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Longitudinal Analysis of Disease Burden in Refractory and Nonrefractory Generalized Myasthenia Gravis in the United States

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Abstract

Objective:
To compare temporal trends in clinical and health care resource utilization (HRU) outcomes in people with refractory and nonrefractory generalized myasthenia gravis (gMG).

Methods:
A retrospective analysis of data from adults with gMG in the Myasthenia Gravis Foundation of America Patient Registry. gMG status (ever-refractory or always nonrefractory) and clinical (Myasthenia Gravis—Activities of Daily Living [MG-ADL] scores, exacerbations) and HRU outcomes were determined from questionnaires self-completed 6-monthly for up to 4 years. The probability of each outcome was compared for the 2 groups over time.

Results:
The mean MG-ADL score and the probability of experiencing each outcome were significantly greater in the ever-refractory versus nonrefractory groups during each year of follow-up. Between-group differences in time trends were statistically significant for intensive care and feeding-tube use.

Conclusions:
People who have ever had refractory gMG may have worse functional status, more exacerbations, and higher HRU than people with consistently nonrefractory disease.

Key Words: myasthenia gravis, refractory, longitudinal, health care resource utilization

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INTRODUCTION

Generalized myasthenia gravis (gMG) is an autoimmune condition that is caused, in most cases, by antibodies against acetylcholine receptors (AChRs) at the neuromuscular junction.[1] This leads to characteristic fatigable weakness of the ocular, bulbar, respiratory, axial, and limb muscles.[2] The symptoms are diverse, including ptosis, diplopia, dysphagia, dysarthria, and weakness of the arms, hands, and legs.[3] It can also have a substantial impact on the quality of life and the ability to conduct everyday tasks.[4,5] Most patients will experience at least one exacerbation during the course of their illness.[2]

As a chronic incurable disease, gMG requires long-term or lifelong treatment in most people with the disease.[6–8] According to the Myasthenia Gravis Foundation of America (MGFA) consensus guidelines, the goal of treatment is to achieve at least "minimal manifestation status" with minimal treatment side effects.[9] These guidelines recommend continuing low-dose steroids over the long term and that nonsteroidal immunosuppressant therapy (IST) should only be tapered after treatment goals have been maintained for 6 months to 2 years.[9]

The symptoms of gMG generally respond to treatment with acetylcholinesterase inhibitors and/or conventional IST (eg, steroids, azathioprine, and mycophenolate mofetil). However, some people continue to endure ongoing symptoms despite multiple therapy attempts or experience intolerable side effects. These people are classified as having treatment-refractory gMG, with prevalence estimates ranging from 5% to 15%.[10–15] Uncontrolled symptoms in people with refractory gMG can have a variety of medical and

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functional sequelae, including malnutrition, sleep disturbances, and inability to work and/or drive.[16] The burden of disease is further compounded by the adverse effects of some of the treatments used in people with refractory gMG. For example, high-dose steroids can have serious long-term side effects such as diabetes and osteoporosis,[17,18] and chronic use of IST is associated with severe bacterial and viral infections.[16] Rituximab may also be associated with chronic B-cell depletion.[19,20] Other issues associated with the management of refractory gMG are the very slow response to some ISTs[21] and the often "trial and error" nature of treatment.[22]

The characterization and burden of refractory gMG need to be improved, particularly regarding its long-term effects. In a US retrospective study of administrative claims data, people with refractory myasthenia gravis (MG) had significantly higher rates of exacerbations, myasthenic crises, and hospitalizations and/or emergency department (ED) visits compared with people with nonrefractory MG.[10] However, the duration of follow-up used to assess these outcomes was only 1 year. The aim of the current study was therefore to compare yearly outcomes and longer-term temporal trends in functional status, MG exacerbations, and health care resource utilization (HRU) in people with refractory and nonrefractory gMG using data from the MGFA Patient Registry.

METHODS

Data Source

Data were obtained from the MGFA Patient Registry, which is open to adults (aged ≥18 years) with gMG living in the United States.[23] Registry participants were invited to complete an initial survey at enrollment and follow-up surveys every 6 months thereafter to collect the following information: demography, gMG medical and treatment history, HRU, and impact on functional status, as assessed by the Myasthenia Gravis—Activities of Daily Living (MG-ADL) questionnaire. All information, including gMG diagnosis, was self-reported.

