En Face Optical Coherence Tomography Imaging of the Photoreceptor Layers in Hydroxychloroquine Retinopathy

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• PURPOSE: To investigate the application of en face optical coherence tomography (OCT) imaging in eyes with hydroxychloroquine (HCQ) retinopathy.
• DESIGN: Retrospective case series.
• METHODS: SETTING: Institutional. PATIENT POPULATION: Sixty-two eyes of 31 Asian patients with HCQ retinopathy. OBSERVATION PROCEDURES: Macular volume scanning using swept-source OCT was performed in 6 × 6-mm and 9 × 9-mm areas centered on the fovea. Segmentation of the photoreceptor layers was automatically performed between the inner border of the ellipsoid zone and that of the retinal pigment epithelium–Bruch membrane complex to obtain en face OCT images. Findings from the en face images were qualitatively and quantitatively evaluated; they were analyzed and correlated with the fundus autofluorescence and visual field findings. MAIN OUTCOME MEASURES: En face OCT findings.
• RESULTS: All eyes with HCQ retinopathy had a beaten-bronze appearance in the areas with photoreceptor defects, whereas those with intact photoreceptors had areas with smooth surfaces, which were occasionally demarcated by hyporeflective margins, on the en face OCT images. The presence and extent of the retinopathy could be quickly determined using the images. They also provided quantitative information on the progression based on the areas of intact photoreceptors compared over several visits. Furthermore, the area of central intact photoreceptors significantly correlated with the mean deviation, pattern standard deviation, and visual field index of 30-2 visual field examinations (all $P < .001$).
• CONCLUSIONS: En face OCT may be useful for visualizing the presence and extent of HCQ retinopathy and its progression. The area of central intact photoreceptors measured on en face OCT images showed a significant association with functional visual field defects. This imaging may be a helpful adjunct for screening and follow-up examinations of HCQ retinopathy. (Am J Ophthalmol 2019;199:71–81. © 2018 Elsevier Inc. All rights reserved.)

HYDROXYCHLOROQUINE (HCQ) RETINOPATHY IS retinal toxicity of HCQ characterized by photoreceptor and retinal pigment epithelium (RPE) defects. It is progressive and irreversible; therefore, early recognition is imperative to minimize the damage.[1,2] The American Academy of Ophthalmology (AAO) has proposed guidelines for screening in which optical coherence tomography (OCT) and visual field examination are the key tests.[1] OCT is an important objective test for screening of HCQ retinopathy owing to its wide availability, excellent specificity, and noninvasive nature.[1–3]

Diverse OCT techniques have been developed to facilitate the visualization of the retinal changes in several retinal diseases.[4–9] For example, en face OCT has been applied in the imaging of the photoreceptor integrity in disorders such as diabetic macular edema and retinal vein occlusion.[4,5,9] Previous studies have shown the usefulness of this imaging technique in the assessment of the photoreceptor integrity and in monitoring disease progression in the diseases.[4,9] Because long-term use of HCQ can be accompanied by characteristic photoreceptor changes, en face OCT imaging may be beneficial in their detection and follow-up of their progression. Several authors applied volumetric mapping and en face visualization of the outer retinal layers to a few patients with HCQ retinopathy.[10,11] The imaging localized the damage and outer retinal thinning caused by the drug. Recently, Arndt and associates showed topographic analyses between multifocal electroretinogram (ERG) and en face OCT in HCQ retinopathy.[12] However, the clinical usefulness of the en face OCT for HCQ retinopathy has not yet been studied extensively.

In the present study, we aimed to document the findings of en face OCT imaging of the photoreceptor layers in eyes with HCQ retinopathy and evaluate its clinical utility in the detection of the presence and progression of the retinopathy.

METHODS

• SUBJECTS: We retrospectively reviewed 68 eyes of 34 patients who presented to Hanyang University Hospital

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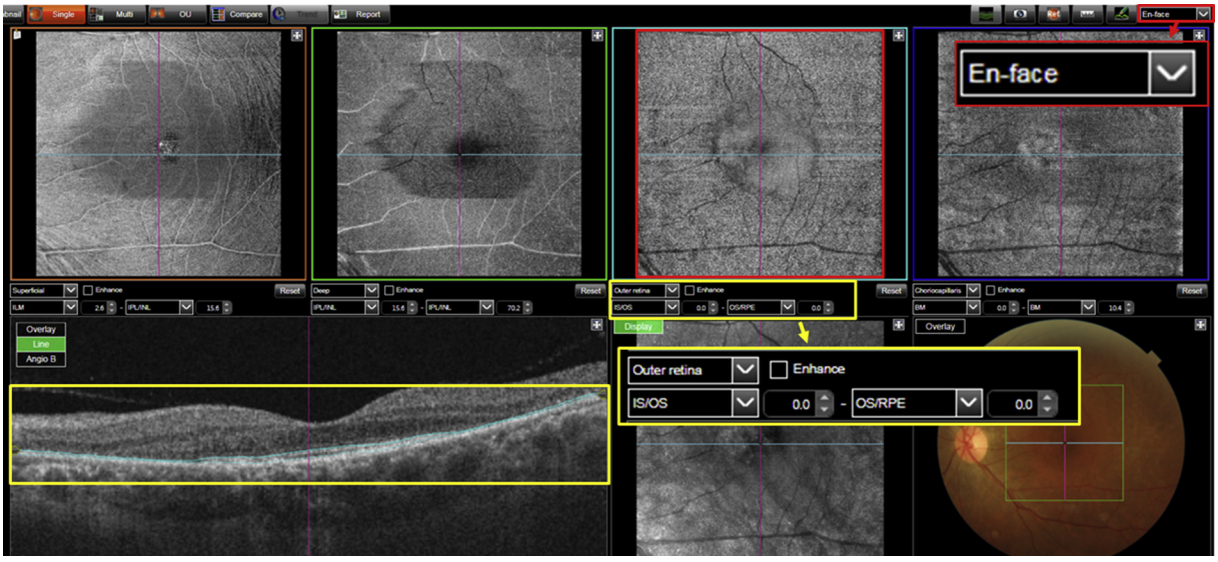

