RESEARCH ARTICLE

Effect of Immunosuppression in Risk of Developing Generalized Symptoms in Ocular Myasthenia Gravis

A Retrospective Cohort Study

Deepak Menon, MD, Mohammed Alharbi, MD, Hans D. Katzberg, MD, MSc, Vera Bril, MD, Meg G. Mendoza, PhD, and Carolina Barnett-Tapia, MD, PhD

Neurology® 2024;103:e209722. doi:10.1212/WNL.0000000000209722

Correspondence
Dr. Barnett-Tapia
c.barnetttapia@utoronto.ca

Abstract

Backgrounds and Objectives

Early use of immunosuppression has been suggested to prevent generalization of ocular myasthenia gravis (OMG), but high-quality evidence is limited in this regard. We examined whether treatment with prednisone and other immunosuppressants reduce the risk of generalization in OMG.

Methods

This is a retrospective study of consecutive adults with pure OMG who had a minimum 6 months of follow-up. The main outcome was the time to developing generalized symptoms. We used propensity scores to create matched data sets of patients treated with prednisone or any immunosuppressant vs controls. We also used unmatched models with inverse probability of treatment weights (IPTW) and variable exposure times. We used Cox proportional hazards model to estimate hazard ratio (HR) for generalization, comparing treated patients vs controls.

Results

A total of 154 patients were included, with a mean follow-up of 87.4 ± 73 months since onset. Forty-three (28%) were generalized, and mean time to generalization from diagnosis was 24.2 ± 24.1 months. Patients who received prednisone had lower risk of generalization than controls, with pooled HR 0.43 (95% CI 0.19–1.06) for the matched model, HR 0.46 (95% CI 0.21–0.89) for the IPTW model, and for HR 0.44 (95% CI 0.23–0.81) for the time-dependent exposure model. Patients who received any immunosuppressant had lower risk of generalization, with HR 0.30 (95% CI 0.11–0.77), 0.32 (95% CI 0.14–0.70), and 0.35 (95% CI 0.15–0.80) for the matched, IPTW, and IPTW-varying exposure models, respectively.

Discussion

Our study provides evidence that steroidal and nonsteroidal immunosuppression in patients with OMG is associated with a reduced risk of developing generalized symptoms over time. This supports the early use of immunosuppression in this population.

Classification of Evidence

This study provides Class III evidence that treatment of OMG with corticosteroids or nonsteroidal immunosuppressants reduces the risk of generalization.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Introduction

The unique structural and physiologic properties of extraocular muscles make them particularly vulnerable to the pathophysiology of myasthenia gravis (MG).[1] This is reflected in the fact that ocular symptoms are the initial manifestations of MG in as many as 85% of patients.[2] However,

From the Department of Neurology (D.M.), National Institute of Mental Health and Neuro Sciences, Bangalore, India; Prosserman Centre for Neuromuscular Disease (D.M., M.A., H.D.K., V.B., M.G.M., C.B.-T.), Toronto General Hospital, University Health Network; and Institute of Health Policy (C.B.-T.), Management and Evaluation, University of Toronto, Ontario, Canada.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AchRAb = acetylcholine receptor antibody; **HR** = hazard ratio; **IPTW** = inverse probability of treatment weight; **MG** = myasthenia gravis; **OMG** = ocular MG; **PS** = propensity score; **REB** = Research Ethics Board; **SMD** = standardized mean difference.

MG is not usually site restricted, and long-term studies have shown that up to 50%–80% of patients progress to generalized MG, and this transition usually takes place within the first 2 years.[2-4] Retrospective studies have identified several factors associated with this progression to generalized MG. Later age at onset, female sex, severity of symptoms, abnormal repetitive nerve stimulation, positive acetylcholine receptor antibody, and thymic hyperplasia are some of the factors favoring generalization; however, these associations have not been consistent across studies.[3-8] Although high-quality evidence is lacking, corticosteroids are advocated in the treatment of ocular MG (OMG).[9,10] Data from retrospective and small prospective studies seem to suggest that early treatment with corticosteroids could prevent generalization of OMG.[4,11-13] However, the generalizability of these results has been questioned because of limited information on the duration of symptoms; variable follow-up times; and initiation, dosage, and timing of steroids.[7] The 2 randomized controlled trials on the use of steroids in OMG had several limitations, such as very short treatment duration (8 days) and restricted outcome measure in one and premature termination because of slow enrollment with just 11 subjects randomized in the other.[14,15] Data from observational studies can be effective in filling these knowledge gaps and statistical techniques such as propensity score (PS) matching can be used to reduce the confounders and bias of treatment inherent to observational studies.[16]

The primary research question in this study was whether treatment of OMG with corticosteroids or nonsteroidal immunosuppressants reduces the risk of generalization.

