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THYMECTOMY MAY NOT BE ASSOCIATED WITH CLINICAL IMPROVEMENT IN MuSK MYASTHENIA GRAVIS

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ABSTRACT: *Introduction:* A randomized trial demonstrated benefit from thymectomy in nonthymomatous acetylcholine receptor (AChR)-antibody positive myasthenia gravis (MG). Uncontrolled observational and histologic studies suggest thymectomy may not be efficacious in anti–muscle-specific kinase (MuSK)-MG. *Methods:* The therapeutic impact of thymectomy was evaluated from data collected for a multicenter, retrospective blinded review of rituximab in MuSK-MG. *Results:* Baseline characteristics were similar between thymectomy (n = 26) and nonthymectomy (n = 29) groups, including treatment with rituximab (42% vs. 45%). At last visit, 35% of thymectomy subjects reached the primary endpoint, a Myasthenia Gravis Foundation of America (MGFA) post-intervention status (PIS) score of minimal manifestations (MM) or better, compared with 55% of controls (P = 0.17). After controlling for age at onset of MG, rituximab, prednisone, and intravenous immunoglobulin/plasma exchange treatment, thymectomy was not associated with greater likelihood of favorable clinical outcome (odds ratio = 0.43, 95% confidence interval 0.12–1.53, P = 0.19). *Discussion:* Thymectomy was not associated with additional clinical improvement in this multicenter cohort of MuSK-MG patients.

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Abbreviations: AChR, acetylcholine receptor; IRB, institutional review board; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MGSTI, Myasthenia Gravis Status and Treatment Intensity; MM, minimal manifestations; MMF, mycophenolate mofetil; MuSK, muscle-specific kinase; PIS, postintervention status; PLEx, plasma exchange

Key words: immunosuppressant therapy; myasthenia gravis; muscle-specific kinase (MuSK) antibodies; rituximab; thymectomy

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Myasthenia gravis (MG) associated with muscle-specific kinase (MuSK) antibodies (MuSK-MG) is a rare subtype of MG, in which patients are more likely to have prominent bulbar, neck, and early respiratory muscle weakness.[1–5] A randomized, controlled trial of thymectomy in nonthymomatous acetylcholine receptor (AChR) antibody-positive generalized MG (AChR-MG) demonstrated improved clinical outcomes with thymectomy, as well as a decreased requirement for immunosuppression.[6] However, there is a paucity of evidence and no consensus on the role of thymectomy in MuSK-MG.[1,5]

Two histologic studies reported lack of thymic changes in MuSK-MG patients; follicular and lymphoid hyperplasia, enlarged perivascular spaces, and prominent germinal centers, typical in AChR-MG, were not observed.[7,8] Instead, the thymus compartment was observed to be similar in appearance to age-matched controls,[8] with some studies reporting only rare cases of lymphoid hyperplasia in MuSK-MG patients.[4,9] These studies suggest the thymus does not play as prominent a role in MuSK-MG as in AChR-MG, thus calling into question the utility of thymectomy.

There are no controlled studies describing the efficacy of thymectomy in MuSK-MG. The few available studies suggest limited improvement in clinical outcomes or reliance on immunosuppression after thymectomy in MuSK-MG.[10–12] Notably, these were

observational, uncontrolled studies with limited sample sizes, which in part reflects the rare occurrence of the MuSK-MG subtype. A few studies noted clinical improvement or reaching a desirable Myasthenia Gravis Foundation America (MGFA) postintervention status (PIS) score in up to 40%–50% of patients after thymectomy.[2,3,9] In those uncontrolled studies, patients were on concurrent immunosuppressant therapy, confounding the ability to attribute reported clinical improvement to thymectomy alone.[2,3] Formal international consensus guidelines for management of MG do not recommend thymectomy in MuSK-MG based on current evidence.[13]

MuSK-MG is considered a separate clinical and histologic entity distinct from AChR-MG, with a paucity of data regarding the efficacy of thymectomy. We present data on thymectomy from a retrospective multicenter study with a cohort of MuSK-MG patients from 10 neuromuscular centers initially designed to evaluate the role of rituximab in MuSK-MG.[14] In this study, we investigated whether thymectomy is associated with favorable clinical outcomes in patients with MuSK-MG.

