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BRIEF COMMUNICATION

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Abstract

We performed a population-based case–control study of United States Medicare beneficiaries age 60–90 in 2009 with prescription data (48,295 incident Parkinson disease cases and 52,324 controls) to examine the risk of Parkinson disease in relation to use of immunosuppressants. Inosine monophosphate dehydrogenase inhibitors (relative risk = 0.64; 95% confidence interval 0.51–0.79) and corticosteroids (relative risk = 0.80; 95% confidence interval 0.77–0.83) were both associated with a lower risk of Parkinson disease. Inverse associations for both remained after applying a 12-month exposure lag. Overall, this study provides evidence that use of corticosteroids and inosine monophosphate dehydrogenase inhibitors might lower the risk of Parkinson disease.

Introduction

Numerous studies have attempted to identify neuroprotective medications to slow the progression of Parkinson disease (PD), but all have failed to meet primary endpoints.[1–5] As a result, there are no approved medications that alter PD progression. One potential reason for the failure of these clinical trials is that all attempts to modify disease course with putative neuroprotective medications were in patients with established PD. In an attempt to identify PD patients during their prodromal phase, we recently developed a PD predictive model that uses administrative data from the Medicare program.[6] In this model, several diagnoses commonly treated with immunosuppressants were inversely associated with PD. In this study, we performed a targeted pharmacoepidemiology analysis to investigate the risk of PD in relation to immunosuppressant use.

Methods

Study design

We conducted a population-based case–control study using Medicare claims data from the United States (U.S.), following approval from the Centers for Medicare and Medicaid (CMS), and the Institutional Review Board at Washington University in St. Louis. Medicare is the U.S. national health insurance for those 65 and older, as well as the disabled, and provides health care for 98% of the U.S. population age 65 and older. Approximately, 25% of those age 65–90 who receive Medicare use a Medicare Advantage plan, which does not report claims data to the CMS. As a result, data from those patients cannot be included in this study. Approximately, 50% of those with traditional fee-for-service Medicare use Medicare Part D to pay for prescription medication costs. All participants were U.S. residents who were age 66–90 years old and relied solely on Medicare for health insurance (Parts A/B) in 2009.[6] For the present analysis, we further focused on beneficiaries with Medicare Part D (pharmacy) coverage with at least one prescription drug claim (medication fill) in 2008–2009.

Among beneficiaries who met these criteria, we determined PD status from comprehensive (inpatient, skilled nursing facility, outpatient, physician/carrier, durable medical equipment, and home health care) Part A and B Medicare claims data for 2004–2009. PD cases (n = 48,295) had at least one International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnosis code for PD (332 or 332.0) in 2009 and no prior PD codes. Using this case definition, we have been able to replicate all of the well-established PD-disease/demographic associations.[6] Controls (n = 52,324) were from a random sample of beneficiaries who met the same criteria, but without PD codes. These beneficiaries represented 54% of cases and 44% of controls from the original case–control study,[6] which included all newly diagnosed PD cases in 2009 and a 0.5% random sample of all noncases who met study criteria. We avoided matching controls to cases so that we could obtain unbiased risk estimates for demographic factors known to be associated with PD and, hence, include them in a predictive model of PD, the primary purpose of the sample.[6] Regression models that adjust for potential matching variables are a suitable alternative to matching,[7] especially when there is sufficient overlap between cases and controls on matching factors, as in our study. This approach also avoids potential loss in statistical power due to matching.[8]

Assessment of covariates and immunosuppressant use

We identified ever/never use of seven immunosuppressant drug classes and 26 specific medications in those classes in 2008–2009, prior to PD diagnosis/reference, using Part D data. The categories included calcineurin inhibitors (cyclosporine, tacrolimus); Inosine monophosphate dehydrogenase (IMDH) inhibitors (azathioprine, leflunomide, mycophenolate); dihydrofolate reductase inhibitors (methotrexate); biologics (abatacept, adalimumab, anakinra, certolizumab, etanercept); corticosteroids (prednisone, prednisolone, methylprednisolone, dexamethasone, cortisone, hydrocortisone); and miscellaneous (hydroxychloroquine, sulfasalazine, mesalamine, interferon beta-1a, thalidomide, lenalidomide, glatiramer acetate, flingolimod, and dimethyl fumarate). Other immunosuppressants were used too infrequently to be included in these analyses. Only oral, rectal, or parenteral forms of medications were considered for these analyses. We used ICD-9 and Current Procedural Terminology (CPT) codes from 2004 to 2009, up to the time of PD diagnosis/reference, to assess ever/never tobacco smoking. Because there were no specific incentives for physicians to code smoking behaviors during the time window of this study, we estimated and validated the probability of having ever smoked based on >600 codes, sex, race/ethnicity, and birth year.[6] The relationship between this smoking variable and PD risk reasonably approximated the known inverse association demonstrated in numerous previous studies.[6,9] We also calculated the total number of unique diagnosis codes prior to PD diagnosis/reference as a measure of overall use of medical care.

