Article

Spectral-Domain Optical Coherence Tomography Is More Sensitive for Hydroxychloroquine-Related Structural Abnormalities Than Short-Wavelength and Near-Infrared Autofluorescence

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Purpose: To analyze the appearance of structural abnormalities due to hydroxychloroquine (HCQ) toxicity by spectral-domain optical coherence tomography (SD-OCT) and short-wavelength autofluorescence (SW-AF) and near-infrared fundus autofluorescence (NIR-AF) imaging.

Methods: This retrospective cohort study included 88 eyes from 44 patients who had a history of or were currently taking HCQ. SD-OCT, SW-AF, and NIR-AF images were analyzed by two independent graders for the detection of HCQ-associated abnormalities.

Results: Sixty eyes (30 patients, 68%) presented with no abnormalities for either imaging modality. Twenty eyes (10 patients, 23%) presented with parafoveal abnormalities (ellipsoid zone attenuation and/or interdigitation zone continuity loss) in SD-OCT scans but with qualitatively normal SW-AF and NIR-AF images. Eight eyes (four patients, 9%) presented with bull's-eye maculopathy in SW-AF and NIR-AF images, with corresponding outer retinal structures disrupted parafoveally in SD-OCT scans ("flying saucer" sign). No patients presented with normal SD-OCT scans and concurrent abnormalities in SW-AF or NIR-AF images.

Conclusions: SD-OCT was more sensitive in detecting structural abnormalities than either SW-AF or NIR-AF imaging, suggesting its superiority as a screening imaging modality for HCQ toxicity. Maculopathy and abnormalities in the retinal pigment epithelium from HCQ toxicity can be appreciated in both SW-AF and NIR-AF images.

Translational Relevance: Although debate exists regarding the best imaging modalities for screening patients for potential HCQ toxicity, our study supports the use of SD-OCT over both SW-AF and NIR-AF imaging as a screening modality.

Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug that has become a cornerstone for the treatment of rheumatological diseases. In systemic lupus erythematosus (SLE), for example, HCQ therapy increases long-term survival and decreases disease flares, and its withdrawal is associated with higher risks of flares and disease exacerbation.[1–3] The popularity of HCQ therapy is based on its effectiveness and low systemic adverse effects.[3] Nevertheless, the most feared adverse effect of HCQ is retinopathy, which leads to vision loss that may even progress after cessation of treatment.[4,5] HCQ retinopathy is considered rare, with previously estimated incidences ranging between 0.5% and 1.8% in long-term users.[6,7] Nevertheless, a recent study reported that HCQ retinopathy is more common

than previously thought, as it found a prevalence of 7.5% in long-term users.[8] Therapy-dependent associated risk factors for the development of HCQ retinopathy include a daily dosage greater than 5.0 mg/kg of real body weight, duration of treatment greater than 10 years, and a cumulative dose greater than 1000 g.[8–10]

Given the concern for vision loss, there is a strong emphasis on screening patients taking HCQ. The current recommended initial screening tests from the American Academy of Ophthalmology (AAO) are spectral-domain optical coherence tomography (SD-OCT) and visual fields appropriate for race (10-2 pattern for non-Asians, 24-2 or 30-2 for Asian patients).[9] Despite the general consensus regarding this screening protocol, multiple studies have evaluated various modalities to determine which of these detects retinopathy the earliest, ranging from structural imaging modalities such as SD-OCT to functional modalities such as automated visual fields, including the Humphrey visual field (HVF), and multifocal electroretinography (mfERG).[10–15]

In this study, we assessed the imaging modalities of short-wavelength autofluorescence (SW-AF) and near-infrared autofluorescence (NIR-AF) in detecting HCQ retinopathy. Both SW-AF and NIR-AF are important imaging modalities in assessing the health of the retinal pigment epithelium (RPE), and multiple studies have explored their use in retinal dystrophies such as retinitis pigmentosa and other retinal pathologies.[16–21] In addition to exploring their role in the detection of HCQ retinopathy, we compared them to SD-OCT, the currently preferred structural imaging modality for screening.

Methods

The study procedures were defined and informed patient consent was obtained as outlined by protocol #AAAB6560 approved by the Institutional Review Board at Columbia University Medical Center. The study followed the tenets of the Declaration of Helsinki. The data presented in the study, including imaging, are not identifiable to individual patients.