Participants

Participants were eligible for inclusion in the study if they reported a physician diagnosis of gMG ≥1 year before enrollment, had completed the enrollment questionnaire between July 2013 and February 2018 and at least one follow-up questionnaire by February 2019, and provided sufficient information to allow for determination of refractory status at enrollment.

On completion of each questionnaire, a participant's gMG status (refractory or nonrefractory) was determined according to his/her responses to questions on the number, class, and duration of current and previous drug treatments (from their current and past questionnaires) and the MG-ADL total score (from their current questionnaire), based on criteria (Table 1) commonly used in the published literature[9,11] to define refractory MG.

To maintain static comparator groups and handle transitions in refractory status during follow-up, 2 distinct participant groups were created: "ever-refractory" and "nonrefractory." The ever-refractory group comprised participants who were classified as having refractory gMG at any point during the study (ie, at enrollment or during follow-up). Once classified as having refractory gMG, from that time onward, participants remained in this group irrespective of their refractory status at subsequent assessments. Follow-up began at the first classification of refractory gMG, and this was defined as the baseline for these participants. If these participants had been classified as having nonrefractory gMG in previous surveys, those surveys were excluded from the analysis to maintain independence between groups. The ever-refractory group therefore included both the prevalent cases at enrollment and the incident cases that occurred during follow-up. The nonrefractory group included participants who were classified as having nonrefractory disease in all completed surveys, ie, baseline for this group was at enrollment.

Study Outcome Measures

Study outcome measures reported in each 6-month assessment questionnaire

Journal of
CLINICAL
NEUROMUSCULAR
DISEASE

Volume 22, Number 1
September 2020

TABLE 1. Criteria Used for Classifying Refractory MG

Criteria	Required for Definition of Refractory Disease
1. Past treatment	Use of at least 2 of the following: azathioprine, cyclophosphamide, ciclosporin, methotrexate, mycophenolate, prednisone, rituximab, and/or tacrolimus for at least 6 months each in the past year; OR use of at least one of the ISTs for any duration AND repeated use of intravenous immunoglobulin or plasmapheresis, defined as at least 4 rounds in the past year
AND	
2. Current treatment	Use of at least one of the following: azathioprine, cyclophosphamide, ciclosporin, intravenous immunoglobulin, methotrexate, mycophenolate, plasmapheresis, prednisone, rituximab, or tacrolimus
AND	
3. MG-ADL total score	Current MG-ADL score ≥6

comprised participants' MG-ADL total score for the preceding 4 weeks, the number of MG exacerbations during the past 6 months, and HRU [overnight hospitalizations, ED visits, intensive care unit (ICU) use, and feeding-tube use] during the past 6 months.

Statistical Analyses

Survey data collected through February 2019 were analyzed, with a maximum possible follow-up of 4 years. Baseline demographic and clinical characteristics were compared for participants with ever-refractory and nonrefractory gMG using the Student *t* test (continuous variables) or a χ^2 test (categorical variables). Generalized estimating equation models were used to assess longitudinal trends in study outcomes and their relationship with refractory status. Interaction terms for refractory status and time were included in the models to investigate time trend differences associated with refractory status. All models controlled for age and the education level at baseline, as well as sex and race. Hypothesis tests were performed at the 0.05 alpha level.

RESULTS

Study Population

Overall, 782 participants met the inclusion criteria and were enrolled in the study. Based on the results of the enrollment survey, 49 participants (6%) had refractory gMG. Based on the results from all surveys, 581 participants (74%) were classified as nonrefractory and 201 (26%) as ever-refractory. At baseline, the ever-refractory group was statistically significantly younger ($P = 0.0008$) and included a greater proportion of women ($P = 0.0001$) versus the nonrefractory group (Table 2). The mean MG-ADL total scores were significantly higher (worse) in participants with ever-refractory versus nonrefractory gMG ($P < 0.0001$). Of participants reporting sufficient data to determine anti-AChR antibody status, 10 (50%) of the ever-refractory group and 168 (66%) of the nonrefractory group reported being positive for the anti-AChR antibody at baseline. Of those reporting sufficient data to determine muscle-specific kinase (MuSK) antibody status, 5 (31%) of the ever-refractory group and 32 (32%) of the nonrefractory group reported being positive for the anti-MuSK antibody at baseline.

