EXPLORING THE IMPACT OF NON-STEROIDAL IMMUNOSUPPRESSIVE DRUGS AND STEROIDS ON THE DEVELOPMENT OF COMORBIDITIES IN PATIENTS WITH MYASTHENIA GRAVIS IN THE NATIONAL VETERANS AFFAIRS HEALTH NETWORK

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INTRODUCTION AND OBJECTIVE

Introduction

- Myasthenia gravis (MG) is an autoimmune neuromuscular disorder characterized by muscle weakness and fatigue that significantly impacts the quality of life for those affected.[1]
- Patients with MG often face the challenge of developing comorbidities such as cardiovascular disease, hyperlipidemia, hypertension, diabetes mellitus, respiratory disorders, and autoimmune diseases.[2-5]
- These challenges are exacerbated by the adverse events associated with the medications utilized for the treatment of MG including steroids and non-steroidal immunosuppressants (NSISTs). In particular, prolonged corticosteroid use can induce conditions like osteoporosis, weight gain, cardiac issues, gastrointestinal malfunction, hypertension, and glucose intolerance.[5]
- Understanding the relationship between treatment strategies and the prevalence of comorbidities can inform treatment decisions for patients.

Study Objective

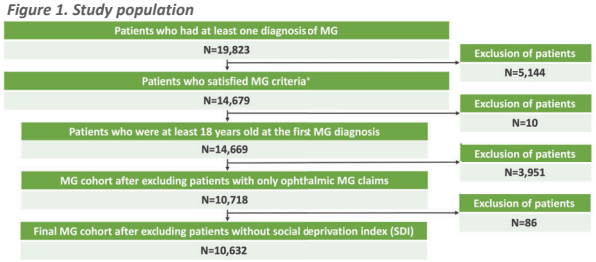
- The purpose of this study was to explore the link between the prevalence of comorbidities in MG and the use of steroids and NSISTs in its treatment.

METHODS

Study Design and Data Source

- This was a retrospective cohort study using de-identified data extracted from the National Veterans Affairs (VA) Health Care Network database from January 1999 to March 2022.
- The database contains electronic medical record (EMR) data from over 1,700 sites of care serving ~8.76 million veterans each year.
- The study cohort comprised of adult patients with 2 or more diagnostic claims related to MG as described in **Figure 1**.
- Patients were followed from index date (defined as the first recorded diagnosis for MG) until enrollment end date, end of the study (03/15/2022), or death.

Figure 1. Study population



*Study population diagnosis criteria referenced the best performing algorithm based on Lee et al. Muscle & Nerve 2021[6]
Abbreviations: MG=myasthenia gravis; SDI=social deprivation index

Study Endpoints

- 14 categories of comorbidities were evaluated: anxiety, autoimmune conditions, cardiovascular disease, depression, diabetes, gastroesophageal reflux disease (GERD), glaucoma, hyperlipidemia/hypercholesterolemia, hypertension, infections, malignancy, osteoporosis, sleeping disorders, and thyroid disorders.
- These comorbidities were selected as either common comorbidities for MG patients or common side effects associated with steroids and NSIST.

Statistical Analysis

- For each comorbidity of interest, a multivariate dynamic time-dependent Cox model was developed to evaluate key drivers of new comorbidity development among those without the comorbidity before index date.
- The key independent variables of interest were adjusted in the model: steroid (yes/no) and NSIST (yes/no) treatment use.
- Demographic characteristics, SDI score, CCI, BMI, comorbidity history, and advanced therapy use were adjusted in the model with comorbidity history, CCI and treatment used as an annual time-dependent variable.

RESULTS

Patient Characteristics

- A total of 10,632 patients with MG were identified and were followed for a median of 7 years (**Table 1**). Most of the patients were elderly with a mean age at diagnosis of 70.5 years.

Drug utilization in MG cohort (Table 1)

- Of the cohort, 51% of patients were on steroids and 14% were on NSISTs.
- Approximately 80% of patients with MG had at least one or more treatments, with 16% of patients treated with more than 3 treatments.

Table 1. Key baseline and treatment characteristics

Characteristics	MG (N=10,632)	
Time to index date by year, (mean, SD)	8.43	5.27
Median (IQR) follow-up in time to index date	7	4-12
Follow-up year (Mean, SD)	7.77	4.91
Age at diagnosis		
Age at index date (mean, SD)	70.47	11.53
Median, IQR	71.92	64.35-78.63
Gender		
Male (N, %)	10,178	95.73%
Race/ethnicity (N, %)		
Caucasian	7,890	74.21%
African American	817	7.68%
Hispanic	447	4.20%
Others (Asian, Native American, Unknown)	1478	13.9%
Social Deprivation Index (mean, SD)	46.98	26.40
Body Mass Index (Mean, SD)	30.18	5.87
Charlson Comorbidity Index (mean, SD)	0.68	1.23
Treatment during follow-up (N, %)		
Acetylcholinesterase inhibitors	8,051	75.72%
Eculizumab	25	0.24%
IVIG/SCIG	1,024	9.63%
Non-steroidal immunosuppressants (NSISTs)	1,485	13.97%
Plasma Exchange (PLEX)	88	0.83%
Rituximab	119	1.12%
Steroids	5,417	50.95%
Baseline comorbidities (N, %)		
Hypertension	7,580	71.29%
Hyperlipidemia/hypercholesterolemia	6,971	65.57%
Cardiovascular disease	5,578	52.46%
Infections	5,836	54.89%
Diabetes	3,906	36.74%
GERD	3,721	35.00%
Depression	2,562	24.10%
Malignancy	1,864	17.53%
Glaucoma	1,809	17.01%
Thyroid-related disorders	1,657	15.59%
Autoimmune-associated conditions*	1,035	9.73%
Sleeping disorder	862	8.11%
Osteoporosis	530	4.98%
Anxiety	386	3.63%