FIGURE 1. The captured image of commercial software provided by the manufacturer. Yellow boxes indicate the automated segmentation for the photoreceptor layers and red boxes represent the en face images used for our analyses.

between January 1, 2013 and February 28, 2018 for evaluation of HCQ retinal toxicity and who were diagnosed to have HCQ retinopathy. The diagnosis of HCQ retinopathy was made based on the presence of at least 1 objective finding, confirming the abnormalities observed on a subjective test (ie, visual field examination).[1] For objective evidence of HCQ retinopathy, characteristic photoreceptor defects with or without RPE disruption were confirmed on OCT B-scan images in all the patients. Other findings suggestive of HCQ retinopathy, such as pericentral or parafoveal hyper- or hypo-autofluorescence on fundus autofluorescence and parafoveal/extramacular ERG depression, were also used for the diagnosis.[1] Three patients were excluded as they did not have OCT en face images (n = 2) or had en face OCT images of poor quality owing to severe motion artifacts (n = 1). Finally, 62 eyes from 31 patients with HCQ retinopathy were included in the present study. The institutional review board of Hanyang University Hospital approved this study. Our study adhered to the tenets of the Declaration of Helsinki.

• **PATIENT EVALUATION:** All patients underwent comprehensive ophthalmic examinations for HCQ toxicity screening at the initial visit. Best-corrected visual acuity evaluation, slit-lamp examination, noncontact tonometry (KT-500 automated tonometer; Kowa, Tokyo, Japan), automated refraction (KW-1500; Kowa), and indirect ophthalmoscopy/fundus photography with pupil dilation were performed. For screening of HCQ toxicity, fundus autofluorescence (FAF), OCT, and Humphrey visual field 30-2 and 10-2 examinations (Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, California, USA) were performed to document subjective and objective abnormalities in patients using HCQ.

Blue-light FAF was performed using a confocal scanning laser ophthalmoscope (F-10; Nidek, Tokyo, Japan). OCT images were obtained using the DRI-triton OCT system (Topcon Inc, Tokyo, Japan) using a 3D macular volume scan protocol that generated a cube of data through a 6 × 6-mm^2 and 9 × 9-mm^2 grid, composed of 320 and 512 clusters of four repeated B-scans centered on the fovea, respectively.

The segmentation of the photoreceptor layers for the en face images was automatically performed from the inner border of the ellipsoid zone to that of the RPE–Bruch membrane complex using software provided by the manufacturer, as shown in Figure 1. All of the segmentation lines in our patients were confirmed by an independent reviewer (S.J.A.), who manually corrected segmentation errors in 2 patients. En face images of the photoreceptor layers indicate the mean signal intensity over the area between the borders. Figure 1 also shows the details on the use of the commercial software, including segmentations and image acquisition, for our analyses.

Grading of the HCQ retinopathy was performed in accordance with previous reports.[3,13] Depending on the severity of retinopathy, eyes were categorized to have early (isolated defects on visual field examinations and patchy photoreceptor loss without RPE involvement on OCT imaging), moderate (damage on the photoreceptors and scotomas constituting a partial [>180 degrees] or full ring), or severe retinopathy (combination of RPE damage on OCT imaging and hypo-autofluorescence on FAF examination). Based on the location of the retinopathy, the eyes were

TABLE. Demographic Data and Clinical Characteristics of Patients Included in This Study

Characteristics	Results
Sex, male: female	0 : 31
Mean age, year	54.3 ± 9.9
Diagnosis, SLE: RA, n (%)	23 : 8 (74.2 : 25.8)
Mean refractive errors, diopter	−1.69 ± 2.25
Follow-up period ≥12 months, n (%) eyes	40 (64.5)
Mean follow-up period (months)	21.9 ± 9.3
Daily dose, mg	279.0 ± 86.4
BMI, kg/m^2	20.7 ± 2.6
IBW,[a] kg	49.9 ± 3.7
Daily dose/Bwt, mg/kg	5.5 ± 1.6
Daily dose/IBW, mg/kg	5.6 ± 1.8
Duration of HCQ use, y	14.2 ± 4.2
Cumulative dose/Bwt, g/kg	26.7 ± 7.8
Severity of retinopathy, early: moderate: severe	20 : 17 : 25
Pattern of retinopathy, pericentral: parafoveal: mixed	42 : 6 : 14

BMI = body mass index; Bwt = body weight; HCQ = hydroxychloroquine; IBW = ideal body weight; RA= rheumatoid arthritis; SLE = systemic lupus erythematosus.

[a]Calculated by Devine formula (IBW = 50 + 2.3 kg per inch over 5 feet [for men] or 45.5 + 2.3 kg per inch over 5 feet [for women]).

graded to have parafoveal (photoreceptor/RPE disruption in a ring, 2-8 degrees from the fovea), pericentral (localized damage, >8 degrees from the fovea), or mixed (both pericentral and parafoveal) pattern of retinopathy.[3,13]

Among the patients who were followed up for equal to or longer than 12 months with both FAF and OCT, progression of retinopathy on OCT B-scans was defined by increase in defect size (also decreased size of intact photoreceptors) or greater extent of outer retinal disruption on 9-mm horizontal and vertical B-scan images crossing the fovea in the following visits. On en face images, increase in defect area (also decreased areas of intact photoreceptors) was considered as retinopathy progression. On FAF, progression was defined as the appearance of new hypofluorescent or hyperfluorescent lesions or the enlargement of existing lesions.[14] Two independent investigators (S.J.A. and J.J.), who were masked to the patients' clinical information, evaluated all the images and measured the distances from the fovea to the intact photoreceptors. In case of any discrepancy between the reviewers, a senior investigator (B.R.L.) was consulted, and consensus was reached among the investigators. The average value of the distances or areas was used in our analyses.