The mean (SD) follow-up period was 2 (1.3) years. During this time, the median number of questionnaires completed per participant was 3 (interquartile range 2–5).

The number of transitions between refractory and nonrefractory status during the study is summarized in **Supplemental Digital Content 1** (see **Supplementary Fig. 1,** http://links.lww.com/JCND/A38).

TABLE 2. Participant Characteristics at Baseline by Refractory Status*

Characteristics	Ever-refractory gMG (n = 201)	Nonrefractory gMG (n = 581)	*P*
Age at diagnosis, y; mean (SD)	45.0 (15.2)	50.6 (17.2)	<0.0001
Age at baseline, y; mean (SD)	51.6 (14.3)	59.2 (13.9)	0.0008
Sex, n (%)			0.0001
Male	55 (27)	252 (43)	
Female	146 (73)	329 (57)	
White, n (%)	46 (23)	533 (92)	<0.0001
MG-ADL total score; mean (SD)	9.1 (2.5)	5.1 (3.9)	<0.0001
Education, n (%)			0.4684
Less than high school	2 (1)	2 (<1)	
High school degree/general education diploma	41 (20)	125 (22)	
Associate's degree	40 (20)	88 (15)	
Technical degree	12 (6)	37 (6)	
Bachelor's degree	50 (25)	171 (29)	
Postgraduate education	55 (27)	152 (26)	
Anti-AChR antibody test performed, n (%)			<0.0001
Yes	45 (22)	391 (67)	
No	5 (2)	45 (8)	
Unsure or missing	151 (75)	145 (25)	
Anti-AChR antibody positive, n (%)†	10 (50)	168 (66)	0.3155
Anti-MuSK antibody test performed, n (%)			<0.0001
Yes	28 (14)	147 (25)	
No	40 (20)	197 (34)	
Unsure or missing	133 (66)	237 (41)	
Anti-MuSK antibody positive, n (%)†	5 (31)	32 (32)	0.9583

*Participants were included in the ever-refractory group from the point at which their disease was defined as refractory; participants were included in the nonrefractory group if their disease was nonrefractory at enrollment and at all timepoints assessed during the study.
†Calculated as a percentage of the patients who reported their antibody test results.

Once participants' disease became refractory, relatively few reverted to nonrefractory status during their follow-up period.

Outcome Measures

Summary statistics for the outcome measures in the ever-refractory and nonrefractory groups during each year of follow-up are presented in Table 3. The proportions of participants with each outcome generally decreased between baseline and years 3–4 in both groups, but were almost always higher in the ever-refractory group versus the nonrefractory group.

MG-ADL

Modest decreases (improvements) in predicted MG-ADL total scores were observed in both groups during the follow-up period (Fig. 1A). Scores were consistently and statistically significantly lower (better) in the nonrefractory group versus the ever-refractory group, but there was no evidence of a difference in the time trend between the groups ($P = 0.2792$) (Table 4). At baseline (after controlling for the confounding factors of sex, race, and baseline age and education level), the predicted mean [95% confidence interval (CI)] MG-ADL score was 62.4% (50.3%–75.3%) higher (worse) in participants with ever-refractory gMG compared with those with nonrefractory disease. At 2 years and 4 years, the differences between the 2 groups [68.6% (53.8%–84.9%) and 75.2% (51.8%–102.1%), respectively] were similar

Journal of CLINICAL NEUROMUSCULAR DISEASE
Volume 22, Number 1
September 2020

TABLE 3. Summary Statistics for MG-ADL Total Score, Exacerbations, and HRU Over Time in the Ever-refractory and Nonrefractory Groups*

