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Minimal manifestation status and prednisone withdrawal in the MGTX trial

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Abstract

Objective
To examine whether sustained minimal manifestation status (MMS) with complete withdrawal of prednisone is better achieved in thymectomized patients with myasthenia gravis (MG).

Methods
This study is a post hoc analysis of data from a randomized trial of thymectomy in MG (Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy [MGTX]). MGTX was a multicenter, randomized, rater-blinded 3-year trial that was followed by a voluntary 2-year extension for patients with acetylcholine receptor (AChR) antibody–positive MG without thymoma. Patients were randomized 1:1 to thymectomy plus prednisone vs prednisone alone. Participants were age 18–65 years at enrollment with disease duration less than 5 years. All patients received oral prednisone titrated up to 100 mg on alternate days until they achieved MMS, which prompted a standardized prednisone taper as long as MMS was maintained. The achievement rate of sustained MMS (no symptoms of MG for 6 months) with complete withdrawal of prednisone was compared between the thymectomy plus prednisone and prednisone alone groups.

Results
Patients with MG in the thymectomy plus prednisone group achieved sustained MMS with complete withdrawal of prednisone more frequently (64% vs 38%) and quickly compared to the prednisone alone group (median time 30 months vs no median time achieved, $p < 0.001$) over the 5-year study period. Prednisone-associated adverse symptoms were more frequent in the prednisone alone group and distress level increased with higher doses of prednisone.

Conclusions
Thymectomy benefits patients with MG by increasing the likelihood of achieving sustained MMS with complete withdrawal of prednisone.

Clinicaltrials.gov identifier
NCT00294658.

Classification of evidence
This study provides Class II evidence that for patients with generalized MG with AChR antibody, those receiving thymectomy plus prednisone are more likely to attain sustained MMS and complete prednisone withdrawal than those on prednisone alone.

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Coinvestigators are listed at links.lww.com/WNL/B137.

Glossary

BMI = body mass index; **IVIg** = IV immunoglobulin; **MG** = myasthenia gravis; **MG-ADL** = Myasthenia Gravis Activities of Daily Living; **MGFA** = Myasthenia Gravis Foundation of America; **MGTX** = Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy; **MMS** = minimal manifestation status; **PLEX** = plasmapheresis; **QMG** = Quantitative Myasthenia Gravis; **SAE** = serious adverse event; **TAC** = treatment-associated complications; **TAS** = treatment-associated symptoms.

Prednisone is an oral corticosteroid that is commonly used as a first-line immunotherapy in myasthenia gravis (MG) due to relatively rapid onset of action and therapeutic effect.[1–8] Usage of prednisone is often limited by short- and long-term adverse effects experienced by a majority of patients.[3–7,9] Prednisone dosing is typically tapered down gradually once the disease is under control to minimize complications; alternate-day dosing may also decrease associated adverse effects.[1,10–14] Although complete withdrawal could be considered ideal, cessation of prednisone is not always possible due to disease relapses.

Despite more than 50 years of usage, questions remain regarding optimal treatment regimens and expected outcomes. Randomized clinical trials of corticosteroids in MG are rare and limited by small sample size.[1,8,15] Randomized clinical trials of other medications provide limited information regarding prednisone due to small sample size, short follow-up periods, or lack of prednisone dose adjustments.[16–19] Retrospective studies have significant bias due to case selection, uncontrolled treatment protocols, inconsistent follow-up, and absence of predefined outcome measures.[3,6,20–25] Moreover, previous studies have not reported outcomes separately in patients with or without thymectomy. Better understanding of outcome after high-dose prednisone with or without thymectomy would further inform international treatment guidelines[26,27] and help identify the target population for other treatment modalities such as steroid-sparing agents, immune modulators, and complement inhibitors.

A randomized trial of thymectomy in MG (Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy [MGTX]) demonstrated the efficacy of thymectomy by comparing thymectomy plus prednisone vs prednisone alone at 36 months.[28] The benefit of thymectomy persisted in an extension study that followed half of the MGTX cohort for an additional 24 months.[29] All participants in the trial received high-dose alternate-day prednisone on a predefined titration and tapering schedule based on achievement of minimal manifestation status (MMS). During the trial, objective and subjective outcome measures were collected along with treatment-associated symptoms and complications. In this study, we further analyzed MGTX trial data to evaluate the clinical impact of high-dose alternate-day prednisone in MG, and how thymectomy modified the course in achieving favorable outcomes and reducing adverse effects.

