Predicting the Progression of Geographic Atrophy in Age-Related Macular Degeneration With SD-OCT En Face Imaging of the Outer Retina

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BACKGROUND AND OBJECTIVE: Spectral-domain optical coherence tomography (SD-OCT) en face imaging was used to measure the growth of geographic atrophy (GA) and identify baseline anatomic changes in the outer retina in eyes with nonexudative age-related macular degeneration (AMD).

PATIENTS AND METHODS: In this prospective study, eyes were imaged using 200 × 200 and 512 × 128 A-scan raster patterns. Outer retinal anatomy was visualized using en face imaging of a 20-µm thick slab encompassing the inner segment/outer segment (IS/OS) band.

RESULTS: En face SD-OCT imaging of the IS/OS region revealed a bilaterally symmetrical pattern of outer retinal disruption extending beyond the borders of GA that accurately predicted the progression of GA over 1 year in 13 of 30 eyes (43.3%). In the remaining cases, the area of disruption was much larger than the area of progression.

CONCLUSION: En face imaging of the outer retina can predict the growth of GA in some eyes. Due to the bilateral symmetry of these findings, this imaging strategy may identify a genetic subset of patients in whom photoreceptor loss precedes the progression of GA. These areas with outer retinal disruption should be followed in clinical trials designed to test treatments for dry AMD.

INTRODUCTION

Geographic atrophy (GA) is the hallmark of advanced nonexudative (dry) age-related macular degeneration (AMD). The characteristic appearance of GA results from the loss of the photoreceptor layer, retinal pigment epithelium (RPE), and choriocapillaris. In most cases, GA first appears in the parafoveal location and progresses around the fovea and then through the fovea with concomitant loss of central visual acuity. Early in the disease process, patients often complain of difficulty with glare, reading, and adjusting to dim light situations even though the GA has not yet progressed through the foveal center. These complaints have been attributed to the presence of parafoveal scotomas from the GA and to dysfunctional rod and cone photoreceptors outside the area directly involved with GA. While the appearance of GA has been associated with the disappearance of drusen, GA can also appear in areas without preexisting drusen. The exact cause for the appearance and progression of GA remains elusive. Current theories to explain the appearance of GA include nutritional deprivation due to the thickened Bruch’s membrane and/or the presence of drusen, oxidative damage to the RPE, the toxic accumulation of lipofuscin within the RPE, inflammatory damage to the retina and/or RPE that may be mediated by the dysregulation of the complement system, and vascular insufficiency of the underlying choroid. Whether GA results from an ini-
tial insult to photoreceptors, RPE, or the choriocapillaris remains unknown.

The appearance and progression of GA has been extensively studied using reflectance fundus imaging, \(8,9\) autofluorescence (AF) imaging, \(10\) and spectral-domain optical coherence tomography (SD-OCT) imaging. \(11\) These imaging strategies have provided some clues regarding the appearance and progression of GA. Reflectance imaging has identified drusen, hyperpigmentation, and reticular pseudo-drusen as risk factors for the appearance and progression of GA. \(1,6,7,12,13\) Autofluorescence imaging has identified different hyperautofluorescence patterns of the RPE, and these patterns have been associated with different growth characteristics of GA. \(14-17\) SD-OCT has identified subretinal drusenoid deposits and abnormalities of the RPE and photoreceptors at the margins of GA that may be associated with the expansion of GA. \(17-22\) However, none of these imaging strategies have reliably predicted an area in the macula where GA is likely to appear or predicted the growth of GA over 1 year once it appears. To help predict where GA is likely to appear and grow, investigators have relied on functional testing of the retina. \(1\)

