AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Linking OCT, Angiographic, and Photographic Lesion Components in Neovascular Age-Related Macular Degeneration

*Cynthia A. Toth, MD,[1,4] Vincent Tai, MS,[1] Stephanie J. Chiu, PhD,[1] Katrina Winter, BS,[1] Monica B. Sevilla, MS,[1] Ebenezer Daniel, MBBS, PhD,[2] Juan E. Grunwald, MD,[2] Glenn J. Jaffe, MD,[1] Daniel F. Martin, MD,[3] Gui-shuang Ying, PhD,[2] Maxwell Pistilli, MS,[2] Sina Farsiu, PhD,[4] Maureen G. Maguire, PhD,[2] for the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group**

Purpose: To develop methods to make precise comparisons of specific retinal features between and within spectral-domain (SD) OCT images, color fundus photography (CFP) images, and fluorescein angiography (FA) images in eyes treated with anti−vascular endothelial growth factor (VEGF) agents for neovascular age-related macular degeneration (nAMD).

Design: Retrospective study.

Participants: Patients with good study-eye images at the 104-week visit in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Methods: Graders reviewed CFP and FA images and delineated areas of fibrotic or nonfibrotic scar and geographic atrophy (GA) or non-GA. Other graders reviewed SD-OCT images and delineated retinal and subretinal lesion characteristics. Using newly developed custom software and graphic user interfaces, the presence and thickness of each feature at each pixel on the en face view was determined.

Main Outcome Measures: Spectral-domain OCT findings versus CFP and FA lesion components from regional overlays.

Results: Per-eye distribution and thickness of SD-OCT features within CFP- and FA-established areas of scar and atrophy can be determined precisely, can be displayed in multiple formats, and can be extracted into pixel-specific data sets. These methods enable statistical analysis of imaging results within eyes and across eyes of different patients. For example, photoreceptor loss, subretinal lesion material, and thicknesses of photoreceptor layer and subretinal material across those SD-OCT features can be related precisely to CFP and FA regions of scar or atrophy.

Conclusions: Methods to integrate qualitative and quantitative retinal and subretinal changes to coincide with photographic and angiographic designations of the nAMD lesion areas and sequelae are integral for accurate assessments of posttreatment retinal morphologic features. These may lead to better understanding of disease progression and improved treatment strategies. *Ophthalmology Retina 2017;■:1−13 © 2017 by the American Academy of Ophthalmology*

Supplemental material available at www.ophthalmologyretina.org.

Eyes with neovascular age-related macular degeneration (nAMD) treated with anti−vascular endothelial growth factor (anti-VEGF) agents demonstrate many interrelated retinal architecture changes. A single eye may have changes related to active neovascularization, atrophy, and scarring. These processes may be monitored by several imaging methods, most often stereoscopic color photography, stereoscopic fluorescein angiography (FA), and OCT. Combining the information from these different methods with high accuracy and precision allows for developing, proving, and disproving hypotheses regarding the development and progression of neovascularization, atrophy, and scarring.

In the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and other longitudinal studies of the outcomes of anti-VEGF treatment for nAMD, both geographic atrophy (GA) and scar have been reported to develop frequently[1−3] and to be associated with poor visual acuity.[4,5] The changes accompanying these processes are poorly understood. Mowatt et al[6] pointed to the need for integrated information on the performance of spectral-domain (SD) OCT compared with FA for diagnosis and monitoring of active and inactive nAMD. Schmidt-Erfurth and Waldstein[7] pointed to the need for integrated analysis of all structural and functional features to determine retinal

https://doi.org/10.1016/j.oret.2017.09.016
ISSN 2468-6530/17

biomarkers that could guide efficient individualized treatment of nAMD. Castillo et al,[8] in a review, recognized the disagreement between OCT and FA in detecting active disease and the paucity of studies directly comparing the tests in the same population. To date, identification of the relative size and regional distribution across the macula of multiple lesion components visible on OCT compared with the relative size and regional distribution of lesion components visible on color fundus photography (CFP) and FA has been performed manually and for only 1 or a few selected lesion components.

To extract this important information from OCT, CFP, and FA imaging in CATT, we developed novel methods and software to register and analyze the regional distribution of SD-OCT retinal and subretinal data and of CFP and FA data. With these methods of registration, pixel-by-pixel analysis, and overview analysis, researchers will be able to integrate the different imaging methods to understand better the range of neovascular lesion components. This will be useful in future studies of the pathophysiologic features of nAMD, because local precursors can be mapped to the regional progression and outcomes of nAMD. Thus, data from future studies using these methods will be useful to clinicians who need to predict and monitor response to nAMD treatment and to those developing novel therapies for nAMD.

