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Steroid Toxicity in Adults With Myasthenia Gravis in the United States Based on Electronic Health Records

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INTRODUCTION

Myasthenia gravis (MG)

- MG is a chronic autoimmune disorder characterized by defective transmission at the neuromuscular junction[1,2]
- Steroids are commonly prescribed in MG due to fast onset of action and their anti-inflammatory and immunosuppressant effects.[3,4] However, the clinical benefits of steroid therapy are tempered by the potential for short- and long-term drug-related AEs, including osteoporosis, hyperglycemia, and adrenal suppression
- While there is increasing evidence of the impact of long-term steroid use on patient burden, there are limited effective tools to support clinicians in continuously monitoring steroid toxicity over time

Glucocorticoid Toxicity Index (GTI)

- GTI is a standardized clinical outcome assessment (COA) of glucocorticoid toxicity that uses 9 health domains in the calculation of its scores (Table 1)
- Correlated highly with the GTI, the GTI-Metabolic Domains (GTI-MD) is an abbreviated version that can assess steroid toxicity using 4 metabolic domains captured directly from electronic health records (EHR). Utilizing GTI-MD with real-world data can help guide clinicians to monitor steroid use and enhance treatment decision-making

Objective

- The objective of the study was to quantify steroid toxicity with GTI-MD in patients with MG using EHR data. We hypothesized that patients receiving multiple courses of steroids and those initiating steroid treatment at 20+ mg/day would have higher steroid toxicity

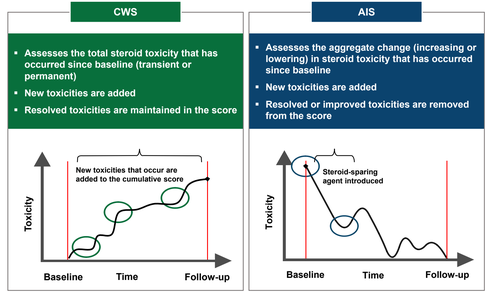
Table 1. Overview of GTI, GTI-MD, and GT-SNAPSHOT Score

GTI	Weighted, standardized COA of steroid toxicity that uses 9 health domains to measure the change in toxicity between two time points
GTI-MD	An abridged and validated version that correlates highly with the GTI to quantify steroid toxicity between two time points
GT-SNAPSHOT score	Assessment of glucocorticoid toxicity at a single point in time (contrasting with the CWS and AIS, which measure change in toxicity between two points in time)

Cumulative Worsening Score (CWS) and Aggregate Improvement Score (AIS)

- The GTI measures toxicity effectively using two scores, the CWS and the AIS (Figure 1). Higher scores (either CWS or AIS) correspond to higher toxicity

Figure 1. Assessment of Toxicity: CWS and AIS

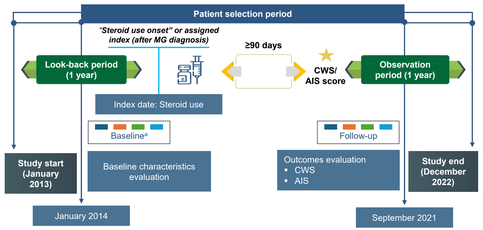


METHODS

Study description and data sources

- A retrospective, real-world study was conducted using Optum® de-identified EHR data set (Optum® EHR), comprising laboratory values needed for the GTI-MD algorithm with data from January 2013 to December 2022 (Figure 2)

Figure 2. Study Design



[a]Lab assessments (lipid metabolism, glucose tolerance, BMI, and blood pressure) were required to be within a 14-day window.
Lipid metabolism Glucose tolerance BMI BP
Data on medication dose *increase, decrease,* or *no change* at time of lab assessments were included in the algorithm.

