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Risk of Serious Infections and Malignancies in Adult Myasthenia Gravis Patients: A US Claims Database Study

Jana Podhorna,[1] Kristin Heerlein,[1] Charlotte Ward,[2] Ikjae Lee,[3] Yuebing Li,[4] Tobias Ruck,[5] Elizabeth Teperov,[1] Ami Shah,[1] Jeffrey Guptill[1]

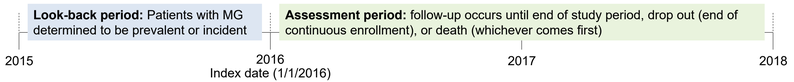
[1]argenx, Ghent, Belgium; [2]ZS Associates, Evanston, Illinois, USA; [3]Columbia University, New York, New York, USA; [4]Cleveland Clinic, Cleveland, Ohio, USA; [5]Department of Neurology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

INTRODUCTION

- MG is a rare and severe autoimmune disease associated with pathogenic autoantibodies directed against components at the NMJ[1,2]
- The autoimmune mechanism of disease, muscular weakness (especially respiratory weakness), and immunosuppressant therapies can increase the risk of infections and malignancies, although reports from the literature vary in their estimations of the magnitude of increased risk[3-10]
- To date, the majority of studies that have investigated the relationship between MG and various infections and malignancies have largely focused on a subset of the MG population and have been mostly non–US-based[7-11]
- This retrospective, propensity score–matched study used Optum's de-identified Market Clarity Data (Market Clarity) to evaluate the incidence rate of infections and malignancies in a real-world setting among patients with MG in comparison with a matched non-MG cohort[12]
  - Optum's de-identified Market Clarity Data deterministically links medical and pharmacy claims with EHR data from providers across the continuum of care for over 80 million patient histories[13]

METHODS

- Adult patients (aged ≥18 years) with continuous insurance enrollment during the look-back and assessment periods were identified for inclusion via ICD-9 and ICD-10 diagnosis codes and assigned an index date (first MG diagnosis) over an identification period between 1/1/2016 and 12/31/2017
  - Patients with malignancies (including malignant thymoma) within the 1-year look-back period were excluded
- Patients were matched (1:1) to patients without MG from a 5% random sample of the general population using propensity score matching (1% random sample previously reported)[a]
- Subgroup analyses based on history of immunosuppressants (1 claim) during the study period was performed[b]



[a]The following baseline characteristics were compared between the MG and general population groups: age at index (continuous), gender (male/female), CCI calculated based on comorbidities discovered in the 12-month period prior to index (continuous), geography at index (northeast, midwest, south, and west), insurance status at index (commercial, Medicare, Medicaid, and multiple), the calendar year of index, non-MG hospitalizations (continuous), presence of another autoimmune condition (yes/no), and presence of obesity (yes/no) in the 12 months prior to index. [b]ISTs included corticosteroids, NSISTs (azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate/mycophenolate mofetil, and tacrolimus), rituximab, and eculizumab.

SUMMARY

Patients with MG have a higher risk for serious infections, opportunistic infections, and infection-related deaths compared with a matched non-MG cohort

Pneumonia, sepsis, cellulitis, and influenza were common serious infections in patients with MG as well as in those with a history of IST use

Besides the expected increased risk for thymic malignancies, patients with MG had an increased risk of certain solid malignancies compared with a matched non-MG cohort

RESULTS

Table 1. Baseline Demographics and Matching Criteria in the Look-Back Period (Study Population)

Characteristic	Matched[a] MG patient population (N=5002)	General population (N=20008)	SMD[b]
Age, years, mean (SD)	61.94 (15.58)	61.67 (15.24)	0.01
18-39, n (%)	511 (10)	1868 (9)	
40-64, n (%)	2084 (42)	9057 (45)	
65+, n (%)	2407 (48)	9083 (45)	
Sex, n (%)			
Female	2703 (54)	11627 (58)	0.08
Male	2298 (46)	8381 (41)	
Unknown	1 (0)	- (0)	
CCI, mean (SD)	1.47 (1.75)	1.51 (1.92)	0.02
0, n (%)	1865 (37)	8154 (40)	
1-2, n (%)	2102 (42)	7417 (37)	
3-4, n (%)	683 (14)	2613 (13)	
≥5, n (%)	352 (7)	1824 (9)	
Coexisting autoimmune condition, n (%)	1234 (24)	5022 (25)	0.01
Obese/overweight, n (%)	1405 (28)	5794 (28)	0.02
Non-MG hospitalizations, n (%)	618 (12)	2768 (13)	0.01
Mean (SD)	0.21 (0.75)	0.27 (0.97)	
Median (range)	0.00 (0-12)	0.00 (0-25)	

