Editorial Commentary

MGTX extension study longitudinally favors early thymectomy in non-thymomatous young-adult patients with AChR antibody-positive myasthenia gravis

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Introduction

Subclass classification and thymic pathology of myasthenia gravis (MG)

MG is an autoimmune neuromuscular disease that presents weakness of the skeletal muscles. The disease is caused by disturbed neuromuscular transmission mediated by autoantibodies (Ab) against acetylcholine receptors (AChR) or other proteins, such as muscle-specific receptor tyrosine kinase (MuSK) (1). Disturbance of synaptic proteins results in fluctuating muscle weakness with easy fatigability. There are various subclass classifications of MG based on demographic (e.g., age of onset), clinical (e.g., ocular or generalized) and pathophysiological (e.g., Ab specificity and thymic pathology) findings (2,3). They distinguish patients with only ocular symptoms from those with generalized symptoms, and patients with and without serum AChR-Abs. Gilhus *et al.* proposed classifying AChR-Ab-positive (AChR-Ab+) generalized MG (gMG) patients into thymoma-associated gMG, early-onset (non-thymomatous) gMG (EOMG) and late-onset (non-thymomatous) gMG (LOMG) (2), while Akaishi *et al.* proposed classification of AChR-Ab+ gMG patients into thymoma-associated gMG, gMG with thymic hyperplasia and gMG without thymic abnormalities using two-step cluster analyses (3). Both classifications classify AChR-Ab+ gMG patients into basically the same populations. The borderline of onset age between EOMG and LOMG or between gMG with thymic hyperplasia and that without thymic abnormalities is reportedly approximately 50 years (2,3), and there seems to be a worldwide consensus about a cut-off of 50 years in clinical settings (2,4).

Autoreactive T cells specific for AChRs are generated in the thymus via non-tolerogenic thymopoiesis by an aberrant function of thymic epithelial cells. However, generation of these AChR-specific T cells is not necessarily the cause of MG, because these cells are also found in healthy individuals (5,6). The pathogenetic step in MG involves activation of potentially AChR-specific T and B cells (6-9); since this type of an activation system is required to develop and maintain the disease, it is a therapeutic target (7,8). Intra-thymic activation of the pathogenesis of MG, which is the therapeutic target of thymectomy, is probably limited to particular types of MG: MG with thymic lymphofollicular hyperplasia is almost the same population as EOMG and a small part of thymoma-associated MG (4,7,8,10). Onset of MG after removal of thymoma is also known, suggesting the probability of a trigger for activation of MG pathogenesis outside the thymus.

Current treatment options against AChR-Ab+ gMG

Treatment options for AChR-Ab+ gMG are of three types: oral medications, non-oral fast-acting therapies, and surgical thymectomy performed under general anesthesia. Oral medications include pyridostigmine, corticosteroids and non-steroid immunosuppressants, such as azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide, etc. (11). Conventional non-oral fast-acting therapies, such as intravenous immunoglobulins, plasmapheresis and high-dose intravenous methylprednisolone, were formerly performed mainly for acute exacerbations, but are now used more aggressively and routinely to quickly achieve sufficient control of the symptoms with sparing oral drugs for long-term use or to maintain once improved disease status (11,12). Recently, it was reported that combined treatment with low-dose oral medications and aggressive non-oral fast-acting therapies from the early stages of treatment enable ≥60% of gMG patients to live a normal lifestyle without worrying about both MG symptoms and complications from oral steroids within 5 years into treatment (13). Furthermore, molecular target therapies have been and continue to be developed for refractory gMG patients (2,4).

Surgical thymectomy is obviously the treatment of choice for removal of tumors in patients with thymoma-associated MG, regardless of the effects against MG. Since the first report of thymectomy against non-thymomatous MG 80 years ago (14), there have been many retrospective studies that reported benefits of thymectomy in patients with non-thymomatous MG. However, the effects varied widely, and it was also shown in some reports that there was no difference in remission rate between thymectomy and medical management (15,16). The possibility that the benefits of thymectomy were negligible as compared to the efficacy of modern immunotherapeutic approaches was also reported (17). Until publication of the results of the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) study (18), the efficacy of thymectomy for non-thymomatous MG had not been conclusively shown. However, it was widely believed that thymectomy has beneficial effects in the early stages of AChR-Ab+ gMG with thymic hyperplasia (i.e., almost the same patient population as EOMG) (2,4,7,8). At the same time, it is well known that even after thymectomy, serum AChR-Ab titers either do not show negative conversion, remain positive but are decreased, or do not decrease, the effect varying in individual cases.

MGTX and MGTX extension studies

The MGTX study, first reported in 2016, was an international, randomized, rater-blinded 3-year prospective study enrolling a total of 126 patients with non-thymomatous AChR-Ab+ gMG (18). The enrolled patients were randomly assigned to either the thymectomy plus prednisone group (thymectomy group: n=66) or oral prednisone alone group (prednisone group: n=60). Only a small fraction of AChR-Ab+ gMG patients above 50 years old (i.e., almost the same age as LOMG patients) were enrolled. The age at enrollment was young [median 33 years (range, 18–64 years) in the thymectomy group and 32 years (range, 18–63 years) in the prednisone group], and disease duration before enrollment was short [1.14 (0.15–4.38) years in the thymectomy group and 1.08 (0.02–4.41) years in the prednisone group]. Around 70% of the enrolled patients were female.

