Association Between Oral Fluoroquinolone Use and Retinal Detachment

Fanny Raguideau, PharmD; Magali Lemaitre, PhD; Rosemary Dray-Spira, MD, PhD; Mahmoud Zureik, MD, PhD

IMPORTANCE Several studies have focused on the current use of oral fluoroquinolones and the risk for retinal detachment (RD), but the existence of this association is under debate. Given the widespread fluoroquinolone use, investigation of this association is essential.

OBJECTIVE To assess the association between oral fluoroquinolone use and the risk for RD, including the rhegmatogenous and exudative types.

DESIGN, SETTING, AND PARTICIPANTS This case-crossover study included 27,540 adults with RD from French health care databases from July 1, 2010, through December 31, 2013. Patients with a history of RD or retinal break, endophthalmitis, intravitreal injection, choroidal retinal vitreal biopsy, and human immunodeficiency virus infection or those hospitalized within 6 months of RD were excluded. The risk period of primary interest was current use, defined as exposure to fluoroquinolones within 10 days immediately before RD surgery, according to previous findings. Oral fluoroquinolone use was assumed to start on the day the prescription was dispensed.

MAIN OUTCOMES AND MEASURES Exposure to fluoroquinolones during the risk period (1-10 days) compared with the control period (61-180 days). The association was also assessed regarding use in the recent (11-30 days) and past (31-60 days) intermediate risk period, type of fluoroquinolone, and type of RD.

RESULTS Of the 27,540 eligible patients (57% men; mean [SD] age, 61.5 [13.6] years), 663 patients with RD were exposed to fluoroquinolones during the observation period, corresponding to 80 cases exposed during the 10-day risk period (≤10 days before RD) and 583 cases exposed during the control period (61-180 days). We found a significant increased risk for RD during the 10-day period after the dispensing of oral fluoroquinolones, with an adjusted odds ratio of 1.46 (95% CI, 1.15-1.87). The risk was significantly increased for rhegmatogenous and exudative RD, with adjusted odds ratios of 1.41 (95% CI, 1.04-1.92) and 2.57 (95% CI, 1.46-4.53), respectively. Recent and past use of fluoroquinolones were not associated with a higher risk for RD, with adjusted odds ratios of 0.94 (95% CI, 0.78-1.14) and 1.06 (95% CI, 0.91-1.24), respectively.

CONCLUSIONS AND RELEVANCE Current oral fluoroquinolone use was associated with an increased risk for RD, including the rhegmatogenous and exudative types. These findings, along with the available literature, suggest an association between fluoroquinolone use and the risk for RD. The nature of this association should be further investigated in future studies.
Retinal detachment (RD), including the exudative type often associated with systemic diseases, for which antibiotics may be prescribed, and the rhegmatogenous type, which requires prompt surgical intervention to reduce the chance of irreversible severe visual loss, has an annual incidence rate of 1 per 10,000 in the general population. The rhegmatogenous type is the most common. Fluoroquinolones are one of the most commonly prescribed classes of antibiotics. Because of their broad-spectrum antibacterial coverage, they are effective in the treatment of a wide variety of community-acquired infections. In France, fluoroquinolones are used mainly to treat urinary tract infections but might be used in the setting of systemic diseases that could have associations with exudative RD. Approximately 5,000,000 oral fluoroquinolone prescriptions were dispensed in 2013, including mainly norfloxacin, ofloxacin, and ciprofloxacin hydrochloride.

A nested case-control study of a cohort of ophthalmologic patients reported a significant 4.5-fold increase in the risk for RD with the current use of oral fluoroquinolones. Apart from this study, a Taiwanese cohort study showed a significant association with a 2-fold increase in risk with the use of fluoroquinolones compared with amoxicillin. Most of the other studies based on health claims databases found a positive but nonsignificant association (eTable 1 in the Supplement); however, most studies were underpowered to exclude a small increase in risk. Further evidence of retinal damage triggered by fluoroquinolones is apparent in several nonclinical studies that show dosage-related retinal toxic effects. Certain forms of ocular toxicity of fluoroquinolones have also been observed in humans. Moreover, the effects of cytotoxic properties on collagen and connective tissue offer a plausible pathophysiologic mechanism for acute fluoroquinolone-associated rhegmatogenous RD. Hence, given the controversial epidemiologic results and the widespread use of fluoroquinolones, we assessed the association between RD and fluoroquinolones using the French health care databases.

