Background and Objective: To compare images of geographic atrophy (GA) obtained using spectral domain optical coherence tomography (SD-OCT) with images obtained using fundus autofluorescence (FAF).

Patients and Methods: Five eyes from patients with dry AMD were imaged using SD-OCT and FAF, and the size and shape of the GA were compared.

Results: GA appears bright on SD-OCT compared with the surrounding areas with an intact retinal pigment epithelium because of increased reflectivity from the underlying choroid. SD-OCT and FAF both identified GA reproducibly, and measurement of the area of GA is comparable between the two methods with a mean difference of 2.7% of the total area.

Conclusion: SD-OCT can identify and quantify areas of GA. The size and shape of these areas correlate well to the areas of GA seen on autofluorescence images; however, SD-OCT imaging also provides important cross-sectional anatomic information.

Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss among the elderly. The advanced form of AMD associated with severe vision loss is characterized by the development of macular neovascularization and geographic atrophy (GA). The vision loss attributable to macular neovascularization results from the growth, leakage, and hemorrhage of abnormal blood vessels leading to disciform scar formation and loss of photoreceptors, whereas the loss of visual acuity in GA results from the loss of the choriocapillaris, retinal pigment epithelium (RPE), and photoreceptors. In patients with GA outside the foveal center, at least 30% will lose an average of three lines of visual acuity over a 2-year period, and within 4 years, 25% of patients with GA who had good visual acuity will decline to 20/200 or worse.

Vitamin supplementation is the only treatment known to slow the progression to advanced AMD; however, two phase 2 clinical trials are underway investigating drugs that may prevent the growth of GA in AMD. These drugs include an oral agent known as...
fenretinide (Sirion Pharmaceuticals, Tampa, FL) and a topical agent known as OT-551 (Othera Pharmaceuticals, Exton, PA), with other drugs being considered and in preclinical or early phase 1 studies.6,7

GA has been defined as an area of partial or complete depigmentation of the RPE as seen in fundus photographs with at least two of the following three characteristics: generally round or oval shape, sharp margins, and visibility of underlying large choroidal vessels.8 Although the existence of GA generally could be detected, graders at reading centers had difficulty reproducibly measuring atrophic areas because of variable fundus pigmentation and the presence of drusen. In test results for consistency among graders, there was agreement for only 30 of the 43 pairs (70%) of fundus photographs when assessing the number of atrophic areas, the number of spared areas, or the configuration of atrophy with less than a 0.5-disc area (DA) difference in total atrophic area.9 In another study, nonstereomydriatic digital fundus photographs were found to have a sensitivity of only 66.0% and a specificity of 86.9% compared with the gold-standard of a clinical exam.10 In yet another study using stereo fundus photographs, the agreement among graders as to the existence of GA ranged between 88% and 98% (κ = 0.60–0.95), whereas the weighted agreement for the area covered by GA ranged between 93% and 99% with weighted kappa values between 0.79 and 0.97.11 These results showed good reproducibility only for lesion sizes with very broad dimensions (ie, 500-1,000 µm vs 1,000-3,000 µm).

Other imaging modalities such as fundus autofluorescence (FAF) may improve the precision and reproducibility of assessing GA compared with fundus photography. FAF is related to lipofuscin in the RPE,12 and areas of GA are visualized as distinct and confluent areas of hypoautofluorescence.13 Although it appears as though FAF could be a more reliable and reproducible technique for the assessment of GA compared with fundus photography, no such comparisons have been reported.

Spectral domain optical coherence tomography (SD-OCT), also known as Fourier domain OCT, high-speed OCT, or high-definition OCT, is another strategy capable of imaging GA. SD-OCT has the ability to noninvasively image the fundus using infrared light. Image acquisition with SD-OCT is accomplished without repeatedly scanning the reference arm mirror to determine depth information as is required in time domain OCT. Instead, the returning signal is measured with a spectrometer in the detection arm of the interferometer and converted by Fourier transformation to obtain the depth information provided previously by the moving reference arm. As a result, SD-OCT has a markedly faster speed of imaging, and it acquires a much larger volume of data.14,15 The three-dimensional data acquired can then be used to create an OCT fundus image (OFI) by summing the signal of each of the A-scans and viewing their relative values en face.16,17

In patients with GA, the OFI appears to demarcate areas of GA by showing an increased total signal in areas where the GA is apparent on clinical examination, fundus photography, and autofluorescence imaging. The increased OCT signal associated with GA arises from the absence of the RPE and choriocapillaris,18 two layers of the eye that normally cause the incident light to scatter, thus preventing deeper transmissions of light. This report describes a comparison between the OFIs obtained using SD-OCT and autofluorescence in AMD patients with GA and serves as proof of concept that GA can be imaged using SD-OCT.