• **ANALYSES:** Descriptive statistics were used for demographic data and details on HCQ usage. The detection of HCQ retinopathy was compared among the imaging modalities, OCT B-scans, OCT en face imaging, and FAF. The frequencies of the progression were also compared among these modalities. The rate of progression of the photoreceptor defects was estimated by calculating the difference in the areas of intact photoreceptors between baseline and the final visit and dividing it by the number of follow-up years. The clinical factors associated with the progression rate were evaluated using multiple regression analyses. To evaluate structure-function relationship between photoreceptors and visual field defects, global indices of visual field test such as mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI) were correlated with the area of central intact photoreceptors using Pearson correlation analysis.

Continuous values are presented as means ± standard deviations. Statistical analyses were performed using PASW Statistics for Windows version 18.0 (SPSS Inc, Chicago, Illinois, USA). *P* values < .05 were considered statistically significant.

RESULTS

• **PATIENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS:** The Table summarizes the demographic data and clinical characteristics of the 31 patients included in this study. All patients were women, and the mean age of the patients was 54.3 ± 9.9 years (range, 35-77 years). Twenty-three (74.2%) and eight (25.8%) patients had systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), respectively. The mean refractive error was -1.69 ± 2.25 diopters; and 20 (32.3%), 17 (27.4%), and 25 (40.3%) eyes with early, moderate, and severe retinopathy, respectively, were included in this study. Pericentral, parafoveal, and mixed patterns of retinopathy were observed in 42 (67.7%), 6 (9.7%), and 14 (22.6%) eyes, respectively. Mean body mass index of the patients was 20.7 ± 2.6 kg/m^2 and ideal body weight was 49.9 ± 3.7 kg on average. The ratio of the cumulative dose to body weight and those of the daily dose to actual and ideal body weights were 26.7 ± 7.8 g/kg, 5.5 ± 1.6 mg/kg, and 5.6 ± 1.8 mg/kg, respectively. Progression of retinopathy was evaluated among the 40 eyes with a follow-up period ≥12 months, in which the mean follow-up period was 21.9 ± 9.3 months.

• **FINDINGS OF EN FACE OPTICAL COHERENCE TOMOGRAPHY IMAGING:** Figure 2 provides examples of a fundus photograph (Top left), FAF image, and 9 × 9-mm OCT en face image (Top right) together with the corresponding B-scans demonstrating the segmentation (Bottom) that was used in this study. In the eyes with severe retinopathy involving the photoreceptor and RPE defects, the FAF images showed a ring-shaped hyper-autofluorescence and hypo-autofluorescence, and the OCT B-scans demonstrated the corresponding photoreceptor and RPE defects in the pericentral area. En face OCT images demonstrated