Patients and Clinical Examination

We conducted a retrospective review of patients that presented to our clinic at the Harkness Eye Institute of Columbia University who had a history of or were currently taking HCQ therapy between 2015 and 2019. The inclusion criteria involved patients with clinic visits during which SW-AF, NIR-AF, and SD-OCT imaging were performed. Clinical examination included a fundoscopic examination, ascertainment of best-corrected visual acuity, imaging with the three aforementioned imaging modalities, and HVF testing. Demographic information, real body weight, and history regarding the use of HCQ were obtained from the clinical record and/or the patient.

Image Acquisition and Analyses

Imaging across all modalities was conducted after pupillary dilation (>7 mm) with tropicamide (1%) and phenylephrine hydrochloride (2.5%). SD-OCT and SW-AF (488-nm excitation) images were acquired using the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). NIR-AF imaging was acquired with the Heidelberg Retina Angiograph 2 (HRA2) scanning laser ophthalmoscope using the indocyanine green angiography mode. For both modalities, scans were acquired with either a 55° or 30° field of view. HVF 10-2 perimetry (Carl Zeiss Meditec, Dublin, CA) was also obtained for each patient. Five patients from this cohort were of Asian descent. As such, SD-OCT imaging was performed to image beyond the parafoveal region, both SW-AF and NIR-AF imaging was performed with a 55° field of view, and wider HVF tests (24-2 or 30-2) were obtained.

Two authors (RJ and RP) analyzed the images independently and noted abnormalities that could be attributed to HCQ therapy. For SD-OCT, these abnormalities involved (1) parafoveal loss of the ellipsoid zone (EZ) and interdigitation zone (IZ) bands with foveal conservation ("flying saucer" sign), and (2) early abnormalities as described by Garrity et al.,[10] including EZ band attenuation and/or loss of a continuous IZ band.[22] For SW-AF and NIR-AF images, we considered an image to be abnormal if the AF pattern deviated from what is observed in healthy subjects. SD-OCT, SW-AF, and NIR-AF images were analyzed per eye and independently from each other to avoid a potential for bias (i.e., when analyzing the SW-AF image from a particular patient, the grader was unaware if abnormalities were present in the SD-OCT and/or NIR-AF images of that particular patient). Given the qualitative nature of our data (presence/absence of abnormalities), inter-grader agreement between RJ and RP was assessed by using Cohen's κ coefficient. The calculated value of κ was 0.901 (95% confidence interval, 0.823–0.979), suggestive of a high level of inter-grader agreement. In the images where disagreement was present between the two authors, a third author (SHT) analyzed the image, and the three authors conjointly arrived at a decision. After the image analyses of the aforementioned three
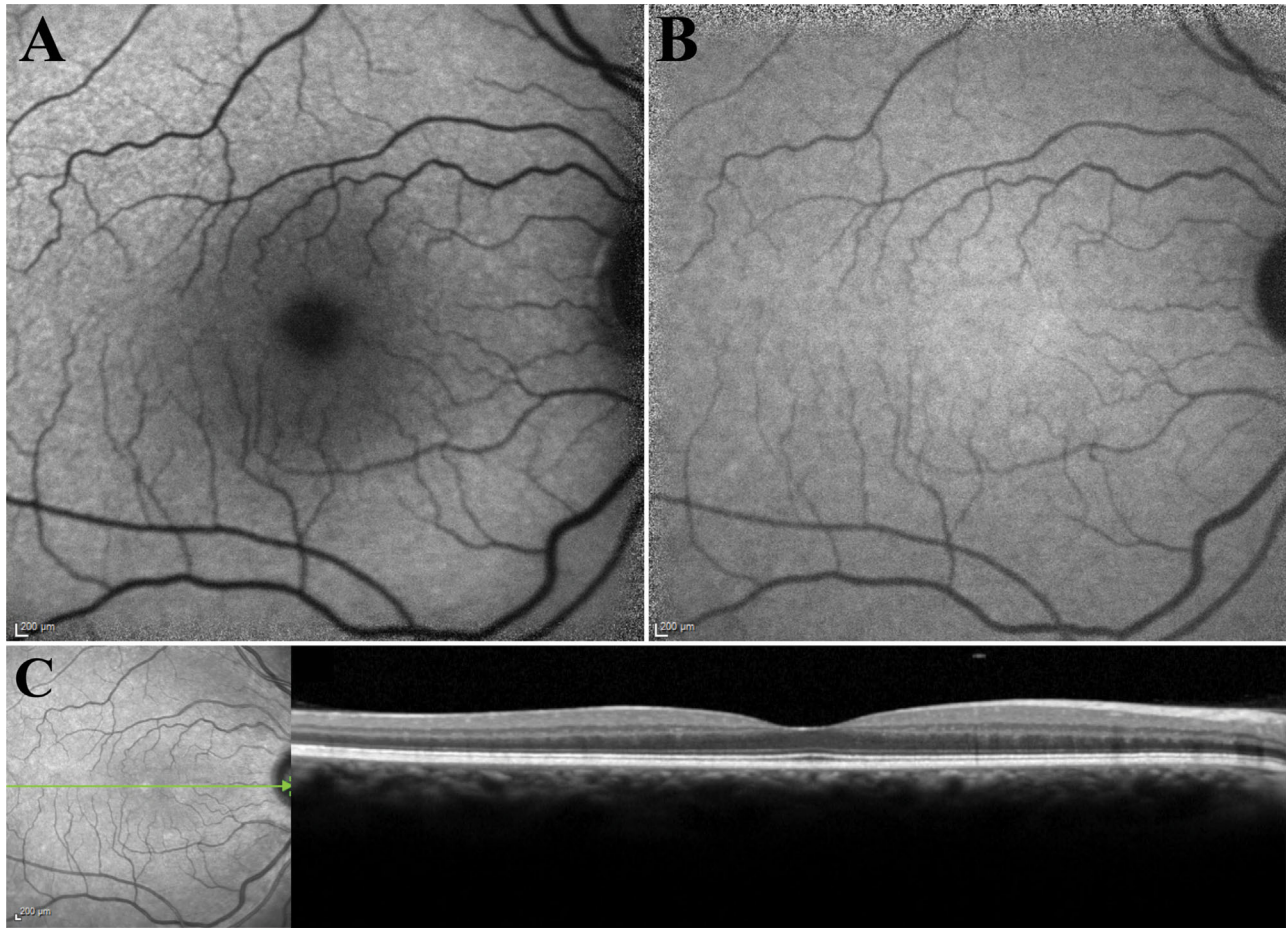
Figure 1. Normal multimodal imaging acquired from a 50-year-old woman treated with HCQ therapy for rheumatoid arthritis. SW-AF and NIR-AF imaging revealed a normal distribution of AF throughout the posterior pole, with typically reduced AF in the central macula in SW-AF images (A) and correspondingly high macular AF in NIR-AF images (B). SD-OCT revealed retinal layers with no abnormalities (C).