Methods

Patients and Clinical Data

This was a retrospective cohort study. We included all consecutive adult patients diagnosed with pure OMG with a visit at the Prosserman Family Centre for Neuromuscular Disease, Toronto, Canada, between 2015 and 2020, and at least 6 months of follow-up since onset. A diagnosis of OMG was confirmed if a patient had symptoms and signs compatible with OMG, such as fatigable ptosis and/or diplopia and no symptoms of generalized disease (with normal strength in all other facial, bulbar, and limb muscles) and either abnormal electrophysiology (decremental response in repetitive nerve stimulation studies or increased jitter in voluntary single-fiber electromyography) or positive acetylcholine antibody (AChRAb) or muscle-specific tyrosine kinase antibody status. The data collected included age, sex, age at onset of symptoms, antibody status, thymic status and thymectomy, time to generalization, duration of follow-up, and severity of MG at the last follow-up in terms of MG Impairment Index. We also collected from our database treatments received during follow-up before generalized symptoms (any definitive symptoms or signs of weakness beyond ocular muscles) appeared, and for patients who had not generalized, up to last assessment, these included pyridostigmine, prednisone, azathioprine, and mycophenolate. For immunosuppressive treatment, we also collected data of start of each treatment (in months) from diagnosis.

Outcomes

The main outcome was development of generalized MG symptoms (i.e., bulbar, respiratory, or limb weakness) after the first clinic visit. For those patients who developed generalized symptoms, we recorded time to generalization from symptom onset in months. We recorded the earliest report of generalized symptoms in the chart, which could be a patient call to the clinic, a report from another physician, a hospital admission, or reported by the patient during routine follow-up. In the latter case, we recorded the earliest date of description of generalized symptoms by the patient; if no clear date was recorded, we used the visit's date. We defined controls as patients with pure ocular symptoms who were not exposed to immunosuppressants. For the patients who developed generalized symptoms, they were considered controls if they were not exposed to immunosuppressants before generalized symptoms occurred.

Statistical Analysis

We used SPSS version 2020 (IBM, Armonk, NY) and R version 3.5.1. The demographic and clinical variables are expressed as means with SD or numbers and percentages. We performed multiple imputation for any missing data using the R package "multivariate imputation by chained equation" (mice), creating 20 imputed data sets; pooled estimates are presented for all analyses.[17]

To assess the treatment effect of prednisone with regard to time to generalization, we first used PS models to predict the use of prednisone. We included age at onset, sex, duration of disease before diagnosis, AChRAb status, and use of azathioprine and mycophenolate to build the PS models. We also analyzed the data considering the use of any immunosuppressant (steroidal or nonsteroidal) during the ocular phase as the exposure.

We used the R package Matchthem to create matched data sets of treated and untreated patients.[18] Matching was done to

Table 1 Clinical, Laboratory, and Treatment Variables According to Prednisone Exposure in Unmatched and Matched Cohorts

	Unmatched cohort (n = 154)			Matched cohort (n = 98)		
	No prednisone (N = 67)	Prednisone (N = 86)	SMD	No prednisone (N = 49)	Prednisone (N = 49)	SMD
Age at onset	57.8 ± 15.9	57.2 ± 15.5	0.03	58.5 ± 14.5	59.1 ± 17.5	0.04
Female	46 (68)	28 (33)	0.75[a]	27 (55)	26 (53)	0.05
Symptom duration[b]	15.9 ± 30.9	15.9 ± 23.4	0.009	14.9 ± 33.9	14.1 ± 15.7	0.04
AchRAb	19 (40)	24 (42)	0.008	24 (49)	23 (47)	0.05
Azathioprine	7 (10)	31 (36)	0.53[a]	7 (14)	8 (16)	0.04
Mycophenolate	1 (2)	19 (22)	0.49[a]	3 (7)	5 (11)	0.09
Any nonsteroidal immunosuppressant	8 (12)	36 (42)	0.61[a]	8 (16)	9 (18)	0.04
Pyridostigmine	54 (79)	62 (72)	0.16[a]	38 (77)	37 (75)	0.05
Thymoma	5 (7.5)	0 (0)	0.40[a]	3 (6)	0 (0)	0.30[a]