Methods

We conducted a nationwide study from July 1, 2010, through December 31, 2013. To consider determinants or potential confounders of RD, we applied a case-crossover design as a means of controlling factors within participants. This self-matched design implies that time-invariant multiplicative confounders are necessarily adjusted. To deal with a possible reverse-causality bias owing to the recurrence of RD and the increasing probability of subsequent events, only first events were used (subsequent events were ignored) and unidirectional analyses were performed (Figure 1). After confirming the absence of any seasonal trend in the occurrence of RD and fluoroquinolone use and after finding no difference in the distribution of fluoroquinolone use before and after RD (Methods in the Supplement), we used a short observation period that was defined as the 180 days leading up to RD surgery (index date). The French Data Protection Agency approved this study. Patient data were deidentified, and informed consent is not required for health care database studies in France.

Given previous findings, current use of fluoroquinolones was the risk period of primary interest and was defined as an exposure to a fluoroquinolone no more than 10 days immediately before an RD procedure. Oral fluoroquinolone use was assumed to start on the day the prescription was dispensed. The probability of exposure in the risk period was compared with the probability of exposure in the earlier control period (61-180 days before the RD procedure). Exposure to fluoroquinolones in the 11 to 60 days before the RD procedure corresponds to the past use of fluoroquinolones that is believed to carry an intermediate risk. Consequently, patients exposed during the intermediate risk period were excluded to retain a suitable control period with a baseline risk. This intermediate risk was explored in a secondary analysis.

Data Sources

We used the SNIIRAM (French National Interscheme Health Insurance Information System) database, which covers the entire French population and offers different plans based on employment situations. We only used the data relating to beneficiaries of the general plan (77% of the population) for whom the SNIIRAM comprehensively records—with dates—outpatient drugs (Anatomical Therapeutic Classification [ATC])
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Original Investigation Research

Figure 2. Study Flowchart

- **45,091** Eligible adults with RD from January 1, 2010, to December 31, 2013, who were affiliated with the general health plan
- **17,551** Excluded
  - 243 With AIDS and/or a history of endophthalmitis
  - 3,046 With a history of RD
  - 12,760 With a history of hospital admission (6 months before RD)
  - 474 With intravitreal injections
  - 697 With a prescription for a fluoroquinolone by an ophthalmologist or any hospital physician
  - 331 With 2 fluoroquinolone prescriptions dispensed within 50 days

- **27,540** Included in study population

RD indicates retinal detachment.

We identified all individuals 18 years or older presenting with RD during the study period. We excluded persons with a history of RD or break, endophthalmitis, intravitreal injection, choroidal retinal vitreal biopsy, and human immunodeficiency virus infection (data were available from 2006) (Figure 2). Because information on in-hospital antibiotic exposure was not available, and to minimize the influence of potential confounders, such as ocular surgeries or trauma, we also excluded persons who had been hospitalized within 6 months before RD.

To minimize the potential prophylactic use of fluoroquinolones before the surgical procedure, we excluded all patients for whom a fluoroquinolone had been prescribed by an ophthalmologist, an anesthetist, or any hospital physician. In our main analysis, we excluded all individuals who had been exposed to a fluoroquinolone during the intermediate risk period (11-60 days). To be comparable between the risk (1-10 days) and control (61-180 days) periods, individuals with 2 fluoroquinolone prescriptions dispensed within 50 days in the control period were also excluded.

**Retinal Detachment**

The outcome was defined as in previous studies as an incident hospitalization for RD in combination with a surgical procedure for RD within 14 days after the date of hospital admission for RD.2-4 The specific types of RD selected were rhegmatogenous (ICD-10 code H330), exudative (ICD-10 code H332), tractional (ICD-10 code H334), and other (ICD-10 code H335). The selected surgical procedures are listed in eTable 3 in the Supplement. Hospital admissions for retinoschisis and retinal cysts (ICD-10 code H331) or retinal tears without detachment (ICD-10 code H333) in combination with a specific RD procedure were also selected.

