Oral Fluoroquinolones and the Risk of Uveitis

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**IMPORTANCE** Fluoroquinolones are the most commonly prescribed antibiotic class in the outpatient setting. Recent reports have implicated an association between oral fluoroquinolones and an increased risk of uveitis.

**OBJECTIVE** To determine the hazard of uveitis with oral fluoroquinolone use.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective cohort study was conducted using medical claims data from a large national US insurer (N = 4,387,651). Cohorts from ambulatory care centers across the United States were created including every new user of an oral fluoroquinolone or β-lactam antibiotic prescription with at least 24 months of data prior to the date of the prescription from January 1, 2000, to January 30, 2013. Exclusion criteria consisted of any previous diagnosis of uveitis or a uveitis-associated systemic illness. Participants were censored for a new diagnosis of a uveitis-associated systemic illness, the end of an observation period, use of the other class of antibiotic, or removal from the insurance plan. Data analysis was performed from January 2 through March 15, 2015.

**MAIN OUTCOMES AND MEASURES** The hazard of a uveitis diagnosis after a fluoroquinolone prescription compared with a β-lactam prescription using multivariate regression with Cox proportional hazards models.

**RESULTS** Of the 4,387,651 patients in the database, 843,854 individuals receiving a fluoroquinolone and 3,543,797 patients receiving a β-lactam were included in the analysis. After controlling for age, race, and sex using multivariate analysis, no hazard for developing uveitis at the 30-, 60-, or 90-day observation windows was seen (hazard ratio [HR] range, 0.96; 95% CI, 0.82-1.13; to 1.05; 95% CI, 0.95-1.16; P > .38 for all comparisons). The 365-day observation period showed a small increase in the HR for the fluoroquinolone cohort (1.11; 95% CI, 1.05-1.17; P < .001). Moxifloxacin produced an increased hazard for uveitis at every time point (HR range, 1.47-1.75; 95% CI, 1.27-2.37; P < .001 for all comparisons). Secondary analysis demonstrated a similar hazard at 365 days for a later diagnosis of a uveitis-associated systemic illness after fluoroquinolone use (HR range, 1.46-1.96; 95% CI, 1.42-2.07; P < .001 for all comparisons).

**CONCLUSIONS AND RELEVANCE** These data do not support an association between oral fluoroquinolone use and uveitis. Instead, this study shows an association between oral fluoroquinolone use and the risk for uveitis-associated systemic illnesses, which is a possible source of bias that could explain the findings of previous studies.

Published online October 29, 2015.
oral fluoroquinolones have been implicated as a cause of uveitis in multiple case reports and case series.1-4 Although the first formal study identified no association between this drug class and uveitis,2 further concern was raised when a recent study6 focusing on ciprofloxacin and moxifloxacin demonstrated a 1.96- to 2.98-fold higher risk of uveitis in patients using these agents compared with nonusers. These results are clinically significant since fluoroquinolones are commonly prescribed in the outpatient setting for many diseases, including respiratory tract, urinary tract, soft-tissue, and gastrointestinal tract infections. At present, fluoroquinolones are the most commonly prescribed class of antibiotic in the ambulatory setting.7

The exact mechanism by which fluoroquinolones may induce uveitis is unclear. Pharmacokinetic studies8 using whole-body scintigraphy have shown that moxifloxacin concentrates in melanin-containing structures in the meninges, skin, and eyes. It is well established that fluoroquinolones can sensitize the skin to phototoxic effects, thereby predisposing it to photodermatitis. Moreover, melanin has been shown9 experimentally to potentiate fluoroquinolone-induced phototoxic effects to the skin. Thus, it has been postulated that moxifloxacin may have some direct toxic effect on the iris pigment.8 This finding is consistent with most previous reports of fluoroquinolone-induced uveitis, which featured few inflammatory cells in the anterior chamber but pigment dispersion in the anterior chamber with diffuse iris transillumination defects and sometimes pupil mydriasis. To our knowledge, almost all reported cases of uveitis thus far have occurred 2 to 4 weeks after administration of the fluoroquinolone and usually within 2 weeks.