		Ever-refractory gMG		Nonrefractory gMG	
Outcomes	**Time from baseline (y)**	**Observed, n†**	**With outcome, n (%)**	**Observed, n†**	**With outcome, n (%)**
MG-ADL total score ≥6‡	0	201	168 (84)	581	185 (32)
	<1 y	146	100 (68)	428	99 (23)
	1–2 y	163	105 (64)	526	115 (22)
	2–3 y	84	55 (65)	348	66 (19)
	3–4 y	55	42 (76)	249	41 (16)
Exacerbation§	0	200	115 (58)	557	253 (45)
	<1 y	146	69 (47)	414	118 (29)
	1–2 y	160	66 (41)	505	94 (19)
	2–3 y	82	32 (39)	344	80 (23)
	3–4 y	54	16 (30)	244	44 (18)
ED visit§	0	201	69 (34)	578	124 (21)
	<1 y	146	41 (28)	426	75 (18)
	1–2 y	163	42 (26)	524	76 (15)
	2–3 y	84	19 (23)	348	45 (13)
	3–4 y	55	14 (25)	249	31 (12)
Overnight hospitalization§	0	201	59 (29)	577	111 (19)
	<1 y	146	38 (26)	427	67 (16)
	1–2 y	163	37 (23)	524	74 (14)
	2–3 y	84	17 (20)	345	39 (11)
	3–4 y	54	12 (22)	248	30 (12)
ICU use§	0	201	48 (24)	572	196 (34)
	<1 y	146	17 (12)	425	15 (4)
	1–2 y	163	11 (7)	526	15 (3)
	2–3 y	83	5 (6)	346	6 (2)
	3–4 y	55	3 (5)	249	1 (<1)
Feeding-tube use§	0	200	19 (10)	575	70 (12)
	<1 y	146	4 (3)	425	5 (1)
	1–2 y	163	4 (3)	526	4 (1)
	2–3 y	84	3 (4)	345	1 (<1)
	3–4 y	55	0 (0)	249	2 (1)

*Participants were included in the ever-refractory group from the point at which their disease was defined as refractory; participants were included in the nonrefractory group if their disease was nonrefractory at enrollment and at all timepoints assessed during the study.
†Based on the number of questionnaires completed and refractory status at time of completion.
‡In the previous 4 weeks.
§In the previous 6 months.

to the between-group difference seen at baseline (Table 4).

Exacerbations

The predicted probabilities for experiencing any exacerbation and for the number of exacerbations were highest at baseline in both groups (Fig. 1B, C), but were significantly lower for the nonrefractory group versus the ever-refractory group at baseline and all timepoints during follow-up (Table 4). At baseline (after controlling for potential confounding factors), the predicted probability of an exacerbation was 55.5% (95% CI 13.0%–113.8%) higher in the refractory group compared with the nonrefractory