Methods

Through post hoc analysis of MGTX trial data, our aim was to generate Class II evidence that thymectomy helps patients with generalized MG reach sustained MMS and completely withdraw from prednisone. MGTX was a multicenter, international, rater-blinded, randomized trial that enrolled 126 participants, 66 into thymectomy plus prednisone and 60 into prednisone alone. Of the 126 randomized participants, 111 (88%) (60 thymectomy plus prednisone, 51 prednisone alone) completed the 36-month study period, and 68 (61%) entered the extension study. Fifty patients completed the month 60 visit. Intention-to-treat was used for the analyses; 8 patients randomized to prednisone alone received thymectomy outside the protocol and 9 patients in the thymectomy plus prednisone group refused thymectomy.

The protocol prescribed thymectomy to be performed within 30 days for those randomized to surgery group. Participants not already receiving prednisone at baseline received an alternate-day dose of oral prednisone starting at 10 mg, which was increased in 10-mg steps to 100 mg on alternate days or to 1.5 mg/kg body weight, whichever was lower; upward dose titration ceased when MMS was achieved. Participants who were already taking prednisone on a daily basis were switched to equivalent alternate-day doses with subsequent dose increase as above, except the maximum dose of 120 mg alternate day was allowed for those who did not reach MMS by month 4. The maximum prednisone dose was maintained until MMS was reached and then reduced by 10 mg every 2 weeks until a level of 40 mg on alternate days was reached, with subsequent slowing of the taper to 5 mg every month, as long as MMS was maintained. If MMS was lost, the alternate-day prednisone dose was increased by 10 mg every 2 weeks until MMS was restored. Tapering could resume 4 weeks later. Once prednisone tapering commenced, the total dose of pyridostigmine could not exceed 240 mg/d. Plasmapheresis (PLEX) or IV immunoglobulin (IVIg) was permitted at the discretion of the unblinded neurologist in patients whose condition was unstable, but it was not permitted to maintain MMS. Patients who did not achieve MMS at 12 months or who had unacceptable side effects from prednisone could receive azathioprine at a dose of 2.5 mg/kg per day or another immunosuppressant such as cyclosporine if azathioprine caused side effects.

Outcome measures

The Quantitative Myasthenia Gravis (QMG) scale is a validated 13-item scale that measures weakness in MG with scores ranging

from 0 to 39, with higher scores indicating more severe disease.[30,31] The Myasthenia Gravis Activities of Daily Living (MG-ADL) scale is a validated simple 8-question survey of MG symptoms with scores ranging from 0 to 24 with higher scores indicating more severe disease.[32] MMS is defined as having "no symptoms or functional limitations from MG, but there may be some weakness on examination of some muscles."[26,33] At the same time, QMG score at the visit had to be lower than baseline and lower than 14 to qualify for MMS in this study. Sustained MMS with complete withdrawal of prednisone was defined as the achievement of MMS on a 0 mg average prednisone dose over 2 or more consecutive follow-up visits at least 3 months apart, excluding month 0. QMG and MG-ADL scores were collected by blinded evaluator at 0, 3, 4, 6, and then every 3 months through month 60. MMS and prednisone dose calculated by pill count were reported to a blinded evaluator at months 0, 1, 2, 3, 4, and 6 and then every 3 months through month 60.

Safety measures

Treatment-associated symptoms (TAS) were recorded via a 29-item survey of prednisone-associated symptoms derived from the transplant literature.[34] Patients reported the symptoms experienced along with distress level (0 = not at all, 1 = a little bit, 2 = moderately, 3 = very much, 4 = extremely). TAS was collected at months 0, 1, 2, 3, 4, and 6 and then every 3 months through month 36. Patients were aware of their prednisone dosage. Treatment-associated complications (TACs) were recorded via a survey of 36 complications from prednisone, immunosuppressants, and thymectomy, which was collected at months 0, 1, 2, 3, 4, and 6 and then every 3 months through month 60. Serious adverse events (SAEs) requiring hospitalization were collected at each follow-up visit during the 60 months.

