Risk of Non-infectious Uveitis or Myasthenia Gravis in Patients on Checkpoint Inhibitors

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Summary

- Exposure to checkpoint inhibitor chemotherapy confers a higher risk for non-infectious uveitis and myasthenia gravis compared to non-checkpoint inhibitor chemotherapy

Background

- Immune checkpoint inhibitors (CPI) target CTLA-4, PD1-, PDL-1 specific to cancer pathways.
- Current checkpoint inhibitors: ipilimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab.
- Cancers: metastatic melanoma, non-small cell lung cancer, gastric cancer, renal cell cancer, small cell lung cancer, head/neck cancer, urothelial carcinoma, hepatocellular carcinoma, cervical cancer, and merkel cell carcinoma.

Background

- Ocular side effects
  - Conjunctivitis, dry eyes, uveitis, myasthenia gravis, optic neuropathy, thyroid ophthalmopathy, Vogt-Koyanagi-Harada-like syndrome, retinal vasculitis, cranial nerve palsies, papillitits and others
- Incidence rates 1-6%.

- **Purpose: To evaluate the risk of developing non-infectious uveitis and myasthenia gravis after use of checkpoint inhibitor chemotherapy using an administrative claims database from a large US insurer.**

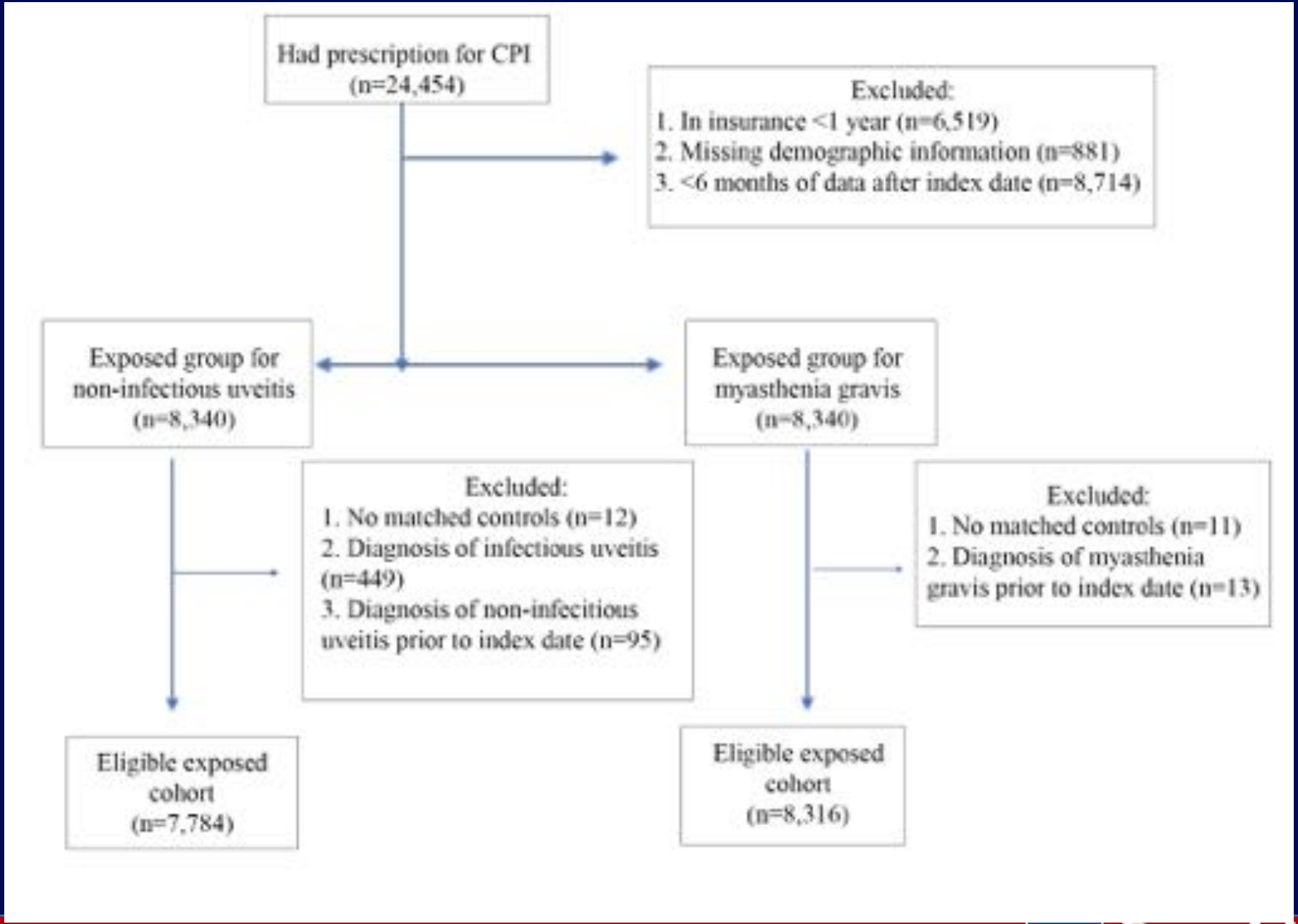
Methods

- Optum's de-identified Clinformatic Data Mart Database
- Dates: 1/1/2010- 6/30/2019
- Exposed group: all patients who used an CPI (NDC/CPT codes)
- Control group: age, gender, race, and index year matched 10-1 for every exposed
- Cox proportional hazards regression analysis

