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Analyzing Relative Blood Flow Speeds in Choroidal Neovascularization Using Variable Interscan Time Analysis OCT Angiography

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Purpose: Longitudinally visualizing relative blood flow speeds within choroidal neovascularization (CNV) may provide valuable information regarding the evolution of CNV and the response to vascular endothelial growth factor (VEGF) inhibitors.

Design: Retrospective, longitudinal case series conducted at the New England Eye Center.

Participants: Patients with either treatment-naïve or previously treated CNV secondary to neovascular age-related macular degeneration.

Methods: Optical coherence tomography angiography (OCTA) was performed using a 400-kHz, 1050-nm swept-source OCT system with a 5-repeat B-scan protocol. Variable interscan time analysis (VISTA) was used to compute relative flow speeds from pairs of B-scans having 1.5- and 3.0-ms separations; VISTA signals then were mapped to a color space for display.

Main Outcome Measures: Quantitative outcomes included OCTA-based area and volume measurements of CNV at initial and follow-up visits. Qualitative outcomes included VISTA OCTA analysis of relative blood flow speeds, along with analysis of contraction, expansion, densification, and rarefication of CNV.

Results: Seven eyes of 6 patients (4 women and 2 men) with neovascular age-related macular degeneration were evaluated. Two eyes were treatment naïve at the initial visit. Choroidal neovascularization in all eyes at each visit showed relatively higher flow speeds in the trunk, central, and larger vessels and lower flow speed in the small vessels, which generally were located at the periphery of the CNV complex. Overall, the CNV appeared to expand over time despite retention of good visual acuity in all patients. In the treatment-naïve patients, slower-flow-speed vessels contracted with treatment, whereas the larger vessels with higher flow speed remained constant.

Conclusions: Variable interscan time analysis OCTA allows for longitudinal observations of relative blood flow speeds in CNV treated with anti-VEGF intravitreal injections. A common finding in this study is that the main trunk and larger vessels seem to have relatively faster blood flow speeds compared with the lesions' peripheral vasculature. Moreover, an overall growth of chronically treated CNV was seen despite retention of good visual acuity. The VISTA framework may prove useful for developing clinical end points, as well as for studying hemodynamics, disease pathogenesis, and treatment response. *Ophthalmology Retina 2017;■:1–14 © 2017 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD) is a leading cause of vision loss for people 50 years of age or older in the developed world.[1,2] Neovascular AMD (nAMD) is a late stage of AMD characterized by the growth of abnormal blood vessels above or below the retinal pigment epithelium (RPE).[1,3–5] The longitudinal changes occurring in the morphologic features of the neovascularization with treatment remain incompletely understood.[1,6,7] Vascular endothelial growth factor (VEGF) plays a role in regulating the growth and exudation of neovascularization, and intravitreal anti-VEGF injections are effective to treat these lesions.[8–10] However, the exact pathophysiologic response of the neovascularization after anti-VEGF injection is a continuing area of research.[7,11–14]

Optical coherence tomography angiography (OCTA) is a noninvasive imaging method that has allowed further insight into the structural anatomic features of neovascularization[15–18] and its response to anti-VEGF treatment.[8,19–22] The underlying principle of OCTA is to use the intrinsic flow contrast provided by moving blood cells to differentiate blood flow

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from surrounding static tissue. Optical coherence tomography angiography works by acquiring repeated OCT B-scans from the same tissue location and then processing the data to extract the time-varying components, which correspond to blood flow. In a standard OCTA display, bright (white) pixels represent motion, corresponding to the presence of flowing blood cells, and dark (black) pixels indicate the absence of flowing blood cells. Artifacts in OCTA from motion and projection may complicate this basic relationship.[23] When OCTA volumes are resliced and viewed along en face planes, the resulting display shows a map of the retinal and choroidal vasculature. Compared with traditional dye-based angiography, OCTA has the advantage of being noninvasive and depth resolved, the latter of which allows the different vascular plexuses to be visualized independently.

