Results from the MGTX Extension Study of Thymectomy in MG

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MDA

Myasthenia Gravis Foundation of America, Inc.

Disclosures

- No relevant disclosures
- Prednisone, azathioprine, IVIg used off-label in myasthenia gravis

GC4

MGTX and BioMG

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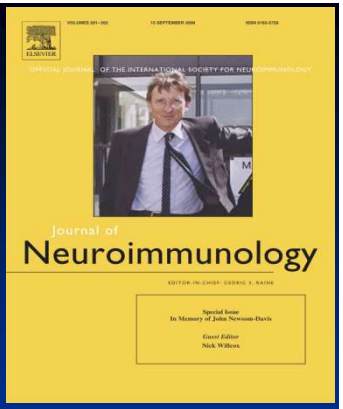

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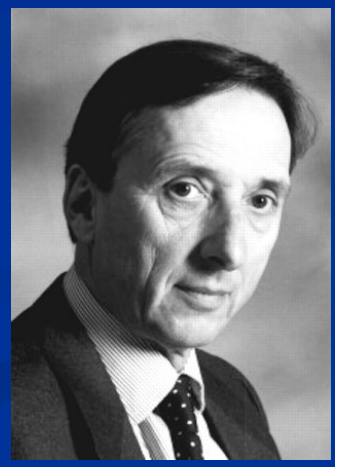

1919-2014

Slide 3

GC4 Gary Cutter, 04/10/2016

MGTX: Single blind, Multicenter, International Randomized Trial

Primary aim: Answer 3 questions in non-thymomatous MG patients followed for 3 years

Compared with prednisone protocol alone, does extended transsternal thymectomy (ETTX) + prednisone protocol result in:

- greater improvement in strength (time-weighted average QMG)?
- lower prednisone requirement (time-weighted average prednisone dose)?
- enhanced quality of life (AEs, TAS, TAC)?

MGTX protocol details

Inclusion criteria

AChR binding Ab pos (≥0.5)
MGFA Class 2-4; disease duration < 5 years
Age at least 18 and < 65 years
Optimal anti-cholinesterase dose
Prednisone naive or not

Main exclusion criteria

Previous thymectomy or sternotomy or thoracotomy
Immunosuppressive therapy (x prednisone) within last year
Rituximab at any time
Medically or psychiatrically unfit for thymectomy
Chest CT or MR evidence of thymoma
Pregnancy or lactation, or considering becoming pregnant
Current prednisone > 0.75 mg/kg or 50 mg/d (or AD equivalent)

MGTX Trial

67 sites in N. America, Europe, S. America, S. Africa, Asia, Australia

AChRAb+, MGFA Clinical Class II-IV, ≤5 yrs, no thymoma, 18-65 yo, +/- prednisone Rx

randomize

ETTX + Prednisone 1.5 mg/kg AD	Prednisone alone 1.5 mg/kg AD
MMS: prednisone taper	MMS: prednisone taper

outcome measures

1° Time-weighted QMG & Prednisone, (AEs at 3 yrs) 2° Time to MMS MG-ADL ΔSF-36 Hospital days	1° Time-weighted QMG & Prednisone, (AEs at 3 yrs) 2° Time to MMS ΔMG-ADL ΔSF-36 Hospital days

MGTX Results

Wolfe GI et al.
***N Engl J Med* 2016;375:511-522**

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Randomized Trial of Thymectomy in Myasthenia Gravis

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ABSTRACT

BACKGROUND

Thymectomy has been a mainstay in the treatment of myasthenia gravis, but there is no conclusive evidence of its benefit. We conducted a multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone.

METHODS

We compared extended transsternal thymectomy plus alternate-day prednisone with alternate-day prednisone alone. Patients 18 to 65 years of age who had generalized nonthymomatous myasthenia gravis with a disease duration of less than 5 years were included if they had Myasthenia Gravis Foundation of America clinical class II to IV disease (on a scale from I to V, with higher classes indicating more severe disease) and elevated circulating concentrations of acetylcholine-receptor antibody. The primary outcomes were the time-weighted average Quantitative Myasthenia Gravis score (on a scale from 0 to 39, with higher scores indicating more severe disease) over a 3-year period, as assessed by means of blinded rating, and the time-weighted average required dose of prednisone over a 3-year period.