modalities, we used HVF testing as an ancillary modality. As such, those results were analyzed in conjunction with SD-OCT images to determine whether HVFs presented with abnormalities related to HCQ therapy, abnormalities equivocal for toxicity, or no abnormalities. Descriptive statistics are presented as mean ± standard deviation where appropriate.

Results

We analyzed a total of 88 eyes (44 patients) in this study. The average age of the cohort was 52 ± 20 years. Of the 44 patients, 41 were female (93%) and three were male (7%). The most common indication for HCQ therapy was SLE (18 patients), followed by rheumatoid arthritis (16 patients), and Sjögren's syndrome (four patients). The average treatment duration was 8 ± 6 years. When considering therapy-dependent risk factors for toxicity, 25 patients had a history of daily dosing > 5 mg/kg (57%), 16 patients had a therapy duration > 10 years (36%), and 21 patients had a total cumulative dose > 1000 g (48%). None of the patients presented with a medical history of kidney or liver dysfunction or tamoxifen use. Detailed demographic information and HCQ dosing history are summarized in the Table for all the patients in the cohort.

Sixty eyes (30 patients, 68%) presented with no abnormalities in any imaging modality (Fig. 1). In SW-AF images, a normal distribution of AF was observed, with low SW-AF intensity in the fovea consistent with the pattern in healthy eyes (Fig. 1A). Similarly, the distribution of NIR-AF, including a high AF intensity in the fovea, was consistent with the pattern observed in healthy eyes (Fig. 1B).[23] In SD-OCT scans, the retinal layers, including the EZ and IZ bands, were intact (Fig. 1C). HVF also revealed no abnormalities. When considering therapy-dependent risk factors for toxicity, nine patients had no risk factors (30%), 13 patients had

Table. Patient Demographics, Usage of Hydroxychloroquine, and Abnormalities in Structural Imaging and Functional Testing

