SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY AND ADAPTIVE OPTICS MAY DETECT HYDROXYCHLOROQUINE RETINAL TOXICITY BEFORE SYMPTOMATIC VISION LOSS

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ABSTRACT

Purpose: To describe spectral-domain optical coherence tomography (SD-OCT) and adaptive optics (AO) imaging in hydroxychloroquine retinal toxicity.

Methods: Two patients with long-term hydroxychloroquine use, subtle perifoveal ophthalmoscopic pigmentary changes, and bilateral perifoveal defects on automated Humphrey visual field (HVF) 10-2 perimetry were imaged using SD-OCT and AO.

Results: SD-OCT images demonstrated loss of photoreceptor inner segment/outer segment (IS/OS) junction and a downward "sink-hole" displacement of inner retinal structures in areas of hydroxychloroquine toxicity corresponding to HVF 10-2 defects and ophthalmoscopic clinical examination findings. SD-OCT irregularities in the IS/OS junction were also seen in areas not detected on HVF 10-2. AO images showed disruption of the cone photoreceptor mosaic in areas corresponding to HVF 10-2 defects and SD-OCT IS/OS junction abnormalities. Additionally, irregularities in the cone photoreceptor density and mosaic were seen in areas with normal HVF 10-2 and SD-OCT findings.

Conclusions: SD-OCT and AO detected abnormalities that correlate topographically with visual field loss from hydroxychloroquine toxicity as demonstrated by HVF 10-2 and may be useful in the detection of subclinical abnormalities that precede symptoms or objective visual field loss.

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INTRODUCTION

Hydroxychloroquine sulfate (Plaquenil; Sanofi-Aventis, Bridgewater, New Jersey) is an antimalarial drug used extensively in treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. Retinal toxicity that may be irreversible[1,2] can develop in some individuals who take hydroxychloroquine, especially when higher-risk criteria are present. Even after the drug is discontinued, retinal degeneration from hydroxychloroquine can continue to progress. For this reason, ophthalmic screening of patients is recommended to detect early retinopathy and discontinue the therapy.

Through the years, multiple modalities have been advocated for screening of hydroxychloroquine retinopathy.[3-8] In response to a diversity of recommended screening regimens, the American Academy of Ophthalmology published preferred practice patterns (PPPs) for hydroxychloroquine retinopathy screening in 2002.[9] These PPPs are based on stratifying risk of retinopathy in a patient based on multiple criteria. A baseline examination is recommended at the beginning of treatment. In low-risk patients in the first 5 years of treatment, screening should be done only as a component of normal ophthalmic examinations. High-risk patients should be screened annually. High-risk criteria consist of any of the following: (1) daily dose exceeding 6.5 mg/kg, (2) greater than 5 years duration of treatment, (3) high body mass index, (4) age 60 years or older, (5) renal or hepatic disease that may impair drug metabolism or excretion, and (6) concurrent retinal disease.[10] Screening examinations for hydroxychloroquine retinopathy as recommended by the PPPs should include a comprehensive ophthalmic examination with either Amsler grid testing or Humphrey visual field (HVF) 10-2 perimetry (Carl Zeiss Meditec Inc, Dublin, California) testing. Other optional testing, including color vision testing, fundus photography, fluorescein angiography, electroretinography, and multifocal electroretinography (mERG), is left to the discretion of the screening clinician.[10]

Ideally, screening for retinopathy would be quick, noninvasive, and very sensitive and specific for detecting early hydroxychloroquine toxicity. New innovations in ocular imaging now allow for unprecedented views of retinal architecture to within microns. Recent advances in spectral-domain optical coherence tomography (SD-OCT) allow for cross-sectional imaging of the retina in vivo to resolutions of 5 to 10 μm.[11-16] Adaptive optics (AO) imaging corrects for ocular aberrations and allows for direct visualization of the photoreceptor mosaic in vivo to resolutions of ≤2 μm.[17-20] This report presents the results of SD-OCT and AO imaging on two patients with known hydroxychloroquine retinopathy.

