Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

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Operative Report

The operative report included information regarding the extent of thymic tissue into pericardial, vena caval, phrenic, diaphragmatic, and cervical regions, the extent of resection in those regions, surgical complications, specimen dimensions, and weight.

Laboratory Monitoring

For patients prescribed azathioprine, liver function tests (LFTs; bilirubin, alkaline phosphatase, aspartate-amino transferase) and complete blood count were checked every 2 weeks for the first 2 months, at month 3, and then every 3 months. Moderate disturbances of LFTs (2-5x the upper limit of normal) resulted in temporary discontinuation of azathioprine. Azathioprine could be restarted when LFTs returned to normal at a dose 50 mg lower than the prior dose. Azathioprine was withdrawn if adverse effects recurred at this lower dose, or for any severe LFT disturbance (> 5x the upper limit of normal). If the white blood cell count (WBC) fell below $3.0x10^9$/L or the absolute neutrophil count below $1.5x10^9$/L, azathioprine was stopped until values normalized, and then restarted at a dose 50 mg below the prior dose. If WBC counts again fell below these values, azathioprine was permanently withdrawn. If cyclosporine was used, BUN/creatinine was added to the laboratory monitoring described above for azathioprine. Cyclosporine doses were reduced appropriately if creatinine exceeded 1.5mg/dl or there was uncontrolled hypertension.

Statistical Analysis

For the primary analysis, the protocol specified that differences were to be assessed by constructing a 99.5% confidence interval for the difference (prednisone alone group minus thymectomy plus prednisone group) in the time-weighted average Quantitative Myasthenia Gravis score. If the confidence interval contained zero, the conclusion would be that the clinical score for the two treatment groups was comparable. Otherwise, one treatment would be considered superior to the other. The second stage would determine if the better treatment was based on the exposure to prednisone using a two sided t-test of the time-weighted average prednisone dose with a Type I error of 0.05 conditional on the time-weighted average Quantitative Myasthenia Gravis score analysis. The null hypothesis for this conditional test was that the mean time-weighted average prednisone dose for thymectomy plus prednisone was equal to the prednisone alone group. Rules were provided *a priori* for each of the 9 possible combinations of outcomes (thymectomy better than prednisone alone, prednisone alone better than thymectomy, or results equivocal). Confirmation of the effectiveness of the two-stage analyses or conclusions if equivocal were to be performed by examining the secondary endpoints, especially the treatment associated complications and symptoms and serious adverse events. Furthermore, subgroup analyses on these primary outcomes were planned as follows: (1) use of corticosteroids vs. no use prior to entering the study; (2) male versus female; and (3) age <40 years and age ≥40 years at disease onset. A post-hoc subgroup analysis based on age above or below 50 years of age at enrollment was also performed at the request of a reviewer (Table S3).

The sample size calculations were based on the analysis being a two-group comparison of the mean time-weighted average prednisone dose at 3 years. A reduction of the time-weighted average prednisone dose of 30% or greater in favor of one treatment was deemed the minimum to be clinically valuable by consensus of the worldwide myasthenia gravis specialists participating in the study. The sample size calculation assumed a two-group comparison of the treatment means, with

the distribution of the time-weighted average prednisone dose values assumed to be approximately normal. This assumption was satisfactorily tested in the Palace et al. trial of azathioprine plus prednisolone vs. prednisolone alone.[1] The sample size was calculated assuming a mean to standard deviation (SD) ratio of 2.0 which was close to the value obtained using the SD pooled from both treatment groups in the Palace et al. trial.[1] For 90% power to obtain a significant result at the 5% two-tailed level, if the true difference between the treatment effects on the time-weighted average prednisone dose at 3 years was 30% of the baseline mean, the trial required 60 subjects in each arm or 120 total. A 99.5% confidence level was used for the first stage for time-weighted average Quantitative Myasthenia Gravis score analysis between months 0 and 36 and a Type I error level of 5% for the second stage for time-weighted average prednisone dose testing between months 0 and 36. No penalty was taken for the Type I error as the result was a conditional result.

The time-weighted average Quantitative Myasthenia Gravis score was computed from the standardized rater-blinded Quantitative Myasthenia Gravis scores. The time-weighted average prednisone dose was computed from pill counts with a secondary analysis based on the prescribed dose for confirmation purposes. As a supplementary analysis, we repeated the primary dosing analysis using a penalty if azathioprine was added to prednisone. The two penalty methods were: (1) taking the prednisone dose at the time azathioprine commenced; and (2) taking the maximum dose of prednisone before azathioprine was added. These dose values were maintained through year 3.