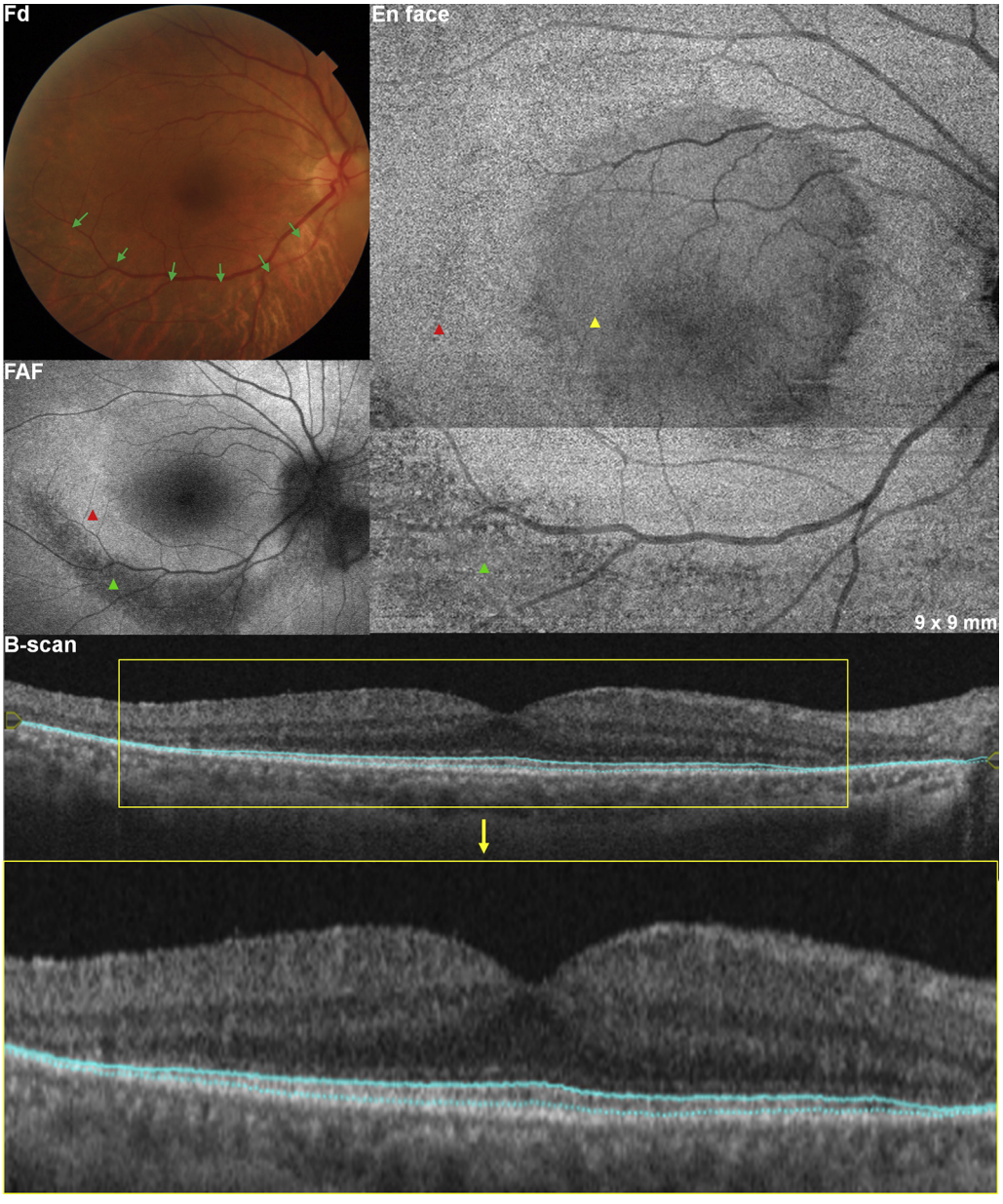

FIGURE 2. Images from (Top left) fundus photography (Fd) and fundus autofluorescence (FAF), (Top right) en face optical coherence tomography (OCT) of the photoreceptor layers, and (Bottom) OCT B-scan of a 58-year-old woman with hydroxychloroquine retinopathy. The fundus photograph shows retinal pigmentary change (green arrows), while FAF shows a hyper-autofluorescent area (red arrowhead) and a hypofluorescent partial ring (green arrowhead) in the paracentral area. A 9 × 9-mm en face OCT image shows a smooth surface in the central area (yellow arrowheads), in contrast to the beaten-bronze appearance (red arrowhead) seen in the pericentral area. The area with hypo-autofluorescence on the FAF corresponds to that of the hyporeflective granular area on the 9 × 9-mm en face OCT image (green arrowhead). The OCT B-scan images demonstrate the characteristic pericentral photoreceptor defects and also the slabs used for en face imaging of the photoreceptor layers. The magnified image (boxed image) shows segmentation lines from the inner border of the ellipsoid zone to the inner border of the retinal pigment epithelium–Bruch membrane complex used for this study.

beaten-bronze appearance (red arrowhead) on the area with photoreceptor defects on B-scan images. In the area combined with RPE defects (green arrowhead), irregular hyporeflectivity was also observed. The Supplemental Figure (Supplemental Material available at AJO.com) shows en face OCT images of age-, sex-, and diagnosis-matched examples of patients with and without HCQ retinopathy, revealing changed texture on the area with photoreceptor

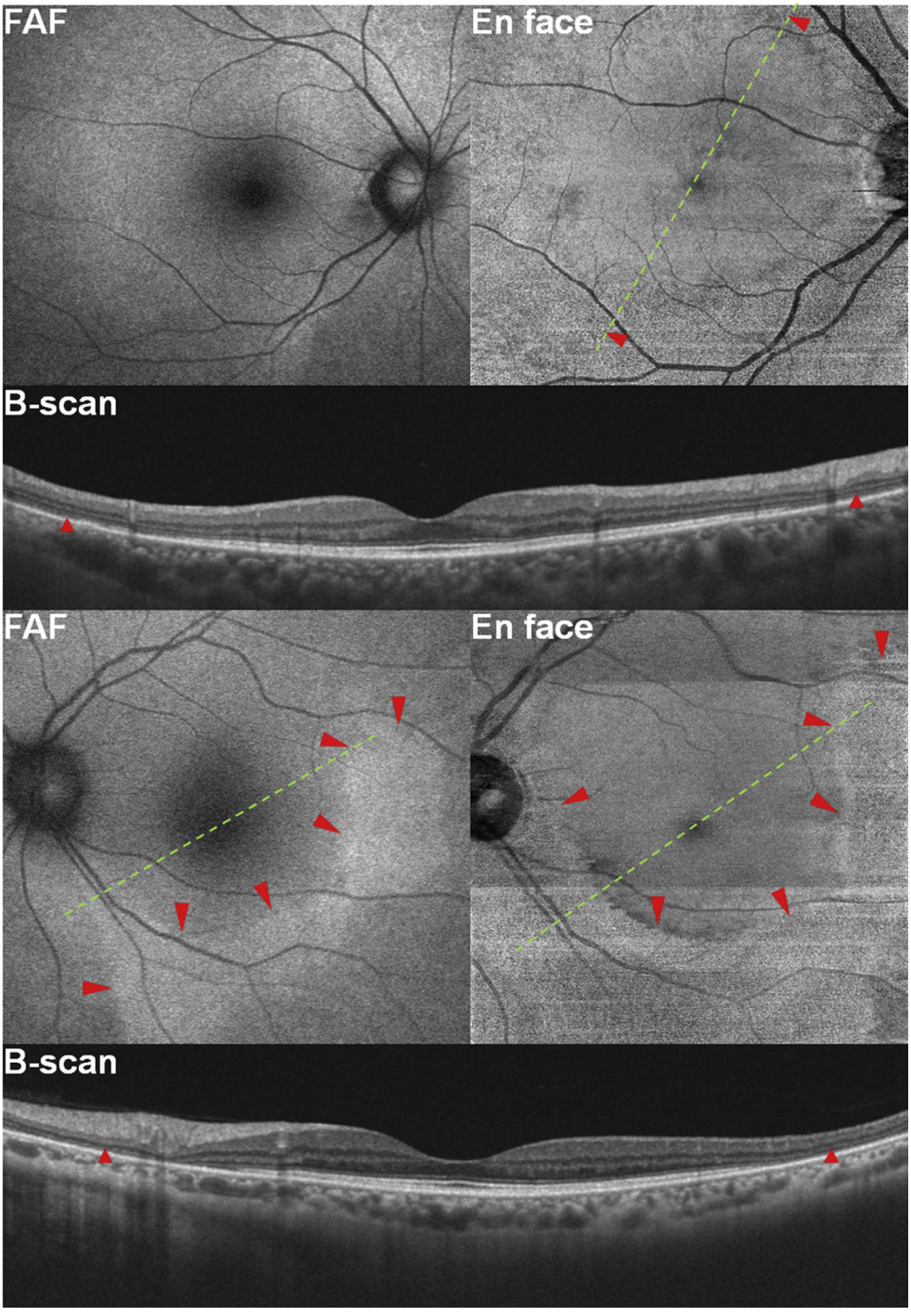

FIGURE 3. Two examples of cases showing discrepancy of the stage of hydroxychloroquine retinopathy in fundus autofluorescence (FAF) and en face optical coherence tomography (OCT). (Top and Second rows) In a 44-year-old systemic lupus erythematosus (SLE) patient, FAF shows no definite hyper- or hypo-autofluorescence, whereas OCT clearly demonstrates a ring-shaped area with irregular, beaten-bronze reflectivity on en face images and photoreceptor defect on B-scan images (red arrowheads). Based on FAF, the eye could not be diagnosed to have HCQ retinopathy, whereas OCT en face imaging diagnosed it as moderate HCQ retinopathy. (Third and Bottom rows) In a 55-year-old SLE patient, the FAF images were evaluated and the condition was differently diagnosed as early and moderate retinopathy by Reviewer 1 and 2, respectively; the senior reviewer evaluated it as early retinopathy, as the extent of the partial ring of hyper-autofluorescence seems to be less than 180 degrees. However, en face and B-scan OCT images show beaten-bronze appearance with a partial ring greater than 180 degrees and nasal and temporal pericentral photoreceptor defects, respectively, which indicates moderate retinopathy stage. Green dotted lines indicate the area scanned for obtaining the OCT B-scan image.

