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

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Abstract

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 two years, patients were released from the clinical trial protocol, and were recalled for examination at 5 years. Trained readers evaluated baseline lesion features, fluid and thickness. Baseline predictors were determined using univariate and multivariate regression analysis.

Main Outcome Measures—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 ($\approx$ 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

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This article contains online-only material. The following should appear online-only: Tables 1, 2, 3, 6.

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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 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 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 SNPs 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, absence of subretinal fluid and treatment with ranibizumab in the first 2 years were independently associated with worse vision outcomes at 5 years.

Graphical Abstract

Five years after initiating treatment with ranibizumab or bevacizumab in CATT participants, cigarette smoking, more severe neovascularization and treatment with ranibizumab in the first 2 years were independently associated with worse vision outcomes at 5 years.

INTRODUCTION

Anti-vascular endothelial growth factor (anti-VEGF) agents are highly effective treatments for neovascular age-related macular degeneration (AMD), and clinical trials have demonstrated their efficacy are 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.^{12–16,17–19} 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). In spite of 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 of 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 paper 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).

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 paper are described here.

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 one of four 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 either 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 or older, the study eye (one 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 optical coherence tomography (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 (EVA) 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 years to 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 SNP in

VEGFR2 (rs2071559, rs4576072, rs6828477). A custom made TaqMan OpenArray loaded with TaqMan SNP genotyping assays (Applied Biosystems) was used for genotyping.^{29–31}

Statistical Analysis

We previously evaluated the baseline predictors for VA response at Year 1, and at 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 four 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 visual acuity 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 using the Fisher exact test for categorical 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 based on the final multivariate linear regression models. The adjusted odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated based on the final multivariate logistic regression models for categorical 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 statistical 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 categorical 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 three genotype groups. Since 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%) patients completed the 5-year follow-up visit. The mean (SD) 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, 2 and 3 (online).

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 two years ($OR=1.62$ for bevacizumab as compared to 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 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 (online). 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 one and two years.^{32–34} 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 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 visual acuity.^{35–38}

At 5-years, we found eyes treated with ranibizumab in the first 2 years had a lower percentage with 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 3-line gain from baseline at 1 year (29.7% vs. 29.5%, $p=0.94$) or at 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 either bevacizumab or aflibercept during the 3 years after the clinical trial.²² The difference in VA improvement at 5-years may be attributable to morphological differences at 5-years between the two drugs, as CATT eyes treated with ranibizumab in the first 2 years tended to have larger lesion area (mean 13.9 vs. 11.9 mm², $p=0.06$),²² and a higher rate of GA growth (0.38 vs. 0.28 mm/year, $p=0.009$).³⁹

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, while smoking in the past was not associated with increased risk of worse VA (VA 20/200 or worse 33%, 20%, 17% in current, former, and non-smokers 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 non-smokers respectively, $p=0.70$) or at Year 2 (9.2%, 7.3% and 7.5% in current, former, and non-smokers respectively, $p=0.82$). The association between smoking and worse long-term VA outcome could be due to the fact that cigarette smoking increases oxidative stress, promotes angiogenesis, damages choroidal vessels and diminishes choroidal blood flow, and reduces choroidal thickness.^{40–44} The Macular Photocoagulation Study found that cigarette smoking was associated with a higher recurrence rate of CNV after laser photocoagulation.⁴⁵ Cigarette smoking may also affect the response to treatment with anti-VEGF agents. Lee et al found that current smoking was independently associated with poor VA improvement (OR=7.3) after 3 months of treatment with ranibizumab for neovascular AMD as compared to non-smokers.⁴¹ Piermarocchi et al also found that smoking was independently associated with worse VA outcomes after 1 year of treatment with ranibizumab.⁴⁶ However, others studies have not found a significant association of smoking with treatment response.^{12;47} 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.^{48;49} 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 GA than in those eyes without subretinal fluid (adjusted hazard ratio 0.52).⁵⁰ Because of the association between subretinal fluid and good VA, a clinical trial is ongoing to evaluate whether tolerating subretinal fluid results in similar visual acuity as compared to treatment for complete resolution of both intra-retinal fluid and subretinal fluid when treating with ranibizumab 0.5 mg.⁵¹

We have previously evaluated baseline predictors for VA score change from baseline at years 1 and 2, VA score and 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 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 morphological or vision outcomes at year 1 or at 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.