RESULTS

A total of 126 patients underwent randomization between 2006 and 2012 at 36 sites. Patients who underwent thymectomy had a lower time-weighted average Quantitative Myasthenia Gravis score over a 3-year period than those who received prednisone alone (6.15 vs. 8.99, P<0.001); patients in the thymectomy group also had a lower average requirement for alternate-day prednisone (44 mg vs. 60 mg, P<0.001). Fewer patients in the thymectomy group than in the prednisone-only group required immunosuppression with azathioprine (17% vs. 48%, P<0.001) or were hospitalized for exacerbations (9% vs. 37%, P<0.001). The number of patients with treatment-associated complications did not differ significantly between groups (P=0.73), but patients in the thymectomy group had fewer treatment-associated symptoms related to immunosuppressive medications (P<0.001) and lower distress levels related to symptoms (P=0.003).

CONCLUSIONS

Thymectomy improved clinical outcomes over a 3-year period in patients with nonthymomatous myasthenia gravis. (Funded by the National Institute of Neurological Disorders and Stroke and others; MGTX ClinicalTrials.gov number, NCT00294658.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wolfe at the Department of Neurology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, State University of New York, 100 High St., Buffalo, NY 14203, or at gilwolfe@buffalo.edu.

*A complete list of the members of the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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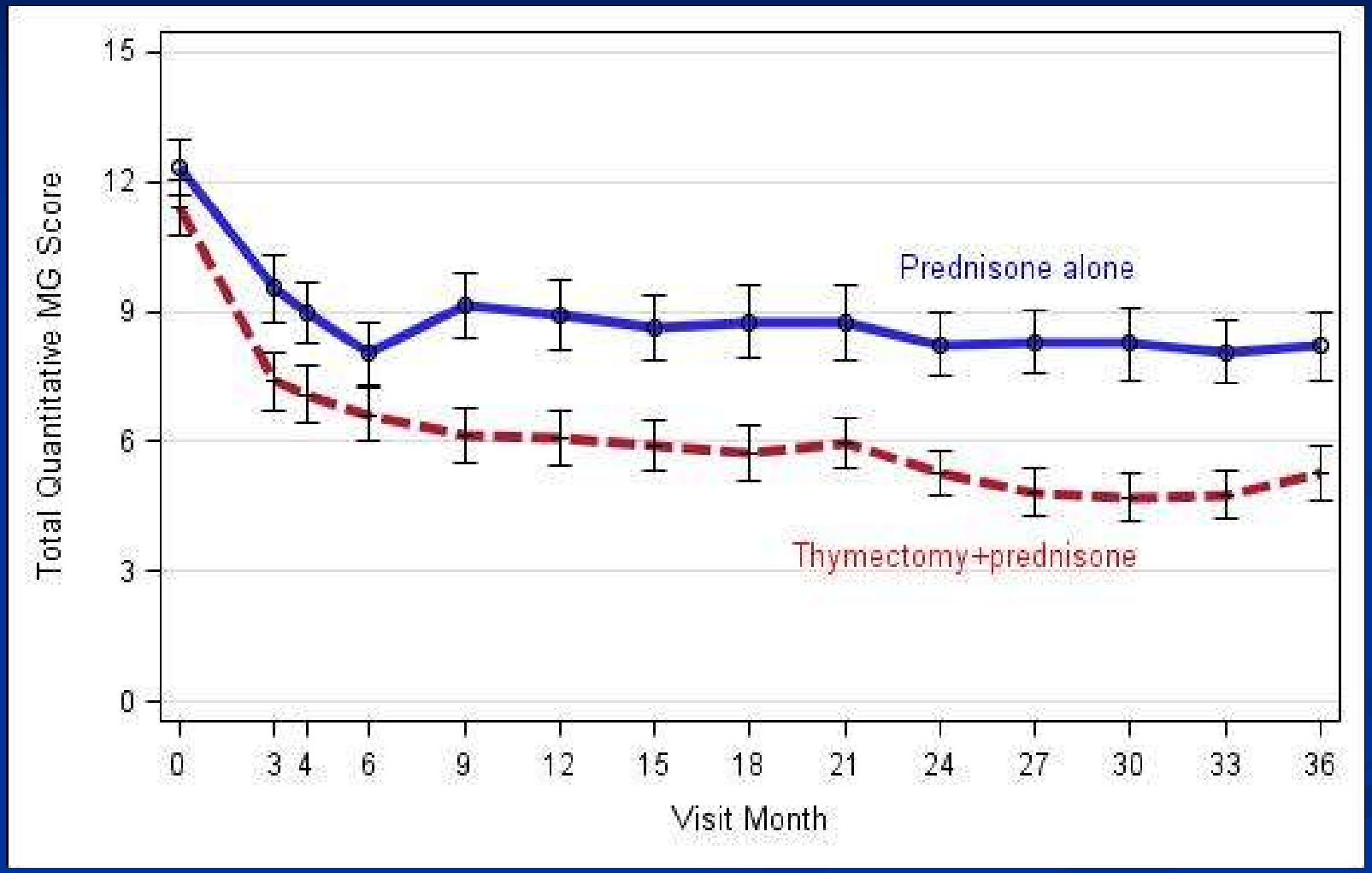
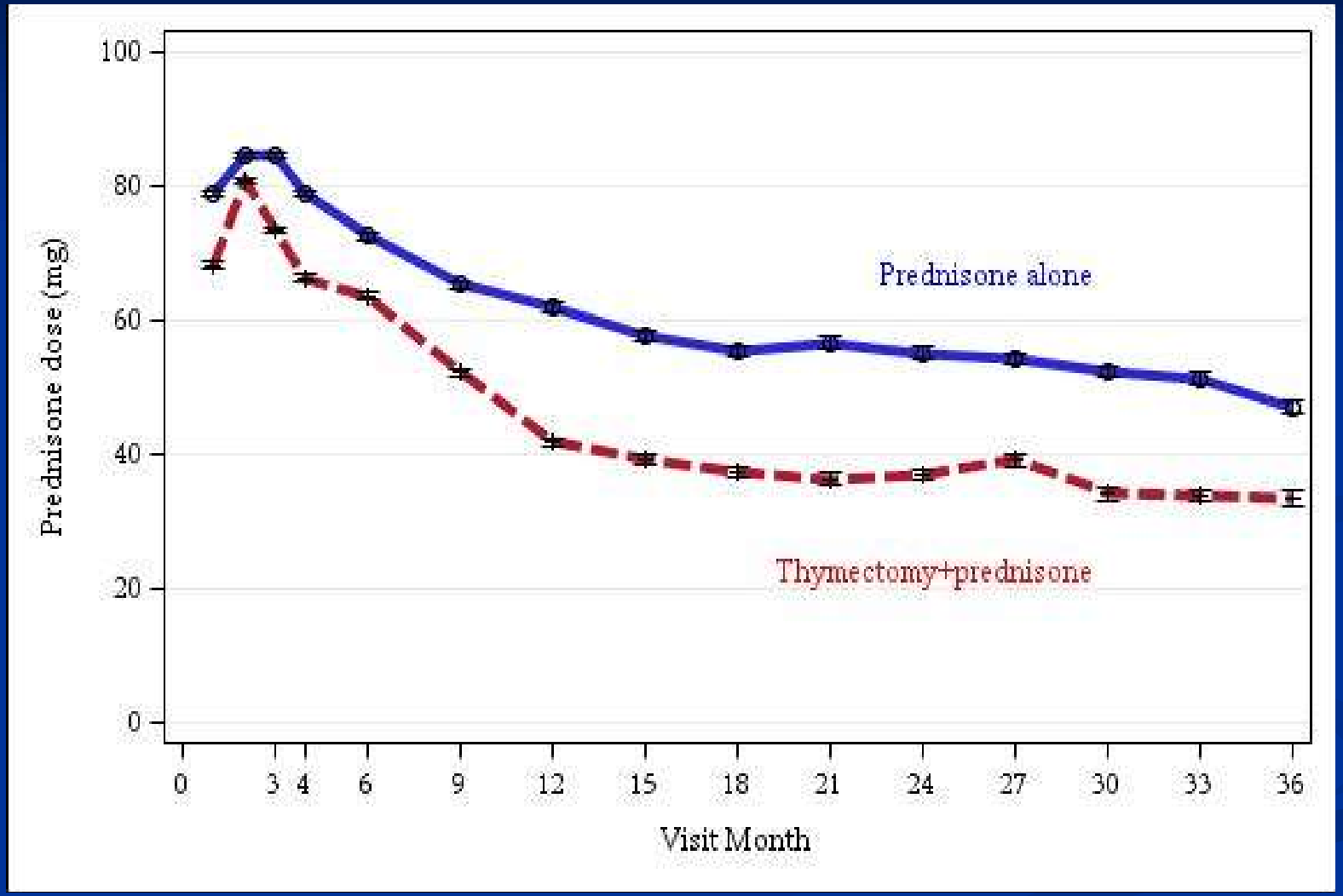
QMG Score (Mean±SE) by Treatment Group



QMG difference: 2.85 pts (99.5% CI 0.47-5.22; p<0.001)

AD Prednisone Dose (Mean±SE) by Treatment Group



Time-weighted average AD prednisone dose difference: 32 mg vs 54 mg (95% CI 12-32 mg; p<0.001)

