Comparison of Geographic Atrophy Growth Rates Using Different Imaging Modalities in the COMPLETE Study

Zohar Yehoshua, MD, MHA; Carlos Alexandre de Amorim Garcia Filho, MD; Renata Portella Nunes, MD; Giovanni Gregori, PhD; Fernando M. Penha, MD, PhD; Andrew A. Moshfeghi, MD, MBA; SriniVas Sadda, MD; William Feuer, MS; Philip J. Rosenfeld, MD, PhD

BACKGROUND AND OBJECTIVE: To compare the measurements and growth rates of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) obtained using different imaging modalities.

PATIENTS AND METHODS: Thirty patients with AMD and GA measuring from 1.25 mm² to 18 mm² based on spectral-domain optical coherence tomography (SD-OCT) fundus imaging were enrolled. Imaging was performed at baseline and at follow-up months 3, 6, 9, and 12, including autofluorescence (AF) imaging with a fundus camera-based flash system (TRC-50DX; Topcon Medical Systems, Oakland, NJ); AF excitation λ: 535-585 nm; detection λ: 605-715 nm), AF and fluorescein angiography (FA) imaging with a confocal scanning laser ophthalmoscopy (SLO) system (Spectralis; Heidelberg Engineering, Heidelberg, Germany); AF excitation λ: 488 nm; detection λ: > 500 nm), and SD-OCT en face imaging (Cirrus; Carl Zeiss Meditec, Dublin, CA).

RESULTS: Average baseline square root measurements and enlargement rates of square root areas appeared similar across all modalities; 0.2 mm was the largest difference between any pair of measurement means. The intraclass correlation coefficients (ICC) were essentially equal to 1 for all comparisons of area measurements but were lower for growth rates than area measurements. Comparison of 26-week average enlargement rates showed no significant difference between the SLO AF image and enhanced SD-OCT en face image (mean difference: 0.01 mm; SD: 0.10; P = .70).

CONCLUSION: Agreement among all imaging modalities in measuring the areas of GA at baseline diminished when the growth rates of GA were compared over 26 weeks, likely because each imaging technique identifies different anatomic features along the border of GA, which may appear similar but change at different rates.

INTRODUCTION

The pathogenesis of age-related macular degeneration (AMD) is a combination of genetic and environmental risk factors. Although neovascularization is the most common cause for severe vision loss, geographic atrophy (GA) is responsible for approximately 35% of all cases of late AMD. As the population ages and patients with neovascular AMD are treated with inhibitors of vascular endothelial growth factor (VEGF), the prevalence of GA is expected to rise sharply. GA often develops as one or several small parafoveal lesions that enlarge and coalesce over time, often sparing the fovea until late in the course of the disease. On funduscopy, GA appears as a sharply demarcated area with exposed choroidal vasculature resulting from the loss of outer neurosensory retina, retinal pigment epithelium (RPE), and choriocapillaris. Multiple imaging modalities have been used to monitor and evaluate GA, including color fundus photography (CFP), fundus autofluorescence (FAF), fluorescein angiography, optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA).

From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida (ZY, CAGF, RPR, GG, FMP, AAM, WF, PJP); the Department of Ophthalmology, Federal University of São Paulo, UNIFESP, São Paulo, Brazil (CAGF, FMP); and Doheny Eye Institute, Keck School of Medicine, Los Angeles, California (SS).