The loss of photoreceptors away from the edge of GA has been identified histopathologically (Alan Bird, personal communication, 2012). \(2,3,23\) and dysfunctional photoreceptors have been detected away from the edge of GA using electrophysiology and microperimetry threshold testing. \(1\) Based on electrophysiological testing, it remains controversial whether rods are primarily affected or both rods and cones are similarly affected. \(24-33\) Microperimetry has detected photoreceptor abnormalities even before GA develops, and this strategy can also predict the area where existing GA will likely progress. \(34-40\) These histopathologic, electrophysiologic, and microperimetric findings in eyes with GA, along with the early visual function deficits and symptoms observed in patients even before GA develops, \(41\) suggest that photoreceptor dysfunction precedes the appearance and progression of GA in some eyes. These findings would also suggest that an anatomic correlate should exist away from the margin of GA that could be visualized using SD-OCT imaging. Such an anatomic correlate could involve the photoreceptor layer. To test this possibility, we focused on the inner segment/outer segment (IS/OS) boundary of photoreceptors that can be easily visualized using SD-OCT imaging. This boundary area would likely be disrupted if photoreceptor function were abnormal. An en face imaging technique was developed that allowed us to visualize the integrity of this region using the advanced visualization feature of the Cirrus HD-OCT instrument (Carl Zeiss Meditec, Dublin, CA). This imaging technique was then used to visualize the area around GA in eyes with nonexudative AMD to determine whether we could predict the appearance and progression of GA.

**PATIENTS AND METHODS**

Patients with nonexudative AMD were enrolled in a prospective SD-OCT study, which was approved by the institutional review board of the University of Miami, Miller School of Medicine, and was compliant with the Health Insurance Portability and Accountability Act of 1996. The study adhered to the tenets of the Declaration of Helsinki. Study participants were recruited from the retina service at the Bascom Palmer Eye Institute and monitored for at least 12 months. Each patient signed an informed consent. To be enrolled in this study, patients had to have at least one eye with GA measuring from 1.25 mm² to 18 mm² and a visual acuity of 20/63 or better (60 letters) as measured using a standard visual acuity testing protocol with the ETDRS chart at 4 meters. The GA could be unifocal or multifocal. Patients were excluded from the study if the study eye demonstrated areas of peripapillary atrophy communicating with the area of macular atrophy. Patients were also excluded if the study eye presented any sign or history of choroidal neovascularization or any confounding ocular conditions such as retinal detachment, severe nonproliferative or worse diabetic retinopathy, retinal vascular occlusion, macular edema, evidence of inherited retinal degeneration, or a history of pars plana vitrectomy. At least two retina specialists at the Bascom Palmer Eye Institute confirmed the clinical diagnosis of nonexudative AMD and that the patient met the inclusion/exclusion criteria for the study.

The ophthalmological examination included best corrected visual acuity measured using the ETDRS chart at 4 meters, low luminance visual acuity testing at 4 meters using a 2.0–log unit neutral density filter (Kodak Wratten filter; Kodak, Rochester, NY). \(41\) slit-lamp biomicroscopy, intraocular pressure measurement, and fundus examination. All examinations were performed by one of the authors (PJR or AAM) at baseline, 12 weeks, 26 weeks, 38 weeks, and 52 weeks of follow-up.

Color fundus imaging was obtained using a fundus camera–based flash system (TRC-50DX; Topcon Medical Systems, Oakland, NJ). Autofluorescence imaging was performed using a confocal scanning laser ophthalmoscopic system with an excitation wavelength of 488 nm and detection wavelength greater than 500 nm (Spectralis; Heidelberg Engineering, Heidelberg, Germany). Autofluorescence images were acquired using the high-speed, low-resolution mode and the automatic real-time mean function. The number of frames
was set to 14 when using the automatic real-time mean function. SD-OCT imaging was performed using the Cirrus HD-OCT instrument, which has an axial resolution of 5 µm and a scanning rate of 27,000 A-scans per second. Each eye was imaged using two different raster scan patterns, the 200 × 200 and 512 × 128. The 200 × 200 protocol resulted in the acquisition of an SD-OCT data set consisting of 40,000 uniformly spaced A-scans organized as 200 A-scans in each B-scan and as 200 horizontal B-scans in each raster array. At this setting, each A-scan is separated by 30 µm. The 512 × 128 pattern was comprised of 512 A-scans in each B-scan and 128 horizontal B-scans lines. All scan patterns measured 6 × 6 mm on the retina, and a montage of overlapping scans was performed when GA extended beyond the central 6 × 6-mm scan area. A single experienced operator who assessed the quality of the scan during its acquisition performed all scans. The GA was assessed using a sub-RPE slab derived from the Cirrus Advanced RPE Analysis software. This slab is formed by axially projecting the OCT image data from a region extending 65 µm to 400 µm below the RPE segmentation line in the 200 × 200 scan pattern. In this commercially available software, image processing is used to reduce noise and suppress the appearance of the choroidal vasculature. Measurements were made at baseline, 3 months, 6 months, 9 months, and 1 year of follow-up. The images were exported as a .bmp file measuring 200 × 200 pixels. The area of GA was quantified using a Cintiq WACOM digitizing tablet (WACOM, Vancouver, WA) and image analysis software (Adobe Photoshop CS2; Adobe Systems, San Jose, CA) as previously described. Three graders outlined the areas of GA, and a consensus image was generated. In those instances in which consensus could not be reached, one of the investigators (PJR) adjudicated the disagreement and a final drawing was generated. The nominal conversion factor of a calibrated SD-OCT instrument (36 mm²/40,000 pixels) was used to convert the number of pixels into the area of GA. The baseline area of GA and the growth rate of GA were measured using the square root transformation strategy previously described.