Although the finding in that case-control study6 was novel, the most robust results are those that are confirmed through different methods across different populations. We aimed to evaluate the risk of uveitis after oral fluoroquinolone use using a retrospective cohort study in a large national US database.

Methods

Data Set
Data were abstracted from the Clininformatics Data Mart Database (OptumInsight), which contains deidentified medical claims of all beneficiaries from a large managed care network in the United States. Included within the database are all outpatient medical claims (office visits and associated diagnoses), all outpatient pharmaceutical prescriptions filled, and demographic data for all beneficiaries during their enrollment in the insurance plan. The subset of data available for this study included all patients in the database from January 1, 2000, to January 30, 2013. The University of Pennsylvania’s institutional review board deemed this study exempt from review owing to the deidentified nature of the data.

Cohorts
For this study, 2 cohorts were created for comparison, consisting of all patients who had received a prescription for either a fluoroquinolone or a β-lactam antibiotic during their time in the plan. β-Lactams were chosen as the comparison group because they share similar medical indications with fluoroquinolones but are not thought to be associated with uveitis. The index date for each patient was considered the first date of either a fluoroquinolone or β-lactam prescription during the coverage period. Patients were required to have been enrolled in the insurance plan for at least 24 months before the index date. Exclusion also occurred if the patient had any previous diagnosis of uveitis or a systemic disease known to be associated with uveitis (eTable in the Supplement lists all International Classification of Diseases, Ninth Revision [ICD-9] codes used during this study) or received a prescription for both a fluoroquinolone and β-lactam on the index date. Owing to the potentially chronic and indolent nature of uveitis, patients were included in a cohort only once during the study regardless of multiple prescriptions.

Outcomes of Interest
The primary outcome of interest was defined as having an ICD-9 incident diagnosis code for uveitis made by an eye-care provider. Next, owing to the pathophysiologic mechanism suggested earlier, a secondary outcome using only cases of incident anterior uveitis was also examined. Because of previous work6 reporting a positive association between specific fluoroquinolones and uveitis, a subanalysis was performed examining individual fluoroquinolone antibiotics. Finally, a sensitivity analysis was performed in which a case was considered to have occurred only when a corticosteroid prescription (oral or topical) was filled by the patient within 30 days of the incident uveitis diagnosis.

Indication bias, which is any association between a drug and an outcome that is the result of reasons underlying why the drug is prescribed rather than a direct effect of the drug, is often a major limitation of these types of studies. Although using β-lactams as a comparator group attempts to reduce this bias, another secondary analysis was done applying an incident diagnosis of a systemic disease known to be associated with uveitis as an outcome measure. This secondary analysis was done because one can be more confident in a potential positive association between fluoroquinolone use and uveitis if there is no association between the drug class and these systemic diseases since these conditions are clearly not caused by fluoroquinolone use (eg, sarcoidosis, lupus, and inflammatory bowel disease). Covariates used in multivariate analysis were age, sex, and race.

Statistical Analysis
Baseline demographic characteristics were assessed at the time of the index date and were analyzed using descriptive statis
Results

In total, 4 387 651 patients were included for analysis (843 854 in the fluoroquinolone cohort and 3 543 797 in the β-lactam cohort) (Figure). Ciprofloxacin was the most commonly prescribed fluoroquinolone, followed by levofloxacin and moxifloxacin (Table 1). In the fluoroquinolone cohort, 58.1% of the patients were female; only 51.7% of the β-lactam cohort was female. Patients ranged in age from birth to 85 years. The mean (interquartile range) age in the fluoroquinolone cohort was 53.2 (40-67) years and 37.1 (18-53) years in the β-lactam cohort. The fluoroquinolone cohort also had a higher percentage of black people than did the β-lactam cohort.