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Address correspondence to Philip J. Rosenfeld, MD, PhD, Bascom Palmer Eye Institute, 900 NW 17th Street, Miami, FL 33136; email: prosenfeld@med.miami.edu. doi: 10.3928/23258160-20150422-03
(FA), and spectral-domain optical coherence tomography (SD-OCT).6-8

High-quality, stereoscopic color fundus imaging has been the gold standard in identifying and evaluating the severity and progression of AMD in epidemiologic eye disease studies.3-15 Due to inter-patient variability of fundus pigmentation, media opacities, variable stereopsis, and the presence of small satellites of atrophy, graders at reading centers have reported difficulty reproducibly measuring GA.14,15 The standard CFP criteria are not always specific enough to differentiate GA from its precursors, such as depigmentation and drusen, which also appear roughly circular, and the borders of GA can be difficult to distinguish in lightly pigmented eyes.16 Other imaging modalities such as FAF using a fundus camera or a confocal scanning laser ophthalmoscope (cSLO) have been used to image GA and may offer improved detection and reproducibility when assessing atrophic lesion size.17-19 RPE lipofuscin20 and a complex mixture of fluorophores that are byproducts of the visual cycle21 dominate fundus autofluorescence generated with short-wave length excitation. These fluorophores accumulate in the RPE as a result of photoreceptor cell outer segment phagocytosis. In FAF imaging, GA is characterized by a loss of FAF due to the loss of lipofuscin contained within the RPE. The difference in contrast intensity between atrophic and intact areas is often very obvious, and the contours of the atrophic areas can be more distinct in FAF images compared with color fundus images. Areas of increased FAF outside the margins of GA may be associated with excessive accumulation of RPE lipofuscin or a reduplication of the RPE and a variable loss of retinal sensitivity.22,23 In addition, FAF characteristics that are not identified by fundus photography or fluorescein angiography may serve as prognostic indicators of disease progression. There is a correlation between the pattern of increased autofluorescence surrounding GA and the growth rate of GA in patients with AMD.22,24-26 Limitations of FAF imaging include the difficulty of detecting GA and its boundaries in the presence of advanced cataracts and when using the cSLO-based imaging system, the difficulty in identifying the boundaries of GA in close proximity to the foveal center because of the retinal xanthophylls that absorb the excitation light and prevent autofluorescence from the underlying RPE.17,27 SD-OCT is an imaging modality capable of producing high-speed, high-resolution, high-density three-dimensional cross-sectional images covering the central macula.6,28 Several studies have used SD-OCT to describe a wide spectrum of morphologic alterations that appear within the atrophy as well as within the surrounding retinal tissue.6,29-31 SD-OCT provides both qualitative information, such as ultrastructural changes, and quantitative parameters, such as the area of GA.31-38 Area measurements can be obtained by summing the signal of each of the A-scans and viewing their relative values using an en face approach known as an OCT fundus image (OFI).29,32,33 GA appears as a bright area in this OFI due to the increased penetration of light into the choroid where atrophy has occurred in the macula.

GA was previously shown to be reproducibly identified and measured using the OFI as well as an enhanced technique known as the sub-RPE slab.34 Advantages of using the SD-OCT fundus images compared with other imaging strategies for GA include the convenience of using only one type of imaging technique for documenting both en face and cross-sectional images of the macula and monitoring patients for conversion from dry to neovascular AMD. This imaging approach ensures that the area of perceived GA actually corresponds to the loss of outer retinal anatomy and RPE, which correlates with the loss of visual function.

Previous studies have compared the measurements of GA obtained using different imaging modalities and found significant correlation between GA areas measured using SD-OCT and FAF35-37 and using FAF and color fundus imaging.38 However, it was unclear whether the growth rates were different using these different strategies. In this study, we compared different imaging modalities to determine whether there was a difference not only in the size of GA but also in the calculated growth rates when using camera-based FAF, cSLO FAF, FA, and SD-OCT imaging.

