Association between cycline antibiotic and development of pseudotumor cerebri syndrome

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Background: Cycline antibiotics (CAs) are commonly used to treat acne, blepharitis, and dry eye syndrome. Prescribers or patients may hesitate to use Cas because they may increase the risk of pseudotumor cerebri syndrome (PTCS).

Objective: We sought to assess whether CA use is associated with an increased risk of PTCS or papilledema and whether the risk depends upon dosage or duration of CA intake.

Methods: We studied patients 12 to 65 years of age who were diagnosed with acne, blepharitis, or dry eye syndrome, who were enrolled in a nationwide managed care network between January 1, 2001 and December 31, 2015, and who had no preexisting diagnosis of papilledema or PTCS. Multivariable Cox regression modeling was used to assess the risk of developing papilledema or PTCS from exposure to CAs.

Results: Among the 728,811 eligible enrollees (mean age, 34.7 years; 72% female), 42.0% filled ≥1 CA prescription. Of the 305,823 CA users, 170 (0.06%) were diagnosed with papilledema or PTCS. By comparison, of the 57.0% with no record of CA use, 121 (0.03%) were diagnosed with papilledema or PTCS ($P < .0001$). In the unadjusted model, every additional year of CA use was associated with a 70% (doxycycline: hazard ratio, 1.70 [95% confidence interval 0.98-2.97]; $P = .06$) or 91% (minocycline: hazard ratio, 1.91 [95% confidence interval 1.11-3.29]; $P = .02$) increased hazard of papilledema/PTCS relative to nonusers of CAs. After adjustment for confounders, the increased hazard of PTCS/papilledema with CA use was no longer statistically significant ($P = .06$, doxycycline; $P = .08$, minocycline).

Limitations: This study relies on claims data, which lack clinical data.

Conclusion: This study offers some evidence that CAs may increase the risk of PTCS/papilledema. However, after accounting for confounding factors in our multivariable models, we found no statistically significant association between CA use and the development of PTCS. Moreover, there was no dose-response effect whereby greater CA use was associated with a higher PTCS risk. (J Am Acad Dermatol 2019;81:456-62.)

Key words: acne; cycline antibiotics; drug reaction; idiopathic intracranial hypertension; papilledema; pseudotumor cerebri.

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INTRODUCTION

Pseudotumor cerebri syndrome (PTCS), also known as idiopathic intracranial hypertension, is a condition characterized by signs and symptoms of intracranial hypertension without structural or systemic causes.[1] A recent revision of the diagnostic criteria for PTCS syndrome published in 2013 indicated a potential association between cycline antibiotics (CAs) and PTCS.[1]

During the 1960s, case reports described infants with bulging fontanels as a complication of tetracycline treatment.[2,3] Since then, numerous case reports and case series have linked use of CAs to PTCS.[4-6] Yet to our knowledge, the largest series describing a potential association between CA and PTCS consists of only 18 cases.[5]

CAPSULE SUMMARY

- This is the first large-scale cohort to investigate the association between cycline antibiotics and the development of pseudotumor cerebri syndrome.
- Cycline antibiotics may increase the risk of pseudotumor cerebri syndrome, but this association was not statistically significant in our models after accounting for confounding factors.

CAs are commonly prescribed for moderate to severe acne, severe dry eye syndrome (DES), and chronic posterior blepharitis.[7,8] In 2011, dermatologists wrote >5 million prescriptions for doxycycline or tetracycline.[9] Given how commonly doctors prescribed CAs, we followed a large cohort of >700,000 beneficiaries with acne, blepharitis, or DES in a large US managed care network for >2 years to determine whether an association exists between CA use and PTCS.

METHODS

Data source

The Clinformatics Data Mart database (OptumInsight, Eden Prairie, MN) contains detailed records of all beneficiaries in a managed care network with members throughout the United States. The dataset contains all individuals with >1 *International Classification of Diseases, Ninth Revision* (ICD-9-CM) codes for eye-related diagnoses (360-379.9), >1 Current Procedural Terminology (CPT) codes for any eye-related visits, diagnostic, or therapeutic procedures (65091-68899 or 92002-92499), or any other claim submitted by an ophthalmologist or optometrist between January 1, 2001 and December 31, 2015. For each enrollee, we had access to all medical claims for ocular and nonocular conditions and sociodemographic information, including age, sex, race/ethnicity, education level, and household net worth. The database also contained records of all filled outpatient pharmacy prescriptions. We have used this data source to study patients with ocular diseases.[10,11] The study, which uses deidentified data, was approved by the Institutional Review Boards of the University of Minnesota and University of Michigan.