Outer retinal anatomy was then visualized using en face imaging of a slab that encompassed the IS/OS boundary. These slabs were generated from the 200 × 200 macular cube volume scans using the advanced visualization software available on the commercial instrument. Several different slab thicknesses and positions were tested to find the en face image that best encompassed the IS/OS region in healthy eyes. The one that was found to be the most useful for visualizing the IS/OS region was a 20-µm thick slab representing the region located between 20 and 40 µm above the RPE segmentation line (Figure 1A). Using Adobe Photoshop CS2 image analysis software, we registered this en face image to the OCT fundus image generated from the 512 × 128 macular cube volume scans at the same visit so that the corresponding B-scans consisting of 512 A-scans could be superimposed on the en face image created from the 20-µm thick outer retinal slab. The B-scan generated from the 512 × 128 scan pattern had higher transverse sampling density and provided better visualization of the IS/OS outer retinal region than the B-scan from the 200 × 200 raster scan pattern used to generate the slab image, which is comprised of 200 A-scans. To better visualize the changes outside the area of GA, we registered the baseline en face image derived from the outer retinal slab with the baseline sub-RPE slab image that showed the area of GA. This baseline area of GA was then filled in with white. The same strategy was used to superimpose the outline depicting the growth of GA at 6 months and 1 year. This approach was used to highlight the correlation between the growth of the GA over 1 year and the patterns identified using the en face image of the outer retinal slab at baseline. The patterns observed on the en face images were then classified as focal (well-demarcated dark area adjacent to the GA) or diffuse (poorly demarcated dark area).

## Results

A total of 30 AMD patients with GA were enrolled, and no patient withdrew from the study during the year. One eye was designated the study eye, and 19 fellow eyes with nonexudative AMD and GA were evaluated as well. The mean age (standard deviation) of the patients was 79.87 years (6.56). For the 30 study eyes, the mean GA square root area at baseline was 2.37 mm (0.90), and after 1 year, the annual growth rate of GA in these study eyes was 0.37 mm per year (0.21). For the 19 fellow eyes, the mean GA square root area at baseline was 2.45 mm (0.76), and after 1 year, the annual growth rate of GA in these fellow eyes was 0.29 mm per year (0.18).

En face slab images encompassing the IS/OS region were generated for both the study and fellow eyes. In normal eyes with an intact IS/OS region (Figure 1), the macula outside the foveal center appears uniformly bright except for the shadows cast by the larger retinal blood vessels. These blood vessels appear dark on the en face image due to the increased reflectivity of these vessels compared with the surrounding retina. The foveal center appears slightly darker than the surrounding retina due to the slight elevation of the IS/OS junction at the foveal center that elevates the IS/OS region outside the slab. The local brightness of the en face image is related to the total OCT signal included.
in the slab. In eyes with GA, the slab en face image contains relatively darker regions that typically surround the GA. These dark regions correspond to areas where the IS/OS band is disrupted.