METHODS

Two female patients with known hydroxychloroquine retinopathy were imaged using SD-OCT and AO imaging. Both patients were referred to the retina service for abnormal HVF 10-2 perimetry findings on hydroxychloroquine screening eye examinations. Comprehensive ophthalmic examinations, fundus photography, and mERG were performed, and both patients were diagnosed as having hydroxychloroquine retinopathy. Prior to SD-OCT and AO imaging, both patients provided informed consent. All research adhered to the tenets of the Declaration of Helsinki, and the study protocol was approved by the Children's Hospital of Wisconsin Institutional Review Board.

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Patient 1 was a 57-year-old woman who had been taking hydroxychloroquine, 400 mg daily, for 20 years at a dose of 6.15 mg/kg per day for systemic lupus erythematosus. She was asymptomatic and denied having red Amsler grid changes. Visual acuity was 20/20 in both eyes. On examination she had subtle perifoveal pigmentary changes in both eyes inferonasal to the fovea. HVF 10-2 showed a paracentral scotoma most apparent superotemporally in both eyes.

Patient 2 was a 61-year-old woman who had been taking hydroxychloroquine, 400 mg daily, for 16 years at a dose of approximately 8 mg/kg per day for Sjögren syndrome. She recently had lost about 10 pounds. Over the last year she had noted more difficulties with seeing. Visual acuity was 20/20 in both eyes. Clinical examination was remarkable for a distinct rim of depigmentation inferiorly in the perifoveal region of both eyes and other granular changes in the paracentral region. HVF 10-2 showed distinct paracentral scotomas most dense superiorly in both eyes.

Spectral domain imaging was performed using both the Spectralis SD-OCT (Heidelberg Engineering, Vista, California) and a Bioptigen SD-OCT (Bioptigen Inc, Durham, North Carolina). For Bioptigen SD-OCT, images were acquired and processed as follows. Each image was 6 or 7 mm in length, and B-scans were composed of 1,000 A-scans. One hundred B-scans were obtained in each scan set. Scan sets were then directly exported from the SD-OCT machine and read into ImageJ (http://rsb.info.nih.gov/ij/) for processing. Frames that were distorted on account of large saccades or eye blinks were removed. A rigid body registration using the ImageJ plug-in "StackReg" was applied to generate a stabilized frame sequence for subsequent averaging, and the scan length was calibrated by correcting for the patient's axial length as measured by a Zeiss IOLMaster (Carl Zeiss Meditec Inc, Dublin, California).

Images of the photoreceptor mosaic were obtained using a newly developed AO ophthalmoscope housed at the Medical College of Wisconsin, Milwaukee. Each patient's head was stabilized using a dental impression on a bite bar, and both eyes were dilated and cyclopleged using a combination of phenylephrine hydrochloride 2.5% and tropicamide 1%. In a continuous closed-loop fashion, the eyes' monochromatic aberrations were measured over a 6.8-mm pupil with a Shack-Hartmann wavefront sensor and corrected for by using a 52-channel deformable mirror (Imagine Eyes, Orsay, France). A fiber-coupled near infrared source was used for imaging, which consisted of a 200-mW SLD (superluminescent diode; center wavelength of 837.8 nm and 14.1-nm spectral bandwidth FWHM [full width at half maximum]) and 110 m of multimode step index fiber (Fiberguide Industries, Stirling, New Jersey) to eliminate speckle noise of images.[21] The patient was then instructed to fixate on a calibrated fixation light that could be translated to image different parts of the macula. Each imaging flash was 500 milliseconds, and the retinal image sequence that was available for processing consisted of 40 frames (6 milliseconds exposure per frame). The pattern of the retinal vasculature was used to confirm the image location, and the acquired images were 1.8° × 0.9°. Individual frames from each image sequence were registered and averaged using custom Matlab software (The MathWorks, Natick, Massachusetts).