Statistical analysis

Of the 126 randomized participants, 123 had at least 1 study visit and were included in the analysis. Basic demographic and disease-related information, MMS, pill counted prednisone dose, other medication use, QMG scores, MG-ADL scores, TAS, TAC, and SAE were retrieved from the MGTX database. Body mass index (BMI) was calculated using baseline height and weight. Obesity was defined as BMI >30. Demographic and clinical characteristics were compared between groups using Student *t* test or Wilcoxon rank-sum test for continuous variables and χ^2 test for categorical variables. Achieving MMS and achieving sustained MMS with complete withdrawal of prednisone were compared with Kaplan-Meier survival curve and log-rank test between groups. Cox proportional hazard regression model was used to investigate association between achievement of sustained MMS with complete withdrawal of prednisone and predictor variables. Treatment group, sex, age, ethnicity, and baseline prednisone and pyridostigmine usage, maximum prednisone dose prior to achieving MMS, usage of IVIg and PLEX prior to enrollment, baseline Myasthenia Gravis Foundation of America (MGFA) class, duration of disease, month 0 QMG score, month 3 QMG score, ΔQMG (changes of QMG score from month 0 to month 3), month 0 MG-ADL score, month 3 MG-ADL score, and ΔMG-ADL (changes of MG-ADL score from month 0 to month 3) were tested as potential predictor variables. The frequency of introducing steroid-sparing agents prior to achieving sustained MMS with complete withdrawal of prednisone was compared using Fisher exact test.

The reported frequency of each item in TAS was compared between the thymectomy plus prednisone and the prednisone alone group using Fisher exact test. Distress index was calculated by adding distress levels of all 28 TAS items for each individual visit. Distress index was correlated with alternate-day mean prednisone dose using mixed model analysis with random intercept. Correlation between distress index and prednisone dose was further tested by categorizing alternate-day mean prednisone dosage into no prednisone, >0–10, >10–20, and >20 mg. TAC data were summarized as the proportion of participants with each complication during the study period and were compared between groups using Fisher exact test. p value less than 0.05 was considered statistically significant without adjustment for multiple comparisons due to the exploratory nature of this study. Analyses were done using SAS version 9.4 and R project version 3.3.2.

Standard protocol approvals, registrations, and patient consents

The trial was registered with ClinicalTrials.gov (NCT00294658). Each trial site received approval from a local institutional review board or ethics committee and each patient provided written informed consent before enrollment.

Data availability

Deidentified data are available to qualified individuals for research purposes by request through the MGTX coordinating center, University of Alabama at Birmingham.

Results

A total of 123 MGTX participants were included in the analysis; 88 were female (72%) and median age was 32 years at enrollment. Among them, 117, 115, 114, 111, and 50 completed months 6, 12, 24, 36, and 60, respectively. Mean follow-up times were 45 months in both groups. There was no significant difference between thymectomy plus prednisone (65) and prednisone alone (58) groups in age, sex, ethnicity, past treatments, MGFA class, duration of disease, follow-up duration, baseline QMG and MG-ADL scores, or frequency of hypertension, diabetes, or obesity at enrollment (table 1).

Of the 123 participants, 112 reported MMS at least once during study participation with comparable frequencies among thymectomy plus prednisone and prednisone alone groups (92% vs 90%). Median time when 50% of participants achieved initial MMS was faster in the thymectomy plus prednisone group compared to the prednisone alone group over the 60-month study period, demonstrated by Kaplan-Meier survival curve (2 vs 3 months, $p = 0.04$; figure 1). With the standardized tapering protocol, 54 of the patients among 123 participants achieved sustained MMS after complete withdrawal of prednisone. The

thymectomy plus prednisone group achieved sustained MMS with complete withdrawal of prednisone more frequently (64% vs 38%) and earlier in the course (median time 30 months vs median time not achieved, $p < 0.001$; figure 2) compared to the prednisone alone group. Cox proportional hazard model demonstrated that thymectomy, lower QMG, and MG-ADL scores at month 3 and improvement in the first 3 months based on larger reductions in the QMG and MG-ADL scores correlated significantly with achieving sustained MMS with complete withdrawal of prednisone when modeled individually. On adjusted model with treatment group as the main predictor of interest, month 3 QMG scores and improvement in the QMG and MG-ADL scores between month 0 and 3 were significant covariates for achieving this target (table 2). Among these 54 patients, steroid-sparing agents were used in 5% (2/37) of the thymectomy plus prednisone and 35% (6/17) of the prednisone alone group ($p = 0.008$) prior to achieving this target. Losing MMS among these 54 patients was noted in 30% (11/37) of thymectomy plus prednisone and 35% (6/17) of the prednisone alone group. Among 17 patients who lost MMS while off prednisone, all but 3 patients regained MMS with less than 20 mg alternate-day doses of prednisone. Two patients lost MMS at the end of the study: 1 in the thymectomy plus prednisone and 1 in the prednisone alone group. A single patient in the prednisone alone group required high-dose prednisone after losing MMS.

