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ORIGINAL PAPER

Is optical coherence tomography angiography a useful tool in the screening of hydroxychloroquine retinopathy?

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Abstract

Purpose To detect the early changes in retinal vasculature via optical coherence tomography angiography (OCTA) by comparing the quantitative OCTA parameters in the group of patients who were using hydroxychloroquine (HCQ) or not.

Methods This was a cross-sectional, comparative, and observational study. The patients who were newly or previously prescribed HCQ for an autoimmune disease were included. OCTA imaging was performed via OCT RT XR Avanti with AngioVue software (Optivue Inc, Freemont, CA). The study group had two groups: a control group (patients newly diagnosed and who were not taking any medication) and a treatment group (patients who were receiving HCQ treatment). The main outcome measure was OCTA parameters.

Results A total of 102 eyes of 102 patients were included. There were 70 patients in the treatment group and 32 patients in the control group. All of the vascular density values were similar between the control and treatment groups ($p > 0.05$ for all). However, the superficial whole thickness, superficial parafoveal thickness, superficial perifoveal thickness, deep whole thickness, deep parafoveal thickness, and deep perifoveal thickness were thinner in the treatment group than the control group ($p < 0.05$ for all).

Conclusion Vascular density parameters did not differ between the control and treatment groups. However, the retinal thickness values were lower in the treatment group.

Keywords Angiography · Hydroxychloroquine · Optical coherence tomography · Retinopathy

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Introduction

Chloroquines which are originally antimalarial drugs are now being widely used in the treatment of autoimmune diseases [1, 2]. Also, they are used as emerging treatment options for skin, oncologic, and pediatric inflammatory disorders [3]. Surprisingly, chloroquines are now widely used as a first-line drug

in the treatment of—new coronavirus infection—COVID-19 [4]. The first drug of the group was chloroquine, and less toxic variant hydroxychloroquine (HCQ) was developed later [3, 5]. Chloroquines have toxic effects on retina and eventually lead to so-called bull's eye maculopathy [3]. The optimum safe dose of the drug is still debatable. Traditionally HCQ was used based on ideal body weight (IBW); however, it was reported that in some cases, actual body weight (ABW) might be better to use. The doses of < 5 mg/kg/day were considered safe [3, 5]. The duration of HCQ use is another important factor for toxicity. In a large epidemiologic study of 2361 patients who used HCQ for > 5 years, the HCQ toxicity was reported to be 7.5% after 5 years of HCQ use and 20% after 20 years of HCQ use [6]. The exact mechanism of retinal toxicity was not exactly revealed [3]. Toxic effects on retinal pigment epithelium (RPE) cells, accumulation of HCQ in pigmented ocular tissues, and degeneration of photoreceptor cells are among the most possible mechanisms underlying HCQ toxicity [3, 7, 8]. Different screening protocols were described in order to detect HCQ toxicity [3, 9, 10]. Screening is recommended in the first year and annually thereafter [3]. The 10-2 visual field testing, spectral domain optical coherence tomography (OCT), and autofluorescence (AF) imaging are accepted as the main screening tools [3]. In some special circumstances, multifocal electroretinography (mfERG) might be essential also [11, 12]. Many studies were conducted on the sensitivity and specificity of the mentioned tests. Combination of mfERG with either 10-2 visual field testing or OCT was reported as the most reliable screening method [3]. The specificity of 10-2 visual field testing alone was reported as 85.7%, and OCT alone was 78.6% [3]. Optical coherence tomography angiography (OCTA) is a new noninvasive tool which can assess the retinal vascular system quantitatively, and the efficacy of OCTA in HCQ retinopathy was previously evaluated by several authors [13–16]. In this study, we aimed to detect the early changes in retinal vasculature via OCTA by comparing the quantitative OCTA parameters in patients who were using HCQ or not.

Materials and methods

This prospective, cross-sectional, and comparative study was conducted in Bakirkoy Training and Research Hospital. A written informed consent for the treatment was obtained from all of the participants. The study adhered to the tenets of the Declaration of Helsinki and local ethics board approval was obtained.