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 visual acuity measurements at centers with in-clinic visit rate of at least 50% provided very similar results. The study is also limited by the multiple testing of four-related VA outcomes, as false positive findings can occur with multiple testing.

In conclusion, 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 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 their long-term VA outcomes from anti-VEGF treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1 (online)

Univariate analysis for association of baseline participant characteristics with visual acuity outcomes at 5 years

# of subjects at 5 years (N=647)												
Baseline Characteristics		VA score (letters) at 5 years			Change in VA score (letters) from baseline at 5 years			3-line gain from baseline at 5 years			VA 20/200 or worse at 5 years	
		n	Mean (SE)	P-value [§]	Mean (SE)	P-value [§]	n (%)	P-value [†]	n (%)	P-value [†]		
Age (years)				0.006 (0.003)		0.40 (0.18)		0.46 (0.54)		0.32		
	50–69	102	62.1 (2.4)		–1.3 (2.2)		22 (21.6%)		20 (19.6%)			
	70–79	260	61.4 (1.4)		–2.8 (1.3)		42 (16.2%)		45 (17.3%)			
	80	285	55.5 (1.5)		–4.5 (1.4)		50 (17.5%)		64 (22.5%)			
	As continuous (per year increase)	647	–0.54 (0.13)	<0.001	–0.32 (0.12)	0.009	–0.02 (0.01)	0.13	0.02 (0.01)	0.08		
Gender				0.75		0.23		0.052		1.00		
	Female	419	59.1 (1.2)		–2.5 (1.1)		83 (19.8%)		84 (20.0%)			
	Male	228	58.5 (1.6)		–4.7 (1.4)		31 (13.6%)		45 (19.7%)			
Cigarette Smoking				0.28		0.50		0.93		0.03		
	Never	274	60.4 (1.4)		–2.2 (1.3)		48 (17.5%)		47 (17.2%)			
	Former	315	58.3 (1.4)		–4.0 (1.3)		57 (18.1%)		63 (20.0%)			
	Current	58	55.2 (3.5)		–5.2 (3.1)		9 (15.5%)		19 (32.8%)			
Hypertension				0.052		0.43		0.74		0.46		
	No	209	61.6 (1.6)		–2.3 (1.4)		35 (16.7%)		38 (18.2%)			
	Yes	438	57.6 (1.2)		–3.8 (1.1)		79 (18.0%)		91 (20.8%)			
Diabetes				0.50		0.57		0.78		1.00		
	No	540	58.6 (1.0)		–3.5 (1.0)		94 (17.4%)		108 (20.0%)			
	Yes	107	60.3 (2.2)		–2.2 (2.2)		20 (18.7%)		21 (19.6%)			
Drug group in first 2 years				0.19		0.17		0.08		0.28		
	Ranibizumab	328	57.7 (1.3)		–4.5 (1.2)		49 (14.9%)		71 (21.6%)			
	Bevacizumab	319	60.2 (1.3)		–2.1 (1.3)		65 (20.4%)		58 (18.2%)			
Treatment regimen in first 2 years				0.60		0.24		0.29		0.44		
	Monthly	164	60.5 (1.8)		–0.8 (1.7)		33 (20.1%)		27 (16.5%)			
	Switched	157	58.6 (2.1)		–4.2 (2.0)		31 (19.7%)		33 (21.0%)			
	PRN	326	58.2 (1.3)		–4.2 (1.2)		50 (15.3%)		69 (21.2%)			

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[§]From one way analysis of variance for comparing mean VA and VA change from baseline.

⁷From Fisher exact test for comparing percent of gaining or losing of 3 lines.

P-value in the parenthesis is from the test of linear trend.

SE = standard error. VA = visual acuity.