PATIENTS AND METHODS

Thirty patients were enrolled from the COMPLETE study from November 2009 to March 2011. Eighteen fellow eyes met the inclusion criteria and were analyzed as a secondary endpoint. The COMPLETE study was an investigator-sponsored prospective, randomized, placebo-controlled, double-masked, single-center study designed to evaluate the safety and efficacy of intravenous eculizumab for the treatment of patients with GA secondary to AMD.39 The study was performed with approval by the Food and Drug Administration (IND #104471). Before the initiation of the study, additional approval was obtained from the institutional review board at the University of Miami, Miller School of Medicine. Informed consent was obtained from all patients before determination of full eligibility, and the study was performed in accordance with the Health Insurance Portability and Accountability Act. Eligibility
Ophthalmological Examination and Imaging Procedures

Imaging techniques used in this study included color and autofluorescence (AF) imaging with a fundus camera-based flash system (TRC-50DX; Topcon Medical Systems, Oakland, NJ; AF excitation λ: 535 to 585 nm; detection λ: 605 to 715 nm), AF and fluorescein angiographic imaging with a cSLO system (Spectralis; Heidelberg Engineering, Heidelberg, Germany; AF excitation λ: 488 nm; detection λ: > 500 nm), and SD-OCT imaging with both the Cirrus (Carl Zeiss Meditec, Dublin, CA) and Spectralis (Heidelberg Engineering, Heidelberg, Germany) instruments. Confocal SLO autofluorescence images were acquired using the high-speed, low-resolution mode and the automatic real time (ART) mean function.

The Cirrus SD-OCT system was used to acquire 200 × 200 cubes centered at the fovea. From these datasets an en face OFI was generated, as well as an enhanced en face OFI, which is obtained from a slab beneath the RPE (sub-RPE slab).34 The OFIs represent virtual fundus images resulting from the en face summation of the reflected light from each A-scan. The OFI uses all of the reflected light, whereas the enhanced OFI (sub-RPE slab) only uses the light from a region beneath the RPE.

The areas of GA observed in the OFI and the sub-RPE slab images were manually outlined by two independent graders (CAAGF and ZY) at the Bascom Palmer Eye Institute using a CintiQ WACOM digitizing tablet (WACOM Corp., Vancouver, WA) and image analysis software (Adobe PhotoshopCS2; Adobe Systems, San Jose, CA) as previously described.40 A consensus grading results was used for subsequent analysis. In the cases in which the two graders could not reach an agreement on the outlines of the GA, a third senior grader (PJR) outlined the lesion, and his measurement was used for the analysis. The Topcon flash AF images were registered to the OFI using custom-built retinal image registration software based on the blood vessels ridges.41 These registered flash-AF images, the cSLO-AF images, and FA images were manually outlined by two certified graders at the Doheny Eye Institute Reading Center (DIRC), and one consensus measurement was used for the analysis. Two graders delineated the region of GA in an independent masked fashion. In accordance with previously published reading center protocols, DIRC separately identified areas of definite and questionable GA on the AF images. A zone of definite decreased autofluorescence (DDAF) is defined as a well-demarcated area (or areas) of decreased autofluorescence where the reduction in AF is at least 90% of the intensity level of the optic nerve or retinal vessels. These areas of DDAF were manually outlined using standard previously described planimetric grading software (GRADOR). The graders also outlined areas of questionable decreased AF (QDAF). The reading center medical director (SS) re-reviewed and confirmed or adjusted the gradings for each case to yield a final result for each case and modality. Both graders were shown to have excellent grading reproducibility for GA lesions in previous clinical trials. To compute the area of GA, we report results using both the DDAF and the combined regions of both definite and questionable AF. The area measurements of GA then underwent a square root transformation. This approach eliminated the influence of lesion size on test-retest variability and growth rates.40 The growth of GA was defined as the difference of the square root of the area measurements at the appropriate time points. Fellow eyes that met inclusion criteria were used as well in the analysis.

