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Vision-Threatening Lesions Developing with Longer-Term Follow-up after Treatment of Neovascular Age-Related Macular Degeneration

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Purpose: To assess the development of vision-threatening lesions at least 3.5 years after initiating anti-vascular endothelial growth factor (VEGF) for choroidal neovascularization (CNV) in eyes with age-related macular degeneration (AMD).

Design: Retrospective cohort study.

Participants: A total of 75 patients (81 eyes) with CNV secondary to AMD who received intravitreous anti-VEGF treatment and were followed for at least 3.5 years after initiating treatment.

Methods: Retrospective record review of patients initiating anti-VEGF treatment between November 2005 and June 2008 at a university-based institution for whom at least 3.5 years of follow-up was available at the same institution.

Main Outcome Measures: Predominantly hemorrhagic lesions or geographic atrophy (GA).

Results: Among 75 patients (81 eyes; 59% were women; median age, 78 years), mean follow-up was 4.9 years and at least 6 years for 40%. Median visual acuity (VA) was 20/80 (interquartile range [IQR], 20/50–20/100) initially, 20/63 (IQR, 20/40–20/160) at 2 years, 20/80 (IQR, 20/40–20/200) at 3.5 years, and 20/63 (IQR 20/32–20/200) at 6 years. Six eyes (7%) had predominantly hemorrhagic lesions initially, whereas this developed in an additional 3 eyes (4%, 95% confidence interval [CI], 1% to 10%) in 3.5 years and in 1 additional eye (1%, 95% CI, 0.03% to 7%) at more than 3.5 years of follow-up. Initially, GA within or overlapping the boundary of the entire CNV was present in 4 eyes (5%) and outside this boundary in 8 eyes (10%). Geographic atrophy enlarged in each eye over time. The only eyes that developed GA outside the CNV boundary were those that had GA outside the lesion at baseline. Additional atrophy within the boundary of CNV defined at baseline, termed "atrophic disciform scars," developed in 5 eyes (6%), all within 4 years of treatment initiation.

Conclusions: Longer-term follow-up of neovascular AMD managed with anti-VEGF therapy suggests that predominantly hemorrhagic lesions may develop within 3.5 years of initiating therapy and more than 3.5 years after initiating therapy. In contrast, new areas of GA beyond the boundaries of the CNV lesion as defined at initiation of anti-VEGF therapy seem unlikely to develop if there is no GA outside of the CNV lesion initially. *Ophthalmology 2014;■:1–9 © 2014 by the American Academy of Ophthalmology.*

On the basis of results from several large-scale randomized clinical trials, anti-vascular endothelial growth factor (VEGF) therapy is the standard of care for most eyes presenting with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).[1–5] These studies have shown that anti-VEGF treatment reduces the risk of visual acuity (VA) loss and increases the chance of VA gain in select cases of CNV through at least 2 years of follow-up. Although intravitreous anti-VEGF treatment is relatively safe, endophthalmitis is a rare but serious ocular complication associated with treatment. More recently, descriptions of other sight-threatening events noted during follow-up, such as geographic atrophy (GA) of the retinal pigment epithelium (RPE), have been reported in eyes receiving these treatments.[6] Randomized trial results have evaluated a variety of dosing regimens, but follow-up typically concluded 2 years after treatment initiation within these trials,[1–5] such that minimal information regarding VA or safety outcomes beyond 2 years has been made available.[7] Most patients with CNV secondary to AMD require treatment beyond 2 years of treatment initiation to try to sustain anatomic improvements and avoid loss in vision that can emerge when treatment is discontinued.[8] To our knowledge when initiating this study, there was little information regarding sight-threatening conditions associated with the disease or the therapy more than 3.5 years after initiating treatment.[7,9–12]

To provide additional information on longer-term ophthalmic outcomes and risks, vision-threatening lesions, specifically predominantly hemorrhagic lesions or GA of the

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RPE, developing at least 3.5 years after initiating anti-VEGF therapy, were identified from a retrospective study. Patient records of individuals for whom bevacizumab (Avastin; Genentech Inc, San Francisco, CA) or ranibizumab (Lucentis; Genentech Inc) was initiated at least 3.5 years before this study were reviewed to identify these events.

Methods

The identities of patients with neovascular AMD treated by 2 retina specialists (S.B.B., N.M.B.) from November 1, 2005, to June 30, 2008, at the Retina Division, Wilmer Eye Institute, were obtained by searching billing records (International Classification of Diseases, 9th Revision code 362.52: exudative senile macular degeneration). The medical records of these individuals were reviewed to select those patients who had CNV due to AMD and had received their initial treatment for neovascular AMD at the Retina Division with at least 1 intravitreous injection of bevacizumab or ranibizumab and had at least 3.5 years of follow-up at the Retina Division after the initial injection. This cutoff was chosen because most of the literature reporting on longer-term results after initiation of anti-VEGF therapy report observations through 4 years after treatment initiation. It was judged that a visit window of plus or minus 6 months around a 4-year time point would be reasonable; as such, we selected the earliest time interval that would be included in a 4-year visit window, specifically, 3.5 years after initiation of anti-VEGF therapy, as the minimum duration of follow-up for inclusion in this study. Patients were excluded from this study if pegaptanib or photodynamic therapy (PDT) or laser photocoagulation had been given or if their study eye had been followed in a clinical trial. Eyes with CNV and evidence of both AMD and retinal abnormalities likely consistent with a coexisting pattern dystrophy primarily involving the RPE were excluded, as were eyes with neovascular AMD and coexisting diabetic retinopathy, retinal vascular occlusion, or other sight-threatening ocular conditions.