**Statistical Analysis**

Data were analyzed from July 1, 2010, to December 31, 2013. If a patient was exposed during a risk period, fluoroquinolone exposure was considered event related. The probability of exposure during a risk period was compared with the probability of exposure in further random control periods of 10 days. Because the case-crossover design used a single case period matched with further control periods, we analyzed the data through conditional logistic regression models to explore the association while controlling for possible residual confounding factors. Given the short observation period (180 days), age and comorbidities were considered fixed during all periods (control and risk). The use of ophthalmologic antibiotics, oral antibiotics, and oral corticosteroids could change between these different periods. An individual was considered exposed when a prescription was dispensed during the risk and control periods. We calculated the odds ratios (ORs) and 95% CIs. Odds ratios were also estimated by stratification according to the type of fluoroquinolone (norfloxacin, levofloxacin, ciprofloxacin, ofloxacin, lomefloxacin hydrochloride, and moxifloxacin hydrochloride) prescribed and the type of RD.

We also assessed the 11- to 60-day intermediate risk period to study the toxic mechanism of the acute vs prolonged association using an exposure definition equivalent to that of Pasternak et al4 for recent (11-30 days preceding RD) and past (31-60 days preceding RD) use. We used the same adjustment variables as in the main analysis.

We performed a sensitivity analysis to test the robustness of our findings using another case-only design, the self-controlled case series.31 In this design, we also looked at first events, and the risk period was defined as the 10-day period after each fluoroquinolone prescription had been dispensed (considered to be the greater risk period for the event), whereas the risk-free period included all other periods when patients were considered to be at baseline risk. Individuals exposed to fluoroquinolones during the intermediate risk period (11-60 days) were excluded. The incidence rate ratio and its 95% CIs were estimated by comparing the incidence of RD during the risk and risk-free periods using a conditional Poisson regression model.
### Table 1. Characteristics of the Population With RD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Group&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RD With Fluoroquinolone Use&lt;sup&gt;+&lt;/sup&gt;</th>
<th>RD Without Fluoroquinolone Use&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.5 (13.6)</td>
<td>63.9 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Age, No. (%), y</td>
<td>10 997 (31.6)</td>
<td>225 (33.9)</td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>16 543 (60.1)</td>
<td>438 (66.1)</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>15 692 (57.0)</td>
<td>295 (44.5)</td>
<td></td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>16 092 (55.5)</td>
<td>292 (43.6)</td>
<td></td>
</tr>
<tr>
<td>Type of retinal detachment, No. (%)</td>
<td>18 629 (67.6)</td>
<td>435 (65.5)</td>
<td></td>
</tr>
<tr>
<td>Rhegmatogenous</td>
<td>2987 (10.8)</td>
<td>87 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Serous or exudative</td>
<td>3291 (11.9)</td>
<td>84 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Tractional</td>
<td>2252 (8.2)</td>
<td>49 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Retinal tears without detachment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>344 (1.2)</td>
<td>7 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Retinoschisis and retinal cysts&lt;sup&gt;c&lt;/sup&gt;</td>
<td>37 (0.1)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Type of surgical procedures, No. (%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>16 424 (59.6)</td>
<td>413 (62.3)</td>
<td></td>
</tr>
<tr>
<td>Retinovitreal&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7646 (27.8)</td>
<td>178 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Retinopexy</td>
<td>3384 (12.3)</td>
<td>70 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>86 (0.3)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic history, No. (%)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>6944 (25.2)</td>
<td>185 (27.9)</td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>1315 (4.8)</td>
<td>38 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Other retinal and choroidal disorder (including retinopathy)</td>
<td>1142 (4.1)</td>
<td>27 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Vitreous disease or degeneration (including degenerative myopia)</td>
<td>433 (1.6)</td>
<td>12 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Other procedures</td>
<td>182 (0.7)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Other medical history, No. (%)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>2958 (10.7)</td>
<td>72 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3308 (12.0)</td>
<td>108 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases&lt;sup&gt;j&lt;/sup&gt;</td>
<td>311 (1.1)</td>
<td>10 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Renal diseases&lt;sup&gt;j&lt;/sup&gt;</td>
<td>3299 (12.0)</td>
<td>82 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Use of antibiotic eyedrops at the index date, No. (%)</td>
<td>579 (2.1)</td>
<td>19 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Use of other oral antibiotics at the index date, No. (%)</td>
<td>499 (1.8)</td>
<td>16 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Reimbursement for eyeglasses or contact lenses, No. (%)</td>
<td>21 351 (77.5)</td>
<td>549 (82.8)</td>
<td></td>
</tr>
<tr>
<td>Any ophthalmologist visit during the year before RD, No. (%)</td>
<td>12 393 (45.0)</td>
<td>302 (45.6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: RD, retinal detachment.

<sup>a</sup> Percentages have been rounded and may not total 100.

