Published in final edited form as:
JAMA Ophthalmol. 2013 January ; 131(1): 91–93. doi:10.1001/jamaophthalmol.2013.559.

Flashes, Floaters, and Oral Fluoroquinolones:

Is Retinal Detachment a Worry?

Dennis P. Han, MD and **Aniko Szabo, PhD**
Medical College of Wisconsin, Milwaukee.

Etminan et al[1] performed a population-based, retrospective case-control study evaluating the association between retinal detachment (RD) and oral fluoroquinolone use in a population of patients under ophthalmological care. Substantial evidence implicates these agents with tendinitis and tendon rupture, raising a concern that an increased risk of RD might follow from a shared mechanism of collagen degradation[2] that could affect the vitreous of the eye. Oral fluoroquinolones are commonly prescribed, possibly even overprescribed,[3] such that a public health risk may be posed. However, until now, only anecdotal reports of RD after oral fluoroquinolone use exist. These drugs penetrate rapidly into the vitreous cavity of the eye.[4]

Clinicians must now grapple with the findings of Etminan et al of a 4.5-fold elevation in RD risk with oral fluoroquinolone use. How convincing is this information, and should we change our prescribing behaviors based on this report? To illuminate this issue, we discuss herein (1) a physiological background for RD; (2) validity and generalizability of the findings of Etminan et al; (3) a perspective on the amount of purported increased risk of RD; and (4) how physicians might currently approach these findings in clinical practice.

Degenerative changes in the vitreous can lead to synchisis (gel liquefaction with fluid cavity formation) and syneresis (collapse of the vitreous body), processes that can lead to dehiscence of the vitreous body from the retinal surface. This sequence of events, termed *posterior vitreous detachment* at its more advanced stages, usually occurs without untoward effects because there is weak vitreoretinal adhesion. In the presence of firm vitreoretinal adhesion, however, vitreous dehiscence can lead to vitreous traction, retinal tears, and rhegmatogenous RD.[5]

It is likely that most of the RDs ascertained in the study were rhegmatogenous, based on the predominance of this mechanism in the general population. These occur mostly in persons older than 50 years,[6] but various genetic collagen disorders affecting the vitreous body, such as Stickler and Marfan syndromes, are associated with RD in both adults and children. It is thus conceivable that a drug in- terfering with collagen integrity may increase risk. Although the molecular mechanism by which fluoroquinolones might affect vitreous humor remains speculative, a study on collagen metabolism in tendon tissue suggests a possible mechanism. Fluoroquinolones upregulate matrix metalloproteinase 2, leading to increased cleavage of

Correspondence: Dr Han, Medical College of Wisconsin, Ophthalmology, Eye Institute, 925 N 87th St, Milwaukee, WI 53226-4812 (dhan@mcw.edu).

Financial Disclosure: None reported.

type I collagen in tendon tissue.[2] Matrix metalloproteinase 2 is also present in vitreous and is capable of cleaving its components of types V, IX, and XI collagen, potentially destabilizing it.[7] Collagen synthesis and breakdown in the vitreous body are in continuous dynamic equilibrium throughout life, such that a disturbance of this equilibrium, including a rapid acceleration of collagen breakdown, may affect its integrity,[8] increasing the risk of retinal tears and detachments through the mechanisms described earlier.

Tendinitis or tendon rupture has been reported to occur from 2 hours to 6 months after oral fluoroquinolone intake,[9] with a median time of occurrence of 6 days after intake. To detect a potentially early onset of RD that might mimic the tendon rupture phenomenon, Etminan et al segregated use of oral fluoroquinolones by estimated termination date of the prescribed course of the drug relative to the date of the service code for RD surgery, which they used as an “index date.” “Recent” and “past” users were defined as having drug termination dates occurring 1 to 7 days before and 8 to 365 days before the index date, respectively. “Current” users were defined as having an estimated drug termination date “overlapping” the index date. Thus, “current” users were a highly select group whose RD surgery likely occurred extremely close to the time of drug discontinuance.

Notably, only “current” use of oral fluoroquinolones was shown to be associated with RD. “Recent” and “past” use showed no association. This observation deserves comment, both from physiological and clinical standpoints. Retinal detachment developing in “current” but not “past” users might be surprising to some, considering that vitreous collagen synthesis and repair is considered a very slow process. A drug-induced toxic injury to the vitreous gel might be expected to persist, and a risk of RD along with it. One must presume that a metastable state is rapidly established in the vitreous, after which RD risk falls to baseline. From a clinical standpoint, RD surgery can only approximate the date of RD onset, and RD itself can sometimes take days to weeks to become symptomatic. Thus, the timing of use categories defined by Etminan et al infers a greater precision than might be applied clinically, though it does not diminish the overall implications of their findings. Nonetheless, the study can only support the possibility that, like tendon rupture, elevated RD risk is a phenomenon that occurs soon after treatment with oral fluoroquinolones, apparently by perhaps days as opposed to many weeks.