METHODS

Study Design. This is a *post-hoc* analysis comparing MuSK-MG patients treated with thymectomy to those not treated with thymectomy. Data were originally collected as part of a multicenter, blinded prospective review of rituximab in MuSK-MG.[14] In the original study, potential participant clinical information from the first year of treatment or until the first dose of rituximab at each participating center was reviewed by an expert panel blinded to the actual treatment received. The panel determined whether it was appropriate to enroll the patients in a clinical trial of rituximab vs. placebo, before collecting full clinical data for the retrospective analysis. In the current study we analyzed the outcomes in patients who received thymectomy vs. patients who did not receive thymectomy, and who were selected for inclusion by the panel in the original rituximab study.[14]

Standard Protocol Approvals and Registrations. The institutional review boards (IRBs) at collaborating institutions approved the protocol. IRB-approved data-sharing agreements were established between the University of Vermont and collaborating sites.

Patients. All patients with laboratory confirmed MuSK-MG treated at 10 collaborating institutions between January 1, 2005 and January 1, 2015 were evaluated for inclusion in the original rituximab study. The inclusion criteria for the protocol have been described previously.[14] Seventy-seven of 119 patients evaluated by the panel were deemed appropriate for enrollment in the original rituximab study (Fig. 1). An additional 22 patients had less than 6 months of clinical follow-up and were excluded due to insufficient follow-up data. Excluded patients had a slightly less severe MG phenotype (median worst MGFA score III). The 55 patients selected for analysis in the original rituximab study were included in this *post-hoc* analysis. The baseline visit in the current analysis was set as the time of first presentation at each clinical center.

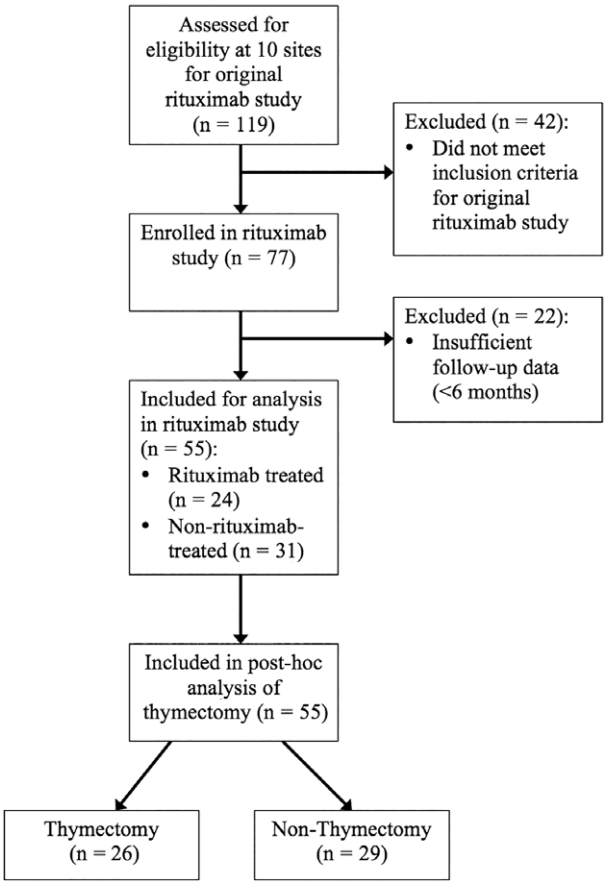

FIGURE 1. Inclusion and exclusion criteria by blinded expert panel for inclusion in original rituximab study. This same cohort was subsequently selected for inclusion in the current *post-hoc* analysis of impact of thymectomy.