Statistical analysis

We used Stata MP version 14.2 (College Station, Texas) to construct logistic regression models with PD as the outcome and specific immunosuppressants as independent variables. We used the odds ratios (ORs) and 95% confidence intervals (CIs) from these models to estimate relative risk (RR), since PD is uncommon. We adjusted for age, sex, race/ethnicity, smoking, and count of unique diagnosis codes a priori.[6] We also examined the effect of lagging medication exposure by 12 months. The purpose of lagging the medication exposure was to minimize any effect on the association with PD due to reverse causation, whereby, symptoms of prodromal PD result in preferential use or avoidance of a medication. We applied this lag by ignoring immunosuppressant use that occurred in the 12 months prior to the PD diagnosis date or control reference date, and excluding cases and controls who

had no fills of any medication prior to that 12-month period. To investigate for potential confounding by indication, we tested the effect of including every ICD-9/CPT code, individually, in the association models for corticosteroids and IMDH inhibitors. We retained in the final model any code that altered the respective PD-immunosuppresant RR by more than 10% and was a code that was a medically appropriate indication for immunosuppressants.

Role of the funding source

The coauthors were solely responsible for all decisions related to statistical analysis, interpretation of results, and decision to publish.

Results

Characteristics of cases and controls

Most cases and controls were non-Hispanic white (Table 1), consistent with demographic characteristics of the general adult and PD population in the U.S. We observed the expected greater risk of PD with increasing age (case mean 78.6 years, control mean 76.4 years), male sex, and lower risk with tobacco use (all $P < 0.001$).

Immunosuppressant class and PD risk

Of the six categories of immunosuppressants, two were clearly associated with a lower risk of PD: Corticosteroids (RR = 0.80; 95% CI 0.77–0.83) and IMDH inhibitors (RR = 0.64; 95% CI 0.51–0.79). (Tables 2 and 3) These findings were consistent when imposing a 12-month lag on medication "exposure" (Tables 2 and 3) or adjusting for indications associated with smoking (e.g., chronic obstructive pulmonary disease and asthma (results not shown)). The other classes of immunosuppressants were not as clearly inversely associated with PD risk, although those taking methotrexate had a borderline lower risk of PD (RR = 0.84; 95% CI 0.74–0.95). When we investigated for confounding by indication, no ICD-9/CPT codes altered the respective PD-immunosuppresant RR by more than 10% and were a medically appropriate indication for immunosuppressant use.

Specific IMDH inhibitors and corticosteroids and PD risk

When we considered medications within the IMDH inhibitor category, each was consistently associated with a lower risk of PD. Mycophenolate was associated with the lowest risk of PD (RR = 0.55; 95% CI 0.31–0.98),

Table 1. Characteristics of incident Parkinson disease (PD) cases and controls with Medicare Part D pharmacy coverage, Medicare 2009.

	PD cases[1] *N* = 48,295 No lag	Controls[1] *N* = 52,324 No lag	PD cases[1] *N* = 43,095 12-month lag	Controls[1] *N* = 46,341 12-month lag
Age, y				
66–69	8.6	16.7	8.4	15.9
70–74	20.1	28.3	20.0	28.2
75–79	24.2	22.3	24.4	22.5
80–84	26.7	19.2	26.7	19.6
85–90	20.4	13.4	20.6	13.8
Range	66–90	66–90	66–90	66–90
Mean (SD)	78.6 (6.1)	76.4 (6.3)	78.7 (6.1)	76.5 (6.3)
Female	57.3	64.6	58.5	65.7
Race/ethnicity				
White	85.5	83.7	85.5	83.8
Black	6.9	7.8	6.8	7.9
Pacific Islander/other	1.1	1.6	1.1	1.5
Asian	2.7	3.4	2.8	3.4
Hispanic	3.3	2.9	3.4	2.9
Native American	0.4	0.4	0.3	0.4
Unknown	0.1	0.1	0.1	0.1
Smoking index[2] ≥ median	38.4	51.5	36.8	49.8

PD, Parkinson disease.

