Photodiagnosis and Photodynamic Therapy 39 (2022) 103013

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Exploration of fluoroquinolone-induced retinal pigment epithelium layer changes in the pathogenesis of macular degeneration

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ARTICLE INFO

Keywords:
Acute retinal degeneration
Contrast sensitivity
Fluoroquinolone
Optic coherence tomography
Photostress recovery time
Phototoxicity

ABSTRACT

Purpose: Fluoroquinolone toxicity studies in animals (cats, rabbits and mice) showed that acute retinal degenerations appear clinically related to phototoxicity. The aim of this study was to evaluate the association between the administration of oral fluoroquinolone and the onset of clinically or subclinically detectable acute retinal degeneration in humans.

Material and Methods: This study included patients that received oral fluoroquinolone treatment (ciprofloxacin, levofloxacin or moxifloxacin) for variable systemic diseases diagnosed by the Department of Urology and Infectious Diseases (study group, n=76), and age and sex matched otherwise healthy subjects (control group, n=50). All the subjects underwent a detailed ophthalmologic examination including tests for visual acuity, intraocular pressures, color vision, photostress recovery time and contrast sensitivity measurements, central foveal thickness, subfoveal choroidal thickness, ganglion cell complex thickness and 10/2 Humphrey visual field test. Color fundus and fundus autofluorescence photographs were also obtained. Examinations and tests were repeated at 1st week and 1st month in the study group.

Results: There was no statistically significant difference among visual acuity, intraocular pressure, photostress recovery time, color vision, contrast sensitivity measurements, central foveal thickness, subfoveal choroidal thickness, average ganglion cell complex thickness, superior ganglion cell complex thickness, inferior ganglion cell complex thickness, focal loss volume, global loss volume, mean deviation, pattern standard deviation values in treatment group at baseline, 1st week and 1st month ($p > 0.05$, for the comparison of each parameters). There was not any alteration among color fundus and fundus autofluorescence photographs obtained at baseline, 1st week and 1st month in treatment group. All parameters within the study and control groups were similar throughout the study period ($p > 0.05$, for the comparison of each parameter).

Conclusion: This study evaluated the association between the administration of oral fluoroquinolone and the onset of acute retinal degeneration. Preliminary results of this study showed that use of oral fluoroquinolone had no detectable impact on retinal degeneration at acute phase.

1. Introduction

The retina is a tissue that is continuously exposed to sunlight throughout life and has a high blood flow; thus, it carries a risk in terms of systemic and light-related toxicity. Systemic use of various drugs may cause toxicity in the retina. However, drug-induced toxic maculopathy is rare. Different drugs have different harmful effects, either directly or through substrates. The mechanisms emphasized in the pathogenesis are metabolic or enzymatic functions affected in the target cell, ischemia, various biochemical abnormalities in the retinal pigment epithelium (RPE), and oxidation and immune allergic reactions [1].

Fluoroquinolones are a class of broad-spectrum antibiotics used to treat various infectious diseases round the world. They play an important role in the treatment of serious bacterial infections, especially those that are hospital acquired. However, a black-box warning was issued by the US Food and Drug Administration (FDA) for fluoroquinolones due to their serious and long-term adverse effects, such as the potential to cause tendon rupture, a permanent syndrome called fluoroquinolone-associated disability (FQAD), and cutaneous adverse reactions. The warning was followed by restrictions on their use [2–4].

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https://doi.org/10.1016/j.pdpdt.2022.103013
Received 4 February 2022; Received in revised form 22 June 2022; Accepted 8 July 2022
Available online 9 July 2022

Fluoroquinolones are acknowledged photosensitizers that trigger various reactions to human skin (photoallergy, photodegradation, phototoxicity, and photocarcinogenesis) caused or exacerbated by exposure to sunlight [5–7]. Previously, animal studies reported that fluoroquinolones caused acute diffuse retinal degeneration, resulting in acute blindness [8]. It was shown that the trigger of retinal degeneration resulting from the phototoxic effect of fluoroquinolones is the dispersion of mitochondria in the inner segment of the photoreceptors. Reactive oxygen radicals and cytochrome c are released from damaged mitochondria, and apoptosis begins with the activation of caspases [9,10]. Ofloxacin taken twice a day for 21 days induced acute degeneration in the RPE layer, which was shown histopathologically in rabbits [11]. In another acute toxicity study, enrofloxacin administered at 50 mg/kg daily for 3 days histopathologically resulted in retinal lesions, ranging from vacuolization to necrosis in the photoreceptors and outer nuclear layers in cats [12].