Table 2 (online)

Univariate analysis for association of baseline ocular and fundus characteristics with visual acuity outcomes at 5 years

Baseline Ocular Characteristics		# of subjects at 5 years (N=647)	VA score (letters) at 5 years		Change in VA score (letters) from baseline at 5 years		3-line gain from baseline at 5 years		VA 20/200 or worse at 5 years	
			n	Mean (SE)	P-value [§]	Mean (SE)	P-value [§]	n (%)	P-value [†]	n (%)
Baseline VA in study eye				<0.001 (<0.001)		0.005 (<0.001)		<0.001 (<0.001)		<0.001 (<0.001)
20/25 – 20/40	268	67.7 (1.2)			–6.4 (1.2)		6 (2.2%)		27 (10.1%)	
20/50 – 20/80	231	58.1 (1.5)			–2.8 (1.5)		57 (24.7%)		42 (18.2%)	
20/100–20/160	110	47.3 (2.3)			0.8 (2.3)		40 (36.4%)		41 (37.3%)	
20/200–20/320	38	35.5 (3.7)			3.6 (3.7)		11 (28.9%)		19 (50.0%)	
Baseline VA in fellow eye				0.07 (0.02)		0.23 (0.10)		0.82 (0.56)		0.29 (0.17)
20/20 or better	229	61.6 (1.6)			–2.0 (1.4)		42 (18.3%)		38 (16.6%)	
20/25–20/40	249	58.3 (1.6)			–2.9 (1.5)		45 (18.1%)		54 (21.7%)	
20/50 or worse	169	56.1 (1.8)			–5.7 (1.7)		27 (16.0%)		37 (21.9%)	
Baseline area of CNV (disc area)				0.02 (0.002)		0.01 (0.001)		0.27 (0.14)		0.10 (0.02)
1	277	63.0 (1.3)			–0.0 (1.2)		56 (20.2%)		42 (15.2%)	
>1 to 2	127	58.7 (2.2)			–3.6 (1.9)		20 (15.7%)		25 (19.7%)	
>2 to 4	116	57.3 (2.4)			–5.0 (2.4)		22 (19.0%)		24 (20.7%)	
>4	52	54.0 (3.7)			–9.9 (3.2)		5 (9.6%)		15 (28.8%)	
Baseline total area of CNV lesion (disc area)				<0.001 (<0.001)		0.01 (0.001)		0.10 (0.28)		0.003 (<0.001)
1	222	63.5 (1.4)			–0.7 (1.3)		39 (17.6%)		32 (14.4%)	
>1 to 2	146	60.3 (1.9)			–1.7 (1.9)		29 (19.9%)		26 (17.8%)	
>2 to 4	148	56.2 (2.1)			–5.0 (2.1)		31 (20.9%)		34 (23.0%)	
>4	109	51.0 (2.6)			–8.7 (2.2)		11 (10.1%)		34 (31.2%)	
Location of lesion				0.02		0.75		0.03		0.04
Not Subfoveal	170	62.7 (1.6)			–2.8 (1.6)		21 (12.4%)		25 (14.7%)	
Subfoveal	469	57.5 (1.2)			–3.4 (1.1)		92 (19.6%)		103 (22.0%)	
Lesion type				0.11		0.10		<0.001		0.053
Occult only	392	60.1 (1.2)			–4.5 (1.1)		50 (12.8%)		69 (17.6%)	