Primary and Subgroup Analyses

	Treatment Group Mean±SD		Estimated Difference (95% CI†)	P Value[a]
	Prednisone alone	Thymectomy+ prednisone		
Primary Analyses				
Time-weighted average Quantitative MG score	8.99 ± 4.93 (N=56)	6.15 ± 4.09 (N=62)	2.85 (0.47-5.22)	< 0.001
Time-weighted average alternate-day prednisone dose (mg)	54 ± 29 (N=56)	32 ± 23 (N=61)	22 (12-32)	< 0.001
Subgroup Analyses				
Time-weighted average Quantitative MG score				
Prednisone use at enrollment (interaction with treatment P value[b]=0.86)				
Not prednisone naïve	9.10 ± 5.06 (N=46)	6.30 ± 3.89 (N=47)	2.80 (0.11-5.49)	0.004
Prednisone naïve	8.84 ± 4.60 (N=9)	5.66 ± 4.79 (N=15)	3.18 (-3.03-9.39)	0.12
Gender (interaction with treatment P value[b]=0.57)				
Female	9.73 ± 5.16 (N=38)	6.47 ± 4.13 (N=46)	3.26 (0.34-6.18)	0.002
Male	7.45 ± 4.11 (N=18)	5.23 ± 3.95 (N=16)	2.22 (-1.96-6.40)	0.12
Age (years) at disease onset (interaction with treatment P value[b]=0.74)				
< 40	9.60 ± 5.32 (N=34)	6.50 ± 4.41 (N=42)	3.10 (-0.13-6.33)	0.007
≥ 40	7.85 ± 3.50 (N=18)	5.33 ± 2.79 (N=18)	2.52 (-0.65-5.69)	0.02
Time-weighted average alternate-day prednisone dose (mg)				
Prednisone use at enrollment (interaction with treatment P value[b]=0.91)				
Not prednisone naïve	56 ± 31 (N=46)	35 ± 25 (N=46)	22 (10-33)	<0.001
Prednisone naïve	45 ± 22 (N=9)	25 ± 17 (N=15)	20 (4-37)	0.02
Gender (interaction with treatment P value[b] =0.79)				
Female	54 ± 27 (N=37)	33 ± 25 (N=45)	21 (9-32)	<0.001
Male	55 ± 34 (N=19)	31 ± 18 (N=16)	24 (5-42)	0.01
Age (years) at disease onset (interaction with treatment P value[b]=0.81)				
< 40	55 ± 30(N=33)	35 ± 25 (N=41)	20 (8-33)	0.002
≥ 40	49 ± 29 (N=19)	27 ± 18 (N=18)	23 (7-39)	0.007

MGTX Extension Study

- Identical prednisone dosing and outcome protocol
- q3 mo assessments to month 60
- MG-QOL15 (initial version) explored
- 68/111 completing MGTX enrolled
  - More severe QMG at month 0
  - Better MG-ADL at month 36
  - Higher proportion of Hispanic subjects
  - Randomization to surgery or not did not predict extension study enrollment

Long-term effect of thymectomy plus prednisone versus prednisone alone in patients with non-thymomatous myasthenia gravis: 2-year extension of the MGTX randomised trial

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Summary

Background The Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX) showed that thymectomy combined with prednisone was superior to prednisone alone in improving clinical status as measured by the Quantitative Myasthenia Gravis (QMG) score in patients with generalised non-thymomatous myasthenia gravis at 3 years. We investigated the long-term effects of thymectomy up to 5 years on clinical status, medication requirements, and adverse events.

Methods We did a rater-blinded 2-year extension study at 36 centres in 15 countries for all patients who completed the randomised controlled MGTX and were willing to participate. MGTX patients were aged 18 to 65 years at enrolment, had generalised non-thymomatous myasthenia gravis of less than 5 years' duration, had acetylcholine receptor antibody titres of 1·00 nmol/L or higher (or concentrations of 0·50–0·99 nmol/L if diagnosis was confirmed by positive edrophonium or abnormal repetitive nerve stimulation, or abnormal single fibre electromyography), had Myasthenia Gravis Foundation of America Clinical Classification Class II–IV disease, and were on optimal anticholinesterase therapy with or without oral corticosteroids. In MGTX, patients were randomly assigned (1:1) to either thymectomy plus prednisone or prednisone alone. All patients in both groups received oral prednisone at doses titrated up to 100 mg on alternate days until they achieved minimal manifestation status. The primary endpoints of the extension phase were the time-weighted means of the QMG score and alternate-day prednisone dose from month 0 to month 60. Analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00294658. It is closed to new participants, with follow-up completed.

