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

Gil I Wolfe, Henry J Kaminski, Inmaculada B Aban, Greg Minisman, Hui-Chien Kuo, Alexander Marx, Philipp Ströbel, Claudio Mazia, Joel Oger, J Gabriel Cea, Jeannine M Heckmann, Amelia Evoli, Wilfred Nix, Emma Ciafaloni, Giovanni Antonini, Rawiphan Witoonpanich, John O King, Said R Beydoun, Colin H Chalk, Alexandru C Barboi, Anthony A Amato, Aziz I Shaibani, Bashar Katirji, Bryan R F Lecky, Camilla Buckley, Angela Vincent, Elza Dias-Tosta, Hiroaki Yoshikawa, Márcia Waddington-Cruz, Michael T Pulley, Michael H Rivner, Anna Kostera-Pruszczyk, Robert M Pascuzzi, Carlayne E Jackson, Jan J G M Verschuuren, Janice M Massey, John T Kissel, Lineu C Werneck, Michael Benatar, Richard J Barohn, Rup Tandan, Tahseen Mozaffar, Nicholas J Silvestri, Robin Conwit, Joshua R Sonett, Alfred Jaretzki III*, John Newsom-Davis*, Gary R Cutter, on behalf of the MGTX Study Group†*

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.

Lancet Neurol 2019; 18: 259–68

Published Online January 25, 2019 http://dx.doi.org/10.1016/S1474-4422(18)30392-2

See Comment page 225

†Members listed in the appendix

Department of Neurology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA (Prof G I Wolfe MD, N J Silvestri MD); **Department of Neurology, George Washington University School of Medicine and Health Sciences, Washington, DC, USA** (Prof H J Kaminski MD); **Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA** (Prof I B Aban PhD, G Minisman MA, H-C Kuo MS, Prof G R Cutter PhD); **Institute of Pathology, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany** (Prof A Marx, MD); **Institute of Pathology, University of Göttingen, Göttingen, Germany** (Prof P Ströbel MD); **Department of Neurology, University of Buenos Aires, Buenos Aires, Argentina** (Prof C Mazia MD); **Division of Neurology, University of British Columbia, Vancouver, BC, Canada** (Prof J Oger MD); **Department of Neurology, University of Chile, Santiago, Chile** (Prof J G Cea MD); **Divisionof Neurology, Department of Medicine, University of Cape Town, Cape Town, South Africa** (J M Heckmann MBChB); **Department of Neurology,**

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

Catholic University, Rome, Italy (A Evoli MD); Department of Neurology, Johanes Gutenberg University, Mainz, Germany (Prof W Nix MD); Department of Neurology, University of Rochester Medical Centre, Rochester, NY, USA (Prof E Ciafaloni MD); Department of Neurology, Mental Health and Sensory Organs, University of Rome Sapienza, Rome, Italy (G Antonini MD); Department of Neurology, Mahidol University, Bangkok, Thailand (Prof R Witoonpanich MD); Department of Neurology, University of Melbourne, Melbourne, VIC, Australia (J O King MD); Department of Neurology, University of Southern California, Los Angeles, CA, USA (Prof S R Beydoun MD); Department of Neurology, McGill University, Montreal, QC, Canada (C H Chalk MD); Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA (A C Barboi MD); Department of Neurology, Harvard Medical School, Boston, MA, USA (Prof A A Amato MD); Nerve and Muscle Centre of Texas, Houston, TX, USA (Prof A I Shiabani MD); Department of Neurology, Case Western Reserve University, Cleveland, OH, USA (Prof B Katirji MD); Walton Centre for Neurology and Neurosurgery, Liverpool, UK (B R F Lecky MD); Nuffield Department of Clinical Neurosciences, Oxford University, Oxford, UK (Prof C Buckley MD, Prof A Vincent MBBS, Prof J Newsom-Davis MD); Unit of Neurology, Hospital de Base do Distrito Federal, Brasília, Brazil (Prof E Dias-Tosta MD); Department of Neurology, Kanazawa University, Kanazawa, Japan (Prof H Yoshikawa MD); Department of Neurology, Federal University, Rio de Janeiro, Brazil (M Waddington-Cruz MD); Department of Neurology, University of Florida, Jacksonville, FL, USA (M T Pulley MD); Department of Neurology, Georgia Regents University, Augusta, GA, USA (Prof M H Rivner MD); Department of Neurology, Medical University of Warsaw,

Research in context

Evidence before this study

We searched PubMed with the terms "randomised", "thymectomy", and "myasthenia gravis" to identify articles published in English between Jan 1, 2012, and Aug 28, 2018. This search overlapped with previous searches done during the design, conduct, and publication stages of the international, multicentre, randomised controlled, rater-blinded Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX). Our search identified one publication of the results of MGTX and one publication from our investigator group reporting biomarker results from the trial. We also identified six letters to the editor or editorials commenting on the MGTX results. No other randomised studies of thymectomy in patients with myasthenia gravis were identified. Before MGTX, the results of observational studies mostly suggested that thymectomy improved outcomes in patients with non-thymomatous myasthenia gravis. Practice guidelines, however, identified several flaws in these studies (including confounding variables of age, sex, and disease severity), showing the need for a randomised controlled trial. The results of MGTX showed that extended transsternal thymectomy combined with a standardised prednisone protocol was superior to prednisone alone at 3 years in improving clinical status and lowering medication requirements in patients with generalised non-thymomatous myasthenia gravis.

Added value of this study

The MGTX extension study, in which patients were followed up under the same protocol until month 60 (5 years) showed that thymectomy plus prednisone treatment continued to confer benefits—including improved disease outcomes, reduced prednisone requirements, and fewer hospitalisations for disease exacerbations—compared with prednisone alone in patients with generalised non-thymomatous myasthenia gravis. Additionally, the extension study results for the thymectomy plus prednisone group are favourable compared with those for other observational long-term outcome studies in patients with myasthenia gravis that tracked minimal manifestation status.

Implications of all the available evidence

Thymectomy within the first few years of the disease course in addition to prednisone therapy confers benefits that persist for 5 years compared with prednisone alone in patients with generalised non-thymomatous myasthenia gravis. Results from the extension study provide further support for the use of thymectomy in management of myasthenia gravis and should encourage serious consideration of this treatment option in discussions between clinicians and their patients.

in 1941.[1] Whether or not thymectomy offered definitive benefits in this patient population has remained a heated topic since then. A practice guideline in 2000 for which all available data about thymectomy were analysed could not conclusively establish the benefit of thymectomy in non-thymomatous myasthenia gravis.[2] The authors of the practice guideline and others who did systematic literature reviews[2,3] called for a prospective, randomised, medication-controlled trial with blinded assessments, a call that was met by the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX).[4]

The results of MGTX,[4] an international, multicentre, randomised controlled study, showed that extended transsternal thymectomy in combination with a standardised prednisone protocol was superior to prednisone alone in improving myasthenic weakness and lowering corticosteroid requirements in patients with non-thymomatous myasthenia gravis who were positive for acetylcholine receptor antibodies. The trial also showed that thymic resection in addition to prednisone resulted in a significantly lower requirement for azathioprine and intravenous immunoglobulin, and significantly lower frequency of hospitalisations for exacerbation of myasthenia gravis, compared with prednisone alone (all were reduced by more than 50% in the thymectomy group).[4]

A 3-year timepoint was chosen for analysis of the MGTX primary endpoint on the basis of studies that showed benefits in the first 2–4 years after thymectomy but also suggested that, after 4 years, surgically and medically managed patients improved at similar rates, with no additional benefit derived from thymectomy itself.[5,6] Thus, the aim of this extension study was to investigate the durability of treatment response related to thymectomy in this population and whether benefits accrue past 3 years.