### PATIENTS AND METHODS

Approval to perform SD-OCT imaging on patients was obtained from the Institutional Review Board at the University of Miami Miller School of Medicine, and all patients signed informed consents. SD-OCT imaging was performed on five left eyes of patients with AMD who had funduscopic exams, color fundus photographs, and FAF imaging showing GA.

SD-OCT images were obtained using the Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA). This SD-OCT device has an axial resolution of 5 µm and can perform 27,000 A-scans per second. The central macula of each patient’s left eye was imaged using a 200 × 200 raster scan pattern (the first number refers to the number of A-scans used to form each horizontal B-scan, whereas the second number is the total number of horizontal B-scans) and was acquired in approximately 1.5 seconds. The SD-OCT was calibrated so that the horizontal and vertical dimensions of the OFI generated from all 40,000 A-scans measured 6 × 6 mm (Fig. 1).
Autofluorescence images were obtained using the Topcon TRC-50IX color fundus camera (Topcon Medical Systems, Paramus, NJ) with either Topcon Imagenet software or Ophthalmic Imaging Systems (OIS, Sacramento, CaA) acquisition software and filters. Filters for each system were made by Spectrotech, Inc. (Saugus, MA) to the specifications described by Spaide, with an excitation filter peak transmission at 580 nm and a barrier filter peak transmission at 695 nm. No averaging or processing of the images was performed after acquisition.

The OFI was registered to the fundus photographs and FAF images by rigidly superimposing the OFI on the retinal vasculature of the fundus image. These images were then pixelated so that structures could be compared on an equal scale. ImageJ, a freeware program developed by the NIH (http://rsb.info.nih.gov/ij/), was then used to manually draw perimeters around the atrophic areas on the FAF images as well as on the OFIs. Color photographs were not analyzed because the borders of the atrophy were not clearly distinguishable in each of the patients. The borders of GA were drawn three times around the central areas of atrophy on the FAF image and the OFI independently by two graders (BJL and FW). In this proof of concept study, neither additional peripheral patches of atrophy nor small islands of intact RPE within the central atrophic region were considered. The area enclosed in the boundary was then computed for each of the pairs of images. The pixel area was then converted back to square millimeters using the same fixed ratio established by the calibrated SD-OCT.

For each patient, there were two sets of three independent drawings of the border around the area of atrophy performed on both the FAF image and the OFI. We compared reproducibility of the area manually identified on OFI and FAF for each of these modalities and between the two modalities, as well as the concordance between the two graders using a linear mixed model analysis.

**RESULTS**

Mean age of the five patients was 80.4 years; three patients were men; and their vision ranged from 20/40 to 20/400 (median, 20/200). All patients were pseudophakic and had a central predominant patch of GA in addition to drusen and RPE hyperpigmentation. Patients in our study had no history of neovascular AMD and no previous treatment with laser photocoagulation, photodynamic therapy, or intravitreal injections.

Figure 1 shows the relationship of the B-scan in...
forming an OFI. The dotted line in the OFI represents the location of the B-scan shown below. Areas that appear bright on the OFI line up exactly with areas of RPE loss and increased signal from the choroid compared with the relatively darker areas where the RPE is intact.

The area of GA identified by the OFI is qualitatively comparable with the area visualized by FAF. Visual inspection of the two images demonstrates a striking similarity in the size and shape of the atrophy (Fig. 2). In these examples, the area of atrophy on both FAF and the OFI are well demarcated compared with the fundus photographs.

The mean area and standard deviation as a percentage of that area for each subject and each of the graders is shown in the Table. The average difference between measurements made with OCT and autofluorescence was highly significant \( P < .001 \), but also small with a mean of 0.25 mm\(^2\) (95% confidence interval, 0.17-0.34 mm\(^2\)) or 2.7% (1.8%-3.6%) of the average lesion size. The average difference between graders, 0.02 mm\(^2\), was not statistically significant \( P = .64 \). The interclass correlation coefficient, which expresses the variability between GA lesions as a percentage of the total measurement variability, including lesions, graders, and measurement type (FAF vs SD-OCT), was 99.8%.