Participants and sample selection

Individuals were included in the analysis if they met the following criteria: they were 12 to 65 years of age at plan enrollment, continuous enrollment in the medical plan for ≥2 years, ≥2 visits to an eye care provider (ophthalmologist or optometrist) to provide each patient with opportunities to get evaluated for and diagnosed with PTCS/papilledema, and >1 diagnosis of acne (ICD-9-CM, 706.1), DES (ICD-9-CM, 370.33 and 375.15), or blepharitis (ICD-9-CM, 373.0). We chose these as conditions of interest because it is common for them to be treated with CAs for an extended period of time. Therefore, these patients may be at increased risk for developing side effects. Persons with preexisting diagnoses of PTCS or papilledema during a 3-year lookback period were excluded. To limit misclassification of the outcome of interest as PTCS/papilledema, we also excluded beneficiaries with conditions that can mimic them, such as optic disc drusen, pseudopapilledema, ischemic optic neuropathy, optic neuritis, meningitis, cerebral venous sinus thrombosis, brain tumor, and hydrocephalus (Fig 1).

Outcome of interest

Our outcome of interest was an incident (new) diagnosis of PTCS (ICD-9-CM, 348.2) along with ≥1confirmatory diagnosis of PTCS on a different date. Some health care professionals code patients with PTCS as papilledema (ICD-9-CM 377.0) instead, and therefore we also considered this diagnosis as an outcome of interest. Our primary analyses considered codes for either PTCS or papilledema as the outcome of interest, but we also performed additional analyses looking separately at the relationship between CA use and PTCS and between CA use and papilledema.

CA use

The key predictor variable of interest was exposure to CAs. Individuals were classified as receiving CAs, which include tetracycline, doxycycline,