The acute phototoxic effect of the fluoroquinolone group drugs on human skin and retina in animal models is known, but no clinical study in the literature has investigated the clinically or subclinically detectable acute retinal degeneration in the human eye. In this study, we examined the effect of fluoroquinolone derivative drugs on the retina in the acute period for the first time; we believe that the results of this clinical study will contribute to the literature.

2. Materials and methods

The study group consisted of subjects who presented to the Urology and Infectious Diseases Polyclinic of Marmara University Faculty of Medicine and who used oral fluoroquinolone therapy (ciprofloxacin, moxifloxacin, and levofloxacin) for various infections. The control group consisted of healthy individuals who presented to the Ophthalmology Polyclinic and who did not use any medication. This prospective controlled study included 152 eyes of 76 patients in the study group, and 100 eyes of 50 subjects in the control group. The study group and the control group were either primary (with no previous exposure) or secondary (with a sufficient wash-out period) fluoroquinolone-naive. The study was conducted in accordance with the principles of the Helsinki Declaration, and approval was obtained from the ethics committee for local clinical trials. Written consent was obtained from each participant.

Subjects in the study and control groups were matched by age, sex, and body mass index (BMI). Subjects using any drug other than fluoroquinolones, smoking, or consuming alcohol were not included in the study. Those with corneal disorders such as keratoconus, corneal scarring, and bullous keratopathy; retinal disorders such as diabetic retinopathy, senile macular degeneration, central serous chorioretinopathy, and vein occlusion; glaucoma or optic disc damage; and uveitis, history of ocular surgery, and refraction values outside the range of -3.00 D to +3.00 D were also excluded from the study. Moreover, subjects with hepatic or renal insufficiency were not included in the study.

The participants' BMIs were derived by measuring their heights and weights. All participants underwent detailed eye examinations including the best corrected visual acuity (BCVA), biomicroscopic anterior segment examination, and intraocular pressure (IOP) measurement with noncontact pneumotonometry (Tonoref III, NIDEK Co. Ltd., Japan). Dilated fundus examinations were performed using a Volk SuperField NC lens, including the entire retinal periphery. The Ishihara test was used to assess color vision under the illumination of fluorescent lamps (38 Plates Edition, 1990). The plates were presented to the subjects' eyes at a distance of approximately 75 cm, and a 4-second response time was allowed for each plate. Contrast sensitivity was measured using a wall-mounted Pelli-Robson chart with 16 triplets of Sloan letters of constant size from a distance of 1 meter under photopic room illumination. Each triplet decreases in contrast by 0.15 log units, ranging from 100% to 0.56% (0.00–2.25 log units). Testing ended when the subject missed 2 of 3 letters in a triplet, and a contrast sensitivity score was recorded. During the photostress test, the subjects' gaze was fixed on a bright light from the ophthalmoscope directed on the macula for 10 seconds. The photostress recovery time was measured as the time taken for acuity to return to within three of the letters of pre-bleach acuity. The same procedures were performed on the other eye for color vision, contrast sensitivity, and photostress recovery time tests. Visual field testing was performed using a Humphrey Visual Field Analyzer (Carl Zeiss Meditec Inc. Dublin, CA, USA) and the white-on-white 10/2 SITA standard algorithm, testing 68 points in the central 10-degree field. A reliable visual field test was considered as <20% fixation losses and <15% false positive or <15% false negative values. The mean deviation and pattern deviation plots were reviewed for abnormalities. A loss of more than 5 dB at three or more adjacent points or a loss exceeding 10 dB at a single point was defined as an abnormality on the 10-2 visual field plots. After full pharmacologic dilation, fundus photographs were taken using a Topcon TRC-50DX fundus camera, and fundus autofluorescence (FAF) examinations were performed (Topcon, Tokyo, Japan) by an experienced technician. At least 5 FAF shots were taken and high-quality images were recorded.

