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Natural History of Drusen Morphology in Age-Related Macular Degeneration using Spectral Domain Optical Coherence Tomography

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Abstract

Purpose—To characterize the natural history of drusen using spectral-domain optical coherence tomography (SDOCT) imaging of eyes from patients with non-exudative age-related macular degeneration (AMD).

Design—Prospective longitudinal natural history study

Participants—One hundred forty three eyes of 100 patients with at least 6 months follow-up.

Methods—Patients with drusen secondary to non-exudative AMD were scanned using the Cirrus SDOCT instrument (Carl Zeiss Meditec, Dublin, CA). Eyes were imaged using the 200×200 A-scan raster pattern contained within a 6×6mm area. Custom software was used to quantify volumetric changes in drusen over a period of at least 6 months and for as long as 24 months. Drusen volume and drusen area were measured within circular regions centered at the fovea having diameters of 3mm and 5mm. The measurements were analyzed using a suitable scale transformation. For drusen volume, a cube root transformation strategy was used.

Main Outcome Measures—The change in drusen volume and area over time.

Results—One hundred forty three eyes of 100 patients were analyzed with 69 eyes followed for 6 months, 106 eyes followed for 12 months, 48 eyes followed for 18 months, and 48 eyes followed for 24 months. The 3mm circle baseline drusen volume ranged from 0.0009mm³ to 0.7479mm³ or 0.10mm to 0.91mm using the cube root scale. On average, drusen volume and drusen area increased over time with the magnitude of the increase dependent on the length of

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follow-up ($p=0.001$, 3mm circle). In the eyes with a decrease in drusen volume, the magnitude of this decrease was dependent on the baseline drusen volume ($p=0.001$, 3mm circle) and independent of the follow-up interval.

Conclusions—SDOCT imaging revealed a dynamic, undulating growth pattern for drusen with a tendency for drusen to increase in volume and area over time. An appreciation of the quantitative changes in drusen volume over time using SDOCT imaging provides a novel strategy for following normal disease progression and for identifying novel clinical trial endpoints to be used when investigating therapies for the treatment of non-exudative AMD.

Keywords

drusen; age-related macular degeneration; optical coherence tomography; progression; natural history

Introduction

Age-related macular degeneration (AMD) continues to be the leading cause for severe visual loss in people over 65 years of age in developed countries.¹ Drusen are one of the earliest signs of AMD and are characterized as hard or soft as well as small ($<63\text{ }\mu\text{m}$), intermediate ($>63\text{ }\mu\text{m}$ but $<125\text{ }\mu\text{m}$) or large ($\geq 125\text{ }\mu\text{m}$).^{2, 3} Different population-based studies and clinical trials have indicated that large, soft, confluent drusen are associated with a higher risk for development of advanced AMD.^{2, 4, 5} These drusen, which present early in the course of AMD, are characterized by variable size and shape and can possess ill-defined borders.

Regression of soft macular drusen has been described in clinical and histopathological studies.^{1, 6–10} Gass first noted that drusen could fade and disappear, leaving only an irregular mottling of the retinal pigment epithelium (RPE), while visual acuity might not be affected. He also observed that most cases of geographic atrophy followed the fading of drusen or the collapse of a serous detachment of the RPE resulting in degeneration and atrophy of the RPE and photoreceptors.⁶ These observations were supported by large population-based studies where it was noted that some patients showed drusen regression without any residual signs.^{1, 8, 9, 11} The Complications of Age-related Macular Degeneration Trial (CAPT) trial reported that over 6 months, 1.2% of eyes had a spontaneous reduction in drusen area by 50% and after 5 years this proportion increased to 31.2%.¹⁰ These reports support the dynamic nature of drusen with resorption of some drusen as well as the formation of new drusen, and both of these activities can occur simultaneously in the same macula.^{11, 12} While the prognostic implications of drusen regression are unknown, this naturally occurring phenomenon raises the possibility that treatments capable of altering drusen morphology could influence disease progression in AMD.