Baseline Ocular Characteristics		# of subjects at 5 years (N=647)	VA score (letters) at 5 years		Change in VA score (letters) from baseline at 5 years		3-line gain from baseline at 5 years		VA 20/200 or worse at 5 years				
			n	Mean (SE)	P-value [§]	Mean (SE)	P-value [§]	n (%)	P-value [†]	n (%)	P-value [†]		
Predominantly or Minimally classic RAP lesion		242	56.9 (1.6)		0.51	-1.5 (1.5)		0.21	62 (25.6%)		58 (24.0%)		0.74
No		575	58.6 (1.0)			-3.6 (0.9)			98 (17.0%)		117 (20.3%)		
Yes		62	60.7 (3.0)			0.1 (2.9)			15 (24.2%)		11 (17.7%)		
Blocked fluorescence lesion					0.39			0.10					0.57
No		547	58.6 (1.0)			-3.8 (1.0)			91 (16.6%)		112 (20.5%)		
Yes		93	60.9 (2.4)		0.03	0.3 (2.2)		0.84	23 (24.7%)		16 (17.2%)		0.26
Fibrotic or atrophic scar													
No		620	59.3 (1.0)			-3.2 (0.9)			107 (17.3%)		122 (19.7%)		
Yes		20	47.4 (6.0)		0.006 (0.004)	-4.3 (6.2)		0.26 (0.57)	7 (35.0%)		6 (30.0%)		0.02 (0.01)
Hemorrhage associated with the lesion													
None		249	61.2 (1.4)			-4.6 (1.4)			27 (10.8%)		42 (16.9%)		
1 disc area		330	58.7 (1.4)			-1.9 (1.3)			77 (23.3%)		66 (20.0%)		
>1 disc area		60	50.2 (3.3)			-5.4 (2.7)			9 (15.0%)		20 (33.3%)		
Geographic atrophy					0.13			0.81					0.57
None		600	59.3 (1.0)			-3.3 (0.9)			104 (17.3%)		118 (19.7%)		
Present		47	53.7 (3.6)			-4.1 (3.3)			10 (21.3%)		11 (23.4%)		
Intraocular pressure (mmHg)					0.15 (0.06)			0.65 (0.44)					0.58 (0.45)
<10		10	62.9 (6.6)			-3.8 (6.8)			2 (20.0%)		2 (20.0%)		
10-20		602	59.3 (1.0)			-3.1 (0.9)			108 (17.9%)		118 (19.6%)		
>20		35	51.4 (5.0)			-6.7 (4.4)			4 (11.4%)		9 (25.7%)		
Glaucoma					0.52			0.51					0.52
No		579	59.1 (1.0)			-3.1 (0.9)			106 (18.3%)		118 (20.4%)		
Yes		68	57.1 (3.0)			-5.0 (2.8)			8 (11.8%)		11 (16.2%)		
CNV in fellow eye					0.35			0.68					0.43
None		460	58.5 (1.2)			-3.1 (1.1)			80 (17.4%)		95 (20.7%)		
Present		170	60.5 (1.7)			-4.0 (1.6)			30 (17.6%)		30 (17.6%)		

[§] From one way analysis of variance for comparing mean VA and VA change from baseline.

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† From Fisher exact test for comparing percent of gain or loss of 3 lines from baseline.

P-value in the parenthesis is from the test of linear trend.

Unknown status for a specific feature was excluded from the univariate analysis for this specific feature.

SE = standard error, VA = visual acuity, CNV = choroid neovascularization, RAP = retinal angiomatous proliferans.

Table 3 (online)

Univariate analysis for association of baseline OCT features with visual outcomes at 5 years

Baseline OCT features	# of subjects at 5 years (N=647)	VA score (letters) at 5 years			3-line gain from baseline at 5 years			VA 20/200 or worse at 5 years
		Mean (SE)	P-value	Mean (SE)	P-value	n (%)	P-Value	
Retinal thickness (microns)			0.02 (0.02)		0.85 (0.65)		0.46 (0.25)	
<120	65	60.2 (3.5)		-4.8 (3.1)		8 (12.3%)		12 (18.5%)
120 to 212	351	61.0 (1.2)		-3.2 (1.1)		62 (17.7%)		64 (18.2%)
>212	229	55.3 (1.6)		-3.0 (1.5)		44 (19.2%)		53 (23.1%)
Subretinal fluid thickness (microns)			0.10 (0.16)		0.63 (0.84)		0.83 (0.77)	0.27 (0.26)
0	410	57.6 (1.2)		-3.6 (1.1)		72 (17.6%)		89 (21.7%)
>0 to 25	54	64.6 (3.2)		-0.5 (2.8)		8 (14.8%)		7 (13.0%)
>25	181	60.2 (1.8)		-3.4 (1.7)		34 (18.8%)		33 (18.2%)
Subretinal tissue complex thickness (microns) by quartile			0.04 (0.005)		0.36 (0.63)		0.06 (0.21)	0.27 (0.06)
1st (>0 to 75)	157	61.7 (1.8)		-5.4 (1.8)		18 (11.5%)		27 (17.2%)
2nd (>75 to 160)	147	61.3 (1.9)		-2.0 (1.8)		30 (20.4%)		25 (17.0%)
3rd (>160 to 275)	172	58.1 (1.9)		-1.6 (1.7)		38 (22.1%)		35 (20.3%)
4th (>275)	169	54.9 (2.0)		-4.3 (1.8)		28 (16.6%)		42 (24.9%)
Retinal + subretinal fluid thickness (microns) by quartiles			0.02 (0.007)		0.91 (0.91)		0.46 (0.19)	0.08 (0.10)
1st (160)	156	61.2 (1.9)		-4.2 (1.7)		23 (14.7%)		29 (18.6%)
2nd (>160 to 225)	164	60.4 (1.8)		-2.4 (1.7)		30 (18.3%)		30 (18.3%)
3rd (>225 to 320)	171	60.1 (1.8)		-3.1 (1.6)		28 (16.4%)		28 (16.4%)
4th (>320)	154	53.5 (2.1)		-3.6 (2.1)		33 (21.4%)		42 (27.3%)
Total foveal thickness (microns) by quartile			<0.001 (<0.001)		0.67 (0.90)		0.01 (0.048)	<0.001 (<0.001)
1st (325)	161	63.1 (1.6)		-4.3 (1.6)		16 (9.9%)		25 (15.5%)
2nd (>325 to 425)	172	63.6 (1.7)		-1.5 (1.8)		38 (22.1%)		22 (12.8%)
3rd (>425 to 550)	144	58.4 (2.1)		-3.5 (1.9)		26 (18.1%)		30 (20.8%)
4th (>550)	168	50.5 (2.0)		-3.9 (1.8)		34 (20.2%)		52 (31.0%)
Intra-retinal fluid			0.003		0.43		0.03	0.06