An RTVue Model RT-100 5.1 SD-OCT (Optovue, Inc. Fremont, CA, USA) device was used. The RTVue RT-100's EMM5 program and reference 3-dimensional macula scanning programs were used for fovea-centered macular measurements. In this program, images were acquired in 0.9 seconds (the outer 6×6-mm grid of 13 horizontal and 13 vertical lines with 803 A-scans each, and the inner 4×4-mm grid of 8 horizontal and 8 vertical lines with 535 A-scans each). The RTVue 100′s GCC program was used to measure the macular ganglion cell complex (GCC) thickness. The GCC protocol consisted of 15 vertical lines and one horizontal line covering an area of 7 mm × 7 mm centered 1-mm temporal to the fovea. Average GCC, superior GCC, inferior GCC, focal volume loss (FVL, %), and global volume loss (GVL, %) parameters were calculated using software provided by the device. The chorioretinal imaging option comprised a horizontal line of 12 mm centered on the fovea. For choroidal thickness, the vertical length between the hyperreflective outer boundary of retinal pigment epithelium (RPE) and chorioscleral junction was manually measured in the subfoveal region 500 microns temporally and nasally (Fig. 1). The average of three choroidal thickness readings (repeated three times and averaged) was recorded. All measurements were performed between 09:00 and 11:00 to avoid diurnal variation in choroidal thickness, as previously reported. Detailed eye examinations and all tests of all participants were repeated before the use of oral fluoroquinolones, an at the 1st week and 1st month of the treatment.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows 21.0 program. The normality of data was verified using the Kolmogorov-Smirnov test. The normally distributed values were expressed as mean ± standard deviation (SD), and the non-normally distributed data, as median (interquartile range; IQR). Normally distributed continuous parameters were assessed with analysis of the parametric tests (student's t-test, analysis of variance [ANOVA]) and non-normally distributed data were compared with the non-parametric tests (Mann – Whitney U, Friedman's tests). Differences between study and control groups were evaluated using student's t-test and Mann – Whitney U test, whereas ANOVA and Friedman's tests were used to compare the data of study group at different time points to the control group. The one-way repeated measures ANOVA test and Friedman's test were used to compare variables at three time points in the study group. The Chi-square test was used in the analysis of categorical variables. A p-value of <0.05 was considered statistically significant.

3. Results

A total of 152 eyes of 76 patients using oral fluoroquinolone antibiotics and 100 eyes of 50 healthy individuals were included in the study. Thirty-seven (48.6%) of the study group were female and 39 (51.3%) were male. In the control group, 26 (52%) were female and 24 (48%) were male. The mean age of the study group was 49.8 ± 11.3

