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COMMENT & RESPONSE

Oral Fluoroquinolone Use and Retinal Detachment

To the Editor We read with interest the recent article by Raguideau et al¹ on the association between the use of fluoroquinolone antibiotics and retinal detachment. The authors chose to use 2 self-controlled study designs to address this question: first, the case crossover method,² and, second, the self-controlled case series.³ The 2 methods appear to give similar answers, suggesting a roughly 50% increased risk of retinal detachment following exposure to a fluoroquinolone. However, we have some concerns about the method underpinning the study.

First, in the case-crossover study, Raguideau et al¹ excluded people who had been exposed to any fluoroquinolone during the intermediate-risk period, and they also excluded all people exposed twice to a fluoroquinolone within any 50-day period during the control period. We believe this may have introduced an important bias, whereby people exposed during the control period were disproportionately excluded. As a consequence, patients would appear to be more likely exposed during the risk period close to the date of retinal detachment, potentially creating a spurious association. This approach is analogous to conducting a case-control study and selecting patients based on prior knowledge of the exposure of interest, which can cause serious bias. We note that 331 of the 994 fluoroquinolone-exposed cases were excluded from the main analysis for this reason, a substantial proportion of the informative cases in this study. It would be helpful to see the results of an analysis with no exclusions.

Second, a recent cohort study⁴ with the same question used a “control” exposure to demonstrate that an effect size of similar magnitude may be driven by bias and confounding; the authors found that fluoroquinolone and amoxicillin had similar associations with the risk of retinal detachment. Although self-controlled designs are less susceptible to individual-level time-invariant confounding than traditional cohort studies, other biases (in particular, indication bias) are not avoided, and a similar control exposure, not hypothesized to be associated with retinal detachment, would have been helpful in the study by Raguideau et al¹ to help exclude such biases.

Finally, the detailed methods used for the self-controlled case series are not presented in the study or the online supplementary material. Correctly implementing this design requires a careful choice of observation and risk periods.⁵ Is it possible for the authors to provide further details on how the self-controlled case-series analysis was performed? This additional information would be helpful in the interpretation of the conclusions.

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In Reply Our main analysis focused on the immediate acute effects of fluoroquinolones. Therefore, as is usually done, we excluded patients exposed during the intermediate risk period. Because the intermediate risk period is not associated with an increased risk, this exclusion is unlikely to have affected the odds ratio. Individuals with a fluoroquinolone prescription during the 10 days preceding retinal detachment (RD) and exposed during the intermediate risk period (ie, during the 50 prior days) were not considered exposed during the risk period. Consistently, individuals with 2 fluoroquinolone prescriptions dispensed within 50 days in the control period were not considered exposed either.

In a complementary analysis, we included the 331 patients exposed during the intermediate risk period. As anticipated, the results were unchanged; exposure to fluoroquinolones remained significantly associated with the occurrence of RD during the 10-day risk period, with an adjusted odds ratio of 1.46 (95% CI, 1.17-1.81).

A potential confounding bias of the systemic disease for which fluoroquinolones may be prescribed is possible. Other studies¹⁻⁵ previously managed this issue using another antibiotic as reference. The cohort study performed by Kuo et al² reported, contrarily to the one performed by Daneman et al,¹

a significant association of fluoroquinolone use with RD after they compared the prescriptions of patients in the fluoroquinolone cohort with those of propensity score-matched adults treated with amoxicillin. Moreover, the study design that we used ensures the minimization of confusion by indication. Indeed, the self-matched design implies that time-invariant multiplicative confounders are necessarily adjusted for. Given the short observation period of our study (180 days), the clinical situations of the patients may be considered fixed during the control and risk periods. Therefore, the prescription of fluoroquinolones for an underlying respiratory, inflammatory, or infectious disease may occur in a nondifferential manner within control or risk periods. In addition, in our study, we excluded all patients who had been hospitalized within 6 months prior to the RD. This likely resulted in excluding patients with severe chronic diseases, including inflammatory diseases, and thus minimizing confounding by indication. Lastly, to control for potential residual bias, we conducted a sensitivity analysis excluding patients with long-term infectious or inflammatory conditions and respiratory failure. Exposure to fluoroquinolones remained significantly associated with the occurrence of RD over the 10-day period, with an adjusted odds ratio of 1.43 (95% CI, 1.11-1.84).

In the self-controlled case series design, we also looked at first event, and we used the same short observation period. The risk period was defined as the 10-day period after each fluoroquinolone prescription had been dispensed, 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 with a logarithmic link function, taking the duration of the different study periods into account. Given the study observation period (180 days), age and comorbidities were considered to be “fixed” during the study period. Corticosteroid treatment was taken into account as a time-dependent variable.

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