<sup>b</sup> Indicates in combination with at least 4 of the following: coagulation, vitrectomy, laser endocoagulation, retinotomy, internal tamponade, fluid-air exchange, dissection of adhesions, and retinectomy or buckling with at least 3 of the previous procedures.

<sup>c</sup> Indicates vitreous procedures involving at least 4 of the following: coagulation, vitrectomy, laser endocoagulation, retinotomy, internal tamponade, fluid-air exchange, dissection of adhesions, and retinectomy or buckling with at least 3 of the previous procedures.

<sup>d</sup> Includes orbital disorders, ocular trauma, and congenital malformation.

### Results

After applying the exclusion criteria to the source population of 45 091 eligible individuals with RD, 27 540 individuals were studied (Figure 2). The main characteristics of the study population are described in Table 1. The mean (SD) age was 61.5 (13.6) years, and most participants were male (57.0%). Rhegmatogenous RD was observed in 18,629 cases (67.6%), and exudative RD was observed in 2987 cases (10.8%). A history of cataract was reported in 6944 cases (25.2%); diabetes mellitus, in 2958 (10.7%); and cardiovascular diseases, in 3308 (12.0%).

During the study period, 6708 individuals (24.4%) received at least 1 fluoroquinolone prescription of a total of 12,232 prescriptions dispensed. More than half of the prescriptions (6896 [56.4%]) were dispensed after RD.

During the observation period (180 days before RD), 663 individuals were exposed to fluoroquinolones with a total of 728 prescriptions dispensed. Norfloxacin was the fluoroquinolone most often dispensed in 198 cases (27.2%). Levofoxacin, ciprofloxacin, and ofloxacin were dispensed in 142 (19.5%), 127 (17.4%), and 117 (16.1%), respectively.

The characteristics of the total patient population and patients exposed to fluoroquinolones during the observation period were globally similar (Table 1). Patients exposed to fluoroquinolones were older and more often women. Surgery for RD was performed in 26,736 cases (97.1%) on the day of the hospital admission (14,970 [54.4%]) or the day after (11,765 [42.7%]).

Regarding patients with RD exposed to fluoroquinolones during the study observation period, 80 were exposed during the risk period (≤10 days before RD) and 583 were exposed during the control period (61-180 days). The following variables with a significance threshold below 0.20 or known risk factors were retained in the final model: age, ophthalmologic history, diabetes mellitus, cardiovascular disease, renal disease, glaucoma, corticosteroid use, and reimbursement for eyeglasses or contact lenses. Oral and ophthalmic antibiotics were associated with RD in the univariate analysis. However, because these antibiotics can be prescribed for the RD surgical procedure, they were not included in the multivariate model to avoid an overadjustment.

Exposure to fluoroquinolones was significantly associated with the occurrence of RD during the 10-day risk period, with an adjusted OR of 1.46 (95% CI, 1.15-1.87) (Table 2). Recent use (11-30 days) and past use (31-60 days) of fluoroquinolones were not associated with a higher risk for RD, with adjusted ORs of 0.94 (95% CI, 0.78-1.14) and 1.06 (95% CI, 0.91-1.24), respectively. The sensitivity analysis using a self-controlled case series design confirms a significantly increased risk for RD associated with the use of oral fluoroquinolones, with an adjusted incidence rate ratio of 1.68 (95% CI, 1.36-2.07).

The risk for RD was studied according to the type of fluoroquinolone and the type of RD (Table 3). We kept the same adjustment variables as those selected for the main analysis. Levofoxacin use was significantly associated with a risk for RD within 10 days, with an adjusted OR of 2.07 (95% CI,
A sensitivity analysis without levofloxacin showed a positive association between fluoroquinolones and RD, which failed to achieve significance after adjustment, with an adjusted OR of 1.26 (95% CI, 0.95-1.69). Current oral fluoroquinolone use was associated with an increased risk for rhegmatogenous and exudative RD, with an adjusted OR of 1.41 (95% CI, 1.04-1.92) and 2.57 (95% CI, 1.46-4.53), respectively. The main characteristics of rhegmatogenous cases are described in eTables 4 and 5 in the Supplement. Results are similar to those of the main analysis. Patients with a history of diabetes mellitus or a previous visit to an ophthalmologist had a stronger association (P < .05 for interaction) (eTable 6 in the Supplement).