One or more adverse symptoms were reported in 93% of TAS surveys. Most commonly reported adverse symptoms were fatigue, mood swings, increased appetite, and sleeplessness. When the frequencies of reported symptoms were compared between the thymectomy plus prednisone and prednisone alone groups, reporting 1 or more adverse symptoms was more frequent in the prednisone alone group. Changed appearance, changed taste, decreased interest in sex, fatigue, headache, painful menstruation, increased appetite, increased hair growth, mood swings, moon facies, palpitations, and poor concentration were more frequently reported in the prednisone alone group; chest pain, painful scar, and bruises were more frequently reported in the thymectomy plus prednisone group (table 3). Distress index (summation of distress level for 28 TAS items) correlated in linear fashion with the alternate-day mean prednisone dose ($p < 0.0001$). When alternate-day prednisone dose was grouped by the 4 dosage intervals, distress index increased between no prednisone and >0–10 mg ($p = 0.0004$) and >0–10 mg and >10–20 mg ($p = 0.03$) alternate-day dosing levels; however, there was no statistically significant increase in distress index between >10–20 and >20 mg alternate-day dosing levels.

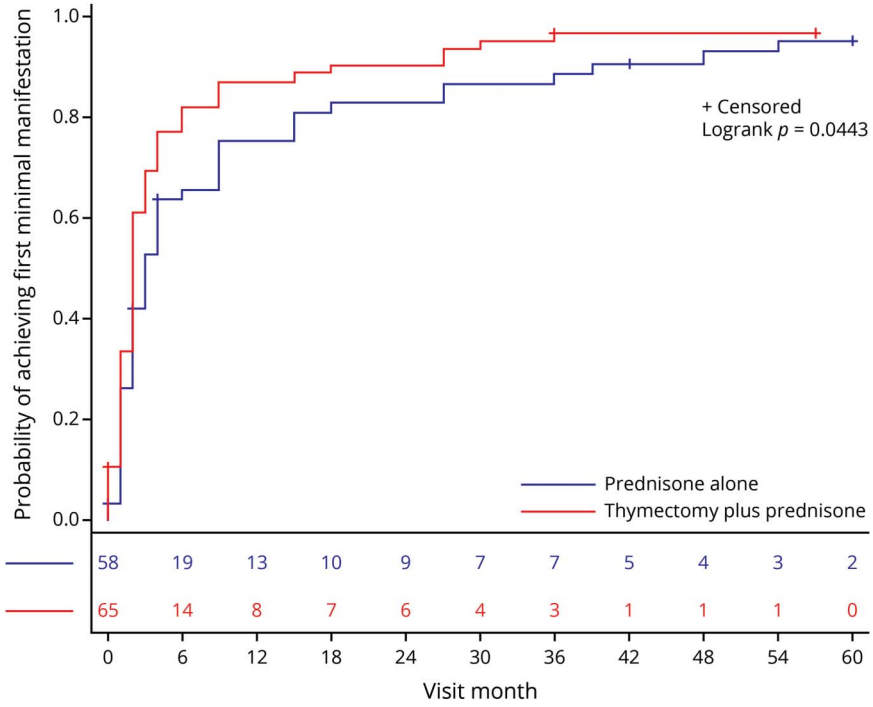
One or more complications were reported in 86% of participants over the entire study period, with such reports being more frequent in the prednisone alone group (93% vs 80%, $p = 0.04$). The most frequently reported complication changed over time from rash (month 1) to sleep disturbance (month 2 and 3) to weight gain (month 4 to month 60). Overall, increased weight (51%) was most frequent, followed by sleep

Table 1 Demographics and clinical characteristics of the participants at enrollment