Findings Of the 111 patients who completed the 3-year MGTX, 68 (61%) entered the extension study between Sept 1, 2009, and Aug 26, 2015 (33 in the prednisone alone group and 35 in the prednisone plus thymectomy group). 50 (74%) patients completed the 60-month assessment, 24 in the prednisone alone group and 26 in the prednisone plus thymectomy group. At 5 years, patients in the thymectomy plus prednisone group had significantly lower time-weighted mean QMG scores (5·47 [SD 3·87] *vs* 9·34 [5·08]; p=0·0007) and mean alternate-day prednisone doses (24 mg [SD 21] *vs* 48 mg [29]; p=0·0002) than did those in the prednisone alone group. 14 (42%) of 33 patients in the prednisone group, and 12 (34%) of 35 in the thymectomy plus prednisone group, had at least one adverse event by month 60. No treatment-related deaths were reported during the extension phase.

Interpretation At 5 years, thymectomy plus prednisone continues to confer benefits in patients with generalised non-thymomatous myasthenia gravis compared with prednisone alone. Although caution is appropriate when generalising our findings because of the small sample size of our study, they nevertheless provide further support for the benefits of thymectomy in patients with generalised non-thymomatous myasthenia gravis.

Funding National Institutes of Health, National Institute of Neurological Disorders and Stroke.

Introduction

There have been doubts about the benefits of thymectomy in patients with non-thymomatous myasthenia gravis since Alfred Blalock and colleagues first reported improvements in clinical status in some patients with non-thymomatous myasthenia gravis after thymectomy