Methods

Study design and participants

MGTX was an international, rater-blinded study done at 36 academic medical centres in 15 countries (Argentina, Australia, Brazil, Canada, Chile, Germany, Italy, Japan, Mexico, the Netherlands, Poland, South Africa, Thailand, the UK, and the USA). Centres screened all patients with myasthenia gravis for possible inclusion in MGTX. Eligible participants were aged 18–65 years, had generalised non-thymomatous myasthenia gravis of less than 5 years' duration, had serum acetylcholine receptor antibody concentrations of 1·00 nmol/L or higher (patients with concentrations of 0·50–0·99 nmol/L were eligible if diagnosis was confirmed by positive edrophonium test, abnormal repetitive nerve stimulation, or abnormal single fibre electromyography), had Myasthenia Gravis Foundation of America Clinical Classification[7] Class II–IV disease (ie, class I [weakness only in ocular muscles] and V [crisis requiring intubation] disease was excluded); and were on optimal anticholinesterase therapy with

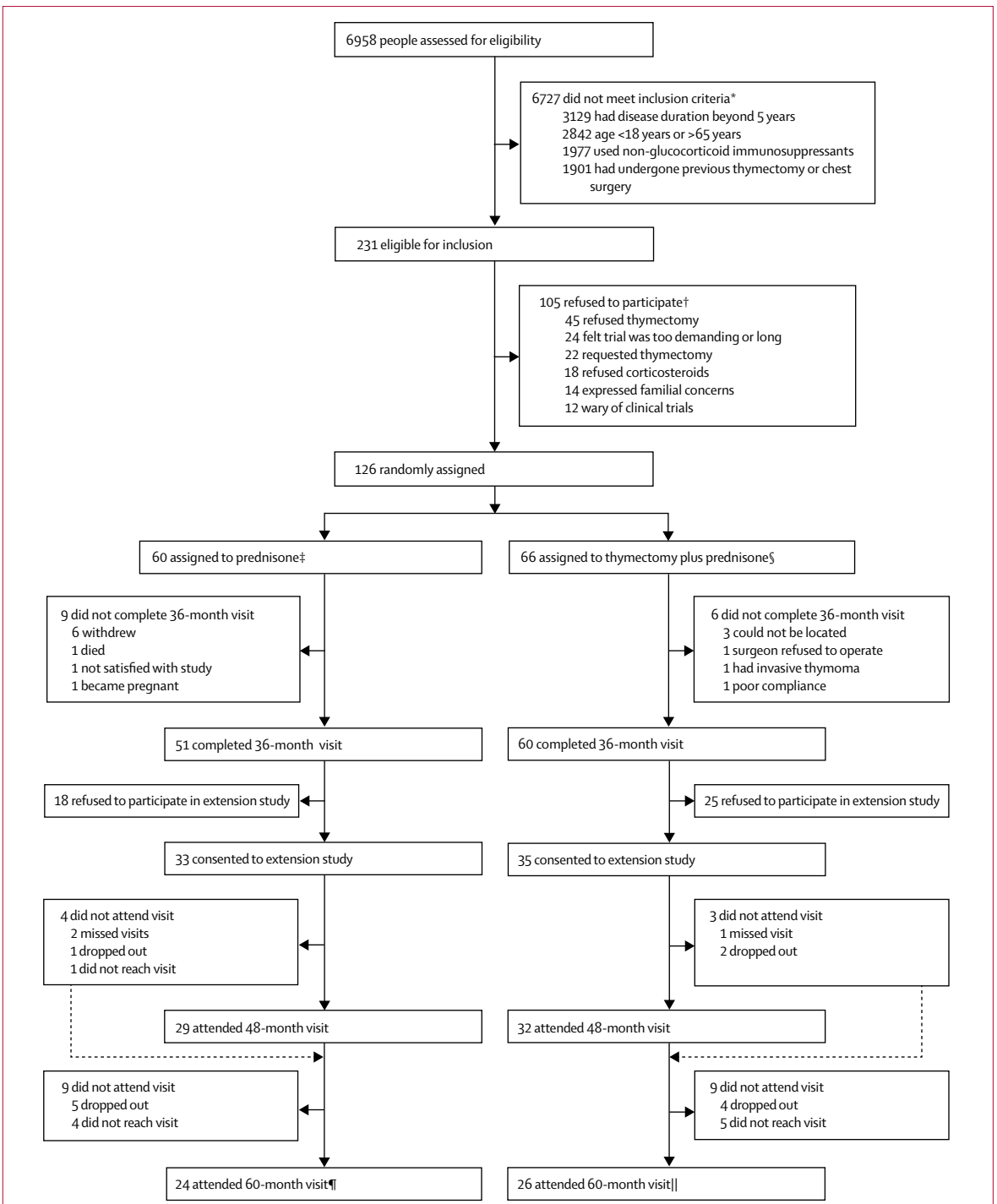

Figure 1: **Trial profile**
Primary and secondary outcomes were assessed at each of the visits listed. *Some patients were excluded for more than one reason; other, less common reasons for exclusion are listed in the text. †Some patients gave more than one reason. ‡Eight patients had thymectomies outside the study protocol. §Eight patients refused to have thymectomies, and a surgeon judged one patient to be unfit to undergo the procedure. ¶22 participants in the prednisone group attended the 36-month, 48-month, and 60-month assessments. ||25 participants in the thymectomy plus prednisone group attended the 36-month, 48-month, and 60-month assessments.

or without oral corticosteroids. Exclusion criteria were thymoma on chest imaging, previous thymectomy, immunotherapy other than prednisone, pregnancy or lactation, unwillingness to avoid pregnancy, contraindications to corticosteroids, and significant medical illness that would prevent participation.

