Association between oral fluoroquinolone use and the development of retinal detachment: a systematic review and meta-analysis of observational studies

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Objectives: Several observational studies have been published investigating the association between oral fluoroquinolone use and the development of retinal detachment; however, the findings are not concordant. This study is a meta-analysis of the existing literature and estimates the overall absolute risk of such an event.

Methods: Electronic databases were searched for observational studies on the association between oral fluoroquinolone and retinal detachment up to August 2014. Studies that did not meet the criteria for meta-analysis were narratively reviewed. Cases of retinal detachment during current fluoroquinolone use were also extracted for absolute risk calculation.

Results: Seven observational studies were included. Three (case–control and self-controlled case series studies) were eligible for meta-analysis and four (cohort studies) were narratively reviewed. The rate ratio of the case–control studies was 1.82 (95% CI 0.67–4.93), $I^2 = 96\%$ and the incidence rate ratio of the self-controlled case series was 1.03 (95% CI 0.84–1.27), $I^2 = 36\%$. Three of the four cohort studies found no significant association between oral fluoroquinolone use and the development of retinal detachment. The pooled absolute risk of retinal detachment whilst on current oral fluoroquinolone treatment is estimated to be 4.85 per 1000000 prescriptions (95% CI 0.78–8.91).

Conclusions: The findings of this systematic review and meta-analysis do not support an association between oral fluoroquinolone use and the development of retinal detachment. Given the low absolute risk, such an event would be rare if there were an association. The current prescribing practice for fluoroquinolones should not be altered because of a previously suggested potential risk of retinal detachment.

Keywords: adverse drug reactions, pharmacoepidemiology, retina

Introduction

Etminan et al.\(^1\) reported a significant association between the current use of oral fluoroquinolones (FQ) and the development of retinal detachment (RD) (i.e. an RD event occurring within the prescription period of FQ). This study caused the US, Canadian and European regulatory authorities to place FQ on their alert list\(^2\)–\(^4\) and since then more observational studies have been published. This systematic review and meta-analysis evaluates these observational studies and the potential for increased risk of RD with oral FQ use.

Methods

A systematic literature search was conducted using keywords, MeSH and Embtree terms. Records were retrieved from databases including PubMed, CINAHL and EMBASE in August 2014. The search terms included were fluoroquinolones AND (retinal detachment OR retinal*). This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)\(^5\) and the Meta-analysis of Observational Studies in Epidemiology\(^6\) to ensure clear and comprehensive reporting.

Inclusion and exclusion criteria

Observational studies that investigated the association between FQ use and the development of RD were included. Animal studies were excluded.

Quality assessment

The included studies were assessed for methodological quality using the Newcastle–Ottawa scale (NOS) as recommended by the Cochrane Collaboration.\(^7\) C. S. L. C. and L. Y. L. W. independently reviewed and scored each of the studies. Study quality is indicated by the number of stars, with a maximum allocation of nine stars.
Data extraction
Data on the outcome of interest, which is the risk or odds of developing RD whilst on FQ treatment, were extracted for analysis. Statistics presenting the period up to 10 days from the first day of prescription were selected. Studies where such statistics could not be extracted or included in the meta-analysis were summarized in the narrative review.

Statistical analysis
A random-effects model was used in the meta-analysis to account for heterogeneity between studies. Statistical analyses were conducted using Review Manager 5.2 (Cochrane Collaboration, 2012).

The number of RD cases that occurred whilst on FQ treatment was extracted from the original list of articles and the absolute risk was estimated using a method previously described. The 95% CI was calculated using the Wilson score interval. The analysis was performed using SAS 9.3 (SAS Inc., USA).

Results
A total of 695 citations were retrieved from the literature search. C. S. L. C. and L. Y. L. W. screened and reviewed relevant articles independently. Seven observational studies were relevant (Figure 1). The quality of the methodology was assessed and the results are presented in Tables 1 and 2.

