Invited Commentary

Does Systemic Fluoroquinolone Use Increase Risk of Retinal Detachment?

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By linking primary care records to hospital admissions data in 2 UK databases (Aurum and GOLD), Brown et al[1] examined the association between systemic fluoroquinolone use and risk of acute uveitis and rhegmatogenous retinal detachment (RD) within 60 days after prescriptions. The authors used 2 analytic designs with different assumptions to test the hypotheses. Based on results of time-to-event analysis that took advantage of the cohort study design, which uses prospective follow-up of patients at risk, the authors found no evidence of associations between first treatment episode of fluoroquinolone and RD in either of 2 patient cohorts prescribed fluoroquinolone (weighted hazard ratio [HR], 1.19 [95% CI, 0.66-2.15] in Aurum; weighted HR, 4.53 [95% CI, 0.48-43.04] in GOLD).[1] Another analysis that considered all treatment episodes of fluoroquinolone led to comparable results (weighted HR, 1.14 [95% CI 0.80-1.64] in Aurum; weighted HR, 1.54 [95% CI, 0.51-4.70] in GOLD).[1] The authors further performed a pre-post analysis (or "case cross-over analysis" as the authors described) to verify the findings using only data from patients with RD in the 2 datasets. Exposure to fluoroquinolone was not associated with an increased risk of RD across different exposure windows (days 1-29, 30-59, or 60 or more).[1]

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Although the study findings of Brown et al were consistent with those of a recent publication using similar study designs,[2] the evidence base supporting current policies on fluoroquinolone use has remained largely inconsistent and unreliable. As a first-line antibiotic, fluoroquinolone is frequently indicated for its broad antimicrobial spectrum in the primary care and hospital setting. However, emerging safety concerns about increased risks for collage-associated complications, such as aortic aneurysm/dissection, RD, and tendon disorders, have restricted fluoroquinolone use by the US Food and Drug Administration and European Medicine Agency.[3]

As early as in 2012, Etminan et al[4] examined the association between oral fluoroquinolone use and the risk of RD in a nested case-control study in Canada. They identified patients with RD based on surgical procedure codes within 2 weeks of a physician service code. Matched on age and time of study entry, 10 controls were selected for each eligible patient with RD. The investigators found an increased risk of RD in current users of fluoroquinolone (patients with active prescription) but not in recent (prescription terminated within 7 days) or past users (prescription terminated in 7-365 days). Because of the relatively low absolute risk (1 in 2500 patient-year), which was presumably outweighed by the benefits of fluoroquinolone, it was suggested that only symptomatic patients at risk for RD might benefit from pretreatment retinal evaluation.[5]

In 2016, a systematic review and meta-analysis that included data from 10 observational studies reported that, although fluoroquinolone was not associated overall with risk of RD, the association differed depending upon study design or definition of exposure windows.[6] In a recently published umbrella review of 7 systematic reviews, Gatti and colleagues[3] concluded that associations between fluoroquinolone and aortic aneurysm/dissection or tendon disorders were supported by highly credible evidence, whereas evidence for RD was inconsistent among the reviews and thus considered weak. In the most recent systematic review identified by the umbrella review,[3] Yu and colleagues included 6 of 8 studies that also were included in the other 2 reviews; authors of both reviews had concluded that there was no association between fluoroquinolone and RD whereas Yu et al found a positive association between RD and past fluoroquinolone use (between 30-365 days) in men and in study participants aged 60 years or older.

At the study level, one of the potential sources of heterogeneous findings may stem from selection bias, that is, different eligibility criteria for selecting study participants, such as including[4] or excluding[1] individuals with diabetic retinopathy or other medical conditions that were associated with fluoroquinolone prescriptions and risk of RD. The exclusion of high-risk individuals from the analysis may have inadvertently led to selecting low-risk participants into the study. Therefore, instead of excluding participants potentially at risk for RD, these individuals could be included in the study and their risk estimated separately in subgroup analysis. Second, varying degrees of residual confounding when using a cohort study design depends on how similarity of characteristics prior to treatment initiation was achieved between comparison groups by statistical analysis. In Brown et al,[1] the authors used inverse probability treatment weighting to create independence between potential confounders and the probability of fluoroquinolone use in the primary time-to-event analysis. However, the weighting scores created for the overall population do not always guarantee comparability within subgroups. Thus, for each subgroup analysis, the study population should have been stratified first and then weighted within each stratum before performing the regression analysis. Also, selection bias introduced by conditioning (or covariate adjustment) must be avoided when time-varying covariates are incorrectly incorporated into the model to adjust for confounding. Lastly, accurate and consistent measurement of time at risk (ie, exposure to fluoroquinolone) is essential for valid estimation of relative and absolute risk.

Use of health claims data to shed light on treatment-associated adverse events, particularly rare events, has gained increasing popularity over the past decade. To optimize the benefits of existing cohort data, analytic plans to emulate clinical trial designs can address selection bias and confounding by indication in observational data and have the potential to provide unbiased estimates of either treatment effectiveness or safety concerns.[7]

ARTICLE INFORMATION

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Published Online: May 30, 2024. doi:10.1001/jamaophthalmol.2024.1948

Conflict of Interest Disclosures: None reported.

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