Baseline OCT features	# of subjects at 5 years (N=647)	VA score (letters) at 5 years		Change in VA score (letters) from baseline at 5 years		3-line gain from baseline at 5 years		VA 20/200 or worse at 5 years		
		n	Mean (SE)	P-value	Mean (SE)	P-value	n (%)	P-Value	n (%)	P-Value
No Fluid	170	64.1 (1.7)			-3.2 (1.6)		25 (14.7%)		24 (14.1%)	
Fluid not in foveal center	179	58.3 (1.9)			-5.2 (1.7)		24 (13.4%)		40 (22.3%)	
Fluid in foveal center	285	56.1 (1.4)			-2.5 (1.3)		63 (22.1%)		64 (22.5%)	
Sub-retinal fluid			0.009			0.19		0.95		0.046
No Fluid	93	52.2 (2.8)			-7.2 (2.7)		16 (17.2%)		27 (29.0%)	
Fluid not in foveal center	302	59.3 (1.3)			-2.5 (1.2)		55 (18.2%)		59 (19.5%)	
Fluid in foveal center	245	61.2 (1.5)			-2.9 (1.5)		42 (17.1%)		41 (16.7%)	
Sub-RPE fluid			0.15			0.10		0.10		0.44
No Fluid	186	59.7 (1.7)			-3.3 (1.6)		30 (16.1%)		34 (18.3%)	
Fluid not in foveal center	216	61.5 (1.6)			-0.9 (1.5)		48 (22.2%)		38 (17.6%)	
Fluid in foveal center	206	57.0 (1.8)			-5.6 (1.6)		30 (14.6%)		46 (22.3%)	
RPE elevation			0.03			0.04		<0.001		0.47
No	85	64.2 (2.5)			1.2 (2.5)		27 (31.8%)		14 (16.5%)	
Yes	551	58.1 (1.0)			-4.1 (0.9)		84 (15.2%)		112 (20.3%)	
RPEE maximum height (mm) by quartiles			0.50 (0.36)			0.45 (0.23)		0.52 (0.79)		0.62 (0.41)
1st (≤3.0)	96	58.5 (2.4)			-3.6 (2.1)		14 (14.6%)		19 (19.8%)	
2nd (>3.0 to ≤5.0)	115	61.5 (2.2)			-1.7 (2.1)		17 (14.8%)		18 (15.7%)	
3rd (>5.0 to ≤11.5)	167	58.1 (1.9)			-3.6 (1.8)		31 (18.6%)		34 (20.4%)	
4th (>11.5)	159	57.2 (1.9)			-6.1 (1.7)		20 (12.6%)		35 (22.0%)	
RPEE maximum width (mm) by quartiles			0.80 (0.41)			0.38 (0.74)		0.38 (0.97)		0.97 (0.86)
1st (≤12.0)	63	60.7 (3.0)			-4.4 (2.6)		8 (12.7%)		11 (17.5%)	
2nd (>12.0 to ≤31.5)	153	59.1 (2.0)			-3.5 (1.8)		24 (15.7%)		31 (20.3%)	
3rd (>31.5 to ≤55.0)	138	59.8 (1.8)			-0.9 (1.8)		28 (20.3%)		26 (18.8%)	
4th (>55.0)	157	57.5 (2.0)			-5.4 (1.9)		21 (13.4%)		31 (19.7%)	

[§]From one way analysis of variance for comparing mean VA and VA change from baseline.