Case–control
Two case–control studies were included in the meta-analysis. Etminan et al.11 reported a positive association between FQ use and the development of RD in a cohort, nested among patients who had visited an ophthalmologist, using the British Columbia Linked Health Database. Cases were defined as those with an RD-related procedure 14 days after the diagnosis date. Cases in FQ users and non-FQ users were compared and the rate ratio (RR) was adjusted for sex, previous history of cataract surgery, myopia, diabetes, number of visits to ophthalmologist, and number of prescription drugs used. In an attempt to replicate the study of Etminan et al., Fife et al. conducted a similar analysis in the US using the MarketScan Commercial Claims and Encounters databases. The results are presented as Fife2014(CCAE-CC) and Fife2014(Optum-CC) respectively in the meta-analysis. Meta-analysis of the three databases did not show a significant association with an OR of 1.82 (95% CI 0.67–4.93), I² = 96% (Figure 2). There was no significant change to the RR [1.25 (95% CI 0.95–1.65)], I² of 0%, following removal of the Etminan et al. study from the sensitivity analysis.

Self-controlled case series
Two studies using four different databases were included in this meta-analysis. Neither study found a significant association between oral FQ use and the development of RD. Of these, one study was performed using the Hong Kong Clinical Data Analysis and Reporting System (CDARS) and Taiwan National Health Insurance Research Database (NHIRD). The incidence RR (IRR) was adjusted for age, history of diabetes and cataract surgery. The meta-analysis results of the Hong Kong and Taiwan

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Figure 1. PRISMA flow chart.
<table>
<thead>
<tr>
<th>Study</th>
<th>Data source</th>
<th>Study period</th>
<th>Region</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Outcome definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etminan</td>
<td>Linked Health Database</td>
<td>01/2000–12/2007</td>
<td>Canada</td>
<td>Case-control</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study had an ophthalmologist visit history of RD diagnosis or procedures; endophthalmitis; intravitreal injection or vitreous biopsy | RD procedure (British Columbia procedure codes) received within 14 days of RD diagnosis (ICD-9) ** |
| Kuo | NHIRD | 1998–2010 | Taiwan | Case-control | 
Study was conducted on the age ≥ 18 years, prescribed FQ or amoxicillin during the prior 90 days; history of RD diagnosis or procedure; blindness; procedure for nucleation or enucleation of eyes | RD diagnosis (ICD-9) within 90 days of follow-up ** |
| Pasternak | Central Person Register, The National Prescription Registry, The Danish National Patient Registry | 1/1/1997–31/12/2011 | Denmark | Case-control | 
Study was conducted on the age ≥ 18 years, prescribed FQ; no history of RD or retinal tear; did not use FQ in the last 180 days; had lived in Denmark for at least 1 year; had filled at least 1 prescription for any medication in the last year; no hospitalization in the last 30 days; had a history of endophthalmitis, intravitreal injection, or choroidal; retinal or vitreal biopsy; cataract surgery; major eye surgery or eye trauma 30 days before RD | RD procedure received within 14 days after RD diagnosis ** |
| Chui | CDARS, NHIRD HK: 1/1/2001–31/12/2012; TW: 1/1/2000–31/12/2010 | HK, TW | HK, TW | Case-control | 
Study was conducted on the age ≥ 18 years, prescribed FQ; head or eye injury 30 days before RD; history of endophthalmitis, RD diagnosis or procedure | RD procedure received during FQ prescription (ICD-9) ** |
| Eftekhari | THIN | 06/1994–01/2012 | UK | Case-control | 
Study was conducted on the age ≥ 18 years, prescribed FQ or b-lactam; registered with GP for at least 365 days before prescription date; had a history of RD or retinal tear; FQ and b-lactam prescribed on the same day; history of intraocular surgery or diagnosis of endophthalmitis 90 days after FQ prescription | RD or retinal tear procedure (Medcodes) within 7, 30, 90 and 365 days after the FQ prescription *** |
<table>
<thead>
<tr>
<th>Study</th>
<th>Data source</th>
<th>Study period</th>
<th>Region</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Outcome definition</th>
<th>NOS&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fife 2014&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CCAE, Optum</td>
<td>CCAE: 1/1/2000 – 31/1/2012; Optum: 1/9/2005 – 31/3/2012</td>
<td>USA</td>
<td>CC</td>
<td>had an ophthalmologist visit and at least 1 year in the cohort</td>
<td>history of RD diagnosis or procedure; endophthalmitis or related procedures such as vitreous biopsy or intravitreal injection; RD event happened during hospitalization or within 10 days after being discharged</td>
<td>RD procedure received within 14 days after RD diagnosis</td>
<td>**   **   ***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SCCS</td>
<td>ophthalmologist visit not required</td>
<td>exclusion criteria in CC; history of inflammatory, infectious, or traumatic retinitis; index date of RD event happened during current or recent use of multiple antibiotic prescription (FQ and/or β-lactam); hospitalization between cohort entry and event date</td>
<td>restricted to codes associated with rheumatogenous RD and within 30 days after the beginning of FQ prescription</td>
<td>**   **   ***</td>
</tr>
<tr>
<td>Kapoor 2014&lt;sup&gt;15&lt;/sup&gt;</td>
<td>REP</td>
<td>1/1/2003 – 30/6/2011</td>
<td>USA</td>
<td>C</td>
<td>prescribed FQ, macrolides or β-lactam</td>
<td>history of endophthalmitis, necrotizing retinitis, ipsilateral intraocular surgery; severe ocular/ head trauma within 90 days of RD; treated with serous/exudative RD or diabetic retinopathy-related tractional RD</td>
<td>RD procedure (Current Procedure Terminology) within 7, 30, 90 and 365 days after the FQ prescription</td>
<td>*    ***</td>
</tr>
</tbody>
</table>

