Commentary

A crucial first randomized controlled trial of thymectomy in non-thymomatous myasthenia gravis

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The much awaited results of a randomized trial of thymectomy in myasthenia gravis (MG) were published in the August 11, 2016 edition of *New England Journal of Medicine* by Wolfe *et al*. on behalf of the "Thymectomy trial in non-thymomatous myasthenia gravis patients receiving prednisone therapy" (MGTX) study group (1). This landmark publication stands as the only controlled randomized thymectomy trial, hoping to end a 75-year-old controversy.

In 1939, Alfred Blalock (2) published a case report on the successful outcome of surgery in MG with thymoma and 5 years later, he extended this observation to non-thymomatous cases (3). In 1966, a large series from the Mount Sinai and Massachusetts General Hospital which described the management of 1,355 MG patients, included 188 non-thymomatous cases treated with thymectomy (4). A striking benefit was reported in the subset of 156 female patients, with total remission without relapse in 38% and improvement in a further 51%. This paper had a lasting impact on medical practice, establishing a practice bias in favor of thymectomy in females less than 40 years with moderate to severe generalized non-thymomatous MG.

In parallel, the rationale for thymectomy in acetylcholine receptor autoantibody (AChRA)-positive MG was bolstered by many lines of evidence suggesting that the thymus likely plays a pivotal immunopathogenic role. Three major subsets of AChRA-positive patients can be distinguished: early onset with thymic lymphofollicular hyperplasia, thymoma-associated, and late onset with thymic atrophy. These subgroups can be delineated based on age and sex distribution, human leukocyte antigen (HLA) association, presence of myoid cells, expression of the autoimmune regulator gene, TNFα homozygosity, and the presence of additional autoantibodies directed against striated muscle, ryanodine receptors or titin (5).

There have been several controlled randomized trials in the medical management of MG, showing positive results for cyclosporine, plasma exchange, pulse methylprednisolone, azathioprine added to prednisone, IVIg and tacrolimus (6), and notably, negative results for mycophenolate (7,8). Some negative trials were clearly underpowered, for example and ironically, an early controlled trial showing no benefit of prednisone 100 mg every other day compared to placebo, which included only 13 patients (9). Controlled trials of oral immunosuppressive agents could be expected to be less challenging to conduct than trials on thymectomy from several points of view: familiarity of potential patient recruits with the rationale for such medications, relatively rapid onset of action, generally favorable short-term side-effect profile, availability of pharmaceutical funding in some cases, and the relative ease of both administration and double-blinding.

Much of the published literature on thymectomy has consisted of non-randomized observational or case-control studies, often relying on remission rates using the Kaplan-Meier method of life table analysis (10). The interpretation of this data is clouded by the lack of reliable information about the rate of spontaneous remission, which is an intrinsic feature of the natural history of MG. Nonetheless, remission rates were arguably the most reliably chosen endpoint, at a time when objectively quantified and reproducible scale of disease severity such as the Quantitative MG (QMG) score had not been

designed and validated in large MG cohorts (11). Results of thymectomy trials have varied substantially in many crucial data elements: duration and severity of baseline MG, choice and intensity of concurrent immunosuppressive therapy, completeness and duration of post-surgical follow-up, inclusion of thymoma cases, failure to report relapses or re-operations. Moreover, these studies have reported on different surgical techniques, including transcervical, unilateral of bilateral videoscopic, infrasternal, standard or extended transsternal thymectomy.

Gronseth and Barohn (12) published an evidence based review of thymectomy for patients with non-thymomatous MG, on behalf of the American Academy of Neurology in 2000. They identified 27 studies where outcome measurements were compared between the operated and medically treated patients. Patients subjected to thymectomy were more often female, with more severe generalized MG. The aggregate analysis did appear to favor thymectomy in several respects: 1.6 times higher rate of asymptomatic status, 1.7 higher rate of improvement, and 2.1 higher rate of medication-free remission. There were numerous methodologic inconsistencies that confounded the interpretation of the data. The practice parameter stated that "thymectomy is recommended as an option to increase the probability of remission or improvement" (class II: evidence provided by well-designed observational studies with concurrent controls e.g., case-control and cohort studies). This practice parameter was reaffirmed in 2014, judging that more recent literature would not alter the conclusions. A 2013 Cochrane review similarly concluded that there no published randomized controlled trials on this topic (13).

The MGTX study group was thus tasked with designing a trial that might provide the first class I level of evidence on thymectomy in non-thymomatous MG (1). Recruitment was expected to be challenging as the majority of MG experts in the medical and surgical community were not in equipoise regarding the benefit of thymectomy. Indeed, the study supplementary appendix reported that in a survey of 133 MGTX study investigators 77 had predicted that the outcome would favor the use of thymectomy, 27 felt the outcome would not and 29 stated they really could not offer a prediction. Additionally, there were concerns about the relatively long duration high dose prednisone protocol in both arms of the study.