Abbreviations: AchRAb = positive acetylcholine receptor antibody; SMD = standardized mean difference.
Tested in 47 patients without prednisone and in 57 with prednisone (unmatched data). Matched data are pooled after multiple imputation.
[a] A value >0.1 indicates imbalance between treatment groups. *p* Values are not sensitive to detect subtle imbalance and thus are not presented.
[b] Duration of symptoms before diagnosis, in months. Continuous variables are presented in mean ± SD. Categorical variables are presented as count and proportion.

balance PS covariates through cardinal matching and a maximum caliper of 0.2 without replacement. We assessed balance of the covariates using standardized mean differences (SMDs) whereby SMD ≤0.1 indicates good balance. We used Cox models to estimate hazard ratio (HR) for time to developing generalized symptoms from symptom onset rather than from diagnosis, because patients with longer time with pure ocular symptoms may have inherently reduced risk of generalization by the time of diagnosis. We ran models with use of prednisone or any immunosuppressant as the main predictor, using frailties to account for matching. Because matching can remove some individuals from analyses (those unmatched), we also used PS as inverse probability of treatment weights (IPTW) in the full cohort and ran models on the weighted data. To account for immortal time bias, we also built time-dependent exposure IPTW models, using the IPW package to estimate time-varying weights.[19,20]

For predicted HR of 0.5, with event probability 40%, 20% power, and alpha 5%, 129 patients were required. All models were run with 2-tailed alpha. Statistical analysis was completed by D. Menon and C. Barnett-Tapia.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Research Ethics Board (REB) of the University Health Network (Toronto, Ontario, Canada). Given the retrospective nature of our study, patient consent was waived by the REB.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

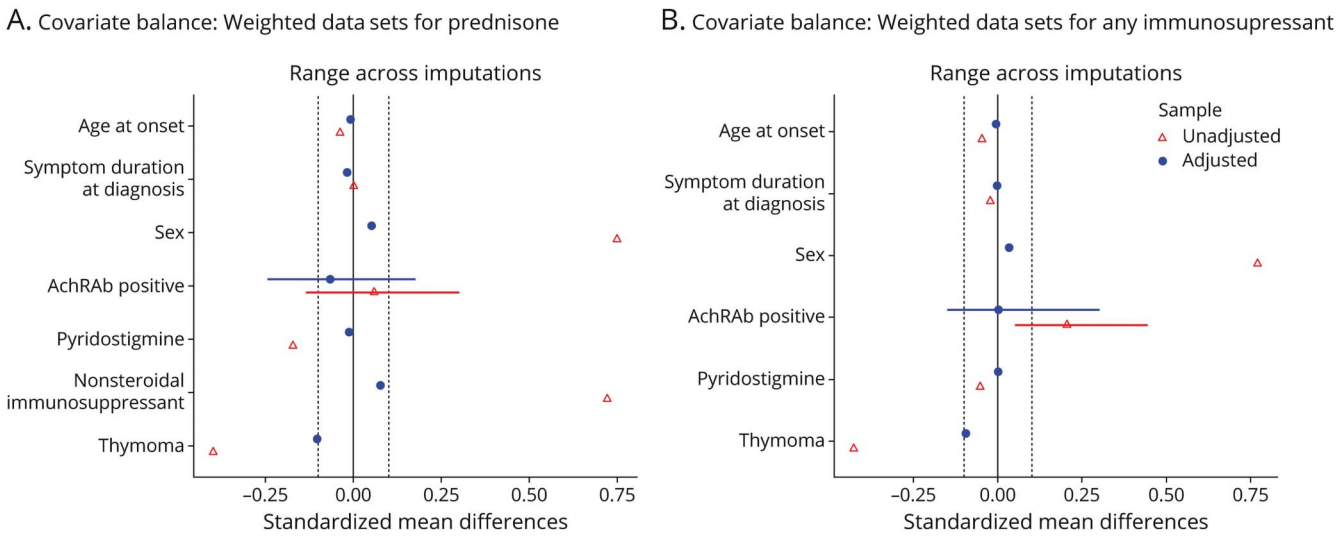
Results

From 186 consecutive patients with OMG who presented to the clinic during the study period, we identified 154 eligible patients based on our inclusion and exclusion criteria. The mean age at onset of symptoms was 57.5 ± 15.8 years (median 60 years). The mean duration of follow-up was 87.4 ± 73 months from symptom onset. Upon the last follow-up, 43 patients (28%) had generalized. The mean number of visits in the first 2 years since diagnosis was 6.8 and median was 8.