Four representative cases with different patterns of outer photoreceptor disruption are shown from Figures 2 to 21. Each case is depicted in five figures. The first figure for each patient shows baseline images: color fundus images, autofluorescence images, sub-RPE slab en face images, and the outer retinal slab en face images of both eyes. These figures highlight the symmetry of the lesions. The second figure represents the growth of the lesion over 1 year as shown using the sub-RPE slab en face images. The baseline areas of GA are filled in with white and superimposed on the baseline outer retinal slab en face image. The growth of GA at 6 months and 1 year is depicted as lines registered to the baseline image. The dark area surrounding the GA on the baseline en face image depicts the area of outer photoreceptor disruption. These images showing the growth of GA demonstrate the correlation between the dark areas seen on the baseline outer retinal slab en face image with the enlargement pattern of the GA. The final three figures of each eye show representative examples correlating the en face image with registered B-scans. These registered images show that the darker areas on the en face image correlate with disruption of the IS/OS region in the outer retina.

Figures 2 to 6 depict the images of an 80-year-old man with bilateral GA. Visual acuity was 70 letters (20/40) in the right (study) eye and 32 letters (20/250) in the left eye. The autofluorescence image of the right eye shows a hyper-autofluorescence pattern extending superiorly, nasally, and temporally (Figure 2C). On the slab en face image at baseline (Figure 2G), a dark area extends from the nasal, superior, and temporal margin of the GA. The extension of this dark area is more evident superiorly. Figure 3 depicts the growth of the GA at week 26 (Figures 3B, 3E) and at week 60 (Figures 3C, 3F). At baseline, the area of GA was measured to be 4.15 mm$^2$. At weeks 26 and 60, the GA had enlarged to 6.50 mm$^2$ and 8.90 mm$^2$, respectively. The square root enlargement rate (ER$sqt$) was 0.82 mm over 1 year. The outlines of the GA at these time points are registered to the baseline outer retinal slab en face image (Figures 3E, 3F). By week 60, the GA had progressed through the dark area identified at baseline (Figure 3F). Figures 4A and 4C show a line on the outer retinal slab en face image depicting the location of a B-scan passing through a normal area of the image above the GA and the dark area. No disruption of the IS/OS region can be detected. Figure 5 shows the dotted lines correlating the disruption of the IS/OS region and the boundaries of the dark area depicted on the outer retinal slab en face image. Figure 6 shows the correlation between the disrupted IS/OS region and thinned outer nuclear layer on the B-scan and the dark area on the outer retinal slab en face image, as well as a correlation between the area of GA and the increased choroidal reflectivity seen on the B-scan. We refer to this type of IS/OS disruption as focal and directional. The term “focal” refers to the well-demarcated appearance of the dark area, and “directional” refers to the asymmetric extension of the dark area from the border of the preexisting GA, which corresponds to the directional extension of GA.

Figures 7 to 11, images of a 78-year-old woman with bilateral GA, show another example of focal and directional IS/OS disruption. Visual acuity was 79 letters (20/25) in the left (study) eye and 78 letters (20/25) in the right eye. Figure 7G shows a dark area on the outer retinal slab en face image of the right eye that closely resembles the area of GA shown in the left eye (Figure 7F, H). Over the next year, the area of GA in the right eye enlarges within the area that appeared dark on the baseline outer retinal slab en face image (Figure 8). The area of GA at baseline was 1.82 mm$^2$ (Figure 8A). At week 26, the area was 2.83 mm$^2$ (Figure 8B), and at week 52, the area was 5.03 mm$^2$ (Figure 8C). The ER$sqt$ over 1 year was 0.89 mm. Figure 9 shows a B-scan passing through a normal area of the retina above the area that appears dark on the en face slab image. No obvious disruption of the IS/OS band is found. Shadowing from the retinal vessels confirms the registration of the B-scan with the en face image (Figure 9B). Figures 10 and 11 show the correlations between the disrupted IS/OS region and thinned outer nuclear layer with the dark areas seen on the outer retinal slab en face image, as well as the correlations between the outer retinal atrophy and the increased choroidal reflectivity with the areas of GA.