Secondary analyses to capture quality-of-life data included a comparison of the occurrence of any of 36 treatment-associated complications and 29 treatment-associated symptoms[2] (Supplementary Appendix, pages 27 & 28 for full listings) that can arise from use of corticosteroids and other immunosuppressive agents. The number of treatment-associated complications and symptoms were separately summed at each visit and analyzed over the periods of 0-12, 0-24 and 0-36 months using generalized linear mixed models with treatment, time (linear) and treatment by time interaction as fixed effects and intercept as random effects to account for repeated measures. We

fitted mixed logit to compare the proportion with at least one complication or symptom; mixed Poisson to compare the number of complications, and mixed Gamma model for level of distress of symptoms.

Serious adverse event frequency was also compared between the two treatment arms. The proportion of patients with hospitalizations and cumulative hospital days for a given period were analyzed using chi-squared test and zero-truncated negative binomial, respectively. However, for hospitalizations due to MG exacerbation, Fisher's exact test and Wilcoxon 2-sample exact test were utilized due to the small sample. There were no planned adjustments on the significance level due to multiple secondary outcomes.

The other secondary outcomes were achievement of Minimal Manifestations Status (Supplementary Appendix, page 25 for definition), MG Activities of Daily Living, and Short Form-36 (SF-36) Health Survey (version 2, Health Assessment Lab, Medical Outcomes Trust and QualityMetric, Inc.). Cox proportional hazards models were used to evaluate the time from month 0 to reach initial Minimal Manifestation Status, while logistic regression with the treatment group in the model was used to compare the proportion achieving Minimal Manifestation Status at months 12, 24, and 36. MG Activities of Daily Living over the period of 0-36 months was analyzed in a similar manner as the Quantitative Myasthenia Gravis score in the primary analyses, i.e., computing time-weighted average scores over 0-36 months. We also performed cross-sectional analyses of MG Activities of Daily Living scores at months 12, 24 and 36 using t-tests.

Stopping rules, even for extremely small P values, were not deemed desirable due to the fluctuating nature of myasthenia gravis, the possibility that improvement may not persist, and the hypothesis that thymectomy provides benefit over the long term. The planned cost analysis has not been completed at this time as it faced challenges posed by different health systems across different countries and continents over a study period lasting 10 years.

The Data Safety Monitoring Board (DSMB) reviewed the data in a masked fashion as Groups A and B from the outset of the trial. However, it quickly became clear that adverse events unblinded the two treatment groups due to issues that arose related to the thymectomy procedure. After the initial reports to the DSMB, primary outcome data were not presented by group once it became clear that blinding was not possible.

Imputations for Missing Data

For patients who dropped out before the month 36 visit, the time-weighted average outcomes were computed based only on the period that they were in the study, i.e., the denominator used to compute the time-weighted average for the Quantitative Myasthenia Gravis score and prednisone dosage was number of days from randomization to the last visit. For missing data due to missing visits before drop out, results were generated by connecting data points for the Quantitative Myasthenia Gravis score and pill counts from the two study encounters on each side of the missed visit. To further test the robustness of results from this analysis, three other imputation methods were used: (1) excluding the missing visit from the computation; (2) replacing missing data with the most favorable value from the prednisone-only group and the least favorable value from the surgery group; and (3) replacing missing data with the least favorable value from the prednisone-only group and the most favorable value from the surgery group. For both the time-weighted average Quantitative Myasthenia Gravis score and prednisone dose analyses, none of these methods of estimation changed the underlying findings.

Analysis of Prednisone by Prescribed Dose

When comparing prednisone requirements based on prescribed dose instead of pill counts from the blister packs, the pattern favoring thymectomy persisted, with a significantly lower cumulative count (4.34 ± 2.31 vs. 5.93 ± 2.84, estimated difference 1.60, 95% CI 0.66-2.54, $p=0.001$). No matter the method used to calculate prednisone exposure, we could conclude that the improved clinical status seen in the surgical group was not at the expense of higher doses of immunosuppressive medication.

Secondary Outcome Analyses

Table S4 summarizes the results of secondary outcomes. If the maximum prednisone dose before starting azathioprine was used as a penalty, the alternate-day prednisone reduction was 36% for the thymectomy group (46.7 mg vs 72.9 mg), whereas if the prednisone dose at the time of starting azathioprine was used as a penalty, the alternate-day prednisone reduction was 33% for thymectomy (45.6 mg vs. 68.1 mg). Similar conclusions (not presented) were obtained when a penalty was attached to the use of intravenous immunoglobulin or plasma exchange. The time-weighted average Myasthenia Gravis Activities of Daily Living score over 36 months was found to be significantly better in the thymectomy group (2.24 vs. 3.41, p=0.008). Plasma exchange use was not significantly different between the groups, but intravenous immunoglobulin was used less frequently in the thymectomy group (17% vs. 40%, p=0.005). The proportion of subjects who achieved Minimal Manifestation Status at month 12 was significantly higher (67% vs 37%, p=0.001) in the thymectomy group. Similar findings were observed at months 24 and 36. Using the Cox model, the time to initial Minimal Manifestation Status was found to be significantly shorter in the thymectomy group (p=0.03). The proportion of patients with hospitalization due to myasthenia gravis exacerbation in the first 24 months was significantly higher in the prednisone alone group (28% versus 9%, p=0.006), and further increased to 37% in the 0-36 month period. The average cumulative days in the hospital was lower in the thymectomy+prednisone group but was only significant for the period of 0-24 months (p=0.004).