**TABLE 1**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrus enhanced OFI</td>
<td>48</td>
<td>2.43</td>
<td>.84</td>
<td>1.11</td>
<td>4.05</td>
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<tr>
<td>Cirrus OFI</td>
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<td>.83</td>
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<td>.00</td>
<td>3.98</td>
</tr>
<tr>
<td>CSLO DDAF+QDAF</td>
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<td>.93</td>
<td>3.98</td>
</tr>
<tr>
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<td>2.29</td>
<td>.90</td>
<td>.00</td>
<td>3.99</td>
</tr>
<tr>
<td>Flash DDAF+QDAF</td>
<td>47</td>
<td>2.33</td>
<td>.85</td>
<td>.97</td>
<td>3.99</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>48</td>
<td>2.28</td>
<td>.84</td>
<td>.88</td>
<td>3.98</td>
</tr>
</tbody>
</table>

*OCT fundus image (OFI), Confocal scanning laser ophthalmoscopic (CSLO), Definitely decreased autofluorescence (DDAF), Questionable decreased autofluorescence (QDAF)"
Statistical Analysis

Previous studies have demonstrated that taking the square-root of area measurements prior to calculating the enlargement rates of GA removed the dependence of growth on baseline area and resulted in a homogeneous test-retest variance across the range of lesion sizes.\(^40,42\) Agreement between measurement obtained using different imaging modalities was examined using intra-class correlation coefficients (ICCs) of agreement and Bland-Altman limits of agreement (LOA). A commonly accepted guide to interpretation of ICC is that less than 0.4 equals poor agreement, 0.4 to 0.75 equals fair to good agreement, and greater than 0.75 equals excellent agreement.\(^43\)

**RESULTS**

Table 1 and Figure 1 show the average square root of area measurements at baseline using each imaging modality. The average square root area measurements were similar, but there were some highly significant differences between them (\(P < .001\), repeated measures analysis of variance followed by post-hoc least significant difference tests). The two OCT-based measurements were slightly larger than all the AF and FA measurements (\(P < .001\)). The DDAF measurements using cSLO were slightly smaller than both of the flash AF measurements (\(P < .005\)). The FA measurements were smaller than the combined (definite plus questionable) flash AF measurements (\(P = .004\)). Table 2 presents ICCs between the measurements made with each pair of modalities. ICCs were all in the range considered to indicate excellent agreement (all \(\geq 0.94\)). Measurements taken at week 12 and week 26 had similar levels of agreement. Bland-Altman LOA were generally within ± 0.35 mm, after accounting for the systematic differences between the averages, which was approximately 15% of the range of measurements. Figure 2 plots the cSLO DDAF versus enhanced OFI measurements. Of note, despite the good agreement, all but one of the cSLO measurements is smaller than its corresponding OCT sub-RPE slab measurements. Evaluation of the enlargement rates for each of the imaging modality at week 26 for 48 eyes (30 study eyes and 18 fellow eyes) are shown in Table 3 and Figure 1B. On average, all modalities measured growth in the range of 6.5% to 10% of baseline averages, and the average growth of square root area did not differ between them except that FA displayed

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Comparison of modalities at baseline growth at 26 weeks. (A) Measurements of geographic atrophy for different imaging modalities at baseline. (B) Growth rate measurements of geographic atrophy at 26 weeks. OFI = OCT fundus image; AF = autofluorescence; CSLO = confocal scanning laser ophthalmoscopic; FA = fluorescein angiography.
more growth than the others (all \( P \leq .005 \)) and that the cSLO images displayed more growth in the regions of definitely decreased AF than did the flash AF (\( P = .022 \)). Negative growth estimates can be assumed to be the effect of measurement error. Figure 2 displays 26-week cSLO DDAF growth measurements versus those made with enhanced OFI.

Table 4 shows that the agreement between pairs of imaging modalities for growth rates, as assessed with ICCs, ranged from fair to excellent. The OCT-based measures of changes tended to show better agreement with combined decreased AF than definitely decreased AF images. FA measurements agreed equally well with both OCT and AF-based measures of area. Figure 1 shows the agreement between the imaging modalities for baseline area and for growth over 26 weeks. Figures 3 and 4 show an example of GA and the corresponding appearance on each of the imaging modalities.