Among the 126 enrolled patients, 111 patients completed the 36-month follow-up (n=60 in the thymectomy group *vs.* n=51 in the prednisone group). The results showed that the primary endpoints, time-weighted average of the Quantitative Myasthenia Gravis (QMG) score (6.15±4.09 *vs.* 8.99±4.93, P<0.001) and time-weighted average of alternate-day prednisone dose (32±23 *vs.* 54±29 mg, P<0.001) both favored the thymectomy group over the 3-year follow-up period. The percentage of patients who achieved minimal-manifestation status (MMS) at month 36 also favored the thymectomy group (67% *vs.* 47%). The study also performed subgroup analyses for the primary endpoints by onset age (i.e., <40 or ≥40 years), which revealed favorable results for thymectomy in both onset age groups, although the significance level was much lower in the group with onset age ≥40 years than onset age <40 years. To be noted here, additional subgroup analyses for subgroups with onset ages ≥50 years and <50 years were also shown in the supplementary data table, which showed no difference in endpoints between thymectomized and non-thymectomized groups of patients with onset age ≥50 years (i.e., LOMG) (P=0.67) due to both the small number of patients (n=9 in the thymectomy group *vs.* n=8 in the prednisone group) and actually small differences between the two groups (e.g., 6.39±2.79 *vs.* 5.74±3.21 in time-weighted average QMG). The MGTX study was an honorable breakthrough study, clearly concluding that early thymectomy has some benefit for non-thymomatous young-adult patients with AChR-Ab+ gMG (i.e., EOMG). However, the efficacy of thymectomy for LOMG with onset age ≥50 years was not shown, and hence, is still controversial.

The MGTX extension study was reported in 2019 (19). Among the 111 patients who completed the preceding 3-year MGTX study, 68 (68/111=61%) patients agreed to participate in the further 2-year extension study (totally 5 years) (thymectomy group: n=35, prednisone group: n=33). Among them, only 50 (50/111=45%) patients eventually completed the 60-month visit (n=26 *vs.* n=24). Since patients who are less responsive to, or tolerant of, study intervention might drop out over time, the possibility that the extension study somewhat overestimated the benefit of thymectomy could not be completely excluded (19). The results showed that both the primary endpoints (i.e., time-weighted mean of QMG score and alternate-day prednisone dose) still favored the thymectomy group compared with the prednisone group even over the extended period of 36–60 months (P<0.001 for both primary endpoints). It was observed that the difference in time-weighted mean of QMG score between the two groups was greater at 5 years in the extension study than that observed at 3 years in the preceding MGTX study; however, Figure 2 (19) showing data limited to the extension study cohort shows that the difference was smaller at 5 years than at 3 years. For some reason, statistical analyses of the differences in the two primary endpoints were performed for the 68 enrolled patients and not for the 50 patients who completed the study. Subgroup analyses after dividing the subjects into those with onset age <40 years and ≥40 years revealed that both the primary endpoints favored the thymectomy group in both subpopulations. Subgroup analyses after dividing the subjects based on the onset age of 50 years, which is equivalent to EOMG *vs.* LOMG, were not reported in the extension study. It seems that there were only a few patients enrolled in the extension study with the onset age ≥50 years, because the median and interquartile ranges (IQR) of the enrolled patients were much lower than 50 years [median age (IQR): 32.0 years (22.0–41.0 years) in the thymectomy group and 33.0 years (25.0–43.0 years) in the prednisone group]. The scores of MG-ADL and MG-QOL15 at month 60 were not different between the two groups (P=0.21 and P=0.96, respectively). Based on these results, positive effects of early thymectomy mainly for non-thymomatous EOMG persisted over the extended period of months 36–60 from the initial random treatment group assignment.

The MGTX and MGTX extension studies were historical and noteworthy as they focused on the long unsolved and controversial issue of whether or not thymectomy is beneficial in non-thymomatous AChR-Ab+ gMG patients, and scientifically concluded the efficacy of thymectomy with a randomized cohort study. The fact that early thymectomy has some benefits in non-thymomatous young-adult patients with AChR-Ab+ gMG (EOMG) is indisputable, and this fact is not likely to change in future. On the other hand, when adapting these results clinically for patients, some caution is required. First, before selecting surgical thymectomy, which is invasive therapy under general anesthesia, patients should be well informed about the many other modern therapeutic options (particularly in developed countries with sufficient medical resources), as well as the possible adverse events related to surgery. Also, patients should be informed of the fact that thymectomy cannot increase the rate of full remission. Second, as the efficacy of thymectomy for LOMG with onset age ≥50 years was not shown and is still controversial, the indications for thymectomy in such patients should be carefully considered.

In conclusion, following MGTX and its extension studies, surgical thymectomy against non-thymomatous MG has once again gained attention and will survive as one of the therapeutic options for young-adult patients with early-stage AChR-Ab+ gMG.

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Footnote

Conflicts of interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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