Patients

The patients who were newly or previously prescribed HCQ for an autoimmune disease were included in the study. Only one eye of each patient was included and the right eye was designated as the study eye in the patients with an even birth month number and the left eye was selected in the patients with an odd birth month number. The patients who had amblyopia or, a retinal disease or, intraocular inflammation or, media opacity or, a history of systemic conditions that could alter the microvasculature (including diabetes, hypertension, cardiovascular disease, and renal disease) were not included.

Examinations

All of the patients underwent a complete ophthalmological examination, including best-corrected visual acuity (BVCA), slit-lamp biomicroscopy, dilated fundus examination. Optical coherence tomography imaging was performed via OCT RT XR Avanti with AngioVue software (Optivue Inc, Freemont, CA). Structural OCT parameters and OCTA parameters for fovea were analyzed. 6×6 scan size was used for OCTA imaging, all of the scans were automatically segmented, and the quantitative values that are FAZ area, FAZ perimeter, flow area, vessel density, and retinal thickness were all calculated via the built-in automated software of the device. All measurements were obtained between 9 a.m. and 11 a.m. as the choriocapillary flow might change diurnally [17]. The scans with a signal strength index of < 40 with motion artifacts and segmentation errors were accepted to have a poor quality and were not analyzed.

Groups and outcomes measures

Firstly, the study group was divided into two groups: a control group (patients newly diagnosed and who were

not taking any medication) and a treatment group (patients who were receiving HCQ treatment). Also, the treatment group was divided into two subgroups for further analysis in terms of treatment duration as follows: the patients who were under HCQ treatment for ≤ 5 years or > 5 years.

The main outcome measure of the study was OCTA parameters of the patients who were under HCQ treatment.

Statistical methods

Sample size calculations were done using the G*Power 3 software (Kiel, Germany). Sample size power was calculated for each of the evaluated OCTA parameters, and a minimum total sample of 16 patients was required to detect the differences between the control and treatment groups of the study with 80% power and $\alpha = 0.05$. Categorical variables were presented as numbers and percentages, while numerical variables were expressed as the mean and standard deviation. Kolmogorov–Smirnov test was used to analyze normality of the data, and the distribution of the data was found to be normal; therefore, independent sample t test was used to compare the numerical variables between the two groups. Categorical variables were compared using Chi-square test. Pearson test was used for correlation analysis. A p value < 0.05 was considered statistically significant.

Results

A total of 102 eyes of 102 patients were included. There were 70 patients in the treatment group and 32 patients in the control group. The patients in the treatment group were using HCQ for a mean of 73.2 ± 44.5 months (ranging between 12 and 180 months). The mean age was 49.2 ± 10.5 years (ranging between 24 and 77 years) in the study and 48.1 ± 16.1 years (ranging between 20 and 69 years) in the control groups, respectively (p = 0.7). Fifty-three (52%) patients had rheumatoid arthritis, 21 (20.6%) had Sjogren's syndrome, and 28 (27.5%) had systemic lupus erythematosus.

The mean values for the OCTA parameters are summarized in Table 1. All of the vascular density values were similar between the study and treatment groups ($p > 0.05$ for all). However, the superficial

whole thickness, superficial parafoveal thickness, superficial perifoveal thickness, deep whole thickness, deep parafoveal thickness, and deep perifoveal thickness were lower in the treatment group than the control group ($p < 0.05$ for all).

Twenty-nine patients were under HCQ treatment for ≤ 5 years, and 41 patients were under HCQ treatment for > 5 years (Table 2). The mean duration of HCQ use was 29.7 ± 14.3 months in the subgroup of patients who were under HCQ treatment for ≤ 5 year and 102.2 ± 32.3 months in the group of patients who were under HCQ treatment for > 5 years. The mean daily dose of HCQ was 221 ± 41 mg in the patients who were under treatment for ≤ 5 years and 228 ± 45 mg in the patients who were under treatment for > 5 years (p = 0.5). Choriocapillaris flow area, superficial whole density, and superficial perifoveal density values were different between patients who were under HCQ treatment for ≤ 5 years and > 5 years ($p < 0.05$ for all). Also, superficial whole thickness, superficial parafoveal thickness, superficial perifoveal thickness, deep whole thickness, deep parafoveal thickness, and deep perifoveal thickness were lower in patients who were under HCQ treatment for > 5 years than those who were under HCQ treatment for ≤ 5 years ($p < 0.05$ for all).