CC, case–control study; C, cohort study; SCCS, self-controlled case series; CCAE, MarketScan Commercial Claims and Encounter database; Optum, Optum ClinFormatics database; REP, Rochester Epidemiology Project.

<sup>a</sup>Quality assessment of the methodology of the included studies. The assessment guideline for case–control studies was used for self-controlled case series studies.

<sup>b</sup>Study quality is indicated by the number of stars. Each study could be allocated a maximum of nine stars.

<sup>c</sup>Replication case–control and self-controlled case series analyses.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Closest ‘current use’ definition</th>
<th>Number of cases in ‘current FQ use’</th>
<th>Result of current FQ use</th>
<th>Absolute risk of RD whilst on FQ treatment (up to 10 days from the first day of prescription)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etminan 2012&lt;sup&gt;1&lt;/sup&gt;</td>
<td>RD case: 4384 control: 43840</td>
<td>within prescription period</td>
<td>145</td>
<td>RR: 4.50 (95% CI 3.56–5.70)</td>
<td>data not available</td>
</tr>
<tr>
<td>Kuo 2013&lt;sup&gt;14&lt;/sup&gt;</td>
<td>FQ prescriptions: 178179 AMX prescriptions: 178179</td>
<td>patients were followed up for 90 days after they entered the cohort</td>
<td>96</td>
<td>HR: 2.07 (95% CI 1.45–2.96)</td>
<td>data not available</td>
</tr>
<tr>
<td>Pasternak 2013&lt;sup&gt;13&lt;/sup&gt;</td>
<td>FQ episodes: 748792 control episodes: 5 520 446</td>
<td>1–10 days starting from the first day of prescription</td>
<td>5</td>
<td>RR: 1.29 (95% CI 0.53–3.13)</td>
<td>5 cases out of 748 792 prescriptions = 6.7 per 1 000 000 prescriptions</td>
</tr>
<tr>
<td>Chui 2014&lt;sup&gt;6&lt;/sup&gt;</td>
<td>FQ prescriptions:&lt;sup&gt;b&lt;/sup&gt; HK: 260 198 TW: 1098 086</td>
<td>within prescription period</td>
<td>HK: 2&lt;sup&gt;b&lt;/sup&gt; TW: 7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IRR: HK: 0.82 (95% CI 0.20–3.36) TW: 1.45 (95% CI 0.68–3.10)</td>
<td>HK: 2 cases out of 260 198 prescriptions = 7.7 per 1 000 000 prescriptions TW: 7 cases out of 1 098 086 prescriptions = 6.4 per 1 000 000 prescriptions</td>
</tr>
<tr>
<td>Eftekari 2014&lt;sup&gt;16&lt;/sup&gt;</td>
<td>FQ prescriptions: 290 393 β-lactam prescriptions: 6 314 030</td>
<td>1–7 days after the prescription</td>
<td>0</td>
<td>data not available</td>
<td>0 cases out of 290 393 prescriptions</td>
</tr>
<tr>
<td>Fife 2014&lt;sup&gt;12c&lt;/sup&gt;</td>
<td>case–control: CCAE: RD case: 7844 control: 77 654 Optum: RD case: 3059 control: 30 230</td>
<td>case–control: within prescription period</td>
<td>case–control: CCAE: 66 Optum: 13</td>
<td>OR (case–control): CCAE: 1.33 (95% CI 0.99–1.80) Optum: 0.93 (95% CI 0.48–1.81)</td>
<td>data not available</td>
</tr>
<tr>
<td></td>
<td>self-controlled case series: 30 days after start of FQ prescription</td>
<td>self-controlled case series: CCAE: 74 Optum: 18</td>
<td>RR (self-controlled case series): CCAE: 1.13 (95% CI 0.99–1.29) Optum: 0.85 (95% CI 0.66–1.09)</td>
<td>data not available</td>
<td>data not available</td>
</tr>
<tr>
<td>Kapoor 2014&lt;sup&gt;15&lt;/sup&gt;</td>
<td>FQ prescriptions: 92 130 macroline prescriptions: 107 086 β-lactam prescriptions: 178 352</td>
<td>within 7 days after the prescription</td>
<td>0</td>
<td>0% (95% CI 0–0.01)</td>
<td>0 cases out of 92 130 prescriptions</td>
</tr>
<tr>
<td>Overall absolute risk</td>
<td></td>
<td></td>
<td></td>
<td>4.85 cases out of 100 000 prescriptions (95% CI 0.78–8.91)</td>
<td>data not available</td>
</tr>
</tbody>
</table>
databases are presented as Chui 2014 (HK) and Chui 2014 (TW), respectively. Fife et al. also conducted a self-controlled case series study in the US. Unlike the case–control analysis, ophthalmology visits were not an inclusion criterion. Cases were defined as those with RD 30 days after the beginning of FQ exposure. The RRs are presented as Chui 2014 (HK) and Chui 2014 (TW), Fife 2014 (CCAE-SCCS) and Fife 2014 (Optum-SCCS). Meta-analysis of the four databases gave a statistically non-significant IRR of 1.03 (95% CI 0.84–1.27), $I^2 = 36\%$ (Figure 3).