- GTI-MD scores (AIS and CWS; higher scores representing higher toxicity) were compared between the MG-steroid initiator (SI) and MG-steroid naïve (SN) cohorts
- Patients in MG-SI cohort were further categorized as per frequency (multiple and one-time user) and strength (20+ mg and <20 mg) of steroids at index

Figure 3. Study Overview

Key patient selection criteria

Inclusion criteria:
- Adult patients of age ≥18 years with MG (>2 MG diagnoses ≥30–≤730 days apart)
- Steroid users identified using NDC and procedure codes for oral and IV steroid use
- Patients with lab values for GTI-MD within a 14-day period during both the baseline and follow-up period[a]

Exclusion criteria:
- Patients with evidence of bariatric surgery post index
- Patients with incomplete steroid prescription information

Study variables
- Baseline characteristics (age [at index])
- CCI (1-year pre index)

Study outcomes

Baseline characteristics
- CWS assesses the total steroid toxicity that has occurred since baseline (transient or permanent)
- AIS assesses the aggregate change (increasing or lowering) in toxicity that has occurred since baseline

Statistical analysis
- Descriptive statistics were used to evaluate patient baseline characteristics and GTI-MD scores
- Chi-square test for assessing the relation between categorical variables
- Student *t*-tests for analyzing continuous variables
- Multivariate regression assessed the relationship of steroid usage, strength, and timing of follow-up assessment to GTI-MD
- A *P* value of <0.05 was considered statistically significant

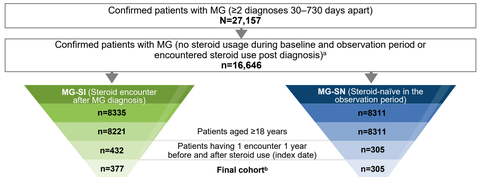
[a]The baseline period was 1 year pre index, and the follow-up period was 1 year post 90-day steroid exposure period post index. The limits of GTI-MD domains include LDL: 20–400 mg/dL; BMI: 15–50 kg/m²; HbA1c: 3%–20%; BP: 40–250 mmHg (systolic) and 30–150 mmHg (diastolic).
List of steroids: Prednisone, prednisone-diphenhydramine HCl methylprednisolone, methylprednisolone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, dexamethasone, hydrocortisone, hydrocortisone cypionate.

RESULTS

Patient selection

- Among 27,157 adults with MG, 377 and 305 were included in the MG-SI and MG-SN cohorts, respectively (Figure 4)

Figure 4. Patient Flow



[a]10,511 patients were excluded as they had 1 year of steroid-free usage. [b]36 patients excluded for bariatric surgery and incomplete steroid information.

Baseline demographics and clinical characteristics

- Mean (SD) age was 68.7 (10.3) for MG-SI and 71.5 (9.0) years for MG-SN cohort with male predominance (MG-SI: 57%; MG-SN: 67%; Table 2)
- Almost half of the patients had Charlson Comorbidity Index (CCI) score 1–2 (MG-SI: 46%; MG-SN: 47%), which is higher in this study compared with typical real-world study in patients with MG (likely due to requirement of lab values in this study)[4]

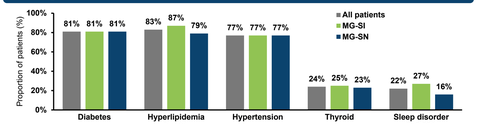
Table 2. Baseline Demographics and Clinical Characteristics