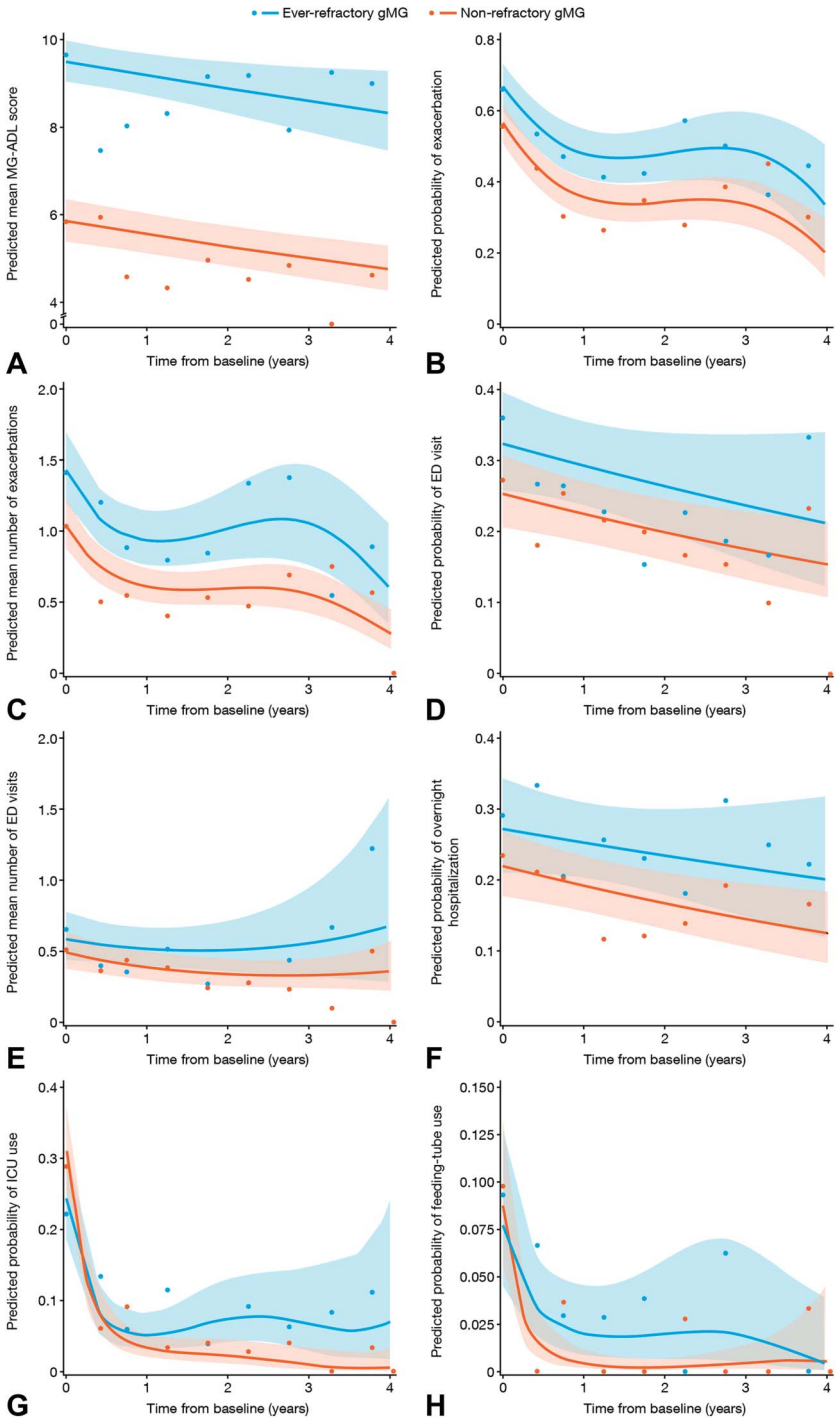

FIGURE 1. Predicted results from generalized estimating equation models according to refractory status* over time for: (A) MG-ADL total scores†; (B) probability of any exacerbation‡; (C) number of exacerbations‡; (D) probability of any ED visit‡; (E) number of ED visits‡; (F) probability of any overnight hospitalization‡; (G) probability of any ICU use‡,§; and (H) probability of any feeding-tube use. ‡,§ Sample means are displayed as dots. Shading indicates 95% CI. *Participants were included in the ever-refractory group from the point at which their disease was defined as refractory; participants were included in the nonrefractory group if their disease was nonrefractory at enrollment and at all timepoints assessed during the study. †Over the previous 4 weeks. ‡In the previous 6 months. §Results should be interpreted with caution owing to the small number of participants who provided data between years 3 and 4.

TABLE 4. Odds Ratios for Differences in MG-ADL Total Scores and HRU Between Participants With Ever-refractory and Nonrefractory gMG Over Time

