OCT ANGIOGRAPHY REVEALS EARLY CHANGES WITH HYDROXYCHLOROQUINE THERAPY

Patients without signs and symptoms of retinopathy may have significant loss of vascular density.

BY DIOGO LOPES, MD; TOMÁS LOUREIRO, MD; ANA RITA CARREIRA, MD; ANA MIRANDA, MD; MAFALDA PEREIRA, MD; INÊS MACHADO, MD; AND NUNO CAMPOS, MD

Hydroxychloroquine (HCQ) is a drug often used effectively in the treatment of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and other connective tissue disorders.[1,2] Although HCQ is associated with a lower incidence of retinal toxicity compared with chloroquine, it still has the potential to cause irreversible vision loss. Given that patients with HCQ-associated retinopathy are initially asymptomatic, screening for this condition plays an important role in its early identification.

The most important risk factors for toxic retinopathy are daily dosage, duration of use, renal disease, tamoxifen use, and concomitant macular disease.[3] Currently, several examination techniques are used to screen for retinopathy because no consensus exists on the most sensitive screening process. The most recent recommendations from the AAO suggest that evaluations should include biomicroscopy, computed static perimetry (protocol 10-2), and one or more objective tests, including spectral domain OCT (SD-OCT), multifocal electroretinogram (mfERG), and background fundus autofluorescence (FAF).[3-5]

OCT angiography (OCTA) is an imaging modality developed to study retinal and choroidal vascular perfusion by detecting capillary blood cell flow without the need for contrast injection.[6] OCTA evaluation of a symptomatic patient with evidence of HCQ-associated retinopathy shows a reduction in vascular density in the deep retinal plexus and choriocapillaris (CC), as reported by Kam et al.[7]

We performed a study to evaluate vascular density in different retinal plexuses using OCTA in asymptomatic patients without evidence of retinal toxicity under treatment with HCQ to understand the tool's utility in early screening for retinal toxicity.

MATERIAL AND METHODS

This retrospective study was conducted between March 2018

AT A GLANCE

- Hydroxychloroquine (HCQ), a drug often used in the treatment of autoimmune diseases, has the potential to cause irreversible vision loss.
- The authors performed a retrospective study using OCT angiography to compare vascular density between asymptomatic patients treated with HCQ and a control group.
- Patients without signs and symptoms of HCQ retinopathy may have significant loss of vascular density compared with controls.

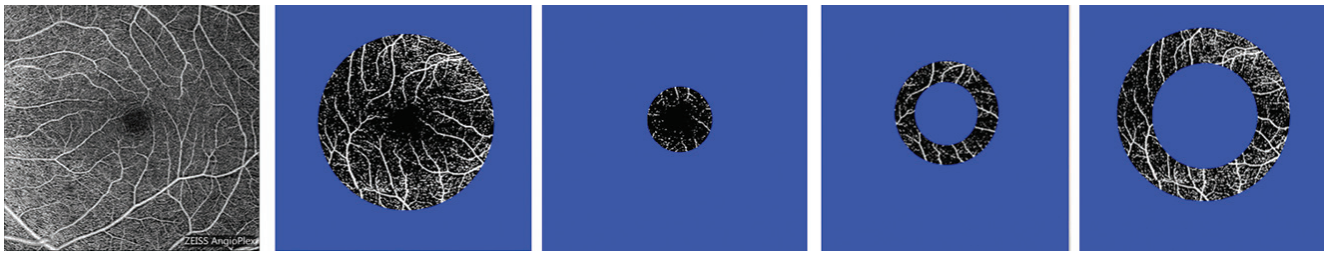

Figure. Methodology for calculating vascular density with the Image J program. From left to right: 6 x 6-mm OCTA image; macular region; foveal region; parafoveal region; perifoveal region.

and January 2019 in accordance with ethical standards and the tenets of the Declaration of Helsinki. Thirty eyes of 15 asymptomatic patients under treatment with HCQ and attending rheumatology consultation were included in the study. Patients showed no signs or symptoms of HCQ-associated retinopathy and showed no evidence of toxicity on screening tests, including 10-2 visual fields, SD-OCT, and FAF. Exclusion criteria included the presence of any retinal or optic nerve pathology or media opacity. An age- and sex-adjusted control group of patients not under treatment with HCQ and without evidence or history of any eye disease was recruited.

Clinical history measures included age, sex, rheumatologic diagnosis, duration of HCQ use, daily and cumulative dose of HCQ, visual symptoms, and other systemic medications and conditions. All patients underwent a complete ophthalmologic evaluation including BCVA, biomicroscopy, IOP measurement via Goldmann applanation tonometry, and fundoscopy. Screening exams included good quality central 10° perimetry with the Octopus automated perimeter (Haag-Streit); SD-OCT and FAF using the Cirrus HD-OCT (Carl Zeiss Meditec); and OCTA using the Cirrus HD-OCT 5000 (Carl Zeiss Meditec).

This last device is an SD-OCT scanner with a resolution depth of 5 µm and an acquisition speed of 27,000 scans per second. Scan volumes with a topographic dimension of 6 x 6 mm centered on the macula were obtained. Automated segmentation of full-thickness retinal scans into the superficial capillary plexus (SCP), deep capillary plexus (DCP), and CC were performed.