ID	Sex	Age (y)	HCQ Indication	Daily Dose (mg)	Daily Dose/RBW (mg/kg)	Duration (y)	Total Dose (g)	Risk Factors for Toxicity			Abnormalities[a]		
								Daily Dose > 5 mg/kg	Duration > 10 y	Total dose > 1000 g	SW-AF	NIR-AF	SD-OCT
1	F	72	Lyme	400	6.8	1	146	X					
2	F	65	SLE	400	5.9	15	2190	X	X	X			
3	F	57	SLE	400	5.5	20	2920	X	X	X	X		X
4	F	78	RA	400	5.4	10	1460	X	X	X		X	X
5	F	53	SLE	400	4.4	13	1898		X	X			
6	F	33	Sjögren's syndrome	300	5.5	2	219	X					
7	M	22	SLE	400	4.8	7	1022			X			
8	F	70	Sjögren's syndrome	400 (200b)	7.4 (3.7b)	10 (10)	2190	X	X	X			X
9	F	10	Sjögren's syndrome	200	7.0	2	146	X					
10	F	75	RA	500	7.3	12	2190	X	X	X			X
11	F	42	MCTD	300	4.41	5	548						
12	F	57	SLE	400	4.8	3	438						
13	F	23	SLE	400	3.9	1	146						
14	F	16	Lyme	200	3.7	0.5	37						
15	F	48	RA	400	5.9	9	1314	X		X			
16	F	69	Sjögren's syndrome	400	5.3	8.5	1241	X		X			
17	F	53	SLE	100	1.5	7	256						
18	F	72	RA	400 (200b)	6.5 (3.3b)	16 (1)	2409	X	X	X			X
19	F	9	Polymyositis	100 (200b)	3.3 (6.7b)	2.67 (0.33)	122						
20	M	51	Psoriatic arthritis	400	5.8	9	1314	X		X			X
21	F	55	RA	200	2.9	0.2	15						
22	F	18	RA	200	4.2	5	365						X
23	F	50	SLE	400	7.2	10	1460	X	X	X			X
24	F	39	SLE	400	3.9	15	2190		X	X	X	X	X
25	F	71	RA	400 (200b)	6.8 (3.4b)	9 (4)	1606	X		X			X
26	F	35	SLE	400	6.8	8	1168	X		X			
27	F	49	SLE	400	4.4	5	730				X	X	X
28	F	45	RA	300	5.6	2	219	X					
29	F	58	Behçet's syndrome	200	4.2	7	511						
30	F	66	RA	400	6.4	14.5	2117	X	X	X			X
31	F	20	SLE	200	4.0	1	73						
32	F	52	SLE	400	8.9	10	1460	X	X	X	X	X	X
33	F	64	SLE	400	5.4	0.08	12	X					
34	M	86	RA	400	6.3	1	146	X					
35	F	80	SLE	200	1.9	20	1460		X	X			
36	F	68	SLE	300	4.9	3	329						
37	F	72	RA	100	1.4	26	949		X				
38	F	68	RA	450	6.5	10	1643	X	X	X			
39	F	67	RA	400	6.5	8	1168	X		X			X
40	F	74	RA	200	3.2	13	949		X				
41	F	43	RA	400	5.8	2	292	X					
42	F	23	SLE	400	7.9	2	292	X					
43	F	50	RA	400	4.6	7	1022			X			
44	F	34	SLE	200	3.7	12	876		X				

Given that all patients presented with bilateral abnormalities, we present this information in a per-patient manner. MCTD, mixed connective tissue disorder; RA, rheumatoid arthritis; RBW, real body weight.

[a] Image analyses were performed per eye.