In total, 86 patients (56%) were exposed to prednisone and 94 (61%) to any immunosuppressant during the ocular phase. Of these, 50 (53%) received only prednisone; 17 (18%) prednisone and azathioprine; 14 (15%) prednisone, azathioprine, and mycophenolate; 7 (7%) only azathioprine; 5 (5%) prednisone and mycophenolate; and 1 (1%) only mycophenolate. The mean maximum dose of prednisone was 25.2 ± 16 mg per day (range 10–80 mg per day), with mean total duration of 34.9 ± 58 months and mean starting time of 4.3 ± 24 months (range 0–192) after diagnosis. The mean start time for azathioprine was 18.4 ± 45 months (range 0–245) after diagnosis and for mycophenolate 20.2 ± 19 months (range 0–84) after diagnosis.

Of the generalized patients, median time to developing generalized symptoms was 22 months from symptom onset, with a mean of 35.1 ± 40 months. From diagnosis, median time to developing generalized symptoms was 15 months, with a mean of 24.0 ± 29 months. From diagnosis, 20 patients (47%) were generalized at ≤ 12 months, 30 (70%) of ≤24 months, and 34 (79%) within 36 months. Of the 9 patients who

Figure 1 Covariate Balance Before and After Inverse Probability of Treatment Weighting



Panel A shows the standardized mean differences for prednisone as exposure. Panel B shows the standardized mean differences for any immunosuppressant as exposure. The dashed line indicates standardized mean difference of 0.1. Differences >0.1 indicate poor balance. AchRAb = acetylcholine receptor antibody.

generalized after 36 months, 3 (33%) had received prednisone and 4 (44%) any immunosuppressant in the ocular phase. Of the patients who developed generalized symptoms, 6 (14%) had at least 1 MG crisis; 4 of these had not received any immunosuppression in the ocular phase.

In the unmatched data set, the patients who received prednisone were more likely male, with a lower proportion of thymoma and higher proportion of treatment with azathioprine and/or mycophenolate. Those who received any immunosuppressant were also most likely male, with positive AchRAbs. Details of the clinical, laboratory, and treatment variables according to prednisone exposure in unmatched and matched cohorts are summarized in table 1.

The PS-matched data set for prednisone had 49 treated and 49 controls, with excellent balance on all covariables except for thymoma. Therefore, the Cox model included thymoma as a covariable. The Cox model on the matched data showed a pooled prednisone HR of 0.43 (95% CI 0.19–1.06).

The weighed data sets had good balance of all covariates (Figure 1). The IPTW model had a pooled HR of 0.46 (95% CI 0.21–0.89), favoring prednisone. When modeling

Table 2 Clinical, Laboratory, and Treatment Variables According to Any Immunosuppressant Exposure in Unmatched and Matched Cohorts

	Unmatched cohort (n = 153)			Matched cohort (n = 100)		
	No IS (N = 60)	IS (N = 94)	SMD	No IS (N = 50)	IS (N = 50)	SMD
Age at onset	57.9 ± 15.5	57.2 ± 15.8	0.05	60.1 ± 14.5	59.4 ± 17.5	0.03
Female	41 (69)	32 (34)	0.75[a]	33 (66)	32 (64)	0.04
Symptom duration[b]	16.3 ± 32.7	15.7 ± 22.6	0.03	17.4 ± 27.5	18.1 ± 35.6	0.03
AchRAb	16 (38)	27 (44)	0.08	16 (32)	16 (32)	0.00
Pyridostigmine	46 (77)	70 (74)	0.04	38 (76)	37 (74)	0.05
Thymoma	5 (8)	0 (0)	0.40[a]	0 (0)	0 (0)	0.00

Abbreviations: AchRAb = positive acetylcholine receptor antibody; IS = immunosuppression (prednisone, azathioprine and/or mycophenolate); SMD = standardized mean difference.
Tested in 62 patients with and 42 without immunosuppression (unmatched data). Matched data are pooled after multiple imputation.
[a] A value >0.1 indicates imbalance between treatment groups. *p* Values are not sensitive to detect subtle imbalance and thus are not presented.
[b] Duration of symptoms before diagnosis, in months. Continuous variables are presented in mean ± SD. Categorical variables are presented as count and proportion.