All OCTA 6 x 6 mm images of the different plexuses were exported into the Image J program (National Institutes of Health) for analysis of vascular density, as the Cirrus software analyzes only SCP. The foveal avascular zone (FAZ) of the superficial vascular plexus was automatically calculated by the OCTA software.

To calculate vascular density with Image J software, a previously described method was used in which images were binarized using a threshold strategy.[8,9] The vascular density value was derived from a ratio of white pixels, representing vessels, to total number of pixels. We analyzed regions of the macula including the foveal region (1.5 mm diameter), parafoveal region (ring between 1.5 and 2.5 mm diameter), and perifoveal region (ring between 2.5 and 4 mm diameter) in both groups (Figure).

Sets of values were compared between the two groups for each layer of segmentation. Statistical analysis was performed using SPSS version 23.0, and statistical significance was defined by *P* value less than .05. The primary outcome measures were vascular density in the macular, foveal, parafoveal, and perifoveal regions in the superficial, deep, and CC layers.

RESULTS

A total of 30 eyes of 15 patients undergoing HCQ treatment were included in the study. Mean patient age was 54.3 ± 19.5 years (range, 26–76 years). The treatment group

TABLE 1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF HCQ GROUP AND CONTROL GROUP

	Patients (n = 15)	Controls (n = 15)
Age (years)		
Mean ± standard deviation (SD)	54.3 ± 19.5	52.4 ± 1.0
Range	26–76	30–70
Gender, n (%)		
Female	15 (100%)	15 (100%)
Male	-	-
Rheumatic disease, n (%)		-
Systemic lupus erythematosus	7 (46.7%)	
Rheumatoid arthritis	4 (26.7%)	
Sjögren syndrome	4 (26.7%)	
Daily dose (mg/kg/day)		-
Mean ± SD	5.81 ± 1.37	
Range	3.50–7.84	
< 6.5 mg/kg/day	10 (67%)	
> 6.5 mg/kg/day	5 (33%)	
Cumulative dose (g)		-
Mean ± SD	1,231 ± 619.3	
Range	438–2,774	
< 1,000 g	6 (40%)	
> 1,000 g	9 (60%)	
Treatment duration (years)		-
Mean ± SD	8.9 ± 4.0	
Range	3–14	

TABLE 2. RESULTS OF SCP ANALYSIS BY IMAGE J PROGRAM

SCP Vessel Density (%)			
	Patients	Control	*P* value
Macular	20.0 ± 5.1	26.6 ± 5.4	< .001*
Foveal	8.1 ± 6.2	12.3 ± 4.8	<. 001*
Parafoveal	16.8 ± 6.7	22.4 ± 6.7	.001*
Perifoveal	23.8 ± 4.8	30.6 ± 5.3	< .001*

*Statistically significant value (*P* < .05)

TABLE 3. RESULTS OF DCP ANALYSIS BY IMAGE J PROGRAM

DCP Vessel Density (%)			
	Patients	Controls	*P* value
Macular	33.7 ± 5.9	37.5 ± 5.2	.010*
Foveal	12.6 ± 6.0	15.6 ± 4.6	.001*
Parafoveal	34.0 ± 7.4	36.7 ± 6.8	.061
Perifoveal	38.0 ± 5.7	41.8 ± 5.1	.008*

*Statistically significant value (*P* < .05)

TABLE 4. RESULTS OF CC ANALYSIS BY IMAGE J PROGRAM

CC Vessel Density (%)			
	Patients	Controls	*P* value
Macular	37.3 ± 5.6	40.2 ± 5.8	.052
Foveal	-	-	-
Parafoveal	30.8 ± 6.6	35.9 ± 8.4	.044*
Perifoveal	41.0 ± 5.2	43.5 ± 4.9	.067

*Statistically significant value (*P* < .05)

TABLE 5. RESULTS OF SCP ANALYSIS BY CIRRUS SOFTWARE

SCP Vessel Density (%)			
	Patients	Controls	*P* value
Central	13.8 ± 17.4	20.2 ± 9.5	.001*
Internal	32.0 ± 8.5	38.5 ± 8.9	.002*
External	37.6 ± 7.4	41.6 ± 7.9	.012*
Total	35.6 ± 7.4	40.3 ± 8.1	.005*

*Statistically significant value (*P* < .05)

comprised seven patients (46.7%) with a diagnosis of systemic lupus erythematosus, four (26.7%) with rheumatoid arthritis, and four (26.7%) with Sjögren syndrome (Table 1). No statistically significant difference was seen in age and sex of the HCQ group and control group (*P* = .441). Five patients (33%) had a cumulative dose greater than 1,000 g, and nine patients (60%) had a daily dose greater than 6.5 mg/kg. No patient reported relevant visual symptoms. Ophthalmologic evaluation revealed no relevant findings in biomicroscopy, fundoscopy, or screening examinations.

OCTA evaluation revealed significant changes in vascular density in all capillary plexuses in the HCQ group compared with the control group. Image J vascular flow analysis showed a significant reduction in the SCP (*P* < .001) and DCP (*P* = .010) in the overall macular region.