[†]From Fisher exact test for comparing percent of gaining or loss of 3 lines.

OCT= Optical coherence tomography, RPE= retinal pigment epithelium, RPEE=RPE elevation.

P-value in the parenthesis is from the test of linear trend.

Unknown status for a specific feature was excluded from the univariate analysis for this specific feature.

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Table 4

Multivariate analysis for baseline predictors of VA score and VA score change from baseline at 5 years

Baseline Characteristics	N*	VA score at 5 years		VA score change from baseline at 5 years	
		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 to 2	145	60.8 (1.8)		-1.8 (1.8)	
>2 to 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)	

* 7 eyes with ungradeable subretinal fluid were excluded.

SE = standard error, VA = visual acuity, CNV = choroid neovascularization.

[§] From the multivariate model that included baseline visual acuity in study eye, baseline total area of CNV lesion, and baseline subretinal fluid.

Table 5
Multivariate analysis for baseline predictors of 3-line gain, and 20/200 or worse in VA at 5 Years

Baseline Characteristics	N	3-line gain from baseline at 5 years		VA 20/200 or worse at 5 years	
		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 years			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 to 2	146			26 (17.8%)	1.15 (0.63, 2.08)
>2 to 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)		

OR=odds ratio, CI=confidence interval, SE = standard error, VA = visual acuity, CNV = choroid neovascularization, RPE= retinal pigment epithelium.

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From the multivariate model that included gender, drug group in first 2 years, baseline visual acuity in study eye, and baseline RPE elevation.
*
§From the multivariate model that included cigarette smoking, baseline visual acuity in study eye, and baseline total area of CNV lesion.

Table 6 (online)

Univariate analysis for association of genotype with VA outcomes

SNP and genotype	# of Subjects at Year 5 (N=539)	VA score (letters) at year 5		Change in VA score (letters) from baseline at year 5		>= 3-line gain from baseline at year 5		VA 20/200 or worse at year 5	
		Mean (SE)	P-value	Mean (SE)	P-value	n (%)	P-Value	n (%)	P-value
7 SNPs related to AMD									
CFH, rs1061170									
TT	102	61.2 (2.4)		-2.0 (2.2)	0.62	15 (14.7%)		19 (18.6%)	0.92
TC	260	57.9 (1.5)		-3.5 (1.4)		51 (19.6%)		50 (19.2%)	
CC	177	60.1 (1.7)		-3.5 (1.6)		24 (13.6%)		34 (19.2%)	
ARMS2, rs10490924									
GG	180	59.6 (1.8)		-3.8 (1.7)	0.51	32 (17.8%)		36 (20.0%)	0.66
GT	253	59.0 (1.5)		-3.3 (1.4)		39 (15.4%)		48 (19.0%)	
TT	106	59.3 (2.1)		-2.0 (2.0)		19 (17.9%)		19 (17.9%)	
HTRA1, rs11200638									
GG	184	59.8 (1.8)		-3.4 (1.7)	0.69	33 (17.9%)		36 (19.6%)	
AG	254	58.9 (1.5)		-3.5 (1.4)		38 (15.0%)		49 (19.3%)	
AA	101	59.2 (2.2)		-2.1 (2.1)		19 (18.8%)		18 (17.8%)	
C3, rs2230199									
CC	291	58.8 (1.4)	0.46	-3.2 (1.3)	0.75	51 (17.5%)	0.70	54 (18.6%)	0.86
CG	208	59.2 (1.6)		-3.8 (1.6)		32 (15.4%)		44 (21.2%)	
GG	40	62.6 (3.1)		-0.5 (2.6)		7 (17.5%)		5 (12.5%)	
LIPC, rs10468017									
TT	32	55.4 (4.4)	0.25	-9.3 (3.6)	0.20	2 (6.3%)	0.91	7 (21.9%)	0.18
CT	220	62.1 (1.4)		0.3 (1.3)		44 (20.0%)		33 (15.0%)	
CC	287	57.5 (1.5)		-5.3 (1.4)		44 (15.3%)		63 (22.0%)	
CFB, rs4151667									
AA	2	38.5 (36.5)	0.28	-16.5 (14.5)	0.38	0 (0.0%)	0.31	1 (50.0%)	0.58
AT	26	56.8 (4.5)		-5.3 (4.1)		3 (11.5%)		5 (19.2%)	
TT	511	59.5 (1.0)		-3.0 (1.0)		87 (17.0%)		97 (19.0%)	

