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Analysis of Serious Infections and Malignancy Risk in Myasthenia Gravis: A US Claims Database Study

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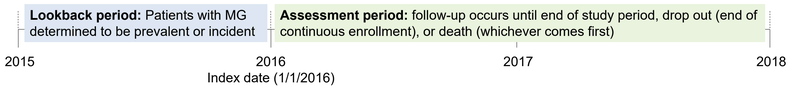
INTRODUCTION

- MG is a rare and severe autoimmune disease associated with pathogenic autoantibodies directed against the NMJ[1]
- The autoimmune nature of MG, associated muscular weakness (especially respiratory weakness), and immunosuppressant therapies can increase the risk of infections and malignancies, although the results are not consistent in the literature[2-9]
- 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[6-10]
- This retrospective, propensity score–matched study used deidentified Optum® Market Clarity claims dataset 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[11]
  - Optum® Market Clarity claims dataset links medical and pharmacy claims across 100 million patient histories in the US[12]

METHODS

- Adult patients (aged ≥18 years) with continuous insurance enrollment during the lookback 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 lookback period were excluded
- Patients were matched (1:1) to patients without MG from a 1% random sample of the general population using propensity score matching[a]
  - Study results are being confirmed using a 5% random sample
- Subgroup analyses based on history of immunosuppressants (2 claims) during the lookback period was performed[b]



[a]The following baseline characteristics were compared between the MG and general population groups: age at index (continuous), sex at index (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

Additional analyses are being conducted to further investigate the relationship between MG and associated therapies with risk for various infections and malignancies

RESULTS

Table 1. Baseline Demographics and Matching Criteria in the Lookback Period (Study Population)

	Matched[a]		
Characteristic	**MG patient population (N=5002)**	**General population (N=3818)**	**SMD[b]**
Age, years, mean (SD)	61.94 (15.58)	60.82 (16.23)	0.09
18-40, n (%)	511 (10)	462 (12)	
40-65, n (%)	2084 (42)	1600 (42)	
65+, n (%)	2407 (48)	1756 (46)	
Sex, n (%)			
Female	2703 (54)	2195 (57)	0.06
Male	2298 (46)	1623 (43)	
Unknown	1 (0)		
CCI, mean (SD)	1.47 (1.75)	1.63 (1.98)	0.05
0, n (%)	1865 (37)	1420 (37)	
1-2, n (%)	2102 (42)	1485 (39)	
3-4, n (%)	683 (14)	545 (14)	
≥5, n (%)	352 (7)	368 (10)	
Coexisting autoimmune condition, n (%)	474 (9)	392 (10)	0.02
Obese/overweight, n (%)	1405 (28)	1245 (33)	0.09
Non-MG hospitalizations, n (%)	618 (12)	493 (13)	0.01
Mean (SD)	0.21 (0.75)	0.24 (0.94)	
Median (range)	0.00 (0-12)	0.00 (0-26)	

[a]All demographic variables were determined at baseline while all clinical variables (CCI, obesity, autoimmune presence, and hospitalizations) were assessed during the 1-year lookback 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

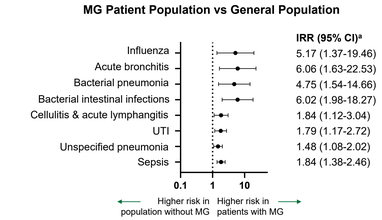
CCI, Charlson comorbidity index; CNS, central nervous system; ED, emergency department; GI, gastrointestinal; ICD, International Classification of Diseases; IR, incidence rate; IRR, incidence rate ratio; IST, immunosuppressant; LRT, lower respiratory tract; MedDRA, Medical Dictionary for Regulatory Activities; 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.