	Thymectomy plus prednisone (n = 65)	Prednisone alone (n = 58)
Female sex, n (%)	49 (75)	39 (67)
Age, y, median (range)	32 (18–63)	33 (18–63)
Ethnicity, white/Hispanic/black/Asian/other, n (%)	30 (46), 17 (26), 7 (11), 6 (9), 5 (8)	29 (50), 17 (29), 5 (9), 4 (7), 3 (5)
Pyridostigmine at enrollment	60 (92)	56 (97)
Prednisone at enrollment, n (%); mean (SD) dose, mg	49 (75); 32 (20)	47 (81); 31 (14)
Previous IV immunoglobulin, n (%)	12 (18)	13 (22)
Previous plasma exchange, n (%)	9 (14)	7 (12)
MGFA class IIa/IIb/III/IV, n (%)	24 (37), 18 (28), 21 (32), 2 (3)	24 (41), 14 (24), 19 (33), 1 (2)
Duration of disease, y, mean (SD)	1.42 (1.04)	1.46 (1.04)
QMG score at month 0, mean (SD)	11.40 (5.1)	12.35 (4.9)
MG-ADL score at month 0, mean (SD)	5.29 (3.4)	5.40 (3.3)
Follow-up duration, mo, mean (SD)	45.1 (15.9)	45.6 (16.9)
Preexisting obesity, n (%)	17 (26)	17 (29)
Preexisting diabetes mellitus, n (%)	3 (5)	3 (5)
Preexisting hypertension, n (%)	4 (6)	3 (5)

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; QMG = Quantitative Myasthenia Gravis.

Figure 1 Achievement of minimal manifestation status (MMS) in thymectomy plus prednisone and prednisone alone groups



disturbance (40%), hypertension (28%), diabetes mellitus (13%), infection (11%), cataract (11%), and psychiatric problems (8%). Hospitalization other than for thymectomy or initiation of prednisone therapy was reported in 34%, with the frequency being higher in the prednisone-only group; the majority of these were related to MG exacerbation (table 4).

Figure 2 Achievement of sustained minimal manifestation status (MMS) with complete withdrawal of prednisone in thymectomy plus prednisone and prednisone alone groups

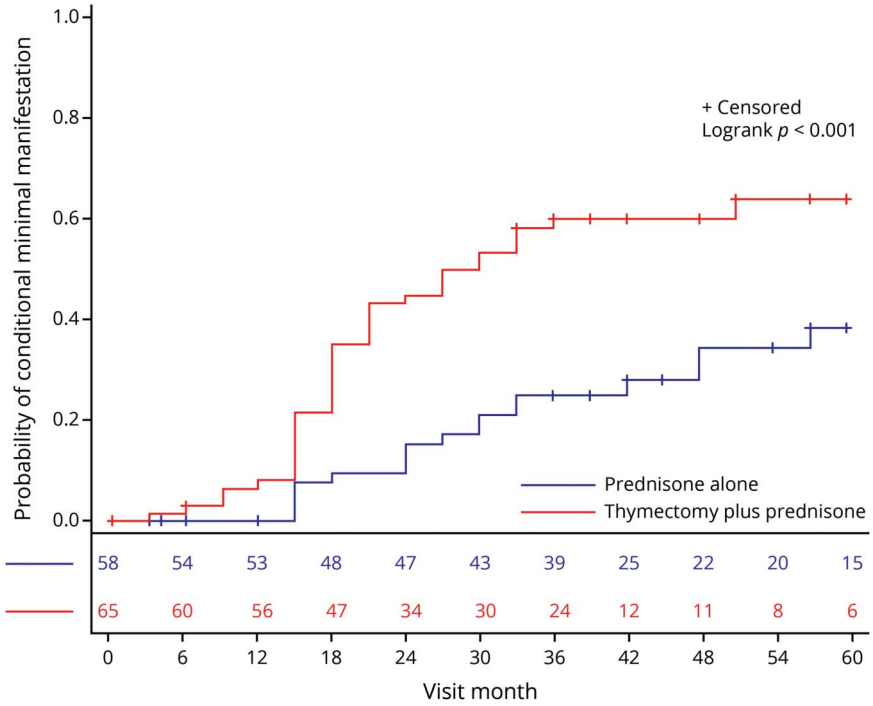


Table 2 Cox proportional hazard model to predict the time to achievement of sustained minimal manifestation status (MMS) with complete withdrawal of prednisone