**Narrative review**

Four cohort studies were also included in this review. However, their study designs were very different and therefore are not appropriate for meta-analysis. Pasternak et al. used the Central Person Register to identify adults living in Denmark from 1997 to 2011. RD cases were defined as incident diagnosis of RD with a related procedure performed within 14 days of the diagnosis date. They reported five cases of RD among current FQ users (1–10 days post first day of FQ prescription and the index date of RD diagnosis was 90 days of the follow-up period. The authors concluded that oral FQ was associated with subsequent occurrence of RD. The FQ risk was independent of age, sex, diabetes, indications for anti-microbials and underlying ophthalmic conditions.

Kapoor et al. examined whether there was an associated increase in subsequent RD and symptomatic retinal breaks and oral FQ. They included adult residents of Olmsted County, Minnesota who were prescribed oral FQ from 2003 to 2011, from the Rochester Epidemiology Project. Patients prescribed oral FQ were compared with those prescribed oral macrolide and $\beta$-lactam antibiotics. Cases were defined as procedures recorded within 1 year of the first prescription. RD repair procedures were performed within 365 days of the first prescription in 0.03% (95% CI 0.01–0.06) of the FQ group, 0.02% (95% CI 0.01–0.03) of the macrolide group, and 0.03% (95% CI, 0.02–0.05) of the $\beta$-lactam group ($P > 0.05$). There were no significant differences in treatment rates within 7, 30 and 90 days of the first prescription between the groups. Kapoor et al. concluded that oral FQ use was not associated with an increased risk of RD and symptomatic retinal breaks in their study.

Eftekhari et al. investigated whether oral FQ use would increase the risk of RD and retinal tear in the UK using The Health Improvement Network database (THIN). Patients prescribed FQ between 1994 and 2012 were compared with those prescribed $\beta$-lactam. Cases were defined as those with a procedure related to retinal break during the observation period. No case was observed 7 days after the prescription among FQ users; therefore, it was not possible to estimate the HR. The adjusted HR was
0.78 (95% CI 0.02–4.74) 30 days after prescription, 1.26 (95% CI 0.40–3.06) at 90 days and 1.35 (95% CI 0.85–2.06) at 365 days. A sensitivity analysis included only cases with a retinal break diagnosis within 30 days of the procedure with no findings of increased risk. Eftekhari et al.16 concluded that no increased risk of retinal break was observed using the THIN database.