Tables S5, S6, and S7 summarize the results of the analyses for outcomes related to quality of life: Short Form-36 (SF-36), treatment-associated complications, and treatment-associated symptoms. SF-36 (both physical and mental components) and treatment-associated complications were not significantly different between the two groups in the different time periods considered.

However, on the treatment-associated symptoms survey, the number of subjects with ≥1 symptom, mean number of symptoms, and distress levels were significantly lower in the thymectomy group over time.

Pill Count Methodology

Prednisone blood levels were deemed impractical, costly, and burdensome due to the need to subject patients to frequent draws to construct exposure over time. Furthermore, the drug has a short half-life[3] that would complicate interpretation of serum levels in a trial with alternate-day dosing of prednisone. Pill counts were based on identical, user-friendly, blister packs containing 10 mg tablets of prednisone that were provided for every alternate-day dose. The blister packs were returned at each study visit to compare with prescribed dose. Pill counts were preferred over recording of the dose prescribed because it better assessed what subjects actually took. Pill counts should not be differentially biased; potential errors in counting missing and remaining tablets from the blister packs should have been broadly similar for the two groups. Furthermore, studies have reported that pill counts correlate well with treatment prescriptions, even in "silent" diseases such as hypertension which are often asymptomatic.[4, 5] MG is not a silent disease, and recurrence of symptoms on inadequate doses of medication can serve as a reminder for patients to be compliant with their prescription.