**Discussion**

This nationwide case-only design study found a significantly increased risk for RD associated with the use of oral fluoroquinolones with an adjusted OR of 1.46. Combining the health insurance database (SNIIRAM) and hospital discharge database (PMSI) has considered all French surgical procedures for RD during the study period (n = 27 540), which, to our knowledge, assesses the largest number of cases to date (compared with other epidemiologic studies available). Therefore, our use of these databases coupled with the study design provides the necessary power to demonstrate an OR of less than 2.00.

Etminan et al\(^2\) first investigated this potential association. They found a 4-fold increase in risk that may be partly explained by the underlying ocular conditions of the study population whose baseline risk for RD might have been higher than that of the general population (inclusion during an ophthalmologist’s visit). Several studies were prompted by this finding. Kuo et al\(^3\) found a 2-fold increase in risk over 90 days, whereas the relevant risk period is deemed to be 10 days. The other studies\(^4-6,8\) found a positive but nonsignificant association. However, most of these studies were underpowered to conclude that an association existed, including the study by Pasternak et al\(^4\) with an adjusted OR of 1.29 (95% CI, 0.5-3.13). Fife et al\(^6\) also found results close to ours, with an adjusted OR of 1.33 (95% CI, 0.99-1.80). However, the use of commercial claims databases allowing entry and dropout of individuals over time might have resulted in reducing the number of exposed cases and therefore diluting the magnitude of the risk. Almost all subsequent studies rely on health care data.

### Table 2. Crude and Adjusted ORs for RD According to Current, Recent, and Past Fluoroquinolone Use

<table>
<thead>
<tr>
<th>Fluoroquinolone Use During Observation Period</th>
<th>Fluoroquinolone Use During Risk Period</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>(P) Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current (1-10 d)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Crude</td>
<td>1.58 (1.25-2.00)</td>
<td>0.97 (0.80-1.17)</td>
<td>1.08 (0.92-1.25)</td>
</tr>
<tr>
<td>Adjusted&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Adjusted</td>
<td>1.46 (1.15-1.87)</td>
<td>0.94 (0.78-1.14)</td>
<td>1.06 (0.91-1.24)</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; RD, retinal detachment.

<sup>a</sup> Indicates total number of dispensings (n = 728). Pefloxacin and enoxacin were not included because of small numbers (n = 14).

<sup>b</sup> Indicates total number of patients with fluoroquinolone use (n = 663).

<sup>c</sup> Multivariate model.

### Table 3. Crude and Adjusted ORs for RD by Current Use Stratified by Type of Fluoroquinolones and Type of RD

<table>
<thead>
<tr>
<th>Type of Fluoroquinolone or RD</th>
<th>Fluoroquinolone Use During Observation Period</th>
<th>Fluoroquinolone Use During Risk Period</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>(P) Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>198</td>
<td>15</td>
<td>0.97 (0.58-1.62)</td>
<td>0.94 (0.55-1.59)</td>
<td>0.23</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>142</td>
<td>25</td>
<td>2.35 (1.51-3.65)</td>
<td>2.07 (1.30-3.32)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Ciprofloxacin hydrochloride</td>
<td>127</td>
<td>12</td>
<td>1.30 (0.71-2.38)</td>
<td>1.17 (0.62-2.21)</td>
<td>0.23</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>117</td>
<td>11</td>
<td>1.25 (0.67-2.36)</td>
<td>1.11 (0.57-2.19)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Lomefloxacin hydrochloride</td>
<td>68</td>
<td>7</td>
<td>1.29 (0.58-2.86)</td>
<td>1.31 (0.59-2.92)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Moxifloxacin hydrochloride</td>
<td>62</td>
<td>8</td>
<td>1.76 (0.83-3.72)</td>
<td>1.47 (0.67-3.22)</td>
<td>0.23</td>
</tr>
<tr>
<td>Rhegmatogenous</td>
<td>435</td>
<td>50</td>
<td>1.47 (1.09-1.98)</td>
<td>1.40 (1.03-1.90)</td>
<td>0.23</td>
</tr>
<tr>
<td>Exudative or serous</td>
<td>87</td>
<td>18</td>
<td>2.96 (1.74-5.01)</td>
<td>2.56 (1.46-4.51)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Tractional</td>
<td>49</td>
<td>4</td>
<td>1.16 (0.41-3.31)</td>
<td>1.14 (0.40-3.27)</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Other or unspecified</td>
<td>92</td>
<td>8</td>
<td>1.13 (0.55-2.28)</td>
<td>0.98 (0.47-2.06)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; RD, retinal detachment.