Table 3 Hazard Ratio Estimates for Different Models

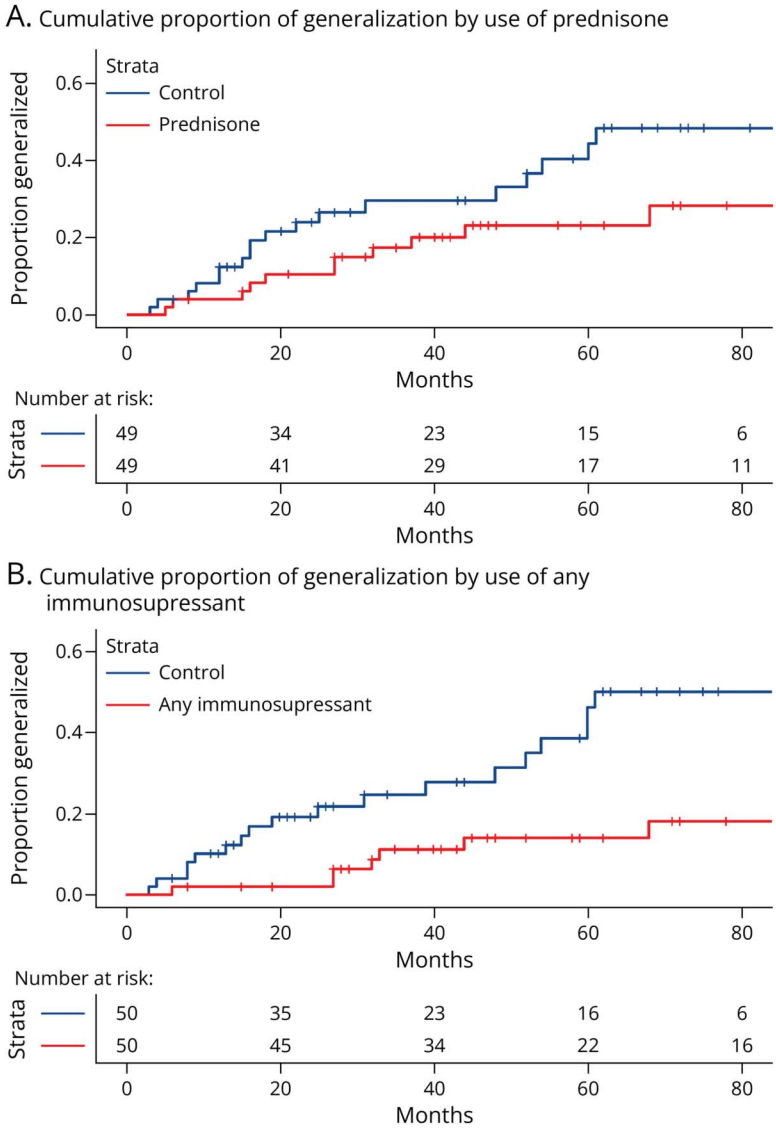
	Prednisone		Any immunosuppressant	
Model	**Hazard ratio**	**95% CI**	**Hazard ratio**	**95% CI**
PS matched	0.43	0.19–1.06	0.30	0.11–0.77
IPTW	0.46	0.21–0.89	0.32	0.14–0.70
IPTW + time-varying exposure	0.44	0.23–0.81	0.35	0.15–0.80

Abbreviations: IPTW = inverse probability of treatment weights; PS = propensity score.

prednisone as a time-dependent exposure on the IPTW model, the prednisone HR was 0.44 (95% CI 0.23–0.81).

When looking at the use of any immunosuppressant, the PS-matched data set had 50 treated patients and 50 controls with balance of all covariates (Table 2). The pooled HR was 0.30 (95% CI 0.11–0.77) favoring immunosuppressants. The weighed data sets had good balance of all covariates (Figure 1). The IPTW model had a pooled HR of 0.32 (95% CI 0.14–0.70) favoring immunosuppressants. In the time-

Figure 2 Cumulative Probabilities of Developing Generalized Symptoms by Treatment



This figure shows the cumulative probability of developing generalized symptoms over time for the model with prednisone (A) and any immunosuppressant (B) in the matched data sets.

varying exposure IPTW model, immunosuppressant HR was 0.35 (95% CI 0.15–0.80). Table 3 summarizes the estimates for all models. Figure 2 depicts survival curves for treated and untreated individuals in the matched data.