Methods

The CATT participants and methods have been described in previous publications.[9,10] CATT was registered with ClinicalTrials.gov (identifier, NCT00593450). Enrollment extended across 43 clinical centers in the United States from February 2008 through December 2009. The study was approved by an institutional review board associated with each center and complied with the Health Insurance Portability and Accountability Act regulations. The study was performed in accordance with the tenents of the Declaration of Helsinki. All participants provided written informed consent. The image analysis methods were developed using a subset of images from CATT.

At baseline in CATT, participants underwent bilateral stereo CFP, FA, and time-domain OCT. Color fundus photography and FA along with OCT were performed again at 1, 2, and 5 years. Spectral-domain OCT imaging was conducted in many of the CATT participants after the year 1 visit.[11] In CATT, year 2 (104-week visit) scans were captured either with time-domain OCT methods or SD-OCT using Cirrus (Carl Zeiss Meditech, Dublin, CA) or Spectralis (Heidelberg Engineering, Heidelberg, Germany) systems. Only Cirrus and Spectralis SD-OCT scans were used in this overlay study. Images were acquired on the Cirrus device with the scan pattern of 6 × 6-mm macular volume cube with 128 horizontal line scans. Images were acquired on Spectralis OCT devices with 3 scan patterns: 20° × 20° macular volume cube with 49 horizontal line scans, 30° × 30° macular volume cube with 49 horizontal line scans, and 30° × 30° macular volume cube with 97 horizontal line scans. All scan patterns have 512 A-scans per line scan.

Photographic images were evaluated by the CATT Fundus Photography Reading Center at the University of Pennsylvania, and OCT images were evaluated by the CATT OCT Reading Center at the Duke Advanced Research in SS/SD-OCT Imaging Laboratory. Graders at each reading center were masked to the assessment from the other reading center. Four main features identifiable on stereo CFP and FA images of eyes treated with anti-VEGF agents were identified for in-depth evaluation (Table 1; see "Photographic Analysis," below): GA, non-GA, fibrotic scar, and nonfibrotic scar. Images of eyes at the 104-week CATT visit with these features present on CFP and with OCT images of sufficient quality to grade were selected for development and illustration of the methods described in this article.

Photographic Analysis

Two graders at the CATT Fundus Photography Reading Center each viewed CFP and FA images at that visit. For each of the features listed in Table 1, the graders outlined the area of the features on a frame from the FA image; this drawing was considered a layer. The same frame from the FA image was used for all layers. The FA frame was selected based on the clarity of the image, the presence of at least three quarters of the optic disc in the image, and having the most features of interest among those present on the entire angiogram. The FA image was imported into Photoshop (Photoshop CS3; Adobe Systems, San Jose, CA), and each of the CFP or FA components was outlined. Delineations on the FA image were performed on one monitor, whereas color, red-free, and fluorescein images of the same visit were viewed on an adjacent monitor. Information from all images was ascertained to mark the foveal center and center of the optic disc and to outline each type of morphologic characteristic. Qualitative and quantitative grading of fundus morphologic and FA characteristics in CATT have been shown to have good reproducibility.[12]

The foveal center was determined by identifying an area of increased pigmentation in the middle of the macular region on the color image and the geometric center of the area surrounded by the termination of the smallest visible perifoveal vessels seen clearly in the early FA transit phase or red-free image. In poor-quality images, baseline images having fluid and hemorrhage, and in follow-up images that had scar or atrophy at the mid-macular region, the best approximation of the foveal center was made and marked. A 6-mm diameter circular template centered on the foveal center was applied, and morphologic features of the total choroidal neovascularization lesion were delineated in 13 (11 components plus the fovea and disc center) labeled layers within that ring. The total choroidal neovascularization lesion components included choroidal neovascularization, hemorrhage, fibrotic scar, nonfibrotic scar, serous pigment epithelial detachment, blocked fluorescence, GA, non-GA, retinal angiomatous proliferation, and retinal pigment epithelium (RPE) tear (Table 1). Each of these 11 components was exclusive at any single location, so that a site could not be assigned 2 components.

The outline of each layer, representing 1 morphologic feature, was a unique color available in the Photoshop software. Outlining a particular morphologic feature was achieved using a single unbroken line. If the same morphologic feature was observed in several areas (e.g., multiple GA lesions), each area was drawn. Any of the defined morphologic features completely or partially within the circular template or touching the circle were drawn, even if they extended beyond the template.

OCT Analysis

Trained readers at the Duke Advanced Research in SS/SD-OCT Imaging Laboratory used proprietary software, the Duke OCT Retinal Analysis Program Marking Code version 61.4.2 (MATLAB R2012a; Mathworks, Natick, MA), to mark the foveal center based on the deepest site in the foveal pit for each scan, the photoreceptor bulge, or the best estimate. Readers also marked the lateral extent of all morphologic features observed across the full extent of each B-scan (Fig 1) using defined criteria listed in