The final visit is the last follow-up at each center during the period of analysis for the original rituximab study.[14]

For the current analysis, the 55 participants chosen for the rituximab study were stratified to the thymectomy or nonthymectomy group. Baseline data included sex, age at MG onset, age at last visit, medical comorbidities, date of thymectomy, thymic pathology if known, and immunosuppressant treatments. At all follow-up visits, we collected modified MGFA PIS score, immunosuppressant dose at beginning of visit, and intravenous immunoglobulin (IVIg) or plasma exchange (PLEx) treatment since last follow-up visit as either rescue therapy (surrogate measure of MG exacerbation) or maintenance therapy. MGFA PIS application was modified to allow scoring based on chart review.[15] Patients were classified into MGFA PIS categories of minimal manifestations (MM), pharmacologic remission, complete stable remission, and symptomatic. Patients were also assigned a myasthenia gravis status and treatment intensity score (MGSTI) at all visits[14] (refer to Fig. S1 in the Supplementary Material online).

Study Outcomes. The primary endpoint was the MGFA PIS score at the final visit, which was defined as the last follow-up visit at each center that occurred before the end of the study period of January 2015. An MGFA PIS score of MM or better was defined *a priori* as a desirable outcome. Secondary outcomes included MGSTI score, which combines the MGFA PIS with immunosuppressant doses.[14] A score of ≤2 for the MGSTI

was defined *a priori* as a favorable clinical outcome, reflecting an MGFA PIS score of MM or better, along with low doses of immunosuppressants. Other secondary outcomes included median prednisone dose, need for other immunosuppressant medications, and IVIg/PLEx treatment.

Statistical Methods. Baseline characteristics and clinical outcomes at the time of the final visit were compared between the thymectomy and nonthymectomy groups. Fisher's exact test was performed to analyze percentages and Wilcoxon's rank sum was used to analyze difference between medians.

Multivariable logistic regression was used to adjust for potential confounding variables. To address potential confounding, we included the following clinical variables: thymectomy status; age at onset of MG; rituximab treatment; prednisone treatment at baseline; and IVIg or PLEx treatment between the previous and final visits. Due to our limited sample size, we limited potential confounders to the variables considered most clinically significant based on expert opinion. A *post-hoc* power analysis was performed to estimate the sample size required to detect statistical significance of the primary outcome with 80% power.

RESULTS

Baseline Characteristics. Baseline characteristics were similar between the thymectomy and nonthymectomy groups (Table 1). About 80% of the cohort was female, with a median age of 32 years at onset of MG. There were no significant differences between the thymectomy and nonthymectomy groups for female sex, median age at onset of MG, median age at last visit, duration of follow-up, and number of rituximab-treated subjects. Both groups had a similar baseline worst MGFA grade (median MGFA class IVB).

In patients who received thymectomy, 65% had thymectomy before the period of observation for this study. The median time to the final visit after thymectomy was 96 months. Thymus pathology was reported as normal in 58%, hyperplasia in 23%, and unknown in 19%.

There was a higher percentage of patients on prednisone in the thymectomy group. However, there was no difference in the median baseline prednisone dose, the percentage of patients on other immunosuppressant medications, the percentage of patients on multiple immunosuppressants, or the percentage of patients on IVIg/PLEx at baseline.

Effect of Thymectomy on Achieving Primary Endpoint. We did not observe a statistically significant difference in clinical outcome between the thymectomy and nonthymectomy groups (Table 2). In univariable analysis, subjects who received thymectomy had 0.43 the odds of reaching the primary endpoint chosen to represent a beneficial clinical outcome, a MGFA modified PIS score of MM or better, compared with subjects who did not undergo thymectomy (Table 3). A *post-hoc* power analysis determined that a sample size of 188 would be required to detect the observed odds ratio of 0.43 as statistically significant at the 5% level, with 80% power. The study was therefore underpowered (power = 0.33) to detect a statistically significant effect.