The case-control design of this study allowed assessment of relative risk of RD by comparing rates of use of oral fluoroquinolones between patients who developed and did not develop RD during selected intervals around intake of the drug. However, the method did not allow calculation of actual rates of RD associated with oral fluoroquinolone use. The rate difference of 3.3% vs 0.6% described in the Abstract applies to the frequency of current oral fluoroquinolone use, not RD, as one might gather from the Abstract. We believe a clarification should be provided by Etminan et al in this regard, lest the Abstract be widely misinterpreted. However, by the abstruse beauty of the case-control study design, the statistically adjusted ratio of drug use rates between the 2 groups equates to the ratio of risk of RD between populations who did and did not take the drug.[10] Their estimate of number needed to harm of 2500 is equivalent to an attributable risk of 0.040% (reciprocal of 2500). Here, Etminan et al apparently presume an absolute baseline risk of about 0.01% of RD in an untreated population, increased 4.5-fold (from their data) to about 0.05% in cases

satisfying “current use” criteria. For perspective, this is about one-twentieth the absolute risk of an RD (estimated at roughly 1%), occurring within 1 year after cataract extraction,[11] a common ophthalmic procedure recommended only if there is a reasonable chance of visual benefit.

So how should clinicians approach the stated elevation of risk of RD? First, we agree with Etminan et al that, because of the retrospective nature of this study and the possibility of undetected biases, further confirmation of this finding is necessary, ideally in a population not limited to those under ophthalmologic care. Second, even a small risk of RD attributable to oral fluoroquinolones should not be considered insignificant, given the large number of patients who take these drugs. Third, physicians should keep in mind that RD is not a life-threatening condition, whereas uncontrolled infection is. Finally, most RDs can be surgically repaired, though even if successful, some degree of permanent visual impairment is common. Early detection can help. New flashes and floaters can forewarn development of RD, and visual field loss can signal an RD in progress; all of these symptoms indicate a need for urgent evaluation. Patients armed with this knowledge have a better chance for a good outcome, whatever the cause of RD.

Should we counsel patients that oral fluoroquinolones can actually cause RD? Confirmatory evidence of this association would help to answer this question. If it is deemed appropriate to discuss RD risk with patients, physicians should be aware of omission and outcome biases, cognitive phenomena whereby the clinician and patient focus on “what could happen, rather than what is most likely to happen following initiation of a therapy.”[12(p178)] This could result in a patient not receiving a much-needed medication. But, we should also make sure there is a need.

Acknowledgments

Funding/Support: This work was supported in part by Research to Prevent Blindness, Inc; the Jack A. and Elaine D. Klieger Professorship, Medical College of Wisconsin (Dr Han); and grant 1UL1RR031973 from the Clinical and Translational Science Award program of the National Center for Research Resources, National Institutes of Health (Dr Szabo).

Additional Contributions: We thank J. Sebag, MD, FRCOphth, for helpful comments on an earlier version of the manuscript.

REFERENCES

1. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. JAMA. 2012; 307(13):1414–1419. [PubMed: 22474205]
2. Tsai W-C, Hsu C-C, Chen CPC, et al. Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen. J Orthop Res. 2011; 29(1):67–73. [PubMed: 20602464]
3. Lautenbach E, Larosa LA, Kasbekar N, Peng HP, Maniglia RJ, Fishman NO. Fluoroquinolone utilization in the emergency departments of academic medical centers: prevalence of risk factors for inappropriate use. Arch Intern Med. 2003; 163(5):601–605. [PubMed: 12622607]
4. Smith A, Pennefather PM, Kaye SB, Hart CA. Fluoroquinolones: place in ocular therapy. Drugs. 2001; 61(6):747–761. [PubMed: 11398907]
5. Sebag J. Anomalous posterior vitreous detachment: a unifying concept in vitreoretinal disease. Graefes Arch Clin Exp Ophthalmol. 2004; 242(8):690–698. [PubMed: 15309558]

6. Haimann MH, Burton TC, Brown CK. Epidemiology of retinal detachment. Arch Ophthalmol. 1982; 100(2):289–292. [PubMed: 7065947]

7. Ponsioen TL, Hooymans JMM, Los LI. Remodelling of the human vitreous and vitreoretinal interface: a dynamic process. Prog Retin Eye Res. 2010; 29(6):580–595. [PubMed: 20621195]

8. Le Goff MM, Bishop PN. Adult vitreous structure and postnatal changes. Eye (Lond). 2008; 22(10): 1214–1222. [PubMed: 18309340]

9. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. Clin Infect Dis. 2003; 36(11):1404–1410. [PubMed: 12766835]

10. Pearce N. Classification of epidemiological study designs. Int J Epidemiol. 2012; 41(2):393–397. [PubMed: 22493323]

11. Coppé AM, Lapucci G. Posterior vitreous detachment and retinal detachment following cataract extraction. Curr Opin Ophthalmol. 2008; 19(3):239–242. [PubMed: 18408500]

12. Kempainen RR, Migeon MB, Wolf FM. Understanding our mistakes: a primer on errors in clinical reasoning. Med Teach. 2003; 25(2):177–181. [PubMed: 12745527]