	All patients (N=682)	MG-SI (n=377)	MG-SN (n=305)	*P* value
Age at index, years, mean (SD)	70.0 (9.8)	68.7 (10.3)	71.5 (9.0)	**<0.001**
Gender, n (%)				
Female	262 (38)	161 (43)	101 (33)	**0.005**
Male	420 (62)	216 (57)	204 (67)	
Insurance type at index, n (%)				
Commercial	162 (24)	104 (28)	58 (19)	**<0.001**
Medicare	200 (29)	126 (33)	74 (24)	
Multiple/other/unknown	320 (47)	147 (39)	173 (57)	
CCI, mean (SD)	2.4 (2.1)	2.6 (2.2)	2.2 (1.9)	**0.003**
Baseline GT-SNAPSHOT score, mean (SD)	90.6 (31.9)	92.0 (31.1)	88.8 (32.8)	0.19
BMI category, n (%)[a]				
Normal (18–<25)	86 (13)	37 (10)	49 (16)	0.06
Overweight (25–<30)	211 (31)	123 (33)	88 (29)	
Obese (30+)	384 (56)	217 (58)	167 (55)	
HbA1c category, n (%)[a]				
Diabetes (HbA1c >6.5%)	317 (46)	175 (46)	142 (47)	0.22
Prediabetes (HbA1c 5.7%–6.5%)	222 (33)	118 (31)	104 (34)	
Normal (HbA1c <5.7%)	143 (21)	84 (22)	59 (19)	
Hypoglycemic medication use, n (%)[b]	383 (56)	212 (56)	171 (56)	0.96
Systolic BP, mmHg, mean (SD)[a]	129 (16)	129 (17)	128 (15)	
Diastolic BP, mmHg, mean (SD)[a]	74 (10)	74 (10)	73 (10)	
Antihypertensive medication use, n (%)[b]	505 (74)	280 (74)	225 (74)	0.88
LDL, mg/dL, mean (SD)[a]	88.3 (34.0)	90.1 (34.3)	86.2 (33.5)	
Lipid-lowering medication use, n (%)[b]	419 (61)	234 (62)	185 (61)	0.71

[a]Test values of the encounter closest to the index date in the pre-steroid period have been considered. [b]Medication capture has been checked for until the encounter date closest to Index date in the pre-period.

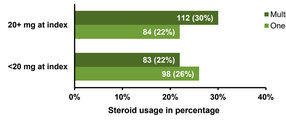
- MG-SI had higher prevalence of hyperlipidemia and sleep disorder than MG-SN cohort (Figure 5)

Figure 5. Baseline Characteristics: Presence of Common MG Comorbidities



- 112 (30%) patients in the MG-SI cohort had multiple prescriptions of 20+ mg strength steroids at index (Figure 6)

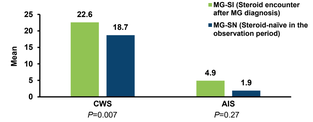
Figure 6. Steroid Usage at Index as per Frequency and Strength



GTI-MD scores

- The mean (SD) GTI-MD scores were higher in MG-SI compared with MG-SN (CWS: 22.6 [22.8] vs 18.7 [21.2], *P*=0.007; AIS: 4.9 [34.5] vs 1.9 [34.3], *P*=0.27; Figure 7)

Figure 7. GTI-MD Scores for MG-SI Versus MG-SN



- MG-SI had more patients exceeding the minimal clinically important difference (MCID) than MG-SN (Table 3)

Table 3. Minimal Clinically Important Difference (MCID)[9]

MCID, n (%)	MG-SI (n=377)	MG-SN (n=305)	*P* value
CWS			
>10 points	**256 (68)**	**180 (59)**	**0.013**
>20 points	**167 (44)**	**110 (36)**	**0.012**
>30 points	141 (37)	98 (32)	0.15
AIS			
>10 points	171 (45)	137 (45)	0.91
>20 points	118 (31)	84 (28)	0.29
>30 points	84 (22)	69 (23)	0.92

Limitations

- The study included a small cohort size and incomplete steroid dosing capture in EHR data
- Additional studies evaluating longer follow-up periods, changes in steroid dosing, and a more diverse MG patient population are needed to assess the further applicability of GTI-MD in clinical practice
- The analysis may include bias as data were not matched for concomitant disease and medication

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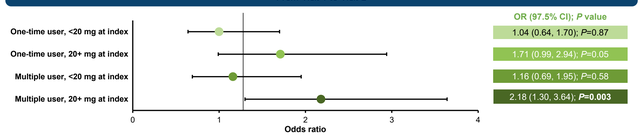
CWS and AIS scores as per frequency and strength of steroid use

