Progression of Retinal Pigment Epithelial Atrophy in Antiangiogenic Therapy of Neovascular Age-Related Macular Degeneration

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• PURPOSE: To monitor retinal pigment epithelial (RPE) atrophy progression during antiangiogenic therapy of neovascular age-related macular degeneration (AMD) over 2 years using polarization-sensitive optical coherence tomography (OCT).

• DESIGN: Prospective interventional case series.

• METHODS: SETTING: Clinical practice. STUDY POPULATION: Thirty patients (31 eyes) with treatment-naïve neovascular AMD. OBSERVATION PROCEDURES: Standard intravitreal therapy (0.5 mg ranibizumab) was administered monthly during the first year and pro re nata (PRN; as-needed) during the second year. Spectral-domain (SD) OCT and polarization-sensitive OCT (selectively imaging the RPE) examinations were performed at baseline and at 1, 3, 6, 12, and 24 months using a standardized protocol. RPE-related changes were evaluated using a semi-automated polarization-sensitive OCT segmentation algorithm and correlated with SD OCT and fundus autofluorescence (FAF) findings. MAIN OUTCOME MEASURES: RPE response, geographic atrophy (GA) progression.

• RESULTS: Atrophic RPE changes included RPE thinning, RPE porosity, focal RPE atrophy, and development of GA. Early RPE loss (ie, RPE porosity, focal atrophy) increased progressively during initial monthly treatment and remained stable during subsequent PRN-based therapy. GA developed in 61% of eyes at month 24. Mean GA area increased from 0.77 mm^2 at 12 months to 1.10 mm^2 (standard deviation = 1.09 mm^2) at 24 months. Reactive accumulation of RPE-related material at the lesion borders increased until month 3 and subsequently decreased.

• CONCLUSIONS: Progressive RPE atrophy and GA developed in the majority of eyes. RPE migration signifies certain RPE plasticity. Polarization-sensitive OCT specifically images RPE-related changes in neovascular AMD, contrary to conventional imaging methods. Polarization-sensitive OCT allows for precisely monitoring the sequence of RPE-related morphologic changes. (Am J Ophthalmol 2015;159(6):1100–1114.

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AGE-RELATED MACULAR DEGENERATION (AMD) IS A progressive disease leading to substantial visual loss.[1–3] Independent of the 2 classic pathways of disease progression with an atrophic or a neovascular development, a leading pathophysiologic role of the retinal pigment epithelium (RPE) has been recognized.[4,5] Defects in the RPE layer continuity with abnormal choroidal vessel growth cause leakage and fluid accumulation resulting in rapid deterioration of vision[5] owing to successive damage to the overlying retina, while clinically masking RPE morphology.

Vascular endothelial growth factor (VEGF)-A is a key factor in the pathogenesis of choroidal neovascularization (CNV).[6–8] Milestone clinical trials have demonstrated significant efficacy in terms of improving visual acuity (VA) with monthly injections of ranibizumab. The antibody fragment inhibits binding of multiple active forms of VEGF-A to their receptors, resolves leakage, and restores retinal morphology and often function, and became the first-line treatment for neovascular AMD.[9–14] Recently, an increased progression rate of geographic atrophy (GA) has been recognized during anti-VEGF therapy.[15,16]

Together with anti-VEGF therapy, high-resolution imaging technologies such as spectral-domain optical coherence tomography (SD OCT) that obtain high-resolution retinal images have become increasingly important modalities in the diagnosis and therapeutic management of neovascular AMD.[17] However, current SD OCT technology visualizes retinal structures exclusively by intensity-based imaging and has substantial limitations in identifying the RPE owing to difficulties in segmenting structures of similar reflectivity. A distinct evaluation of RPE morphology would be of major relevance to gain insight into the primary pathophysiology of AMD, the biologic response to anti-VEGF therapy, and long-term prognosis.