Figures 12 to 16 show the images of an 83-year-old woman with bilateral GA, reticular pseudo-drusen, and subretinal drusenoid deposits. Visual acuity was 84 letters (20/20) in the right (study) eye and 37 letters (20/200) in the left eye. The characteristic pattern of reticular pseudo-drusen can be appreciated on the autofluorescence images shown in Figures 12C and 12D. The outer retinal slab en face image shows a lacy undulating pattern that surrounds the GA in both eyes. This undulating pattern represents the areas of the reflective subretinal drusenoid deposits that are found between the RPE and the photoreceptor outer segments and identified on the B-scans shown in Figures 14 to 16. Figure 13 shows the sub-RPE slabs depicting the growth of GA over 1 year. At baseline, the GA measured 6.52 mm$^2$. By 26 weeks, the GA had enlarged to 8.14 mm$^2$, and by 52 weeks, the GA had en-
larged to 9.29 mm², for an annual ERsqt of 0.49 mm. The baseline outer retina slab en face image shows a diffuse, undulating dark pattern distributed around the foci of GA (Figures 12G, 13D). Over the next year, the foci grew uniformly into these dark areas (Figures 13E, 13F). Figure 14B shows the B-scan appearance that corresponds to the outer retinal slab en face image with this dark, lacy pattern. In this B-scan, an undulating IS/OS band can be visualized that is associated with subretinal drusenoid deposits. Figures 15 and 16 correlate the dark areas on the outer retinal slab en face image with the disruption of the IS/OS band on the B-scans. These figures also correlate the areas of GA with the outer retinal atrophy and the increased choroidal reflectivity seen on the corresponding B-scans. We refer to this type of IS/OS disruption as diffuse based on the widespread appearance of this dark, lacy pattern and the poorly demarcated boundary between normal and abnormal retina.

Figures 17 to 21 show the images of a 70-year-old man with bilateral GA and reticular pseudo-drusen with larger subretinal drusenoid deposits in the outer retina. Visual acuity was 68 letters (20/40) in the left (study) eye and 29 letters (20/250) in the right eye. The characteristic pattern of the reticular pseudo-drusen can be appreciated on the autofluorescence images shown in Figures 17C and 17D. The outer retinal slab en face images show a darker, speckled pattern surrounding the GA in both eyes that correlates with the extension of the subretinal drusenoid deposits into the outer retina above the RPE as shown on the B-scans in Figures 19 to 21. Figure 18 shows the sub-RPE slabs depicting the growth of GA over 1 year. At baseline, the GA measured 6.21 mm². By 26 weeks, the GA had enlarged to 7.32 mm², and by 52 weeks, it had enlarged to 7.89 mm², for an annual ERsqt of 0.32 mm. The baseline outer retina slab en face image shows a diffuse area of speckling in the macula distributed around the multifocal areas of GA (Figures 18G, 18D), and over the next year, the lesion grew into this darkly speckled area (Figures 18E, 18F). The B-scan appearance of this darkly speckled area seen on the outer retinal slab en face image is shown in Figure 19B, where it is possible to visualize subretinal drusenoid deposits and hyper-reflective material within the outer retina. As a result of these deposits, the IS/OS band is irregular, which along with the deposits is responsible for the speckled appearance on the slab en face images. Figures 19 to 21 correlate the dark areas on the outer retinal slab en face image with the disruption of the IS/OS region, and the areas of GA can be appreciated on the corresponding B-scans. We also refer to this type of IS/OS disruption as diffuse based on the widespread poorly defined area that appears dark in both eyes.

The Table shows the distribution of the different disruption patterns for the 30 study eyes. The disruption patterns were symmetrical for the 19 fellow eyes with nonexudative AMD. The focal pattern, in which the well-demarcated dark area predicts where the GA is going to grow, was observed in 13 patients (43.3%), and the diffuse pattern, in which the dark area was much larger than the area where the GA grew to, was observed in 17 patients (56.7%). There was no significant difference in growth rate over a year between these two groups (P = .70). Using blue-light autofluorescence imaging, we identified reticular pseudo-drusen in 46% of the eyes with the focal pattern and 77% of the eyes with the diffuse pattern. The prevalence of reticular pseudo-drusen in both groups was not significantly different (P = .13).
Figure 2. Baseline images of geographic atrophy (GA) from both eyes of an 80-year-old man with nonexudative age-related macular degeneration and focal disruption of the outer retina. (A,B) Color fundus images with a superimposed square depicting the area scanned with spectral domain optical coherence tomography (SD-OCT) imaging. (C,D) Fundus autofluorescence images with a superimposed square depicting the area scanned with SD-OCT imaging. (E,F) Sub-RPE slabs. (G,H) En face images derived from the outer retinal slab described in Figure 1 with the superimposed images of GA (white) derived from the corresponding sub-RPE slabs at baseline.