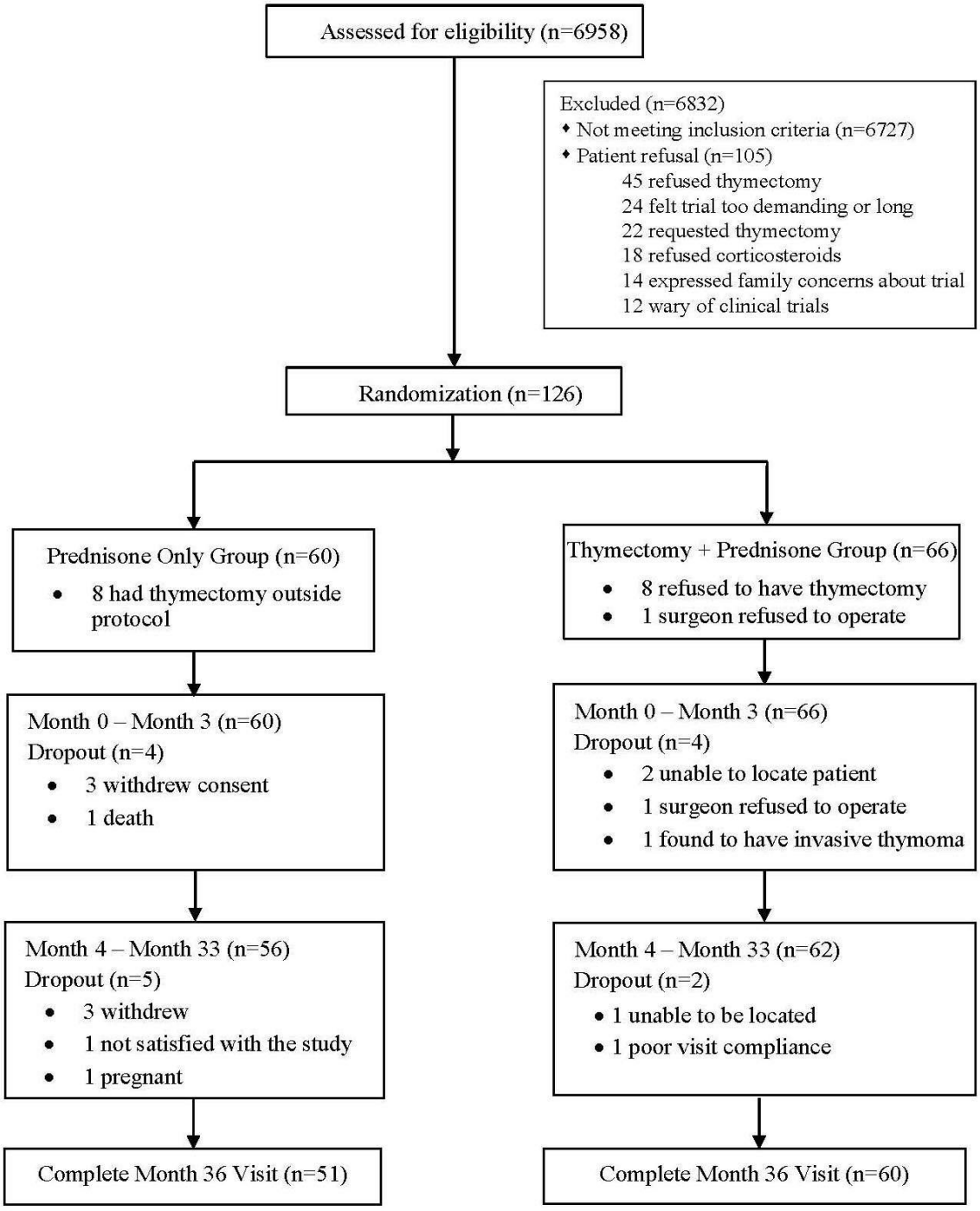

Figure S1. **MGTX Participant Flow and Reasons for Declining MGTX (Cited by ≥2 subjects).**

Table S1. **Predictions of Investigators on Outcome of MGTX.**

Outcome will not favor the use of thymectomy	27
Outcome will favor the use of thymectomy	77
in all patients	44
in patients not receiving prednisone at entry	14
in patients receiving prednisone at entry	19
I really do not know	29
TOTAL	133

Table S2A. **Thymic Histology from 46* Patients Randomized to Surgery**.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Thymic follicular hyperplasia (CD23)[a]	15	18	6	5	2
Overall atrophy[b]	1	7	6	18	14
Cortical atrophy[c]	5	10	15	12	4

Table S2B. **Thymic Histology of 4 Patients who Crossed over to Surgery before Month 36.**

Patient	Age	Sex	Thymic follicular hyperplasia[a]	Overall atrophy[b]	Cortical atrophy[c]
#1	20	F	Grade 2	Grade 2	Grade 2
#2	45	M	Grade 0	Grade 4	Grade 4
#3	42	F	Grade 1	Grade 4	Grade 4
#4	33	F	Grade 1	Grade 2	Grade 1

*46 subjects with non-thymomatous thymus provided informed consent to have their specimens evaluated at a centralized laboratory at the Institute of Pathology, University of Heidelberg, Mannheim, Germany, as part of the Biomarker in Myasthenia Gravis ancillary study. There were 34 women and 12 men, age range 18-63 years. An additional specimen that harbored a WHO type B2 thymoma was excluded from this analysis. None of these features differed in patients with disease onset of <40 and ≥40 years of age. Cortical atrophy was significantly greater in patients ≥50 years of age than in younger ones (P=0.0038; Kolmogorov-Smirnov test), while TFH and overall atrophy were not different. TFH was encountered in 2 of 8 patients over age 50 years. Four patients who crossed over to surgery also consented to the centralized histological evaluation.

[a]Thymic follicular hyperplasia was defined by counting CD23-positive follicular dendritic cell networks and graded as: Grade 0, no follicles; Grade 1, follicles in ≤1/3 of thymic lobules; Grade 2, follicles in >1/3 and ≤ 2/3 of thymic lobules; Grade 3, follicles in >2/3 of thymic lobules; Grade 4, lymph node-like transformation of the thymus with >4 follicles per low power field (x50 magnification).

[b] Overall atrophy of the thymus was graded according to fat content following morphometric determination of the areas of adipose tissue and thymic parenchyma (epithelial and lymphocytic) per slide: Grade 0, 0-20% fat; grade 1, 21-40% fat; grade 2, 41-60% fat; grade 3, 61-80% fat; grade 4, >80% fat.

[c] Cortical atrophy was semi-quantitatively graded as follows: Grade 0, cortex adequate for age; grade 1, slight atrophy as indicated by a starry sky pattern; grade 2, moderate atrophy (cortical remnants easily detected); grade 3, severe atrophy (cortical remnants difficult to identify); grade 4, no cortical remnants.

Table S3. **Additional Post-Hoc Subgroup Analyses on the Primary Outcomes.**

	Treatment Group Mean±SD		Estimated Difference (95% CI[†])	P Value[a]
	Prednisone alone	Thymectomy +prednisone		
Outcome: Time-weighted average Quantitative MG score				
Age (yrs) at enrollment (interaction with treatment P value[b] =0.28				
< 50	9.43 ± 5.09 (N=48)	6.22 ± 4.24 (N=53)	3.21 (0.55-5.88)	< 0.001
≥ 50	6.39 ± 2.79 (N=8)	5.74 ± 3.21 (N=9)	0.65 (-4.17-5.47)	0.67
Outcome: Time-weighted average alternate-day prednisone dose (mg)				
Age (yrs) at enrollment (interaction with treatment P value[b] =0.97)				
< 50	60.93 ± 26.60 (N=48)	44.69 ± 21.57 (N=52)	16.23 (6.65-25.81)	0.001
≥ 50	53.29 ± 32.93 (N=8)	37.59 ± 18.99 (N=9)	15.69 (-11.67-43.06)	0.24

[†]95% confidence intervals except for Quantitative MG score where confidence intervals are 99.5% level per protocol.
[a] P values of these post-hoc subgroup analyses were based on two independent sample t-tests.
[b] P value for interaction with treatment was based on fitting a general linear model separately for each outcome.
MG denotes myasthenia gravis.