RESULTS

SD-OCT images of all four eyes revealed abnormalities in the outer retina corresponding to areas of hydroxychloroquine retinopathy as identified by clinical funduscopic findings and HVF 10-2 defects. These changes included complete loss of the photoreceptor inner segment/outer segment (IS/OS) junction with relative preservation of the retinal pigment epithelium (RPE) and external limiting membrane and downward displacement, or "sink-hole effect," of overlying inner retina layers in perifoveal areas corresponding to HVF 10-2 defects and ophthalmoscopic clinical examination findings (Figure 1). Additionally, outer retinal changes with a "moth-eaten" appearance to the photoreceptor IS/OS layer but with preservation of inner retinal layers were also identified in areas in which HVF 10-2 appeared normal (Figure 2). Central foveal architecture was preserved in both patients.

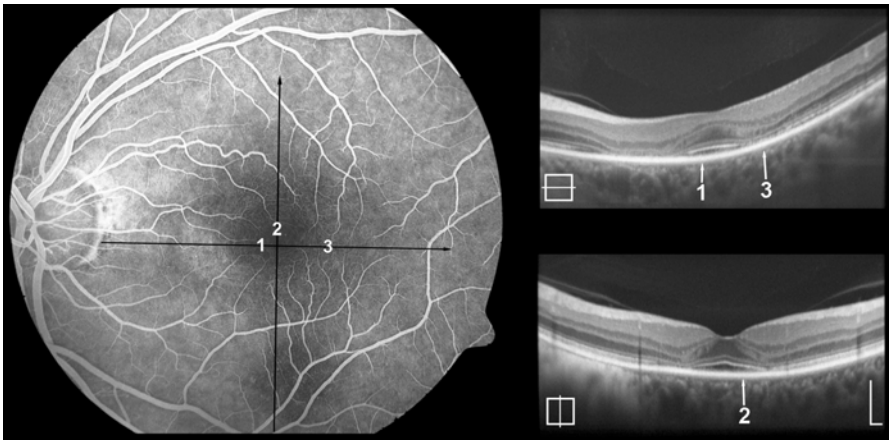

FIGURE 1

Patient 1. Fluorescein angiogram (FA) and Bioptigen SD-OCT images of left eye. SD-OCT images are registered onto FA fundus photo. Upper SD-OCT image is the horizontal scan, and the lower SD-OCT image is the vertical scan. Numbers 1, 2, and 3 on the fundus photo represent locations where adaptive optics imaging was done. These same locations are also registered on the SD-OCT images. SD-OCT images show loss of photoreceptor inner segment/outer segment junctions and a "sink-hole" effect of the inner retinal structures in the perifoveal area.

AO images were taken at precise locations in the perifoveal area and registered to fundus images and SD-OCT images. Patient 1 had both eyes imaged. Patient 2 had the right eye imaged.

In patient 1, AO images were taken in the right eye 2° nasal to the fovea in an area that corresponded to the margin where outer segment photoreceptor IS/OS abnormalities were identified on SD-OCT. AO images confirmed there was a dramatic disruption of the cone mosaic in this location.