Warsaw, Poland (Prof A Kostera-Pruszczyk MD); **Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA** (Prof R M Pascuzzi MD); **Department of Neurology, University of Texas Health Science Centre, San Antonio, TX, USA** (Prof C E Jackson MD); **Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands** (Prof J J G M Verschuuren MD); **Department of Neurology, Duke University Medical Centre, Durham, NC, USA** (Prof J M Massey MD); **Department of Neurology, Ohio State University Wexner Medical Centre, Columbus, OH, USA** (Prof J T Kissel MD); **Department of Neurology, Universidade Federal do Parana, Curitiba, Brazil** (Prof L C Werneck MD); **Department of Neurology, University of Miami, Miami, FL, USA** (Prof M Benatar MD); **Department of Neurology, University of Kansas Medical Centre, Kansas City, KS, USA** (Prof R J Barohn MD); **Department of Neurological Sciences, University of Vermont College of Medicine, Burlington, VT, USA** (Prof R Tandan MD); **Department of Neurology, University of California, Irvine, Orange, CA, USA** (Prof T Mozaffar MD); **Division of Extramural Research, National Institutes of Health/ National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA** (R Conwit MD); **and Section of General Thoracic Surgery, Columbia University Medical Centre, New York, NY, USA** (Prof J R Sonett MD, Prof A Jaretzki III MD)

*Prof Mazia, Prof Jaretzki III, and Prof Newsom-Davis are dead

Correspondence to:
Prof Gil I Wolfe, Department of Neurology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, State University of New York, 1010 Main Street, Buffalo, NY 14202, USA
gilwolfe@buffalo.edu

	Prednisone group (n=33)	Thymectomy plus prednisone group (n=35)
Sex		
Female	24 (73%)	27 (77%)
Male	9 (27%)	8 (23%)
Median age, years (IQR)	33·0 (25·0–43·0)	32·0 (22·0–41·0)
Median disease duration, years (IQR)	1·2 (0·7–2·1)	1·1 (0·7–1·7)
Ethnicity		
Asian	3 (9%)	5 (14%)
Black or African American	3 (9%)	2 (6%)
Hispanic	15 (45%)	12 (34%)
White (non-Hispanic)	10 (30%)	13 (37%)
Other (mixed, Native American, or Alaskan)	2 (6%)	3 (9%)
Myasthenia Gravis Foundation of America Class*		
IIa	12 (36%)	12 (34%)
IIb	8 (24%)	9 (26%)
III	12 (36%)	12 (34%)
IV	1 (3%)	2 (6%)
Treatment		
Current pyridostigmine†	32 (97%)	33 (94%)
Current corticosteroids†	24 (73%)	26 (74%)
Previous intravenous immunoglobulin	7 (21%)	2 (6%)
Previous plasma exchange	4 (12%)	5 (14%)
Quantitative Myasthenia Gravis score	13·0 (4·7)	12·3 (5·1)
Alternate-day prednisone dose, mg	48·5 (30·7)	46·3 (32·7)
Myasthenia Gravis Activities of Daily Living score	5·5 (3·0)	5·37 (3·46)

Data are n (%) or mean (SD), unless otherwise stated. *Class II corresponds to mild weakness, class III to moderate weakness, and class IV to severe weakness; a denotes predominantly limb and axial presentation, whereas b denotes predominantly bulbar presentation. †At trial entry.

Table 1: **Baseline demographic and clinical characteristics of patients in the extension study**

The extension study was open to all patients who completed the initial 36 months of MGTX and were willing to participate. Additional exclusion criteria for the extension study were a desire to pursue thymectomy after the 36-month visit, or enrolment in another experimental clinical trial. Local institutional review boards or ethics committees approved the extension phase of the study at all sites. All participants provided written informed consent before enrolment in the extension study.

Procedures

Patients in MGTX were originally randomly assigned (1:1) to either extended transsternal thymectomy plus prednisone or prednisone only as previously described.[1] There was no randomisation related to the extension study (ie, patients remained in their originally assigned groups). In MGTX, extended transsternal thymectomy was done within 30 days of randomisation in patients assigned to the thymectomy plus prednisone group. All patients in both groups followed the same prednisone protocol. When first enrolled, patients not already taking prednisone received an alternate-day dose of oral prednisone starting at 10 mg, which was increased by 10 mg with each subsequent dose until a dose of 100 mg on alternate days or 1·5 mg/kg (whichever was lower) was reached. For patients who were already taking prednisone at enrolment, the dose could be increased up to 120 mg on alternate days if by month 4 they had not reached Minimal Manifestation Status[7] (MMS), which was defined as no symptoms or functional limitations from myasthenia gravis (although minor weakness could be present on examination) and is an accepted goal of myasthenia gravis therapy.[8] Prednisone doses were maintained until MMS was achieved and the Quantitative Myasthenia Gravis (QMG) score[9]—which comprises 13 items and has a score range of 0–39, with higher scores suggesting more severe weakness—was less than 14 and had fallen at least one point below baseline. Assessments were done by masked raters from month 4 onwards every 2–3 months. Patients in the thymectomy group wore black, high-collared shirts to conceal transsternal incisions when they underwent assessments. Once these conditions were met, the prednisone dose was then reduced by 10 mg every 2 weeks until a dose of 40 mg on alternate days was reached. Thereafter, the dose was further reduced by 5 mg every month as long as MMS was maintained. In patients in whom MMS was not maintained, the prednisone dose was increased by 10 mg on alternate days every 2 weeks until MMS was regained. Tapering could resume 4 weeks after MMS was restored. Once prednisone tapering began, patients could not take more than 240 mg pyridostigmine per day. Patients who had not reached MMS at 12 months or who had intolerable side-effects from prednisone could be given azathioprine 2·5 mg/kg per day (or a substitute immunosuppressant if they could not tolerate azathioprine).

Patients in the extension phase maintained the same prednisone protocol used in the original study. In both MGTX and its extension study, plasmapheresis or intravenous immunoglobulin was permitted to stabilise patients at the discretion of their neurologist (who was not masked to group assignment) but could not be used to maintain MMS. Laboratory monitoring in the extension study was left to the discretion of site investigators. From month 36 (ie, the beginning of the extension study) to month 60, rater-blinded QMG scores and prednisone requirements were recorded at study visits every 3 months. Prednisone intake was measured by pill counts throughout the entire study; blister packs of 10 mg tablets were used, with separate sheets provided for each dose. The alternate-day dosing was recorded in a patient diary, which allowed comparison with pill counts derived from the blister packs that were checked at each visit. Pill cutters were provided for 5 mg dosing, and unused half pills were returned to the pouches.

Outcomes

The primary outcome was a staged assessment of the time-weighted mean QMG score and time-weighted mean required dose of prednisone from month 0 to month 60. This approach enabled assessment of a potential effect of thymectomy on clinical status and how thymic resection might affect long-term prednisone requirements. The rationale for a two-stage primary outcome was that improved clinical status could be secondary to higher prednisone dosing, and poorer clinical status could be due to lower dosing. In the first stage of the analysis, we compared the clinical outcomes (as measured by the time-weighted QMG score) between the two groups. On the basis of results of this between-group comparison of clinical outcomes (ie, improvement, worsening, or no change), the difference in total prednisone requirements was analysed. QMG scores and prednisone doses were collected locally, but data were centrally assessed at the University of Alabama at Birmingham (Birmingham, AL, USA).