**DISCUSSION**

This prospective study compared the measurements and growth rates for the areas of GA obtained using different imaging techniques. SD-OCT en face imaging was found to be significantly correlated with more traditional modalities for monitoring the growth of GA. This comparison demonstrated that all the methods tested could be used to quantify the extent of GA progression, but there were small systematic differences in the average measurements. The calculation of ICCs showed that most of the variance in the measurements was due to differences between eyes and less than 6% of the variance was due to differences between the measurement modalities. While the agreement between the different imaging modalities was good at any given time point, the measurements with respect to the change over a 26-week period was not as good. There are at least
three reasons that could explain why the agreement assessed with the ICC for growth was not as good as for individual measurements. First, since growth was calculated as the difference between baseline and follow-up measurements, the variability in both of the individual measurements contributes additively to the variability in growth. Second, the differences between eyes in growth over 26 weeks were much smaller than the differences between eyes in measurements at a given time point. Bland-Altman LOA provide a range in which 95% of the differences between measurements made with different modalities

Figure 3. Example of a patient with geographic atrophy using different imaging modalities. (A) Fundus photograph. (B) OCT B-scan (corresponding to the red line on fundus photo). (C) OCT fundus image (OFI). (D) Topcon (Oakland, NJ) autofluorescence (AF). (E) Heidelberg AF (Heidelberg Engineering, Heidelberg, Germany). (F) Fluorescein angiography. (G) Enhanced OFI.

Figure 4. Example of a patient with geographic atrophy using different imaging modalities. (A) Fundus photograph. (B) OCT B-scan (corresponding to the red line on fundus photograph). (C) OCT fundus image (OFI). (D) Topcon (Oakland, NJ) autofluorescence (AF). (E) Heidelberg AF (Heidelberg Engineering, Heidelberg, Germany). (F) Fluorescein angiography. (G) Enhanced OFI.
should fall. LOA between measurements made with different modalities, less than ±0.35 µm, is about 15% of the average measurements (Table 1); however, this range is larger than the average growth estimates (Table 2) during the admittedly short 26-week follow-up period, which is one of limitations of the study. We expect that with longer follow-up, the increase in lesion area (ie, a stronger signal) would outweigh the small differences between instruments and agreement would improve, especially as assessed by ICC. This is consistent with the observations of Brader et al. They evaluated the combined use of FA and CFP to detect early changes of GA growth and emphasized the importance of longer trials for the detection of especially small lesions of GA using CFP and the benefit of at least two imaging modalities for improved detection of small and new lesions. In their study, roughly 20% of new areas of GA were missed when CFP alone was used; however, this decreased to less than 10% for areas of GA present for at least 2 years and 5.5% for areas present for 3 years. A third explanation is the intrinsic differences between the imaging modalities. Khanifar et al evaluated measurements of GA using CFP and FAF. They demonstrated that as the average size of GA increased, CFP tended to measure more GA area than FAF. Conversely, as average GA size decreased, FAF tended to measure more GA area than CFP. Although this was not statistically significant, this discrepancy can be explained by properties intrinsic to both imaging types. For example, there is markedly improved contrast when measuring GA on FAF, which provides increased sensitivity for detecting small areas of atrophy in early stages of disease. This is evidenced by the larger number of foci of GA identified by graders on FAF compared with CFP. This improved contrast

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<tr>
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<th>OCT</th>
<th>Autofluorescence</th>
<th>Fluorescein angiography</th>
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<tbody>
<tr>
<td>ICC (LOA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrus OFI</td>
<td>1.00</td>
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</tr>
<tr>
<td></td>
<td>(-0.09,0.09)</td>
<td>(-0.29,0.67)</td>
<td>(-0.07,0.37)</td>
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<tr>
<td>Cirrus OFI</td>
<td>0.94</td>
<td>0.97</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>(-0.28,0.68)</td>
<td>(-0.15,0.44)</td>
<td>(-0.07,0.37)</td>
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<tr>
<td>CSLO DDAF</td>
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<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
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<td>(-0.18,0.10)</td>
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</tr>
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<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
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<td>(-0.17,0.19)</td>
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<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
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<td>(-0.35,0.10)</td>
<td>(-0.15,0.24)</td>
</tr>
<tr>
<td>Flash DDAF+QDAF</td>
<td>0.99</td>
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</table>

All areas analyzed on square root scale.