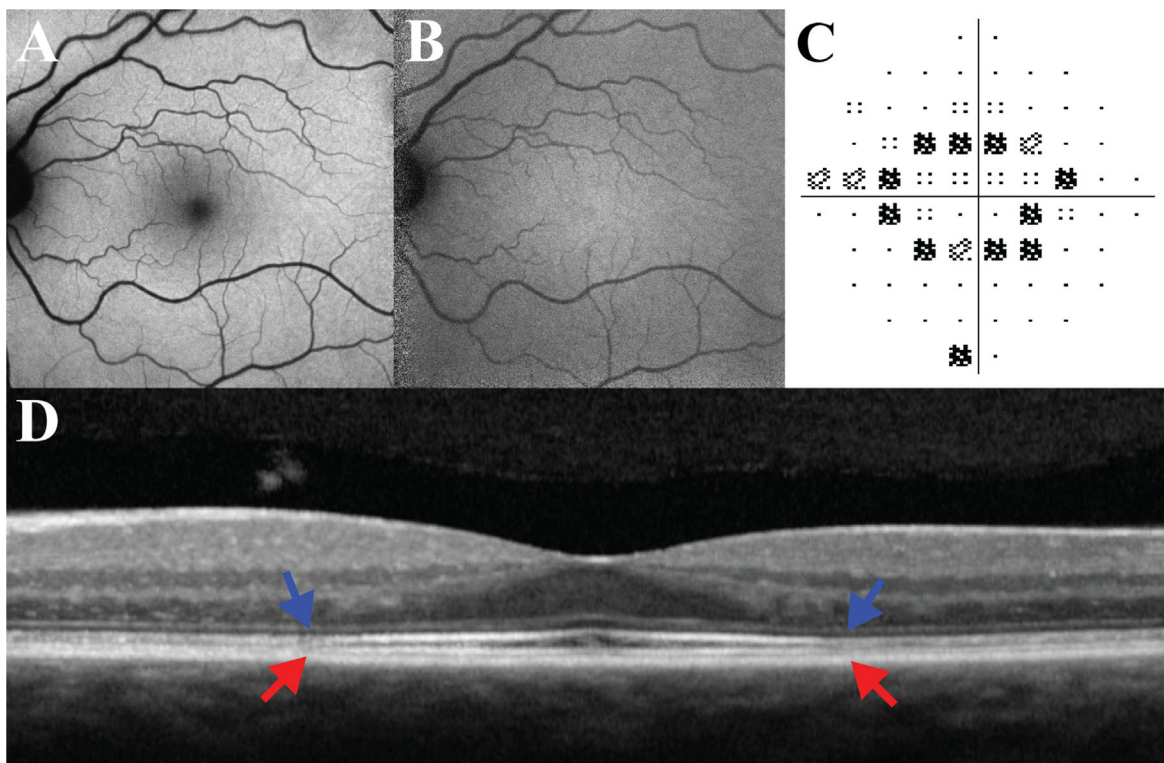[b] Denotes the current dose of HCQ that the patient was taking.

Figure 2. Multimodal imaging in patients with early changes in SD-OCT. SW-AF (A) and NIR-AF (B) imaging in patient 3 (P3) revealed no abnormalities. However, SD-OCT (D) revealed parafoveal shortening and loss of continuity of the IZ band (*red arrows*), and the EZ band (*blue arrows*) was also attenuated. Visual field testing revealed abnormalities in the shape of a ring scotoma in (C).

one risk factor (43%), six patients had two risk factors (20%), and two patients had all three (7%) (Table).

Twenty eyes (10 patients, 23%) presented with abnormalities in SD-OCT images, whereas SW-AF and NIR-AF images were unremarkable (Fig. 2). These abnormalities included attenuation of the EZ band and/or loss of continuity of the IZ band in a parafoveal location (Fig. 2D). From this subgroup of 20 eyes, eight eyes (four patients) presented with abnormalities in the form of a ring scotoma on HVF testing (Fig. 2C). The rest presented with either no abnormalities (four eyes from two patients) or abnormalities deemed equivocal (eight eyes from four patients) (Fig. 3). No eyes presented with normal SD-OCT scans and abnormalities in either SW-AF or NIR-AF images. One patient had no risk factors for toxicity (10%), one had one risk factor (10%), two had two risk factors (20%), and six had all three risk factors (60%) (Table).

Eight eyes (four patients, 9%) presented with abnormalities in all imaging modalities (Fig. 4). In both SW-AF and NIR-AF images, three of the four patients (patients 23, 27, and 32) exhibited overt bull's-eye maculopathy characterized by a parafoveal ring of hyperautofluorescence (hyperAF) that was surrounded by a pericentral area or arc of pronounced

hypoautofluorescence (hypoAF) in both modalities (Figs. 4A, 4B). In the remaining patient (patient 4), an early-stage bull's-eye phenotype was observed. In SD-OCT scans, the structures of the outer retina were significantly disrupted in the parafoveal region, including loss of the EZ and IZ bands, with conservation of the foveal area, creating the appearance of a "flying saucer" (Fig. 4D).[22] Three of these patients (4, 23, and 32) presented with three therapy-dependent risk factors for toxicity, and one patient (27) presented with no therapy-dependent risk factors (Table). On HVF testing, all patients presented with ring scotomas (Fig. 4C).