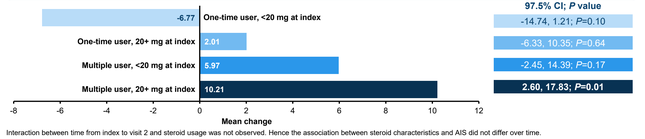
- In MG-SI cohort, patients with multiple records and prescriptions of 20+ mg at index had 2.2-times higher odds of worsening than MG-SN cohort per CWS analysis at the first set of labs in follow-up (Figure 8)

Figure 8. CWS as per Frequency and Strength of Steroid Use in MG-SI Cohort With Reference to MG-SN Cohort
From Visit 1 to Visit 2



- Similarly, patients in MG-SI cohort with multiple records and steroid records of 20+ mg strength at index had an average AIS 10.2 points higher than patients in MG-SN cohort at the first set of labs in follow-up (*P*=0.01; Figure 9)

Figure 9. AIS as per Frequency and Strength of Steroid Use in MG-SI Cohort With Reference to MG-SN Cohort
From Visit 1 to Visit 2



Interaction between time from index to visit 2 and steroid usage was not observed. Hence the association between steroid characteristics and AIS did not differ over time.

- Each additional month of follow-up since index was associated with a decrease of 1.5 AIS (*P*<0.001; Table 4)

Table 4. AIS per Outcome and Time of Steroid Use

Outcome: AIS (visit 1 to visit 2)	Mean change	97.5% CI	*P* value
Commercial insurance			
Medicaid	3.65	-20.52, 27.83	0.77
Medicare	-6.05	-13.74, 1.64	0.12
Multiple	-4.88	-12.60, 2.85	0.22
Unknown	-7.25	-15.89, 1.40	0.10
Age	0.06	-0.25, 0.36	0.72
CCI	-0.72	-2.04, 0.60	0.28
Time from index to visit 2 (days)	-0.05	-0.08, -0.02	**0.001**
Time from visit 1 to index (days)	-0.01	-0.04, 0.02	0.57
Baseline GT-SNAPSHOT score	-0.18	-0.26, -0.09	**0.001**

Time from index to visit 2 (days) = -0.05 was extrapolated to 1 month.

SUMMARY

The results of our study indicate that patients with MG who initiated steroids demonstrated evidence of steroid toxicity in little as 90 days after initial exposure, which was significant for patients with 20+ mg at index with repeated use

Our results demonstrated that steroid toxicity was significantly greater in patients with steroid records of 20+ mg at index and repeated steroid usage in the follow-up period, with patients experiencing consistent elevation in steroid toxicity over time. The GTI-MD score was higher in the MG-SN than expected, which could be explained by age, previous steroid exposure, comorbidities, and side effects from other medications

These findings suggest the GTI-MD can be used in EHR data as a surrogate measure for steroid toxicity. Future studies should analyze the utility of the GTI-MD in managing patients on steroids more effectively

ABBREVIATIONS
AE, adverse event; AIS, Aggregate Improvement Score; BMI, body mass index; BP, blood pressure; CCI, Charlson Comorbidity Index; CI, confidence interval; COA, clinical outcome assessment; CWS, Cumulative Worsening Score; EHR, electronic health record; GT, glucocorticoid toxicity; GTI, Glucocorticoid Toxicity Index; GTI-MD, GTI-Metabolic Domains; GT-SNAPSHOT score, Glucocorticoid Toxicity SNAPSHOT score; HbA1c, glycated hemoglobin; IV, intravenous; LDL, low-density lipoprotein; MCID, minimal clinically important difference; MG, myasthenia gravis; NDC, National Drug Code; OR, odds ratio; SD, standard deviation; SI, steroid initiator; SN, steroid naïve.

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