defects on the en face OCT image of the eye with HCQ retinopathy. There was point-by-point correlation between the B-scan and en face OCT images.

Figure 3 shows the representative cases showing discrepancy among the imaging modalities. In a 56-year-old woman with HCQ retinopathy (Top), OCT B-scan images revealed photoreceptor defects in the pericentral area. OCT en face images also revealed a pericentral beaten-bronze appearance, which was matched with the photoreceptor defects on B-scan images (arrowheads). However, FAF imaging did not show definite abnormal hyper- or hypo-autofluorescence. Furthermore, a 55-year-old woman (Figure 3, Bottom) had discrepant results between FAF and OCT en face images with respect to the extent of the retinopathy. Based on FAF, the eye was graded to have early retinopathy, whereas it was considered to have moderate retinopathy based on the en face OCT findings. OCT B-scan images corresponded better with en face OCT images, implying that the extent of photoreceptor defects was greater than 180 degrees, which suggests that the severity of the retinopathy was moderate.

Overall, all patients with HCQ retinopathy had photoreceptor defects on the 9-mm horizontal or vertical line scan OCT images. All the patients had abnormal findings on en face OCT imaging, a beaten-bronze appearance in the areas with photoreceptor defects with or without hyporeflective demarcations, whereas FAF showed hyper- or hypo-autofluorescence in 53 of 62 eyes, resulting in a sensitivity of 85.5%. There were 4 eyes showing discrepancies in the judgment of retinopathy severity between FAF (early) and en face OCT imaging (moderate).

• **PROGRESSION OF HYDROXYCHLOROQUINE RETINOPATHY IN EN FACE IMAGING:** Figure 4 depicts the photographic examples of eyes with retinopathy showing progression. On B-scan images, the eyes showed decreased distance from the fovea to the border of photoreceptor defects, 2340 to 2217 μm, which can be considered as progression of photoreceptor defects. On the en face images, the inferior margin of intact photoreceptors could be easily determined, and the evaluation of progression was much easier by comparing the en face images between patients' visits. In contrast, FAF shows no definite change in pericentral hyper-autofluorescence between the visits. Figure 5 also demonstrate the case showing central progression of photoreceptor defects, which could be determined more easily in en face OCT images. In this case, the central progression could be quantified by calculating and comparing the area of intact photoreceptors. The progression rate in this example was 0.94 mm^2/year. Overall, the mean progression rate within the central 9 × 9-mm area was 0.59, ranging from -0.02 to 2.6 mm^2/year. OCT B-scans should be registered strictly to ensure that the same areas were compared for the progression evaluation; however, slightly different scan areas do not significantly affect the evaluation of the area of intact photoreceptors in en face imaging, and the areas can be measured and compared using scan areas that are not strictly registered.

Progression of retinopathy was noted in 72.5% (29/40), 75% (30/40), and 55% (22/40) of eyes followed up for ≥12 months according to, respectively, B-scan (increase in defect size or greater extent of outer retinal disruption), en face imaging (decreasing area of the central intact photoreceptors), and FAF (new appearance or increased area of hypo- or hyper-autofluorescence) criteria, during the follow-up period. There were marginally significant differences in the rate of progression between en face OCT imaging and FAF ($P = .061$), in contrast to the nonsignificant difference between en face and B-scan images ($P = .799$).

The Supplemental Table (Supplemental Material available at AJO.com) shows the factors associated with progression rates within the central 9 × 9-mm area obtained from the en face OCT images. Multiple regression analyses showed significant association of progression rates with severity of retinopathy (regression coefficient [B] = 0.488, $P < .001$) and pattern of retinopathy (B = -0.508, $P = .040$), suggesting that the eyes with more severe retinopathy and pericentral pattern were likely to have greater rates of progression of photoreceptor defects.

• **CORRELATION BETWEEN STRUCTURAL AND FUNCTIONAL (VISUAL FIELD) ABNORMALITIES:** Figure 6 shows the association between the area of central intact photoreceptor layers, measured on 9 × 9-mm en face images, and several indices obtained by 30-2 visual field examinations. Correlation analysis showed significant association of the photoreceptor areas with the 3 global indices of 30-2 visual field tests: MD (correlation coefficient r = 0.753, $P < .001$), PSD (r = -0.601, $P < .001$), and VFI (r = 0.730, $P < .001$). Correlation was also significant between the areas and MD (r = 0.516, $P < .001$) and between the areas and PSD (r = -0.558, $P < .001$) of 10-2 visual field tests. These associations represent a structure-function relationship between visual field results and photoreceptor status, which could be quantified by en face OCT imaging in HCQ retinopathy.