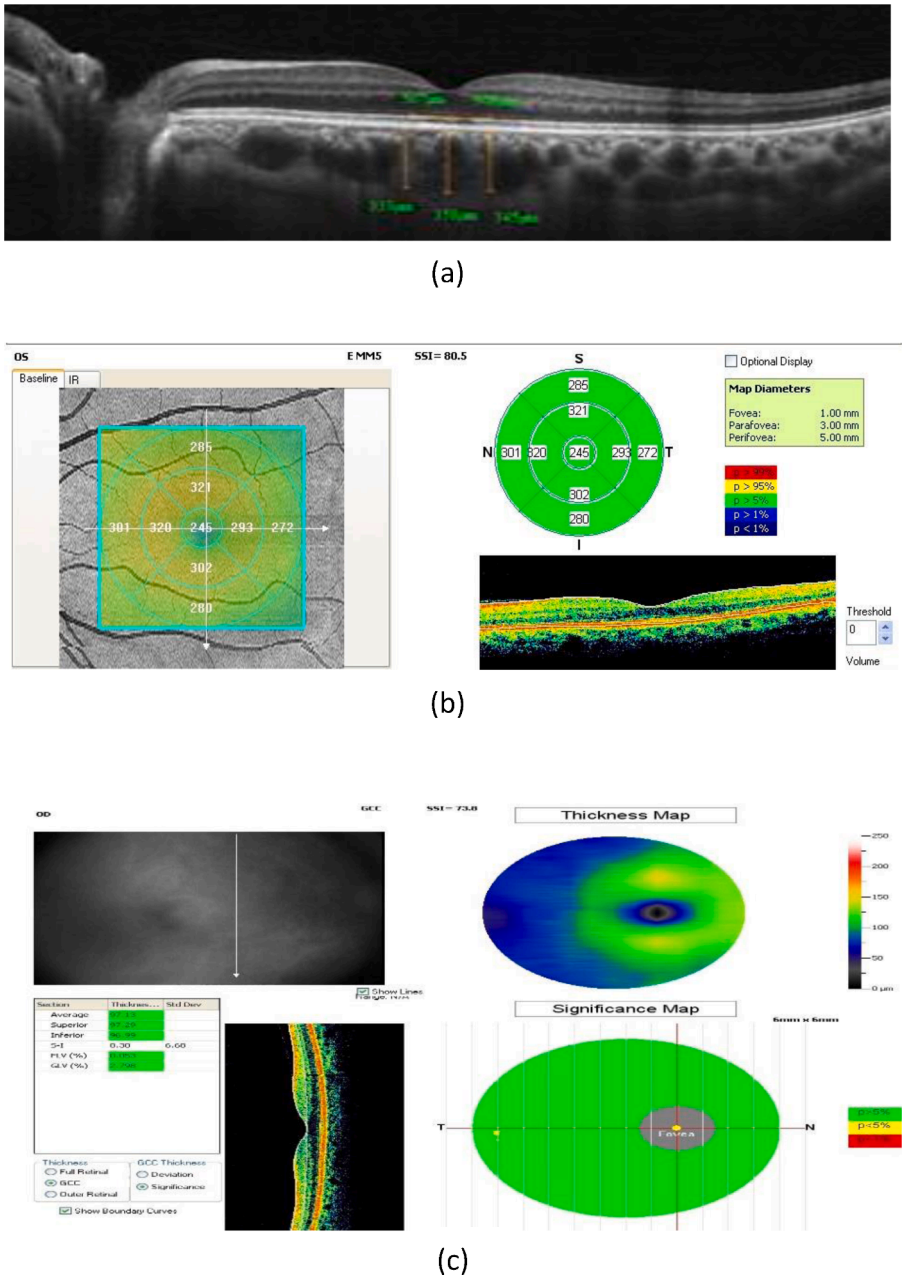

Fig. 1. Optic cohorence tomography imaging: (a) choroidal thickness measurement on the EDI-OCT, (b) central macular thickness on the 100′s EMM5 program, (c) ganglion cell complex measurements on the 100′s GCC program.

years, and it was 48.9 ± 11.2 years for the control group. The mean BMI of the study group was 26.1 ± 3.3 kg/m2, and the BMI of the control group was 26.4 ± 2.9 kg/m2. There was no significant difference between the groups in terms of age, sex, and BMI ($p > 0.05$). The baseline characteristics of the study and control groups are summarized in Table 1.

None of the patients had drug use other than oral fluoroquinolone, systemic disease or chronic eye disease. The types of infections and the types, dosages, and durations of treatment are reported in Table 2.

The comparison of values of pre-treatment and post-treatment 1st-week and 1st-month BCVA, IOP, photostress recovery time, contrast sensitivity, color vision, CMT, SFCT, mean GCC, superior GCC, inferior GCC, FLV, and GLV of the patients in the study group are shown in Table 3. The mean BCVA at baseline was 0.03 ± 0.14 LogMAR units and there was no significant difference at the 1st week and 1st month of the treatment ($p = 0.975$). In terms of IOP, there was no significant

Table 1
Characteristics of subjects.

	Study group	Control Group	p
Age (y±SD)	49.8 ± 11.3	48.9 ± 11.2	0.70*
Male/female	37/39	26/24	0.51#
BCVA, logMAR (median, IQR)	0 (0 - 0.3)	0 (0 – 0.4)	0.10**
SE, (D±SD)	0.64 ± 1.05	0.60 ± 1.32	0.84*
IOP, mmHg (median, IQR)	16 (11–20)	15 (9–20)	0.10**
BMI, (kg/m^2±SD)	26.1 ± 3.3	26.4 ± 2.9	0.72*

* Student's t-test
** Mann-Whitney test
\# Chi square test. BCVA, best-corrected visual acuity; BMI, body mass index; D, diopter; IOP, intraocular pressure; logMAR, logarithm of the minimal angle of resolution.

Table 2
Infections and treatment of patients.

