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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 2018;2:525-530 © 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

Table 5. Multivariate Analysis for Baseline Predictors of 3-Line Gain and 20/200 or Worse in Visual Acuity at 5 Years

Baseline Characteristics	N	≥3-Line Gain from Baseline at 5 Yrs		VA 20/200 or Worse at 5 Yrs	
		n (%)	*Adjusted OR (95% CI)**	*n (%)*	*Adjusted OR (95% CI)†*
Gender			$P = 0.03$		
Female	419	81 (19.6%)	1.0		
Male	228	30 (13.5%)	0.56 (0.34–0.93)		
Cigarette smoking					$P = 0.02$
Never	274			47 (17.2%)	1.0
Quit	315			63 (20.0%)	1.21 (0.78–1.88)
Current	58			19 (32.8%)	2.61 (1.32–5.15)
Drug group in first 2 yrs			$P = 0.04$		
Ranibizumab	328	46 (14.2%)	1.0		
Bevacizumab	319	65 (20.8%)	1.62 (1.01–2.58)		
Baseline VA in study eye			$P < 0.001$		$P < 0.001$
68–82 letters, 20/25–20/40	268	6 (2.3%)	1.0	6 (2.2%)	1.0
53–67 letters, 20/50–20/80	231	55 (24.0%)	13.5 (5.6–32.5)	57 (24.7%)	1.95 (1.15–3.31)
38–52 letters, 20/100–20/160	110	40 (37.4%)	33.9 (13.4–85.7)	40 (36.4%)	5.16 (2.93–9.09)
23–37 letters, 20/200–20/320	38	10 (27.8%)	17.0 (5.6–51.9)	11 (28.9%)	8.03 (3.73–17.3)
Baseline total area of CNV lesion (disc area)					$P = 0.045$
≤1	222			32 (14.4%)	1.0
>1–≤2	146			26 (17.8%)	1.15 (0.63–2.08)
>2–≤4	148			34 (23.0%)	1.60 (0.91–2.83)
>4	109			34 (31.2%)	2.35 (1.31–4.21)
Unknown	22			3 (13.6%)	1.02 (0.27–3.79)
RPE elevation			$P < 0.001$		
No	85	27 (31.8%)	1.0		
Yes	551	84 (15.2%)	0.26 (0.14–0.48)		

CI = confidence interval; CNV = choroidal neovascularization; OR = odds ratio; RPE = retinal pigment epithelium; SE = standard error; VA = visual acuity.
*From the multivariate model that included gender, drug group in first 2 years, baseline VA in study eye, and baseline RPE elevation.
†From the multivariate model that included cigarette smoking, baseline VA in study eye, and baseline total area of CNV lesion.

models for categoric VA outcomes (≥3-line gain from baseline, VA 20/200 or worse). All data analyses were performed using SAS (v9.4, SAS Institute Inc, Cary, NC), and $P < 0.05$ (without correction for multiple testing) was considered to be statistically significant.

In addition, we evaluated the association between SNPs and each VA outcome by using the linear regression model for continuous VA outcomes and logistic regression for categoric VA outcomes. For each SNP, the genotype was summarized as the number of risk alleles present, and a linear trend test was performed to compare VA outcomes across the 3 genotype groups. Because we evaluated a total of 21 SNPs for their association with vision outcomes, $P < 0.002$ was considered as statistically significant.

Results

Among 914 living CATT participants, 647 (71%) completed the 5-year follow-up visit. The mean (standard deviation) VA score in the study eye was 58.9 (24.1) letters, the mean loss from baseline was 3.3 (22.3) letters, 114 (17.6%) eyes gained ≥3 lines from baseline, and 129 (19.9%) eyes had VA 20/200 or worse.[22] The univariate analysis results for baseline predictors of each of VA outcomes are shown in Tables 1 to 3 (available at www.ophthalmologyretina.org).

In the multivariate analysis (Table 4), the statistically significant baseline predictors for worse VA score at 5 years were worse baseline VA in study eye ($P < 0.0001$), larger baseline total area of CNV lesion ($P = 0.001$), and absence of subretinal fluid ($P = 0.03$).

The statistically significant baseline predictors for more VA loss from baseline at 5 years were better baseline VA in study eye ($P < 0.001$), larger baseline total area of CNV lesion ($P = 0.002$), and absence of subretinal fluid ($P = 0.03$) (Table 4).