DISCUSSION

THE PRESENT STUDY EVALUATED THE CLINICAL USE OF EN face OCT imaging in HCQ retinopathy. En face OCT imaging provided images of the photoreceptor layers in a retinal plane, which led to easy and fast recognition of the presence and extent of HCQ retinopathy. Compared with FAF, which provides retinal images in a coronal plane, en face imaging was sensitive in the detection of the presence and progression of retinopathy, and its images matched well with characteristic photoreceptor defects on B-scan images and functional defects on visual field examinations. Our results suggest that en face OCT imaging may be useful in the screening and follow-up

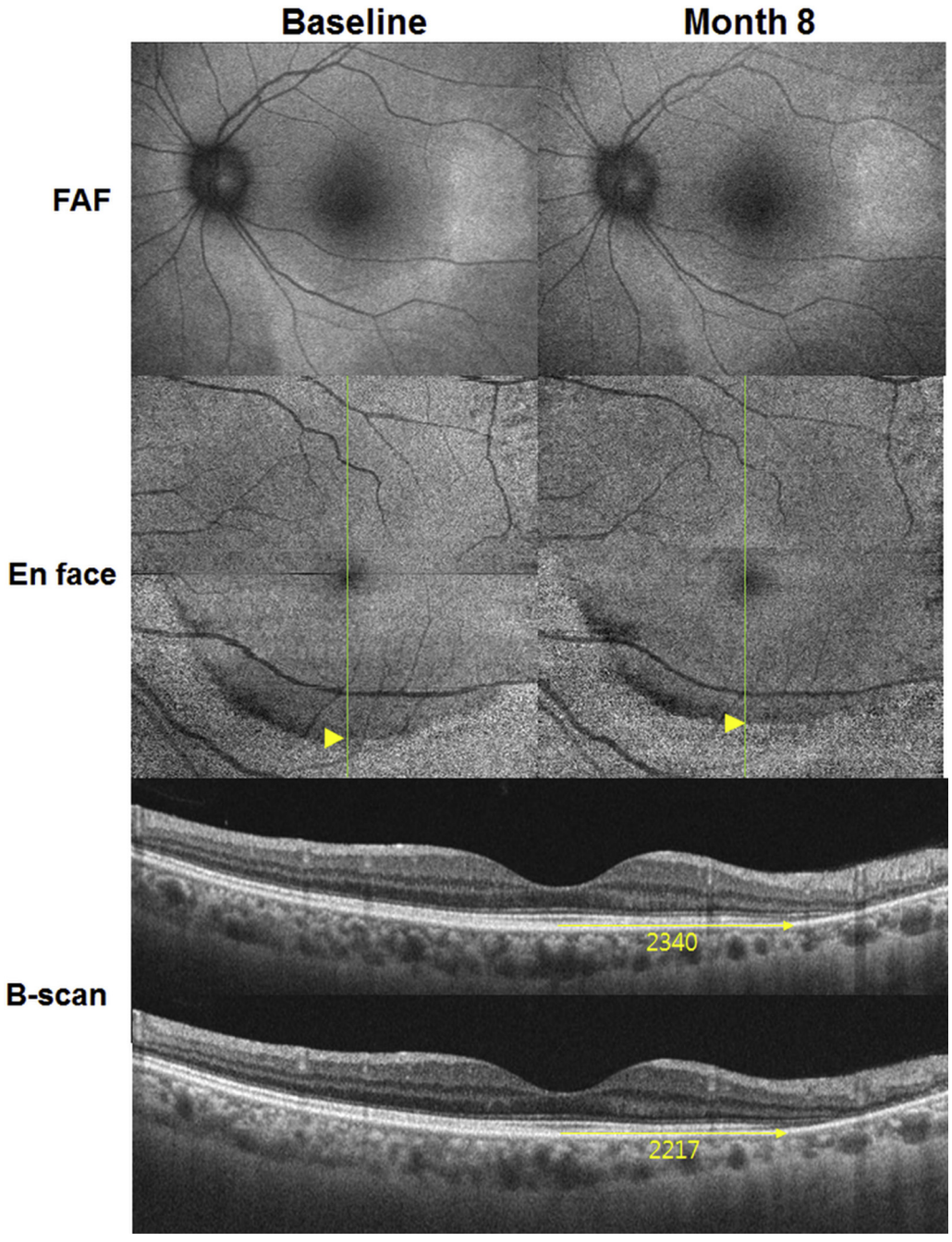

FIGURE 4. The representative case shows mild progression of the retinopathy (centripetal manner) during 8-month follow-up and its detection using (Top) fundus autofluorescence (FAF), (Middle) optical coherence tomography (OCT) en face imaging, and (Bottom) B-scan. Fundus autofluorescence shows no definite change in pericentral hyper-autofluorescence between the 2 visits. On en face images, however, the inferior margin (arrowheads) between intact and defective photoreceptors is more central to the fovea at the 8-month visit. While the B-scan images show no definite progression over the 8-month period, the measurement of the distance from the fovea to the defective photoreceptors (arrows) reveals a decrease in the length of intact photoreceptors from 2340 to 2217 μm.

examinations of HCQ retinopathy and that there is functional correlation of the photoreceptor findings on en face OCT imaging with visual field defects.

En face OCT technology is one of the newly developed visualization methods to reconstruct C-scan images of the posterior pole. Cross-sectional OCT scanning is the conventional method for visualizing retinal abnormalities; however, a review of multiple scans, including foveal and eccentric scans, is required to identify the retinal abnormalities in the posterior pole. Patients taking HCQ