The median final MGFA modified PIS score was symptomatic in the thymectomy group and MM in the nonthymectomy group (Table 2). Of those receiving thymectomy, 27% had an improvement in their MGFA PIS score from baseline, compared with 45% of nonthymectomy subjects ($P = 0.26$).

The multivariable logistic regression model included the variables thymectomy status, age at onset of MG, rituximab treatment, prednisone treatment at baseline, and IVIg or PLEx treatment between the previous and final visits, to control for effect on the primary endpoint, an MGFA PIS score of MM or better. After controlling for these variables, those receiving thymectomy had 0.43 times the odds of reaching the primary endpoint compared with those not receiving thymectomy. Consistent with our previous study,[14] patients treated with concurrent rituximab therapy were 7 times more likely to achieve a favorable clinical outcome when compared with those who did not receive rituximab (Table 3).

Secondary Outcomes. At last visit, patients who received thymectomy were less likely to achieve a favorable MGSTI status and were more likely to be treated with prednisone at the time of the final visit, with a significantly higher median final prednisone dose when compared with patients who did not receive thymectomy (Table 2). There were no significant differences between treatment groups in the outcomes of use of other immunosuppressant medications (i.e., mycophenolate mofetil, azathioprine, other) or IVIg/PLEx at final visit.

Subjects with Thymectomy during Period of Observation. Nine of the 26 subjects in the thymectomy arm received thymectomy during the period of observation for this study. They had a mean follow-up of 54 months. Median baseline MGFA score, recorded for 8 of 9 subjects, was II (MGFA II: 50%; III: 37.5%; IV: 12.5%). All 9 patients were classified as having a MGFA PIS score of symptomatic at time of thymectomy. At the visit closest to 12 months after thymectomy (10–14 months), all 9 subjects were classified as MGFA PIS symptomatic. At the visit closest to 12 months, median MGFA score of all 9 subjects remained II (MGFA II: 77%; III: 23%). At the final visit, 1 subject reached the prespecified beneficial clinical status of MGFA PIS score of MM or better. This subject received rituximab after thymectomy. Two other subjects also received rituximab and continued with an MGFA PIS score of symptomatic. At the final visit, median MGFA score was II (MGFA 0: 11%; II: 78%; III: 11%).

Table 1. Baseline characteristics.

Variable	Thymectomy (n = 26)	Nonthymectomy (n = 29)	P-value
Sex, female [% (n)]	88% (23 of 26)	79% (25 of 29)	0.48*
Median age at onset [years (range)]	29 (8–58)	34 (12–69)	0.12†
Median age at last visit [years (range)]	47 (21–67)	43 (16–78)	0.70†
Median months followed (range)	70 (6–184)	36 (6–148)	0.11†
MGFA worst grade [n (%)]			
Median MGFA	IVB	IVB	0.79†
IIA	1 (4%)	1 (3%)	
IIB	1 (4%)	3 (10%)	
IIIA	1 (4%)	1 (3%)	
IIIB	8 (33%)	7 (24%)	
IVA	2 (8%)	1 (3%)	
IVB	5 (19%)	8 (28%)	
V	8 (31%)	8 (28%)	
Baseline MGFA modified PIS score			
Median PIS	Symptomatic	Symptomatic	0.28†
Baseline MGSTI [n (%)]			
Median level	Level 4	Level 4	0.83†
Level 6	2 (8%)	2 (7%)	
Level 5	6 (23%)	8 (28%)	
Level 4	16 (61%)	14 (48%)	
Level 3	0 (0%)	4 (14%)	
Level 2	2 (8%)	0 (0%)	
Level 1	0 (0%)	1 (3%)	
Level 0	0 (0%)	0 (0%)	
Rituximab treated [% (n)]	42% (11 of 26)	45% (13 of 29)	>0.9*
Baseline immunosuppressant use [% (n)]			
On prednisone	92% (24 of 26)	69% (20 of 29)	0.04*
On MMF	27% (7 of 26)	34% (10 of 29)	0.57*
On AZA	27% (7 of 26)	14% (4 of 29)	0.31*
On other immunosuppressant	12% (3 of 26)	10% (3 of 29)	>0.9*
On multiple immunosuppressants	69% (18 of 26)	55% (16 of 29)	0.4*
On IVIg/PLEx‡	31% (8 of 26)	28% (8 of 29)	>0.9*
Median baseline prednisone (range)	20 (0–60) mg/day	15 (0–60) mg/day	0.28†

AZA, azathioprine; IVIg, intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; MGSTI, Myasthenia Gravis Status and Treatment Intensity; MMF, mycophenolate mofetil; PLEx, plasma exchange.