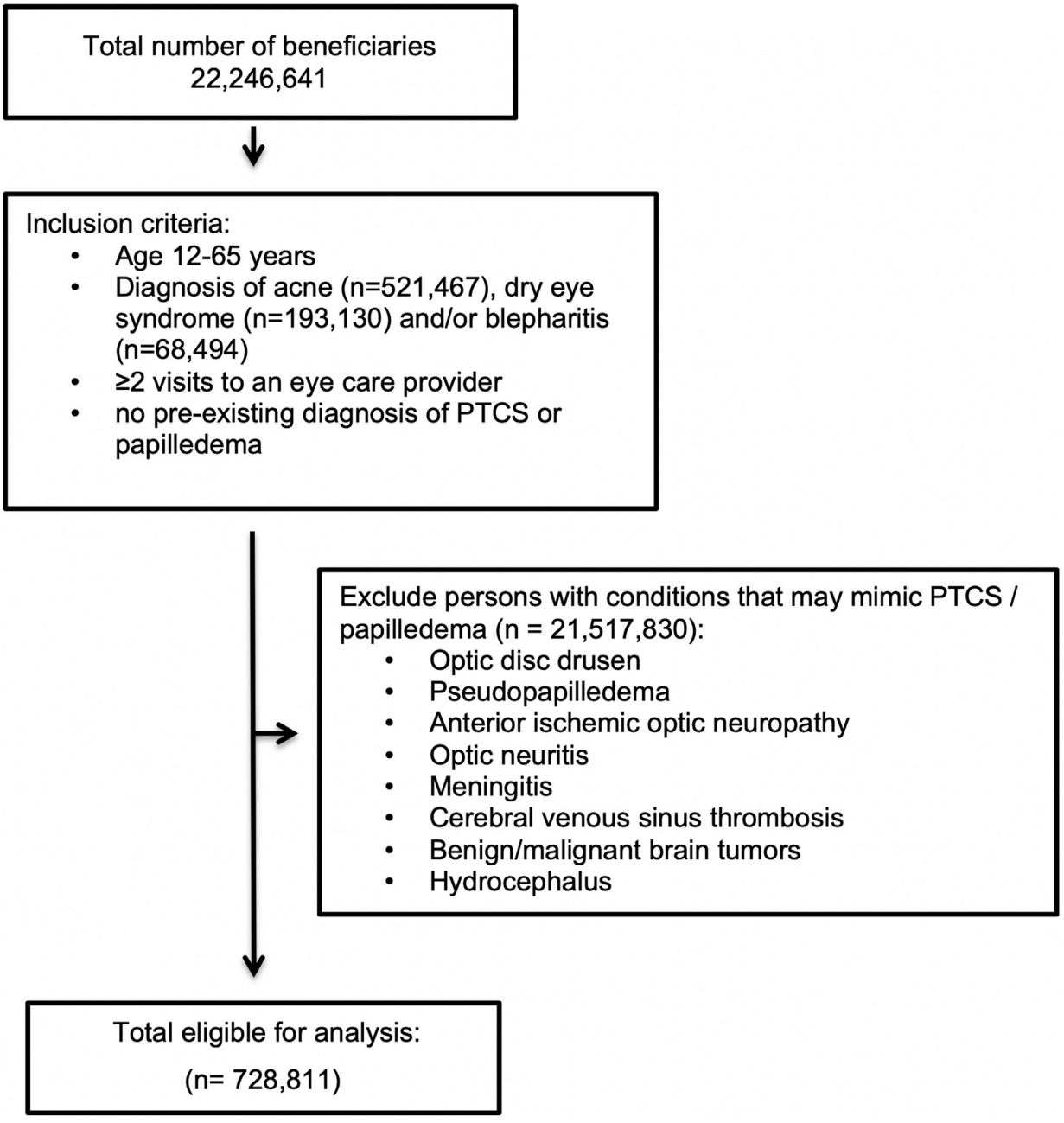

Fig 1. Sample selection. *PTCS*, Pseudotumor cerebri syndrome.

minocycline, or oxytetracycline, if they had ≥1 outpatient pharmacy prescription filled for any of these medications during their time in the plan. Chlortetracycline and demeclocycline are not available in the United States and were not considered. The database contains information on the number of days' supply of all filled prescriptions, so we could quantify the amount of CA each beneficiary received during their time in the plan.

Analyses

SAS software (v 9.4; SAS Institute, Cary, NC) was used to perform the statistical analyses. Frequencies and percentages were used to describe categorical variables and means and standard deviations were used to describe continuous variables. First, we identified the number of incident diagnoses of PTCS or papilledema and used a chi-squared test to assess for differences between users and nonusers of CAs.

Table I. Demographic characteristics of the study sample

Variable	Value	Papilledema/PTCS			
		No, n (%)	Yes, n (%)	Total, n (%)	*P* value (*t* test)
Total, N		728,520 (100.0)	291 (100.0)	728,811	
Mean age at plan enrollment, y (SD)		34.7 (16.1)	28.3 (14.7)	34.7 (16.1)	<.0001
Sex	Male	207,646 (28.5)	39 (13.4)	207,685 (28.5)	<.0001
	Female	520,874 (71.5)	252 (86.6)	521,126 (71.5)	
Race/ethnicity	White	522,859 (79.7)	212 (77.4)	523,071 (79.7)	.003
	Black	47,383 (7.2)	34 (12.4)	47,417 (7.2)	
	Latino	55,688 (8.5)	22 (8.0)	55,710 (8.5)	
	Asian	30,209 (4.6)	6 (2.2)	30,215 (4.6)	
Indication for CA use*	Acne	521,233 (71.5)	234 (80.4)	521,467 (71.6)	.0008
	DES	193,066 (26.5)	64 (22.0)	193,130 (26.5)	.08
	Blepharitis	68,471 (9.4)	23 (7.9)	68,494 (9.4)	.38
CA use†	Tetracycline	41 (0.0)	0 (0.0)	41 (0.0)	1.00
	Doxycycline	200,335 (27.5)	118 (40.5)	200,453 (27.5)	<.0001
	Minocycline	124,540 (17.1)	101 (34.7)	124,641 (17.1)	<.0001
	Oxytetracycline	1 (0.0)	0 (0.0)	1 (0.0)	1.00
	Any CA use	305,653 (42.0)	170 (58.4)	305,823 (42.0)	<.0001
Income	<$40,000	44,142 (9.6)	27 (12.3)	44,169 (9.6)	.09
	$40,000-<$60,000	50,173 (10.9)	29 (13.2)	50,202 (10.9)	
	$600,000-<$100,000	111,386 (24.3)	61 (27.7)	111,447 (24.3)	
	> $100,000	253,234 (55.2)	103 (46.8)	253,337 (55.2)	
Education	Less than high school	2895 (0.4)	2 (0.7)	2897 (0.4)	.001
	High school diploma	125,765 (18.3)	62 (21.6)	125,827 (18.3)	
	Some college	346,232 (50.3)	165 (57.5)	346,397 (50.3)	
	Bachelor's degree or higher	212,822 (30.9)	58 (20.2)	212,880 (30.9)	

CA, Cycline antibiotic; *DES*, dry eye syndrome; *PTCS*, pseudotumor cerebri syndrome.
*Some eligible persons had ≥1 condition(s), so percentages add to >100%.
†Some enrollees filed prescriptions for >1 type of CA.