Classification of Evidence

This study provides Class III evidence that treatment of OMG with corticosteroids or nonsteroidal immunosuppressants reduces the risk of generalization.

Discussion

In this study, we found that in individuals with comparable age, sex, disease duration, antibody status, and use of acetylcholinesterase inhibitors, the use of immunosuppression, steroidal or nonsteroidal, resulted in a significantly reduced risk of generalized symptoms over time. Our HR estimates ranged between 0.43 and 0.46 for prednisone and between 0.30 and 0.35 for any immunosuppressant. The lower HR for any immunosuppressant use compared with prednisone may reflect the combined effect of steroids plus nonsteroidal treatment, especially considering that 38% of treated patients received >1 treatment. However, our study was not powered to detect differences between different treatment combinations.

We found evidence of indication bias, with marked differences noted in the clinical and demographic features between individuals who received immunosuppression. For example, individuals were more likely to receive immunosuppression if they were male and were seropositive for AChRAb. The latter is not surprising because several studies have shown that seropositivity is an independent risk factor of generalized disease.[5,6,21-23] Therefore, it is possible that physicians take this into consideration when deciding on immunosuppressive use.

Overall, our generalization rate (28%) is within the ranges previously published in the literature.[3,24-26] Interestingly, we found that in the small number of individuals who had a longer time (>3 years) to develop generalized disease ~40% had received immunosuppression. This suggests that in some cases, immunosuppression may be able to significantly delay generalization but not prevent it altogether.

Despite the well-known autoimmune pathophysiology of MG, the protective ability of immunosuppression in OMG has not been sufficiently supported by literature evidence. This is largely because of difficulties conducting controlled studies in the OMG population. For example, a previous randomized clinical trial aimed to assess the treatment effect of prednisone in OMG was terminated early because of difficulty enrolling patients and included only 11 patients.[15] Furthermore, the study was aimed at assessing the clinical benefit of prednisone and not its effect on generalization. A recent systematic review from retrospective studies concluded that steroids and other immunosuppressants reduce the risk of generalization.[24] However, most of the retrospective studies have limitations because of the lack of adjustment of confounders.[4,12,27] In addition, there was a marked heterogeneity across studies in the meta-analysis, and odds ratios were reported despite notable differences in follow-up times. Our study fills some of these gaps, by using multiple models balancing variables that can affect generalization and using time-to-event analysis given different follow-up times, likely providing a more accurate estimate of treatment effect.

PS matching is one of several statistical methods that can mitigate the major drawback of observational studies, that is, the inherent bias in treatment selection. Through PS matching, the covariate imbalance can be reduced and is particularly effective while examining the effect of an intervention through observational studies.[28] Because of limitations of PS matching, we also ran full-cohort models using IPTW and with time-dependent exposures to minimize immortal time bias.

Despite the strengths of our approach, there are some limitations. PSs work well to balance known covariates, but there is always a possibility of residual imbalance in unobserved variables, as opposed to an RCT where randomization balances observed and unobserved.[28,29] Therefore, there may be other factors that may affect treatment decisions and the risk of generalization. One example is disease severity at onset; our clinic had different outcome measures used at the time of the first visit for this cohort, so we could not incorporate this into the models. Presumably, more severely affected individuals may have received immunosuppression earlier. We incorporated the starting time of immunosuppression to account for different exposure times; however, we did not have data for all the doses at different times for each immunosuppressant used, and we did not model sequential use of different medications. Therefore, we cannot compare the effect of timing of different immunosuppressant treatments on risk of developing generalized symptoms. In addition, we had more treated than untreated individuals and our matched cohort was smaller than the unmatched; this may limit generalizability of the findings. However, the latter was mitigated with the unmatched models using PS weights where we found similar estimates. Finally, this cohort is from a tertiary neuromuscular academic clinic and may not reflect patients who receive longitudinal care at community neurology or neuro-ophthalmology clinics.

In summary, this study shows that steroidal and nonsteroidal immunosuppressant treatment, in patients with OMG, is associated with a reduced risk of developing generalized symptoms over time and supports the early use of immunosuppression in patients with pure ocular disease.

Study Funding

No targeted funding reported.