Figure 3. Growth of GA in the right eye of the patient described in Figure 2. Sub-RPE slab at baseline (A), week 26 (B), and week 60 (C). (D) Baseline en face image with the superimposed image of GA (white) derived from the corresponding sub-RPE slab at baseline (same as Figure 2G). (E) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 26. (F) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 60. The square root enlargement rate (ERsqt) at 1 year was 0.82 mm.
Figure 4. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 2G) and blue line depicting location of B-scan shown in B. (B) B-scan through normal area above GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. No disruption of the IS/OS band is observed.

Figure 5. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 2G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area above GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Red dashed lines show correlation between dark area on en face image and IS/OS disruption on B-scan.

Figure 6. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 2G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area and GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Red dashed lines show correlation between dark area on en face image and IS/OS disruption on B-scan and between GA and outer retinal atrophy and increased choroidal reflectivity seen on B-scan.
Figure 7. Baseline images of GA from both eyes of a 78-year-old woman with nonexudative age-related macular degeneration and focal disruption of the outer retina. (A,B) Color fundus images with a superimposed square depicting the area scanned with spectral-domain optical coherence tomography (SD-OCT) imaging. (C,D) Fundus autofluorescence images with a superimposed square depicting the area scanned with SD-OCT imaging. (E,F) Sub-RPE slabs. (G,H) En face images derived from the outer retinal slab described in Figure 1 with the superimposed images of GA (white) derived from the corresponding sub-RPE slabs at baseline.

Figure 8. Growth of GA in the right eye of the patient described in Figure 7. Sub-RPE slab at baseline (A), week 26 (B), and week 52 (C). (D) Baseline en face image with the superimposed image of GA (white) derived from the corresponding sub-RPE slab at baseline (same as Figure 7G), (E) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 26. (F) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 52. The square root enlargement rate (ERsqt) at 1 year was 0.89 mm.
**Figure 9.** Correlation between individual B-scan and the pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 7G) and blue line depicting location of B-scan shown in B. (B) B-scan through area above GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. No obvious disruption of the IS/OS band was observed.

**Figure 10.** Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 7G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area and GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Red dashed lines show correlation between dark area on en face image and IS/OS disruption on B-scan and correlation between GA and outer retinal atrophy and increased choroidal reflectivity seen on B-scan.

**Figure 11.** Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 7G) and blue line depicting location of B-scan shown in B. (B) B-scan through GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Red dashed lines show correlation between GA and outer retinal atrophy and increased choroidal reflectivity seen on B-scan.
Figure 12. Baseline images of GA from both eyes of an 83-year-old woman with nonexudative age-related macular degeneration and diffuse disruption of the outer retina. (A,B) Color fundus images with a superimposed square depicting the area scanned with spectral-domain optical coherence tomography (SD-OCT) imaging. (C,D) Fundus autofluorescence images with a superimposed square depicting the area scanned with SD-OCT. (E,F) Sub-RPE slabs. (G,H) En face images derived from the outer retinal slab described in Figure 1 with the superimposed images of GA (white) derived from the corresponding sub-RPE slabs at baseline.

Figure 13. Growth of GA in the right eye of the patient described in Figure 12. Sub-RPE slab at baseline (A), week 26 (B), and week 52 (C). (D) Baseline en face image with the superimposed image of GA (white) derived from the corresponding sub-RPE slab at baseline (same as Figure 12G). (E) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 26. (F) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 52. The square root enlargement rate (ERsqt) at 1 year was 0.49 mm.
Figure 14. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 12G) and blue line depicting location of B-scan shown in B. (B) B-scan through area above GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Subretinal deposits and undulating IS/OS band can be visualized.

Figure 15. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 12G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area and GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Red dashed lines show correlation between dark area on en face image and IS/OS disruption on B-scan and between GA and outer retinal atrophy and increased choroidal reflectivity seen on B-scan.