Table 2 reports the overall number of cases found at each time point for incident cases of uveitis, anterior uveitis, and systemic illnesses associated with uveitis. In the fluoroquinolone cohort, the percentage of patients with uveitis increased from 0.03% to 0.22% from the 30-day to the 365-day observation period. The β-lactam cohort had a similar increase in diagnoses from 0.02% to 0.15%.

Univariate analysis showed that female sex had a protective effect with regard to the hazard of developing uveitis. Older age and black race had higher hazards for developing uveitis at all time points. With multivariate analysis, there remained an association between black race and uveitis at 365 days (HR, 1.3; 95% CI, 1.06-1.60; \( P = .013 \)), as did an association between older age and uveitis at 365 days (HR, 1.11; 95% CI, 1.06-1.17; \( P = .001 \)). No confounding or effect modification by these variables was seen in the association between fluoroquinolone use and the hazard for developing uveitis.

With multivariate analysis, reported as HR and 95% CI, an association was not identified between fluoroquinolones and uveitis at the 30-, 60-, or 90-day time points (range, 0.96-1.05; 0.82-1.16; \( P > .38 \) for all comparisons) (Table 3). However, a small effect was seen at 365 days (1.11; 1.05-1.17; \( P < .001 \)) (Table 3). A subanalysis demonstrated that anterior uveitis constituted fewer of the total uveitis diagnoses in the fluoroquinolone cohort (788 of 1894 [41.6%]) than in the β-lactam cohort (2402 of 5227 [45.9%]) (Table 2). Multivariate analysis similarly showed no increased hazard at the 30-, 60-, and 90-day time points (range, 1.05-1.10; 0.84-1.30; \( P > .19 \) for all comparisons) but, similar to the all-uveitis result, demonstrated a slightly increased HR at 365 days (1.11; 1.03-1.21; \( P = .01 \)) (Table 3). Sensitivity analysis with a stricter definition of a case that also required a prescription for corticosteroids in addition to the incident diagnosis of uveitis had similar results to the main analysis, with the 30-, 60-, and 90-day observation periods showing no association (range, 1.06-1.09; 0.84-1.34; \( P > .32 \) for all comparisons),
and an increased HR (1.13; 1.03-1.24; *P* = .01) at the 365-day observation period.

Of all the fluoroquinolones prescribed, only ciprofloxacin, moxifloxacin, and levofloxacin included sufficient numbers for multivariate analysis. An association was not identified between ciprofloxacin and uveitis at the 60-, 90-, or 365-day time points (range, 0.88-1.03; 0.77-1.10; *P* > .09 for all comparisons) (Table 4). Within 30 days, ciprofloxacin showed a protective effect against developing uveitis (0.75; 0.61-0.92; *P* = .005). An association was not identified between levofloxacin and uveitis at the 30-, 60-, and 90-day time points (range, 1.03-1.29; 0.80-1.72; *P* > .09 for all comparisons), but there was an increased HR (1.17; 1.04-1.31; *P* = .007) demonstrated at 365 days (Table 4). Moxifloxacin showed an association with uveitis at every time point (1.75; 1.28-2.37 at 30 days that decreased to 1.47; 1.30-1.65 at 365 days; *P* < .001 for all comparisons) (Table 4).

Multiple systemic conditions have well-known associations with uveitis (eTable in the Supplement). A final secondary analysis was performed using any incident diagnosis of a known uveitis-associated systemic illness as the outcome. This analysis mirrored closely the results of the moxifloxacin-specific analysis reported above and revealed that any oral fluoroquinolone use was significantly associated with an incident diagnosis of one of these conditions at all time points (HR range, 1.46-1.96; 95% CI, 1.42-2.07; *P* < .001 for all comparisons) (Table 3).