Disclosure

H. Katzberg has received consulting fees or research support from Grifols, CSL Behring, Octapharma, Takeda, Pfizer,

Biogen, Akcea, Alexion, Terumo, UCB, Roche, Argenx, Dyne, Merz, and Syneos. V. Bril serves on the international and the Canadian scientific advisory boards for the Myasthenia Gravis Foundation of America, and has served as a Consultant for Akcea Therapeutics Inc., Alexion Pharmaceuticals Inc., Alnylam Pharmaceuticals Inc., argenX, AstraZeneca, CSL, F. Hoffmann-La Roche Ltd., Grifols, Immunovant Inc., Ionis Pharmaceuticals, Janssen Global Services LLC, Japan Tobacco, Johnson & Johnson Services Inc., Momenta, Novo Nordisk A/S, Octapharma USA Inc., Pfizer Inc., Powell Mansfield Inc., Sanofi, and Takeda Pharmaceutical Company Ltd, and has received research support from Akcea Therapeutics Inc., Alexion Pharmaceuticals Inc., argenx, AstraZeneca, CSL, Grifols, Immunovant Inc., Ionis Pharmaceuticals, Johnson & Johnson Services Inc., Momenta, Octapharma USA Inc., Takeda Pharmaceutical Company Ltd., and UCB S.A. C. Barnett-Tapia has served as member of the advisory board for argenx, Alexion, UCB, and Janssen, has been a consultant for argenx, Janssen, and UCB, has received research support from the US Department of Defense, Muscular Dystrophy Canada and MGNet, Grifols, and Octapharma, and is the primary developer of the MGII and may receive royalties. The other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 3, 2023. Accepted in final form May 29, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Brian C. Callaghan, MD, MS, FAAN.

Appendix Authors

Name	Location	Contribution
Deepak Menon, MD	Department of Neurology, National Institute of Mental Health and Neuro Sciences, Bangalore, India; Prosserman Centre for Neuromuscular Disease, Toronto General Hospital, University Health Network, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Mohammed Alharbi, MD	Prosserman Centre for Neuromuscular Disease, Toronto General Hospital, University Health Network, Ontario, Canada	Major role in the acquisition of data
Hans D. Katzberg, MD, MSc	Prosserman Centre for Neuromuscular Disease, Toronto General Hospital, University Health Network, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Vera Bril, MD	Prosserman Centre for Neuromuscular Disease, Toronto General Hospital, University Health Network, Ontario, Canada	Major role in the acquisition of data; revision of the manuscript for content
Meg G. Mendoza, PhD	Prosserman Centre for Neuromuscular Disease, Toronto General Hospital, University Health Network, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Carolina Barnett-Tapia, MD, PhD	Prosserman Centre for Neuromuscular Disease, Toronto General Hospital, University Health Network; Institute of Health Policy, Management and Evaluation, University of Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

