Emergent Comorbid Events in First Year of Immunomodulatory Treatment in Adults with Generalized Myasthenia Gravis treated in a Neurology Clinic: A Retrospective Review

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ABSTRACT

Background: Current treatments for myasthenia gravis, including immunomodulatory therapies, are associated with significant comorbid events.

Method: Retrospective chart review of all adults diagnosed with generalized myasthenia gravis in our clinic over 5 years to evaluate potential associations between treatment regimens and emergent comorbid events according to system organ class. Comorbid events were categorized by affected system organ class as endocrine, neuropsychiatric, musculoskeletal, gastrointestinal, pulmonary, cardiovascular, urologic, infectious, and hematologic. MG treatment regimens at the latest available date during the 1-year follow-up were categorized by corticosteroid use and further stratified by medication class and combination therapy.

Result: A total of 68 patients were included in the analysis (corticosteroid group, n = 43; non-corticosteroid group, n = 25). We found no significant differences in the frequencies of comorbid events between patients whose regimens included corticosteroids and patients with corticosteroid-free regimens.

Conclusion: Patients who received corticosteroid treatments did not experience higher comorbid events than those receiving non-corticosteroid treatments.

Keywords: Corticosteroids; immunoglobulins; immunomodulation; myasthenia gravis; pyridostigmine

Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by chronic fatigable skeletal muscle weakness caused by dysfunction at the neuromuscular junction that affects 14 to 20 per 100,000 individuals in the United States.[1,2] While traditional treatments for MG, including acetylcholinesterase inhibitors, immunosuppressants, and immunomodulatory drugs, can be effective and enable most patients to achieve a normal life expectancy, these treatments are associated with multiple side effects and comorbid events that can significantly impact patient quality of life, compounding the social and quality-of-life burdens imparted by the disease itself.[3-8] The risk of these events depends on medication choice, drug dosage, treatment duration, and patient characteristics.[9] The impact of MG treatments on the emergence of comorbid events within the first year of diagnosis is poorly understood. In this study, we conducted a retrospective chart review of patients with generalized MG diagnosed and treated for at least 1 year at a single neurology clinic to examine potential associations between treatment regimens and emergent comorbid events.

Materials and Methods

Participants

We retrospectively examined electronic medical records (EMRs) for all adult patients (≥18 years of age) diagnosed with MG from 2011 to 2015 with ≥1 year of follow-up at a single neurology clinic (University Hospital Neurology and Sleep Disorders Clinic at University of Missouri, Columbia, MO, USA). Institutional review board approval was obtained prior to study. IRB #2010001HS. Patients were included if their EMR reflected acetylcholine receptor (AChR) antibody detection, decremental response on low-frequency repetitive nerve stimulation, or abnormal jitter on single-fiber electromyography.[10] The population was limited to those with a Myasthenia Gravis Foundation of America class II to IV clinical classification. Patients with muscle-specific tyrosine kinase antibodies were not included. Patient and disease characteristics, preexisting conditions, medication history, treatment regimens, and comorbid events recorded after diagnosis were extracted from EMRs (Table 1).

Treatments

Our clinic used oral corticosteroid therapy for patients with AChR-positive and seronegative (ie, AChR- and muscle-specific tyrosine kinase-negative) MG. The initial dose (5 mg/day) was gradually increased as needed (low dose, 10–20 mg/day; high dose, 40–50 mg/day). Corticosteroid-sparing agents (mycophenolate 1000 mg twice daily or azathioprine 200 mg/day) were typically added unless there was a contraindication or the patient refused. Pyridostigmine (60 mg 3 times daily)

was used as symptomatic therapy for all patients unless they chose to discontinue because of poor tolerability or efficacy. Intravenous immunoglobulin (IVIg) was added to maintenance treatment (1000 mg/kg every 4 weeks) when the corticosteroid dose could not be increased to an effective level or used as a rescue treatment (1 mg/kg as needed) from worsening symptoms. IVIg could be used alone if the patient refused or was nonadherent to corticosteroid treatment.

Data Analysis

For this analysis, MG treatment regimens at the latest available date during the 1-year follow-up were categorized by corticosteroid use and further stratified by medication class and combination therapy. Patients included in the corticosteroid group were categorized into the following MG treatment cohorts: (1) high-dose corticosteroids only; (2) pyridostigmine and high-dose corticosteroids; (3) pyridostigmine, high-dose corticosteroids, and corticosteroid-sparing agents; or (4) IVIg, low-dose corticosteroids, and corticosteroid-sparing agents (**Table 1**). Patients included in the non-corticosteroid group were categorized into the following MG treatment cohorts: (1) pyridostigmine only; (2) pyridostigmine, corticosteroid-sparing agents, and IVIg as needed; (3) maintenance IVIg only; or (4) maintenance IVIg and pyridostigmine.