In the multivariate analysis (Table 5), the statistically significant baseline predictors of a ≥3-line gain from baseline at 5 years were female gender (OR, 1.79; $P = 0.03$), drug treatment in the first 2 years (OR, 1.62 for bevacizumab compared with ranibizumab; $P = 0.04$), baseline VA in study eye (OR, 33.9 for VA 20/100 to 20/160 vs. 20/40 or better, $P < 0.001$), and absence of retinal pigment epithelium (RPE) elevation (OR, 3.85; $P < 0.001$).

In the multivariate analysis (Table 5), the statistically significant baseline predictors for VA 20/200 or worse at 5 years were current smoking (OR, 2.61; $P = 0.02$), worse baseline VA in study eye (OR, 8.0 for VA 20/200 or worse vs. 20/40 or better; $P < 0.001$), and larger baseline total area of CNV lesion (OR, 2.35 for total lesion area >4 vs. ≤1 disc area; $P = 0.045$).

The associations of 21 SNPs in 6 genes related to the risk of AMD and 3 genes that regulate VEGFA expression with VA outcomes are shown in Table 6 (available at www.ophthalmologyretina.org). Among 539 CATT participants who had genetic data and completed the 5-year follow-up visit, none of the SNPs were significantly associated with VA outcomes.

Discussion

This study evaluated baseline predictors for long-term VA outcomes among the CATT participants who were treated with ranibizumab or bevacizumab in the 2-year clinical trial and followed up for an additional 3 years after exiting from

the clinical trial. We found that worse baseline VA, larger baseline total area of CNV lesion, and presence of baseline RPE elevation, which were associated with 1- or 2-year VA outcomes, remained independently associated with worse VA at 5 years. In addition, we found that male gender, cigarette smoking, absence of subretinal fluid, and treatment with ranibizumab in the first 2 years were independently associated with worse vision outcomes at 5 years.

Despite the reduced sample size and substantial variation in treatment pattern after exiting from the 2-year CATT clinical trial,[22] some of the baseline predictors for year 1 and year 2 VA outcomes remained, including baseline VA in the study eye, baseline total area of CNV lesion, and RPE elevation. Worse baseline VA and larger CNV lesion have been consistently demonstrated to be significantly associated with worse VA outcomes at 1 and 2 years.[18,32,33] Consistent with our study findings, the results from the HORIZON study of 388 patients who completed 4 years of follow-up beyond their 2-year clinical trial showed that younger age, worse baseline VA, and smaller area of CNV lesion were associated with a gain of $\geq$3 lines from baseline.[25] Early detection of CNV and timely treatment before substantial loss of VA and lesion growth are important to maximize the patient's VA.[34–37]

At 5 years, we found eyes treated with ranibizumab in the first 2 years had a lower percentage with $\geq$3-line gain from baseline than patients treated with bevacizumab (20.4% vs. 14.9%, $P = 0.08$), and the difference was statistically significant (adjusted OR, 1.62; $P = 0.04$) in the multivariate analysis after accounting for gender, study eye baseline VA score, and RPE elevation at baseline. During the clinical trial, there was no difference between bevacizumab and ranibizumab in the percentage with $\geq$3-line gain from baseline at 1 year (29.7% vs. 29.5%, $P = 0.94$) or 2 years (28.8% vs. 30.6%, $P = 0.53$).[7,8] The interpretation of this finding should be cautious, because two thirds of these eyes received treatment with bevacizumab or aflibercept during the 3 years after the clinical trial.[22] The difference in VA improvement at 5 years may be due to morphologic differences at 5 years between the 2 drugs, because CATT eyes treated with ranibizumab in the first 2 years tended to have larger lesion area (mean 13.9 vs. 11.9 mm^2, $P = 0.06$)[22] and a higher rate of geographic atrophy growth (0.38 vs. 0.28 mm/year, $P = 0.009$).[38]