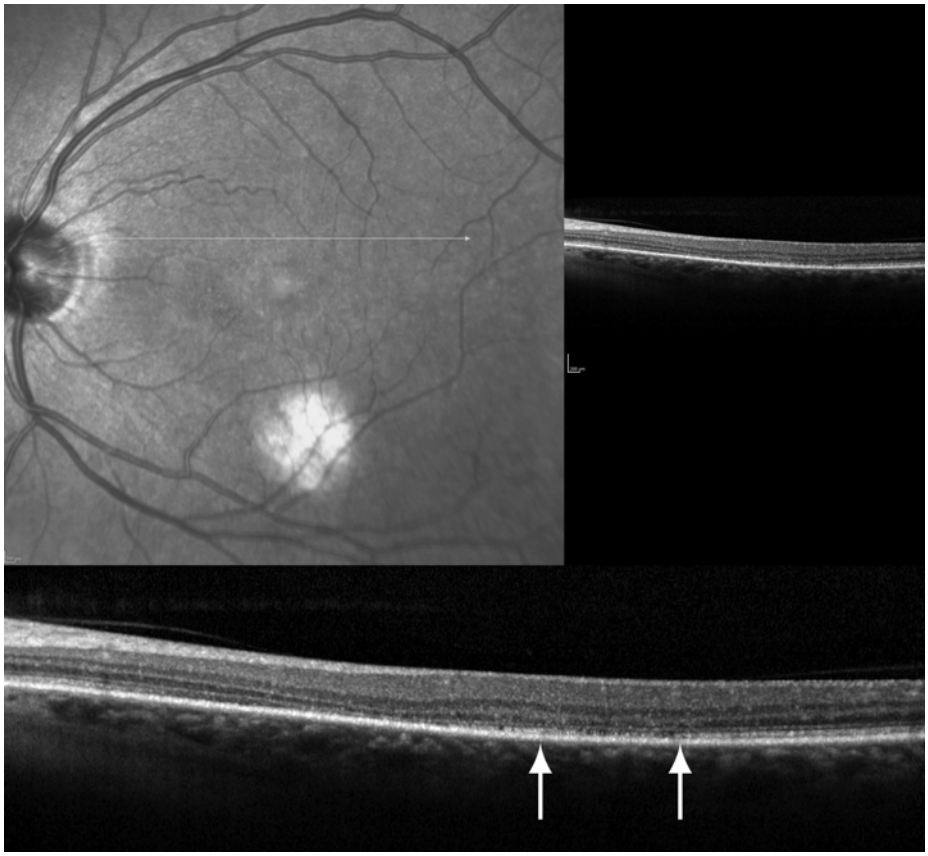

FIGURE 2

Patient 1. Spectralis SD-OCT of left eye. Area of "moth-eaten" photoreceptor inner segment/outer segment abnormalities can be seen between the arrows in an area that appeared normal on funduscopic examination and Humphrey visual field (HVF) 10-2.

In the left eye of patient 1, three different areas were imaged by AO (Figures 1 and 3). Location 1 in Figure 1 is 1° nasal to the fovea. Photoreceptor spacing at this location is 0.881 ± 0.12 minutes of an arc (arc min) (mean ± 1 SD), which is normal[18] (Figure 3A). Corresponding SD-OCT photoreceptor IS/OS findings also appear normal at this location (Figure 1).

Location 2 in Figure 1 is 0.75° superior to the fovea. Outer retinal photoreceptor IS/OS findings appear normal on SD-OCT at this location. AO images show that the cone mosaic has patches of contiguousness (Figure 3D); however, the cone spacing in this area is 1.10 ± 0.15 arc min (mean ± 1 SD). The average spacing for normal retinas at this retinal eccentricity is approximately 0.8 arc min.[18] The photoreceptor spacing at this location falls more than 2 SDs from the mean of normative cone data obtained from histological samples.[22] : Increased photoreceptor spacing indicates less photoreceptors are present.

Location 3 in Figure 1 is 3° temporal to the fovea in an area of photoreceptor IS/OS "moth-eaten" appearance as seen on SD-OCT and borderline HVF 10-2 abnormalities. The photoreceptor spacing was 0.727 ± 0.13 arc min (mean ± 1 SD). Normal cone spacing at this location is about 1.5 arc min.[18] If completely packed, this cone spacing would correspond to a cone density of about 23,000 cones/mm^2, whereas a spacing of 0.727 arc min would correspond to a cell spacing of 98,000 cells/mm^2 (Figure 3B and C) This increased density suggests that structures imaged are actually rod photoreceptors.