[1]Excludes cases and controls from the original study[6] who had no Part D (pharmacy) coverage in 2008–2009 or who had coverage but no medication fills in the respective time period.

[2]Predicted probability of ever smoking divided by the person's total number of unique diagnosis codes.

Table 2. Relative risk and 95% confidence intervals for corticosteroids in relation to Parkinson disease (PD), by medication class[1] and exposure lagging.

	No lag[1,2]	12-month lag[1,2]
PD Cases, *N*	48,295	43,095
Controls, *N*	52,324	46,341
Drug class/medication		
Any corticosteroids[3]		
PD cases, *N* (%)	8793 (18.21)	3862 (8.96)
Controls, *N* (%)	9318 (17.81)	4263 (9.20)
RR (CI)[4]	0.80 (0.77–0.83)	0.81 (0.77–0.85)
Prednisone		
PD cases, *N* (%)	6113 (12.66)	2748 (6.38)
Controls, *N* (%)	6219 (11.89)	2961 (6.39)
RR (CI)[4]	0.81 (0.78–0.85)	0.81 (0.77–0.86)
Prednisolone		
PD cases, *N* (%)	56 (0.12)	24 (0.06)
Controls, *N* (%)	31 (0.06)	12 (0.03)
RR (CI)[4]	1.47 (0.92–2.35)	1.67 (0.81–3.43)
Methylprednisolone		
PD cases, *N* (%)	3232 (6.69)	1173 (2.72)
Controls, *N* (%)	3720 (7.11)	1377 (2.97)
RR (CI)[4]	0.80 (0.76–0.84)	0.80 (0.74–0.87)
Dexamethasone		
PD cases, *N* (%)	384 (0.80)	100 (0.23)
Controls, *N* (%)	441 (0.84)	158 (0.34)
RR (CI)[4]	0.76 (0.66–0.88)	0.60 (0.46–0.79)
Hydrocortisone		
PD cases, *N* (%)	79 (0.16)	38 (0.09)
Controls, *N* (%)	67 (0.13)	30 (0.06)
RR (CI)[4]	0.75 (0.53–1.06)	1.08 (0.65–1.79)

PD, Parkinson's disease; RR, relative risk; CI, confidence interval; IMDH, Inosine monophosphate dehydrogenase.

[1]Overall category counts may not add to the total of individual medications in the category due to the potential for use of more than one medication.

[2]Excludes cases and controls from the original study who had no Part D (pharmacy) coverage in 2008–2009 or who had coverage but no medication fills in the respective time period: No lag means that we included in the analysis any medication prescribed up to PD diagnosis/control reference date while 12-month lag means that we included any medication prescribed up to the year prior to this date.

[3]Also includes cortisone, but RRs could not be estimated due to small numbers.

[4]Adjusted for age (two linear splines with a knot at 85 years), sex, race/ethnicity (7 categories), probability of ever/never smoking (continuous), and total count of unique diagnosis codes (continuous for the respective period, that is, up to PD diagnosis/control reference date or up to 12 months prior to that date).

although the number of patients taking this drug was small, and the CIs were relatively wide. Within the corticosteroid category, the steroids most strongly associated with PD were those used commonly for long-term immunosuppression: Prednisone (RR = 0.81; 95% CI 0.78–0.85); dexamethasone (RR = 0.76; 95% CI 0.66–

Table 3. Relative risk and 95% confidence intervals for immunosuppressants in relation to Parkinson disease (PD), by medication class[1] and exposure lagging.