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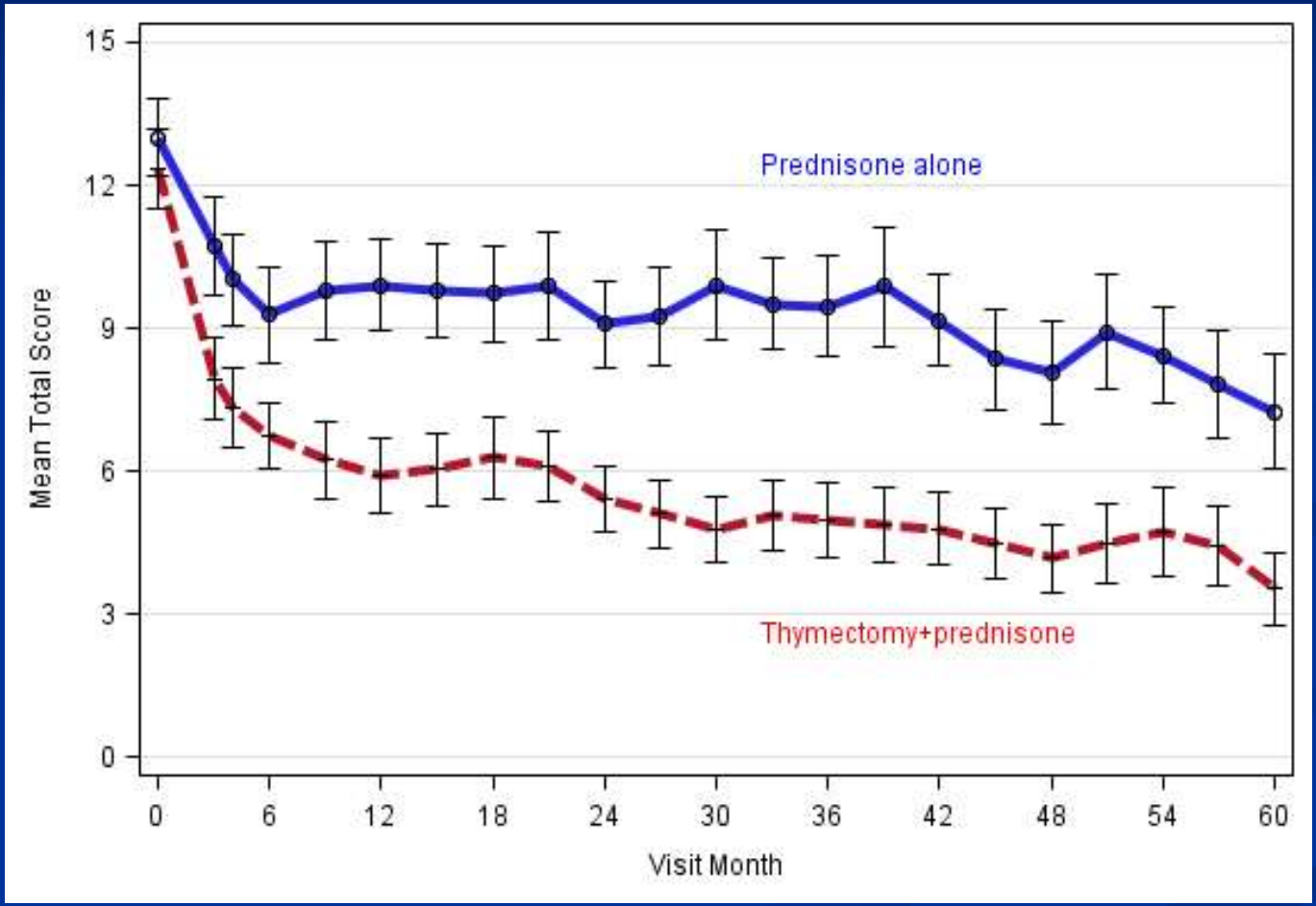
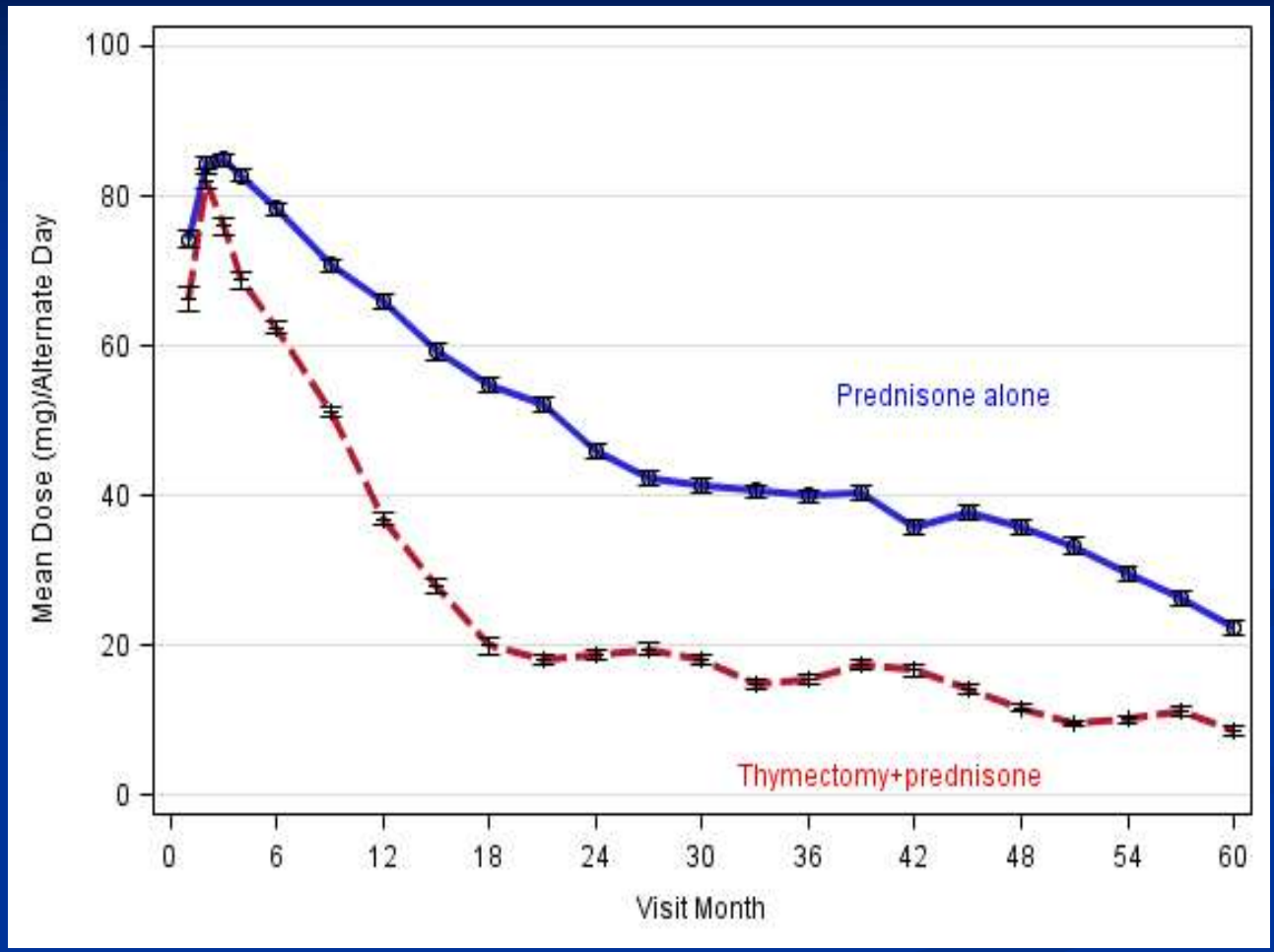
Wolfe GI, Kaminski HJ, Aban IB, et al. *Lancet Neurology* 2019; epub 1/25/19

QMG Score (Mean±SE) by Treatment Group (Extension study subjects only)



QMG difference: 3.87 pts (95% CI 0.71-7.04; p<0.001)