Secondary outcomes measured from month 0 to month 60 were scores on the Myasthenia Gravis Activities of Daily Living scale[10] (MG-ADL; range 0–24; higher scores suggest more severe disease), the proportion of patients reaching MMS, and use of non-steroid immunosuppressants, plasma exchange, and intravenous immunoglobulin. A novel Myasthenia Gravis Quality of Life questionnaire[11] (MG-QOL15; range 0–60; higher scores suggest more severe disease) that was developed after MGTX began was used to assess quality of life in an exploratory manner at months 39, 48, and 60. For another secondary outcome, we repeated the primary dosing analysis but included a prespecified penalty if azathioprine was added to prednisone. That is, either the maximum dose of prednisone before addition of azathioprine (method 1), or the dose of prednisone at the time azathioprine treatment was initiated (method 2), were inputted for all assessment points until month 60 or the time of study withdrawal. Other secondary outcomes assessed from months 0 to 60 focused on safety and adverse events, including days of hospitalisation and treatment-associated complications, which was assessed with surveys adapted from the cardiac transplant literature[12] to assess 36 potential complications associated with corticosteroid use. Medical Dictionary for Regulatory Activities coding was used to classify hospitalisations. A data safety monitoring board that was assembled by the US National Institute of Neurological Disorders and Stroke oversaw MGTX and the extension study until the last study assessment was completed.

Statistical analysis

Data management was done at the University of Alabama at Birmingham via a web-based system. Notification of adverse events and visit tracking were done electronically. All analyses were done by intention to treat. The protocol prespecified analysis of three subgroups: previous corticosteroid use (yes *vs* no), sex, (female *vs* male), and age at disease onset (<40 years *vs* ≥40 years). There were no planned adjustments for multiple secondary outcomes. For MGTX, sample size calculations were based on a reduction in the time-weighted mean prednisone dose of 30% or more in favour of one treatment. This reduction was deemed the minimum that would be clinically valuable by a consensus of international specialists in myasthenia gravis who were part of the trial study group. For the sample size calculation, we assumed a two-group

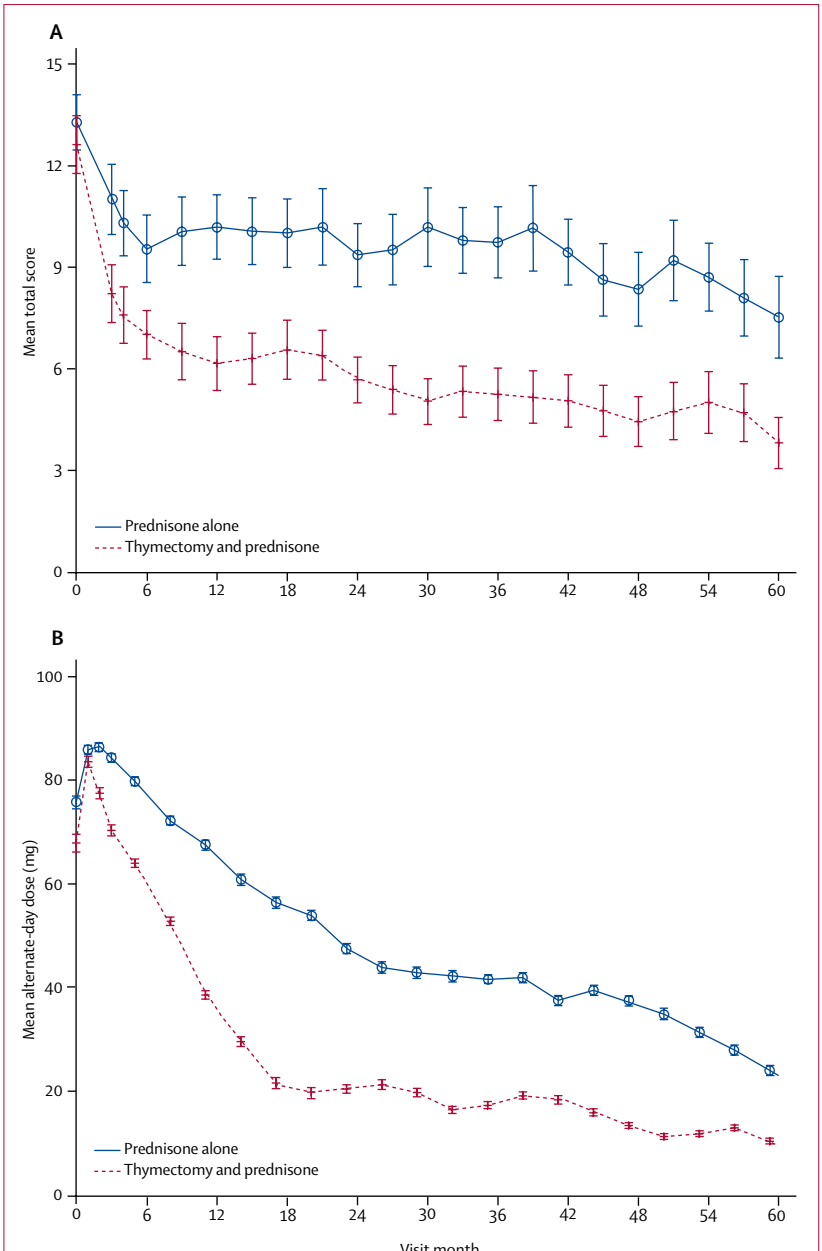

Figure 2: **Mean Quantitative Myasthenia Gravis score (A) and mean alternate-day prednisone dose (B) by treatment group during the 5-year study period**
Error bars represent SEs.

	Prednisone group (n=33)		Thymectomy plus prednisone group (n=35)		Estimated difference (95% CI*)	p value
	Mean (SD)	n (%)	Mean (SD)	n (%)		
Primary outcomes						
Time-weighted mean QMG score	9·34 (5·08)	33 (100%)	5·47 (3·87)	35 (100%)	3·87 (0·71 to 7·04)	0·0007
Time-weighted mean alternate-day prednisone dose, mg	48 (29)	33 (100%)	24 (21)	35 (100%)	24 (12 to 36)	0·0002
Subgroup analyses						
Time-weighted mean QMG score						
Prednisone use at month 0						0·69†
Yes	9·71 (5·25)	24 (73%)	5·56 (3·55)	26 (74%)	4·16 (0·45 to 7·86)	0·0022
No	8·36 (4·75)	9 (27%)	5·21 (4·92)	9 (26%)	3·15 (–4·26 to 10·56)	0·16
Sex						0·71†
Female	9·96 (5·34)	24 (73%)	6·20 (4·02)	27 (77%)	3·76 (–0·10 to 7·63)	0·0092
Male	7·70 (4·13)	9 (27%)	3·00 (1·92)	8 (23%)	4·70 (–0·55 to 9·95)	0·0274
Age at disease onset						0·81†
<40 years	9·53 (5·69)	23 (70%)	5·87 (4·24)	23 (66%)	3·66 (–0·72 to 8·03)	0·0213
≥40 years	8·92 (3·53)	10 (30%)	4·69 (3·05)	12 (34%)	4·22 (–0·20 to 8·64)	0·0056
Time-weighted mean alternate-day prednisone dose, mg						
Prednisone use at month 0						0·40†
Yes	54 (31)	24 (73%)	26 (21)	26 (74%)	27 (12 to 42)	0·0005
No	34 (19)	9 (27%)	18 (20)	9 (26%)	16 (-4 to 35)	0·0400
Sex						0·36†
Female	47 (26)	24 (73%)	26 (23)	27 (77%)	21 (7 to 35)	0·0024
Male	51 (38)	9 (27%)	17 (8)	8 (23%)	34 (5 to 64)	0·0592
Age at disease onset						0·78†
<40 years	48 (29)	23 (70%)	26 (23)	23 (66%)	23 (7 to 38)	0·0031
≥40 years	48 (31)	10 (30%)	21 (16)	12 (34%)	26 (5 to 48)	0·0112