Table S4. **Analyses of Secondary Outcomes.**

	Treatment Group Mean±SD or no./N (%)		Estimated Difference (95% CI)	P Value
	Prednisone Alone	Thymectomy +prednisone		
Time-weighted average prescribed AD prednisone dose (mg)[a]	59.3 ± 28.4 (N=56)	43.4 ± 23.1 (N=62)	16.0 (6.6-25.4)	0.001
Penalized time-weighted average AD prednisone dose (mg; Method 1)[a,b]	72.9 ± 37.4 (N=56)	46.7 ± 24.9 (N=61)	26.3 (14.7-37.8)	< 0.001
Penalized time-weighted AD average prednisone dose (mg; Method 2)[a,c]	68.1 ± 38.3 (N=56)	45.6 ± 24.3 (N=61)	22.5 (10.6-34.4)	< 0.001
Time-weighted average MG Activities of Daily Living[a,d]	3.41 ± 2.58 (N=55)	2.24 ± 2.09 (N=61)	1.17 (0.31-2.03)	0.008
MG ADL at month 12	3.33 ± 3.40 (N=54)	1.92 ± 2.73 (N=61)	1.42 (0.28-2.55)	0.01
MG ADL at month 24	3.11 ± 2.93 (N=53)	2.02 ± 2.78 (N=59)	1.10 (0.03-2.17)	0.04
MG ADL at month 36	2.69 ± 2.80 (N=51)	2.14 ± 2.92 (N=59)	0.55 (-0.53-1.63)	0.32
Azathioprine use[f]	28/58 (48)	11/65 (17)	31.4% (15.6%,47.1%)	< 0.001
Plasma exchange use[f]	9/58 (16)	10/65 (15)	0.1% (-12.7%,12.9%)	~1
Intravenous immunoglobulin use[f]	23/58 (40)	11/65 (17)	22.7% (7%,38.3%)	0.005
Minimal Manifestation Status[e]				
at month 12[f]	20/54 (37)	41/61 (67)	30.2% (12.7%-47.6%)	0.001
at month 24[f]	20/53 (38)	39/59 (66)	28.4% (10.6%-46.2%)	0.003
at month 36[f]	24/51 (47)	39/58 (67)	20.2% (1.9%-38.5%)	0.03
Hospitalization for MG exacerbation				
Months 0-24: # of patients[g]	17/60 (28)	6/66 (9)	19.2% (5.9%, 32.6%)	0.006
Cumulative days[h]	26.4 ± 28.9	5.5 ± 2.9		0.004
Months 0-36: # of patients[g]	22/60 (37)	6/66 (9)	27.6% (13.6%, 41.6%)	<0.001
Cumulative days[h]	22.5± 27.1	8.7 ± 7.7		0.21

[a] P value based on two sample t-test.
[b] Method 1: penalized using maximum dose before azathioprine.
[c] Method 2: penalized using dose at time of starting azathioprine.
[d] Myasthenia Gravis Activities of Daily Living scores 0,1, 2, 3, where 0=normal and higher score is worse.
[e] P value=0.03 based on the Cox model on modeling time to first Minimal Manifestation Status over the period of 0-36 months.
[f] P values based on logistic regression.
[g] P values based on Fisher's exact test.
[h] P values based on Wilcoxon 2-sample exact test.
AD denotes alternate day, ADL Activities of Daily Living, MG myasthenia gravis.

Table S5: **Short Form-36 by Treatment Group and Month.**

Visit	Standardized Physical Component[†] median (min-max)		Standardized Mental Component[#] median (min-max)	
	Prednisone alone	Thymectomy+ prednisone	Prednisone alone	Thymectomy+ prednisone
Month 0	37.9 (13.5-64.3)	41.4 (18.2-60.0)	41.7 (7.6-64.4)	39.1 (17.6-66.7)
Month 12	44.4 (21.2-58.8)	48.4 (11.5-64.4)	46.2 (22.4-70.7)	49.1 (14.6-65.3)
Month 24	43.0 (25.3-59.6)	50.3 (11.2-60.5)	46.7 (21.3-69.1)	49.9 (14.4-62.3)
Month 36	44.2 (20.4-58.9)	48.2 (9.8-61.8)	48.2 (24.1-69.2)	51.7 (29.9-65.1)

[†]Treatment by month interaction P value=0.70 (Normal mixed model with random intercept).
[#]Treatment by month interaction P value=0.81 (Normal mixed model with random intercept).
None of the time points (Months 0, 12, 24, or 36) showed significant treatment group differences except the standardized physical component at Month 24 based on two independent sample t-test, P value=0.04.