Patient 2 had AO images at a location 2° temporal to the fovea. SD-OCT images at this location show that this is right at the margin of outer retinal photoreceptor IS/OS abnormalities. AO images at this area show an irregular, disrupted, patchy cone mosaic with areas of intermittent, near normal cone spacing in some areas. Cone spacing in this area was 1.13 ± 0.15 arc min (mean ± 1 SD) with normal retinal spacing in this area being 1.2 arc min,[18] indicating that spacing in this individual at this location is within the normal range.

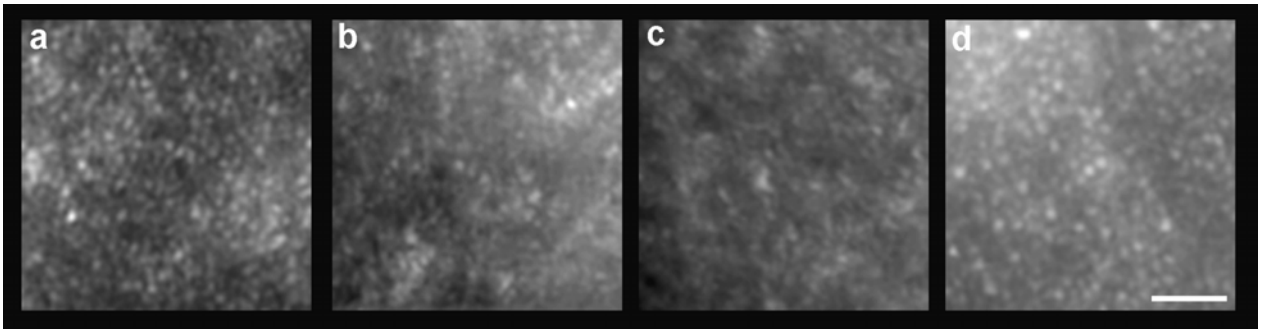

FIGURE 3

Adaptive optics (AO) images taken at locations 1, 2, and 3 as shown in Figure 1. A, Location 1 is 1° nasal to the fovea. Normal cone mosaic and normal cone spacing are seen. B and C, Location 3 is 3° temporal to the fovea. Photoreceptor spacing is 0.727 ± 0.13 arc min (mean ± 1 SD), which is decreased. Normal cone spacing is approximately 1.5 arc min at this location.[18] D, Location 2 is 0.75° superior to the fovea. Cone mosaic shows patches on contiguousness. Cone spacing is 1.10 ± 0.15 arc min (mean ± 1 SD), which is increased. Normal cone spacing is approximately 0.8 arc min at this location.[18]

DISCUSSION

In the two patients described here, SD-OCT and AO imaging detected abnormalities from hydroxychloroquine retinopathy that correlate topographically with clinical funduscopic findings and visual field loss as demonstrated by HVF 10-2 perimetry. SD-OCT images showed complete loss of the photoreceptor IS/OS junction with relative preservation of the RPE and external limiting membrane as previously described by Rodriguez-Padilla and colleagues[23]; however, our SD-OCT images were acquired on two different commercially available SD-OCT machines instead of a research prototype. Additionally, our SD-OCT images reveal a distinct downward displacement, or "sink-hole effect," of inner retina layers in areas overlying outer retinal abnormalities. Areas of outer retinal loss were very precise and localized to areas of toxicity in perifoveal areas corresponding to HVF 10-2 defects and ophthalmoscopic clinical examination findings. Adaptive optics images from an area with hydroxychloroquine retinopathy as seen both clinically and with HVF 10-2 defects showed disruption of the normal cone mosaic and quantitative alterations in cone packing.

