American Academy of Ophthalmology
The Eye M.D. Association

Drusen Volume and Retinal Pigment Epithelium Abnormal Thinning Volume Predict 2-Year Progression of Age-Related Macular Degeneration

Francisco A. Folgar, MD,[1] *Eric L. Yuan, BSE,*[1] *Monica B. Sevilla, MS,*[1] *Stephanie J. Chiu, PhD,*[1,2] *Sina Farsiu, PhD,*[1,2] *Emily Y. Chew, MD,*[3] *Cynthia A. Toth, MD,*[1,2] *for the Age Related Eye Disease Study 2 Ancillary Spectral-Domain Optical Coherence Tomography Study Group**

Purpose: To analyze the value of novel measures of retinal pigment epithelium–drusen complex (RPEDC) volume to predict 2-year disease progression of intermediate age-related macular degeneration (AMD).

Design: Prospective, observational study.

Participants: Three hundred forty-five AMD and 122 non-AMD participants enrolled in the Age Related Eye Disease Study 2 Ancillary Spectral-Domain (SD) Optical Coherence Tomography (OCT) study.

Methods: High-density SD OCT macular volumes were obtained at yearly study visits. The RPEDC abnormal thickening (henceforth, OCT drusen) and RPEDC abnormal thinning (RAT) volumes were generated by semi-automated segmentation of total RPEDC within a 5-mm-diameter macular field.

Main Outcome Measures: Volume change and odds ratio (OR) with 95% confidence intervals (CI) for progression to advanced AMD with choroidal neovascularization (CNV) or central geographic atrophy (GA).

Results: Complete volumes were obtained in 265 and 266 AMD eyes and in 115 and 97 control eyes at baseline and at year 2, respectively. In AMD eyes, mean (standard deviation) OCT drusen volume increased from 0.08 mm^3 (0.16 mm^3) to 0.10 mm^3 (0.23 mm^3; $P < 0.001$), and RAT volume increased from 8.3×10^{-4} mm^3 (20.8×10^{-4} mm^3) to 18.4×10^{-4} mm^3 (46.6×10^{-4} mm^3; $P < 0.001$). Greater baseline OCT drusen volume was associated with 2-year progression to CNV ($P = 0.002$). Odds of developing CNV increased by 31% for every 0.1-mm^3 increase in baseline OCT drusen volume (OR, 1.31; 95% CI, 1.06–1.63; $P = 0.013$). Greater baseline RAT volume was associated with significant 2-year increase in RAT volume ($P < 0.001$), noncentral GA ($P < 0.001$), and progression to central GA ($P < 0.001$). Odds of developing central GA increased by 32% for every 0.001-mm^3 increase in baseline RAT volume (OR, 1.32; 95% CI, 1.14–1.53; $P < 0.001$). In non-AMD eyes, all volumes were significantly lower than AMD eyes and showed no significant 2-year change.

Conclusions: Macular OCT drusen and RAT volumes increased significantly in AMD eyes over 2 years. These quantitative SD OCT biomarkers predict 2-year AMD progression and may serve as useful biomarkers for future clinical trials. *Ophthalmology 2015;■:1–12 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

In age-related macular degeneration (AMD), extracellular deposits accumulate within Bruch's membrane and between the retinal pigment epithelium (RPE) and Bruch's membrane, thickening the RPE and eventually forming drusen.[1] Similar material accumulates on the apical side of the RPE in eyes with subretinal drusenoid deposits.[2] Eyes with AMD, when categorized by color fundus photography (CFP) or fundus examination, progress from an early stage with small drusen, through intermediate stages with large drusen and pigmentary RPE changes, to advanced stages characterized by choroidal neovascularization (CNV) or central geographic atrophy (CGA).[3,4] Recent expert reviews have classified late AMD by the presence of CNV or any geographic atrophy (GA).[5] Although patients may progress to advanced AMD without evidence of preceding intermediate disease, CFP assessments of large drusen size, extensive drusen area, and hyperpigmentary changes have been recognized as risk factors for progression to advanced AMD in patients with intermediate AMD in both eyes or in the second eye of patients with advanced AMD in the first eye.[6–9]

Two-dimensional CFP does not provide complete information regarding the structure and volume of drusen and the RPE. Spectral-domain (SD) optical coherence tomography (OCT) generates detailed cross-sectional and 3-dimensional retinal images in vivo with less than 5 μm of axial resolution.[10,11] We have categorized the SD OCT microstructure of

http://dx.doi.org/10.1016/j.ophtha.2015.09.016
ISSN 0161-6420/15

drusen and correlated drusen area by SD OCT segmentation with drusen area by CFP grading.[10–13] Semiautomated computer algorithms now can perform SD OCT segmentation of retinal layers accurately and reproducibly in AMD eyes with drusen and GA.[14,15] With SD OCT segmentation of the RPE–drusen complex (RPEDC), we have developed novel quantitative biomarkers for RPE thickening from drusen and RPE thinning that identify intermediate AMD from healthy controls with 99% precision.[16]