**Discussion**

This study found no increased hazard of developing uveitis within 30, 60, or 90 days of use of an oral fluoroquinolone. There was a small increased hazard at the 365-day observation period. Similar results were found by examining only anterior uveitis cases. Also, when moxifloxacin was studied alone, an increased hazard was seen at all time points. When uveitis-associated systemic illnesses were used as an outcome measure, there was an association between fluoroquinolones and a later diagnosis of these illnesses that closely mirrored the association between moxifloxacin and uveitis.

Because fluoroquinolones achieve a high steady-state concentration in the serum shortly after onset of use and then quickly decay after discontinuation, one would expect adverse effects of the drug to occur within a short time after initiating treatment. With increasing time after use, the rate of adverse effects due to the drug should decrease as it is excreted from the body. The findings in this study were not consistent with this pattern since no significant association was seen for oral fluoroquinolones as a class and uveitis or anterior uveitis until the 365-day observation period.
A large case-control series found that patients with newly diagnosed uveitis were more likely to currently be receiving a fluoroquinolone than were patients serving as controls. Specifically, there was a rate ratio of 2.98 for moxifloxacin and 1.98 for ciprofloxacin. That study used patients receiving finasteride, a nonantibiotic, as the control group. The use of a nonantibiotic control may have introduced a source of bias known as indication bias. The medical indications for fluoroquinolones are considerably different from those for finasteride therapy. Thus, the varying underlying medical reasons for prescribing these drugs, rather than the drugs themselves, may differentially influence the outcome of interest. Our study also evaluated specific fluoroquinolones, finding an increased hazard for uveitis at all time points for moxifloxacin but no increased hazards for ciprofloxacin at any time point or for levofloxacin through the first 90 days. Prima facie, the moxifloxacin data would seem to confirm the findings of the previous study; however, these increased HRs for moxifloxacin closely mirrored the HR at all time points for the fluoroquinolone class and an incident diagnosis of a uveitis-associated systemic disease.

We interpret these data to mean that fluoroquinolones are unlikely to cause uveitis; rather, a prescription for a fluoroquinolone is a marker of patients with some broader immune dysregulation that predisposes them to an infection for which a fluoroquinolone would be prescribed, which is then followed by uveitis. To be more specific, a patient with an inflammatory condition could have signs or symptoms that mimic infection, which is subsequently treated with antibiotics. For instance, a patient with a lung opacity noted on chest radiography that is due to sarcoidosis might mistakenly receive moxifloxacin treatment for pneumonia. Were that patient to develop uveitis following use of the antibiotic, one might falsely attribute a causal role to the fluoroquinolone when the patient’s underlying disease before diagnosis is more likely the culprit. It is highly unlikely that fluoroquinolones cause inflammatory bowel disease, Behçet disease, or a myriad of other autoimmune diseases. Still, the data show this association. Finally, another possibility is that infectious disease syndromes more commonly treated with fluoroquinolones may be more likely to elicit a lasting immune response that could eventually manifest as uveitis, much in the way that acute infections with Yersinia or Salmonella are thought to trigger a lasting immune response in reactive arthritis and its associated uveitis.

We also suspect that indication bias is responsible for the association seen between moxifloxacin and uveitis at all time points in the present study. One argument against this association would be that levofloxacin (also a third-generation fluoroquinolone) did not have similar results; however, although the 2 medications’ indications overlap, they are not identical. Moxifloxacin is typically used for respiratory tract and skin infections; levofloxacin has a broader range of indications. It is this difference in patient populations that we suspect has a higher propensity for an underlying uveitis-associated systemic disease. Hence, moxifloxacin is prescribed for this group and appears to cause uveitis when the results have been confounded by the indications for the drug.

There were several strengths to this study. First, the source is a large national database, decreasing the likelihood that outlying prescribing patterns by a majority of physicians could influence the results of the study. Second, if assessing drug safety is the goal of a study, a cohort design is a somewhat more robust method than a case-control design because of the ability to examine all patients who received an oral fluoroquinolone. Using the entire cohort causes less data loss compared with evaluating only the small fraction of patients with uveitis who used oral fluoroquinolones in a case-control study. Next, the multiple subanalyses examined within the present study help to clarify potential associations noted in previous reports.