The MGTX randomization period spanned 6 years [2006–2012], and complete results were available for analysis 3 years later, following the prescribed 36 months assessment protocol. The original inclusion criteria were: duration of MG of less than 3 years, age range of 18–60 years, elevated serum AChRA level, and a MG Foundation of America (MGFA) clinical classification of II to IV. Thus study participants had mild to severe generalized MG (class II–IV). Patients were excluded if they had purely ocular manifestations (class I) or critically severe disease requiring intubation (class V). Patients in both arms of the trial were started on prednisone at the time of randomization with an incremental alternate-day regimen starting at 10 mg and increasing to 100 mg, or to 1.5 mg/kg, whichever was the lesser amount. The prednisone administration was targeted to achieve a "minimal-manifestation status" where patients reported no significant symptoms or functional limitations from myasthenia, even though there could be residual weakness detected on examination of some muscles. The alternate prednisone dose was then slowly tapered the lowest level required to maintain minimal-manifestation status. Azathioprine was allowed for patients with unacceptable steroid side effects or failing to achieve minimal manifestation status on prednisone alone at 12 months. Because sham sternotomy was felt to be neither ethical nor feasible, this trial was single blinded. Thymectomy was performed within 30 days of randomization by means of an extended median sternotomy approach. The aim was complete resection of all mediastinal tissue that could anatomically contain gross or microscopic thymus. The operative report had to provide information about the extent of thymic tissue into pericardial, vena caval, diaphragmatic and cervical regions. Neither the main article nor the supplementary appendix provides data about the observed frequency of ectopic thymic tissue in locations such as the perithymic and pericardial fields.

Recruitment into the trial indeed proved challenging, despite changes to eligibility criteria 2 years after the original enrollment date, which increased the allowed disease duration from 3 to 5 years, and extended the upper age limit from 60 to 65 years. Only 36 of 67 participating centers successfully recruited patients. A total of 6,958 persons were screened, yielding only 231 eligible patients. Of the 105 eligible patients who declined to partake, the majority justified their refusal by a concern about either undergoing [45] or being denied [22] thymectomy. The 126 study participants were randomized to prednisone alone (N=60) and thymectomy plus prednisone (N=66). The two arms were well matched at baseline with regard to sex, age, prednisone use at baseline, MGFA class and QMG score. The MGTX trial showed a statistically significant benefit

at 3 years favoring thymectomy for both primary outcomes: a 2.85 absolute reduction in the average QMG score and a lower average alternate-day prednisone requirement (44 *vs*. 60 mg in the prednisone only group). The reduction in QMG score was likely meaningful, as a reduction of 2.3 points was previously found to be reflective of clinical improvement by neurologists assessing the longitudinal validity of this scale (11). Secondary outcome measures provided additional supportive evidence. There were fewer hospitalizations for MG exacerbation, as well as a reduced cumulative number of hospital days in the thymectomy group. Only one of 66 patients had a complication attributed to thymectomy.

The MGTX trial will stand as the landmark proof-of-concept randomized clinical trial supporting thymectomy in non-thymomatous MG. It must be emphasized that the study population was limited to patients with mild to severe generalized MG, of relatively recent onset, concurrently treated with prolonged high dose steroids. The surgical procedure was an extended transsternal thymectomy performed by highly skilled surgeons, with an extremely low operative morbidity. Whether a less invasive surgical approach, such as transcervical or thoracoscopic thymectomy can offer the same benefit will require additional randomized controlled investigation. The MGTX trial did not include ocular or AChRA-negative patients. It has also been commented that the relative benefit conferred by thymectomy in this trial may become less prominent over time: the remission remained stable at 67% in the surgical group but increased from 37% at year 1 to 47% at year 3 in the prednisone-only group (14). The MGTX trial was not primarily powered or designed to assess the response of thymectomy based on duration of illness or sex. The subgroup analyses did however suggest that thymectomy was not associated with an improved QMG score in males and did not lead to a significant reduction of prednisone use in patients with an age of MG onset greater than 40 years.

There have been great strides in the understanding of the pathogenesis of the different subtypes of non-thymomatous MG, leading to increasingly effective and targeted immunotherapy. Chimeric monoclonal antibodies directed against B-cells such as rituximab, offer great promise, particularly for anti-MUSK MG (15). Immunoglobulin infusions may play an increasing role as a costly but low morbidity intervention for both crisis and chronic therapy (16). For severe disease refractory to conventional therapy, autologous stem cell therapy may offer rescue therapy (17). In this changing environment, thymectomy is likely to remain an important therapeutic option, and the MGTX trial provides much awaited high-quality validation of its benefit.

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Footnote

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