Discussion

In this study, we evaluated the patients who were using HCQ for the treatment of several autoimmune diseases via OCTA. We first divided the patients into two groups as the control and treatment groups. Then, we further divided the treatment group into two subgroups according to HCQ use duration (≤ 5 years vs. > 5 years). The vascular density values were similar between the control and treatment groups. However, in line with previous OCT studies [18–21], the thickness values of the treatment group were statistically lower than the control group. We observed some interesting outcomes when we divided the patients into two subgroups depending on the HCQ treatment duration. Superficial whole density and perifoveal density were higher in the subgroup of patients who were using HCQ for ≤ 5 years. Also, most of the thickness values showed difference between the two subgroups and were better in the patients who were using HCQ for ≤ 5 years.

Table 1 The optical coherence tomography angiography outcomes of the two study groups

	Control group, 32 eyes	Treatment group, 70 eyes	p
FAZ area (mm^2)	0.29 ± 0.09	0.31 ± 0.11	0.5
FAZ perimeter (mm)	2.12 ± 0.37	2.16 ± 0.43	0.6
Flow area (outer retina, mm^2)	0.86 ± 0.55	0.73 ± 0.46	0.2
Flow area (choriocapillaris, mm^2)	2.06 ± 0.14	2.06 ± 0.14	0.9
Superficial whole density (%)	51.1 ± 2.2	49.7 ± 3.8	0.06
Superficial whole thickness (μm)	**287 ± 8**	**279 ± 12**	**0.002***
Superficial foveal density (%)	19.7 ± 6.2	18.1 ± 7.6	0.2
Superficial foveal thickness (μm)	245 ± 23	240 ± 19	0.2
Superficial parafoveal density (%)	53.1 ± 2.9	52.1 ± 4.5	0.2
Superficial parafoveal thickness (μm)	**322 ± 11**	**315 ± 16**	**0.02***
Superficial perifoveal density (%)	51.8 ± 2.5	50.4 ± 3.9	0.06
Superficial perifoveal thickness (μm)	**285 ± 8**	**278 ± 13**	**0.004***
Deep whole density (%)	49.8 ± 5.5	49.7 ± 6.2	0.8
Deep whole thickness (μm)	**287 ± 8**	**279 ± 12**	**0.002***
Deep foveal density (%)	36.0 ± 6.5	34.2 ± 8.1	0.2
Deep foveal thickness (μm)	245 ± 23	240 ± 19	0.2
Deep parafoveal density (%)	54.2 ± 4.9	54.0 ± 4.5	0.8
Deep parafoveal thickness (μm)	**322 ± 11**	**315 ± 16**	**0.03***
Deep perifoveal density (%)	51.3 ± 5.7	50.8 ± 6.7	0.7
Deep perifoveal thickness (μm)	**285 ± 8**	**278 ± 13**	**0.004***

FAZ foveal avascular zone

*$p < 0.05$. Bold values represent the variables which shows statistical significance

Table 2 The optical coherence tomography outcomes of the two subgroups of treatment group

