Editorial

Thymectomy for myasthenia gravis: what's next?

Marc de Perrot, Laura Donahoe

Division of Thoracic Surgery, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada

Correspondence to: Marc de Perrot, MD, MSc. Division of Thoracic Surgery, Toronto General Hospital, 9N-961, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada. Email: marc.deperrot@uhn.ca.

Provenance: This is an invited Editorial commissioned by the Section Editor Jianfei Shen (Taizhou Hospital of Zhejiang Province, Wenzhou Medical University, Wenzhou, China).

Comment on: Wolfe GI, Kaminski HJ, Aban IB, *et al.* Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med 2016;375:511-22.

Submitted Jan 09, 2017. Accepted for publication Jan 09, 2017.

doi: 10.21037/jtd.2017.02.32

View this article at: http://dx.doi.org/10.21037/jtd.2017.02.32

Thymectomy for myasthenia gravis (MG) has been performed since Alfred Blalock observed in 1936 that a young woman had remission of her myasthenia after a thymectomy for a cystic tumor of the thymus. Over the ensuing 80 years, multiple retrospective series of thymectomy for non-thymomatous MG have been published suggesting the potential benefit of thymectomy in patients with MG. However, the role of thymectomy in non-thymomatous MG remained a topic of controversy due to the absence of a randomized trial.

In the August 11, 2016 issue of the *New England Journal of Medicine* (1), Wolfe and colleagues reported the results of the first randomized trial to assess the role of thymectomy in MG, the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX). This was an international, randomized, single-blinded, trial comparing thymectomy with prednisone to prednisone alone. This trial enrolled 126 patients at 36 sites between 2006 and 2012. The two primary endpoints were the time-weighted average quantitative myasthenia gravis score and the average prednisone requirements.

The trial demonstrated that patients who underwent thymectomy had a lower time-weighted average quantitative myasthenia gravis score over a 3-year period and a lower requirement for prednisone than patients receiving prednisone alone. In addition, far fewer patients in the thymectomy group required additional immunosuppression with azathioprine and the rate of complications from immunosuppressive medications was also significantly lower. Interestingly, the beneficial impact of thymectomy was most predominantly seen 6 to 12 months after surgery with a rapid decline in the mean dose of prednisone associated with stability in the average quantitative myasthenia gravis score. In contrast, between 6 and 9 months after entering the clinical trial, patients in the prednisone alone group demonstrated worsening of the average quantitative myasthenia gravis score with a relatively stable mean dose of prednisone. Beyond 12 months, the rate of improvement on average was relatively similar between the two groups with a mean dose of prednisone that decreased progressively over time.

The rate of complete remission and the number of patients who were completely weaned from prednisone was not reported. Hence, the contribution of patients with complete remission on the results can not be determined. The rate of minimal manifestations of MG symptoms at 12, 24 and 36 months demonstrated that 67% of the patients undergoing thymectomy had minimal manifestations of their MG at 12 months and this rate remained stable over time. In contrast, the rate of remission was 37% at one year in the prednisone alone group, increasing to 47% at 3 years. Subgroups analysis was limited due to the small number of patients.

The MGTX trial therefore demonstrates the benefit of thymectomy in the treatment paradigm of MG. However, questions remain as to the selection of patients for surgery, the timing of surgery, the types of surgical approach and the extent of surgery.

The majority of patients who underwent thymectomy in the clinical trial were women (76%) with a median age of 32 years and a median duration of disease of 1.1 year. In addition, a serum acetylcholine-receptor-antibody (AchR-Ab)

level of more than 1.0 nmol per liter was required for all patients. Patients with positive AchR-Ab and patients with shorter disease duration have consistently been reported to derive the most benefit from thymectomy in non-thymomatous MG (2-4). However, the benefit of thymectomy in patients with late onset MG remains less clear and no further insight is provided by the trial for that group of patients. Historically, women have been thought to have better outcomes after thymectomy, although that result has been called into question with studies that found no difference in outcome based on gender (5,6). The subtype of antibody present may affect that finding as patients with anti-muscle-specific tyrosine kinase (anti-MuSK) are more commonly female (7).

