1.02	0.7078
High vs Low DB	0.11	0.06	0.19	<0.0001	0.11	0.06	0.21	<0.0001	0.2	0.11	0.39	<0.0001
MG-ADL improved vs not (6 months)	2.45	1.62	3.69	<0.0001	2.03	1.32	3.12	0.0012	2.6	1.54	4.4	0.0004
AChR antibody: positive vs other	1.59	1.05	2.39	0.027248	1.44	0.94	2.22	0.0948	1.65	0.98	2.77	0.06
MuSK antibody: positive vs other	1.11	0.46	2.68	0.822934	1.09	0.43	2.78	0.8527	1.53	0.56	4.17	0.4071
Thymectomy: positive vs other	1.38	0.89	2.15	0.150062	1.39	0.88	2.21	0.1621	1.37	0.78	2.39	0.2727
Thymoma: positive vs other	1.98	1.05	3.73	0.035878	1.76	0.9	3.44	0.0956	1.26	0.54	2.94	0.5983
Prednisone: all 3 visits vs none	0.94	0.59	1.5	0.882537	1.04	0.64	1.69	0.8171	0.69	0.38	1.27	0.4997
Prednisone: 1-2 visits vs none	0.88	0.52	1.47		0.87	0.5	1.52		0.86	0.45	1.64	
Steroid-sparing agent: all 3 visits vs none	0.68	0.43	1.07	0.049698	0.68	0.42	1.09	0.0517	0.53	0.29	0.96	0.0895
Steroid-sparing agent: 1-2 visits vs none	0.53	0.31	0.91		0.5	0.28	0.9		0.62	0.32	1.22	
Azathioprine: all 3 visits vs none	1.07	0.6	1.93	0.034988	1.03	0.55	1.92	0.126	0.96	0.45	2.05	0.1007
Azathioprine: 1-2 visits vs none	0.37	0.17	0.8		0.45	0.21	0.98		0.27	0.08	0.9	
Mycophenolate: all 3 visits vs none	0.91	0.55	1.53	0.658995	0.92	0.54	1.58	0.4363	0.6	0.28	1.28	0.2881
Mycophenolate: 1-2 visits vs none	0.76	0.42	1.37		0.65	0.34	1.25		1.22	0.63	2.4	
IVIg: all 3 visits vs none	0.21	0.09	0.5	<0.0001	0.21	0.08	0.54	<0.0001	0.31	0.11	0.89	0.007
IVIg: 1-2 visits vs none	0.33	0.18	0.6		0.33	0.17	0.64		0.35	0.16	0.8	
Plasma exchange: all 3 visits vs none	0.63	0.13	2.95	0.021432	0.77	0.16	3.63	0.064	0	0		0.9985
Plasma exchange: 1-2 visits vs none	0.24	0.08	0.67		0.29	0.1	0.82		0	0	0	
Rituximab: all 3 visits vs none	0	0		0.585269	0	0		0.5985	0	0		0.7314
Rituximab: 1-2 visits vs none	0.62	0.25	1.53		0.61	0.23	1.6		0.61	0.18	2.06	
Pyridostigmine: all 3 visits vs none	0.17	0.1	0.3	<0.0001	0.16	0.1	0.28	<0.0001	0.2	0.11	0.37	<0.0001
Pyridostigmine: 1-2 visits vs none	0.31	0.16	0.59		0.36	0.19	0.69		0.31	0.14	0.68	
Treatment escalation (6 months): de-escalate vs none	2.05	1.01	4.15	0.001228	2.06	1	4.26	0.0061	2.17	0.97	4.85	0.0017
Treatment escalation (6 months): escalate vs none	0.57	0.37	0.88		0.63	0.4	1		0.47	0.26	0.85	
Treatment escalation (12 months): de-escalate vs none	0.94	0.58	1.5	0.022531	0.94	0.57	1.54	0.0734	0.61	0.31	1.17	0.1566
Treatment escalation (12 months): escalate vs none	0.43	0.24	0.79		0.49	0.26	0.91		0.57	0.27	1.18	

TABLE A2 Multivariable logistic regression results for minimal symptom expression (N = 472) by MG-ADL score <2, MG-QOL15R score <2, and either of those criteria (sensitivity analysis)