[a]All demographic variables were determined at baseline while all clinical variables (CCI, obesity, autoimmune presence, and hospitalizations) were assessed during the 1-year look-back period. [b]SMD was used to assess the success of matching. A cutoff of 0.1 denotes acceptable balance.[13]

Table 2. MG Subgroup Population Baseline Characteristics

Characteristic of MG patient population	History of immunosuppressants (N=2215)	No history of immunosuppressants (N=2787)
Age, years, mean (SD)	60.85 (15.41)	62.8 (15.66)
Sex, n (%)		
Female	1205 (54)	1498 (54)
Male	1010 (46)	1288 (46)
Unknown	- (0)	1 (0)
CCI, mean (SD)	1.56 (1.84)	1.41 (1.68)
Coexisting autoimmune condition, n (%)	278 (13)	196 (7)
Obese/overweight, n (%)	658 (30)	747 (27)
Non-MG hospitalizations, n (%)	330 (15)	288 (10)

ABBREVIATIONS
CCI, Charlson comorbidity index; CNS, central nervous system; ED, emergency department; GI, gastrointestinal; ICD, International Classification of Diseases; IR, incidence rate; IRR, incidence rate ratio; IST, immunosuppressant; LRT, lower respiratory tract; MedDRA, Medical Dictionary for Regulatory Activities; MG, myasthenia gravis; NMJ, neuromuscular junction; NSIST, nonsteroidal immunosuppressive therapy; PY, person-year; SMD, standardized mean difference; URT, upper respiratory tract; UTI, urinary tract infection.

Table 3. Infections and Infection-Related Death[a]

	MG patient population (N=5002)			General population (N=20008)			IRR[b]	
	Number of events	PY[c]	IR per 1000 PY	Number of events	PY[c]	IR per 1000 PY	IRR	95% CI
Serious infection	454	8596	52.81	1040	33060	31.46	1.61	1.44-1.80
Opportunistic infection	722	8254	87.48	1835	32187	57.01	1.47	1.35-1.60
Infection by location								
Skin	1588	7187	220.96	5048	28359	178	1.18	1.12-1.25
Urine and kidney	1170	7726	151.44	3435	30334	113.24	1.28	1.20-1.36
Systemic	357	8713	40.97	967	33092	29.22	1.35	1.19-1.52
GI/liver/gallbladder	360	8675	41.50	1016	32915	30.87	1.29	1.15-1.46
Bone/joint/muscle	194	8830	21.97	641	33282	19.26	1.10	0.94-1.29
CNS	21	9026	2.33	24	33956	0.71	3.17	1.78-5.66
Pulmonary, URT	1818	6946	261.73	5698	27741	205.40	1.21	1.15-1.28
Pulmonary, LRT	1558	7315	212.99	4368	29563	147.75	1.37	1.30-1.45
Bronchitis	999	7934	125.91	2956	30906	95.65	1.26	1.17-1.35
Pneumonia	663	8382	79.10	1509	32637	46.24	1.64	1.50-1.80
Infection-related death[d]	35	9050	3.98	66	33978	1.94	1.93	1.28-2.90

[a]All infections were categorized based on ICD-10 classification. [b]To calculate IRR (95% CI), the Haldane-Anscombe correction factor (0.5) was used to define the IRR and correct zero cells. Only IRRs ≥1 with 95% CIs ≥1.00 are shown. [c]Person-years was defined as the total number of years all individuals were at risk of experiencing the outcome of interest. [d]We attributed death to the outcome by making the assumption that if the outcome happened in the same month/year or 2 weeks prior to the month/year of death, and if the visit was a hospitalization or ED visit, death was indeed related to the outcome of interest.

Table 4. Malignancy

Malignancies	MG patient population (N=5002)			General population (N=20008)			IRR[a]	
	Number of events	PY[b]	IR per 1000 PY	Number of events	PY[b]	IR per 1000 PY	IRR	95% CI
Thymic	53	8984	5.90	0	33977	0	388.98	24.02-6299.97
Eye, brain, and CNS	19	9032	2.10	29	33958	0.85	2.39	1.35-4.23
Male genital organs	67	8983	7.46	163	33812	4.82	1.49	1.12-1.98
Melanoma and other skin	267	8790	30.38	736	33230	22.15	1.32	1.15-1.52
Any malignancy	619	8416	73.55	1619	32376	50.01	1.41	1.29-1.55
Malignancy-related death[c]	5	9050	0.55	11	33978	0.29	1.73	0.67-5.31

[a]To calculate IRR (95% CI), the Haldane-Anscombe correction factor (0.5) was used to define the IRR and correct zero cells. [b]Person-years was defined as the total number of years all individuals were at risk of experiencing the outcome of interest. [c]We attributed death to the outcome, by making the assumption that if the outcome happened in the same month/year or 2 weeks prior to the month/year of death, and if the visit was a hospitalization or ED visit, death was indeed related to the outcome of interest.