	Number of patients (%)	FQ (type, dosage, mg)	Treatment duration (day)
Complicated uriner tract infection	30 (39.4)	ciprofloxacin 500*	10
Prostatitis	35 (46)	ciprofloxacin 500*	14
Uncomplicated pyelonephritis	2 (2.6)	levofloxacin 500 *	14
Bladder infection	2 (2.6)	ciprofloxacin 500*	14
Acute sinusitis	1 (1.3)	moxifloxacin 400**	14
Chronic sinusitis	3 (3.9)	levofloxacin 500 *	14
Community acquired pneumonia	2 (2.6)	moxifloxacin 400**	14

* twice a day
** once a day, FQ, fluoroquinolones.

Table 3
Comparison of the effect of FQ treatment on eye examination findings, OCT and VF parameters.

	Baseline	1 week	1 month	p
BCVA, logMAR	0 (0– 0.3)	0 (0– 0.3)	0 (0–0.3)	0.975**
IOP, mmHg	16 (11–20)	16 (10–20)	15 (10–20)	0.147**
Photostress recovery time, second	5 (3–54)	4 (2–58)	5 (3–54)	0.874**
Contrast sensitivity function, %	4.4 (1.6–12.5)	3.1 (1.6–12.5)	3.1 (2.1–12.5)	0.725**
Number of plates in Ishihara' test	19.9 (16–20)	19.9 (16–20)	19.9 (16–20)	1.000**
CMT, μm	242 (203–279)	240 (212–277)	240 (205–275)	0.758**
SFCT, μm	296.5 (148–532)	288 (150–520)	296.5 (158-530)	0.792**
GCC avg, μm	97.05 (85.5–120.7)	97.7 (78.7–126.4)	97.4 (82.4–121.7)	0.765**
GCC sup, μm	96.54 ± 7.82	96.6 ± 8.07	97.1 ± 7.57	0.295*
GCC inf, μm	97.75 ± 8.02	97.98 ± 8.40	97.91 ± 7.60	0.102*
FLV, %	0.45 (0.002–7.7)	0.43 (0.002–10.0)	0.41 (0.001–7.7)	0.997**
GLV, %	3.21 (0.001–15.3)	3.39 (0.001–16.7)	3.19 (0.001–15.8)	0.848**
MD, dB	-1.47 (-6.4–2.5)	-0.96 (-3.1–2.08)	-0.82 (-2.6–2.04)	0.063**
PSD, dB	1.36 (0.6–3.9)	1.17 (0.7–2.4)	1.16 (0.7–2.5)	0.509**

* One-way repeated measures ANOVA test
** Friedman test. Avg, average; BCVA, best-corrected visual acuity; CMT, central macular thickness; FLV, focal loss volume; GCC, ganglion cell complex; GLV, global loss volume; IOP, intraocular pressure; inf, inferior; logMAR, logarithm of the minimal angle of resolution; MD, mean deviation; PSD,, pattern standard deviation; SFCT, subfoveal choroidal thickness; sup, superior.

difference between baseline, 1st week, and 1st month of treatment ($p = 0.147$). The photostress recovery time was 11.7 ± 13.1 seconds at baseline, whereas it was 10.5 ± 11.4 seconds at the 1st week and 10.3 ± 10.9 seconds at the 1st month of the treatment ($p = 0.874$). Contrast sensitivity and color vision measurements showed no change before and after treatment ($p = 0.725$ and $p = 0.999$, respectively). There was no statistically significant change in the CMT, SFCT, mean GCC, superior GCC, inferior GCC, FLV, GLV, MD, PSD, and there was no ellipsoid zone disruption by OCT scans at the end of treatment ($p > 0.05$). No hypo-autofluorescence or hyperautofluorescence due to drug use was observed in the FAF imaging. The FAF images of a patient before the treatment, and at the 1st week and 1st month of the treatment are shown in Fig. 2.

The comparison of all parameters of the control and study groups are summarized in Table 4. In comparison with the normal participants, patients using fluoroquinolone had no statistically significant differences in terms of all parameters at baseline, and at the 1st week and 1st month of the treatment ($p > 0.05$).

4. Discussion

Our study aimed to examine the clinically and sublinically detectable acute changes in the retina and RPE layer of patients who were treated with ciprofloxacin, levofloxacin, and moxifloxacin for various infections. The preliminary results of this study showed that the use of oral fluoroquinolone had no detectable impact on retina in the acute phase.