**TABLE 3**

**Average Square Root Areas at Baseline by Measurement Modality**

<table>
<thead>
<tr>
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<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
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</thead>
<tbody>
<tr>
<td>Cirrus OFI OFI</td>
<td>48</td>
<td>0.16</td>
<td>0.11</td>
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<td>0.51</td>
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<td>Cirrus OFI</td>
<td>48</td>
<td>0.17</td>
<td>0.12</td>
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<tr>
<td>CSLO DDAF+QDAF</td>
<td>48</td>
<td>0.17</td>
<td>0.14</td>
<td>0.00</td>
<td>0.67</td>
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<tr>
<td>CSLO DDAF</td>
<td>48</td>
<td>0.19</td>
<td>0.18</td>
<td>-0.04</td>
<td>0.90</td>
</tr>
<tr>
<td>Flash DDAF+QDAF</td>
<td>46</td>
<td>0.17</td>
<td>0.14</td>
<td>0.00</td>
<td>0.67</td>
</tr>
<tr>
<td>Flash DDAF</td>
<td>46</td>
<td>0.16</td>
<td>0.14</td>
<td>-0.04</td>
<td>0.66</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>48</td>
<td>0.23</td>
<td>0.15</td>
<td>-0.04</td>
<td>0.80</td>
</tr>
</tbody>
</table>

OFI = OCT fundus image; cSLO = confocal scanning laser ophthalmoscopic; DDAF = definitely decreased autofluorescence; QDAF = questionable decreased autofluorescence.
of small GA on FAF may result in underestimating GA on CFP as compared with FAF.\(^38\)

Lujan et al were the first to compare the area of GA using SD-OCT and FAF.\(^28\) They compared five eyes by superimposing both imaging modalities and delineating the borders of the disease without analyzing the retinal layer morphology. Their findings indicated that there was good correlation between atrophic GA lesions seen in both imaging modalities, but a full range of lesion sizes were not evaluated. Schmitz-Valckenberg et al\(^45\) compared the appearance of eyes with GA using both FAF and SD-OCT and showed that the mean length of an atrophic lesion measured on the FAF images had the closest agreement with the appearance of choroidal hyperreflectivity on the SD-OCT B-scan, and the reduction of the FAF signal seen from GA was spatially correlated with the abrupt transition on the SD-OCT B-scan from a hyporeflective choroid to a hyperreflective choroid. Sayegh et al\(^35\) compared SD-OCT with cSLO FAF for monitoring patients with GA. The authors evaluated and graded characteristic morphologic changes in GA as choroidal signal enhancements and alterations at the level of RPE, external limiting membrane, and outer plexiform layer and compared it to equivalent planimetric measurements on FAF images. They found a good correlation between the decreased FAF signal and SD-OCT quantification of the sub-RPE choroidal signal enhancement. The area with increased penetration of light below Bruch’s membrane where the choroid showed hyperreflectivity was the closest to represent the area of GA in SD-OCT and coincided with the complete loss of FAF.\(^55\)

While CFP imaging was the historical gold standard for identifying GA, FAF and SD-OCT imaging offer an advantage over traditional CFP imaging due to the improved contrast at the margins of GA, which allows easier detection of GA and the ability to use automated measuring strategies. While FA imaging provides a high degree of contrast, it has a disadvantage over SD-OCT and FAF imaging because it is an invasive technique requiring the infusion of fluorescein. While there have been multiple studies showing the usefulness of FAF imaging as the primary or sole means of detecting and measuring GA as well as predicting the growth rates of GA based on surrounding hyperautofluorescence patterns,\(^19,45-51\) there have been fewer reports documenting the benefits of SD-OCT en face imaging for identifying and following the progression of GA.\(^6,29,34,40,52,53\) However, there are advantages and disadvantages of SD-OCT imaging over FAF imaging. SD-OCT provides in vivo cross-sectional imaging of the actual structural layers of the retina and allows for viewing and grading of all retinal layers, so that the presence or absence of RPE can be determined anatomically, rather than presumed by using an indirect measure such as a difference in pigmentation seen on CFP imaging or an