Historically, reading center evaluation of high-quality stereoscopic color fundus photographs have been the gold standard for the manual assessment of drusen to describe drusen natural history, disease severity, and the likelihood of disease progression in AMD.^{5, 13–15} However, even when color fundus photos were read by experts at a reading center, two independent area measurements often showed considerable variation and it was often difficult to delineate indistinct soft drusen.^{16–19} Many computer algorithms are now available for automated and semi-automated drusen analysis from fundus color images. Most of these automated drusen segmentation approaches are based on thresholding in the brightness domain, but their overall accuracy appears to be inadequate for clinical use.^{12, 14, 20}

The recent introduction of spectral domain optical coherence tomography (SDOCT), also known as Fourier domain or high definition OCT, has provided the opportunity to study drusen morphology. SDOCT is able to acquire high-speed, high-resolution, high-density three dimensional images which can capture the true geometry of the retina and retinal pigment epithelium (RPE) in three dimensions. SDOCT can generate high quality individual B-scans that show fine details of the drusen structure and morphology.²¹ SDOCT can also be used to obtain datasets that uniformly sample large regions of the macula and these datasets contain information on the macroscopic features of drusen.^{22, 23, 24} Segmentation algorithms can be used to extract quantitative information describing the three dimensional geometry of the RPE from the SDOCT datasets. In particular, this approach can be used to study the RPE deformations associated with drusen. We developed a novel algorithm, which produced a fully automated, quantitative assessment of these RPE deformations resulting in the measurement of drusen volume and area. This quantitative algorithm has been shown to lead to highly reproducible drusen measurements of drusen area and drusen volume.²⁴ In this study, SDOCT imaging and this novel algorithm were used to investigate the natural history of drusen morphology in the absence of geographic atrophy to determine if changes in drusen morphology can be used as a surrogate clinical trial endpoint in clinical studies designed to investigate treatments for non-exudative AMD.

Methods

This prospective study 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. This study included 143 eyes of 100 patients with a clinical diagnosis of non-exudative AMD. The patients were recruited from the retina service at the Bascom Palmer Eye Institute between 1/2/07 and 11/18/09, and followed for at least 6 months. Each patient signed an informed consent. The clinical diagnosis of non-exudative AMD was confirmed by the Bascom Palmer Eye Institute retina faculty. Biomicroscopic examination as well as digital color fundus photography and SDOCT (Cirrus HDOCT, Carl Zeiss Meditec Inc, Dublin, California) imaging were obtained to document the absence of CNV prior to including patients in the study. Eyes with geographic atrophy were excluded from this study. Patients with other concomitant retinal pathologies including pathologic myopia, diabetic retinopathy, hypertensive retinopathy, and central serous chorioretinopathy were excluded as well.

A Cirrus SDOCT instrument (Carl Zeiss Meditec, Dublin, CA) was used in this study. Macular cube scans were obtained after pupil dilatation using one drop of 2.5% phenylephrine hydrochloride and 1% tropicamide. Each eye was imaged 5 separate times in a single session using a raster scan protocol (200×200 A-scans). This protocol resulted in the acquisition of a SDOCT dataset 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. Each scan covered a retinal area of 6×6mm centered on the fovea. All scans were performed by a single experienced operator, who assessed the quality of the scan during its acquisition. Whenever possible, an effort was made to delete datasets with poor signal strength or with significant motion artifacts. The patient was repositioned during the scanning session as necessary, but there was no specific requirement to reset the patient or the instrument after acquiring each of the five separate datasets.

The raw OCT datasets were exported to a personal computer and analyzed using the algorithm described in our previous publication.²⁴ The RPE layer was segmented using a proprietary algorithm commercially available on the Cirrus SDOCT instrument. A separate algorithm was used to automatically determine the RPE floor. The RPE floor is an extrapolated virtual RPE surface representing the geometry of an RPE free of the local

deformations associated with drusen. The drusen thickness map was defined as the difference between the actual RPE segmentation and the RPE floor.²⁴ This drusen thickness map (which can be more generally referred to as the RPE deformation map) is generated from each of the 40,000 data points and was automatically calculated as previously reported.²⁴ In order to reduce spurious noise, the algorithm ignores RPE deformations with height below a given threshold. This threshold was set to 10 pixels (19.5 μm).