The phytotoxic effect of fluoroquinolone group drugs on human skin is known, and it has been shown in animal studies to cause acute retinal degeneration as a result of phototoxic effects [8,13]. Phototoxicity is associated with the formation of reactive oxygen radicals and mitochondrial damage. The UVA-fluoroquinolone interaction leads to the generation of reactive oxygen radicals and mitochondrial membrane damage. The released cytochrome-c activates the caspase 3 pathway and apoptosis occurs. At the same time, reactive oxygen radicals cause DNA damage [14–16]. Retinal cells do not replicate throughout life. The resulting DNA damage is not repaired and accumulates. Another important process that leads to DNA damage is oxidation. RPE cells exist in an environment rich in light and oxygen, which leads to exposure to reactive oxygen radicals. Antioxidant defense mechanisms limit oxidative damage, but the weakening of these mechanisms with age increases the occurrence of macular degeneration [17,18].

In a study by Verna et al. DNA oxidation in human RPE cells after exposure to hydrogen peroxide (H2O2) or sparfloxacin was monitored. When H2O2- or sparfloxacin-exposed cells were further exposed to UVA irradiation, the oxidative damage to the DNA of these cells was greatly increased over baseline values. In another prospective study, 50 mg/kg of enrofloxacin was administered to 12 cats. In the histopathologic examination performed 3 days later, retinal lesions were found in the retina of all cats, ranging from vacuolization to necrosis in the photoreceptor and outer nuclear layers [19]. Gelatt et al. conducted an ophthalmoscopic examination of 17 cats receiving oral or intravenous

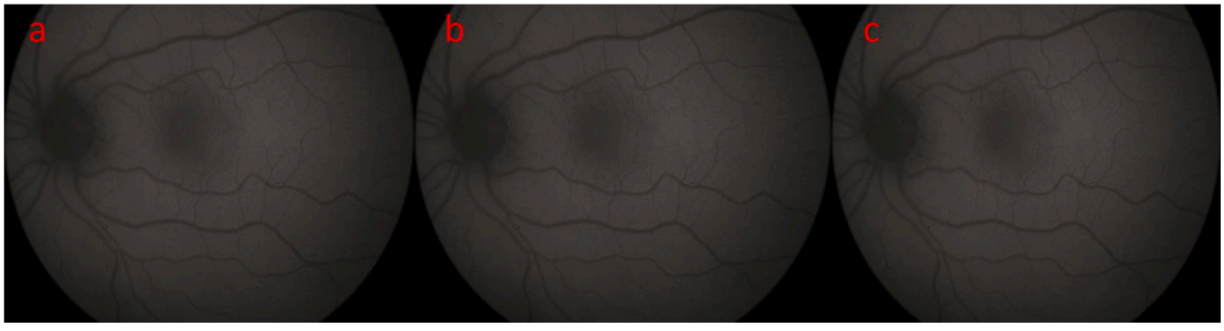

Fig. 2. Fundus autofluorescence imaging of a patient (a) before fluoroquinolone treatment (b) first week of treatment (c) first month of treatment.

Table 4
Comparison of eye examination findings, OCT and VF parameters between study and control groups.

	Control group	Study group			
		Baseline	1 week	1 month	p
BCVA, logMAR	0 (0–0.4)	0 (0–0.3)	0 (0–0.3)	0 (0–0.3)	0.102**
IOP, mmHg	15 (9–20)	16 (11–20)	16 (10–20)	15 (10–20)	0.254**
Photostress recovery time, s	6 (3–49)	5 (3–54)	4 (2–58)	5 (3–54)	0.153**
Contrast sensitivity function, %	4.4 (3.1–12.5)	4.4 (1.6–12.5)	3.1 (1.6–12.5)	3.1 (2.1–12.5)	0.725**
Number of plates in Ishihara' test	20.0 (20–20)	19.9 (16–20)	19.9 (16–20)	19.9 (16–20)	1.000**
CMT, μm	242.5 (203–330)	242 (203–279)	240 (212–277)	240 (205–275)	0.409**
SFCT, μm	296 (172–452)	296 (148–532)	288 (150–520)	297 (158–530)	0.816**
GCC avg, μm	96.6 (81.5–109.6)	97.0 (85.5–120.7)	97.7 (78.7–126.4)	97.4 (82.4–121.7)	0.765**
GCC sup, μm	96.6 ± 6.9	96.5 ± 7.8	96.6 ± 8.1	97.1 ± 7.6	0.980*
GCC inf, μm	97.9 ± 6.3	97.8 ± 8.0	97.9 ± 8.4	97.9 ± 7.6	0.947*
FLV, %	0.40 (0.001–9.5)	0.45 (0.002–7.7)	0.43 (0.002–10)	0.41 (0.001–7.7)	0.482**
GLV, %	3.71 (0.004–12.9)	3.21 (0.001–15.3)	3.39 (0.001–16.7)	3.19 (0.001–15.8)	0.638**
MD, dB	-0.92 (-6.38–2.4)	-1.47 (-6.4–2.5)	-0.96 (-3.1–2.08)	-0.82 (-2.6–2.04)	0.714**
PSD, dB	1.19 (1.01–3.27)	1.36 (0.6–3.9)	1.17 (0.7–2.4)	1.16 (0.7–2.5)	0.307**