Figure 16. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 12G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area and GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Red dashed lines show correlation between dark area on en face image and IS/OS disruption on B-scan and between GA and outer retinal atrophy and increased choroidal reflectivity seen on B-scan.
Figure 17. Baseline images of GA from both eyes of a 70-year-old man with nonexudative age-related macular degeneration and diffuse disruption of the outer retina. (A,B) Color fundus images with a superimposed square depicting the area scanned with spectral-domain optical coherence tomography (SD-OCT) imaging. (C,D) Fundus autofluorescence images with a superimposed square depicting the area scanned with SD-OCT imaging. (E,F) Sub-RPE slabs. (G,H) En face images derived from the outer retinal slab described in Figure 1 with the superimposed images of GA (white) derived from the corresponding sub-RPE slabs at baseline.

Figure 18. Growth of GA in the right eye of the patient described in Figure 17. Sub-RPE slab at baseline (A), week 26 (B), and week 52 (C). (D) Baseline en face image with the superimposed image of GA (white) derived from the corresponding sub-RPE slab at baseline (same as Figure 17G). (E) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 26. (F) Baseline en face image with the superimposed baseline GA and an outline showing the growth of GA at week 52. The square root enlargement rate (ERsqt) at 1 year was 0.32 mm.
Figure 19. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 17G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area above GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Subretinal drusenoid deposits and hyperreflective material within outer retina and irregular IS/OS band are observed.

Figure 20. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 17G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area and GA corresponding to blue line on en face images in A and C. (C) Magnified portion of the en face image with blue line depicting location of B-scan shown in B. The red dashed lines show correlation between dark area on en face image and IS/OS disruption on B-scan and between GA and outer retinal atrophy and increased choroidal reflectivity seen on B-scan.

Figure 21. Correlation between individual B-scan and pattern observed on outer retinal en face image. (A) Baseline en face image with superimposed baseline GA (same as Figure 17G) and blue line depicting location of B-scan shown in B. (B) B-scan through dark area and GA corresponding to blue line on en face images in A and C. (C) Magnified portion of en face image with blue line depicting location of B-scan shown in B. Red dashed lines show correlation between dark area on en face image and IS/OS disruption on B-scan and between GA and outer retinal atrophy and increased choroidal reflectivity seen on B-scan.
DISCUSSION

En face imaging of the outer retina appears to be a novel and useful strategy for identifying areas at risk for the appearance and progression of GA in eyes with nonexudative AMD. The potential usefulness of this imaging strategy in predicting disease progression can be appreciated in the two cases shown in Figures 2 through 11. In these cases, the areas that appeared dark on the en face slab images at baseline correlated with the growth of GA over the next year. These focal dark areas predicted the asymmetric, directional growth characteristics of the GA. The GA tended to grow into these dark areas rather than grow uniformly around the border of the GA. Moreover, the dark areas recapitulated the areas of GA depicted in the fellow eyes, suggesting that this IS/OS disruption of the photoreceptors might represent an early defect leading to GA and may be a feature of the GA that corresponds to a particular genetic subtype of nonexudative AMD. Previous studies have suggested that photoreceptor dysfunction was a harbinger of disease progression in nonexudative AMD, and this en face SD-OCT imaging approach confirms that the IS/OS region and outer nuclear layer can appear abnormal in areas that are destined to develop atrophy. While this disruption of the IS/OS region does not always result in the appearance of atrophy within a year, it appears to be an anatomic change that may correlate with the functional deficits that have been previously reported to predict the appearance and progression of GA in some eyes. Based on the hyperautofluorescence pattern seen in these areas at risk for forming GA, it is still not possible to separate the roles of the photoreceptors and the RPE in promoting the appearance of GA; however, it is striking how closely the IS/OS disruption corresponded with the extent of progression of GA at 1 year in these two cases. This en face imaging strategy was able to accurately predict the growth of GA over a defined period of time in these eyes with the focal pattern.