Regarding the macular regions, in the SCP there was a statistically significant reduction in vascular density in the foveal, parafoveal, and perifoveal regions (Table 2). Analysis of the DCP showed a statistically significant reduction in the foveal and perifoveal regions (Table 3). In the CC layer, there was a significant reduction in vascular density only in the parafoveal region (Table 4).

Quantitative vascular analysis with the Cirrus OCTA software in the SCP confirmed the results obtained by Image J evaluation. The data reveal a significant reduction in vascular density in the overall macula (*P* = .005) as well as each specific region of the macula: foveal, *P* = .001; parafoveal, *P* = .002; and perifoveal, *P* = .012 (Table 5).

In the HCQ group, the FAZ did not show a statistically significant difference from the control group (*P* = .940). There was also no significant correlation between vascular density in the different plexuses and cumulative dose of HCQ or duration of treatment (*P* > .05).

DISCUSSION

Although rare, HCQ retinopathy is potentially irreversible, and cellular damage may continue even after the medication is discontinued; thus, early detection is essential to prevent serious retinal damage.[10,11] In 2016, the AAO published a review of screening recommendations for HCQ retinopathy that suggested patients treated with a daily HCQ dose above 5 mg/kg/day (the most important toxicity factor) and those with renal disease, macular disease, or concomitant tamoxifen treatment should be evaluated frequently.[3] The AAO also recommended that subjective findings of toxicity be confirmed with at least one objective screening test.[3] Even though visual fields are potentially more sensitive, they depend on several factors, and isolated scotoma points are often found in patients taking HCQ with no evidence of retinopathy.[12]

In our study, we aimed to evaluate OCTA as a new, objective screening test. To the best of our knowledge, this is one of the first retrospective studies to analyze and compare vascular density using OCTA in patients under HCQ treatment without evidence of retinopathy and age- and sex-matched

healthy controls.

Similar to other studies, patients treated with HCQ in our study showed reduced vessel density in the SCP and DCP in the overall macular region and also significant reduction in vascular density in the parafoveal region of the CC layer. Goker et al found a larger FAZ and reduced vessel density of the fovea in the SCP and DCP in patients undergoing daily use of HCQ for more than 5 years compared with healthy individuals.[13] In 10 patients treated with HCQ, Forte et al showed reduced vessel density in the central, nasal, and temporal subfields of the DCP, enlargement of the FAZ, and reduced CC density in the central subfield compared with healthy controls.[14]

Studies comparing patients taking HCQ for more than 5 years with patients taking HCQ for less than 5 years also show a positive correlation with reduced vessel density. Ozek et al found that the parafoveal deep temporal and deep hemi-inferior vascular plexus densities were reduced in patients taking HCQ for more than 5 years despite having normal perimetry.[15] Bulut et al found significantly reduced vascular density (SCP and DCP) and wider FAZ in high-risk patients under treatment with HCQ compared with a low-risk group.[16]

Our study revealed a significant reduction in vascular density in the DCP, supporting the structural changes found in high-resolution OCT analysis and in the superficial layers.[17]

The pathophysiology of retinopathy secondary to HCQ is still unclear. Some studies suggest that retinal toxicity could be detected at an earlier stage through the measurement of the inner layer thickness using SD-OCT.[18,19] However, other studies that use SD-OCT show a distinctive loss of the perifoveal inner segment/outer segment photoreceptor junction, suggesting that HCQ retinal toxicity mainly affects the external retina/photoreceptor layer, particularly in the parafoveal and perifoveal regions, before causing structural damage involving the retinal pigment epithelium and the inner retinal layers.[17,20-23]

Patients treated with HCQ but without symptoms or signs of retinopathy appear to have a significant loss of vascular density. These OCTA findings may help clinicians to monitor patients and eventually stratify their risk of retinal damage. Future work with larger sample sizes will be important to reinforce the potential role of OCTA in screening for and detecting the progression of HCQ-associated retinopathy. ■

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NUNO CAMPOS, MD
- Head of Ophthalmology Department, Hospital Garcia de Orta, Almada, Portugal

ANA RITA CARREIRA, MD
- Ophthalmology Resident, Ophthalmology Department, Hospital Garcia de Orta, Almada, Portugal

DIOGO LOPES, MD, CORRESPONDING AUTHOR
- Ophthalmology Resident, Department of Ophthalmology, Garcia de Orta Hospital, Almada, Portugal
- cdiogolopes@gmail.com

TOMÁS LOUREIRO, MD
- Ophthalmology Resident, Ophthalmology Department, Hospital Garcia de Orta, Almada, Portugal
- loureiro.tomas@gmail.com

INÊS MACHADO, MD
- Ophthalmology Consultant, Ophthalmology Department, Hospital Garcia de Orta, Almada, Portugal

ANA MIRANDA, MD
- Ophthalmology Consultant, Ophthalmology Department, Hospital Garcia de Orta, Almada, Portugal

MAFALDA PEREIRA, MD
- Ophthalmology Consultant, Ophthalmology Department, Hospital Garcia de Orta, Almada, Portugal

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