One of the authors performed a post-hoc review of the scans done during the same session; each scan was reviewed for quality and scans with signal strength less than 7, as well as scans with motion artifacts, were categorized as low-quality scans and discarded. The scan which appeared to have the best quality was chosen for drusen measurements, and if there were several scans of similar quality, then one was randomly selected. The position of the fovea was determined manually by scanning through the OCT dataset and finding the spot where the geometry of the inner retinal layers best matched the known anatomical configuration in the fovea. The relative location of the foveal center in the OCT dataset was then reported in x and y coordinates based on pixel position within the 200×200 array of A-scans. Drusen area and volume measurements were obtained for the macular areas within circles centered on the fovea with diameters of 3 mm (C3) and 5 mm (C5) as well as for the full dataset. Quantitative measurements of drusen were performed in the same areas contained within these circles at baseline and at each follow up visit.

In a previous study²⁴ the rationale for using scale appropriate transformations of the data prior to statistical analysis was introduced. A square root transformation was used for drusen area, and a cube root transformation was used for drusen volume. This approach was shown to have several advantages over using the non-transformed measurements. The most significant advantage was the ability to establish constant test-retest tolerance limits that were independent of drusen size. Using this strategy, we found the 95% test-retest tolerance limits for the cube root of drusen volume to be 0.025 mm for the 3mm circle (C3) and 0.028 mm for the 5mm circle (C5).²⁴

In this study, data were collected prospectively according to the patients' routine clinical care schedule and not according to a strict protocol follow-up schedule. Therefore, for each eye, all follow-up visits separated by intervals of 6 months (± 1 month), 12 months (± 1 month), 18 months (± 1.5 months), and 24 months (± 2 months) were explored. Each eye could contribute measurements to more than one interval and two different follow-up intervals from the same eye need not share the same initial measurement. However, no eye could contribute more than one measurement to an interval. This led to 271 observations of the 148 eyes included in the study. Changes in drusen volumes were summarized as population means ($\pm$ standard deviations) and also as the percent of eyes with increased, decreased, or stable measurements with respect to the test-retest limits. To account for correlated data from the same eye, statistical significance was assessed with mixed models for interval level dependent variables and generalized estimating equations (GEE) with logistic link and exchangeable covariance structure for dichotomous dependent variables.²⁵ Kaplan-Meier time to progression analyses did not employ the visit window methodology. The follow-up experience of each eye was used only once in these calculations.

Results

One hundred forty three eyes from 100 patients were enrolled. The mean age of the subjects was 77 years (range 55–93) and 60% were women. Measurements from the C3 region were obtained on all 143 eyes at all time points and measurements from the C5 region were obtained on 141 eyes at all time points. Two eyes were removed from the C5 measurements at certain time points because the corresponding available scans were not well centered on

the fovea. As a result, for those eyes and those visits, the entire C5 circle centered on the fovea extended outside the 6×6mm scan area and these measurements were not available.

Table 1 (Table 1 available at <http://aaojournal.org>) shows the incidence of progression to wet disease or development of geographic atrophy. At the 12 months follow-up, none of the eyes had developed CNV while 6 of the 143 eyes (5.1%) developed geographic atrophy. After 24 months, 5 eyes (6.7%) developed neovascular disease and 14 eyes (17.3%) developed geographic atrophy. Over time, the incidence of conversion to CNV or geographic atrophy increased, but most of the disease progression occurred after the first 12 months. Once an eye progressed to either CNV or geographic atrophy it was censored from the study.

Baseline drusen volume measured using the 3mm circle ranged from 0.0009 mm³ to 0.7479 mm³ or 0.10 mm to 0.91 mm using the cube root scale. Figures 1 and 2 (Figures 1, 2 available at <http://aaojournal.org>) show the changes in transformed drusen area and drusen volume at 6, 12, and 24 months of follow-up as a function of the baseline values. At 12 and 24 months of follow-up, there were more obvious changes in drusen area and volume than were observed at 6 months of follow-up. Negative changes appeared to occur more frequently among drusen with the larger initial volume and area measurements.

Table 2 (Table 2 available at <http://aaojournal.org>) shows the average changes in drusen measurements at 6-month intervals through 24 months expressed in terms of the cube root of the drusen volume ($\pm$ SD) and the square root of the drusen area ($\pm$ SD)²⁴ Sample sizes vary depending on the follow-up interval. Average changes were small and only achieved statistical significance for the 12 and 24 month intervals.