Data are n (%) and mean (SD). QMG=Quantitative Myasthenia Gravis score. *Denotes CI for the mean; we used 95% CIs in all analyses except for analyses of the QMG score, for which we used 99·5% CIs per protocol. †p values for interaction with treatment were based on fitting a general linear model separately for each variable.

***Table 2*: Changes in time-weighted mean QMG score and time-weighted alternate day prednisone dose between baseline and 60 months**

comparison of the treatment means and that the distribution of the time-weighted mean prednisone dose values would be approximately normal. This assumption of an approximately normal distribution was satisfactorily tested in Palace and colleagues' trial[13] of azathioprine plus prednisolone versus prednisolone alone. For 90% power to obtain a significant result at the 5% two-tailed level, MGTX required 60 participants in each group. A separate power calculation was not done for the extension study.

An objective of the extension study was to maximise the amount of information collected to gain better insight into how patients fared after month 36 of MGTX. Patients who were enrolled at later stages were not expected to complete all visits until month 60, and there was no minimum number of visits that patients had to attend to be included in the study. Statistical analyses were adjusted for the amount of follow-up contributed per patient.

Time-weighted outcomes were based on the area under the curve averaged up to the final visit available for that patient. For analyses of time-weighted mean QMG scores, prednisone doses, and MG-ADL scores, we computed the area under the curve using the trapezoidal rule divided by the number of days from randomisation to the last visit. To compare the two treatment groups with respect to these outcomes, we used *t* tests for the main analyses and the Wilcoxon two-sample exact test for subgroup analyses. In addition to these tests, 99·5% CIs of the mean difference were constructed. For the analysis of MMS and the time from month 0 to reach initial MMS, we used a Cox proportional hazards model in which the outcome was censored if the event did not happen by the end of the study or the patient dropped out before the outcome was reached; logistic regression with treatment group in the model was used to compare the proportion achieving MMS at months 48 and 60. For the MG-QOL15 questionnaire data, we used the Wilcoxon two-sample test at each timepoint. We used SAS (version 9.4) for all analyses. The trial is registered with ClinicalTrials.gov, number NCT00294658.

Role of the funding source

The study funder contributed to development of the dual primary outcome throughout the review process, but had no role in study conduct; data collection, analysis, or

interpretation; or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

For MGTX, 6958 patients were assessed for eligibility, 6727 of whom did not meet the inclusion criteria, mainly because of duration of disease beyond 5 years (3129 [47%]), age limits (2842 [42%]), use of non-glucocorticoid immunosuppressives (1977 [29%]), and previous thymectomy or chest surgery (1901 [28%]; figure 1). Of the 231 patients eligible for inclusion, 126 (55%) were randomly assigned between July 26, 2006, and Nov 28, 2012, and 111 completed the 36-month assessment (figure 1; appendix). 68 (61%) of these 111 patients entered the extension study between Sept 1, 2009, and Aug 26, 2015, 33 in the prednisone alone group and 35 in the thymectomy plus prednisone group (figure 1). Three participants who had been randomly assigned to the thymectomy plus prednisone group refused thymectomy, and three randomly assigned to the prednisone alone group insisted on thymectomy, which was done before month 36 in two patients and after month 36 in one. 26 (74%) of the 35 patients in the thymectomy plus prednisone group and 24 (73%) of the 33 patients in the prednisone alone group completed the 60-month visit (figure 1). Patients who entered the extension study were more likely to be Hispanic and had more severe QMG scores at baseline of MGTX but lower MG-ADL scores and fewer treatment-associated complications at month 36 (ie, entry to the extension study) than those who did not participate in the extension study. Baseline characteristics were similar between groups in the extension study (table 1).

Patients in the thymectomy plus prednisone group had significantly improved time-weighted mean QMG scores from month 0 to month 60 compared with those in the prednisone alone group (5·47 [SD 3·87] *vs* 9·34 [5·08]; p=0·0007; figure 2; table 2). Similarly, the time-weighted mean alternate-day prednisone dose from month 0 to month 60 was significantly lower in the thymectomy plus prednisone group than in the prednisone alone group (24 mg [SD 21] *vs* 48 mg [29]; p=0·0002; figure 2; table 2). Prespecified subgroup analyses of the time-weighted mean QMG score by age at disease onset (ie, <40 years *vs* ≥40 years) showed that scores were significantly lower in the thymectomy plus prednisone group than in the prednisone alone group for both age groups (5·87 [SD 4·24] *vs* 9·53 [5·69], p=0·0213 for disease onset <40 years; 4·69 [3·05] *vs* 8·92 [3·53], p=0·0056 for disease onset ≥40 years). Likewise, in other prespecified subgroup analyses by sex, scores were significantly lower in the thymectomy plus prednisone group than in the prednisone alone group in both men and women (table 2). Time-weighted mean prednisone doses were also significantly lower in the thymectomy plus prednisone group than in the prednisone alone group for all subgroup analyses, except for the analysis in men only, in which doses did not differ significantly between groups (table 2). In patients who were naive to prednisone at initial entry into MGTX, time-weighted prednisone doses were significantly lower in the thymectomy plus prednisone group than in the prednisone alone group, but time-weighted mean QMG scores did not differ significantly between groups (table 2).

