



If Thymectomy Reduces the Risk of Progression of Ocular to Generalized Myasthenia Gravis, Who Should Receive it?

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Abstract

In this issue of Neurotherapeutics, Li et al. report a large retrospective study of the beneficial effects of thymectomy on the progression of ocular myasthenia gravis (OMG) to generalized MG (GMG) (Huanhuan et al. in Neurotherapeutics XX, 2021). This paper demonstrates a more than 50% reduction in the risk of GMG when a thymectomy was performed on these patients. The authors conclude with the recommendation that well-designed clinical trials be performed to evaluate the potential that thymectomy in OMG reduces the burden of GMG.

Keywords Ocular Myasthenia Gravis · Generalized Myasthenia Gravis · Progression from Ocular to Generalized Myasthenia Gravis

The authors are careful to not overinterpret their retrospective data and do acknowledge the elephant in the room, that of thymoma. Of the reported patients who underwent a thymectomy, almost 73% had a thymoma, compared to 11% in the non-thymectomy cohort. This difference is both critical and cautionary for the potential of overinterpretation of these results. While patients who were thymectomized had 7 times the incidence of thymoma, they were only twice as likely not to generalize (57% vs 28%). While few would argue that thymectomy is important in the presence of a thymoma in OMG or GMG, and some would argue that thymectomy is also warranted when there is thymic hyperplasia, the issue of thymectomy in OMG for those free of thymoma needs careful consideration.

The confounding due to the large imbalance of patients with thymoma (72.5% in the thymectomy group vs. 10.8% in the nonsurgical group) requires careful evaluation, and the risk reduction in each subgroup becomes important. In those without a thymoma, thymectomy lowered the conversion to GMG from 28% in the nonsurgical group to 11% in the thymectomy group, slightly over a 60% reduction and an

adjusted hazard rate of 0.31, showing an estimated reduced risk of 69%.

In the cumulative conversion to GMG, 32.7% of those with a thymectomy converted compared to 45.9% in the non-surgical group. From the Kaplan–Meier estimated results, a difference of 33% is observed, yielding a number needed to treat of 7.6 and an adjusted hazard rate of 0.42 or a 58% reduction. This suggests that improvement conveyed by thymectomy is slightly less in patients with thymoma than in non-thymoma patients. These numbers raise additional questions for both a clinical trial and the widespread use of thymectomy to prevent GMG.

A trial as the authors recommend would have to exclude thymoma patients because of the ethics of randomizing them. It would probably also have to exclude patients with thymic hyperplasia, assuming this can be identified or suspected on screening. This begs the question of the criteria for a trial in non-thymoma OMG patients and whether to treat all OMG with thymectomy, or only some subset. This is a far more complicated decision than thymoma versus hyperplasia versus normal thymus.

Often researchers will mine existing data for respondents who had a thymectomy or those with thymic hyperplasia in whom the thymectomy might have been thought to be preventive [2]. Unfortunately, these analyses are enriched for false positives, that is, finding individuals who received a thymectomy but would have never progressed to GMG irrespective of the thymectomy. These individuals would be

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considered responders in such a retrospective analysis. Such a group always exists because of factors such as over-zealous use of thymectomy and misdiagnosis.

As the move to artificial intelligence and deep data mining to find successfully treated individuals and recruit them to trials or to consider them a target for personalized medicine, the planners of such trials or individualized treatment recommendations should be very cautious.

In conclusion, while heavily confounded by thymoma and hyperplasia in the comparisons presented, the results of this paper by Li et al. show the benefit of thymectomy in OMG with and without thymoma or hyperplasia, with a slightly greater benefit among the patients without thymoma and/or hyperplasia.

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Declarations

Conflict of Interest D.B.S. is a consultant to Accordant Health Services and serves on Data and Safety Monitoring Boards of Janssen Pharmaceuticals, Roche Pharmaceutical Co., and VielaBio, Inc.

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