While the average drusen volume and area increased, Table 3 (Table 3 available at <http://aaojournal.org>) shows that individual drusen volume or area measurements can increase, decrease, or remain stable over time. Drusen measurement were designated as stable if the value at follow-up was within the 95% test-retest tolerance limits for the baseline measurement. If a drusen measurement at follow up was outside the 95% test-retest tolerance limits for the baseline measurement, then the drusen measurement was designated as having increased or decreased. The proportion of eyes that increased in volume or area measurements correlated with length of the follow-up interval for both C3 and C5 ($p<0.001$). Of note, the percentage of eyes that decreased in volume or area did not appear to change significantly over time. For example, after 6 months of follow up, 15 % of eyes had a decrease in the volume of drusen in the central 3mm of the macula compared with 13% at 24 months of follow up.

Tables 4 and 5 (Table 4, 5 available at <http://aaojournal.org>) show the distribution of significant changes in drusen measurements with respect to the initial drusen size for all follow-up intervals. Initial drusen volumes were divided into quintiles which did not differ with respect to average follow-up months ($p=0.33$), ranging from 14.9 months for the smallest quintile to 12.4 months for the largest quintile. In the C3 cohort, a decrease in drusen volume was observed in only 2% of the eyes with the smallest drusen volume (< 0.012 mm³) compared with 27% of eyes with the largest drusen volume (0.095–0.375 mm³). Drusen area showed the same tendency with a decrease in drusen area observed in only 2% of the eyes with the smallest drusen area (< 0.34 mm²) compared with 22% of eyes with the largest drusen area (1.87–4.01 mm²). Thus, the likelihood that drusen volume or area will decrease over time showed a strong dependence on initial volume or area, respectively (C3: volume $p=0.001$, area $p<0.001$). This increased likelihood for larger lesions to decrease over time is consistent with the observation that there was an increased risk of progression to either CNV or to geographic atrophy based on initial drusen volume among eyes with larger

drusen at baseline, in particular those with lesion volumes initially $\geq 0.1\text{mm}^3$. The increase in drusen volumes or areas did not show any dependence on the initial drusen volumes or areas, respectively (C3: volume $p=0.63$; area $p=0.58$). The results and trends were similar for the 5mm circle and the full dataset.

Figures 3 through 6 display the types of natural history changes in drusen morphology observed during the follow-up period. Figure 3 shows drusen that initially increase in size and then spontaneously regress without any apparent disturbance of the outer retina or RPE. In this case, the drusen volume increased over 3 months and then the drusen regressed spontaneously after 6 months of follow-up. There was a corresponding change on color fundus image which was consistent with the morphologic change in the RPE as seen on the SDOCT B-scan. This change coincided with the resolution of drusen seen on the drusen thickness map. Figure 4 shows an example of drusen which have a stable volume for over 18 months of follow-up. Figures 5 and 6 demonstrate spontaneous drusen regression with subsequent formation of CNV and geographic atrophy, respectively. In Figure 5, the drusen volume increased then decreased but there were no corresponding changes on the color fundus images even though the B-scan and drusen thickness maps showed resolution of the drusen. Three months after the drusen volume decreased, the drusen area on the color fundus image dramatically decreased, and then fluid was identified under the retina and found to be secondary to CNV.

One possible clinical trial endpoint when studying the effect of experimental treatments on drusen morphology would be to focus on a decrease in drusen area or volume over a given time period. Of the 143 eyes with drusen volume measurements from the central 3 mm of the macula, 22 (15%) decreased 50% or more of their baseline volume using the cube root scale (mm). This is equivalent to loss of at least 88% of the baseline drusen volume when expressed as mm^3 . During our follow up, fourteen (64%) of these eyes progressed to geographic atrophy, five (23%) progressed to wet AMD, and three (14%) experienced resorption of drusen without any apparent outer retinal abnormality as assessed using SDOCT, fundus photography, and autofluorescence. After dividing the drusen population into quintiles by volume, it was determined empirically that the second quintile (Table 4 available at <http://aaojournal.org>), which represented drusen with a baseline volume of at least 0.03mm^3 (cube root volume 0.31mm), could serve as a population of drusen for clinical trials because this volume of drusen were easily visualized and measured by using color fundus photography and SDOCT, and this population of drusen could decrease by 88% and still be accurately measured using the automated algorithm. As shown in Table 6 (Table 6, available at <http://aaojournal.org>), 82 eyes with a drusen volume of at least 0.03mm^3 or greater at baseline were identified and included in a Kaplan –Meier analysis. At 24 months, 17 eyes had a decrease of more than 50% of their initial volume; 14/17 developed either GA or CNV and 3/17 had a decrease of at least 50% without progression to advanced disease.