SD-OCT and AO imaging also exhibited abnormalities in areas that appeared unaffected on HVF 10-2 and clinical funduscopic examination. These changes may represent a potential "preclinical" state of hydroxychloroquine toxicity. The exact mechanism of hydroxychloroquine retinal toxicity is not fully understood. Animal studies have shown that the first evidence of toxicity with chloroquine is seen in the retinal ganglion cells.[24] However, histology has shown that perifoveal photoreceptor cells are most severely affected[25] and that this may be a secondary effect due to disruption of RPE metabolism. Chloroquine and hydroxychloroquine are known to disrupt lysosomal function of the RPE, leading to increased accumulation of lipofuscin.[26,27] Daily phagocystosis of photoreceptor outer segments occurs in the lysosomal apparatus of the RPE, and alterations in RPE metabolism may play a role in retinal toxicity.[26,27] Mahon and associates[27] also found an apparent accumulation of autophagic granules in cone photoreceptor cells exposed to chloroquine in an animal model. Rod photoreceptors did not show these granules, and the investigators hypothesize that this defective degradative capacity that appears more predominant in cone photoreceptors could also play a role in toxicity. Given this information, it makes sense that early toxicity would present with subtle changes in the photoreceptor mosaic, and that this would precede the dramatic loss of outer retinal structures seen with more severe hydroxychloroquine retinopathy. Evidence of a defective degradative capacity in cones may also suggest that they are preferentially affected more than rod photoreceptors, and this may be apparent even in early stages of toxicity.

In areas that appeared unaffected by funduscopic examination and with no visual field defects as seen on automated perimetry, our SD-OCT imaging showed areas of a characteristic "moth-eaten" appearance in the photoreceptor IS/OS layer with preservation of inner retina architecture (eg, Figure 1, location 3). AO imaging done at this same location (Figure 3B and C) showed a decrease in photoreceptor spacing, indicating an increased density of photoreceptor cells of approximately 98,000 cells/mm^2. Normal cone density in this location is approximately 23,000 cones/mm^2, making it more likely that most photoreceptors imaged at this location are rod photoreceptors instead of the cone photoreceptors. Densities calculated from AO imaging are similar to histological samples of normative rod photoreceptor data at this retinal eccentricity.[22] This suggests that cone photoreceptors are missing or significantly diminished in number at this location and also that cone photoreceptors may be more susceptible to plaquenil toxicity than rod photoreceptors. This decrease of cone photoreceptors may be responsible for the "moth-eaten" photoreceptor IS/OS appearance seen on SD-OCT. These areas likely represent a "preclinical" stage of hydroxychloroquine retinopathy that with time will develop a severe loss of outer retinal structures and become apparent on clinical examination and visual field testing.

Adaptive optics imaging may also be more sensitive than SD-OCT in identifying these "preclinical" areas of retinal toxicity. In AO images taken at location 2 in the left eye of patient 1, the cone mosaic had patches of contiguousness, but cone spacing was increased to 1.10 ± 0.15 arc min (mean ± 1 SD). Average cone spacing at this retina eccentricity is approximately 0.8 arc min.[18]

Increased cone spacing indicates a reduced density of photoreceptors at this location. The photoreceptor spacing at this location also falls more than 2 SDs from the mean of normative cone data obtained from histological samples.[22] This suggests that the structures imaged are morphologically compromised swollen cones or that the overall number of cone photoreceptors in this location is decreased. This may represent the first signs of hydroxychloroquine toxicity with cone photoreceptor dropout. SD-OCT images were normal at this location.

Current screening methods for hydroxychloroquine retinopathy are limited in that they detect toxicity only after retinal damage has occurred as seen on funduscopic abnormalities and visual field defects. Furthermore, funduscopic changes can be subtle and tend to be a late finding, Amsler grid testing is highly subjective, and automated perimetry can show a steep learning curve. Recently mERG has been shown to be abnormal in hydroxychloroquine retinopathy, and it may be able to detect subtle changes in earlier stages of toxicity.[28-30] However, mERG is limited by clinical availability, patient cooperation, specialized training for administration and interpretation, and cost.