<table>
<thead>
<tr>
<th>ICC (LOA)</th>
<th>OCT</th>
<th>Autofluorescence</th>
<th>Fluorescein angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrus enhanced OFI</td>
<td>0.91 (–0.10,0.10)</td>
<td>0.57 (–0.30,0.24)</td>
<td>0.77 (–0.17,0.17)</td>
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<td>Cirrus OFI</td>
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<td>0.66 (–0.28,0.18)</td>
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<tr>
<td>Flash DDAF+QDAF</td>
<td>0.65 (–0.29,0.18)</td>
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</table>

ICC = intraclass correlation; LOA = limits of agreement; OFI = OCT fundus image; cSLO = confocal scanning laser ophthalmoscopic; DDAF = definitely decreased autofluorescence; QDAF = questionable decreased autofluorescence.
absence of fluorescence on FAF imaging, which is an indirect measure of whether the RPE is present. SD-OCT imaging also offers the opportunity to perform fine detailed evaluation of the borders of GA at different stages of progression. In addition, en face imaging can be used to identify disruptions in the outer retinal layers, which can extend thousands of microns from the edge of GA and serve as early indicators of lesion enlargement, asymmetric growth, and progression through the fovea.52 The disruption of photoreceptor outer segments identified using en face SD-OCT imaging provides evidence of the disease extending out from the edge of GA, much as the patterns of hyperautofluorescence on FAF imaging show evidence of disease surrounding GA. One of the main disadvantages of using SD-OCT is the limited field of view that you can image compared with FAF imaging. However, the information about surrounding abnormalities in the RPE and photoreceptors provided by SD-OCT en face imaging and FAF provide complementary evidence about disease severity and likelihood of GA progression.

The major limitations of this study include its small size, the absence of CFP grading, and the comparison of growth data only through 26 weeks. The size of the study and the duration of the study were based on the COMPLETE study, which was a prospective study using an intravenous complement inhibitor known as eculizumab.59 We included different imaging modalities as a way of validating SD-OCT imaging for use in clinical trials of GA. Due to the known difficulty of measuring small changes in GA using CFP imaging, the relatively short study duration, the appreciation that FAF had replaced CFP as the accepted standard in clinical trials designed to measure GA, and the additional cost of CFP grading, we elected to forgo the expense and just compare the four imaging modalities (flash and cSLO FAF, FA, and SD-OCT) that provide the highest degree on contrast and are thought to provide the best opportunity to detect the margins of GA. Although imaging was obtained through 52 weeks, we only have reading center data for FAF and FA imaging through 26 weeks. This is due to the fact that eculizumab failed to slow the progression of GA at the primary endpoint of 26 weeks, so funding was not available to obtain reading center grading for an additional 26 weeks of images.

SD-OCT imaging was found to be equivalent to FAF imaging for measuring the progression of GA without the potential risk of blue-light damage from the use of cSLO autofluorescence imaging.54,55 SD-OCT imaging has the added benefit of identifying the anatomic changes that precede the progression of GA. When exploring novel therapies for the treatment of GA, SD-OCT imaging should be used in the hope of identifying the anatomic site where the drug may have an effect before enlargement of GA can even be detected. Because SD-OCT imaging will always be used to study the anatomy of GA in clinical trials, we propose the standard use of SD-OCT en face imaging of GA to assess its size and growth rate as well.

REFERENCES