One option for a successful outcome in clinical trial could be defined as a decrease of at least 50% in the baseline cube root volume without progression to geographic atrophy or neovascular disease. If this clinical trial endpoint is to be used in a study, then it is necessary to know the incidence of spontaneous shrinkage of drusen at different time points to determine the number of patients needed for a study of a particular duration. As shown in Table 5 (Table 5, available at <http://aaojournal.org>), the incidence of at least a 50% decrease in drusen volume without disease progression at 6 and 12 months is less than 5 percent, and at 18 and 24 months, it is 7 percent.

In a clinical trial, if a positive outcome is the reduction in the cube root volume by 50% without progression to CNV or geographic atrophy, then Table 7 provides the minimum

sample size requirements for treatment and control groups assuming a particular power to detect a positive outcome if one exists. The table shows the number of patients needed for a treatment based on three different assumed efficacies over a 6 or 12 month follow-up period. A study could be designed with 90% power to detect a treatment effective in 75% of patients receiving it with about 24 subjects given a 2:1 randomization and this treatment effect could be established in as little as 6 months. A less effective treatment, such as one effective in 25% of patients receiving it given the same randomization scheme, would require approximately 274 patients in total.

Discussion

SDOCT can reliably measure drusen morphology over time and this quantitative assessment of drusen could be used as a clinical trial endpoint. In this study, a computerized algorithm was used to automatically measure drusen volume contained within circles having diameters of 3mm and 5mm centered at the fovea. The natural history of drusen was studied using this algorithm and the average drusen volume was found to increase over time. The likelihood of an 88% decrease in volume (50% decrease in the cube root of volume) increased as the drusen volume increased. At each time interval studied, the fraction of the drusen that showed an increase in volume compared with baseline got larger while the fraction of drusen with a decrease in volume remained the same. These observations suggest that drusen are morphologically dynamic with an undulating growth pattern in which drusen can go through repeated cycles of growth and shrinkage, with growth more likely than shrinkage. These results are consistent with a model where drusen have a higher probability of growing rather than shrinking over any given time interval.

The overall dynamic nature of drusen was not previously appreciated. In prior studies using color fundus photography, drusen were shown to regress dramatically over a short period of time, but these reports could only focus on the qualitative appearance and disappearance of drusen. Our SDOCT study demonstrates that the likelihood of such a dramatic collapse in the drusen volume appears to be dependent on drusen volume, with spontaneous drusen regression more commonly associated with larger baseline volumes; however, this event occurs over a range of drusen volumes and could not be predicted based on volume measurements or time of follow-up alone. Moreover, color fundus photographic assessment of drusen was unable to pick up the subtlety of how drusen morphology changes over time. It is entirely possible for drusen volume to decrease by more than 50% of the cube root volume yet have no apparent change on color fundus photography as shown in Figure 5.

Drusen size has been reported as an important risk factor of progression to advanced AMD.^{2, 26} In this current report, eyes with bigger drusen volumes were also more likely to spontaneously regress with the possibility of progressing to geographic atrophy or CNV. Following drusen regression, geographic atrophy was the more common outcome when compared with the incidence of CNV. In contrast to our results, Cukras et al. reported that the incidence of CNV in the first 2 years was markedly higher than the progression to geographic atrophy, but after 3 years the number of new progressions to geographic atrophy increased relative to CNV, and by 5 years, the incidence of geographic atrophy approached that of CNV.¹⁵ The most likely explanation for the difference in outcomes can be found in the difference in the patient populations and the imaging modalities used in the studies. The current study excluded patients at baseline with any evidence geographic atrophy in eyes with drusen. Moreover, the progression to geographic atrophy was defined as the appearance of geographic atrophy within the 5 mm circle. Other possible differences between the studies include the likelihood that the current cohort of eyes may represent an earlier stage of non-exudative AMD, and the fact that SDOCT may have greater sensitivity to detect the

onset of geographic atrophy compared with color fundus photography alone, thus resulting in a higher incidence rate of geographic atrophy compared with the rate of CNV.