This study has shown that both SD-OCT and AO imaging are able to demonstrate abnormalities in the outer retina in hydroxychloroquine retinopathy. Furthermore, both SD-OCT and AO may be able to detect abnormalities at an early, "preclinical" stage of hydroxychloroquine toxicity. Obvious limitations of the study include its small sample size and its retrospective nature that allows one to look for abnormalities that may or may not be attributed to hydroxychloroquine. That being said, the noninvasive, amazing resolution and quantitative aspects of SD-OCT and AO imaging make them attractive as possible screening options for hydroxychloroquine toxicity. SD-OCT machines are becoming more common in clinical settings, and AO imaging development will likely result in a clinical model soon. These modalities may prove to be useful and effective tools for hydroxychloroquine retinal toxicity screening. Further research is needed.

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Author Contributions: *Design and conduct of the study* (K.S., J.C.); *Collection and management of data* (K.S., D.H., J.C., J.R., P.G., J.S.); *Analysis of data* (K.S., J.C., P.G., J.S.); *Preparation and review of manuscript* (K.S., D.H., J.C., J.R., P.G., J.S.).

Conformity With Author Information: All research adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the Children's Hospital of Wisconsin Institutional Review Board.

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PEER DISCUSSION

DR. T. MICHAEL NORK: Recently we have seen impressive advances in fundus imaging. However, it appears that this is only the beginning of an exciting new era. In 1999 Roorda and Williams reported on the stunning capabilities of adaptive optics.[1] Since then, several laboratories around the world have built their own systems. Optical coherence tomography (OCT) is also advancing rapidly. Spectral domain (SD) OCTs are now common in clinical practice and latest generation of laboratory OCTs are capable of resolving individual photoreceptors.

The paper by Dr. Stepien and coworkers illustrates the promise of these new technologies. Hydroxychloroquine is a highly effective drug used for the chronic treatment of certain autoimmune diseases. Initially, there are few ocular side effects, but with time the drug causes retinal toxicity—especially to the perifoveal photoreceptors. Unfortunately, because there are no early signs or symptoms, irreversible damage may occur before the drug is discontinued. Bernstein and Ginsberg [2] described the histopathologic findings in a patient with advanced chloroquine retinopathy, which are qualitatively similar in appearance to the SD-OCT scans of the patients in current paper.

Rodriguez-Padilla and associates[3] previously reported outer retinal injury using a research OCT. However, the present study, although limited to 2 patients, uses commercially available SD-OCTs and adds the results of adaptive optics. Of particular note is that both the SD-OCTs and adaptive optics were able to identify early photoreceptor defects even in regions of normal visual field testing.

Another relatively new method for detecting early hydroxychloroquine retinopathy is the multifocal electroretinogram (mfERG). This functional test of the retina shows a characteristic ring of depressed responses in the perifoveal region in early retinopathy. Stepien and colleagues note that mfERG testing was performed on their patients. However they do not discuss the results of this testing in their paper.

After struggling for years to diagnose early hydroxychloroquine toxicity, clinicians now have several testing modalities available to them. Future studies comparing the costs and benefits of each of these tests will be important in this era of increasing fiscal constraints. For example, only the mfERG gives an objective measure of retinal function. Yet, mfERG testing is relatively expensive

and available at only a few large centers. It may turn out that the new morphologic measures, such as the SD-OCT, will give clinicians all of the information they need to recommend continuing or stopping this important medication.

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DR. ALLAN J. FLACH: I also enjoyed your paper very much. I have no disclosures of vested interest. Would you please describe for us your multifocal ERG results that were mentioned? In addition, one of the biggest problems at least I have with patients on hydroxychloroquine is that if they have a little bit of macular degeneration, then I cannot figure out a way to pickup toxicity or the possibility thereof in those patients. Many of my retinal colleagues cannot determine possible toxicity, either. Does your technology offer us a little hope for these macular degeneration patients to whom I must say, "I just can't follow you".