Outcomes	Odds Ratios (95% CI) for Ever-refractory* vs. Nonrefractory† gMG					Time Trend Analysis
	Baseline‡	Year 1	Year 2	Year 3	Year 4	
MG-ADL total score§	1.624 (1.503, 1.753)	1.655 (1.531, 1.788)	1.686 (1.538, 1.849)	1.719 (1.532, 1.928)	1.752 (1.518, 2.021)	$P = 0.2792$
	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	
Any exacerbation¶	1.555 (1.130, 2.138)	1.657 (1.271, 2.159)	1.765 (1.271, 2.452)	1.881 (1.184, 2.989)	2.005 (1.074, 3.743)	$P = 0.5020$
	$P = 0.0067$	$P = 0.0002$	$P = 0.0007$	$P = 0.0075$	$P = 0.0290$	
No. of exacerbations¶	1.377 (1.117, 1.698)	1.532 (1.262, 1.860)	1.705 (1.305, 2.229)	1.898 (1.295, 2.782)	2.112 (1.267, 3.521)	$P = 0.1398$
	$P = 0.0027$	$P < 0.0001$	$P < 0.0001$	$P = 0.0010$	$P = 0.0041$	
Any ED visit¶	1.740 (1.246, 2.429)	1.762 (1.327, 2.339)	1.785 (1.230, 2.590)	1.808 (1.059, 3.086)	1.831 (0.889, 3.773)	$P = 0.9057$
	$P = 0.0011$	$P < 0.0001$	$P = 0.0023$	$P = 0.0300$	$P = 0.1011$	
No. of ED visits¶	1.447 (1.038, 2.016)	1.628 (1.231, 2.153)	1.832 (1.256, 2.671)	2.061 (1.189, 3.572)	2.319 (1.098, 4.896)	$P = 0.2912$
	$P = 0.0291$	$P = 0.0006$	$P = 0.0017$	$P = 0.0100$	$P = 0.0274$	
Any overnight hospitalization¶	1.614 (1.145, 2.276)	1.736 (1.320, 2.283)	1.867 (1.309, 2.662)	2.008 (1.193, 3.379)	2.160 (1.058, 4.409)	$P = 0.5105$
	$P = 0.0063$	$P < 0.0001$	$P = 0.0006$	$P = 0.0086$	$P = 0.0345$	
Any ICU use¶‖	0.712 (0.491, 1.034)	1.579 (0.998, 2.497)	3.498 (1.514, 8.081)	7.753 (2.178, 27.592)	17.181 (3.091, 95.483)	$P = 0.0007$
	$P = 0.0745$	$P = 0.0509$	$P = 0.0034$	$P = 0.0016$	$P = 0.0012$	
Any feeding-tube use¶‖	0.863 (0.491, 1.518)	8.549 (1.741, 41.984)	84.639 (3.328, 2152.581)	837.988 (6.161, >10,000)	8296.725 (11.318, >10,000)	$P = 0.0079$
	$P = 0.6101$	$P = 0.0082$	$P = 0.0072$	$P = 0.0072$	$P = 0.0073$	

*Participants were included in the ever-refractory group from the point at which their disease was defined as refractory.

†Participants were included in the nonrefractory group if their disease was nonrefractory at enrollment and at all timepoints during the study.

‡For participants with refractory gMG, "baseline" refers to the point at which their disease was defined as refractory, whereas for participants with nonrefractory gMG, it refers to time of enrollment.

§In the 4 weeks before questionnaire completion.

¶In the 6 months before questionnaire completion.

‖Results should be interpreted with caution owing to the small number of participants who provided data between years 3 and 4.

Journal of CLINICAL NEUROMUSCULAR DISEASE
Volume 22, Number 1
September 2020

group. At 2 years, the predicted probability was 76.5% higher (95% CI 27.1%–145.2%) in the refractory versus nonrefractory group; at 4 years, it was 100.5% higher (95% CI 7.4%–274.3%). Corresponding probabilities for the mean number of exacerbations were 37.7% higher (95% CI 11.7%–69.8%) at baseline in the ever-refractory group versus the nonrefractory group, 70.5% higher (30.5%–122.9%) at 2 years, and 111.2% higher (26.7%–252.1%) at 4 years (Table 4). However, there was no evidence of a difference in the time trend between the groups for probability of an exacerbation or the number of exacerbations (Table 4).

HRU

The proportion of patients with recent ED visits was highest at baseline and decreased slowly during the follow-up period in both groups (Table 3 and Fig. 1D). Probabilities of having any ED visit were significantly higher in the ever-refractory versus the nonrefractory group at baseline and at years 1, 2, and 3, but there was no significant between-group difference in the time trend ($P = 0.9057$) (Table 4). At baseline (after controlling for potential confounding factors), the predicted probability of at least one ED visit during the previous 6 months was 74.0% (95% CI 24.6%–142.9%) higher in participants with ever-refractory disease versus those with nonrefractory disease. Between-group differences in predicted probabilities were similar at 2 years [78.5% (95% CI 23.0%–159.0%)] and 4 years [83.1% (−11.1% to 277.3%)] (Table 4).