Table S6: **Treatment Associated Complications**.

Visit Month	Treatment Group	No. of Patients	No. of Patients with ≥1 Complication (%)[a]	Mean Number of Complications[b]
Month 0	Prednisone Alone	58	17 (29.3)	0.5
	Thymectomy+prednisone	65	22 (33.8)	0.6
Month 1	Prednisone Alone	56	15 (26.8)	0.3
	Thymectomy+prednisone	58	15 (25.9)	0.3
Month 2	Prednisone Alone	55	20 (36.4)	0.4
	Thymectomy+prednisone	61	22 (36.1)	0.6
Month 3	Prednisone Alone	55	16 (29.1)	0.4
	Thymectomy+prednisone	61	21 (34.4)	0.4
Month 4	Prednisone Alone	56	23 (41.1)	0.5
	Thymectomy+prednisone	62	23 (37.1)	0.5
Month 6	Prednisone Alone	55	22 (40.0)	0.7
	Thymectomy+prednisone	61	21 (34.4)	0.6
Month 9	Prednisone Alone	54	26 (48.1)	0.7
	Thymectomy+prednisone	61	37 (60.7)	1.0
Month 12	Prednisone Alone	54	28 (51.9)	0.7
	Thymectomy+prednisone	61	35 (57.4)	0.9
Month 15	Prednisone Alone	53	24 (45.3)	0.8
	Thymectomy+prednisone	60	29 (48.3)	0.7
Month 18	Prednisone Alone	53	24 (45.3)	0.7
	Thymectomy+prednisone	59	28 (47.5)	0.8
Month 21	Prednisone Alone	52	20 (38.5)	0.7
	Thymectomy+prednisone	60	22 (36.7)	0.7
Month 24	Prednisone Alone	53	23 (43.4)	0.7
	Thymectomy+prednisone	59	28 (47.5)	0.8
Month 27	Prednisone Alone	53	17 (32.1)	0.4
	Thymectomy+prednisone	61	25 (41.0)	0.7
Month 30	Prednisone Alone	53	19 (35.8)	0.5
	Thymectomy+prednisone	58	23 (39.7)	0.6
Month 33	Prednisone Alone	52	23 (44.2)	0.7
	Thymectomy+prednisone	61	24 (39.3)	0.6
Month 36	Prednisone Alone	51	23 (45.1)	0.7
	Thymectomy+prednisone	59	23 (39.0)	0.5

[a]Treatment by month interaction P value is 0.61 over 0-12 months; P value is 0.88 over 0-24 months; P value is 0.73 over 0-36 months (Logistic regression with random intercept).
[b]Total number of complications is 36; Treatment by month interaction P value is 0.62 over 0-12 months; P value is 0.59 over 0-24 months; P value is 0.40 over 0-36 months (Poisson regression with random intercept).

Table S7: **Treatment Associated Symptoms.**

Visit Month	Treatment Group	No. of Patients	No. of Patients with ≥1 Symptom (%)[a]	Mean No. of Symptoms[b]	Mean Distress Level of Symptoms[c]
Month 0	Prednisone Alone	57	53 (93.0)	8.6	20.7
	Thymectomy+prednisone	65	63 (96.9)	10.4	23.8
Month 1	Prednisone Alone	56	52 (92.9)	8.3	19.2
	Thymectomy+prednisone	58	55 (94.8)	8.5	19.0
Month 2	Prednisone Alone	55	53 (96.4)	8.8	19.4
	Thymectomy+prednisone	61	61 (100)	9.1	20.5
Month 3	Prednisone Alone	55	54 (98.2)	8.9	20.2
	Thymectomy+prednisone	61	60 (98.4)	8.6	18.8
Month 4	Prednisone Alone	56	54 (96.4)	9.4	21.5
	Thymectomy+prednisone	62	59 (95.2)	8.3	16.9
Month 6	Prednisone Alone	55	53 (96.4)	9.1	20.6
	Thymectomy+prednisone	61	60 (98.4)	9.3	20.2
Month 9	Prednisone Alone	54	50 (92.6)	9.9	23.1
	Thymectomy+prednisone	61	59 (96.7)	9.5	21.1
Month 12	Prednisone Alone	54	52 (96.3)	9.7	22.2
	Thymectomy+prednisone	61	56 (91.8)	8.4	18.7
Month 15	Prednisone Alone	53	51 (96.2)	9.5	22.8
	Thymectomy+prednisone	60	56 (93.3)	8.8	20.2
Month 18	Prednisone Alone	53	51 (96.2)	9.3	21.2
	Thymectomy+prednisone	59	52 (88.1)	8.0	17.5
Month 21	Prednisone Alone	52	50 (96.2)	8.8	20.4
	Thymectomy+prednisone	60	52 (86.7)	8.1	17.5
Month 24	Prednisone Alone	53	51 (96.2)	8.9	20.0
	Thymectomy+prednisone	59	52 (88.1)	8.2	18.0
Month 27	Prednisone Alone	53	50 (94.3)	7.7	17.4
	Thymectomy+prednisone	61	50 (82.0)	7.3	16.3
Month 30	Prednisone Alone	53	50 (94.3)	8.1	18.0
	Thymectomy+prednisone	58	49 (84.5)	7.1	14.6
Month 33	Prednisone Alone	51	48 (94.1)	8.4	17.3
	Thymectomy+prednisone	61	51 (83.6)	7.0	16.2
Month 36	Prednisone Alone	51	47 (92.2)	8.6	17.8
	Thymectomy+prednisone	60	49 (81.7)	6.7	15.3