The Age-Related Eye Disease Study 2 (AREDS2; ClinicalTrials.gov identifier, NCT00345176) is a prospective, multicenter, randomized trial that tested the effect of oral supplementation with antioxidant vitamins, minerals, and omega-3 fatty acids on the progression of AMD.[17] The AREDS2 Ancillary SD OCT Study (ClinicalTrials.gov identifier, NCT00734487) is an ancillary prospective, observational study of eyes enrolled in AREDS2, designed to identify whether SD OCT features change over time and predict progression to advanced AMD.[18] Prior reports from this study analyzed the relationship between macular pigmentary changes on CFP and hyperreflective foci on SD OCT at baseline, as well as risk of AMD progression based on presence, number, and location of hyperreflective foci at baseline.[19,20] In this report, we present the AREDS2 Ancillary SD OCT Study results of validated RPEDC segmentation and volume change at the predetermined 2-year primary end point in intermediate AMD eyes and a cohort of healthy age-controlled eyes. We compared the 2-year change in RPEDC-derived volumes between AMD and control eyes and correlated these quantitative biomarkers with 2-year growth of drusen, increase in RPE thinning, development of any noncentral GA, and progression from intermediate to advanced AMD, based on the presence of neovascular AMD or CGA.

Methods

Study Participants

The study population originated from all participants in the prospective AREDS2 Ancillary SD OCT Study, which included 345 participants with AMD from the AREDS2 at 4 clinical sites (National Eye Institute, Duke Eye Center, Emory Eye Center, and Devers Eye Institute) and 122 elderly non-AMD participants from the Duke and Emory sites.[18] All participants provided informed written research consent. The study followed the tenets set forth by the Declaration of Helsinki and was approved by the Duke University Health System Institutional Review Board and by the institutional review board for each clinical site. Data collected from SD OCT scans for all enrolled eyes were stored and managed in compliance with guidelines from the Health Insurance Portability and Accountability Act.

The AREDS2 design, methods, and grading protocol for CFP readers have been described previously.[17,21] In brief, study participants were enrolled who met the inclusion criteria of age between 50 and 85 years, intermediate AMD with large drusen (≥125 μm) in both eyes or large drusen in one eligible eye and advanced AMD in the fellow eye, and no history of vitreoretinal surgery in either eye. The AREDS2 participants could have noncentral GA in the study eye. The age-appropriate control participants were eligible for AREDS2, except that they had no evidence of drusen, GA, or other characteristics of AMD in either eye.[18]

Color Fundus Photography and Optical Coherence Tomography

As part of AREDS2, CFP of AMD eyes were obtained at each annual study visit with 30° fundus cameras (Carl Zeiss Meditec, Dublin, CA) and then graded by certified readers at the Wisconsin Fundus Photography Reading Center (University of Wisconsin, Madison, WI).[21] Clinical trial end points at the year 2 visit were determined by progression to advanced AMD, as previously defined in AREDS2.[17] The advanced AMD end point of CNV was based on (1) the presence of CNV resulting from visible neovascular membrane, hemorrhage, hard exudate, or serous exudation on CFP grading; or (2) the decision to treat for CNV based on the clinical judgment of the treating ophthalmologist. The advanced AMD end point of CGA was based on the appearance of definite GA involving the foveal center on CFP grading, regardless of CNV treatment.

We previously described the study design, methods, grading protocol for certified SD OCT readers, and baseline participant characteristics in the AREDS2 Ancillary SD OCT Study.[18] At baseline and yearly study intervals, certified imagers obtained SD OCT scans with a commercial system adapted for tabletop office imaging (Bioptigen SDOIS, Morrisville, NC). Two high-density SD OCT raster scan patterns captured 100 line scans of 1000 A-scans each, oriented at 0° and 90° across a 6.7 × 6.7-mm area centered on the fovea. Certified SD OCT readers assigned a scan quality designation of good, fair, or poor based on foveal centration; low resolution or saturation; patient blinking; patient fixation or motion artifacts; image registration or flipping; or the presence of any tilted, clipped, or blank frames not related to blinking. Good- or fair-quality scans with lines oriented at 0° were selected by default for SD OCT segmentation. Poor-quality scans at 0° were replaced by good or fair scans at 90° from the same visit; however, if both scans were poor, then the study visit was excluded altogether.

Three-dimensional SD OCT scans underwent semiautomated segmentation with the Duke Optical Coherence Tomography Retinal Analysis Program (DOCTRAP, Duke University, Durham, NC) proprietary software that has been validated in normal and AMD eyes.[14,15] The RPEDC inner border was defined by segmentation of the inner surface of the RPE layer, including the apical surface of drusen, subretinal drusenoid deposits, and pigment epithelial detachments. The RPEDC outer border was defined by segmentation of the inner surface of Bruch's membrane. Segmentation lines were generated across the entire SD OCT scan and then reviewed for accuracy and corrected manually for gross segmentation errors of the RPEDC inner and outer borders within a 5-mm-diameter circular field centered on the fovea, as previously published[16] (Fig 1).

In AMD eyes, macular RPEDC volumes were calculated from RPEDC thickness measurements obtained at each A-scan test point. The same procedure was performed on non-AMD eyes to generate a normative data set for all OCT A-scan test points, previously described in detail.[16] For the purpose of this study, 2 abnormal RPEDC volume measurements were calculated from outlier RPEDC thicknesses: (1) RPEDC abnormal thickening (henceforth, OCT drusen) volume derived from RPEDC thickness of 3 or more standard deviations higher than the mean of the normative data set and (2) RPEDC abnormal thinning (henceforth, RAT) volume derived from RPEDC thickness of 2 or more standard deviations less than the mean of the normative data set (Fig 2).

Statistical Analysis

Volume measurements for total RPEDC, OCT drusen, and RAT were reported as mean volume and standard deviation and were