	Unadjusted		Adjusted with treatment group	
Variable	**Hazard ratio (95% confidence interval)**	***p* Value**	**Hazard ratio (95% confidence interval)**	***p* Value**
Treatment group, thymectomy plus prednisone vs prednisone alone	4.57 (2.32–8.99)	<0.0001	NA	NA
QMG score at month 0	1.00 (0.95–1.06)	0.9580	NA	NA
QMG score at month 3	0.90 (0.85–0.96)	0.0011	0.92 (0.87–0.98)	0.0062
ΔQMG	0.87 (0.82–0.93)	<0.0001	0.90 (0.85–0.95)	<0.0001
MG-ADL score at month 0	1.02 (0.94–1.12)	0.6299	NA	NA
MG-ADL score at month 3	0.86 (0.77–0.97)	0.0147	0.89 (0.80–1.00)	0.0570
ΔMG-ADL	0.88 (0.80–0.96)	0.0040	0.91 (0.84–0.99)	0.0308
Sex, female vs male	1.18 (0.63–2.22)	0.5980	NA	NA
Age, y	0.99 (0.97–1.02)	0.5137	NA	NA
Ethnicity				
African American vs Asian	2.65 (0.81–8.59)	0.1058	NA	NA
Hispanic vs Asian	0.67 (0.21–2.09)	0.4868	NA	NA
Other, mixed/Native American/Alaskan vs Asian	0.53 (0.10–2.87)	0.4582	NA	NA
White vs Asian	0.96 (0.33–2.81)	0.9402	NA	NA
Prednisone usage at enrollment	0.57 (0.30–1.08)	0.0834	NA	NA
Maximum prednisone dose prior to achieving MMS, mg	0.99 (0.98–1.00)	0.4446	NA	NA
Pyridostigmine usage at enrollment	1.07 (0.33–3.43)	0.9165	NA	NA
IV immunoglobulin	0.94 (0.45–1.95)	0.8659	NA	NA
Plasma exchange at enrollment	1.18 (0.53–2.63)	0.6927	NA	NA
MGFA class				
IIb vs IIa, mild generalized weakness	1.18 (0.58–2.42)	0.6480	NA	NA
III vs IIa, moderate vs mild generalized weakness	0.91 (0.45–1.83)	0.7854	NA	NA
IV vs IIa, severe vs mild generalized weakness	0.63 (0.08–4.75)	0.6538	NA	NA
Disease duration. y	0.96 (0.70–1.30)	0.7783	NA	NA

Abbreviations: MG-ADL = Myasthenia Gravis Activities of Daily Living; MGFA = Myasthenia Gravis Foundation of America; QMG = Quantitative Myasthenia Gravis.

Compliance with prednisone dosing was excellent. Employing a 10-mg difference between the prescribed dose and the dose derived from pill count as noncompliant, noncompliance was observed in only 5% of follow-up visits. Of 2,188 study visits, there were 69 visits (3%) where patients took less than the prescribed dose and 37 visits (2%) where they took more.

Discussion

Our supplemental analysis of MGTX trial data demonstrates treatment benefits of extended transsternal thymectomy in nonthymomatous AChR antibody-positive, generalized MG on multiple fronts, extending the positive observations beyond specified primary and secondary outcomes.[28,29] Whereas the majority of participants achieved MMS, the thymectomy plus prednisone group reached this status more quickly than the prednisone alone group. Complete withdrawal of prednisone while maintaining MMS also occurred significantly faster and more frequently in thymectomy plus prednisone group compared to the prednisone alone group, indicating that disease relapses during prednisone tapers were less frequent after thymus removal. Steroid-sparing immunosuppressive agents had to be utilized significantly more frequently in the prednisone alone group; 35% of these patients required these agents to achieve sustained MMS with complete prednisone withdrawal

Table 3 Treatment-associated symptoms from the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) cumulative over all visits