The following data were collected from the record review of the baseline visit (the first visit at which the study eye received initial anti-VEGF treatment) and all follow-up visits through July 2012: demographic data, VA, intravitreous injection administration, presence of a predominantly hemorrhagic lesion, and presence of GA. Visual acuity was recorded in Snellen equivalents from Early Treatment Diabetic Retinopathy Study back-lit charts and converted to logMAR scores for analysis (logMAR = $-\log_{10}$[Snellen equivalent]). Because of the lack of precision when obtaining VA measurements <20/250 in this clinic setting, all VA measurements <20/250 were recorded as ≤20/400 and considered as a logMAR of 1.3. Follow-up visits are reported at 2, 3.5, and 6 years after initiation of anti-VEGF therapy using a 6-month window around the visit date. When data were available from more than 1 visit within a visit window, data from the date that came closest to the biennial visit were used.

An independent review of stereoscopic color fundus photographs, stereoscopic fluorescein angiograms (FAs), and optical coherence tomography (OCT) images of both eyes of all eligible patients was conducted by 2 retina specialists (V.C., N.M.B.) to look for predominantly hemorrhagic lesions and GA at baseline and during all follow-up visits. Categorization of follow-up visits by length of time after treatment initiation for these events was considered as follows: up to 2 years after treatment initiation, 2 to 3.5 years, and after 3.5 years. A predominantly hemorrhagic lesion was defined as a lesion in which 50% or more of the CNV lesion was hemorrhage that obscured the ability to determine whether that area was occupied by CNV.[13,14] Geographic atrophy was defined as an area of partial or complete depigmentation of the RPE with thinning of the overlying neurosensory retina with the addition of at least 2 of the following 3 characteristics: roughly round or oval shape, sharp margins, and visibility of underlying large choroidal vessels,[15] based on color fundus photographs, and when available, red-free fundus photographs, and when available, FA images. Geographic atrophy was subdivided further into 2 categories: (1) GA outside the present or previous boundary of the entire CNV lesion and (2) GA within or overlapping the boundary of the CNV lesion as defined before the initiation of therapy or within or overlapping the area of the boundary of the CNV lesion if it grew at follow-up. Growth of GA was growth in size of the atrophy when comparing all available images side-by-side between any 2 visits. The area occupied by the entire CNV lesion was determined from FA, as defined in previous publications.[16,17] Any discrepancies between graders were openly adjudicated.

Delivery of intravitreous anti-VEGF therapy in this cohort typically included repeating monthly treatment until the managing ophthalmologist was confident that there was no longer successive improvement taking into account the patient's symptoms, ophthalmic examination, OCT, and FA.[18] In some instances, 1 or 2 years after initiating therapy, if the patient was not showing further improvement, even in the setting of CNV activity reflected on clinical examination, OCT, or FA, the managing ophthalmologist often would withhold treatment cautiously while continuing monthly follow-up. Intravitreous therapy would be resumed in these eyes if evidence of CNV activity was suspected with worsening of the clinical examination results, OCT, or FA.

Table 1. Demographic and Baseline Characteristics of Choroidal Neovascularization in Participants with Age-Related Macular Degeneration

Study Subject Characteristics	N = 75 Patients
Gender, No. (%)	
Women	44 (59%)
Men	31 (41%)
Age	
Median (IQR), yrs	78 (72–83)
Range, yrs	55–99
Study Eye Characteristics	**N = 81 Eyes**
VA (Snellen equivalent)	
Median (IQR)	20/80 (20/50–20/100)
Range	20/25–20/400
Predominantly hemorrhagic lesion*	6 (7%)
GA	
Within boundary of CNV lesion	4 (5%)
Not within or contiguous to boundary of CNV lesion	8 (10%)
Fellow Eye Characteristics	**N = 69 Eyes†**
Drusen (no GA, no CNV)	28 (34%)
GA (no CNV)	7 (9%)
CNV	34 (57%)

CNV = choroidal neovascularization; GA = geographic atrophy; IQR = interquartile range; VA = visual acuity.
*Predominantly hemorrhagic lesion was defined as a lesion in which at least 50% of the CNV lesion was blood.
†Characteristics of 69 fellow eyes in 69 patients, each of whom contributed 1 study eye; excludes data on 6 patients who contributed 2 study eyes.