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Long-Term Assessment of Macular Atrophy in Patients with Age-Related Macular Degeneration Receiving Anti–Vascular Endothelial Growth Factor

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Purpose: Although intravitreal anti-vascular endothelial growth factor (VEGF) injection has become the mainstay treatment for neovascular age-related macular degeneration (nAMD), emerging studies suggest that anti-VEGF may be correlated with the development of macular atrophy (MA) in chronic therapy. The purpose of the current study is to determine the prevalence and progression of MA in nAMD treated with chronic anti-VEGF in a routine clinical practice.

Design: Retrospective cohort.

Participants: Patients with nAMD who were previously treatment-naïve and treated with anti-VEGF at the Cole Eye Institute for at least 4 years.

Methods: This is chart review on anti-VEGF treated patients with nAMD with baseline and yearly follow-up spectral domain-OCT for at least 4 years. Retinal pigment epithelium subillumination analysis was used to automate identification of atrophy. Segmentation errors were manually corrected by 4 expert raters using a standardized grading protocol to quantify MA size. Patient baseline characteristics and treatment course were analyzed to identify predictive factors for the development of MA.

Main Outcome Measures: MA growth rate and prevalence in cohorts with and without baseline atrophy.

Results: A total of 79 eyes from 66 patients (79.8±7.4 years, 63% were female) with nAMD and 4 years of follow-up with anti-VEGF injections were identified. The mean baseline visual acuity was 0.48±0.25 logarithm of the minimum angle of resolution (20/60 Snellen equivalent), and the mean final visual acuity was 0.48±0.49 logarithm of the minimum angle of resolution (20/44 Snellen equivalent, $P = 0.23$). The average number of injections was 19.8±9.8. MA was observed in 12.7% of eyes at baseline with an average annual growth rate of 0.7±0.5 mm^2. In eyes without baseline MA, atrophy developed in 53.6% eyes by year 4 with a growth rate of 0.2±0.4 mm^2 per year. Multiple linear regression analysis revealed that the progression of MA was positively correlated with age ($R = 0.02$, $P = 0.009$).

Conclusions: More than half of patients with nAMD treated with anti-VEGF injections for 4 years developed new MA. Atrophy progression was most strongly correlated with age, which suggests that baseline disease characteristics may be more predictive of MA progression than cumulative anti-VEGF treatment. *Ophthalmology Retina 2017;■:1–8 © 2017 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly in the United States.[1,2] In exudative AMD, patients develop choroidal neovascularization (CNV), which accelerates vision loss. Intravitreal anti–vascular endothelial growth factor (VEGF) injection has been shown to prevent early loss of vision due to CNV and is the current gold standard treatment for neovascular AMD (nAMD).[3–8]

Geographic atrophy is the process of retinal pigment epithelium (RPE) loss that causes irreversible vision loss in end-stage nonexudative AMD. Emerging studies have raised the question of whether long-term anti-VEGF therapy may be correlated with a similar but separate process of outer retinal atrophy in nAMD.[3,4,9–14] A cohort within the Comparison of AMD Treatments Trial (CATT) trial showed that treatment with monthly injections was associated with an increased risk of atrophy development in comparison with pro re nata (PRN) treatment.[9,15] Lois et al[16] and Abdelfattah et al[17] similarly showed an association between total number of anti-VEGF injections and the development of atrophy with follow-up times of 1.3 years and 2 years respectively.[16] The IVAN,[18] SEVEN-UP,[19] and PACORES[20] studies and Gillies et al[21] demonstrated that the prevalence of atrophy increased with long-term anti-VEGF therapy. Abdelfattah et al[17] coined the phrase "macular atrophy" as a general descriptor for this

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phenomenon in nAMD to distinguish from geographic atrophy in dry AMD because the mechanism of atrophy development with and without CNV may not be the same.