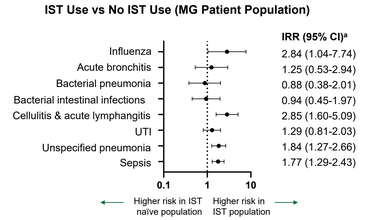
Table 3. Infections and Infection-Related Death[a]

	MG patient population (N=5002)			General population (N=3818)			IRR[b]	
	Number of events	**PY[c]**	**IR per 1000 PY**	**Number of events**	**PY**	**IR per 1000 PY**	**IRR**	**95% CI**
Serious infection	454	8596	52.81	188	6386	29.44	1.83	1.54-2.16
Opportunistic infection	722	8254	87.48	356	6190	57.51	1.55	1.36-1.76
Infection by location								
Skin	1343	7479	179.57	814	5576	146.00	1.26	1.15-1.37
Urine and kidney	1167	7729	150.99	647	5867	110.28	1.40	1.27-1.54
Systemic	357	8714	40.97	197	6355	31.00	1.35	1.13-1.60
GI/liver/gallbladder	306	8744	34.99	139	6404	21.70	1.64	1.34-2.00
Bone/joint/muscle	194	8831	21.97	113	6420	17.60	1.27	1.01-1.60
CNS	21	9026	2.33	4	6545	0.61	3.53	1.28-9.76
Pulmonary, URT	1818	6946	261.73	1108	5323	208.14	1.28	1.19-1.38
Pulmonary, LRT	1555	7320	212.43	864	5655	152.77	1.42	1.30-1.54
Bronchitis	999	7934	125.91	571	5956	95.87	1.34	1.21-1.48
Pneumonia	659	8388	78.56	308	6253	49.26	1.62	1.42-1.86
Infection-related death[d]	36	9050	3.98	10	6547	1.53	2.57	1.29-5.10

[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.

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.

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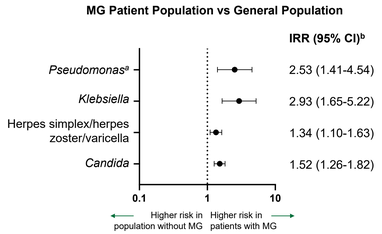
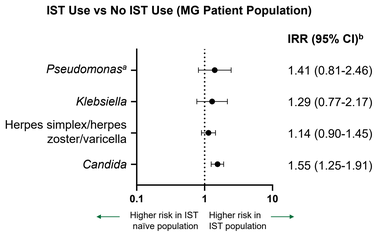
1. Conti-Fine BM, et al. *J Clin Invest*. 2006;116(11):2843-2854. **2.** Gilhus NE, et al. *Eur J Neurol*. 2015;22(1):17-23. **3.** Prior DE, et al. *Muscle Nerve*. 2018;57(6):927-931. **4.** Gilhus NE, Verschuuren JJ. *Lancet Neurol*. 2015;14(10):1023-1036. **5.** Fardet L, et al. *PLoS Med*. 2016;13(5):e1002024. **6.** Yeh JH, et al. *Neuromuscul Disord*. 2014;24(3):245-249. **7.** Pedersen EG, et al. *Eur J Neurol*. 2014;21(5):773-778. **8.** Liu CJ, et al. *Eur J Neurol*. 2012;19(5):746-751. **9.** Su M, et al. *Front Cell Infect Microbiol*. 2022;12:1016728. **10.** Tiamkao S, et al. *Neurosciences*. 2014;19(4):286-290. **11.** Non-interventional Study Protocol v1.0, 25 Apr 2023. **12.** Optum ® Market Clarity Product Sheet. 2020. Accessed March 7, 2024. optum.com/marketclarityadata. **13.** Austin PC. *Stat Med*. 2009;28(25):3083-3107.

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.

Table 4. Malignancy

	MG Patient Population (N=5002)			General Population (N=3818)			IRR[a]	
Malignancies	**Number of events**	**PY[b]**	**IR per 1000 PY**	**Number of events**	**PY**	**IR per 1000 PY**	**IRR**	**95% CI**
Thymic	53	8984	5.90	0	6547	0.00	79.50	4.91-1287.63
Eye, brain, and CNS	19	9032	2.10	2	6544	0.31	5.76	1.54-21.51
Male genital organs	67	8983	7.46	32	6511	4.91	1.54	1.01-2.33
Melanoma and other skin	267	8790	30.38	136	6405	21.23	1.46	1.19-1.79
Any malignancy	619	8416	73.55	298	6251	47.67	1.57	1.37-1.80
Malignancy-related death[c]	5	9050	0.55	1	6547	0.15	2.71	0.44-16.46

[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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