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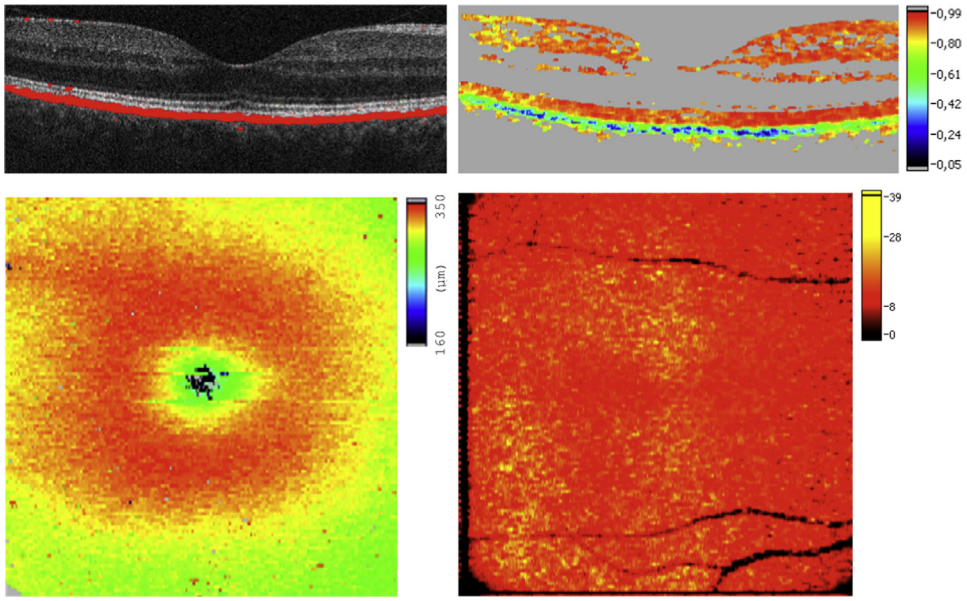

FIGURE 1. Polarization-sensitive optical coherence tomography imaging allows for selective differentiation of the retinal pigment epithelium based on intrinsic tissue-specific polarization contrast. An overlay of an intensity image and the segmented retinal pigment epithelium (RPE; red) in a healthy subject is shown (Top left). The degree of polarization uniformity (DOPU) image selectively delineates the RPE morphology (Top right). Central retinal thickness (CRT) maps may be generated (Bottom left), as well as a selective RPE thickness map (Bottom right).

Recently, polarization-sensitive OCT has been introduced,[18–20] providing morphologic information beyond nonspecific back-scattered intensity patterns, selectively identifying the RPE by measuring several intrinsic tissue qualities simultaneously with spectral-domain high-resolution imaging (reflectivity, retardation, optic axis orientation, degree of polarization uniformity [DOPU]).[18–20] Polarization-sensitive OCT provides distinct identification of the RPE condition in AMD with drusen,[21,22] advanced dry AMD,[22,23] and neovascular AMD.[24] The purpose of the current study was to identify characteristic RPE changes in patients with neovascular AMD undergoing continuous anti-VEGF therapy from early to advanced changes using polarization-sensitive OCT together with conventional SD OCT.

METHODS

• **INCLUSION AND EXCLUSION CRITERIA:** Thirty treatment-naïve patients (31 eyes) with neovascular AMD were included in this prospective interventional case series. The mean age of patients was 82 (standard deviation [SD]: 8) years; 18 patients were female and 12 were male. The character and possible consequences of the study were explained in detail prior to inclusion. Each patient gave signed informed consent. Ethics Committee approval (Medical University of Vienna) was obtained. The study adhered to the tenets of the Declaration of Helsinki and to all federal laws of Austria. This study is registered at https://eudract.ema.europa.eu/, number 2006-005684-26.

Active subfoveal CNV was identified using protocol fluorescein angiography (FA) and conventional SD OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) that showed retinal thickening >250 µm. Exclusion criteria were other retinal diseases including primary GA, retinal dystrophies, and severe media opacities. All patients underwent a standardized ophthalmologic examination including best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) letters, slit-lamp biomicroscopy, fundus photography, and FA.

• **RETINAL PIGMENT EPITHELIUM IMAGING:** Patients were imaged by conventional SD OCT, by fundus autofluorescence (FAF), and by a polarization-sensitive OCT prototype specifically imaging the RPE, developed by the Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, used previously.[21–24] Retinal and RPE morphology was assessed prior to anti-VEGF treatment (baseline) and at 1, 3, 6, 12, and 24 months following baseline.

Polarization-sensitive OCT measures reflectivity, retardation, optic axis orientation, and DOPU[18] simultaneously and images retinal morphology, the RPE, and related depolarizing structures containing melanin. Details of the instrument have been published.[22] RPE identification is based on its depolarizing quality, scrambling the polarization state of back-scattered light, while light back-scattered from