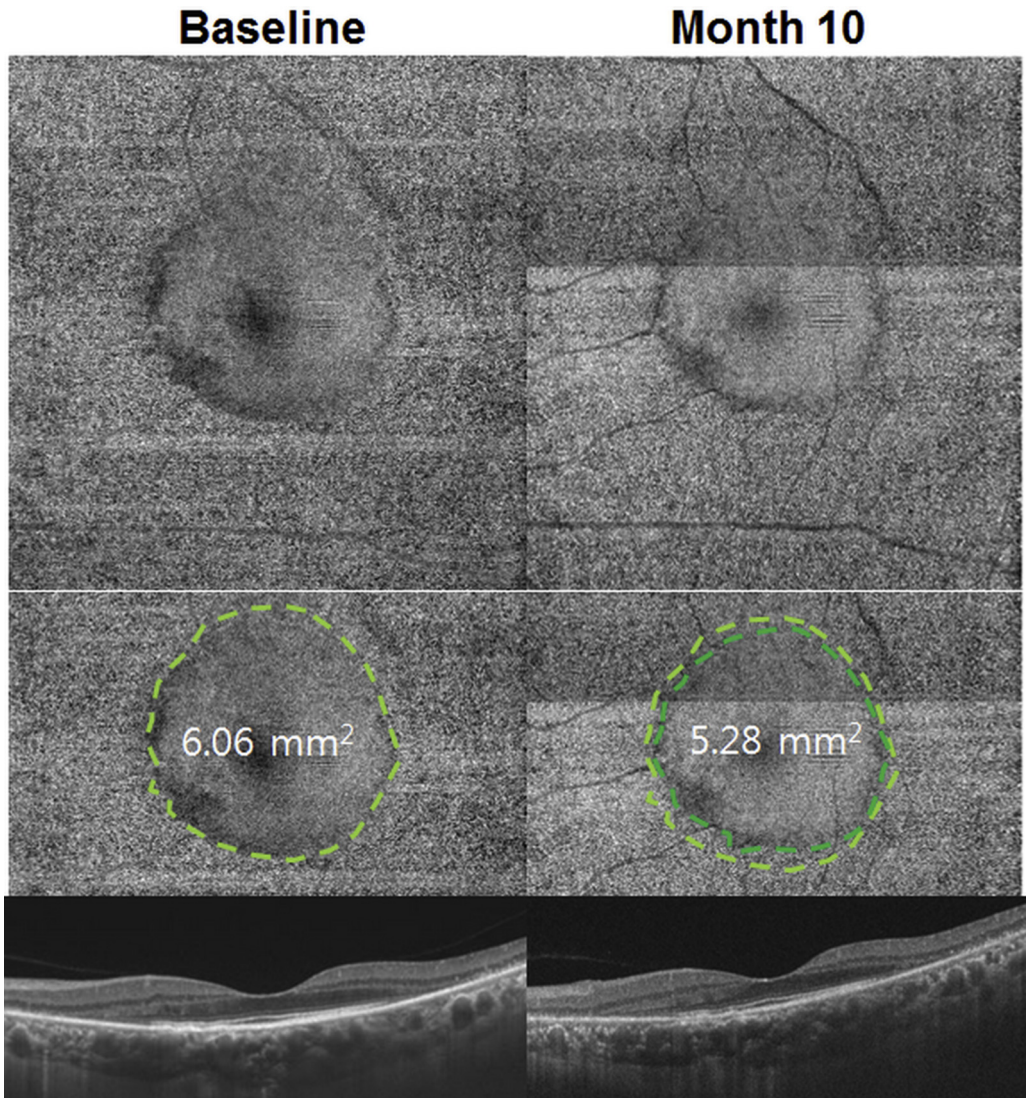

FIGURE 5. Evaluation of retinopathy progression by measuring areas of central intact photoreceptors. Using en face optical coherence tomography (OCT) images (Top and Middle), the area with intact photoreceptor layers (dotted area) can be measured and compared between the baseline (6.06 mm^2) and follow-up (5.28 mm^2) visits. The decrease in the area in the 10-month visit is easily identifiable (Top), whereas the progression is not obvious in the length of intact photoreceptor layers on B-scan images (Bottom).

medication particularly require multiple OCT scans for screening because the retinopathy can occur in diverse patterns, such as the parafoveal and pericentral types.[1,13] In contrast to the cross-sectional B-scan images, an en face OCT image depicts the photoreceptor defects within 1 image in the retinal plane. As this image can cover a wide retinal area, it may enable quick determination of the presence and extent of the retinopathy without reviewing multiple images.

However, the issue of practicality is very important in en face OCT imaging of the retina because this can be a notable obstacle to the use of this imaging modality in real-world clinical practice.[15] Our methods required an additional time of less than 30 seconds per eye, as only 3 parameters ("en face" setting and 2 borders for segmentation) needed to be set; therefore, we considered that our methods were practically feasible. The most important factor influencing the practicality of our methods was automated segmentation on the photoreceptor slab by setting of both (anterior and posterior) borders of segmentations. If manual adjustment is required for segmentation in each eye, greater time and effort is required and may significantly bias the images by introducing subjective judgment of the images. Accordingly, we believe that automated segmentation is an important factor influencing the practicality of en face OCT imaging for specific retinal layers.

Staging of HCQ retinopathy is performed on the basis of the degree of retinopathy and RPE involvement.[3,13]

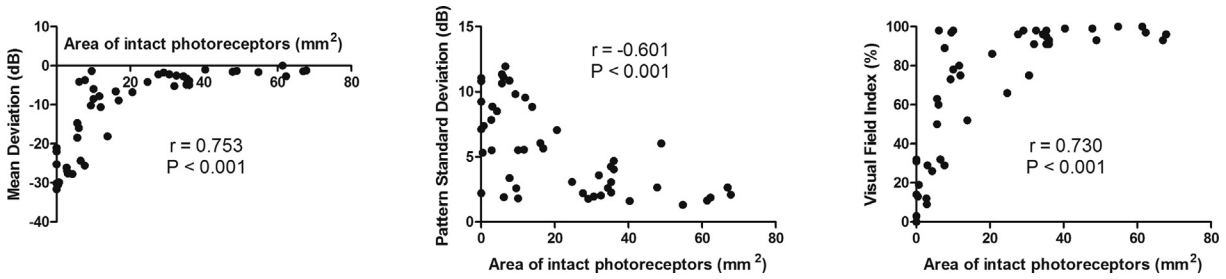

FIGURE 6. Graphs indicating correlation of area of central intact photoreceptors with global visual indices of mean deviation, pattern standard deviation, and visual field index. All these indices show significant correlation (all $P < .001$) with the area of central intact photoreceptors measured on 9 × 9-mm en face optical coherence tomography images.

However, it has not been specified which imaging modality should be used for the staging. Because the abnormal findings on FAF can be variable in early or moderate retinopathy,[3] there may be a discrepancy between FAF and OCT findings with respect to the extent of photoreceptor defects, as shown in Figure 3. Although OCT B-scan imaging may visualize the photoreceptor defects most sensitively, discrimination between early and moderate retinopathy based on the current staging system may not be straightforward using the imaging; this is because it is sometimes difficult to determine whether the extent of outer retinal defects is greater than 180 degrees around the macula on a B-scan image. En face images may be very useful for staging because the images in a coronal (retinal) plane can be used easily to identify the extent of retinopathy; thus, they can be used to determine the stage, and particularly to distinguish between the early and moderate retinopathy.