* One-way ANOVA test
** Friedman test. Avg, average; BCVA, best-corrected visual acuity; CMT, central macular thickness; FLV, focal loss volume; GCC, ganglion cell complex; GLV, global loss volume; IOP, intraocular pressure; inf, inferior; logMAR, logarithm of the minimal angle of resolution; MD, mean deviation; PSD,, pattern standard deviation; SFCT, subfoveal choroidal thickness; sup, superior.

enrofloxacin at various doses (4 mg/kg to 27 mg/kg) (recommended daily dose 11 mg/kg). Acute blindness and abnormal behavior were noted in some cats. Fundus examinations revealed increased tapetal reflectivity, attenuation of retinal vessels, gold spots, and pigmentary changes. These effects were observed between 2 days and 12 weeks after drug administration. Both eyes of a cat with blindness were histologically examined. Diffuse retinal degeneration was seen, primarily affecting the outer nuclear and photoreceptor layer. Focal areas where both the peripheral and central retinas were affected and retinal pigment epithelial hypertrophy were detected [8].

Shimoda et al. administered a single intravenous dose of 5, 10, 20, 40, and 80 mg/kg cytafloxacin to Balb/c mice and exposed them to UVA at various doses and durations. In mice administered 40 and 80 mg/kg cytafloxacin + UVA, it was observed that the photoreceptor segments were lost, the cells in the outer nuclear layer had a pycnotic nucleus, and this layer was thinned, and the pigment epithelial cells were vacuolized [20]. In another study, albino Balb/c and pigmented DBA/2 mice were given a single oral administration of ciprofloxacin, levofloxacin, enoxacin, lomefloxacin or sparfloxacin, followed by UVA irradiation at 1.5 mW/cm2 for 4 hour (21.6 J/cm2). Histologic retinal degeneration was observed in mice receiving 200 or 400 mg/kg enoxacin, 200 or 400 mg/kg lomefloxacin, 50 or 100 mg/kg sparfloxacin [9]. It has been shown that the trigger in retinal degeneration resulting from the phytotoxic effect is the dispersion of mitochondria in the inner segment of photoreceptors. Reactive oxygen radicals and cytochrome-c are released from damaged mitochondria and apoptosis begins with the activation of caspases [9,10].

In a study by Ramirez et al. in 2011, the molecular genetic basis of retinal degeneration due to fluoroquinolones in cats was examined. To reveal the defect in ABCG2, the transport protein in the blood-retinal barrier that prevents the passage of drugs to the retina, researchers prepared HEK-293 cells (FC-7, cat; PC, plasmid control; R2 human) and cat ABCG2, human ABCG2, and a plasmid control, and some of these cells were exposed to enrofloxacin (0, 1, 10, 20 and 50 μmol/l) for 1 hour and then to UV light for 1 hour, and some were treated with enrofloxacin in the dark only. While no effect on viability was observed in any cells in the dark environment, they observed phototoxicity and related cell death in all cells at increased concentrations of UV exposure and enrofloxacin and reported that the greatest cell death was in PC cells without ABCG2, and the least cell death was in human cells [21].