The time-weighted mean MG-ADL score was significantly lower in the thymectomy plus prednisone group than in the prednisone alone group for month 0 to month 48 (1·10 [SD 1·51] *vs* 2·55 [3·02]; p=0·0245) but not for month 0 to month 60 (table 3). The proportion of patients achieving MMS at month 60 was significantly higher in the thymectomy plus prednisone group (23 [88%] of 26 participants) than in the prednisone alone group (14 [58%] of 24 participants; estimated difference 30·1% [95% CI −53·4 to 6·9%; p=0·0236; table 3). From month 0 to month 60, the proportion of patients requiring azathioprine or intravenous immunoglobulin was also significantly lower in the thymectomy plus prednisone group than in the prednisone alone group (table 3). Use of plasma exchange did not differ significantly between groups at 60 months (table 3). Compared with patients in the prednisone alone group, patients in the thymectomy

	Prednisone group	Thymectomy plus prednisone group	Estimated difference (95% CI)	p value
Time-weighted mean alternate-day prednisone dose, mg	49·0 (29·2; 33)	25·9 (20·7; 35)	23·1 (10·9 to 35·2)	0·0003*
Penalised time-weighted mean alternate-day prednisone dose, mg				
Method 1†	66·2 (36·7; 33)	31·0 (31·8; 35)	35·2 (18·6 to 51·9)	<0·0001*
Method 2‡	60·6 (34·6; 33)	28·3 (27·9; 35)	32·3 (17·2 to 47·5)	<0·0001*
Time-weighted and time-specific mean Myasthenia Gravis Activities of Daily Living score§				
Month 0–60	3·26 (2·77; 32)	1·61 (1·46; 34)	1·65 (0·54 to 2·75)	0·0044*
Month 48	2·55 (3·02; 29)	1·10 (1·51; 31)	1·45 (0·20 to 2·71)	0·0245*
Month 60	2·04 (2·63; 24)	1·23 (1·75; 26)	0·81 (−0·48 to 2·07)	0·21*
Azathioprine use	19/33 (58%)	7/35 (20%)	37·6% (16·1 to 59·0%)	0·0014¶
Plasma exchange use	4/33 (12%)	5/35 (14%)	−2·1% (−18·2 to 13·9)	0·73¶
Intravenous immunoglobulin use	11/33 (33%)	3/35 (9%)	24·8% (6·2 to 43·3)	0·0162¶
Minimal Manifestation Status‖				
Month 48	15/29 (52%)	23/31 (74%)	−22·5% (−46·3 to 1·4)	0·07¶
Month 60	14/24 (58%)	23/26 (88%)	−30·1% (−53·4 to 6·9)	0·0236¶
MG-QOL15				
Month 39	13·1 (14·0; 32)	4·8 (9·2; 33)	8·2 (2·3 to 14·1)	0·0029**
Month 48	9·0 (10·1; 29)	4·9 (7·9; 30)	4·1 (0·6 to 8·8)	0·13**
Month 60	7·7 (9·24; 24)	7·8 (10·9; 26)	−0·1 (−5·9 to 5·6)	0·96**

Data are mean (SD; N) or n/N (%). MG-QOL15=Myasthenia Gravis Quality of Life questionnaire. *Calculated with the two-sample *t* test. †Penalised based on maximum dose before azathioprine. ‡Penalised based on dose at time of starting azathioprine. §Scores range from 0 to 3, with 0 corresponding to normal (ie, the patient does not experience that particular impairment of daily living) and higher scores indicating worse impairment of daily activities. ¶Calculated based on logistic regression. ‖p=0·03 based on the Cox model of modelling time to first Minimal Manifestation Status over the period 0–60 months. **p values were calculated with the Wilcoxon two-sample test but CIs were based on the difference in means.

Table 3: **Summary of secondary outcomes measures**

See Online for appendix

	Prednisone group (n=33)	Thymectomy plus prednisone group (n=35)
Number of events up to month 60*	37	29
Patients with one or more events up to month 60*	14 (42%)	12 (34%)
Classification		
Life threatening	5 (15%)	1 (3%)
Disability or incapacity†	0	6 (17%)
Required medical or surgical intervention	2 (6%)	5 (14%)
Death	0	0
Hospitalisation for all causes	16 (48%)	5 (14%)
Cumulative hospital days‡	29·2 (22·3)	26·0 (21·2)
Hospitalisation by MedDRA codes		
Gastrointestinal disorders	1 (3%)	1 (3%)
Hepatobiliary disorders	1 (3%)	0
Infections and infestations	2 (6%)	2 (6%)
Injury, poisoning, and procedure complications	0	1 (3%)
Metabolism and nutrition disorders	0	1 (3%)
Nervous system disorders	10 (30%)	3 (9%)
Respiratory, thoracic, and mediastinal disorders	2 (6%)	0
Surgical and medical procedures	2 (6%)	0
Vascular disorders	1 (3%)	0
Hospitalisation for exacerbation of myasthenia gravis		
Months 0–60	10 (30%)	2 (6%)
Cumulative hospital days‡	26·4 (22·9)	26·0 (21·2)

Data are n, n (%), or mean (SD). MedDRA=Medical Dictionary for Regulatory Activities. *As recorded by the treatment-associated complications survey. †Causes of disability or incapacity were worsening swallowing difficulties and myasthenia gravis in the prednisone group, and osteoporotic thoracic fracture, ocular muscle involvement due to relapsing myasthenia gravis, post-thymectomy diaphragmatic hemiparesis, rib fracture, impending myasthenic crisis, Pott's fracture, tear of left knee meniscus, and low back pain with possible stenosis in the thymectomy plus prednisone group. ‡Data are for patients who were hospitalised.

Table 4: **Adverse events**

plus prednisone group had significantly lower scores on MG-QOL15 at month 39 (4·8 [SD 9·2] *vs* 13·1 [14·0]; p=0·0029) but not at months 48 or 60 (table 3). Analyses including the prespecified penalties on prednisone dosing for initiation of azathioprine showed significantly lower time-weighted mean prednisone requirements from month 0 to month 60 in the thymectomy plus prednisone group than in the prednisone alone group, irrespective of whether the maximum prednisone dose before starting azathioprine (31·0 mg [SD 31·8] *vs* 66·2 mg [36·7]; p<0·0001) or the actual dose at the time of azathioprine initiation (28·3 mg [27·9] *vs* 60·6 mg [34·6]; p<0·0001) was used (table 3).

Cumulative days spent in hospital among participants who required hospitalisation for exacerbations of myasthenia gravis from month 0 to month 60 were similar between the two groups (table 4). Hospitalisations graded according to the Medical Dictionary for Regulatory Activities coding were of low frequency (≤6%) through month 60 for all disorder categories except for nervous system disorders, which primarily reflected exacerbations of myasthenia gravis (data not shown; table 4). Hospitalisations for nervous system disorders occurred in ten (30%) of 30 patients in the prednisone alone group compared with three (9%) of 35 patients in the thymectomy plus prednisone group (table 4). In the treatment-associated complications survey, we recorded 29 events in the thymectomy plus prednisone group and 37 in the prednisone alone group (table 4). These events were primarily related to complications of prednisone therapy (data not shown).

Between months 36 and 60, only four patients (two in each group) had an increase of 2 points or more in the QMG score (data not shown), the threshold widely accepted as indicative of clinical worsening.[14] No deaths occurred during the extension study.