HCQ treatment duration	≤ 5 years, 29 eyes	> 5 years, 41 eyes	p
FAZ area (mm^2)	0.33 ± 0.14	0.30 ± 0.09	0.2
FAZ perimeter (mm)	2.19 ± 0.54	2.15 ± 0.34	0.6
Flow area (outer retina, mm^2)	0.76 ± 0.47	0.71 ± 0.46	0.6
Flow area (choriocapillaris, mm^2)	**2.01 ± 0.15**	**2.09 ± 0.12**	**0.01***
Superficial whole density (%)	**51.3 ± 3.6**	**48.7 ± 3.6**	**0.005***
Superficial whole thickness (μm)	**290 ± 7**	**272 ± 8**	**> 0.0001***
Superficial foveal density (%)	19.1 ± 9.9	17.4 ± 5.6	0.3
Superficial foveal thickness (μm)	245 ± 24	237 ± 14	0.1
Superficial parafoveal density (%)	52.9 ± 4.2	51.6 ± 4.7	0.2
Superficial parafoveal thickness (μm)	**327 ± 12**	**308 ± 13**	**< 0.0001***
Superficial perifoveal density (%)	**52.0 ± 3.8**	**49.3 ± 3.7**	**0.004***
Superficial perifoveal thickness (μm)	**290 ± 8**	**270 ± 9**	**< 0.0001***
Deep whole density (%)	50.6 ± 6.5	49.0 ± 6.0	0.3
Deep whole thickness (μm)	**290 ± 7**	**272 ± 8**	**< 0.0001***
Deep foveal density (%)	35.3 ± 10.5	33.4 ± 6.0	0.3
Deep foveal thickness (μm)	244 ± 24	237 ± 14	0.1
Deep parafoveal density (%)	54.2 ± 5.3	53.9 ± 4.0	0.8
Deep parafoveal thickness (μm)	**327 ± 12**	**308 ± 13**	**< 0.0001***
Deep perifoveal density (%)	51.8 ± 6.8	50.1 ± 6.6	0.3
Deep perifoveal thickness (μm)	**290 ± 8**	**270 ± 9**	**< 0.0001***

HCQ hydroxychloroquine; *FAZ* foveal avascular zone

*$p < 0.05$. Bold values represent the variables which shows statistical significance

The exact mechanism of HCQ retinal toxicity is still debatable. A possible mechanism is the inhibition of uptake of all-trans-retinol leading to a negative effect on the visual cycle [22]. Chloroquine was detected in pigmented ocular diseases in rhesus monkeys after a long-term use [23]. The accumulation in RPE cells seems to be important as the retinal toxicity might continue even after the cessation of the drug [3, 24]. The parafoveal and perifoveal regions are the two most common sites vulnerable to the HCQ toxicity [25]. Fovea is generally affected later. There is an ongoing debate regarding the primary site of the toxicity. Some studies suggest RPEs might be the primary affected tissue; some other suggest the outer retina/photoreceptor complex as the primary affected tissue [3, 25]. Screening guidelines are very important in the follow-up examinations of the patients who are under HCQ treatment. The latest guidelines suggest the physicians to screen the patients via routine ophthalmologic examination, central visual field testing, OCT, and sometimes fundus autofluorescence imaging [10]. Optical coherence tomography is a very useful tool in the screening examinations of the patients using HCQ [3]. Structural OCT was widely studied to reveal the early findings of HCQ toxicity, and now OCTA, another noninvasive tool that has been used to show the retinal circulation, is being studied to detect early HCQ toxicity. In two previous studies, it was revealed that the inner and outer retinal layer was significantly thinner in the group of patients who were under HCQ [18, 26]. In concordance with these studies, we found that both superficial thickness and deep retinal thickness were decreased in the group of patients who were under HCQ treatment. In detail, the perifoveal and parafoveal regions were especially affected from the treatment and showed significant thinning. OCTA studies regarding the changes in vascular density in patients who are under HCQ treatment showed variable outcomes [13–16]. The retinal thickness decrease is a common finding in all of the OCT-based studies; however, there is not a consensus in the differences in vascular density detected via OCTA. Goker et al. showed that the vascular density in fovea in superficial and deep capillary plexus was significantly lower in patients who were under HCQ treatment than the patients who were not [14]. As a well-known fact, the first changes in HCQ toxicity begin from the perifoveal and parafoveal regions; therefore, if some change is