Discussion

SD-OCT is considered the first-line modality of choice for structural screening of HCQ toxicity, with abnormalities in functional testing usually being used to confirm that the SD-OCT changes are indicative of HCQ toxicity. We were thus interested in comparing SW-AF and NIR-AF imaging to SD-OCT scans. A previous study from Cukras et al.[15] used mfERG
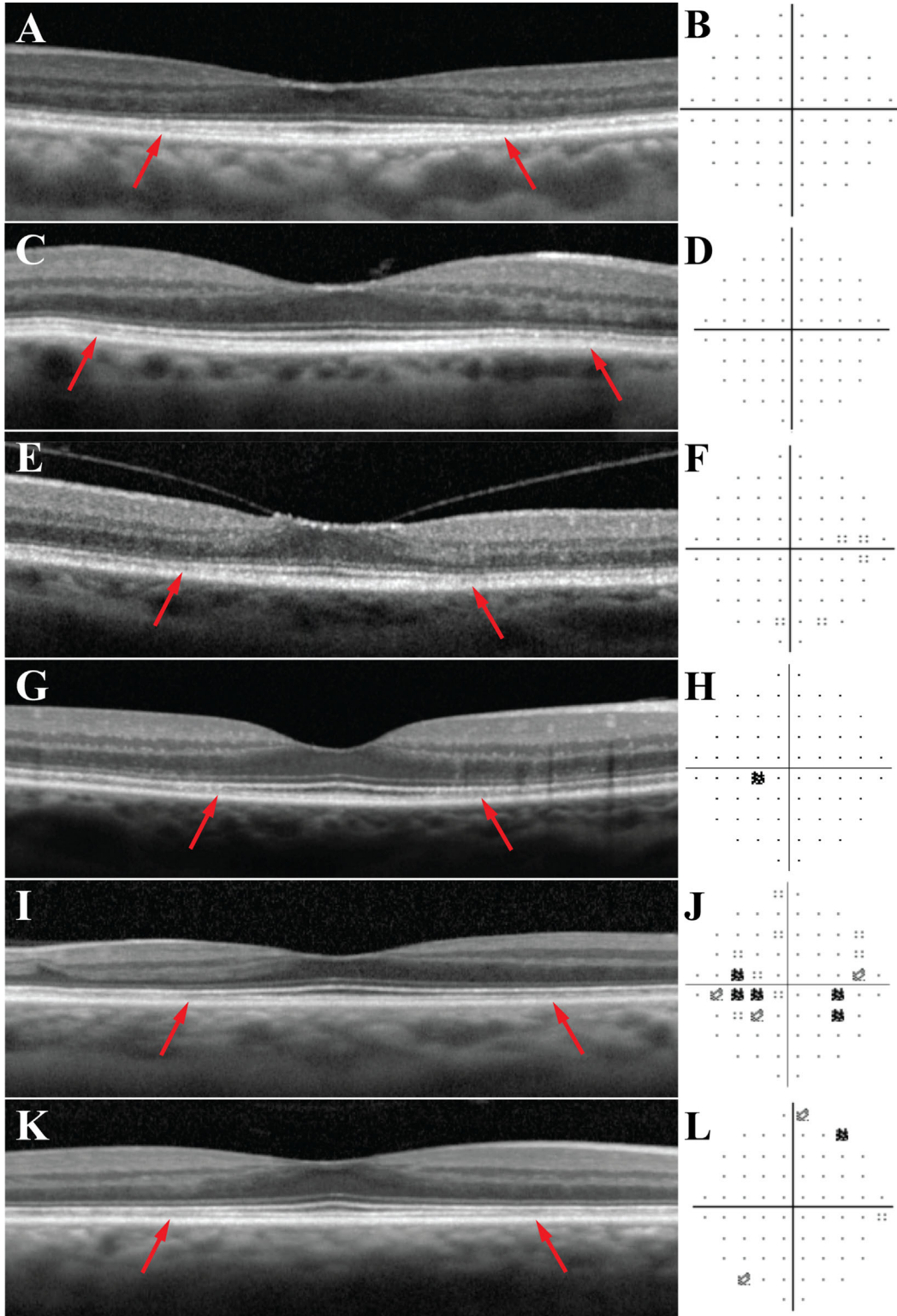
Figure 3. Patients with abnormalities noted in SD-OCT imaging. Six patients (A, B; C, D; E, F; G, H; I, J; K, L) presented with loss continuity of the IZ band (*red arrows*) in SD-OCT scans; yet, findings on visual field testing ranged from no abnormalities (B, D) to abnormalities deemed equivocal for toxicity (F, H, J, L).