ICD 9 and ICD 10 diagnosis codes

Diagnosis	ICD9 Code	ICD10 Code
Non-infectious uveitis	01x.xx, 017.3, 053.2x, 054.4x, 078.5, 088.81, 09x.xx, 091.51, 098.41, 104.00, 115.92, 115.02, 130.2, 135, 137.xx, 360.x, 360.11, 360.12, 360.13, 360.18, 360.19, 362. 18, 363.00, 363.01, 363.02, 363.03, 363.04, 363.05, 363.06, 363.07, 363.10, 363.11, 363.12, 363.13, 363.15, 363.2, 363.21, 363.22, 363.08, 363.13, 364.00, 364.01, 364.02, 364. 03, 364.04, 364.05, 364.10, 364.11, 364.21, 364.23, 364.24, 364.3, 647.0x, 647.3x, 771.2, 871.7, 906.3, 908.8, 921.x, E 930.6, E946.5	A15.x, A17.x, A18.x, A18.53, A19.x, A50.x, A 51.x, A52.x, A51.43, A54.32, A69.2x, B00.5x, B02.3x, B25.9 B39.4, B39.9, B58.x, D86.83, H20.00, H20.01x, H20.02x, H20.03x, H20.05x, H20.1x, H20.2x, H20.04x, H20.81x, H20.82x, H20.9, H30.01x, H30.02x, H30.03x, H30.04x, H30.1x, H30.13x, H30.2x, H30.89x, H30.9x, H32,H33.00x, H35.06x, H44.00x, H44.11x, H44.12x, H44.13x, H44.19, P37.1x, S05.x, T36.6x5a, T49.5x5a,
Myasthenia gravis	358.00, 358.01	G70.00, G70.01
	CPT	
Checkpoint inhibitors	J9228, J9271, J9299, J9022, C9491, C9399, J9023, C9492, J9173	
Non- CPI chemotherapy	96401, 96402, 96403, 96404, 96405, 96406, 96407, 96408, 96409, 96410, 96411, 96412, 96413, 96414, 96415, 96416, 96417, 96420, 96421, 96422, 96423, 96424, 96425, 96440, 96446, 96450, 96521, 96522, 96523, 96542, 96549	

Results


Had prescription for CPI (n=24,454)
Excluded:
1. In insurance <1 year (n=6,519)
2. Missing demographic information (n=881)
3. <6 months of data after index date (n=8,714)
Exposed group for non-infectious uveitis (n=8,340)
Exposed group for myasthenia gravis (n=8,340)
Excluded:
1. No matched controls (n=12)
2. Diagnosis of infectious uveitis (n=449)
3. Diagnosis of non-infecitious uveitis prior to index date (n=95)
Excluded:
1. No matched controls (n=11)
2. Diagnosis of myasthenia gravis prior to index date (n=13)
Eligible exposed cohort (n=7,784)
Eligible exposed cohort (n=8,316)

Results

Non-Infectious Uveitis				
	Checkpoint (N=7784)	**Chemotherapy (N=56661)**	**Total (N=64445)**	**p value**
Age Mean (SD)	72.11 (9.90)	70.92 (10.41)	71.06 (10.36)	< 0.001
Gender				< 0.001
Female	3372 (43.3%)	26357 (46.5%)	29729 (46.1%)	
Male	4412 (56.7%)	30304 (53.5%)	34716 (53.9%)	
Race				< 0.001
White	6013 (77.2%)	44561 (78.6%)	50574 (78.5%)	
Asian	187 (2.4%)	991 (1.7%)	1178 (1.8%)	
Black	867 (11.1%)	6085 (10.7%)	6952 (10.8%)	
Hispanic	482 (6.2%)	3848 (6.8%)	4330 (6.7%)	
Unknown	235 (3.0%)		1411 (2.2%)	
Uveitis				0.016
No Uveitis	7758 (99.7%)	56548 (99.8%)	64306 (99.8%)	
Uveitis	26 (0.3%)	113 (0.2%)	139 (0.2%)	

Myasthenia Gravis				
	Checkpoint (N=8316)	**Chemotherapy (N=60464)**	**Total (N=68780)**	**p value**
Age Mean (SD)	72.23 (9.85)	71.01 (10.36)	71.16 (10.31)	< 0.001
Gender				< 0.001
Female	3591 (43.2%)	28290 (46.8%)	31881 (46.4%)	
Male	4725 (56.8%)	32174 (53.2%)	36899 (53.6%)	
Race				< 0.001
White	6420 (77.2%)	47499 (78.6%)	53919 (78.4%)	
Asian	201 (2.4%)	1066 (1.8%)	1267 (1.8%)	
Black	932 (11.2%)	6537 (10.8%)	7469 (10.9%)	
Hispanic	508 (6.1%)	4072 (6.7%)	4580 (6.7%)	
Unknown	255 (3.1%)	1290 (2.1%)	1545 (2.2%)	
Myasthenia				0.009
No Myasthenia	8305 (99.9%)	60431 (99.9%)	68736 (99.9%)	
Myasthenia	11 (0.1%)	33 (0.1%)	44 (0.1%)	

Results

- After multivariate analysis controlling for age, gender, race, index year, exposure to CPI conferred:
  - increase hazard for uveitis (HR=1.83; 95% CI 1.19-2.82, p=0.006)
  - increase hazard for myasthenia gravis (HR=2.37; 85% CI 1.21-4.65, p=0.012)

Discussion

- First epidemiologic study to assess incidence of uveitis and myasthenia gravis in checkpoint inhibitors.
- The incidence rates in a large healthcare database are low for both non-infectious uveitis and myasthenia gravis in patients exposed to checkpoint inhibitors.
- Exact mechanism of ocular side effects is unknown but likely related to T–cell activation and cross reactivity of tumor cells and normal tissue.
- Caution is advised when managing patients with ocular side effects on checkpoint inhibitors.

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