expected in vascular density, it should be in this area. In our study, the vessel density parameters did not show statistically significant difference between the patients who were under HCQ treatment or not. But our subgroup analysis showed that the perifoveal density and parafoveal density in both superficial and deep capillary plexuses were decreased in the group of patients who were under HCQ treatment for more than 5 years. Also, Goker et al. reported increase in FAZ perimeter and FAZ area in superficial capillary plexus and full retinal vasculature which was postulated to be associated with the accumulation of the drug in the RPE cells. Forte et al. compared the OCTA findings between the patients who were under HCQ treatment for > 5 years (20 eyes of 10 patients) and a control group (36 eyes of 18 healthy volunteer) [15]. They reported that the vascular density in fovea in deep capillary plexus and choriocapillaris was decreased. Again, the main affected zone was reported to be central fovea in this study. Bulut et al. conducted a study to evaluate the additional benefit of OCTA in the screening of HCQ-induced retinal alterations [13]. They divided the patients into two groups as low risk (receiving HCQ for < 5 years) and high risk (receiving HCQ for > 5 years). This study also showed us some controversial outcomes. Surprisingly, the thickness results did not show statistical difference between the low-risk and high-risk groups. Foveal, parafoveal, and perifoveal retina thickness values were similar, and only choroidal thickness was found to be decreased in the group of high-risk patients. In contrast to thickness outcomes, all of the vascular density parameters (whole, superficial, deep and foveal, parafoveal, perifoveal) were found to be decreased in the high-risk group of patients. Ozek et al. evaluated the OCTA findings in rheumatoid arthritis patients receiving HCQ treatment [16]. The authors divided the study population into three groups: patients who received HCQ for > 5 years (24 patients), those who received HCQ for < 5 years (16 patients), and healthy volunteers (20 patients). This study had also controversial outcomes. Nearly none of the retinal thickness outcomes differed between the three study groups except for inferior superficial plexus and hemi-inferior deep capillary plexus thickness values which were lower in the group of patients who were receiving HCQ treatment for > 5 years. The vessel density analysis showed some positive outcomes, and deep temporal and hemi-inferior vascular density was found

to be decreased in patients who were receiving HCQ treatment for > 5 years. In summary, only some OCTA studies were able to detect retinal alterations in patients receiving HCQ treatment [13–16]. It seems that retinal thickness decreases both topographically and tomographically after HCQ treatment. Retinal circulation might also be affected by some means. In our study, we found that, after HCQ use, the retinal thickness was decreased. Additionally, superficial parafoveal density and perifoveal vascular density were decreased in patients who were under HCQ treatment for > 5 years as compared to those who were under HCQ treatment for ≤ 5 years. The blood supply of inner retinal layers comes from superficial retinal circulation [27]. The OCTA outcomes of our study might point to a possible pathologic process underlying early HCQ toxicity in the inner retinal circulation. In line with our results showing superficial retinal circulation impairment in the patients who were under HCQ treatment for > 5 years, some data suggest that the earliest changes following HCQ exposure occur in the cytoplasm of ganglion cells and photoreceptors. The RPE seems to be affected later with the binding of the drug to melanin. Hydroxychloroquine might also influence the retinal cell's metabolism and can cause slowly the chronic toxic effects [19, 23]. Rosenthal et al. have performed an animal study on Rhesus monkeys [23]. They have evaluated the chloroquine toxicity administered 5 days a week for as long as 4.5 years. They have found that chloroquine caused an initial toxic effect on ganglion cells and photoreceptors which was followed by alterations in choroid and RPE. In line with this animal study data, Kan et al. demonstrated a significant thinning in the macular ganglion cells and inner plexiform layer complex via OCT in patients who received HCQ treatment for at least 5 years and who had a normal VF testing [19].

The main limitation of our study was its cross-sectional design. A well-conducted longitudinal study will be essential to clarify the usefulness of OCTA in HCQ retinal toxicity. The most important strength of our study was the good number of patients. We divided our HCQ using patients into two subgroups and revealed some positive outcomes regarding superficial vascular plexus density values.

In conclusion, our results indicated a decrease in the superficial capillary plexus at the parafoveal and perifoveal regions in patients were receiving HCQ treatment for > 5 years. The OCTA imaging may thus be beneficial indirectly in the early detection of HCQ toxicity which is mainly located in the inner retinal layers such as ganglion cells. Our findings need to be confirmed in longitudinal studies.

Author contribution HNT, AO and UY were involved in design and conduct of the study and preparation and review of the study; HNT and UY contributed to data collection; and AO was involved in statistical analysis.

Compliance with ethical standards

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