Randomized Trial of Thymectomy in Myasthenia Gravis

NEJM 2016 August 11; 375 (6): 511-522

At the time of this trial, prior studies had shown a potential benefit of thymectomy (vs. medical mgmt. alone) in nonthymomatous myasthenia gravis (MG). However, conclusive data regarding the true benefit of thymectomy, as well as the clinical characteristics of patients who might benefit most from thymectomy, remained lacking. Given the risks and adverse side effects inherent to prolonged steroid use (i.e., standard of care) for MG, more definitive data regarding the benefit of thymectomy was, therefore, indicated, at least for the purpose of potentially limiting chronic steroid exposure. For this reason, the goal of this study was to compare the efficacy (over a 3yr period) of thymectomy + standard prednisone therapy vs. standard prednisone therapy alone in non-thymomatous MG.

Experimental design and statistics: This study was a multicenter, international, rater-blinded, randomized trial conducted from 2006 to 2012. Inclusion criteria included MG duration of <5yrs, age 18-65yrs, an AchR Ab lvl of >1.00 nmol/L, and an MG classification score of II – IV.[1] Participants could be on prednisone +/- acetylcholinesterase therapy. Exclusion criteria included presence of a thymoma, use of immunotherapy other than prednisone, prior thymectomy, and others.[2] Eligible patients were randomized 1:1 to receive thymectomy + a standard prednisone protocol OR standard prednisone alone. Thymectomy was performed via a median sternotomy and resection by trained thoracic surgeons, and prednisone was given on an alternate day schedule, with 10mg increases every other day until patients achieved "minimal-manifestation status" or no functional limitations due to their MG (max allowed dose: 100 – 120mg daily). Once minimal-manifestation status was achieved, a prednisone taper followed, as long as patients maintained a minimal-manifestation status. Pyridostigmine dosing could not exceed 240mg daily during tapering, IVIG/PLEX were permitted only if patients were unstable, and azathioprine could be started if patients did not achieve minimal-manifestation status by 12 mos. Patients were followed thereafter by Neurologists aware of treatment groups and an evaluator blinded to treatment groups. The primary outcomes included both the average Quantitative MG score (range: 0-39, high scores = worse function) and the average required dose of prednisone over a 3yr period. Secondary outcomes included quality of life surveys related to treatment, the MG ADL score and proportions of patients who achieved minimal-manifestation status and who used other forms of immunotherapy. Statistically, data were analyzed via superiority analyses and Student's t-tests.

Results: A total of 6958 patients across 67 centers, internationally, underwent screening, of which 231 met inclusion/exclusion criteria. Of these patients, 126 were willing to participate and underwent randomization. Baseline characteristics between both treatment groups were similar (**Table 1**). In terms of primary outcomes, average Quantitative MG scores over 3yrs were significantly lower in the thymectomy vs. prednisone-alone group (avg score difference of 2.85 pts, $p < 0.001$) as was the average, alternate-day prednisone dose in the thymectomy vs. prednisone-alone group (32mg vs. 54mg, $p < 0.001$; **Fig 1 and Table 2**). Subgroup analyses (prior steroid use, sex, age, age of disease onset) yielded some differences in primary outcomes (Table 2[3]) though no significant interactions. In terms of secondary outcomes, treatment-associated effects over 3yrs were lower in the thymectomy group, and the thymectomy group had both fewer hospitalizations (9% vs. 37%) and fewer hospital days than the

[1] Class I: ocular weakness only; Class II: mild generalized; Class III: moderate generalized; Class IV: severe generalized; Class V: requiring intubation.

[2] Other exclusion criteria: pregnancy, contraindication to steroids, substantial medical illness

[3] In men and in patients with prior prednisone use pre-trial, Quantitative MG scores did not differ between treatment groups

prednisone-alone group (8.4 vs. 19.2 days). Finally, MG ADL scores also favored the thymectomy group, requirements for azathioprine were lower in the thymectomy group, and the overall % of patients who achieved a minimal-manifestation status by 3yrs was higher in the thymectomy group.

Conclusions: Overall, data from this trial supported the use of thymectomy (with standard prednisone therapy) in nonthymomatous MG, as thymectomy both improved clinical outcomes and reduced cumulative prednisone exposure over 3yrs. This additionally provided support for a role of the thymus in MG disease pathogenesis. The authors note that the trans-sternal approach for thymectomy used here is more invasive, though less invasive techniques may not sufficiently remove all thymic tissue; further data comparing different techniques is warranted. Finally, the authors did highlight the lack of a sham thymectomy procedure as a main limitation to the trial, though a sham procedure was deemed unethical by the study authors. Regardless, data from this trial confirmed the efficacy of thymectomy in non-thymomatous MG, and thymectomy is now considered in the appropriate patient population[4].

Summary created by Elaine Sinclair, D.O.

[4] Based on a patient's antibody-type, age, and type of MG (ocular vs. generalized)