*Fisher's exact test.

†Wilcoxon's rank sum test.

‡Treatment with IVIg or PLEx since last follow-up visit as rescue or maintenance therapy.

Subjects Excluded from Original Rituximab Study. We separately analyzed clinical characteristics and outcomes in the first year of observation for the 42 patients excluded by the committee from the original rituximab study to explore whether patients with good clinical outcomes attributable to a thymectomy were excluded from the original rituximab study. Only data about the first year of treatment were collected for the excluded patients based on the design of the previous rituximab trial. These patients therefore could not be added to the main study analysis because data from their complete clinical course were not collected. Ten of these patients only had 1 visit during the first year of observation, so they did not have enough time-points to be included in this subanalysis; 2 of these patients received thymectomy at the time of first visit. Of the remaining 13 patients treated with thymectomy compared with the 19 patients not treated with thymectomy, both groups had a median level of MGFA PIS symptomatic at first visit and a median worst MGFA score of III, compared with a median worst MGFA score of IV in the patients included in the main analysis. The median duration of follow-up after thymectomy was 60 months (refer to Table S1 in the Supplementary Material online). Among the patients excluded from the rituximab study, those receiving thymectomy did not reach better outcomes than those who did not receive thymectomy in the first year of treatment at each center. At the visit closest to 12 months after the first visit, 62% (8 of 13) of patients treated with thymectomy reached the primary outcome of a MGFA PIS score of MM or better compared with 58% (11 of 19) of those not treated with thymectomy ($P > 0.99$, Fisher's exact test). The median MGFA PIS score was MM in both groups, and the median final MGSTI was level 4, which corresponds to a PIS status of symptomatic while taking higher doses of immunosuppressant medications. There were 6 patients who received thymectomy during the period of observation; these patients had a median follow-up of 10 months after thymectomy and had no differences in outcomes from the remainder of the group. There were no significant differences in use of immunosuppressant medications across groups (refer to Table S2 in the Supplementary Material online).

Table 2. Outcomes at time of last visit.

Outcome	Thymectomy (n = 26)	Nonthymectomy (n = 29)	P-value
MGFA modified PIS MM or better at final visit [% (n)]	35% (9 of 26)	55% (16 of 29)	0.17*
Final MGFA modified PIS score:			
Median PIS [n (%)]	Symptomatic	Minimal manifestations	0.09†
Symptomatic	17 (65%)	13 (45%)	
Minimal manifestations	6 (23%)	8 (28%)	
Pharmacologic remission	1 (4%)	3 (10%)	
Complete stable remission	2 (8%)	5 (17%)	
Final MGSTI [% (n)]			
Level 2 or better at end of period	23% (6 of 26)	45% (13 of 29)	0.15*
Level 1 or better at end of period	15% (4 of 26)	38% (11 of 29)	0.076*
Final MGSTI [n (%)]			
Median level	Level 4	Level 3	0.16†
Level 6	1 (4%)	2 (7%)	
Level 5	5 (19%)	4 (14%)	
Level 4	13 (50%)	8 (27%)	
Level 3	1 (4%)	2 (7%)	
Level 2	2 (8%)	2 (7%)	
Level 1	1 (4%)	4 (14%)	
Level 0	3 (11%)	7 (24%)	
Immunosuppressant use at final visit [% (n)]			
On prednisone	69% (18 of 26)	41% (12 of 29)	0.058*
On MMF	23% (6 of 26)	34% (10 of 29)	0.39*
On AZA	15% (4 of 26)	17% (5 of 29)	>0.9*
On other immunosuppressant	4% (2 of 26)	7% (2 of 29)	>0.9*
On multiple immunosuppressants	50% (13 of 26)	45% (13 of 29)	0.79*
On IVIg/PLEx‡	23% (6 of 26)	17% (5 of 29)	0.74*
Median prednisone dose (range)	10 (0–45) mg/day	0 (0–25) mg/day	0.04†