The numbers of ED visits remained relatively constant across the follow-up period in both groups, but were significantly higher in participants with ever-refractory disease at all timepoints (Table 4 and Fig. 1E). At baseline (after controlling for potential confounding factors), the predicted mean number of ED visits was 44.7% (95% CI 3.8%–101.6%) higher in participants with ever-refractory disease versus those with nonrefractory disease. The predicted probabilities at 2 years and 4 years were 83.2% (95% CI 25.6%–67.1%) higher and 131.9% (9.8%–389.6%) higher, respectively, in the ever-refractory disease group, but there was no significant between-group difference in the time trend ($P = 0.2912$) (Table 4).

The probabilities for any recent overnight hospitalization were significantly higher in the ever-refractory group at baseline and at all timepoints during follow-up (Table 4 and Fig. 1F), but there was no significant between-group difference in the time trend ($P = 0.5105$) (Table 4). At baseline (after controlling for confounding factors), the predicted probability of a recent overnight hospitalization was 61.4% (95% CI 14.5%–127.6%) higher in participants with ever-refractory disease compared with those with nonrefractory disease. Predicted probabilities at 2 years and 4 years were 86.7% (95% CI 30.9%–166.2%) higher and 116.0% (5.8%–340.9%) higher, respectively, in the ever-refractory group (Table 4).

ICU use decreased between baseline and year 1 in both groups (Fig. 1G). Thereafter, it was significantly higher in the ever-refractory group, and the time trend was also significantly different between the groups ($P = 0.0007$) (Table 4). At baseline (after controlling for confounding factors), recent ICU use was comparable between the 2 groups ($P = 0.0745$). At 2 years, the predicted probability of recent ICU use was 249.8% (95% CI 51.4%–708.1%) higher in participants with ever-refractory disease. At 4 years, the difference between groups increased further, but estimates are less precise due to the small number of participants reporting ICU use (<1% of participants with nonrefractory gMG and 5% of those with refractory gMG during years 3–4) (Table 4).

Recent feeding-tube use was similar in the 2 groups at baseline (Fig. 1H). Thereafter, it was significantly higher in the ever-refractory group, and the time trend was significantly different between the groups ($P = 0.0079$) (Table 4). Estimates at later timepoints were less precise due to the small number of participants reporting feeding-tube use (<1% of participants with

Journal of
CLINICAL
NEUROMUSCULAR
DISEASE

Volume 22, Number 1
September 2020

nonrefractory gMG and 0% of those with refractory gMG during years 3–4) (Table 4).

DISCUSSION

The current study evaluated temporal trends in functional status, MG exacerbations, and HRU in people with refractory and nonrefractory gMG. The results suggested that both clinical and HRU outcomes were consistently and significantly worse in participants with ever-refractory versus nonrefractory disease during the follow-up; this may reflect the impact of the disease itself and/or the short-term and long-term effects of the prescribed MG medication on participants' health. The time-trend analysis showed there was a significant increase in the probability of ICU use and possibly feeding-tube use in the ever-refractory versus nonrefractory groups over the time course of the study; however, these results should be interpreted with caution owing to the small number of participants who provided data between years 3 and 4. The differences in the number and rate of exacerbations, ED visits, and overnight hospitalizations between the ever-refractory and nonrefractory groups increased over time (baseline vs. 2 years vs. 4 years), but the time trends for these outcome measures were not significantly different. Again, this may reflect the decreasing number of patients with increasing duration of follow-up and highlights the challenges associated with longitudinal data analysis for rare diseases.

The results of the current study are consistent with previous publications describing increased HRU in people with refractory versus nonrefractory MG.[10,24,25] The current study extended the duration of follow-up by at least 1 year compared with the study by Engel-Nitz et al[10] and suggested longer-lasting effects of experiencing refractory disease.

Estimates of the proportion of the gMG population with refractory disease vary according to the source of the data. Results from administrative health plan databases provide estimates of 5%–10%[10,12] compared with 15%, based on cases presenting at outpatient or neuromuscular clinics.[14,15] In the current study, the proportion of refractory cases at enrollment was 6%. This potentially low value may be due to the limited amount of treatment history data available at enrollment on which to base the classification of refractory status. The cumulative prevalence of refractory gMG—based on the prevalence at enrollment and incident cases during the follow-up period—was 26%.