Absolute risk of RD whilst on current FQ treatment

The absolute risks of developing RD whilst on current FQ treatment among the included studies are presented in Table 2. No RD cases in current FQ users were reported in Kapoor et al.15 and Eftekhari et al.16 The total number of FQ prescriptions was not reported by Etminan et al.1 and Fife et al.12 therefore the absolute risk cannot be estimated. The pooled absolute risk of the five database analyses is estimated to be 4.85 per 1000000 prescriptions (95% CI 0.78–8.91) (Figure 4).

Discussion

The results of this meta-analysis do not support an association between oral FQ use and the development of RD. Three of the four cohort studies13,15,16 in the narrative review do not support an association either. Although two studies1,14 reported significant results, they do not concur. Etminan et al.1 reported that the effect of FQ on RD is of an acute nature, i.e. current FQ users. However, Kuo et al.14 reported that the median interval between the prescription and the index date of RD diagnosis was 35.5 days, i.e. not acute.

Farioli and Kriebel17 estimated the incidence rate of RD in the study of Kuo et al.14 to be 218.5 per 100000 patient-years with a mean age of 47 years. The incidence of RD is age-dependent with <19–27 cases per 100000 person-years in the sixth decade of life.18 They questioned the validity of the findings of Kuo et al.14 since the study’s incidence rate was much higher with a lower mean age. This discrepancy may be explained by significant differences in the RD case definition in the study of Kuo et al.,14 where procedure codes were not required to confirm RD cases. It is worth noting that the RR reported by Etminan et al.1 was much higher than that reported by other included studies. Fife et al.12 replicated the analysis using two datasets from two databases and estimated an OR of almost 1. Since both studies had similar settings, it is unclear why this discrepancy occurred. However, differences in clinical practice and the coding system may account for this. Fife et al.12 validated their results with additional analyses; however, they did not find a significant association, which concurs with the findings of this meta-analysis.

The meta-analysis for self-controlled case series gave an RR of almost 1 [1.03 (95% CI 0.84–1.27)] with moderate variability among the studies from different countries ($I^2 = 36\%$). With such a narrow confidence interval around 1, the results clearly reject an association between the use of FQ and RD. Finally, it is important to note that the pooled absolute risk of developing RD whilst on FQ treatment was minimal (Figure 4). Such an event would be very rare if there were an association.

Strengths and limitations

Disease codes such as ICD-9 were used to identify cases among the included studies. Although the case definitions varied, all (except Kuo et al.14) included a procedure code to confirm the RD case. The codes of the included databases have been validated in other settings,19–21 thus ensuring the quality of the analysed data. In addition, the study designs of all of the included studies are of satisfactory quality, obtaining more than six of nine stars from the NOS quality assessment.
The results of this meta-analysis are compiled from available observational studies and attempts to draw a conclusion on the potential for increased risk of RD with oral FQ use. Variability may have an effect on heterogeneity, which is demonstrated in the meta-analysis of the case-control studies. However, the result remains non-significant in the sensitivity analysis with reduced heterogeneity. Furthermore, the heterogeneity of the self-controlled case series studies analyses was not significant and supports the validity of the conclusion.

Conclusions
The results of the meta-analysis do not support an association between oral FQ use and the development RD. However, if there were an association, such events would be rare given the small absolute risk estimated in the available literature. Based on the evidence from this meta-analysis, the use of oral FQ should not be precluded.

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Transparency declarations
We declare there was no support from any organization for the submitted work, no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work. C. S. L. C., E. W. C. and I. C. K. W. are authors of one of the included studies.

Author contributions
C. S. L. C., E. W. C., L. Y. L. W. and I. C. K. W. had the original idea for this study and contributed to the development of the idea and the study design. C. S. L. C. and L. Y. L. W. independently conducted a systematic review and reviewed the literature for relevance. C. S. L. C., E. W. C. and I. C. K. W. undertook the primary analysis. C. S. L. C., E. W. C. and I. C. K. W. contributed to the interpretation of the analysis. C. S. L. C., E. W. C. and L. Y. L. W. wrote the first draft of the paper. E. W. C., L. Y. L. W. and I. C. K. W. critically reviewed the paper. E. W. C. and I. C. K. W. provided oversight of all aspects of this project. C. S. L. C. and I. C. K. W. are the guarantors. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

References