IQR-interquartile range; IVIG=Intravenous Immunoglobulin, SCIG=Subcutaneous Immunoglobulin, SD=standard deviation

Treatment impact on comorbidity development (Figures 2 and 3)

- After adjusting for key patient demographic, disease-related characteristics, and treatments (steroids, NSISTs, IVIG/biologics), the administration of steroids was associated with a significantly higher risk of developing osteoporosis (HR:1.35), autoimmune conditions (HR:1.23), glaucoma (HR:1.22), diabetes (HR:1.22), malignancy (HR:1.19), infection (HR:1.18), thyroid disorders (HR:1.17), and depression (HR:1.15) (all p<0.05).
- Use of NSISTs were associated with a significantly elevated risk of anxiety (HR:1.26) and sleep-disorders (HR:1.28) (all p<0.05).

Figure 2. Risk of developing new comorbidities (steroid use vs no steroid use)

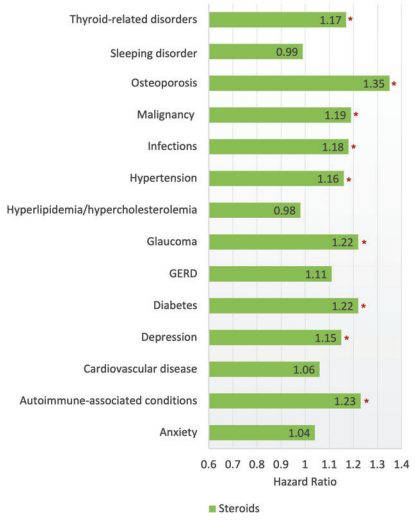
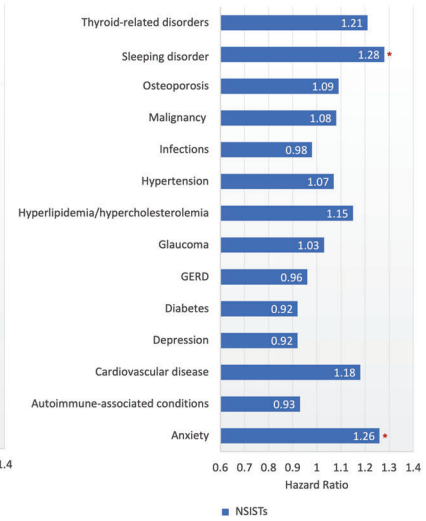


Figure 3. Risk of developing new comorbidities (NSIST use vs no NSIST use)



*Note: Statistically significant

Other factors associated with new comorbidity development

- Older age at MG diagnosis significantly increased the risk of developing comorbidities (p<0.001).
- An increase in the CCI significantly heightened the risk of overall comorbidity development (p<0.001), while the SDI did not play a significant role in comorbidity development.

CONCLUSIONS

- Conventional immunosuppressive therapies like steroids and NSISTs substantially increased the risk of developing several comorbidities in patients with MG, including diabetes, infections, malignancy, glaucoma, and osteoporosis.
- This result suggests it is important to consider the potential impact of comorbidities in treatment choice selection for patients with MG.

Limitations

- The study's main limitation is that due to the homogeneity of the VA populations it reduces the external validity and limits the application of findings to larger, more diverse population.

References

1. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren J. Myasthenia gravis. Nat Rev Dis Primers. May 2, 2019;5(1):30.
2. Cacho-Diaz B, Flores-Gavilán P, Garcia Ramos G. Myasthenia Gravis and Its Comorbidities. Journal of Neurology & Neurophysiology. 01/01 2015;06
3. Harris L, Graham S, MacLachlan S, Exuzides A, Jacob S. A retrospective longitudinal cohort study of the clinical burden in myasthenia gravis. BMC Neurology. 2022/05/09 2022;22(1):172
4. Klimiec-Moskal E, Quirke M, Leite MI. Comorbidities in older patients with myasthenia gravis — Comparison between early- and late-onset disease. Acta Neurologica Scandinavica. 2022;145(3):371-374
5. Misra UK, Kalita J, Singh VK, Kumar S. A study of comorbidities in myasthenia gravis. Acta Neurol Belg. Feb 2020;120(1):59-64
6. Lee I, Schold JD, Hehir MK, Claytor B, Silvestri N, Li Y. Validation of myasthenia gravis diagnosis in the older Medicare population. Muscle & Nerve. 2022;65(6):676-682.

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