Limitations of the present study include a non-standardized follow-up interval for each patient. However, the behavior of drusen appears to be more dependent on their baseline volume rather than on the length of follow-up. Another limitation is the absence of an exact one-to-one correspondence between drusen on fundus photography and the RPE deformations shown using SDOCT imaging, although drusen measurements made with SDOCT appear to correlate well with fundus photography.^{21, 22} In contrast to the drusen seen on color fundus images, the SDOCT drusen detection algorithm ignores deformation of the RPE below a 19 microns noise threshold. It should be kept in mind that drusen thickness maps from OCT datasets are representations of areas with significant disruption in the RPE geometry and not all drusen seen on color fundus images substantially affect the RPE geometry. Therefore, the SDOCT algorithm identifies a subset of drusen that are elevated and does not identify flat drusen or subretinal drusenoid deposits above the RPE. While the SDOCT algorithm cannot identify these flat drusen or the pigmentary changes seen on color fundus photography, it can and often does show the presence of RPE deformations that are not immediately evident on fundus photography. SDOCT can provide a reliable, reproducible method for measuring a particular subset of drusen that may be useful by itself or in conjunction with color fundus photography when developing improved severity scales to determine the likelihood of disease progression and when developing novel endpoints for clinical trials.

We propose that the change in drusen volume should be investigated as a novel surrogate clinical study endpoint when investigating treatments for non-exudative AMD in early stage trials. By using the change in drusen volume as an endpoint, investigators might be able to run smaller and shorter early phase clinical trials to explore therapies that would have otherwise required many more patients and much longer follow-up.

PRÉCIS

Spectral domain optical coherence tomography and a novel automated quantitative algorithm were used to study drusen over time revealing dynamic, undulating growth patterns with area and volume measurements more likely to increase than to decrease.

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Figure 1.

Relationship between the change in the square root of drusen area at 6, 12, and 24 months, and the square root of drusen area at baseline.

A. Scatter plot showing the change in the square root of drusen area (3mm circle) after 6 months, as a function of the square root of drusen area at baseline.

B. Scatter plot showing the change in the square root of drusen area (3mm circle) after 12 months, as a function of the square root of drusen area at baseline.

C. Scatter plot showing the change in the square root of drusen area (3mm circle) after 24 months, as a function of the square root of drusen area at baseline.

Figure 2.

Relationship between the change in the cube root of drusen volume at 6, 12, and 24 months, and the cube root of drusen volume at baseline

- A. Scatter plot showing the change in the cube root of drusen volume (3mm circle) after 6 months, as a function of the cube root of drusen volume at baseline.
- B. Scatter plot showing the change in the cube root of drusen volume (3mm circle) after 12 months, as a function of the cube root of drusen volume at baseline.
- C. Scatter plot showing the change in the cube root of drusen volume (3mm circle) after 24 months, as a function of the cube root of drusen volume at baseline.

Figure 3.

Right eye of a 64 year old woman with drusen followed over 6 months. Drusen were found to increase in volume and then regress spontaneously with resolution of the drusen on color fundus photo but without progression to advanced AMD. Color fundus photo with a line representing the location of the Optical Coherence Tomography (OCT) B scan (A,E,I), horizontal B-scan (B,F,J), Retinal pigment epithelium segmentation map (C,G,K), and hybrid map made of OCT fundus image and drusen thickness map (D,H,L). Images are shown at baseline (A–D), at 3 months of follow-up (E–H), and at 6 months of follow-up (I–L). Drusen volume was calculated to be 0.21 mm^3 at baseline (D), 0.26 mm^3 at 3 months of follow-up (H), and 0.001 mm^3 at 6 months of follow up.

Figure 4.

Right eye of a 75 year old woman with drusen followed over 6 months. Drusen were found to remain stable over 18 months of follow-up. Color fundus photo with a line representing the location of the Optical Coherence Tomography (OCT) B scan (A,E), horizontal B scan (B,F), Retinal pigment epithelium segmentation map (C,G), and hybrid map made of OCT fundus image and drusen thickness map (D,H). Images are shown at baseline (A–D) and at 18 months (E–H). Drusen volume was calculated to be 0.15 mm^3 at baseline (D) and 0.15 mm^3 at 18 months (H).

Figure 5.