AD Prednisone Dose (Mean±SE) by Treatment Group (Extension study subjects only)



Time-weighted average AD prednisone dose: 25 mg vs 48 mg (95% CI 11-36 mg; p<0.001)

Extension Study Primary and Subgroup Analyses

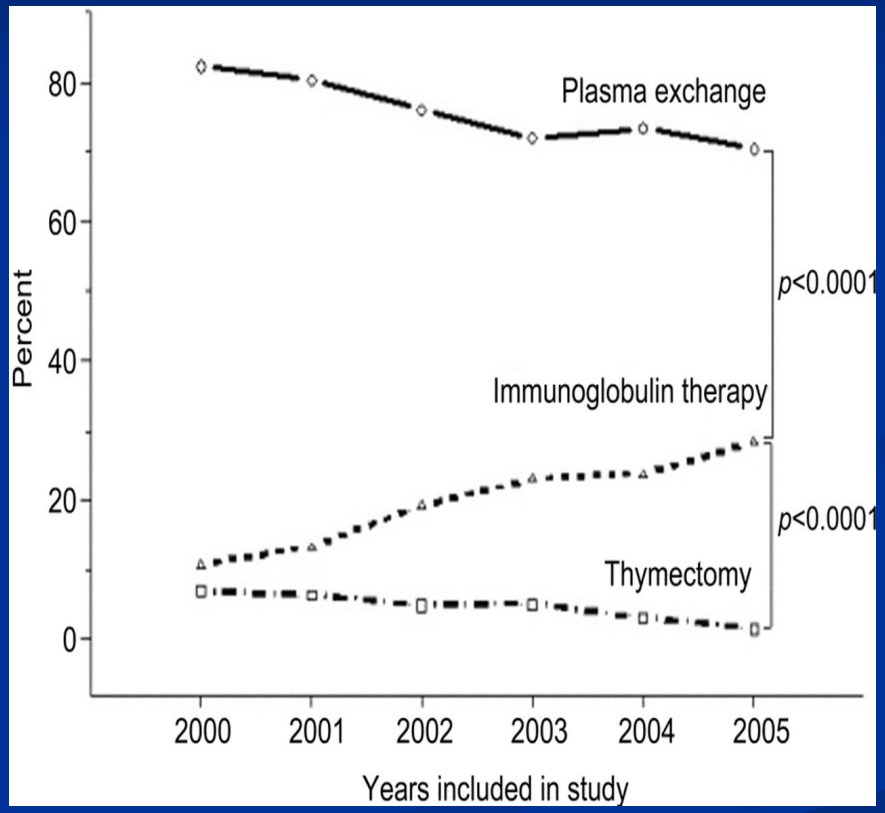
Outcome	Prednisone Alone		Thymectomy plus Prednisone		Estimated Difference (95% CI*)†	P Value‡
	Mean ± SD	No. of patients	Mean ± SD	No. of patients		
Primary Analyses						
Time-weighted average QMG score over 5-yr period	9.34 ± 5.08	33	5.47±3.87	35	3.87 (0.71 to 7.04)	0.0007
Time-weighted average alternate-day prednisone dose over 5-yr period (mg)	48 ± 29	33	24 ± 21	35	24 (12 to 36)	0.0002
Subgroup Analyses						
Time-weighted average QMG score						
Prednisone use at month 0						
Yes	9.71 ± 5.25	24	5.56 ± 3.55	26	4.16 (0.45 to 7.86)	0.0022
No	8.36 ± 4.75	9	5.21 ± 4.92	9	3.15 (-4.26 to 10.56)	0.16
Sex						
Female	9.96 ± 5.34	24	6.20 ± 4.02	27	3.76 (-0.10 to 7.63)	0.0092
Male	7.70 ± 4.13	9	3.00 ± 1.92	8	4.70 (-0.55 to 9.95)	0.0274
Age at disease onset						
< 40 yr	9.53 ± 5.69	23	5.87 ± 4.24	23	3.66 (-0.72 to 8.03)	0.213
≥ 40 yr	8.92 ± 3.53	10	4.69 ± 3.05	12	4.22 (-0.20 to 8.64)	0.0056
Time-weighted average alternate-day prednisone dose (mg)						
Prednisone use at month 0						
Yes	54 ± 31	24	26 ± 21	26	27 (12 to 42)	0.0005
No	34 ± 19	9	18 ± 20	9	16 (-4 to 35)	0.0400
Sex						
Female	47 ± 26	24	26 ± 23	27	21 (7 to 35)	0.0024
Male	51 ± 38	9	17 ± 8	8	34 (5 to 64)	0.0592
Age at disease onset						
< 40 yr	48 ± 29	23	26 ± 23	23	23 (7 to 38)	0.0031
≥ 40 yr	48 ± 31	10	21 ± 16	12	26 (5 to 48)	0.0112