Next, Cox proportional hazard regression analyses were used to estimate the hazard of developing PTCS/papilledema associated with CA use. The first 3 years that each eligible enrollee was in the plan was considered a lookback period. Persons with any record of PTCS/papilledema identified in the lookback period were excluded to eliminate those with preexisting disease. Each enrollee was required to have seen an eye care provider at least once and to have received a diagnosis of acne, blepharitis, or DES during the lookback period. CA use at the time of the index date (3 years after plan entry) was recorded. Enrollees were followed in the model from the index date until they were diagnosed with PTCS or papilledema or were censored. Censoring occurred when the beneficiary left the plan or on December 31, 2015. The diagnosis of PTCS/papilledema could have been given by any provider; however, enrollees were required to have ≥1 visit(s) to an eye care provider in the follow-up period to help confirm this. In the Cox models, the dependent variable was development of PTCS/papilledema. First, we performed univariate models. Next, we created multivariable regression models, adjusting for several potential confounding factors, including age, sex, race/ethnicity, income, education, residence (urban vs. rural), and the following medical comorbidities: hypertension, diabetes, renal disease, depression, sleep apnea, anemia, malnutrition or anorexia, failure to thrive, Arnold–Chiari malformation, and connective tissue diseases. In the models, we treated CA use as a time-dependent covariate. For each enrollee, we quantified the amount of CA use in the 2 years before their initial diagnosis of acne, blepharitis, or DES. For each day of follow-up, we also computed the total amount of exposure to CAs during the previous 2 years. We performed additional Cox regression models studying the association between CA use and PTCS/papilledema, PTCS alone, and papilledema alone. Finally, we looked for a dose-response effect by stratifying CA use into 4 quartiles of use and compared each quartile with nonusers of CAs with adjustment for the above-mentioned potential confounding factors. Each of the models generated hazard ratios (HRs) with 95% confidence intervals (CIs). For all analyses, we considered $P < .05$ to be statistically significant.

RESULTS

A total of 728,811 enrollees with acne, DES, or blepharitis met the inclusion criteria. The mean (SD) age of these enrollees was 34.7 (16.1) years and 520,874 (71.5%) were women. The racial/ethnic distribution included 523,071 (79.7%) whites, 47,417 (7.2%) blacks, 55,710 (8.5%) Latinos, and 30,215 (4.6%) Asian Americans. There were 253,234 (55.2%) persons with incomes >$100,000 and 212,822 (30.9%) were college educated (Table I).

CA use

A total of 305,823 (42.0%) of the enrollees filled >1 prescription for CAs. Doxycycline was the most common CA prescription filled (n = 200,335 [65.5%]), followed by minocycline (n = 124,540 [40.8%]). Some enrollees filled prescriptions for multiple different CAs. Most of the eligible enrollees had acne (n = 521,233 [80.4%]), while some had DES (n = 193,066 [22.0%]), or blepharitis (n = 68,471 [7.8%]). Some enrollees had records of ≥1 of these indications (Table I). Among CA users, the median days of doxycycline use was 52 days (interquartile range, 25-125 days) and minocycline use was 90 days (interquartile range, 30-196 days).

New diagnosis of papilledema/PTCS

Among 728,811 eligible enrollees, 291 (0.04%) received an incident diagnosis of PTCS or papilledema. The incidence of PTCS/papilledema among CA users (n = 170 [0.056%]) was nearly double that for persons with no record of CA use (n = 121 [0.029%], $P < .0001$). Beneficiaries who were diagnosed with papilledema/PTCS were, on average, significantly younger than those who did not (mean [SD] age, 28.3 [14.7] years vs. 34.7 [16.1] years, $P < .0001$) and a significantly greater proportion of persons who were diagnosed with PTCS/papilledema were female (n = 252 [86.6%] vs. n = 520,874 [71.5%], $P < .0001$).