	MG-ADL < 2 or MG-QOL15R < 2				MG-ADL < 2				MG-QOL15R < 2			
	OR	LCL	UCL	*P* value	OR	LCL	UCL	*P* value	OR	LCL	UCL	*P* value
Sex: male vs female	0.988	0.545	1.793	0.9693	1.173	0.642	2.142	0.6039	0.615	0.297	1.27	0.1886
Disease duration (years)	1.026	0.989	1.066	0.1725	1.007	0.969	1.047	0.7149	1.067	1.022	1.113	0.0029
Age (symptom onset, years)	1.019	0.996	1.041	0.1036	1.018	0.995	1.041	0.12	1.019	0.992	1.047	0.1599
Baseline DB: high vs low	0.129	0.066	0.254	<.0001	0.154	0.076	0.309	<.0001	0.301	0.135	0.67	0.0033
MG-ADL: improved vs not (6 months)	3.739	2.136	6.546	<.0001	2.755	1.576	4.817	0.0004	2.924	1.526	5.603	0.0012
AChR antibody: posititve vs other	1.453	0.845	2.499	0.1765	1.371	0.788	2.387	0.2641	1.62	0.839	3.129	0.1507
Thymectomy: positive vs other	0.964	0.4	2.322	0.9341	1.415	0.591	3.39	0.4356	0.54	0.185	1.579	0.2604
Thymoma: positive vs other	2.528	0.878	7.278	0.0857	1.591	0.562	4.509	0.382	1.267	0.364	4.413	0.7097
Prednisone: 1-2 visits vs none	1.347	0.628	2.886	0.332	1.221	0.559	2.668	0.2201	1.908	0.78	4.668	0.3603
Prednisone: all 3 visits vs none	1.6	0.858	2.982		1.737	0.925	3.261		1.159	0.541	2.481	
Azathioprine: 1-2 visits vs none	0.498	0.18	1.377	0.3427	0.592	0.212	1.648	0.4536	0.417	0.087	2.004	0.5176
Azathioprine: all 3 visits vs none	0.737	0.331	1.643		0.694	0.306	1.573		0.81	0.303	2.164	
Mycophenolate: 1-2 visits vs none	0.937	0.402	2.184	0.5522	0.668	0.277	1.612	0.4001	2.442	0.918	6.496	0.025
Mycophenolate: all 3 visits vs none	0.675	0.332	1.373		0.645	0.313	1.331		0.457	0.176	1.188	
IVIg: 1-2 visits vs none	0.809	0.339	1.932	0.0486	0.739	0.299	1.824	0.0861	1.342	0.449	4.012	0.4004
IVIg: all 3 visits vs none	0.225	0.069	0.741		0.237	0.065	0.864		0.453	0.116	1.773	
Pyridostigmine: 1-2 visits vs none	0.357	0.148	0.861	0.0005	0.393	0.164	0.942	0.0002	0.506	0.175	1.465	0.0067
Pyridostigmine: all 3 visits vs none	0.246	0.122	0.497		0.225	0.112	0.453		0.28	0.126	0.622	
Treatment de-escalation vs none (6 months)	2.112	0.779	5.73	0.1418	2.051	0.75	5.61	0.2318	2.328	0.781	6.941	0.0464
Treatment escalation vs none (6 months)	0.713	0.327	1.552		0.808	0.367	1.779		0.521	0.194	1.4	
Treatment de-escalation vs none (12 months)	1.374	0.668	2.824	0.0448	1.475	0.706	3.08	0.0844	0.537	0.211	1.369	0.2087
Treatment escalation vs none (12 months)	0.404	0.159	1.026		0.493	0.194	1.256		0.417	0.141	1.233	

TABLE A3 Use of medication during 1-year follow-up (current at any time-point) (N = 520)

	Males, n = 228	Females (18-45 years old), n = 61	Females (>45 years old), n= 231	*P* value
Pyridostigmine (%)	199 (87.28%)	54 (88.52%)	191 (82.68%)	.2881
Prednisone (%)	157 (68.86%)	40 (65.57%)	124 (53.68%)	.0030[a]
Steroid-sparing immunosuppressants (%)	152 (66.67%)	36 (59.02%)	135 (58.44%)	.1669
Azathioprine (%)	59 (25.88%)	14 (22.95%)	63 (27.27%)	.7855
Mycophenolate (%)	101 (44.30%)	21 (34.43%)	67 (29.00%)	.0029*
IVIg (%)	70 (30.70%)	25 (40.98%)	85 (36.80%)	.2100
Plasma exchange (%)	27 (11.84%)	8 (13.11%)	29 (12.55%)	.9533
Rituximab (%)	14 (6.14%)	9 (14.75%)	20 (8.66%)	.0912

[a]The only significant pairwise comparison was male vs female (>45 years).