	No lag[1,2]	12-month lag[1,2]
PD Cases, *N*	48,295	43,095
Controls, *N*	52,324	46,341
Drug class/medication		
Any calcineurin inhibitor[3]		
PD cases, *N* (%)	26 (0.05)	22 (0.05)
Controls, *N* (%)	20 (0.04)	18 (0.04)
RR (CI)[4]	0.91 (0.49–1.70)	1.10 (0.58–2.09)
Any IMDH Inhibitor		
PD cases, *N* (%)	172 (0.36)	108 (0.25)
Controls, *N* (%)	220 (0.42)	140 (0.30)
RR (CI)[4]	0.64 (0.51–0.79)	0.73 (0.56–0.94)
Azathioprine		
PD cases, *N* (%)	82 (0.17)	51 (0.12)
Controls, *N* (%)	98 (0.19)	64 (0.14)
RR (CI)[4]	0.71 (0.52–0.96)	0.79 (0.54–1.16)
Leflunomide		
PD cases, *N* (%)	70 (0.14)	42 (0.10)
Controls, *N* (%)	97 (0.19)	55 (0.12)
RR (CI)[4]	0.59 (0.43–0.82)	0.71 (0.47–1.08)
Mycophenolate		
PD cases, *N* (%)	24 (0.05)	15 (0.03)
Controls, *N* (%)	29 (0.06)	22 (0.05)
RR (CI)[4]	0.55 (0.31–0.98)	0.55 (0.28–1.08)
Any dihydrofolate reductase inhibitor[5]		
PD cases, *N* (%)	506 (1.05)	352 (0.82)
Controls, *N* (%)	562 (1.07)	411 (0.89)
RR (CI)[4]	0.84 (0.74–0.95)	0.86 (0.74–0.99)
Any Biologics[6]		
PD cases, *N* (%)	82 (0.17)	61 (0.14)
Controls, *N* (%)	99 (0.19)	71 (0.15)
RR (CI)[4]	0.76 (0.56–1.04)	0.90 (0.63–1.28)
Adalimumab		
PD cases, *N* (%)	41 (0.08)	30 (0.07)
Controls, *N* (%)	48 (0.09)	31 (0.07)
RR (CI)[4]	0.83 (0.53–1.29)	1.04 (0.62–1.75)
Etanercept		
PD cases, *N* (%)	47 (0.10)	31 (0.07)
Controls, *N* (%)	54 (0.10)	41 (0.09)
RR (CI)[2]	0.75 (0.50–1.15)	0.79 (0.48–1.28)
Any Miscellaneous[7]		
PD cases, *N* (%)	730 (1.51)	480 (1.11)
Controls, *N* (%)	750 (1.43)	490 (1.06)
RR (CI)[4]	0.85 (0.76–0.95)	0.93 (0.81–1.06)
Hydroxychloroquine		
PD cases, *N* (%)	328 (0.68)	220 (0.51)
Controls, *N* (%)	373 (0.71)	252 (0.54)
RR (CI)[4]	0.77 (0.65–0.90)	0.83 (0.68–1.00)
Sulfasalazine		
PD cases, *N* (%)	143 (0.30)	92 (0.21)
Controls, *N* (%)	145 (0.28)	90 (0.19)
RR (CI)[4]	0.88 (0.69–1.13)	0.99 (0.73–1.34)
Mesalamine		
PD cases, *N* (%)	220 (0.46)	144 (0.33)

(*Continued*)

Table 3. Continued.

	No lag[1,2]	12-month lag[1,2]
Controls, *N* (%)	230 (0.44)	145 (0.31)
RR (CI)[4]	0.79 (0.64–0.96)	0.89 (0.70–1.13)
Thalidomide/lenalidomide		
PD cases, *N* (%)	40 (0.09)	20 (0.05)
Controls, *N* (%)	39 (0.07)	18 (0.04)
RR (CI)[4]	0.85 (0.54–1.34)	0.92 (0.47–1.79)

PD, Parkinson's disease; RR, relative risk; CI, confidence interval; IMDH, Inosine monophosphate dehydrogenase.

[1]Overall category counts may not add to the total of individual medications in the category due to the potential for use of more than one medication.

[2]Excludes cases and controls from the original study who had no Part D (pharmacy) coverage in 2008–2009 or who had coverage but no medication fills in the respective time period: No lag means that we included in the analysis any medication prescribed up to PD diagnosis/control reference date while 12-month lag means that we included any medication prescribed up to the year prior to this date.

[3]Includes cyclosporine and tacrolimus, but RRs could not be estimated due to small numbers.

[4]Adjusted for age (two linear splines with a knot at 85 years), sex, race/ethnicity (7 categories), probability of ever/never smoking (continuous), and total count of unique diagnosis codes (continuous for the respective period, that is, up to PD diagnosis/control reference date or up to 12 months prior to that date).

[5]Includes methotrexate.