Extension Study Secondary Analyses

Outcome	Treatment Group Mean±SD or Count (%)		Estimated Difference (95% CI)	P Value
	Prednisone Alone	Thymectomy +prednisone		
Time-weighted average prescribed AD prednisone dose (mg)[a]	49.0 ± 29.2 (N=33)	25.9 ± 20.7 (N=35)	23.1 (10.9 to 35.2)	0.0003
Penalized time-weighted average AD prednisone dose (mg; Method 1)[a,b]	66.2 ± 36.7 (N=33)	31.0 ± 31.8 (N=35)	35.2 (18.6 to 51.9)	< 0.001
Penalized time-weighted AD average prednisone dose (mg; Method 2)[a,c]	60.6 ± 34.6 (N=33)	28.3 ± 27.9 (N=35)	32.3 (17.2 to 47.5)	< 0.001
Time-weighted average MG Activities of Daily Living to month 60[a,d]	3.26 ± 2.77 (N=32)	1.61 ± 1.46 (N=34)	1.65 (0.54 to 2.75)	0.0044
at month 48	2.55 ± 3.02 (N=29)	1.10 ± 1.51 (N=31)	1.45 (0.20 to 2.71)	0.0245
at month 60	2.04 ± 2.63 (N=24)	1.23 ± 1.75 (N=26)	0.81 (-0.48 to 2.07)	0.21
Azathioprine use[f]	19/33 (58)	7/35 (20)	37.6% (16.1% to 59.0%)	0.0014
Plasma exchange use[f]	4/33 (12)	5/35 (14)	-2.1% (-18.2% to 13.9%)	0.73
Intravenous immunoglobulin use[f]	11/33 (33)	3/35 (9)	24.8% (6.2% to 43.3%)	0.0162
Minimal Manifestation Status[e]				
at month 48[f]	15/29 (52)	23/31 (74)	-22.5% (-46.3% to 1.4%)	0.07
at month 60[g]	14/24 (58)	23/26 (88)	-30.1% (-53.4% to 6.9%)	0.0236
MG-QOL15[g]				
at month 39	13.1 ± 14.0 (N=32)	4.8 ± 9.2 (N=33)		0.0029
at month 48	9.0 ± 10.1 (N=29)	4.9 ± 7.9 (N=30)		0.13
at month 60	7.7± 9.2 (N=24)	7.8 ± 10.9 (N=26)		0.96
Hospitalization for MG exacerbation				
Months 0-36: # of patients[h]	10/33 (30)	2/35 (6)	24.6% (7.1% to 42.1%)	0.01
Months 0-60: # of patients[h]	10/33 (30)	2/35 (6)	24.6% (7.1% to 42.1%)	0.01

Thymectomy in U.S.
2000 to 2005

- Nationwide Inpatient Sample (NIS)
  - 1000 hospitals (20% of community facilities)
  - Can search database for ICD-9-CM codes
  - IC and HIPAA waivers possible
- n=5502
- Thymectomy rate fell from 7% to 1.5%



Alsheklee A ,et al. *Neurology* 2009;72:1548

MGTX in Context
Statements for non-thymomatous MG

- Cochrane Collaboration
  - "There is no randomized controlled trial literature that allows meaningful conclusions about the efficacy of thymectomy on MG. Data from several class III observational studies suggest that thymectomy could be beneficial in MG. An RCT is needed…"
    - Cea G, et al. *Cochrane Library* 2013;10:1-20
- Intl MG Treatment Recommendations
  - "In non-thymomatous MG, thymectomy is performed as an option to potentially avoid or minimize the dose or duration of immunotherapy, or if patients fail to respond to an initial trial of immunotherapy or have intolerable side effects from that therapy."
    - Sanders DB, Wolfe GI, Benatar M, et al. *Neurology* 2016; 87:419-425

MGTX Deeper Dive Summary

- Class I evidence: ETTX has favorable impact on AChRAb+ generalized MG
  - Clinical outcomes
  - Corticosteroid exposure
  - Adverse events
- Benefit can be additive through 5 years
  - MMS achievement — at 5 yrs: 88% vs. 58%; at 3 yrs: 67% vs. 47%
  - Time-weighted QMG — at 5 yrs: Δ3.87; at 3 yrs: Δ2.85
- Current investigations
  - Predictive role of thymic histology
  - Prednisone cessation
  - BioMG

Many Thanks!

- Study subjects: Trust in randomization; up to 5 yrs
- MGTX Investigators/DSMB/NINDS/Patients

March 2006
SF / Oxford