Comorbid events that occurred within 1 year of MG diagnosis were categorized by affected system organ class: endocrine, neuropsychiatric, musculoskeletal, gastrointestinal, pulmonary, cardiovascular, urologic, infectious, and hematologic. Once categorized, an independent, board-certified neurologist reviewed all events to ensure proper classification. The comorbid events were recorded in a systematic and uniform fashion in every clinic visit. Using the comorbid event categories, we compared event incidences between the corticosteroid and non-corticosteroid groups and the MG treatment cohorts.

Continuous and categorical data were summarized with descriptive statistics including means with standard deviations and frequencies. Categorical analyses were performed using GraphPad Prism software (version 7.0; La Jolla, CA, USA) and are presented as odds ratios (ORs) and 95% confidence intervals (CIs); differences were considered statistically significant at $P < 0.05$.

Results

Patient Characteristics

A total of 68 patients were included in the analysis (corticosteroid group, n = 43; non-corticosteroid group, n = 25). The demographic and disease characteristics of the groups were generally well balanced, although preexisting medical conditions and medication history were more common among patients in the non-corticosteroid group (**Table 1**). Most patients across both groups had preexisting conditions and were taking non-MG medications at baseline.

Emergent Comorbid Events

The patient EMRs contained 47 comorbid events (corticosteroid group, n = 27; non-corticosteroid group, n = 20) (**Table 2**). Two patients in each group experienced >1 event, and no patients reported >2 events. A smaller proportion of patients in the corticosteroid group experienced ≥1 event versus the non-corticosteroid group (25 of 43 [58.1%] vs 18 of 25 [72.0%], respectively); however, there was no statistically significant difference between groups in the overall incidence of comorbid events. Most comorbid events occurred in the neuropsychiatric, infections, endocrine, and musculoskeletal system organ class categories. The majority of endocrine emergent comorbid conditions in the corticosteroid group were likely to be steroid-related. Similar to the overall results, there was no statistically significant difference in the incidence of comorbid events within each system organ class between both groups.

There were no statistically significant differences between corticosteroid treatment cohorts for the other system organ classes. We found no statistically significant differences when comparing the frequencies of system organ class events in the non-corticosteroid treatment cohorts.

Discussion

The tolerability challenges of corticosteroids for the treatment of MG are well established, particularly over the long term, and are a motivation for combining corticosteroids with other immunomodulatory and corticosteroid-sparing agents.[3,11] Previous studies suggest that the development of corticosteroid-related comorbid events positively correlates with the duration of corticosteroid treatment and may emerge as late as 3 years after treatment initiation.[12,13] In our study, patients who received corticosteroid treatments did not experience higher comorbid events than those receiving non-corticosteroid treatments. Given the need for many patients with MG to maintain long-term corticosteroid use and the limited 1-year follow-up of our analysis, additional follow-up time in our population may have yielded a higher frequency of corticosteroid-related comorbid events.

We observed higher proportions of patients in the non-corticosteroid group that reported preexisting conditions and medication histories in comparison to the corticosteroid group, which may have influenced the frequency of emergent comorbid events in this group.

TABLE 1. Patient Demographics, Disease Characteristics, and Treatments

	Corticosteroid Group (n = 43)	Non-corticosteroid Group (n = 25)
Age at diagnosis, mean (SD), y	60.5 (16.8)	63.7 (15.7)
Male	28 (65.1)	11 (44.0)
Race		
White	42 (97.7)	23 (92.0)
Black	1 (2.3)	2 (8.0)
Antibody status		
AChR-positive	37 (86.0)	21 (84.0)
AChR- and MuSK-negative	6 (14.0)	4 (16.0)
Thymectomy status		
Yes	8 (18.6)	6 (24.0)
No	35 (81.4)	19 (76.0)
MGFA class		
Class II	20 (46.5)	13 (52.0)
Class III	13 (30.2)	7 (28.0)
Class IV	10 (23.3)	5 (20.0)
Preexisting conditions		
Pulmonary	22 (51.2)	15 (60.0)
Cardiovascular	31 (72.1)	25 (100.0)
Gastrointestinal	12 (27.9)	13 (52.0)
Endocrine	17 (39.5)	15 (60.0)
Hematologic	4 (9.3)	3 (12.0)
Medication history		
Antihypertensives	26 (60.5)	22 (88.0)
Antiplatelets	12 (27.9)	10 (40.0)
Inhalational bronchodilators	18 (41.9)	13 (52.0)
Lipid-lowering medications	15 (34.9)	10 (40.0)
Proton pump inhibitors	18 (41.9)	14 (56.0)
Diabetes medications	16 (37.2)	19 (76.0)
MG treatment regimen		
Pyridostigmine only	—	10 (40.0)
Pyridostigmine + corticosteroid	34 (79.1)	—
Pyridostigmine + CSA	—	11 (44.0)
Pyridostigmine + corticosteroid + CSA	4 (9.3)	—
Corticosteroid only	3 (7.0)	—
IVIg only	—	2 (8.0)
IVIg + pyridostigmine	—	2 (8.0)
IVIg + pyridostigmine + corticosteroid	2 (4.7)	—