Left eye of a 64 year old woman with drusen followed over 6 months. Drusen were found to increase in volume and then regress spontaneously but without resolution of the drusen on color fundus photo and eventual development of choroidal neovascularization with intraretinal fluid. Color fundus photo with a line representing the location of the Optical Coherence Tomography (OCT) B scan (A,E,I,M), horizontal B scan (B,F,J,N), Retinal pigment epithelium segmentation map (C,G,K,O), and hybrid map made of OCT fundus image and drusen thickness map (D,H,L,P). Images are shown at baseline (A–D), at 6 months of follow-up (E–H), at 12 months of follow-up (I–L), and at 15 months of follow-up. Drusen volume was calculated to be 0.19 mm³ at baseline (D), 0.23 mm³ at 6 months (H), and 0.028 mm³ (L) at 12 months.

Figure 6.

Right eye of a 76 year old woman with drusen followed over 6 months. Drusen were found to change to geographic atrophy over 12 months. Color fundus photo with a line representing the location of the Optical Coherence Tomography (OCT) B scan (A,F), horizontal B scan (B,G), Retinal pigment epithelium segmentation map (C,H), hybrid map made of OCT fundus image and drusen thickness map (D,I) and fundus autofluorescence (E,J). Images are shown at baseline (A–E), and at 12 months (F–J). Drusen volume was calculated to be 0.45 mm^3 at baseline (D) and 0.016 mm^3 at 12 months (H). At 12 months geographic atrophy appears with an area of 1.28 mm^2 .

Table 1

Incidence of progression to choroidal neovascularization or geographic atrophy in drusen-only eyes

Months Followed [Window] N=143	Cumulative Number with Neovascular disease	Cumulative Kaplan-Meier Percent Progression to Neovascular disease	Cumulative Number with Geographic Atrophy	Cumulative Kaplan- Meier percent Progression to Geographic Atrophy
6 [5–7]	0	0	1	0.7%
12 [11–13]	0	0	6	5.1%
18 [16.5–19.5]	1	1.3%	9	8.4%
24 [22–26]	5	6.7%	14	17.3%

Mean change ($\pm$ standard deviation) in cube root of drusen volume and square root of drusen area measurements (3 mm circle) as a function of follow-up period.

Table 2

	Cube Root of Volume (3mm)			Square Root of Area (3mm)		
	Initial	Final	Change *	Initial	Final	Change *
Month 6 N=69	0.381 $\pm$ 0.134	0.385 $\pm$ 0.139	0.005 $\pm$ 0.046	1.110 $\pm$ 0.425	1.126 $\pm$ 0.444	0.016 $\pm$ 0.149
Month 12 N=106	0.342 $\pm$ 0.133	0.359 $\pm$ 0.143	0.016 $\pm$ 0.059	0.974 $\pm$ 0.256	1.256 $\pm$ 0.428	0.052 $\pm$ 0.018
Month 18 N=48	0.375 $\pm$ 0.151	0.393 $\pm$ 0.168	0.018 $\pm$ 0.104	1.064 $\pm$ 0.454	0.100 $\pm$ 0.470	0.037 $\pm$ 0.337
Month 24 N=48	0.315 $\pm$ 0.130	0.344 $\pm$ 0.159	0.028 $\pm$ 0.085	0.892 $\pm$ 0.408	0.967 $\pm$ 0.450	0.075 $\pm$ 0.265

* Statistical significance of changes within each follow-up interval from 6 to 24 months was 0.37, 0.006, 0.24, 0.027 (volume) and 0.37, 0.005, 0.18, 0.060 (area).

Table 3

Incidence of drusen with decreased, increased, or stable measurements as a function of follow up duration *

	Cube Root of Volume (3mm)			Square Root of Area (3mm)		
	Decreased	Stable	Increased	Decreased	Stable	Increased
Month 6 N=69	10 (15%)	42 (61%)	17 (25%)	10 (15%)	44 (64%)	15 (22%)
Month 12 N=106	13 (12%)	42 (40%)	51 (48%)	14 (13%)	41 (39%)	51 (48%)
Month 18 N=48	8 (17%)	11 (23%)	29 (60%)	8 (17%)	13 (27%)	27 (56%)
Month 24 N=48	6 (13%)	9 (19%)	33 (69%)	6 (13%)	10 (21%)	32 (67%)

Generalized estimating equation p-values for the change in the proportion of decreased drusen compared with increased/stable drusen by follow-up: 3mm volume, 0.869; 3mm area, 0.872. P-values for the change in the proportion of increased drusen compared with the decreased/stable drusen by follow-up: 3mm volume, <0.001; 3mm area <0.001.