Discussion

The MGTX extension study shows a continued benefit for thymectomy plus prednisone compared with prednisone alone on time-weighted mean QMG scores, a validated measure of clinical status, and reductions in time-weighted mean prednisone requirements for up to 5 years after thymic resection in patients with generalised non-thymomatous myasthenia gravis positive for acetylcholine receptor antibodies. The extension study reinforces the benefit of thymectomy noted in the randomised controlled MGTX,[4] shows continued benefits at 5 years, and dispels doubts about the procedure's benefits or the longevity of its effects.[2]

For the QMG score, either a 2-point or 3-point reduction (depending on the baseline score) has been established by a group at the University of Toronto as a minimal clinically important difference,[14] and a reduction of 2·3 points has been associated with clinical improvement by neurologists with expertise in myasthenia gravis.[15] In the extension study, the time-weighted mean QMG score was 3·87 points lower at 5 years in the thymectomy plus prednisone group than in the prednisone alone group, a larger estimated difference than that at 3 years in MGTX (2·85 points).[4] Likewise, the proportion of patients achieving MMS at 5 years was significantly higher in the thymectomy plus prednisone group than in the prednisone alone group (23 [88%] of 26 patients *vs* 14 [58%] of 24); the corresponding figures at 3 years for all patients in MGTX were 39 (67%) of 58 in the thymectomy plus prednisone group and 24 (47%) of 51 in the prednisone alone group. Based on the proportions achieving MMS, it is reasonable to conclude that benefits conferred by thymectomy persist beyond a 3-year window and could even increase during the subsequent 2 years. Beyond clinical outcomes, both patient populations needed less prednisone to maintain MMS during the 2-year extension study. In the thymectomy plus prednisone group, the mean prednisone dose fell to 11·9 mg at month 60—a dosing level of roughly 5 mg per day or lower, which was associated with quality-of-life metrics similar to those in patients who were in complete stable remission and off all therapy in a Japanese multicentre study.[16] A prednisolone dosing level of 5 mg a day or less has been adopted by

Japanese experts as a goal of therapy in their national guideline for myasthenia gravis.[17,18]

Several studies[19–21] have focused on long-term outcomes of treatments for patients with myasthenia gravis and on which management strategies might better control disease over time if used early in the disease course. Although full remission after treatment is uncommon,[19] two large-scale retrospective studies have shown that outcomes in patients with myasthenia gravis have improved substantially during the past 50 years,[20] and that 95% of patients have either no weakness, purely ocular weakness, or only mild generalised weakness after several years of treatment.[21] These studies did not include formally defined outcome categories such as MMS, as was used in MGTX and its extension study.

An international panel of experts convened by the Myasthenia Gravis Foundation of America produced treatment guidelines in 2016, in which the goal of management of myasthenia gravis is achievement of MMS or remission with no greater than mild adverse events.[8] Several retrospective studies have tracked the achievement of MMS or better in varied myasthenia gravis subpopulations treated with a wide range of therapies, including thymectomy. In a retrospective survey[22] across Japan, an aggressive treatment strategy in the first month after diagnosis that incorporated plasma exchange, intravenous immunoglobulin, or methylprednisolone individually or in combination resulted in persistent MMS or better at a mean of 6 years in 123 (49%) of 249 patients who were taking prednisolone at doses of 5 mg per day or less. Of 439 patients treated less aggressively with oral corticosteroids, 185 (42%) also achieved MMS, but over a mean of 11 years.[22] In a retrospective single-centre study,[23] MMS or better outcomes were achieved in 60 (81%) of 74 patients with myasthenia gravis at a mean follow-up of 6 years who were given conventional treatments including thymectomy, pyridostigimine, prednisone, mycophenolate mofetil, azathioprine, and ciclosporin. Similarly, in a retrospective study[24] of 268 patients with myasthenia gravis given a range of treaments (often in combination), MMS or better, with no more than mild side-effects, was reported in 155 (73%) of 213 patients with complete data at 5 years and 87 (75%) of 116 at 10 years. Of the many demographic and therapeutic variables tested, only disease onset after 50 years and thymectomy were predictive of achieving MMS or better at 10 years.[24] All the studies described here included a full range of patients, with variable antibody statuses and even thymoma. The proportion of patients who underwent thymectomy ranged from 20%[23] to 49%,[22] and thymectomy was clearly recommended as part of management in only one of the retrospective studies.[24] Compared with MGTX, therapeutic options were not strictly defined in these studies, with various immunosuppressives used. Still, the proportion of patients in the MGTX extension study who achieved a desired outcome (ie, MMS or better) compares favourably with that in those studies.

The extension study had several limitations, and caution is needed in predicting such a high likelihood of favourable outcome for all patients with myasthenia gravis who undergo thymectomy. The extension study included 68 (61%) of 111 patients who completed the 36-month MGTX trial, and only 50 (45%) reached the month 60 assessment, which raises some concerns about generalisability of the favourable outcomes to a larger myasthenia gravis population. Compared with the entire MGTX population, the extension study cohort at 36 months had lower MG-ADL scores and fewer treatment-associated complications, which could be predictive of a better outcome at month 60 (appendix). The possibility that the extension study overestimates the benefit of thymectomy is akin to other long-term observations, because patients who are less responsive to, or tolerant of, study interventions might drop out over time. Although MG-ADL scores at 36 months were lower in patients in the extension study than in those who did not participate, absolute mean scores were very low in both populations, with the difference amounting to slightly more than 1 point on the 24-point scale. Although we cannot exclude the possibility that the patients enrolled in the extension study would have had better outcomes than those in the MGTX trial who did not participate, medication requirements and most outcome measures were similar for the two populations at month 36. Therefore, we think the extension study enrolment was generally representative of the entire MGTX cohort.

Hospital data show a substantial reduction in myasthenia-gravis-related admissions for thymectomy after 2000.[25] This reduction in admissions is probably related to increased use of intravenous immunoglobulin and other pharmacological approaches, in addition to the questions that surrounded the true effects of thymectomy. The results of the MGTX extension study provide further evidence for the positive effect of thymectomy in patients with generalised non-thymomatous myasthenia gravis who are positive for acetylcholine receptor antibodies, the largest subpopulation of patients with the disease.[19] This benefit from thymectomy persists for 5 years and extends beyond clinical status alone to include substantial reductions in prednisone requirements and hospital admissions for disease exacerbations. Our results should lead to revision of clinical guidelines in favour of thymectomy and could potentially reverse downward trends in the use of thymectomy in overall management of myasthenia gravis.

Contributors

GIW wrote the Article, finalised all figures and tables, did the literature search, and assisted with data interpretation. GM, AM, PS, JO, JGC, JMH, AE, WN, EC, GA, RW, JOK, SRB, CHC, ACB, AAA, AIS, BK, BRFL, CB, AV, ED-T, HY, MW-C, MTP, MHR, AK-P, RMP, CEJ, JJGMV, JMM, JTK, LCW, MB, RJB, RT, TM, NJS, RC, and JRS reviewed the Article and made critical suggestions; GIW then revised the paper in line with these comments. HJK and GRC critically reviewed the Article, made important suggestions to improve it, and assisted with data interpretation. IBA did the data analysis, created the figures and tables, and made important suggestions to improve the Article. H-CK assisted

with data analysis and reviewed the Article. All authors who are not deceased approved the submitted Article.