References

1. Porter JD, Baker RS. Muscles of a different "color": the unusual properties of the extraocular muscles may predispose or protect them in neurogenic and myogenic disease. *Neurology*. 1996;46(1):30-37. doi:10.1212/WNL.46.1.30
2. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle and Nerve*. 2008;37(2):141-149. doi:10.1002/mus.20950
3. Oosterhuis HJGH. The natural course of myasthenia gravis: a long term follow up study. *J Neurol Neurosurg Psychiatry*. 1989;52(10):1121-1127. doi:10.1136/jnnp.52.10.1121
4. Kupersmith MJ, Latkany R, Homel P. Development of generalized disease at 2 years in patients with ocular myasthenia gravis. *Arch Neurol*. 2003;60(2):243-248. doi:10.1001/archneur.60.2.243
5. Galassi G, Mazzoli M, Ariatti A, Kaleci S, Valzania F, Nichelli PF. Antibody profile may predict outcome in ocular myasthenia gravis. *Acta Neurol Belg*. 2018;118(3):435-443. doi:10.1007/s13760-018-0943-7
6. Mazzoli M, Ariatti A, Valzania F, et al. Factors affecting outcome in ocular myasthenia gravis. *Int J Neurosci*. 2018;128(1):15-24. doi:10.1080/00207454.2017.1344237
7. Wong SH, Huda S, Vincent A, Plant GT. Ocular myasthenia gravis: controversies and updates. *Curr Neurol Neurosci Rep*. 2014;14(1):421. doi:10.1007/s11910-013-0421-9
8. O'hare M, Doughty C. Update on ocular myasthenia gravis. *Semin Neurol*. 2019;39(6):749-760. doi:10.1055/s-0039-1700527
9. Benatar M, Kaminski HJ. Evidence report: the medical treatment of ocular myasthenia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2007;68(24):2144-2149. doi:10.1212/01.wnl.0000263481.14289.90
10. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of myasthenia gravis. *Neurol Clin*. 2018;36(2):311-337. doi:10.1016/j.ncl.2018.01.011
11. Mee J, Paine M, Byrne E, King J, Reardon K, O'Day J. Immunotherapy of ocular myasthenia gravis reduces conversion to generalized myasthenia gravis. *J Neuroophthalmol*. 2003;23(4):251-255. doi:10.1097/00041327-200312000-00002
12. Monsul NT, Patwa HS, Knorr AM, Lesser RL, Goldstein JM. The effect of prednisone on the progression from ocular to generalized myasthenia gravis. *J Neurol Sci*. 2004;217(2):131-133. doi:10.1016/j.jns.2003.08.017
13. Sommer N, Sigg B, Melms A, et al. Ocular myasthenia gravis: response to long term immunosuppressive treatment. *J Neurol Neurosurg Psychiatry*. 1997;62(2):156-162. doi:10.1136/jnnp.62.2.156
14. Mount FW. Corticotropin in treatment of ocular myasthenia. *Arch Neurol*. 1964;11(2):114. doi:10.1001/archneur.1964.00460200010002
15. Benatar M, Mcdermott MP, Sanders DB, et al. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): a randomized, controlled trial. *Muscle Nerve*. 2016;53(3):363-369. doi:10.1002/mus.24769
16. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. In: *Matched Sampling for Causal Effects*. Cambridge University Press; 2006:170-184. doi:10.1017/CBO9780511810725.016
17. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):1-67. doi:10.18637/jss.v045.i03
18. Zhao Q-Y, Luo J-C, Su Y, Zhang Y-J, Tu G-W, Luo Z. Propensity score matching with R: conventional methods and new features. *Ann Transl Med*. 2021;9(9):812. doi:10.21037/atm-20-3998
19. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679. doi:10.1002/sim.6607
20. Chesnaye NC, Stel VS, Tripepi G, et al. An introduction to inverse probability of treatment weighting in observational research. *Clin Kidney J*. 2022;15(1):14-20. doi:10.1093/ckj/sfab158
21. Díaz-Maroto I, García-García J, Sánchez-Ayaso PA, et al. Ocular myasthenia gravis and risk factors for developing a secondary generalisation: description of a Spanish series. *Neurologia*. 2023;38(4):229-235. doi:10.1016/j.nrl.2020.09.004
22. Wong SH, Petrie A, Plant GT. Ocular myasthenia gravis: toward a risk of generalization score and sample size calculation for a randomized controlled trial of disease modification. *J Neuroophthalmol*. 2016;36(3):252-258. doi:10.1097/WNO.0000000000000350

23. Witthayaweerasak J, Rattanalert N, Aui-Aree N, Subramanian N. Prognostic factors for conversion to generalization in ocular myasthenia gravis. *Medicine (Baltimore)*. 2021;100(19):e25899. doi:10.1097/MD.0000000000025899
24. Li M, Ge F, Guo R, et al. Do early prednisolone and other immunosuppressant therapies prevent generalization in ocular myasthenia gravis in Western populations: a systematic review and meta-analysis. *Ther Adv Neurol Disord*. 2019;12(14): 1756286419876521. doi:10.1177/1756286419876521
25. Sanders DB, Raja SM, Guptill JT, Hobson-Webb LD, Juel VC, Massey JM. The Duke myasthenia gravis clinic registry: I. Description and demographics. *Muscle and Nerve*. 2021;63(2):209-216. doi:10.1002/mus.27120
26. Kamarajah SK, Sadalage G, Palmer J, Carley H, Maddison P, Sivaguru A. Ocular presentation of myasthenia gravis: a natural history cohort. *Muscle and Nerve*. 2018; 57(4):622-627. doi:10.1002/mus.25971
27. Mittal MK, Barohn RJ, Pasnoor M, et al. Ocular myasthenia gravis in an academic neuro-ophthalmology clinic: clinical features and therapeutic response. *J Clin Neuromuscul Dis*. 2011;13(1):46-52. doi:10.1097/CND.0b013e31821c5634
28. Kane LT, Fang T, Galetta MS, et al. Propensity score matching: a statistical method. *Clin Spine Surg*. 2019;33(3):120-122. doi:10.1097/BSD.0000000000000932
29. Sainani KL. Propensity scores: uses and limitations. *PM R*. 2012;4(9):693-697. doi: 10.1016/j.pmrj.2012.07.002