SD-OCT outer retinal slab imaging may also provide a unique opportunity to conveniently and accurately follow photoreceptor abnormalities during clinical trials designed to test novel therapies for nonexudative AMD. Currently, the most utilized clinical trial endpoint is to prevent or slow the enlargement of GA over a defined period of time. This SD-OCT outer retinal imaging strategy suggests that photoreceptor damage may have already occurred at quite a distance from the edge of GA, and that this edge of GA where the IS/OS region is disrupted may be more likely to progress. If this photoreceptor damage is irreversible, then any trial designed to test a new drug by following the progression of GA might need to take these areas into account at baseline and determine if additional damage to photoreceptors can be prevented. However, if this disruption of the IS/OS region is reversible, then certain treatments might even show a regression of these dark areas seen on SD-OCT outer retinal slab imaging even though some progression of GA might occur. It is also possible that certain treatment strategies may prove to be beneficial depending on whether these outer retinal abnormalities are present or absent at the start of the study. For example, certain emerging treatments, such as visual cycle modulators, may have more of an effect on eyes with or without existing photoreceptor dysfunction that already have significant disruption of the IS/OS region compared with eyes with very little of this outer retinal abnormality. These visual cycle modulators might even cause a detectable change in the length of the outer photoreceptors that can be imaged using this SD-OCT slab approach, and this imaging strategy might serve as a useful way to determine if an appropriate dose of the drug has been achieved. Currently, electrophysiological testing is used to monitor suppression of the visual cycle using these drugs.

Subretinal drusenoid deposits can also be identified qualitatively using this SD-OCT outer retinal slab en face approach. In the early stages of the disease, the subretinal drusenoid deposits correspond to a lacy undulating pattern when imaged using this outer retinal slab strategy. As the deposits enlarge and disrupt the IS/OS region, the en face approach shows more of a speckled appearance due to the hyperreflective material in the region contained within the slab. While autofluorescence and reflectance imaging will remain a sensitive way to detect the presence of reticular pseudo-drusen, the only way to confirm the presence of subretinal drusenoid deposits is by SD-OCT imaging, and en face SD-OCT imaging of the IS/OS region may prove useful as a way of showing the distribution of subretinal drusenoid deposits in the posterior pole.
While this study provided comprehensive follow-up over 1 year and evidence to suggest that outer retinal changes can predict the growth and progression of GA in some eyes, the sample size was small and additional patients are needed to determine the incidence rates of these different slab patterns in eyes with nonexudative AMD. Currently, this imaging strategy is limited by the lack of an automated algorithm that registers the area of GA observed on the sub-RPE slabs to the outer retinal slab en face images so that the surrounding dark areas can be appreciated in relation to the GA. When the slab image is viewed in the absence of the superimposed GA, the boundaries of the dark area are more difficult to appreciate due to both the disruption of the normal retinal anatomy and the segmentation artifacts that occur within the area of the GA. These problems are concealed when the area of GA is filled in with white and registered to the en face image.

Currently, not all SD-OCT instruments are capable of outer retinal slab en face imaging. A recent study using en face images derived from manual segmentation of the IS/OS band in eyes with macular telangiectasis type 2 demonstrated the usefulness of this strategy in measuring the area of IS/OS disruption. Most likely, as the usefulness and popularity of this en face imaging strategy grows, more manufacturers will provide algorithms to permit this type of fundus visualization.

While full-field ERG, multifocal ERG, and micro-perimetry can provide functional testing of eyes with nonexudative AMD, these functional techniques are time-consuming and do not offer the same level of spatial resolution as SD-OCT imaging. The advantage of using SD-OCT imaging to follow nonexudative AMD patients, especially in clinical trials, is that the same SD-OCT scan that is used to quantitate GA, drusen, and the appearance of choroidal neovascularization can also be used to assess the integrity of the photoreceptor inner and outer segments. While we have chosen to use slab imaging to visualize the IS/OS region as a surrogate for photoreceptor integrity, it is theoretically possible to develop automated algorithms to visualize the integrity or thickness of any structure within the retina that can be detected using SD-OCT imaging. As the resolution, speed, and depth of OCT imaging improve, we should be able to perform highly detailed en face imaging of the retina, RPE, and choroidal vasculature. Slab en face imaging should help us identify the early changes responsible for the progression of AMD in different patients and improve our ability to phenotype, genotype, and follow our patients in therapeutic trials.