Declaration of interests

GIW, HJK, IBA, GM, H-CK, AM, PS, JO, JGC, JMH, AE, WN, EC, GA, RW, JOK, SRB, CHC, ACB, AAA, AIS, BK, BRFL, CB, AV, ED-T, HY, MW-C, MTP, MHR, AK-P, RMP, CEJ, JJGMV, JMM, JTK, LCW, MB, RJB, RT, TM, NJS, RC, JRS, and GRC report grants from the US National Institutes of Health National Institute of Neurological Disorders and Stroke, the Muscular Dystrophy Association, and the Myasthenia Gravis Foundation of America. GIW reports personal fees from Grifols, Shire, and Alexion Pharmaceuticals, and grants from CSL-Behring and ArgenX. AE reports personal fees from Grifols. MTP reports personal fees from Grifols and CSL-Behring. JJGMV reports grants from Myasterix (project ID 602420) and Princes Beatrix Fonds. JMM reports paid consultancy for QuatroBio. MB reports per-patient reimbursement from UCB Pharma, Alexion Pharmaceuticals, and the National Institute of Neurological Disorders and Stroke for the NeuroNEXT 103 trial, and personal fees from Ra Pharmaceuticals. GRC has served on data and safety monitoring boards for AMO Pharmaceuticals, Biolinerx, Horizon Pharmaceuticals, Merck, Pfizer, Opko Biologics, Neurim, Orphazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos, Celgene, and Teva; protocol review committees for the National Heart, Lung, and Blood Institute; and the Obstetric-Fetal Pharmacology Research Unit oversight committee for the Eunice Kennedy Shriver National Institute of Child Health and Human Development. GRC also reports consultancy or advisory board activity for Atara Biotherapeutics, Axon, Biogen, Biotherapeutics, Argenix, Brainstorm Cell Therapeutics, Charleston Labs, Click Therapeutics, Genzyme, Genentech, GW Pharma, Klein-Buendel Incorporated, Medimmune, Medday, Novartis, Roche, Scifluor, Somahlution, Teva, TG Therapeutics, and UT Houston.

Data sharing

The MGTX investigators have established a policy for data sharing. Researchers wishing to access the data collected in the MGTX extension study should contact the corresponding author.

Acknowledgments

The MGTX extension study was partly supported by Clinical and Translational Science Award grants from the National Center for Advancing Translational Sciences of the US National Institutes of Health awarded to the University of Alabama at Birmingham (UL1TR001417; Birmingham, AL, USA), the University of Kansas Medical Centre for Frontiers: the Heartland Institute for Clinical and Translational Research (UL1TR000001; Kansas City, KS, USA), the University at Buffalo State University of New York (UL1TR001412; Buffalo, NY, USA), and the University of Texas Health Science Center at San Antonio (UL1TR001120 and 8UL1TR000149 [from the National Centre for Research Resources and National Center for Advancing Translational Sciences]; San Antonio, TX, USA). The Muscular Dystrophy Association and Myasthenia Gravis Foundation of America provided support for initial planning of the MGTX trial. We acknowledge the efforts and valuable input provided by the MGTX data safety monitoring board members: Steven Keller (Chairman), Alan Dyer, Donald Schotland, John Winer, and Peter Gilbert. The contents of this Article are solely the responsibility of the authors and do not necessarily represent the views of the National Institutes of Health or the National Center for Advancing Translational Sciences.

References

1 Blalock A, Harvey AM, Ford FR, Lilienthal JL. The treatment of myasthenia gravis by removal of the thymus gland. *JAMA* 1941; **117:** 1529–33.

2 Gronseth GS, Barohn RJ. Thymectomy for non-thymomatous autoimmune myasthenia gravis (an evidence-based review). *Neurology* 2000; **55:** 7–15.

3 Cea G, Benatar M, Verdugo RJ, Salinas RA. Thymectomy for non-thymomatous myasthenia gravis. *Cochrane Database Syst Rev* 2013; **10:** CD008111.

4 Wolfe GI, Kaminski HJ, Aban IB, et al. Randomised trial of thymectomy in myasthenia gravis. *N Engl J Med* 2016; **376:** 511–22.

5 Oosterhuis HJ. Observations of the natural history of myasthenia gravis and the effect of thymectomy. *Ann NY Acad Sci* 1981; **377:** 678–90.

6 Rodriguez M, Gomez MR, Howard FM, Taylor WF. Myasthenia gravis in children: long-term follow-up. *Ann Neurol* 1983; **13:** 504–10.

7 Jaretzki III A, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. *Neurology* 2000; **55:** 16–23.

8 Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for the management of myasthenia gravis. *Neurology* 2016; **87:** 419–25.

9 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:** 769–72.

10 Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology* 1999; **52:** 1487–89.

11 Burns TM, Conaway MR, Cutter GR, Sanders DB, Muscle Study Group. Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. *Muscle Nerve* 2008; **38:** 957–63.

12 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:** 315–25.

13 Palace J, Newsom-Davis J, Lecky B. A randomised double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. *Neurology* 1998; **50:** 1778–83.

14 Katzberg HD, Barnett C, Merkies ISJ, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomised trial. *Muscle Nerve* 2014; **49:** 661–65.

15 Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. Quantitative myasthenia gravis score: assessment of responsiveness and longitudinal validity. *Neurology* 2005; **64:** 1968–70.

16 Masuda M, Utsugisawa K, Suzuki S, et al. The MG-QOL15 Japanese version: validation and associations with clinical factors. *Muscle Nerve* 2012; **46:** 166–73.

17 Utsugisawa K, Suzuki S, Nagane Y, et al. Health-related quality-of-life and treatment targets in myasthenia gravis. *Muscle Nerve* 2014; **50:** 493–500.

18 Murai H. Japanese clinical guidelines for myasthenia gravis: putting into practice. *Clin Exp Neuroimmunol* 2015; **6:** 21–31.

19 Gilhus NE. Myasthenia gravis. *N Engl J Med* 2016; **375:** 2570–81.

20 Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008; **37:** 141–49.

21 Kawaguchi N, Kuwabara S, Nemoto Y, et al. Treatment and outcome of myasthenia gravis: retrospective multi-centre analysis of 470 Japanese patients, 1999–2000. *J Neurol Sci* 2004; **224:** 43–47.

22 Utsugisawa K, Nagane Y, Akaishi T, et al. Early fast-acting treatment strategy against generalised myasthenia gravis. *Muscle Nerve* 2017; **55:** 794–801.

23 Salins S, Teter B, Kavak K, Wolfe GI, Silvestri NJ. Low-dose medication and long-term outcome in myasthenia gravis. *J Clin Neuromusc Dis* 2016; **18:** 61–66.

24 Andersen JB, Gilhus NE, Sanders DB. Factors affecting outcome in myasthenia gravis. *Muscle Nerve* 2016; **54:** 1041–49.

25 Alshekhlee A, Miles JD, Katirji B, Preston D, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. *Neurology* 2009; **72:** 1548–54.