* Drusen are considered stable if the transformed endpoint measurement is within the 95% test-retest reproducibility limits from the transformed baseline value, otherwise they are classified as increased or decreased according to the direction of the change.

Incidence of significant decreases or increases in drusen volume measured using a 3mm circle as a function of initial lesions size for all follow-up periods

Table 4

Quintile	Range		N	# (%) Decreased*	# (%) Increased*
	Volume(mm ³)	Cube root Volume(mm)			
1	≤ 0.012	≤ 0.23	54	1 (2%)	26 (48%)
2	0.012 – 0.028	0.23 – 0.30	53	3 (6%)	27 (51%)
3	0.028 – 0.059	0.30 – 0.39	53	7 (13%)	23 (43%)
4	0.059 – 0.095	0.39 – 0.46	55	11 (20%)	25 (46%)
5	0.095 – 0.375	0.46 – 0.72	56	15 (27%)	29 (52%)

Generalized estimating equation p-values for the statistical significance of a linear trend in proportions with decreased (increased) volume by quintile: P=0.001 (0.59) and P=0.001 (0.92) if follow-up time was included in the model.

* Drusen are considered stable if the transformed endpoint measurement is within the 95% test-retest reproducibility limits from the transformed baseline value, otherwise they are classified as increased or decreased according to the direction of the change.

Incidence of significant decreases or increases in drusen area measured using a 3mm circle as a function of initial lesions size for all follow-up periods.

Table 5

Quintile	Range		N	# (%) Decreased	# (%) Increased
	Area (mm ²)	Square Root Area (mm)			
1	≤ 0.34	≤ 0.58	54	1 (2%)	27 (50%)
2	0.34 – 0.82	0.58 – 0.94	54	2 (4%)	24 (44%)
3	0.82 – 1.30	0.94 – 1.09	55	11 (20%)	24 (44%)
4	1.30 – 1.87	1.09 – 1.23	54	12 (22%)	25 (46%)
5	1.87 – 4.01	1.23 – 1.59	54	12 (22%)	25 (46%)

Generalized estimating equation p-values for the statistical significance of a linear trend in proportions with decreased (increased) area by quintile: P<0.001 (0.58) or P<0.001 (0.87) if follow-up time was included in the model.

* Drusen are considered stable if the transformed endpoint measurement is within the 95% test-retest reproducibility limits from the transformed baseline value, otherwise they are classified as increased or decreased according to the direction of the change.

Table 6

Incidence of progression to geographic atrophy or choroidal neovascularization and spontaneous shrinkage in a subset of drusen with baseline volume $\geq 0.03 \text{ mm}^3$.

Window (months)	Baseline Volume $\geq 0.03 \text{ mm}^3$ [Cube root volume $\geq 0.31 \text{ mm}$] (N=82)		
	Cumulative Number with Geographic Atrophy or Choroidal Neovascularization	Cumulative Kaplan-Meier Percent Progression to Geographic Atrophy or Choroidal Neovascularization	Number (%) [†] Shrinking to $<50\%$ of Baseline Cube root Volume Without Progression
6	0	0	1 (4%)
12	4	6.1%	1 (2%)
18	7	11.8%	2 (7%)
24	14	28.2%	3 (7%)

[†]denominator is defined as all lesions with follow-up in this window plus all those with prior progression to geographic atrophy or neovascular disease. Denominators were 27 for 6 months, 50 for 12 months, 29 for 18 months, and 44 for 24 months.

Table 7

Sample size table for comparing successful outcomes in treatment and control groups depending on the presumed percent treatment success* and the percent power of a study to detect a positive outcome if one exists

Ratio of Experimental to Control Randomized Eyes	Percent with Successful Outcomes in Control Group	Number of Eyes Needed in Each Group Based on the Anticipated Percent with Successful Outcomes* and the Desired Power to Detect the Outcome†					
		75%*		50%*		25%*	
		80% Power	90% Power	80% Power	90% Power	80% Power	90% Power
1:1	5%	9:9	11:11	18:18	23:23	59:59	75:75
2:1	5%	14:7	16:8	28:14	34:17	92:46	116:58

* Successful outcome was defined as shrinkage to <50% of baseline cube root volume without progression to geographic atrophy or neovascular disease.

† The number of eyes needed in each group was the same whether the follow-up interval was 6 or 12 months.