It has been reported that progression of retinopathy depends on the severity and it can occur even after drug cessation.[14,16] In previous reports, the progression was evaluated qualitatively and observed to correlate with the severity of retinopathy.[14,16] In this study, however, we could quantify the progression rates of photoreceptor defects and correlate these with the demographic data and details on HCQ usage. Our analysis reinforced the observation that there is an association between retinopathy progression and the stage of retinopathy.[16] For evaluation of retinopathy progression, conventional B-scan OCT images should be acquired accurately to ensure that the compared scanned areas are identical (and thus comparable). However, en face OCT images do not require strict registration of the compared scans because slightly different scanned areas may not significantly affect the calculation of area of central intact photoreceptors.

Screening tests should be widely available, noninvasive, and reliable. Because en face imaging is based on OCT, a noninvasive test that is the most widely used in HCQ retinopathy screening,[17] en face OCT imaging may be effective and also convenient as a screening test because OCT is commonly performed and the en face imaging does not require any additional instrument for the screening. However, we do not believe that the imaging should replace FAF as a screening test. For example, FAF can show the degree of damage in the form of hyper-autofluorescence, which indicates photoreceptor defects, and hypo-autofluorescence, which represents additional RPE damage (referred to as severe retinopathy). Thus, FAF provides information on the severity of the outer retinal defect, particularly RPE involvement, which may not be easily obtained from en face OCT images of the photoreceptor layers. In this context, FAF and en face OCT imaging of the photoreceptor layers may serve as complementary wide-field noninvasive screening tests that can show outer retinal damage in the retinal plane in eyes with HCQ retinopathy.

En face imaging showed sensitivities and specificities comparable to those of the retro-mode imaging we recently reported, as both imaging modalities showed the same sensitivities (100%) and similar specificities (80.2% [89 of 111] and 76.4% in en face OCT imaging and retro-mode imaging, respectively).[18] Our patients showed photoreceptor defects on OCT B-scans, and these defects were represented by abnormal findings on en face OCT imaging; however, segmentation errors on the retinal periphery in patients with less reflective ellipsoid zone line on the area and the recently reported subretinal drusenoid deposits in young SLE patients[19] were the main sources of false positivity in en face OCT imaging. As Browning and Lee showed excellent specificities of SD-OCT B-scans for HCQ retinopathy screening,[20] we could exclude such cases with false-positives using OCT B-scans. Particular attention for false-positives on OCT en face imaging is required as a compromise for the reduced time and effort for evaluation of photoreceptor layers as with retro-mode imaging.

Although en face imaging offers advantages in the detection of retinopathy and its progression, this imaging modality has several limitations that require careful interpretation. If the photoreceptor defects are not evident on structural B-scan images, en face images may not reveal any abnormality because en face images are reconstructed from B-scan images. Thus, the patients suspected to have

HCQ retinopathy but not showing abnormal OCT findings may require other objective or subjective tests for the retinopathy screening. Because individual cross-sectional OCT scans are obtained in sequence and then reconstructed in postprocessing, eye movements can create significant image artifacts. These artifacts can be minimized through fixation tracking, postprocessing registration of the projected OCT volume using retinal blood vessels, or generation of OCT volume scan composed of vertical and horizontal raster scans, which are some of the approaches that are used by different OCT manufacturers. The scan area in this study was confined to a 9 × 9-mm area centered on the fovea; therefore, the retinal toxicity outside of the area may not be covered using this imaging. This may lead to a limitation in the calculation of the progression rate because only the central progression rate could be obtained using the current study settings, as the peripheral margin of the intact and defective photoreceptors could not be imaged using the 9 × 9-mm volume scan in some cases with pericentral retinopathy. Because the retinopathy can extend to more peripheral areas as it progresses, evaluation of the peripheral progression rate may require a more extensive area of coverage for macular volume scan. En face OCT images obtained by wider scans may further enhance detection of retinopathy, particularly in Asian patients.[3] However, in addition to the practicality issue, we used 9 × 9 mm en face images, as the area covered by the current standard tests for HCQ retinopathy, 30-degree FAF and HVF 30-2, corresponded to the area and thus the results obtained by all the tests could be correlated. Furthermore, progression in the central retina is more visually significant than that in the periphery; hence, we considered the retinopathy progression within the area as clinically significant.

Further, this study has several limitations that should be considered when interpreting the results. The study's retrospective design resulted in an intrinsic selection bias. The inclusion of a relatively small number of patients with HCQ retinopathy made it challenging to draw a final conclusion regarding the findings of en face OCT imaging in the eyes. Ethnic diversity in the presentation, particularly with respect to the patterns of retinopathy,[3,13,21] should be carefully considered when interpreting our results. Our subjects were all of Asian ethnicities; therefore, our results might not be applicable to non-Asian populations because of the differences in retinopathy patterns among different ethnicities. Therefore, multinational studies, incorporating a larger number of patients from multiple ethnicities, may be required to substantiate our findings and confirm the value of en face imaging. Finally, measurement of the area with central intact photoreceptors was manually performed in this study and may be prone to random errors or bias. Automated detection and calculation of the areas may provide a more accurate evaluation of the area of photoreceptor defects and their progression.

In conclusion, this study showed that en face OCT imaging of the photoreceptor layers may facilitate quick and sensitive detection of retinopathy and its extent. Because en face imaging may quantify the area of central intact photoreceptors, quantitative evaluation and monitoring of progression of the retinopathy may also be possible by measuring the area. Alongside current imaging modalities, en face OCT imaging of the photoreceptor layers may serve as a useful supplementary screening and follow-up examination technique in patients taking HCQ medication. Furthermore, the imaging may be applicable to other retinal diseases primarily affecting the photoreceptors.

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