Several imaging modalities have been used to measure macular atrophy: colored fundus photographs, fluorescein angiogram, fundus autofluorescence, and spectral domain OCT (SD-OCT). Fundus autofluorescence has been the historical standard for detecting RPE loss because it directly visualizes the distribution of the autofluorescent lipofuscin in the RPE.[22,23] Spectral domain OCT also may be used to identify macular atrophy. Direct inspection of the B-scan can detect outer retinal loss and RPE loss consistent with atrophy. In addition, increased subillumination has been described as due to RPE atrophy, and automated software detection of sub-RPE subillumination is now available. This auto-detection of atrophy accelerates data processing and has high agreement with measurements calculated by fundus autofluorescence.[24,25] Subillumination analysis is emerging in current literature as the imaging technique of choice in studying nAMD atrophy.[17,18,26,27]

Data from studies designed to evaluate atrophy in eyes with nAMD receiving anti-VEGF therapy beyond 2 years are limited. Longer follow-up of macular atrophy is needed to accurately reflect the experience of chronic therapy. The main purpose of this study is to determine the prevalence and progression of macular atrophy in eyes with nAMD receiving anti-VEGF injections and to identify risk factors for the development of macular atrophy.

Methods

Study Design

The study was performed at Cole Eye Institute, Cleveland, Ohio, and received approval from the Cleveland Clinic Investigational Review Board. Because of the retrospective nature of the study, written informed consent was not required. All study-related procedures were performed in accordance with the Health Insurance Portability and Accountability Act.

Study Population

Data from patients with nAMD who received intravitreal injections of anti-VEGF therapy with bevacizumab, ranibizumab, or aflibercept at the Cleveland Clinic Cole Eye Institute were collected. Only treatment-naïve patients receiving treatment for at least 4 consecutive years were included in this study. Eligibility criteria included (1) the diagnosis of nAMD in at least 1 eye and (2) SD-OCT at baseline and at yearly follow-up intervals. These imaging requirements were necessary for macular atrophy grading. Eyes were excluded if any of the following were present: prior photodynamic therapy, laser photocoagulation, RPE tear, or other causes of CNV. Demographic data, including presence of systemic disease, smoking status, age, gender, and CNV type (for those with baseline fluorescein angiography), were collected for each eligible patient in addition to the total number of anti-VEGF injections received within the follow-up period. Choice of anti-VEGF drug and treatment intervals were based on the treating physician's discretion. During the chart review, the number of anti-VEGF injections received and the best-corrected visual acuity with refractive correction at each visit were noted for each study eye.

Macular Atrophy Measurement

Retinal pigment epithelium (RPE) subillumination analysis on SD-OCT (Cirrus Software Version 7.0; Carl Zeiss Meditec, Jena, Germany) was used to automate identification of atrophy by segmenting regions of increased reflectivity in the choroidal layer on the B-scans and quantifying this area on the en face fundus images. Segmentation errors were manually corrected by trained graders. Three graders at first independently provided manual measurements of macular atrophy on SD-OCT using stringent criteria that included disruption of the outer retina (RPE or ellipsoid zone loss) and increased signal transmission into the choroid.[17] Cases with more than 20% of difference in measurements among 2 or more graders were reviewed together by all graders until a consensus was achieved. For cases in which consensus could not be achieved, a senior imaging expert provided the final adjudication.

Statistical Analyses

The cumulative number of intravitreal anti-VEGF injections received over time and baseline demographics were correlated

Table 1. Baseline Characteristics of Patients

Age, yrs	80±7 (mean ± SD)	Range, 62–94
Left eye	47%	
Female gender	63%	
Never smoker	39%	
Diabetes mellitus	11%	
Hypertension	71%	
Coronary artery disease	23%	
Baseline BCVA	0.48±0.25 logMAR (20/60 Snellen equivalent)	
Last visit BCVA	0.48±0.49 logMAR (20/44 Snellen equivalent)	$P = 0.23$
Baseline CNV type (n = 37)	Occult: 78%	
	Classic: 22%	
	Retinal angiomatous proliferation: 0%	
Initial anti-VEGF agent	Bevacizumab: 49%	
	Ranibizumab: 33%	
	Aflibercept: 18%	
Mean No. of injections	19.8±9.8 (mean ± SD)	Range, 3–62

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; VEGF = vascular endothelial growth factor.