DR. DOUGLAS R. ANDERSON: I disclose that I am a consultant for Carl Zeiss Meditech, which has no impact on my question about whether the findings of some of these tests might be found in all people who are taking the drug - - those are going to develop visual problems and those who are not. Or, does the finding such as this mean that it is going to progress into a visually significant problem? Also, noting for example, that your findings were in the normal areas the retina that had not degenerated yet, are those areas ones that you would expect might degenerate? With regard to cost effectiveness, what is the actual incidence of visual deficits with this drug and how many people would you have to test in order to find one person who was about to become visually affected?

DR. SEAN P. DONAHUE: I have no conflicts. I have always wondered why patients with hydroxychloroquine toxicity develop a little ring scotoma, 21/2 to3 degrees out and what would be the mechanism by which those cells would be most selectively damaged. I believe there is an alternative hypothesis here. The cones are being universally damaged and that you have a relatively reduced redundancy there and so it produces what looks like a scotoma in that location, which is really a full field depression. I wonder if you are going to have any thoughts on that possibility from a mechanistic viewpoint?

DR. ARTHUR JAMPOLSKY: No conflicts. Very nice paper. I wonder if you have compared your results to the normal naso-temporal retinal dominance differences in physiology, and the upper-lower retinal differences, the upper retina being far superior to the lower retina. It would seem to me that the findings that you already have may contain additional interesting dominance differences, particularly the upper retina compared to the lower.

DR. KIMBERLY E. STEPIEN: Thank you very much for the questions. First, both patients did have multifocal ERGs done and, as one would expect in people who do have hydroxychloroquine retinopathy, the multifocal ERGs did show deficits. Patients with both plaquenil use and macular degeneration are challenging. The SD-OCT of these two patients with hydroxychloroquine retinopathy showed the dropout of the outer retina layers. We can sometimes see similar changes in macular degeneration, but it would be very interesting to study patients with macular degeneration and hydroxychloroquine to determine if there is a distinct abnormality we could attribute specifically to hydroxychloroqine toxicity. Unfortunately, our patient sample here of two patients is very small and we cannot answer this definitively, but we hope to look into this a little more into the future. The estimated percent of patients on hydroxychloroquine who do develop retinopathy is about 0.5%, so obviously we do have to study many more patients. However, our data and some of the multifocal ERG data suggests that toxicity probably starts at an earlier stage and we may be able to see this toxicity earlier using adaptive optics and SD-OCT. If we can identify the toxicity that does not necessarily mean that we must change the treatment regimen. For many patients, being on plaquenil is a life altering therapy that allows them to enjoy a high quality of life. I believe that having a test would give us a better direction in how often we need to screen these patients and to determine if they are developing changes that would influence the decision of when to stop plaquenil.

In response to the question of why we see toxicity changes in the perifoveal area, I agree our data suggest that perhaps the cones are more significantly affected and the cone density is very high in the region where the retinopathy is found. It makes sense that we would see abnormal changes from hydroxychloroquine toxicity both on the adaptive optics and SD-OCT in these regions with high cone density where retinopathy develops.

Lastly, to address comparing this information to normative data, we are lucky that we have the normative adaptive optics data of Dr. Duncan that gives us the normal cone average spacing in areas surrounding the fovea. We are able to compare our adaptive optics cone spacing data found in our two patients with hydroxychloroquine toxicity to normative data and to indeed show cone spacing abnormalities. Although we did not perform this examination, it would be interesting to compare different parafoveal regions in the same eye. This may give us more information on the timing and locations of the earliest toxicity changes. Normative SD-OCT data of the fovea at different ages or changes seen with aging is still in the process of being completed and we do not know exactly how the different layers of the retina change with time. This data will help us interpret our SD-OCT data from the hydroxychloroquine retinopathy a little better. Thank you.