Despite the widely recognized issue of refractory MG and its burden, a broadly accepted, consensus-based definition does not exist. In this study, a definition of refractory gMG was used that took into account previous and current therapies and current MG-ADL scores, which is broadly consistent with previously used definitions. However, we acknowledge that the results obtained may be sensitive to the definition of treatment-refractory disease and to classification error stemming from the self-reported nature of the data.

A few observations deserve closer attention. At baseline, more participants in the nonrefractory group had recently used the ICU (34% vs. 24%), but this difference was not statistically significant ($P = 0.07$). Interestingly, ICU use decreased substantially in both groups between baseline and the next completed survey. This may be because participants with greater ICU use were less able or motivated to complete the next survey, potentially introducing selection bias. Alternatively, it may be because they were more likely to be referred to enter the registry after a "significant" clinical event. Participants may be more closely monitored after such an event and receive improved care or better access to medication. The latter may also explain why other outcome measures were worst at baseline and improved thereafter. The self-reported rates of positive anti-AChR and anti-MuSK antibody tests in the current study are at variance with previous findings; for example, Suh et al[15] noted anti-AChR antibodies in 53% and 75% and anti-MuSK antibodies in 47% and 2% of patients

with refractory and nonrefractory gMG, respectively. However, the results in the current study may be affected by self-report, missing data, and lack of informed discussion with physicians regarding antibody status. Surprisingly, the nonrefractory group had a higher percentage of participants of white race, perhaps due to self-reporting biases or differences in care.

One limitation of the study is the reliance on participants' recall to accurately assess exacerbations and HRU outcomes. However, this was assumed to be minimal because of the short period of recall (6 months) and the significance of the events being assessed, both of which reduce recall bias.[26] There are also limitations associated with the classification of refractory status over time in the current study. Once a participant was classified as having refractory gMG, for the purposes of the analysis, their data were included in the ever-refractory group for the remainder of the follow-up period. It is possible that the disease became nonrefractory in some of these participants. However, the number of participants whose status changed from refractory to nonrefractory was relatively small (see **Supplementary Fig. 1**, **Supplemental Digital Content 1**, http://links.lww.com/JCND/A38). Furthermore, assigning participants' disease as refractory if it was, in fact, nonrefractory would result in an underestimate of the burden of refractory disease and therefore would result in a conservative estimate of the burden impact. Several other options were considered, including analyses according to baseline refractory status (ie, where it was assumed that participants maintained the same status throughout follow-up as determined at the first questionnaire completion), a consistent refractory status (where participants were classified as refractory if they had refractory disease in a majority of completed questionnaires), or time-varying refractory status (in which actual refractory status at each assessment was used). Use of the ever-refractory classification simplified the model interpretations by maintaining static comparator groups and providing adequate sample sizes of participants with extended longitudinal treatment histories in both the ever-refractory and nonrefractory groups. We also acknowledge the potential impact of a lack of dosing information when classifying refractory status. Another limitation of the current analysis was the shorter duration of follow-up in those participants with disease classified as refractory after enrollment. The potential unreliability of reported anti-AChR and anti-MuSK antibody status may also limit interpretation of the results; large proportions of participants provided no response or responded as unsure, and a low percentage reported positive antibody status.

Strengths of the study include the large number of participants treated in real-life clinical practice, which increases the generalizability of the results. The characteristics of the population were consistent with the known risk factors for refractory MG, ie, younger age at onset and female sex.[11,14,15] It is acknowledged that those with refractory MG may have been more motivated to participate in the registry, potentially introducing selection bias.

In conclusion, based on real-world longitudinal data, this study suggests that people with gMG who have refractory disease at any time may have worse functional status, more exacerbations, and higher HRU than people with consistently nonrefractory disease during a mean follow-up of 2 years. The results also suggest that over time, the probabilities of ICU use and possibly feeding-tube use are increasingly greater in those with refractory versus nonrefractory disease. These results highlight the substantial and potentially long-lasting impact of refractory MG. They also emphasize the importance of identifying and carefully managing people with refractory gMG to limit the detrimental long-term effects on outcomes and HRU in this subgroup.

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