Limitations of this study must also be noted. Although the fluoroquinolone and β-lactam groups in general have similar indications for use, the exact diagnosis for which each prescription was written cannot be identified in this database. In addition, this study included only outpatient prescriptions. Many fluoroquinolones and β-lactams are prescribed orally or intravenously in the inpatient setting, and none of these prescriptions was captured in the database. Moreover, the database cannot confirm that, once patients filled their antibiotic prescriptions, the full course was completed. Diagnoses were made based on ICD-9 codes used in billing data and cannot be verified with medical records. Finally, iris transillumination defects may be a sign of fluoroquinolone-associated uveitis, but these defects do not have a specific ICD-9 code and thus cannot be identified in this database. It is possible that some of these cases were not coded as uveitis by eye care providers and thus were not captured in these data.

Conclusions

The findings of this study do not support the association between oral fluoroquinolone use and uveitis risk. Although there was an increased risk of uveitis 1 year after fluoroquinolone use, this time frame is not consistent with an expected adverse effect for a drug that is used sporadically and quickly eliminated from the body after cessation. Given the systemic illness findings in this study, it is more probable that fluoroquinolone use is a marker that identifies a group of patients who are more likely to develop a disease associated with uveitis rather than causing uveitis.
Controversy Surrounding the Proposed Ocular Adverse Events of Fluoroquinolones

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In the current issue of JAMA Ophthalmology, Sandhu et al report a retrospective cohort study of medical claims data in order to determine the association between fluoroquinolones and uveitis. The authors should be commended on their excellent analyses and interpretation of the results. Their study did not find an association between fluoroquinolones and uveitis. Their conclusions are both in keeping and in contrast with the findings of recent similar studies.  

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The differing conclusions derived from these studies highlight some topics that need to be considered when interpreting the results of medical claims database research: the importance of using proper controls, accounting for confounding bias, replication and validation of results, and the inherent limitations of this type of research. Uveitis is a heterogeneous disease, and can be caused by a variety of infectious and noninfectious (inflammatory) etiologies. Patients can also develop noninfectious uveitis following an unrelated systemic infection (eg, poststreptococcal uveitis). Furthermore, patients with early signs of a systemic inflammatory disease that is associated with uveitis may present with nonspecific systemic symptoms that can be misdiagnosed as a systemic infectious process. Thus, in any study that attempts to examine the association between fluoroquinolones and uveitis, the potential confounding bias of this systemic process needs to be properly accounted for. Forooghian et al previously published a large, retrospective case-control study examining the association between fluoroquinolones and uveitis. The study used β-lactam and macrolide antibiotics as controls and excluded patients with 9 different systemic diseases known to be associated with uveitis. The investigators found that all 3 classes of antibiotics (fluoroquinolones, β-lactams, and macrolides) were associated with uveitis. They concluded that the systemic processes for which fluoroquinolones are prescribed, and not the fluoroquinolones themselves, are the likely inciting factors for uveitis. Following the publication of these results, another group published a report in JAMA Ophthalmology (using a database of older men) claiming an association between the fluoroquinolones moxifloxacin and ciprofloxacin and uveitis. The control used by Edie et al in this report was finasteride, and they adjusted for only 3 different systemic diseases known to be associated with uveitis. It is unclear why they did not use other antibiotics as controls or adjust for a more comprehensive list of systemic inflammatory diseases.

The current report by Sandhu et al appropriately addresses the issue of potential confounding bias in their analyses. They used β-lactams as a control group and excluded patients with 18 different systemic diseases that are known to be associated with uveitis. Furthermore, they performed a secondary analysis using incident diagnosis of a systemic disease known to be associated with uveitis as an outcome measure. When they examined fluoroquinolones as a group, Sandhu and colleagues found no increased hazard of uveitis within 30-, 60-, or 90-day treatment periods. A specific exp...