Over the past 15 years, new auto-immune antibodies affecting the neuromuscular junction have been discovered, the most prominent of which is the anti-MuSK antibody (7). Different pathogenic mechanisms have also been evidenced based on the antibody target and isotypes. These findings led to a new classification determined by the type of antibodies that has implications for diagnosis, therapy and prognosis. While the breaking of tolerance in early onset MG associated with AchR-Ab does involve the thymus (correlating with the role of thymectomy demonstrated in this clinical trial), the role of the thymus in the development of other antibodies such as muscle specific kinase (MuSK) antibodies is less clear and increasing evidence suggests that thymectomy is not beneficial in patients with anti-MuSK MG (4). In the future, it is likely that refinements in patients' selection for surgery will come from better understanding of the different subtypes of disease and thymectomy may be limited to patients with AchR antibody, while the remaining patients may benefit from other targeted therapies such as rituximab, which has shown promise in the treatment of anti-MuSK positive patients (8).

In this trial, the thymectomy had to be done through a complete median sternotomy with *en bloc* resection of all tissue in the mediastinum that anatomically may contain gross and/or microscopic thymus. The resection had to include removal of both sheets of mediastinal pleura and sharp dissection on the pericardium. Over the past 10 years, there has been a major shift from open surgery to video-assisted surgery and robotic assisted surgery in non-thymomatous MG. Minimally invasive surgery can be done through a cervicotomy, a transcervical-subxyphoid approach or unilateral or bilateral video-assisted or robotic assisted thoracic surgery (VATS). Considering the benefit of a minimally invasive approach and the comparable results obtained by open and minimally invasive surgery (9-13), it is unlikely that a randomized trial between open and minimally invasive surgery will take place in the future and minimally invasive approach will increasingly be preferred (14).

The extent of thymectomy remains a controversial topic. Although the presence of extra-capsular thymic tissue is frequent and well described (15), the accessibility of these ectopic thymic foci as well as their function and impact on outcome have been unclear. Ectopic thymic foci are found more frequently in patients with an atrophic thymus and their presence carries a poor outcome even after maximal thymectomy with resection of all potential sites of ectopic thymic foci in the neck and mediastinum (16,17). Since ectopic thymic foci are usually isolated to one or two sites and are most frequently found in the anterior mediastinal fat, an extended thymectomy involving the fat located between the pericardium, both pleura and the diaphragm can be safely accessible and should be routinely resected regardless of the type of surgical approach. Extending the surgery to resect tissues in the pericardiophrenic angles, aorto-pulmonary window, aorto-caval groove and along the thyroid gland carry a risk of phrenic or recurrent nerve injury and there is currently limited evidence to suggest that it should be done routinely. A randomized clinical trial would be needed to answer this question. Interestingly, positron emission tomography (PET) has shown a correlation between parathymic standardized uptake value and presence of ectopic thymic tissue, but future research is needed to determine the clinical utility of this test for patients with MG (18).

In conclusion, the MGTX clinical trial finally confirms the importance of thymectomy in the treatment armamentarium of MG, particularly in young women with AChR-Ab. In the future, refinements in our understanding of the disease and its relations to the thymus will certainly help refine the selection of patients for thymectomy. The extent of thymectomy remains an open question that may lead to the next surgical trial in MG.

Acknowledgements

None.