	Thymectomy plus prednisone (968 visits)	Prednisone alone (861 visits)	*p* Value[a]
Any associated symptoms	91	95	0.0016
Acne	39	37	0.5
Back pain	46	48	0.3
Bruises	27	22	0.01
Changed appearance	34	42	<0.001
Changed taste	21	25	0.02
Decreased interest in sex	21	27	0.001
Depression	35	39	0.07
Diarrhea	31	31	1
Fatigue	56	66	<0.001
Fragile skin	22	17	0.018
Gingival hyperplasia (gum swelling)	11	11	1
Headache	44	50	0.01
Impotence/painful menstruation	17	22	0.007
Increased appetite	48	60	<0.001
Increased hair growth	28	34	0.007
Inflammation	7	4	0.04
Mood swings	50	57	0.002
Moon face	33	43	<0.001
Painful/inflamed/ prominent scar	16	2	<0.001
Palpitations	24	28	0.04
Persistent chest pain	19	8	<0.001
Poor appetite	15	10	0.003
Poor concentration	34	44	<0.001
Poor vision	32	33	0.4
Sleeplessness	49	44	0.03
Stomach complaint	35	39	0.1
Swollen ankles	20	20	0.9
Tremor	22	24	0.3

[a] *p* Value based on Fisher exact test, which does not account for repeated measures.
Values are percentages.

compared to only 5% needing steroid-sparing agents in the thymectomy plus prednisone group. These results further demonstrate the superiority of thymectomy plus prednisone compared to prednisone alone in disease control, while lowering prednisone and other immunosuppressive agent requirements. Assignment to thymectomy, lower disease severity at month 3, and a favorable treatment response at month 3 predicted the achievement of sustained MMS with full withdrawal of prednisone. Other factors such as age, sex, ethnicity, previous treatments, and baseline disease severity were not predictive.

In both treatment groups, adverse symptoms were almost universally reported and distress level increased with higher prednisone doses. We further demonstrated that the distress level was significantly higher with higher prednisone dose even in lower dose ranges (0 mg vs > 0–10 and >0–10 vs > 10–20 mg) while there was no statistically significant difference of distress level when compared between >10–20 mg and >20 mg alternate-day dose ranges. As would be anticipated given decreased prednisone requirements in the thymectomy group, prednisone-associated symptoms such as changed appearance, increased appetite, and moon facies were less frequent in this group.

One or more complications were reported in a majority of the patients, more frequently in the prednisone alone group. Metabolic complications including over 7% weight gain, hypertension, and diabetes were reported in 70% of MGTX participants. This is especially concerning given the increasing number of elderly patients with MG. Decreased activity due to MG and increased caloric intake prompted by prednisone fosters an environment of increased body fat that has metabolic consequences such as insulin resistance, diabetes, and hypertension, critical risk factors for vascular and nonvascular morbidity and mortality.[35,36]

An international consensus statement defines the goal of MG treatment as MMS or better with no more than grade 1 Common Terminology Criteria adverse events.[26] In this study, we extended this treatment objective to be MMS or better with complete withdrawal of prednisone as a means to minimize treatment-related side effects. Although the quality of life study by a large Japanese group has shown that a small dose of corticosteroids (prednisolone ≤5 mg a day) does not affect quality of life,[37] we found that the TAS distress level does increase even at very low dosing levels. Literature on the safety of chronic low-dose steroid treatment is scarce and inconclusive.[38–40]

We found that the majority of patients with MGTX with sustained MMS and complete withdrawal of prednisone remained stable. Most of those who lost MMS regained it after reintroducing low-dose prednisone, supporting a strategy of slowly tapering prednisone completely off in patients with sustained MMS. Since MGTX only allowed for the addition of steroid-sparing agents when a participant did not achieve MMS by 12 months or developed intolerable adverse effects from prednisone, it does not reflect conventional practice,

Table 4 Treatment-associated complications from the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX)