AZA, azathioprine; IVIg, intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; MGSTI, Myasthenia Gravis Status and Treatment Intensity; MMF, mycophenolate mofetil; MM, minimal manifestations; PIS, postintervention status; PLEx, plasma exchange.

*Fisher's exact test.

†Wilcoxon's rank sum test.

‡Treatment with IVIg or PLEx since last follow-up visit as rescue or maintenance therapy.

DISCUSSION

In this *post-hoc* analysis of MuSK-MG patients, we did not detect a more favorable clinical outcome for patients receiving thymectomy compared with those receiving immunosuppression alone. The percentage of patients reaching the primary endpoint of an MGFA PIS score of MM or better was lower for the thymectomy group compared with nonthymectomy subjects, although this difference was not statistically significant. The secondary outcome of the MGSTI endpoint, which incorporates immunosuppressant dose and clinical status, also did not detect a more favorable clinical outcome for subjects in the thymectomy arm compared with those receiving immunosuppression alone. Although there were no differences between groups in the percentage of patients receiving various immunosuppressant medications at final visit or on IVIg/PLEx, the thymectomy group had a significantly higher median final prednisone dose.

Table 3. Predictors of reaching primary endpoint of MGFA PIS score of MM or better.

Variable	OR	95% CI	P-value
Univariable analysis			
Thymectomy	0.43	0.14–1.28	0.13
Multivariable logistic regression			
Thymectomy	0.43	0.12–1.53	0.19
Age at onset of MG	1.00	0.96–1.05	0.99
Rituximab treatment	7.01	1.81–27.11	0.005
On prednisone at baseline	0.98	0.94–1.02	0.33
Final IVIg/PLEx treatment	0.28	0.05–1.47	0.13

CI, confidence interval; MGFA, Myasthenia Gravis Foundation of America; MM, minimal manifestations; OR, odds ratio; PIS, postintervention status.

After controlling for age at onset of MG, rituximab treatment, prednisone treatment at baseline, and IVIg or PLEx treatment between previous and final visits, thymectomy patients continued to be less likely to achieve a beneficial clinical status at the time of the last visit. Although thymectomy was associated with lower odds of reaching the primary endpoint, conclusions about harm of thymectomy are limited by broad confidence intervals and a small sample size, making the study underpowered to detect a significant negative effect.

Baseline characteristics were typical of the MuSK phenotype,[1–4] and were matched between groups, with the exception of the percentage of patients on prednisone. The larger number of patients treated with prednisone at baseline in the thymectomy group could be indicative of a more severe phenotype at baseline. However, the 2 treatment groups had the same baseline median MGFA PIS and MGSTI ratings, and worst MGFA status. It is also possible that, despite similar MGFA PIS and MGSTI

ratings, something about the individual phenotypes in the thymectomy group prompted treating physicians to suggest the more drastic intervention of thymectomy. It is notable that there was no difference in the percentage of patients receiving rituximab in each group, as rituximab has been associated with a favorable clinical outcome in MuSK-MG.[14]

The benefit of thymectomy in AChR-MG may plateau about 12 months after the surgery.[6] In some cohorts, improvement after thymectomy has been reported after years of follow-up.[16] Although the median duration of follow-up in the thymectomy cohort was 70 months, the majority of the thymectomy arm subjects in our cohort received thymectomy before the period of observation, which prevents a full time-to-event analysis of the observed effect at the 12-month mark and final visit. In the 9 subjects who did receive thymectomy during the period of observation, none achieved our primary endpoint around 1 year postsurgery. One of the 9 achieved the primary endpoint at the time of last visit in association with rituximab treatment within 6 months of this final visit. These observations add to our impression that thymectomy does not appear to be associated with an increased chance of beneficial clinical outcomes in patients with anti-MuSK MG.