Although current cigarette smoking at enrollment was uncommon (9%) in CATT participants, current cigarette smoking at baseline was independently associated with a 2.6 times higher risk of VA 20/200 or worse in the study eye at 5 years, whereas smoking in the past was not associated with increased risk of worse VA (VA 20/200 or worse, 33%, 20%, and 17% in current, former, and nonsmokers, respectively). Current smokers had only a slightly higher proportion with VA 20/200 or worse at year 1 (8.5%, 6.3%, and 7.2% in current, former, and nonsmokers, respectively, $P = 0.70$) or at year 2 (9.2%, 7.3%, and 7.5% in current, former, and nonsmokers, respectively, $P = 0.82$). The association between smoking and worse long-term VA outcome could be because cigarette smoking increases oxidative stress, promotes angiogenesis, damages choroidal vessels, diminishes choroidal blood flow, and reduces choroidal thickness.[39–43] The Macular Photocoagulation Study found that cigarette smoking was associated with a higher recurrence rate of CNV after laser photocoagulation.[44] Cigarette smoking also may affect the response to treatment with anti-VEGF agents. Lee et al[40] found that current smoking was independently associated with poor VA improvement (OR, 7.3) after 3 months of treatment with ranibizumab for neovascular AMD compared with nonsmokers.[40] Piermarocchi et al[45] also found that smoking was independently associated with worse VA outcomes after 1 year of treatment with ranibizumab. However, other studies have not found a significant association of smoking with treatment response.[12,46] Overall, these findings provide further support for encouraging patients to quit smoking.

We found that presence of subretinal fluid at baseline was associated with better VA score at 5 years and less VA loss from baseline. In our previous cross-sectional analysis, we also found that presence of subretinal fluid was associated with better VA at year 1 and year 2.[47,48] Possible explanations for these effects include that subretinal fluid may protect the photoreceptors from toxicity related to direct contact with underlying diseased RPE or that subretinal fluid may contain neuroprotective substances. We have previously found that in eyes with subretinal fluid there was a lower risk of developing geographic atrophy than in those eyes without subretinal fluid (adjusted hazard ratio, 0.52).[49] Because of the association between subretinal fluid and good VA, a clinical trial is ongoing to evaluate whether tolerating subretinal fluid results in similar VA compared with treatment for complete resolution of both intraretinal fluid and subretinal fluid when treating with ranibizumab 0.5 mg.[50]

We have previously evaluated baseline predictors for VA score change from baseline at years 1 and 2, VA score, and $\geq$3-lines gain from baseline at year 1.[14,15] However, we did not evaluate the baseline predictors for worse VA outcomes because of the small number of eyes with worse VA outcome at years 1 or 2 during the clinical trial. With more eyes losing vision by 5 years, we evaluated VA 20/200 or worse in the study eye. We found that current smoking, worse baseline VA, and larger CNV lesion area were independently associated with higher risk of VA 20/200 or worse at 5 years.

The role of single nucleotide polymorphisms (SNPs) on the response to anti-VEGF treatment for neovascular AMD has been evaluated in many studies, including genes related to incidence of AMD, genes associated with VEGF, and *EPAS1* genes. However, the findings from these studies are inconsistent.[12] In CATT, we have previously evaluated these genetic associations with the morphologic or vision outcomes at year 1 or year 2 and did not find any significant associations.[29–31] Consistent with our previous findings, we found that none of these genetic factors were significantly associated with vision outcomes at year 5.

Study Limitations

The results of this study are limited by the fact that only 71% of living patients from the original clinical trial population returned for VA measurement, and patients who did not return had a mean age 2 years older and mean baseline VA 3 letters worse than patients who returned.[22] This may limit the generalizability of our study findings. However, our sensitivity analysis among 518 participants who underwent in-clinic VA measurements at centers with an in-clinic visit rate of at least 50% provided

similar results. The study is also limited by the multiple testing of 4 related VA outcomes, because false-positive findings can occur with multiple testing.

Conclusions

Similar to the previous findings for the predictors of VA outcomes at 1 or 2 years in CATT, worse baseline VA and larger CNV lesion size were strongly associated with worse long-term VA, and none of the studied genetic factors were associated with VA outcomes at 5 years. Current smoking was not associated with VA outcomes at 1 or 2 years but was associated with a higher risk of VA 20/200 or worse at 5 years. Early detection and treatment of neovascular AMD and quitting smoking may improve the long-term VA outcomes from anti-VEGF treatment.

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*A listing of the Comparison of Age-Related Macular Degeneration Treatments Trials Research Group is available at www.ophthalmology-retina.org.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CATT** = Comparison of AMD Treatments Trials; **CNV** = choroidal neovascularization; **OR** = odds ratio; **PRN** = pro re nata; **RPE** = retinal pigment epithelium; **SNP** = single nucleotide polymorphism; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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