<sup>a</sup> Indicates total number of dispensings (n = 728). Pefloxacin and enoxacin were not included because of small numbers (n = 14).

<sup>b</sup> Indicates total number of patients with fluoroquinolone use (n = 663).
with limited information regarding confounders and thus limited ability to adjust for important confounding factors (eg, myopia).

In accordance with biological plausibility, we found an increased risk for rhegmatogenous RD. We also found an increased risk for exudative RD that was usually due to underlying inflammatory mechanisms. To consider a potential confounding bias, we performed a sensitivity analysis that excluded patients with long-term infectious or inflammatory conditions and respiratory failure. Exposure to fluoroquinolones remained significantly associated with the occurrence of RD, with an adjusted OR of 1.43 (95% CI, 1.11-1.84). In addition, exudative RD captured in our study is only severe RD, for which prior drug therapies failed and a first-time surgical intervention was required. In this context and in line with some case reports, fluoroquinolones might play a role in rechallenge of serous RD.32 The numbers of other types of RD are too few to facilitate a robust conclusion. Moreover, tractional RDs are usually due to underlying fibrotic mechanisms. Therefore, the reported increased risk in patients with diabetes mellitus might be explained by this underlying mechanism. However, an effect on the direction of the results could not be identified with the exclusion of the few tractional RDs found. Although a plausible pathophysiologic mechanism for these findings exists, as associations they cannot be considered definitive cause-and-effect relationships.

We found a significant increase in the risk for RD with levofloxacin. Kuo et al33 found that the increase in risk varied depending on the type of fluoroquinolones. The risk was multiplied by 10 for ciprofloxacin and by 2 for levofloxacin or norfloxacin, whereas it was not increased for ofloxacin. Compared with previous studies in which participants were mainly ciprofloxacin users,2-4 our study had a balanced use of fluoroquinolones that might explain our finding. Nevertheless, given the small number of cases exposed to some fluoroquinolones, our study probably does not have sufficient statistical power to draw conclusions that rely on the type of fluoroquinolone. In addition, published data on the risk for tendinopathy,19,33,34 which is thought to have a similar mechanism to RD, do not show any association with a specific fluoroquinolone.

The main strength of our study lies in the self-matched design, which allows us to control for time-invariant factors. This design is particularly useful for studies conducted with health care databases in which few items of clinical data are recorded. Moreover, given the short observation period (180 days), we may reasonably assume that confounding risk factors, such as myopia (not available in the study database), diabetes mellitus, history of cataract, and even age effect, were the same during the risk and control periods. Thus, the study design has allowed us to overcome limitations of previous studies.

The self-controlled case series design was used in previous studies in the United States6 and Hong Kong and Taiwan.9 Both studies have shown a positive link, with results close to significance for Fife et al.6 The difference in risk could be explained by the integration of the intermediate risk period in the control period, which tends to underestimate the true risk. However, designs were not described in sufficient detail to allow a detailed comparison.35

Our study presents some limitations. Like all studies that use health care databases, exposure to treatment is derived from drug-dispensing data instead of effective drug intake. However, this classification bias is nondifferential, and, given the indications for fluoroquinolones, we can reasonably assume that the dispensing date was the effective start-of-treatment date.

Given the unidirectional design, exposure-trend bias is likely. We performed an additional analysis to compare the exposure distribution of fluoroquinolones between 2 symmetric periods (outside the potential prophylactic use of fluoroquinolones) framing RD (eMethods in the Supplement). No difference was identified between these periods. We therefore assume that an exposure-trend bias, if it existed, would be minimal and without any effect on our results.

We have no information regarding the in-hospital use of fluoroquinolones. Therefore, patients hospitalized during the 180 days before RD were excluded. We have no information on the therapeutic indication. Using the specialty of the prescribing physician, we were able to exclude patients receiving prophylactic fluoroquinolone treatment from the surgical procedure. However, we were not able to study the association between the cumulative dose and the occurrence of RD. Although we have information about the number of reimbursed fluoroquinolone packs, we cannot calculate the end of treatment because the posology and duration of treatment differ with the therapeutic indication.

Conclusions

Our results suggest a significant increased risk for RD, which includes the rhegmatogenous and exudative types, after the current use of oral fluoroquinolones. These findings, together with the available literature, suggest an association between fluoroquinolone use and the risk for RD. The nature of this association should be investigated further in future studies.
Association Between Oral Fluoroquinolone Use and Retinal Detachment

REFERENCES