Footnote

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

References

1. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized Trial of Thymectomy in Myasthenia Gravis. N Engl J Med 2016;375:511-22.
2. Venuta F, Rendina EA, De Giacomo T, et al. Thymectomy for myasthenia gravis: a 27-year experience. Eur J Cardiothorac Surg 1999;15:621-4; discussion 624-5.
3. Maggi G, Casadio C, Cavallo A, et al. Thymectomy in myasthenia gravis. Results of 662 cases operated upon in 15 years. Eur J Cardiothorac Surg 1989;3:504-9; discussion 510-1.
4. Ponseti JM, Caritg N, Gamez J, et al. A comparison of long-term post-thymectomy outcome of anti-AChR-positive, anti-AChR-negative and anti-MuSK-positive patients with non-thymomatous myasthenia gravis. Expert Opin Biol Ther 2009;9:1-8.
5. Bachmann K, Burkhardt D, Schreiter I, et al. Thymectomy is more effective than conservative treatment for myasthenia gravis regarding outcome and clinical improvement. Surgery 2009;145:392-8.
6. Luo Y, Pan DJ, Chen FF, et al. Effectiveness of thymectomy in non-thymomatous myasthenia gravis: a systematic review. J Huazhong Univ Sci Technolog Med Sci 2014;34:942-9.
7. Binks S, Vincent A, Palace J. Myasthenia gravis: a clinical-immunological update. J Neurol 2016;263:826-34.
8. Keung B, Robeson KR, DiCapua DB, et al. Long-term benefit of rituximab in MuSK autoantibody myasthenia gravis patients. J Neurol Neurosurg Psychiatry 2013;84:1407-9.
9. Siwachat S, Tantraworasin A, Lapisatepun W, et al. Comparative clinical outcomes after thymectomy for myasthenia gravis: Thoracoscopic versus trans-sternal approach. Asian J Surg 2016. [Epub ahead of print].
10. Liu CW, Luo M, Mei JD, et al. Perioperative and long-term outcome of thymectomy for myasthenia gravis: comparison of surgical approaches and prognostic analysis. Chin Med J (Engl) 2013;126:34-40.
11. Meyer DM, Herbert MA, Sobhani NC, et al. Comparative clinical outcomes of thymectomy for myasthenia gravis performed by extended transsternal and minimally invasive approaches. Ann Thorac Surg 2009;87:385-90; discussion 390-1.
12. Zahid I, Sharif S, Routledge T, et al. Video-assisted thoracoscopic surgery or transsternal thymectomy in the treatment of myasthenia gravis? Interact Cardiovasc Thorac Surg 2011;12:40-6.
13. Lin MW, Chang YL, Huang PM, et al. Thymectomy for non-thymomatous myasthenia gravis: a comparison of surgical methods and analysis of prognostic factors. Eur J Cardiothorac Surg 2010;37:7-12.
14. Orsini B, Santelmo N, Pages PB, et al. Comparative study for surgical management of thymectomy for non-thymomatous myasthenia gravis from the French national database EPITHOR. Eur J Cardiothorac Surg 2016;50:418-22.
15. Klimek-Piotrowska W, Mizia E, Kuzdzał J, et al. Ectopic thymic tissue in the mediastinum: limitations for the operative treatment of myasthenia gravis. Eur J Cardiothorac Surg 2012;42:61-5.
16. Ponseti JM, Gamez J, Vilallonga R, et al. Influence of ectopic thymic tissue on clinical outcome following extended thymectomy in generalized seropositive nonthymomatous myasthenia gravis. Eur J Cardiothorac Surg 2008;34:1062-7.
17. Ambrogi V, Mineo TC. Active ectopic thymus predicts poor outcome after thymectomy in class III myasthenia gravis. J Thorac Cardiovasc Surg 2012;143:601-6.
18. Mineo TC, Ambrogi V, Schillaci O. May positron emission tomography reveal ectopic or active thymus in preoperative evaluation of non-thymomatous myasthenia gravis? J Cardiothorac Surg 2014;9:146.

Cite this article as: de Perrot M, Donahoe L. Thymectomy for myasthenia gravis: what's next? J Thorac Dis 2017;9(2):237-239. doi: 10.21037/jtd.2017.02.32