Visualization of retinal microvasculature obtained with OCTA continues to improve our understanding of neovascularization in AMD. In an OCTA study, Spaide[8] proposed that, as a result of anti-VEGF injection for neovascularization, newly sprouted vessels are pruned, resulting in increased vascular resistance in the remaining vessels and higher flow in the main vascular trunk. Although current OCTA systems provide insight into the presence, absence, and structure of the neovascular lesions, they provide limited information about blood flow speeds within the vessels. Our research group from the Massachusetts Institute of Technology and New England Eye Center (NEEC) recently developed a general hardware–software framework, termed *variable interscan time analysis* (VISTA), capable of computing relative blood flow speeds from time-series OCTA data.[24,25] Variable interscan time analysis works by acquiring more than 2 repeated OCT B-scans at each retinal location and then computationally forming OCTA images of different interscan times using subsets of these repeated scans.[24] The key concept is that OCTA images at different interscan times capture different flow information.[26–29] Optical coherence tomography angiography signals in these images with different interscan times then can be compared in a variety of ways to derive information about the relative blood flow speeds in the vasculature. For example, a recent publication by Ploner et al[25] demonstrated a ratio-based VISTA scheme that mapped these relative flow speeds into a color-coded map for easy visualization.

In the current study, VISTA OCTA was used to evaluate choroidal neovascularization (CNV) secondary to nAMD longitudinally and to follow the progression of vessel maturation after anti-VEGF treatment. The aim of this analysis was to gain a better understanding of the structural and hemodynamic changes that occur in CNV with anti-VEGF therapy.

Methods

Participants

This retrospective longitudinal study was conducted at the NEEC of Tufts Medical Center (Boston, Massachusetts). The study was approved by the Tufts Medical Center Institutional Review Board. Participants underwent a complete ophthalmic examination by a trained retina specialist (either NKW, CRB, JSD, or AJW) at the NEEC. Select patients with a new diagnosis of CNV secondary to nAMD, or a known history of CNV secondary to nAMD, were imaged on a prototype swept-source (SS) OCT device after written informed consent was obtained. This research adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act of 1996.

Swept-Source OCT and Swept-Source OCT Angiography

Optical coherence tomography and OCTA were performed using an ultrahigh-speed SS-OCT research prototype device developed at the Massachusetts Institute of Technology and deployed at the NEEC. This OCT system has been described previously in detail.[30] Briefly, the prototype SS-OCT device uses a vertical cavity surface-emitting laser with a 400-kHz A-scan rate. Compared with commercial spectral-domain OCT devices, which use a 840-nm center wavelength, the vertical cavity surface-emitting laser light source has a 1050-nm center wavelength, which enables better penetration through opaque media and deeper penetration through the RPE and choroid.[31] Recent studies also have found that longer-wavelength SS-OCT and OCTA better visualizes and detects CNV compared with shorter-wavelength spectral-domain OCT and OCTA systems.[32–34] The full-width-at-half-maximum axial and transverse optical resolutions in tissue were approximately 8 to 9 μm and 20 μm, respectively.

Optical coherence tomography angiography imaging was performed over both 3 × 3- and 6 × 6-mm fields of view, centered on the fovea. For each acquisition, 5 repeated B-scans were obtained at 500 uniformly spaced locations. Each B-scan consisted of 500 A-scans. For each B-scan, the acquisition time, accounting for the mirror scanning duty cycle, was approximately 1.5 ms; the total volume acquisition time was approximately 3.9 seconds. The volumetric scan pattern yields isotropic transverse sampling of the retina at 12- and 6-μm intervals for the 6 × 6- and 3 × 3-mm field sizes, respectively. To compensate for patient motion and to improve image quality, 2 orthogonally scanned volumes were acquired from each eye and subsequently were registered and merged using a previously published algorithm.[35,36] To assess repeatability of the VISTA OCTA images, 3 × 3- and 6 × 6-mm VISTA OCTA images, acquired one after the other, were compared (Fig 1).

Choroidal Neovascularization OCT Angiography and Variable Interscan Time Analysis OCT Angiography Image Generation

Volumetric OCTA data corresponding to 1.5- and 3.0-ms interscan times were formed using the VISTA framework and an amplitude-based decorrelation scheme.[24,25] These data then were projected (using mean projection) through the depths spanned by the CNV to generate en face OCTA images corresponding to the 1.5- and 3.0-ms interscan times. Specifically, for each CNV, the axial (depth) position of the anterior-most aspect of the CNV and the axial (depth) position of the posterior-most aspect of the CNV were used as the boundaries for projection (Fig 2, available at www.ophthalmologyretina.org); note that because the volumes were not segmented, the projection bounds intersected different layers at locations away from the lesions. Because of this, for clarity of presentation, these areas away from the lesion boundaries were set to black in the displayed en face images.

The projected en face OCTA images of the CNV then were mapped to a color-coded display using the published ratio-based VISTA OCTA scheme.[25] The methodology has been described previously by Choi et al[24] and Ploner et al.[25] In brief, this