Steroid toxicity in adults with myasthenia gravis in the United States based on electronic health records

EPO-409

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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 adverse events (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 its 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

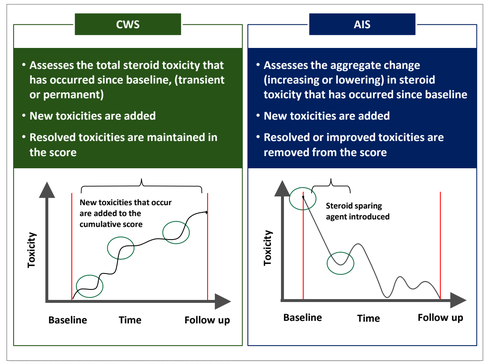
GTI	Weighted, standardized COA of steroid toxicity that uses 9 health domains to measure the change in toxicity between two time points.
GTI-MD	An abridged and validated version that correlates highly with the GTI to quantify steroid toxicity between two time points
GT-SNAPSHOT score	Assessment of glucocorticoid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

AIS, Aggregate Improvement Score; COA, clinical outcome assessment; CWS, Cumulative Worsening Score; GT-SNAPSHOT score, Glucocorticoid Toxicity SNAPSHOT score; GTI-MD, Glucocorticoid Toxicity Index-Metabolic Domain.

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



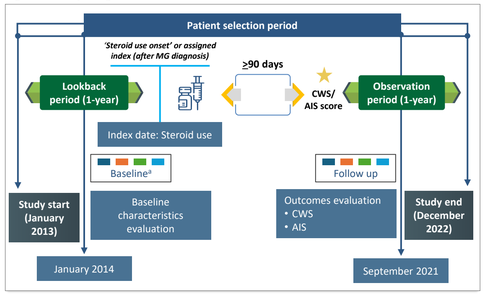
AIS, Aggregate Improvement Score; CWS, Cumulative Worsening Score.

Methods

Study description and data sources:

- A retrospective, real-world study was conducted using Optum® de-identified Electronic Health Record 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.
AIS, Aggregate Improvement Score; BMI, body mass index; BP, blood pressure; CWS, Cumulative Worsening Index; GTI-MD, Glucocorticoid Toxicity Index-Metabolic Domain; MG, myasthenia gravis.

- 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
- Cumulative Worsening Score assesses the total steroid toxicity that has occurred since baseline (transient or permanent)
- Aggregate Improvement Score 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

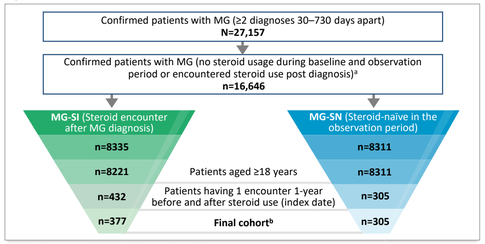
[a]The baseline period was 1-year pre-index, and the follow-up period was 1-year post-90-day steroid exposure period post-index. The limits of GTI-MD domains include LDL: 20–400 mg/dL; BMI: 15–50 Kg/m^2; HbA1c: 3%–20%; BP: 40–250 mmHg (systolic) and 30–150 mmHg (diastolic).
List of steroids: Prednisone, prednisone-diphenhydramine HCl methylprednisolone, methylprednisolone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, dexamethasone, hydrocortisone, hydrocortisone cypionate.
AE, adverse event; AIS, Aggregate Improvement Score; BMI, body mass index; BP, blood pressure; CCI, Charlson Comorbidity Index; CWS, Cumulative Worsening Score; GTI-MD, Glucocorticoid Toxicity Index-Metabolic Domain; HbA1c, glycated hemoglobin; IV, intravenous; LDL, low-density lipoprotein; NDC, National Drug Code.

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.
MG, myasthenia gravis; SI, steroid initiator; SN, steroid naïve.

Baseline demographics and clinical characteristics:

- Mean (standard deviation [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]

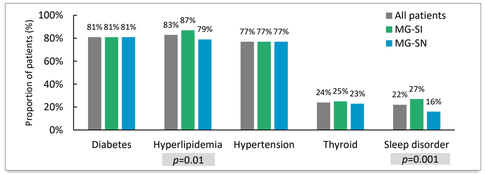
Table 2: Baseline demographics and clinical characteristics

	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 (%)[b]				
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 (%)[b]				
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 (%)[a]	383 (56)	212 (56)	171 (56)	0.96
Systolic BP, mean (SD) mmHg[b]	129 (16)	129 (17)	128 (15)	
Diastolic BP, mean (SD) mmHg[b]	74 (10)	74 (10)	73 (10)	
Antihypertensive medication use, n (%)[a]	505 (74)	280 (74)	225 (74)	0.88
LDL, mean (SD) mg/dL[b]	88.3 (34.0)	90.1 (34.3)	86.2 (33.5)	
Lipid-lowering medication use, n (%)[a]	419 (61)	234 (62)	185 (61)	0.71

[a]Medication capture has been checked for until the encounter date closest to Index date in the pre-period. [b]Test values of the encounter closest to the index date in the pre-steroid period has been considered.
BMI, body mass index; BP, blood pressure; CCI, Charlson Comorbidity Index; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; MG, myasthenia gravis; SD, standard deviation; SI, steroid initiator; SN, steroid naïve.