Partial thickness OFIs were generated for each of the five patients using a volume of data from within the choroid that was based on the geometry of the intact RPE (Fig. 3). This resulted in enhanced contrast of the area of GA but was not analyzed separately.

**DISCUSSION**

The reconstructed OFI integrates each A-scan and shows the spatial distribution of the signal intensity within the macula. The areas of increased signal intensity identified by the OFI correlate with the absence of the RPE and represent areas of GA. Each B-scan shows an increased signal from areas of atrophy compared with adjacent areas where the anatomy is more intact. This area is brighter on the OFI because the absence of melanin granules within the RPE and the absence of blood in the choriocapillaris allow for less light scatter and an increased amount of signal to be recorded from the deeper choroidal structures.

In this study of five GA lesions, the areas of atrophy measured using the OFIs were reproducible and comparable with those areas measured using FAF images. The differences in lesion size estimates with the two imaging techniques was small at 2.7% of the total lesion size with minimal difference in the discrepancies between repeat measurements made using both imaging modalities by separate graders. However, the major limitation of this study is that only a small number of eyes with GA were analyzed.

As a proof of concept, manual identification of the GA using the OFI has been shown to be
reproducible in this small number of patients and could be used as a practical method to quantify the presence and progression of GA in a large clinical trial. An automated tool could be developed to help quantify GA from either full or partial thickness OFIs. Partial thickness OFIs have been described previously and are generated by using a subset of the data collected in each SD-OCT scan. This approach has been used previously to visualize choroidal vessels. The thickness and position of the image could be adjusted to reduce the noise generated from the overlying retinal structures and optimize the visualization of the GA.

The advantages of imaging GA using SD-OCT is that most clinicians will be purchasing a system in the near future and no additional equipment will be necessary. However, to obtain FAF images using a standard digital fundus camera, a special set of filters need to be obtained. Even once these filters are in place, the image quality is highly variable depending on the resolution of the camera system, the dilation of the pupil, the presence and severity of a cataract, and the expertise of the photographer. In contrast to these limitations, SD-OCT is easier to operate with fewer limitations in reference to pupil size or cataract. Another option is to obtain a dedicated FAF imaging system using a scanning laser ophthalmoscope; however, these tend to cost as much as an SD-OCT system and provide planar information only. An apparent disadvantage to the

### Table

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<th>Patient (Grader)</th>
<th>SD-OCT Area</th>
<th>FAF Area</th>
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SD-OCT = spectral domain optical coherence tomography; FAF = fundus autofluorescence; SD = standard deviation.

Figure 3. A, B-scan through GA. Dotted lines represent contour of the intact RPE. B, Partial OFI derived from area between dotted lines from each B-scan. The location of the B-scan shown in A is indicated with horizontal line. C, Standard OFI.
scan protocol used by this SD-OCT system is the relatively small (6 × 6 mm) scan area compared with an FAF image. However, overlapping SD-OCT scans could be acquired and, in principle, a montage could be created that covers a larger area within the macula. Another advantage of FAF imaging over SD-OCT may be the capability to detect areas of hyperautofluorescence using FAF imaging. The patterns of hyperautofluorescence may be predictive of an increased rate of progression for GA; however, the reproducibility of these patterns and their predictive value remain controversial.20,21 Currently, there does not appear to be an SD-OCT correlate for areas of hyperautofluorescence.

Now that growth of GA has become a primary endpoint in clinical trials of drugs for the treatment of dry AMD, the need to reliably quantitate GA and the progression of GA has become increasingly important. In our study, both FAF and SD-OCT appear to be reproducible methods to precisely measure the central area of GA. SD-OCT, however, collects a three-dimensional dataset that can be analyzed beyond its en face image. This is useful in assessing the true cross-sectional anatomy of the retina and determining the full extent of macular atrophy and other dry AMD pathology. After all, when assessing the progression of disease, it may be important to look at all the layers of the macula rather than just the lipofuscin content of the RPE. The true utility of SD-OCT and the OFI will be tested in ongoing prospective clinical trials.

REFERENCES