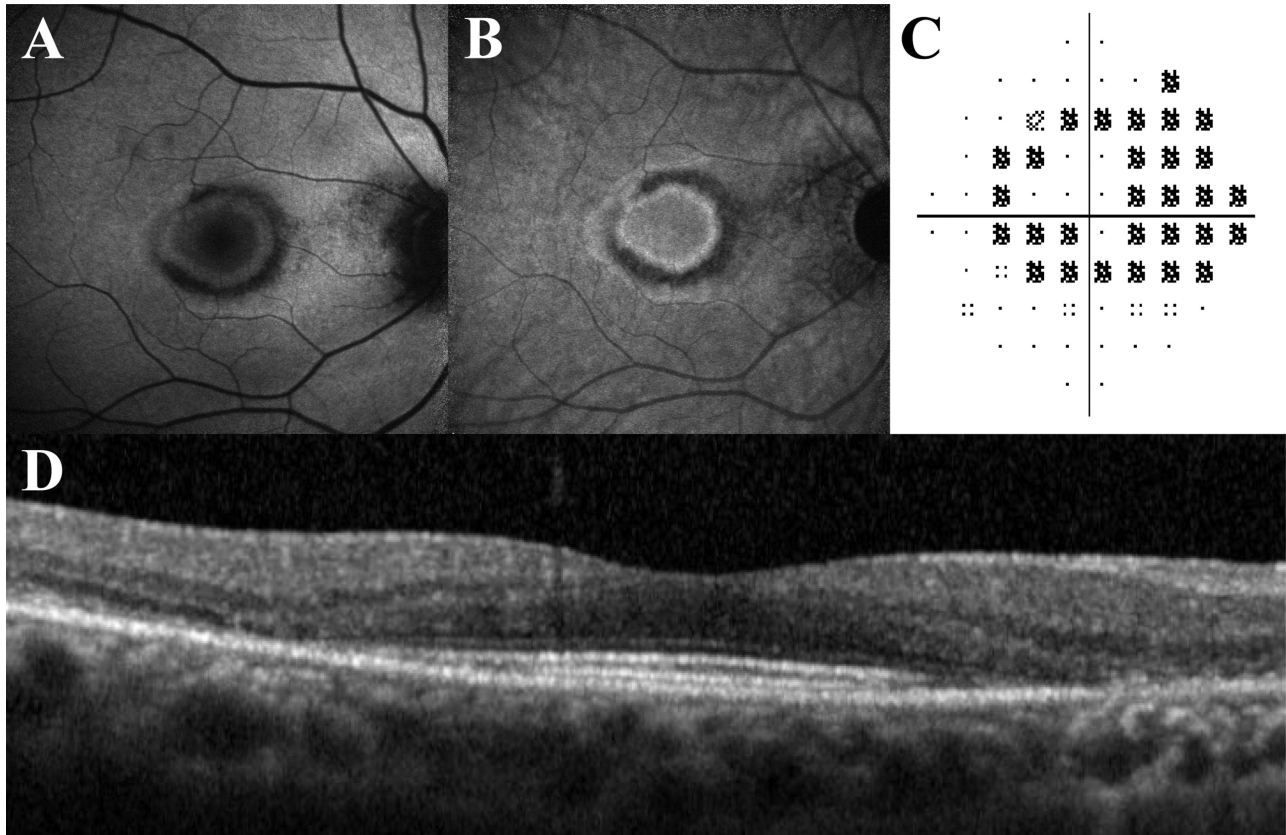
Figure 4. Multimodal imaging in a patient with HCQ retinopathy. Patient 23 (P23) was treated with 400 mg/day of HCQ for 10 years. SW-AF (A) and NIR-AF (B) imaging revealed normal patterns of AF centrally surrounded by a ring of hyperAF, which was surrounded by a region or ring of hypoAF (bull's-eye pattern). Visual field testing revealed a ring scotoma (C). On SD-OCT scans (D), the structures of the outer retina were noted to be significantly disrupted in a parafoveal manner, including loss of the EZ and IZ bands, with conservation of the fovea ("flying saucer" phenotype).