In another study by Rampal et al. the development of ofloxacin-induced retinopathy in rabbits was investigated. Nine pigmented rabbits were divided into three equal groups; the first group was the control group, the second group was given 10 mg of ofloxacin twice per day for 21 days, and the third group was given 20 mg of ofloxacin daily for 21 days. Glutathione, lipid peroxidation, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, catalase, and superoxide dismutase activities were measured by collecting blood samples from the ear veins of rabbits on days 0, 7, 14, and 21 of the treatment. It was shown that reactive oxygen radicals increased and antioxidant enzymes decreased from the 7th day in both treated groups. Histopathologic examinations revealed various degenerative changes in both treated groups. Cellular damage was detected in the retina, and it was observed that this damage was more in the third group, and it was reported that the RPE cells migrated to the photoreceptor layer and lined up like a rosary [11].

Schimoda et al. examined phototoxic lesions caused by fluoroquinolones in 100 Balb/c mice, dividing the mice into five groups. The groups were arranged as follows: the first group was treated with sparfloxacin (50, 100 mg/kg), the second group was treated with enoxacin (400, 800 mg/kg), the third group was treated with levofloxacin (400, 800 mg/kg), the fourth group was the control group, and the fifth group received UVA treatment. Retinal degeneration occurred in the sparfloxacin and enoxacin + UVA groups (at all doses); no retinal changes were observed in the levofloxacin, control, and UVA groups. Histopathologic examinations revealed vacuolization in photoreceptor segments, swelling of RPE cells, thickening and irregularity in the outer nuclear layer, and necrotic cells. They reported that these changes later caused degeneration and thinning of the retina [13].

In a study by Sobolewska et al. retinal ganglion cell cultures were obtained in rats and these cultures were diluted with moxifloxacin 5, 15, 50, 150, 300, 500 and 1500 μg/mL, respectively, and after exposure for 24 hours, a significant difference between 5-50 μg/mL was obtained. Although no cytotoxic effect was observed, it was observed that 15.5% of the cells lost their viability in the culture with 50 μg/mL moxifloxacin, and also a significant decrease in viable cell count was observed at concentrations of 150, 500 and 1500 μg/mL (26.8%, 50.7% and 63.4%, respectively). Histopathologically, it was seen that morphologic changes in retinal ganglion cells due to moxifloxacin were dose-dependent [22].

Previous researches have showed that the use of oral fluoroquinolones causes retinal degeneration in animal models but there is no human study. In present study, we examined whether oral fluoroquinolones are associated with clinically and sublinically detectable acute retinal degeneration in patients who were relatively young and healthy. The population was important because they might be less likely to be suffered from the side effects of the fluoroquinolones. The patients with diabetes mellitus, older ages or poor renal/hepatic function might be prone to fluoroquinolone-related complications. We found that the

use of oral fluoroquinolones had no detectable association with retinal degeneration at acute phase and to the best of our knowledge our study is the first prospective clinical study to investigate this effect.

This study is preliminary and has some limitations. Electrophysiologic tests could not be performed due to laboratory limitations and difficulties in finding volunteer patients. The number of patients using levofloxacin and moxifloxacin is insufficient. A long-term study using a larger number of patients and different fluoroquinolones, including the effect at cumulative doses, would be more useful to demonstrate the subtle changes of oral fluoroquinolones in the human retinas. Another limitation was that we included both eyes of the patients to the study. This approach was reported to be a bias that can result in type 2 error in statistics and inappropriately increase statistical power [23,24]. Despite these factors there was still no statistically significant difference between the groups corfiming the lack of short-term retinal toxicity in the study group following fluoroquinolone use.

In conclusion, no clinically and sublinically detectable acute alterations were found in the human retina and RPE association with oral fluoroquinolones during the study period. In this study, the usage of fluoroquinolones and the follow-up time were relatively short. Prospective studies with higher cumulative dosage of oral fluoroquinolones and longer follow-up time might detect retinal degeneration.

5. Funding

Authors declare that this study received no financial support.

CRediT authorship contribution statement

Alev Ozcelik-Kose: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Osman Cekic:** Writing – review & editing, Methodology. **Cevdet Kaya:** Writing – review & editing, Data curation.

Declaration of Competing Interest

Authors declare that there are no conflicts of interest.

Acknowledgments

We want to thank Dr. Zekaver Odabası from Infectious Diseases Department, Marmara University Faculty of Medicine, for presenting the patients.

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