Factors associated with developing PTCS/papilledema

In the univariate regression model, every additional year of doxycycline use was associated with a 70% increased hazard of PTCS/papilledema (HR 1.70 [95% CI 0.98-2.97], $P = .06$). Every additional year of minocycline use was associated with a 91% increased hazard of papilledema/PTCS relative to those with no exposure to CAs (HR 1.91 [95% CI 1.11-3.29], $P = .02$). In the multivariable Cox regression models, after adjusting for age, other sociodemographic factors, and ocular and systemic comorbidities, there was no significant association between doxycycline use (HR 1.90 [95% CI 0.96-3.75], $P = .06$) or minocycline use (HR 1.83 [95% CI 0.93-3.63], $P = .08$) and the development of papilledema/PTCS (Table II).

Next, we looked to determine whether a dose-response effect could be observed such that more exposure to CAs carried a greater risk of PTCS/papilledema. After accounting for the aforementioned potential confounders, we found no statistically significant increase in the hazard of developing PTCS/papilledema among the highest quartile of doxycycline (HR 0.64 [95% CI 0.38-1.10], $P = .11$) or minocycline users (HR 1.25 [95% CI 0.73-2.15], $P = .42$) compared with nonusers of CAs.

DISCUSSION

While there have been case reports and small series in the literature linking CA use to the development of PTCS/papilledema, to our knowledge, this is the first large-scale analysis aimed at addressing this topic. The results of our analyses offer a mixed message. The incidence of PTCS/papilledema among CA users was nearly double that of nonusers. Moreover, in our unadjusted regression models, we determined that users of doxycycline or minocycline had a markedly elevated hazard of developing PTCS/papilledema (70% and 91%, respectively, with each additional 365 days of use of either of these agents). However, after adjustment for confounding factors, while the magnitude of the elevated hazard of PTCS/papilledema continued to remain quite high for both doxycycline and minocycline, neither was statistically significant. Likewise, when we checked for a dose-response relationship, we found no increased hazard of developing PTCS/papilledema for enrollees with the highest quartile of minocycline or doxycycline use compared with nonusers of these medications. On one hand, these findings might suggest that CAs do not confer increased risk of PTCS. On the other hand, they may also indicate a strong trend that they do, but that this remains a clinically relevant association that did not reach statistical significance.

A review of the literature identified >3 dozen reports capturing 100 patients who were diagnosed with PTCS/papilledema after taking CAs. These case reports include infants who developed bulging fontanelles only a few hours after receiving CAs to adults who had been taking CAs for >1 year before they were diagnosed with PTCS. While these case reports and case series offer some evidence that PTCS is associated with CA use, to more definitively explore this potential association requires identifying a much larger cohort of patients, some of

Table II. Factors affecting the hazard of developing pseudotumor cerebri syndrome or papilledema

Model no.*	Variable	Value	HR (95% CI)	*P* value
1	Doxycycline use†		1.70 (0.98-2.97)	.06
	Minocycline use†		1.91 (1.11-3.29)	.02
2	Doxycycline use†		1.90 (0.96-3.75)	.06
	Minocycline use†		1.83 (0.93-3.63)	.08
	Age at enrollment		0.95 (0.94-0.96)	<.0001
	Sex	Male		
		Female	4.67 (2.89-7.55)	<.0001
	Race/ethnicity	White		
		Black	1.36 (0.88-2.10)	.17
		Latino	1.02 (0.63-1.67)	.93
		Asian	0.40 (0.13-1.25)	.11
	Education	Less than high school		
		High school diploma	0.49 (0.07-3.66)	.48
		Some college	0.56 (0.08-4.16)	.57
		Bachelor's degree or higher	0.36 (0.05-2.78)	.33
	Income	<$40,000		
		$40,000-<$60,000	0.91 (0.53-1.57)	.74
		$60,000-<$100,000	0.92 (0.57-1.49)	.74
		≥$100,000	0.69 (0.43-1.12)	.13
	Location of residence	Urban		
		Large rural	0.88 (0.43-1.81)	.73
		Small rural	0.76 (0.33-1.74)	.51
	Hypertension‡	None		
		Uncomplicated	2.37 (1.63-3.44)	<.0001
		Complicated	2.19 (1.00-4.82)	.051
	Diabetes‡	None		
		Uncomplicated	0.77 (0.44-1.35)	.36
		Complicated	0.77 (0.26-2.22)	.62
	Anemia		0.93 (0.57-1.50)	.75
	Arnold—Chiari malformation		7.31 (2.70-19.77)	<.0001

CI, Confidence interval; *HR*, hazard ratio.