[6]Includes abatacept, anakinra, certolizumab, but respective RRs could not be estimated due to small numbers.

[7]Includes interferon beta-1a, glatiramer acetate, flingolimod, dimethyl fumarate but respective RRs could not be estimated due to small numbers.

0.88); methylprednisolone (RR = 0.80; 95% CI 0.76–0.84). For those taking both a corticosteroid and an IMDH inhibitor, risk of PD was 0.53 (95% CI 0.40–0.70) in the unlagged model and 0.60 (95% CI 0.42–0.84) in the 12-month lagged model.

Discussion

In this large population-based study, use of immunosuppressants, namely corticosteroids and IMDH inhibitors, was associated with a lower risk of PD, even after imposing an "exposure" lag. This relationship was consistent across most of drugs in these two classes. IMDH inhibitors appeared to be the most strongly protective, although RRs for medications within this class were imprecise because these medications were used infrequently. The potentially protective effect from corticosteroids was somewhat weaker, and we cannot completely rule out the possibility that this inverse association is due to confounding by smoking, since corticosteroids are used frequently for pulmonary symptoms related to smoking. Although both IMDH inhibitors and corticosteroids are associated with serious potential morbidity with long-term use, physicians often employ corticosteroid-sparing strategies, in patients requiring chronic immunosuppression, to avoid morbidities such as metabolic dysfunction, osteoporosis, and cardiovascular disease.[10] As such, the IMDH inhibitors may be the preferable category of immunosuppressants to consider pursuing for potential PD neuroprotection.

While corticosteroids affect both acute and chronic inflammation by multiple mechanisms, the IMDH inhibitor mechanism is much more specific. IMDH inhibitors block DNA synthesis by inhibition of inosine monophosphate dehydrogenase, the rate-limiting step in synthesis of guanosine nucleotides, which preferentially impacts T-cells.[11] This inhibition synthesis of cellular adhesion receptors involved in cell-to-cell contacts. The immunosuppressant effects of these medications are likely due to suppression of T-cell response to allogeneic cells and antigens.[12] Although it is not clear that these medications cross an intact blood–brain barrier,[12,13] the potential neuroprotective mechanism could be entirely due to peripheral suppression of T-cell activity. For example, suppression of T-cell activity might suppress propagation of peripheral α-synuclein aggregation in the gastrointestinal tract, which may be an important peripheral site that initiates the PD neurodegenerative cascade.[14,15] Alternatively, there is growing evidence that neuroinflammation may play a critical role in the pathogenesis of neurodegenerative diseases, including PD, and these drugs could impact the neuroinflammatory component of PD neurodegeneration through peripheral T-cell immunomodulation.[16–18] Although we can only speculate as to the potential mechanism of these immunomodulatory drugs on PD, this pharmacoepidemiology study provides additional evidence of a potential role of the immune system in disease risk and potential therapeutic targets to modify risk of PD and possibly even PD progression.

While our study has considerable strengths, including size and comparability of cases and controls, there are a few limitations. Since Medicare provides insurance coverage for the elderly U.S. population, we could not estimate the risk of PD in relation to these immunosuppressants in younger patients. We were also limited to a relatively narrow window of exposure and have to assume that patients took these medications for extended periods during their lives, limiting our ability to make causal inference and to conduct analyses that consider cumulative dose. While this assumption of long-term use may be true for IMDH inhibitors, it is probably less true for corticosteroids, which are used more episodically for numerous conditions. As with any administrative data study, we also could not confirm patient adherence, although

prescriptions filled are a reasonable proxy for use, and it is unlikely that lack of patient adherence could have created the particularly strong inverse association for IMDH inhibitors. Nonetheless, we acknowledge that the number of patients taking IMDH inhibitors and some of the other individual medications was quite small relative to the overall size of the dataset, making some of the estimated ORs imprecise. Future studies with longer windows of exposure will be necessary to investigate dose-response relations between these medications and PD risk.

Finally, there are likely multiple mechanisms to the corticosteroid immunosuppressant effects,[10] making potential neuroprotective mechanisms less targeted. Therefore, the IMDH inhibitors may represent the most promising potential drug class for PD neuroprotection.

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Author Contributions

Study concept and design: BAR, SSN.
Data acquisition and analysis: All authors.
Drafting of the manuscript and figures: All authors.

Conflict of Interest

The authors have no conflicts to report.

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