Data are shown as n (%) unless specified otherwise.
AChR, acetylcholine receptor; CSA, corticosteroid-sparing agent; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; SD, standard deviation.

TABLE 2. Emergent Comorbid Events Stratified by System Organ Class

System/Complication, n (%)	Corticosteroid Group (n = 43)	Non-corticosteroid Group (n = 25)	Odds Ratio (95% CI)	P
Endocrine				
Glucose intolerance	3 (7.0)	—	7.28 (0.5182–186.9000)	0.128
Diabetes mellitus	1 (2.3)	—		
Pancreatitis	1 (2.3)	—		
Neuropsychiatric				
Peripheral neuropathy	1 (2.3)	5 (20.0)	0.41 (0.2100–1.2356)	0.132
Anxiety	2 (4.7)	—		
Cramp fasciculation	1 (2.3)	—		
Depression	1 (2.3)	—		
Headache	—	1 (4.0)		
Multiple sclerosis	1 (2.3)	—		
Sciatica	1 (2.3)	—		
Sleep apnea	—	1 (4.0)		
Stroke	—	1 (4.0)		
Musculoskeletal				
Osteoporosis	3 (7.0)	—	3.16 (0.3600–23.4960)	0.317
Bicep tendon tear	1 (2.3)	—		
Osteopenia	1 (2.3)	—		
Rotator cuff tear	—	1 (4.0)		
Gastrointestinal			0.57 (0.0342–9.5568)	0.690
Gastritis	—	1 (4.0)		
Peptic ulcer	1 (2.3)	—		
Cardiovascular			3.07 (0.1417–66.5951)	0.470
Hypertension	2 (4.7)	—		
Urologic			0.10 (0.0050–2.3400)	0.150
Acute kidney injury	—	1 (4.0)		
Renal stone	—	1 (4.0)		
Hematologic			0.18 (0.0342–9.5568)	0.690
Pancytopenia	—	1 (4.0)		
Pulmonary			0.10 (0.0050–2.3400)	0.150
Bronchitis	—	1 (4.0)		
COPD	—	1 (4.0)		
Infections				
Pneumonia	2 (4.7)	1 (4.0)	0.78 (0.2890–2.2950)	0.697
Urinary tract infection	—	3 (12.0)		
Chronic sinusitis	1 (2.3)	—		
Clostridioides difficile	—	1 (4.0)		
Disseminated varicella sepsis	1 (2.3)	—		
Epididymitis	1 (2.3)	—		
Necrotizing fascitis	1 (2.3)	—		
Otitis media	1 (2.3)	—		
Total*	27	20	0.42 (0.1324–1.3441)	0.144

*Patients may have experienced >1 emergent comorbid event.
CI, confidence interval; COPD, chronic obstructive pulmonary disorder.

The existence of comorbidities has contributed to poorer outcomes in patients with MG and is considered a risk factor for infections in most autoimmune disorders.[14,15] In our study, the decision to start a patient on a specific medication regimen was made after reviewing their preexisting comorbidity profile and choosing the best available medication option. Preexisting comorbidities and patient age can influence the identified medication related comorbid events [14,15]

Although generally well tolerated, treatment with pyridostigmine has been associated with muscarinic and nicotinic side effects,[3,6,11] and azathioprine can cause flu-like symptoms,[3] which may have compounded the corticosteroid side effects. The use of high-dose corticosteroids in combination with corticosteroid-sparing agents shortly after diagnosis to achieve early symptom control may have potentiated corticosteroid-related endocrine and neuropsychiatric effects.[9]

The prevalence of comorbid events associated with immunomodulatory treatment underscores the importance of oversight by an experienced neurological center.[9] In one study, outcomes for patients with MG were rated as significantly improved when care was provided by neuromuscular specialists versus other physician types despite clinical severity at onset.[16]

There are some limitations to our study. The findings of this retrospective study of EMRs at a single institution may not be reflective of outcomes in other care settings. Moreover, the analysis was limited to the first year after MG diagnosis, which may have excluded comorbid events that emerged after long-term treatment. Lastly, the small sample size and lack of control group limit the robustness of our findings.

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