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Baseline Predictors for Five-Year Visual Acuity Outcomes in the Comparison of AMD Treatment Trials

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Purpose: To determine baseline predictors of visual acuity (VA) outcomes at 5 years after initiating treatment with ranibizumab or bevacizumab for neovascular age-related macular degeneration (AMD).

Design: Secondary analysis of data from a cohort study.

Participants: Patients enrolled in the Comparison of AMD Treatments Trials (CATT) who completed a 5-year follow-up visit.

Methods: Participants were randomly assigned to ranibizumab or bevacizumab and to 1 of 3 dosing regimens. After 2 years, patients were released from the clinical trial protocol and recalled for examination at 5 years. Trained readers evaluated baseline lesion features, fluid, and thickness. Baseline predictors were determined using univariate and multivariate regression analyses.

Main Outcome Measures: The VA score and change from baseline, ≥3-line gain, and VA 20/200 or worse at 5 years.

Results: Among 647 patients with VA measured at 5 years, mean VA score in the study eye was 58.9 letters (≈20/63), mean decrease from baseline was 3.3 letters, 17.6% eyes gained ≥3 lines, and 19.9% had VA of 20/200 or worse. In multivariate analysis, worse baseline VA was associated with worse VA, more VA gain, higher percentage with ≥3-line gain, and higher percentage with 20/200 or worse at 5 years (all $P < 0.001$). Larger baseline choroidal neovascularization (CNV) lesion area was associated with worse VA, greater VA loss, and higher percentage with 20/200 or worse at 5 years (all $P < 0.05$). Absence of baseline subretinal fluid was associated with worse VA ($P = 0.03$) and more VA loss ($P = 0.03$). Female gender, bevacizumab treatment in the first 2 years, and absence of retinal pigment epithelium (RPE) elevation were associated with higher percentage with ≥3-line gain. Cigarette smoking was associated with a higher percentage with 20/200 or worse. None of the 21 single nucleotide polymorphisms evaluated were associated with VA outcomes.

Conclusions: Five years after initiating treatment with ranibizumab or bevacizumab in CATT participants, worse baseline VA, larger baseline CNV lesion area, and presence of baseline RPE elevation remained independently associated with worse VA at 5 years. In addition, male gender, cigarette smoking, and absence of subretinal fluid and treatment with ranibizumab in the first 2 years were independently associated with worse vision outcomes at 5 years. *Ophthalmology Retina 2017;■:1–6 © 2017 by the American Academy of Ophthalmology*

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Anti–vascular endothelial growth factor (VEGF) agents are highly effective treatments for neovascular age-related macular degeneration (AMD), and clinical trials have demonstrated their efficacy is similar within 1- or 2-year follow-up.[1–11] However, vision response to anti-VEGF treatment varies substantially among individual patients. Several studies have evaluated baseline demographic, clinical, genetic, or behavioral factors that may predict visual acuity (VA) outcomes.[12–19] These studies have consistently found that patient age, baseline VA, and choroidal neovascularization (CNV) lesion size predict VA outcomes. However, almost all of these studies evaluated factors associated only with short-term treatment response (within 2 years after treatment). Despite the good short-term VA response from anti-VEGF treatment for neovascular AMD, mean VA declines with longer follow-up.[20–25] Factors that predict short-term VA changes may differ from those that predict long-term VA changes.

We recently completed 5-year follow-up of a well-defined cohort of patients who underwent treatment with ranibizumab or bevacizumab during 2 years of a clinical trial followed by approximately 3.5 years of clinical care according to best medical judgment. Long-term (mean, 5.5 years) mean VA declined to 3 letters worse than at baseline and 11 letters worse than at 2 years.[22] The aims of this article are to evaluate baseline predictors for both long-term favorable VA outcomes and poor VA outcomes at 5 years among the participants of the Comparison of AMD Treatments Trials (CATT).

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Table 4. Multivariate Analysis for Baseline Predictors of Visual Acuity Score and Score Change from Baseline at 5 Years

Baseline Characteristics	N*	VA Score at 5 Yrs		VA Score Change from Baseline at 5 Yrs	
		Adjusted Mean (SE)	*P Value*	*Adjusted Mean (SE)*	*P Value*
Baseline VA in study eye			<0.001		<0.001
20/25–20/40	267	66.9 (1.4)		−7.2 (1.4)	
20/50–20/80	229	58.4 (1.5)		−2.6 (1.5)	
20/100–20/160	107	48.6 (2.1)		2.0 (2.1)	
20/200–20/320	37	36.7 (3.6)		4.6 (3.6)	
Baseline total area of CNV lesion (disc area)			0.001		0.002
≤1	218	62.7 (1.5)		0.3 (1.5)	
>1–≤2	145	60.8 (1.8)		−1.8 (1.8)	
>2–≤4	147	56.8 (1.8)		−5.4 (1.8)	
>4	108	52.2 (2.1)		−10.1 (2.1)	
Unknown	22	59.1 (4.7)		−1.4 (4.7)	
Baseline subretinal fluid			0.03		0.03
No fluid	93	53.2 (2.3)		−9.1 (2.3)	
Fluid not in foveal center	302	59.8 (1.3)		−2.4 (1.3)	
Fluid in foveal center	245	60.3 (1.4)		−2.2 (1.4)	