*Model 1 provides univariate results. Model 2 adjusts for sociodemographic factors and medical comorbidities.

†These models show the increased hazard of a given cycline antibiotic with every 365 days of use. For example, in model 1, every 365 days of use was associated with a 70% increased hazard of developing pseudotumor cerebri syndrome/papilledema.

‡"Complicated" refers to end-organ damage (ie, neuropathy, nephropathy, and retinopathy) from the condition. "Uncomplicated" means no record of any end-organ damage. The model was also adjusted for the following nonsignificant variables: connective tissue disease, depression, sleep apnea, malnutrition, failure to thrive, renal disease, and Charlson comorbidity index.

whom are receiving CAs and others who are not and following them longitudinally to see whether there are differences between the 2 groups as we found here.

A few mechanisms have been proposed to explain CA-associated increased intracranial pressure (ICP). CAs may affect the cyclic adenosine monophosphate pathway at the arachnoid granulations, which can disturb the filtering function of the choroid plexus and lead to decreased absorption of cerebrospinal fluid.[12] A genetic predisposition has also been proposed when dizygotic twin sisters were diagnosed with PTCS while taking tetracycline for acne.[13] However, the exact mechanism by which CAs could cause increased ICP remains unidentified.

Our analysis also found a significant association between papilledema/PTCS and female sex, younger age, and hypertension. Of the 252 subjects with PTCS/papilledema, 86.6% were female compared with 71.5% of control subjects ($P < .0001$). This is consistent with the reported demographics of idiopathic intracranial hypertension[1] and those with alleged increased ICP from CAs. Beneficiaries who were diagnosed with papilledema/PTCS had a mean age of 28.3 versus 34.7 years for control subjects, which is consistent with PTCS where patients are typically between 20 and 40 years of age.[1] Among the 100 reported patients with increased ICP from CAs, the mean age was 17.2 years, likely reflecting the young age of individuals with acne who are taking CAs.

Our database comprises a large national sample of insured individuals throughout the United States, making our results generalizable. In contrast to the small number of cases without control data, having each beneficiary's sociodemographic profile and detailed claims data on ocular and nonocular medical conditions allowed us to control for numerous potential confounding variables.

Limitations

This study has several limitations. We relied on claims data—a source that lacks information on clinical parameters. As such, we were unable to adjust for potential confounding factors, such as body habitus, which has been independently associated with developing PTCS/papilledema. We have no reason to believe that the users of CAs differed from nonusers with respect to body habitus or other unmeasured variables. We also did not have details on the degree of elevated ICP for those diagnosed with PTCS/papilledema or findings from lumbar punctures or magnetic resonance imaging scan results to confirm the presence of this outcome. Our findings would only be affected if there was differential misclassification of these outcomes among users and nonusers of CAs, which we doubt occurred. Third, we quantified exposure to CAs based on prescription fills. While more frequent prescription fills likely represents a good surrogate of actual use of these agents, it does not account for nonadherence. However, if patients who were prescribed CAs were nonadherent and did not take them, this would bias our findings as well. Finally, these study findings may not be generalizable to those with other forms of health insurance or patients without health insurance.

CONCLUSION

This is the first large-scale analysis to investigate the incident (0.056%) development of papilledema and PTCS among individuals taking CAs using health care claims data from a large, national US managed care network. Dermatologists can use these data to assess risk as they prescribe CAs. In a univariate model, those who received CAs were at increased hazard of developing papilledema/PTCS compared with nonusers. Using multivariable Cox regression controlling for confounding variables, the association between CA use and papilledema/PTCS disappeared.

Our data raise the question of whether a true association between CA use and PTCS exists. Ultimately, a large-scale prospective study would best identify the potential relationship, but this is unlikely to occur. The decision to continue treatment with CAs in the setting of PTCS involves careful consideration of the risks, benefits, and alternatives and should be done on a patient-by-patient basis. Careful counseling of those high-risk patients who are obese, female, or hypertensive may be warranted before prescribing CAs. For some patients, the risk of avoiding these medications may outweigh the potential benefits.

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