	Total (123)	Thymectomy plus prednisone (65)	Prednisone alone (58)	*p* Value[a]
Any complications	106 (86)	52 (80)	54 (93)	0.04
Metabolic complications (weight gain or hypertension or diabetes mellitus)	87 (71)	42 (65)	45 (78)	0.2
Avascular necrosis	2 (2)	0 (0)	2 (3)	0.2
Assisted ventilation	9 (7)	2 (3)	7 (12)	0.08
Bone marrow suppression requiring withdrawal of medication	1 (1)	1 (2)	0 (0)	1
Cataract	14 (11)	5 (8)	9 (16)	0.3
Cyclosporine-associated encephalopathy	1 (1)	1 (2)	0 (0)	1
Death due to MG	0 (0)	0 (0)	0 (0)	1
Diabetes mellitus requiring medication	16 (13)	6 (9)	10 (17)	0.3
Empyema	1 (1)	1 (2)	0 (0)	1
Fractures	6 (5)	5 (8)	1 (2)	0.2
Glaucoma	6 (5)	5 (8)	1 (2)	0.2
Hemothorax	0 (0)	0 (0)	0 (0)	1
Herpes zoster	9 (7)	5 (8)	4 (7)	1
Hospitalization other than for thymectomy and/or initiation of prednisone therapy	43 (35)	16 (25)	27 (47)	0.02
Hypertension (>150/90 mm Hg or requiring hypotensive therapy)	34 (28)	15 (23)	19 (33)	0.3
Infection requiring IV antibiotics	13 (11)	4 (3)	9 (16)	0.1
Intestinal perforation	0 (0)	0 (0)	0 (0)	1
Liver function test abnormalities requiring withdrawal of medication	5 (4)	2 (3)	3 (5)	0.7
Lymphoma	0 (0)	0 (0)	0 (0)	1
Pancreatitis	2 (2)	1 (2)	1 (2)	1
Persistent thoracic pain (more than 4 weeks)	13 (11)	9 (14)	4 (7)	0.3
Phrenic nerve dysfunction	0 (0)	0 (0)	0 (0)	1
Pneumothorax	1 (1)	1 (2)	0 (0)	1
Prominent (keloid) scar	15 (12)	13 (20)	2 (3)	0.005
Rash	42 (34)	19 (29)	23 (40)	0.3
Recurrent laryngeal nerve injury	0 (0)	0 (0)	1 (2)	0.5
Renal failure	3 (2)	1 (2)	2 (3)	0.6
Reoperation, any cause	2 (2)	1 (2)	1 (2)	1
Serious mental symptoms requiring psychiatric referral	10 (8)	5 (8)	5 (9)	0.9
Sleep disturbance requiring referral or treatment	49 (40)	27 (42)	22 (38)	0.7
Skin cancer	4 (3)	1 (2)	3 (5)	0.3
Sternal dehiscence	0 (0)	0 (0)	0 (0)	1
Sternal wound infection	1 (1)	1 (2)	0 (0)	1

Continued

Table 4 Treatment-associated complications from the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) *(continued)*

	Total (123)	Thymectomy plus prednisone (65)	Prednisone alone (58)	*p* Value[a]
Tendon rupture	3 (2)	1 (2)	2 (3)	0.6
Thoracic duct injury	0 (0)	0 (0)	0 (0)	1
Tracheotomy	4 (3)	2 (3)	2 (3)	1
Upper GI hemorrhage	1 (1)	0 (0)	1 (2)	1
Weight gain >7 pounds above baseline weight at study entry, 2 consecutive visits	63 (51)	32 (49)	31 (53)	0.7

Abbreviations: GI = gastrointestinal; MG = myasthenia gravis.
Values are n (%).
[a] *p* Value based on Fisher exact test.

where there are fewer restrictions on their use. In practice, steroid-sparing agents and other treatment modalities such as IVIg, PLEX, and eculizumab can be considered within the objective of achieving MMS or better status in a timely fashion while limiting treatment-related side effects.[16–18]

Potential weaknesses of the MGTX study are the strict entry criteria, perhaps limiting the relevance of the results to the broader generalized MG populations, including those without AChR antibodies. Patients were not blinded as sham surgery was considered unethical, and elements of a placebo effect cannot be excluded. However, such effects tend to decrease over time, and MGTX remains the longest randomized study in MG. Selection bias may have been introduced as we combined data from the main and extension study. Extension study participants had better disease control and fewer adverse effects compared to participants who were not followed beyond month 36.[29] However, this bias does not affect our major conclusions. Data for this study were generated by post hoc analysis and are not intended to prove the principal hypothesis. Further, since MGTX only permitted alternate-day prednisone dosing, it does not shed light on whether such dosing is as effective as daily administration. A recent survey indicates that most US patients are treated with daily prednisone, especially in early stages when control of disease manifestations is paramount.[9] How high to either start or titrate corticosteroids in individual patients remains a question, and current practice may lead to unnecessarily high doses and their attendant risk for more adverse events. Further study is needed to address these questions.

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Disclosure

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Appendix 1 *(continued)*

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Continued

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Coinvestigators are listed at links.lww.com/WNL/B137

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