CNV = choroidal neovascularization; SE = standard error, VA = visual acuity.
From the multivariate model that included baseline VA in study eye, baseline total area of CNV lesion, and baseline subretinal fluid.
*Seven eyes with ungradable subretinal fluid were excluded.

Methods

Details on the study design and methods of the CATT have been reported in previous publications[7,8,22] and on ClinicalTrials.gov (NCT00593450). Only the major features related to this article are described.

Study Participants

The institutional review board associated with each clinical center approved the study protocol, and informed consent was obtained from each patient. Between February 20, 2008, and December 9, 2009, patients were enrolled from 43 clinical centers in the United States and randomized to 1 of 4 treatment groups at baseline: (1) ranibizumab monthly; (2) bevacizumab monthly; (3) ranibizumab as needed (pro re nata [PRN]); and (4) bevacizumab PRN. At the end of year 1, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly to monthly or PRN treatment. Patients initially assigned to PRN treatment retained both their drug and regimen for year 2.

The study enrollment criteria included age of 50 years or older, the study eye (1 eye per patient) having untreated active choroid neovascularization (CNV) due to AMD, and baseline study eye VA between 20/25 and 20/320 on electronic VA testing.

Study Procedures

During the initial visit, patients provided information on demographic characteristics and medical history. Certified photographers obtained stereoscopic, color fundus photographs, fluorescein angiograms, and time-domain OCT images. Both photographic and OCT images were evaluated at reading centers using standardized protocols.[26,27]

At baseline and during follow-up visits every 4 weeks through 104 weeks, study eyes were treated following the CATT protocol. Certified VA examiners, masked to the treatment assignment, measured VA after refraction in both eyes using the Electronic Visual Acuity Tester following the protocol used in the Diabetic Retinopathy Clinical Research Network.[28]

After the visit at 104 weeks, patients were released from their assigned treatment protocol, and all treatments were administered according to best medical judgment. At approximately 5.5 years (range, 4.3–7.1 years) after the date of treatment assignment in the clinical trial, patients were recalled for eye examination and VA measurement by study-certified personnel following the same protocol used during the clinical trial.

A subgroup of 835 CATT participants provided blood samples for genotyping including 7 single-nucleotide polymorphisms (SNPs) associated with risk of AMD: *CFH Y402H* (rs1061170), *ARMS2* (also called *LOC387715*), *A69S* (rs10490924), *HTRA1* (rs11200638), *C3 R80G* (rs2230199), *LIPC* (rs10468017), *CFB* (rs4151667), *C2* (rs547154); 4 *EPAS1* SNPs (rs6726454, rs7589621, rs9679290, rs12712973); 7 SNPs in *VEGFA* (rs699946, rs699947, rs833069, rs833070, rs1413711, rs2010963, and rs2146323); and 3 SNPs in *VEGFR2* (rs2071559, rs4576072, rs6828477). A custom-made TaqMan OpenArray loaded with TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA) was used for genotyping.[29–31]

Statistical Analysis

We previously evaluated the baseline predictors for VA response at year 1 and year 2 using univariate and multivariate regression models.[14,15] Following a similar analysis approach, we evaluated the same candidate baseline predictors for 5-year VA outcomes.

We analyzed baseline predictors for 4 clinically relevant VA outcomes in the study eye at 5 years, including VA score, change in VA score from baseline, ≥3-line (i.e., 15 letters) gain from baseline, and VA 20/200 or worse at 5 years.

We evaluated baseline predictors, including demographic, ocular characteristics, and OCT findings. Each baseline predictor was first evaluated by univariate analysis (without adjustment for other covariates) using generalized linear models for continuous VA outcomes (i.e., VA score and change in VA score from baseline) and the Fisher exact test for categoric VA outcomes (i.e., ≥3-line gain from baseline, VA 20/200 or worse). The baseline predictors with a P value <0.20 in the univariate analysis were included in a multivariate analysis so that the independent effect of each predictor could be assessed. The final multivariate model was created by applying a backward selection procedure that retained only those predictors with a P value ≤0.05. Adjusted means of VA score and VA score change from baseline were calculated on the basis of the final multivariate linear regression models. The adjusted odds ratios (ORs) and their 95% confidence intervals were calculated on the basis of the final multivariate logistic regression