[a]Treatment by month interaction P value is 0.22 over 0-12 months; P value is 0.002 over 0-24 months; P value <0.001 over 0-36 months (Logistic regression with random intercept).
[b]Total number of symptoms is 29; Treatment by month interaction P value is 0.007 over 0-12 months; P value is 0.02 over 0-24 months; P value <0.001 over 0-36 months (Poisson regression with random intercept).
[c]Treatment by month interaction P value is 0.04 over 0-12 months; P value is 0.003 over 0-24 months; P value is 0.003 over 0-36 months (Gamma regression with random intercept); distress levels for each symptom were assigned scores 0, 1, 2, 3, and 4 (0="not at all" and 4="extremely" distressful).

Table S8: **Visit Status by Treatment Group.**

	Prednisone alone			Thymectomy+prednisone		
Visit	**No. of Actual Visits**	**No. of Missed Visits**	**Cumulative No. Who Withdrew**	**No. of Actual Visits**	**No. of Missed Visits**	**Cumulative No. Who Withdrew**
Month 0	57	1	2	65	0	1
Month 1	56	1	3	60	2	4
Month 2	55	2	3	62	0	4
Month 3	56	0	4	61	1	4
Month 4	56	0	4	62	0	4
Month 6	55	0	5	61	1	4
Month 9	54	0	6	61	0	5
Month 12	54	0	6	61	0	5
Month 15	53	0	7	61	0	5
Month 18	53	0	7	60	1	5
Month 21	53	0	7	60	1	5
Month 24	53	0	7	59	2	5
Month 27	53	0	7	61	0	5
Month 30	53	0	7	59	2	5
Month 33	52	0	8	61	0	5
Month 36	51	0	9	59	1	6
Total	**864**	**4**	**9**	**973**	**11**	**6**

References

1. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Neurology 1998;50:1778-1783.
2. Moons P, De Geest S, Abraham I, Van Cleemput J, Vanhaecke J. Symptom experience associated with maintenance immunosuppression after heart transplantation: patient's appraisal of side effects. Heart Lung 1998;27:315-325.
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4. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. Med Care 1999;37:846-857.
5. Shulman N, Cutter G, Daugherty R, et al. Correlates of attendance and compliance in the hypertension detection and follow-up program. Control Clin Trials 1982;3:13-27.

Myasthenia Gravis Foundation of America Definitions

Clinical Classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

From: Jaretzki III A, Barohn RJ, Ernstoff RM, et al. Neurology 2000;55:16–23.

***Table 4** MGFA Postintervention Status*

Complete Stable Remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR)	The same criteria as for **CSR** except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of **CSR** or **PR** do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
	Change in Status
Improved (I)	A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U)	No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W)	A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.
Exacerbation (E)	Patients who have fulfilled criteria of **CSR, PR,** or **MM** but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause (see Morbidity and Mortality table).

From: Jaretzki III A, Barohn RJ, Ernstoff RM, et al. Neurology 2000;55:16–23.