Our results showing no observed additional clinical improvement with thymectomy are consistent with previous histologic studies that demonstrated absent or nonspecific thymic changes and lymphoid hyperplasia in MuSK-MG.[4,7–9] These findings are consistent with the absence of a pathogenic association between the thymus and MuSK-MG.[1,7,8,10–12] Consistent with these findings, the majority of subjects in our cohort for whom thymus pathology was available had normal tissue. A small number were reported to have thymic hyperplasia, consistent with previously described nonspecific thymic hyperplasia in anti-MuSK MG.[4,9] Due to the retrospective nature of this trial and original design to address effects of rituximab, we did not collect AChR antibody status. It is possible, although unlikely, that some of the subjects in our cohort were seropositive for AChR in addition to MuSK.

The goal of care for MG patients is to use minimal doses of immunosuppressants while reaching greatest clinical benefit.[5,13] Patients with MuSK-MG have been shown to respond well to corticosteroids, PLEx,[1,3,10,13] and more recently to rituximab,[14] but respond poorly to acetylcholinesterase inhibitors when compared with AChR-MG.[1–3,10,13] Given the differences in response to various treatments and interventions between different subtypes of MG, this speaks to the importance of a comprehensive initial work-up of MG and dedicated management based on immunological subtype.[13]

We acknowledge the important limitation that our analysis was *post hoc*, utilizing data retrospectively collected for the purpose of evaluating rituximab efficacy in a blinded prospective review. The 55 patients selected for the study may not be representative of all MuSK-MG patients, as less severely affected patients were excluded from analysis.[14] We analyzed data about the patients excluded from the rituximab study to explore the possibility that they had achieved a good clinical status due to thymectomy. Although the patients excluded from the rituximab study had a more mild worst MGFA score than those included in the rituximab study, the excluded patients treated with thymectomy had similar clinical severities at first visit as the excluded patients not treated with thymectomy. In addition, among the patients excluded from the rituximab study, those receiving thymectomy did not achieve better outcomes than those treated with medical therapy alone in the first year. Another source of bias may be related to the clinical characteristics of patients that led to the recommendation of thymectomy. However, the analyzed thymectomy and nonthymectomy cohorts had similar disease severities at baseline. Although our study may have been underpowered to detect a statistically significant difference between the thymectomy and nonthymectomy groups, our multicenter collaboration between 10 neuromuscular centers allowed us to maximize the sample size to study a rare subtype of MG.

Another limitation is the lack of data on thymectomy technique. Maximal resection of thymus tissue, along with early timing of thymectomy, may be associated with better outcomes.[16] Although our results do not suggest a benefit of thymectomy, it would be of interest to have assessed whether thymectomy technique correlated with clinical outcome. Evaluating surgical complications, quality-of-life measurements, and complications related to long-term immunosuppressant use would be informative in further weighing the risks and benefits of these interventions.

A strength of our study compared with previous analyses of thymectomy in MuSK-MG is the use of a control arm. Like previous uncontrolled, observational studies, which reported modest clinical improvement in some patients after thymectomy,[2,3,9] we observed clinical improvement and reduction in prednisone dose in both the thymectomy and nonthymectomy cohorts in this study. The observed improvement in both groups over time is likely more reflective of the effects of long-term immunosuppressant medication and long-term management of the disease, rather than thymectomy alone.

In conclusion, this study has provided evidence that thymectomy may not be associated with increased likelihood of a favorable clinical outcome in MuSK-MG. Given the low likelihood that a future randomized, controlled trial will be performed in

MuSK-MG, the data from this study may help to inform treatment decisions.

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Ethical Publication Statement: We (the authors) 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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