test results as reference and reported that SD-OCT and HVF showed clinically useful specificity and sensitivity for the detection of HCQ toxicity, but SW-AF did not. A study by Kellner et al.[24] correlated changes in SW-AF and NIR-AF imaging with those observed in SD-OCT scans in a cohort of eight long-term users of chloroquine. In a later study, Kellner et al.[25] also used both SW-AF and NIR-AF imaging in a study reporting the incidence of cystoid macular edema and epiretinal membrane formation after cessation of chloroquine/hydroxychloroquine treatment; progression of disease was also revealed with both imaging modalities. By studying a large cohort of patients, we found that 10 patients presented with early changes in the outer retinal layers in SD-OCT scans along with normal SW-AF and NIR-AF images. Our results suggest that, because SD-OCT is more sensitive in detecting structural abnormalities than either SW-AF or NIR-AF imaging, it is a superior imaging modality for screening patients for early retinopathy. Nevertheless, both SW-AF and NIR-AF play

an important role in HCQ imaging as modalities to monitor HCQ-mediated RPE damage.

The most significant risk to HCQ therapy is the potential for vision loss; thus, emphasis is placed on identifying the imaging modality that can provide the earliest detection of retinopathy. The AAO recommends SD-OCT imaging and HVF as primary initial tests,[9] with mfERG and SW-AF imaging being considered ancillary.[9] Results from multiple studies differ as to whether SD-OCT or HVF detects retinopathy the earliest. Some groups have reported HCQ-associated HVF changes in patients before SD-OCT abnormalities.[11–13] In addition, a study by Browning et al.[14] analyzed the sensitivity and specificity of SD-OCT, HVF, and mfERG in detecting retinopathy, and they reported SD-OCT to be the most specific but least sensitive. Yet, a recent study by Garrity et al.[10] reported that patients may develop early SD-OCT abnormalities despite normal HVFs. These abnormalities included parafoveal attenuation of the EZ band and/or loss of a continuous IZ band.[10]

Ten of our patients presented with such abnormalities, and of this subgroup, two presented with no abnormalities in HVF, four presented with equivocal abnormalities, and four presented with visual field abnormalities resembling ring scotomas. Although we cannot definitely conclude that abnormalities in SD-OCT always precede HVF changes without a prospective follow-up of patients, our cohort demonstrates that abnormalities in SD-OCT scans can be observed before they appear in HVF testing.

Not only is HCQ an essential drug in the treatment of rheumatological diseases, but its use has also expanded to other fields such as dermatology and oncology.[26–30] As the use of HCQ therapy has expanded, the development of toxicity has also increased. The guidelines set by the AAO recommend a daily dose less than 5 mg/kg of real body weight.[9] Yet, some studies have reported a large number of patients whose therapy has exceeded this dose. A recent study by Sandhu et al.[31] analyzed a group of 138 SLE patients taking HCQ and reported that 41% exceeded the recommended maximum dose. A similar study by Wallace et al.[32] reported that, in 2696 SLE patients, 26% were on exceeding doses. From the 44 patients we analyzed in this study, 25 were taking a higher dose than recommended (57%), and 11 of these 25 presented with HCQ-associated structural abnormalities in fundus images (44%). Physicians involved in the care of patients taking HCQ should be alert to dosages greater than 5 mg/kg, which are especially common for non-rheumatological diseases. These diseases often require high dosages, and cases from the literature have presented rapid-onset retinopathy associated with high-dosage HCQ therapy for cancer and graft-versus-host disease.[29,33] Treatment duration greater than 10 years poses a significant risk factor for toxicity, and, even if treatment is kept at recommended dosages, there is a 20% risk of toxicity after 20 years.[8–10] Among our 44 patients, 16 patients had received HCQ therapy for longer than 10 years (36%), and nine of these patients presented with structural abnormalities (56%).

Our study presents some limitations. The cross-sectional design allowed for characterization of the patients' images at a single clinic visit, but longitudinal follow-up would be necessary to potentially observe the development of these early SD-OCT abnormalities into the "flying saucer" phenotype. Furthermore, longitudinal data are necessary for the correlation of these early SD-OCT abnormalities and their temporal appearance in SW-AF and NIR-AF images. The qualitative nature of the study could also be seen as a limitation, as attenuation of layers can sometimes be observed independent of pathology, such as in poor-quality SD-OCT scans. Future studies with longitudinal follow-up of these early lesions should provide greater temporal insight and allow for accurate assessment of quantitative markers of toxicity. Another limitation is the lack of mfERG data in this study, as such data could help complement the presented HVFs in the characterization of the patients that presented with abnormalities only on SD-OCT imaging. Despite these limitations, we believe that it is essential for practitioners to be aware that SD-OCT is more sensitive in detecting these early abnormalities than either SW-AF or NIR-AF images.

In conclusion, our findings suggest the greater sensitivity of SD-OCT scans in detecting early HCQ-related abnormalities compared to both SW-AF and NIR-AF imaging. Thus, SD-OCT should be the preferred first-line, objective structural screening modality for HCQ-associated retinopathy. Both SW-AF and NIR-AF imaging effectively demonstrate the topography of HCQ-associated RPE damage.

Acknowledgments

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