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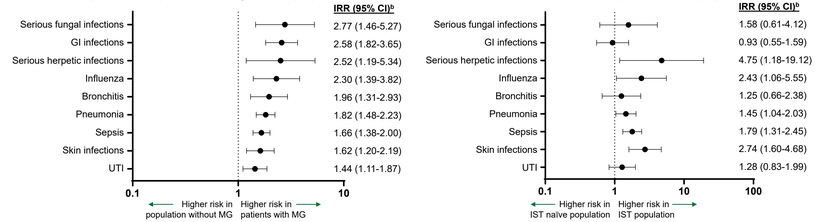
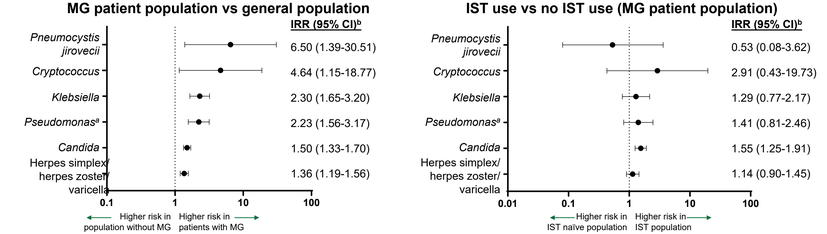
1. Conti-Fine BM, et al. *J Clin Invest.* 2006;116(11):2843-2854. **2.** Behin A, Le Panse R. *J Neuromuscul Dis.* 2018;5(3):265-277. **3.** Gilhus NE, et al. *Eur J Neurol.* 2015;22(1):17-23. **4.** Prior DE, et al. *Muscle Nerve.* 2018;57(6):927-931. **5.** Gilhus NE, Verschuuren JJ. *Lancet Neurol.* 2015;14(10):1023-1036. **6.** Fardet L, et al. *PLoS Med.* 2016;13(5):e1002024. **7.** Yeh JH, et al. *Neuromuscul Disord.* 2014;24(3):245-249. **8.** Pedersen EG, et al. *Eur J Neurol.* 2014;21(5):773-778. **9.** Liu CJ, et al. *Eur J Neurol.* 2012;19(5):748-751. **10.** Su M, et al. *Front Cell Infect Microbiol.* 2022;12:1018728. **11.** Tlamkao S, et al. *Neurosciences.* 2014;19(4):286-290. **12.** Non-interventional Study Protocol v2.0, 25 Apr 2023. **13.** Market Clarity Product Sheet. 2024. Accessed August 30, 2024. https://www.optum.com/content/dam/o4-dam/resources/pdfs/sell-sheets/mc-sell-sheet.pdf. **14.** Austin PC. *Stat Med.* 2009;28(25):3083-3107.

Figure 1. Serious Infections[a]



[a]Serious infections were defined as requiring an ED visit or hospitalization with an admitting diagnosis or "most" responsible (primary) diagnosis of infection or resulting in death [b]To calculate IRR (95% CI), the Haldane-Anscombe correction factor (0.5) was used to define the IRR and correct zero cells.

Figure 2. Opportunistic Pathogens



Due to the limited mapping between MedDRA and ICD codes for opportunistic infections, the current approach used MedDRA as a guide, but largely relied upon what was used in the ICD along with medical judgment to select pathogens that are known to cause opportunistic infections

[a]Including *Burkholderia* and *Stenotrophomonas*. [b]To calculate IRR (95% CI), the Haldane-Anscombe correction factor (0.5) was used to define the IRR and correct zero cells.

ACKNOWLEDGMENTS AND DISCLOSURES: **CW** is a consultant with ZS associates. **IL** has received research funding from the National Institutes of Health, Myasthenia Gravis Foundation of America, American Academy of Neurology, CTeATe consortium, and American Brain Foundation, and received consulting fees/honoraria from AmyArx, Alexion, Regeneron, Roche/Genentech, MedLink, and Medscape. None of the funders influenced the study design or analysis. **YL** has received research support from argenx and served as a consultant for argenx, UCB Pharma, Alexion, Catalyst, and Immunovant. **TR** has received consulting fees/honoraria or support for meeting participation from Abbott, Alexion Pharmaceuticals, Inc, argenx BV, Biogen Inc, Celgene, Merck, Novartis, Roche, Teva, and UCB. **JP, ET, AS,** and **JG** are employees of argenx. Medical writing and editorial support for this presentation was provided by PrAssion AG and funded by argenx.

Presented at the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting; October 15-18, 2024; Savannah, Georgia