Outcome Scales

QMG score

TEST ITEMS WEAKNESS(SCORE)	NONE (0)	MILD (1)	MODERATE (2)	SEVERE (3)	Item Score (0,1,2 or 3)	
1. Double vision on lateral gaze right or left (**circle one**), seconds	61	11-60	1-10	Spontaneous		
2. Ptosis (upward gaze), seconds	61	11-60	1-10	Spontaneous		
3. Facial Muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete		
4. Swallowing 4 oz./ 120 ml water	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)		
5. Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9		Score Subtotal for Items 1-5 **S1 =**
6. Right arm outstretched (90° sitting), seconds	240	90-239	10-89	0-9		
7. Left arm outstretched (90° sitting), seconds	240	90-239	10-89	0-9		
8. Vital Capacity (% predicted) mouthpiece or facemask (**circle one; best of 3**)	≥80%	65-79%	50-64%	< 50%		
9. Right hand grip: (**best of 2**) male (KgW) female	≥45 ≥30	15-44 10-29	5-14 5-9	0-4 0-4		
10. Left hand grip: (**best of 2**) male (KgW) female	≥35 ≥25	15-34 10-24	5-14 5-9	0-4 0-4		Score Subtotal for Items 6-10 **S2 =**
11. Head, lifted (45° supine), seconds	120	30-119	1-29	0		
12. Right leg outstretched (45° supine), seconds	100	31-99	1-30	0		
13. Left leg outstretched (45° supine), seconds	100	31-99	1-30	0		Score Subtotal for Items 11-13 **S3 =**
				Score Total (Items 1-13) =		**S1+S2+S3 =**

TOTAL QMG SCORE (range 0-39) _____

Note: Total QMG score must match with the SCORE TOTAL and SUBSCORE TOTAL.

QMG Score At Month 0 =

From: Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the Quantitative Myasthenia Gravis Score. Ann NY Acad Sci 1998;841:769-772.

A minimally important difference has been calculated at 2.3 points.

MG-ADL

Grade	0	1	2	3	Score (0,1,2 or 3)	
1 Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech		
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube		
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube		
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence		Score Subtotal for Items 1-4 =I
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions		
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance		
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant		
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant		Score Subtotal for Items 5-8 =
				Score Total (Items 1-8) =		**Subscore Total =**

TOTAL MG-ADL SCORE (range 0-24) _____

Note: Total MG-ADL score must match with the SCORE TOTAL and SUBSCORE TOTAL.

From: Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. Neurology 1999;52:1487-1489.

A minimally important difference has been calculated at 2 points.

Treatment Associated Complications

A. Treatment Associated Complications	YES	NO	Comments
1. Avascular necrosis (Osteonecrosis)			
2. Assisted ventilation			
3. Bone marrow suppression requiring withdrawal of medication			
4. Cataract (patient reports impaired vision; ophthalmological opinion to confirm)			
5. Cyclosporin associated encephalopathy			
6. Death due to MG			
7. Diabetes mellitus requiring medication (oral hypoglycaemic agents or insulin)			
8. Empyema			
9. Fractures (number of bones)			
10. Glaucoma (ophthalmological opinion to confirm)			
11. Hemothorax			
12. Herpes zoster			
13. Hospitalization other than for ETTX and/or initiation of prednisone therapy			
14. Hypertension (>150/90 or requiring hypotensive therapy)			
15. Infection requiring intravenous antibiotics			
16. Intestinal perforation			
17. Liver function test abnormalities requiring withdrawal of medication			
18. Lymphoma			
19. Pancreatitis			
20. Persistent thoracic pain (more than 4 weeks)			
21. Phrenic nerve dysfunction			
22. Pneumothorax (needle aspiration, or a chest tube after the initial chest tubes have been removed)			
23. Prominent (keloid) scar			
24. Rash			
25. Recurrent laryngeal nerve injury			
26. Renal failure			
27. Re-operation, any cause			
28. Serious mental symptoms requiring psychiatric referral			
29. Sleep disturbance requiring referral or treatment			
30. Sternal dehiscence			
31. Sternal wound infection			
32. Tendon rupture			
33. Thoracic duct injury			
34. Tracheotomy			
35. Upper gastrointestinal hemorrhage			
36. Weight gain >7% above baseline weight at study entry (scores positive if present on two consecutive visits)			

Adapted from Reference #2.

Treatment Associated Symptoms

Adverse Symptoms	Frequency of Symptoms (please check one only)					Symptom distress from 0-4 (not distressing at all to very much distressing)
	Never	Sometimes	Regularly	Almost Always	Always	
1. acne						
2. back pain						
3. bruises						
4. changed appearance						
5. changed taste						
6. decreased interest in sex						
7. depression						
8. diarrhea						
9.fatigue						
10. fragile skin						
11. gingival hyperplasia (gum swelling)						
12. headache						
13.impotence/painful menstruation						
14. increased appetite						
15. increased hair growth						
16. inflammation						
17. mood swings						
18.moon face						
19. muscle weakness						
20. painful/inflamed /prominent scar						
21. palpitations						
22.persistent chest pain.						
23. poor appetite						
24. poor concentration						
25. poor vision						
26. sleeplessness						
27. stomach complaints						
28. swollen ankles						
29. tremor						

Adapted from Reference #2.

Short Form-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
C	Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Had difficulty performing the the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
C Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time <u>during the past 4 weeks</u>…

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!