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

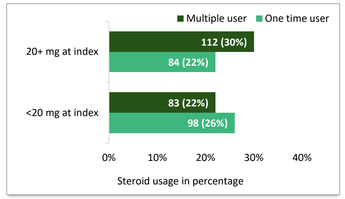
Figure 5: Baseline characteristics: Presence of common MG comorbidities



MG, myasthenia gravis; SI, steroid initiator; SN, steroid naïve.

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

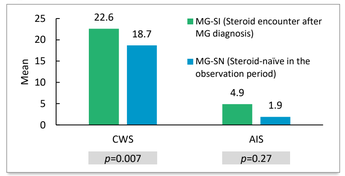
Figure 6. Steroid usage at index as per frequency and strength



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



AIS, Aggregate Improvement Score; CWS, Cumulative Worsening Score; GTI-MD, Glucocorticoid Toxicity Index-Metabolic Domains; MG, myasthenia gravis; SI, steroid initiator; SN, steroid naïve.

- 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

AIS, Aggregate Improvement Score; CWS, Cumulative Worsening Score; MCID, minimal clinically important difference; MG,, myasthenia gravis; SI, steroid initiator; SN, steroid naïve.

Limitations

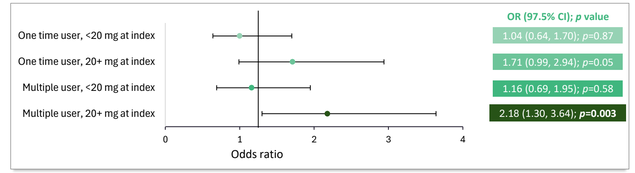
- The study was comprised of a small cohort size and incomplete steroid dosing capture in EHR data.
- Additional studies evaluating longer follow up periods, changes in steroid dosing, and a more diverse MG patient population are needed to assess the further applicability of GTI-MD in clinical practice.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

Conflict of interest: This study was funded by argenx US, Inc. (Boston, MA, USA). TR received honoraria and/or research support from Alexion, argenx, Biogen, Merck, Novartis and Roche. NG has served as a paid consultant for argenx, UCB, Janssen, and Alexion, and has grant support from argenx. MH consults for argenx, Alexion, Janssen, UCB, and Immunovant; received compensation as Guest Editor for Continuum Lifelong Learning in Neurology 2023; and is supported by UVM Medical Center grant for unrelated work. GP, CQ, and DG are employees of argenx. JS has consulted for argenx on glucocorticoid toxicity. JS's employer, the Massachusetts General Hospital, owns the intellectual property of the Glucocorticoid Toxicity Index (GTI). The intellectual property of the GTI-MD (Metabolic Domains) is co-owned by the Massachusetts General Hospital and Steritas, LLC. JS co-founded Steritas and is the chair of the Scientific Advisory Board but has no fiduciary responsibility at the company. MS is an employee of Steritas and AC is a consultant to Steritas. DA, RK, and AW are employees of ZS Associates (Evanston, IL, USA) and serve as paid consultants for argenx.

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).

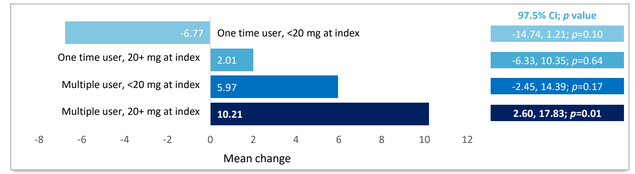
Figure 8. CWS as per frequency and strength of steroid use in MG-SI cohort with reference to MG-SN cohort (from visit 1 to visit 2)



CI, confidence interval; OR, Odds ratio.

- Similarly, patients in MG-SI cohort with multiple records and steroid records of 20+ mg strength at index have 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.
AIS, Aggregate Improvement Score; CCI, Charlson Comorbidity Index; CWS, Cumulative Worsening Score; GT, glucocorticoid toxicity.

- 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
AIS, Aggregate Improvement Score; CCI, Charlson Comorbidity Index; CI, confidence interval; GT, Glucocorticoid Toxicity.

Conclusion

- **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.**

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References:
1. Meriggioli MN, et al. *Expert Rev Clin Immunol.* 2012;8(5):427-38; 2. Sanders DB, et al. *Neurology.* 2016 Jul 26;87(4):419-25; 3 Farmakidis C, et al. *Neurol Clin.* 2018;36(2):311-37; 4. van Enkhuizen J, et al. *Ther Adv Neurol Disord.* 2024 Apr 16;17:17562864241237495.