SNP and genotype	# of Subjects at Year 5 (N=539)	VA score (letters) at year 5		Change in VA score (letters) from baseline at year 5		>= 3-line gain from baseline at year 5		VA 20/200 or worse at year 5	
		Mean (SE)	P-value	Mean (SE)	P-value	n (%)	P-Value	n (%)	P-value
C2, rs547154			0.37		0.95		0.79		0.79
	TT					0 (0.0%)		0 (0.0%)	
	GT	55.5 (4.5)		-10.0 (13.0)		17 (18.5%)		19 (20.7%)	
	GG	57.5 (2.5)		-2.9 (2.3)		73 (16.5%)		82 (18.5%)	
4 EPAS1 SNPs									
	rs6726454		0.51		0.24		0.02		0.50
	AA	57.4 (2.1)		-5.0 (1.8)		16 (11.6%)		25 (18.1%)	
	AG	60.2 (1.4)		-3.0 (1.4)		44 (16.6%)		49 (18.5%)	
rs7589621			0.69		0.93		0.19		0.12
	GG	59.3 (2.1)		-1.8 (1.9)		30 (22.1%)		29 (21.3%)	
	GG								
	AG	59.4 (1.4)		-3.4 (1.3)		41 (14.6%)		49 (17.5%)	
rs9679290			0.76		0.42		0.10		0.60
	AA	59.7 (1.6)		-2.9 (1.6)		40 (18.6%)		41 (19.1%)	
	AA	56.7 (3.8)		-3.6 (3.5)		9 (20.5%)		13 (29.5%)	
	GG								
rs12712973			1.00		0.74		0.10		0.25
	CC	57.9 (1.9)		-5.0 (1.7)		20 (12.3%)		31 (19.1%)	
	CG	60.5 (1.4)		-2.1 (1.3)		49 (18.2%)		48 (17.8%)	
	CC	58.3 (2.5)		-3.3 (2.2)		21 (19.4%)		24 (22.2%)	
7 SNPs in VEGFA									
	rs12712973		1.00		0.74		0.10		0.25
	CC	58.3 (2.1)		-2.8 (1.9)		30 (20.7%)		33 (22.8%)	
	AC	60.3 (1.4)		-3.2 (1.3)		44 (16.1%)		49 (17.9%)	
rs699946			0.17		0.43		0.72		0.09
	AA	58.1 (2.2)		-3.7 (1.9)		16 (13.2%)		21 (17.4%)	
	GG								
	AG	62.8 (4.2)		-4.6 (4.4)		5 (23.8%)		2 (9.5%)	
rs699947			0.88		0.91		0.98		0.64
	AA	60.8 (1.7)		-1.6 (1.5)		28 (16.0%)		29 (16.6%)	
	AA	58.2 (1.3)		-4.0 (1.2)		57 (16.6%)		72 (21.0%)	
	CC								
	155	59.7 (1.8)		-3.0 (1.6)		23 (14.8%)		27 (17.4%)	

SNP and genotype	# of Subjects at Year 5 (N=539)	VA score (letters) at year 5		Change in VA score (letters) from baseline at year 5		>= 3-line gain from baseline at year 5		VA 20/200 or worse at year 5	
		Mean (SE)	P-value	Mean (SE)	P-value	n (%)	P-Value	n (%)	P-value
AC	266	58.9 (1.5)		-3.3 (1.4)		50 (18.8%)		53 (19.9%)	
AA	118	59.4 (2.3)		-3.2 (2.0)		17 (14.4%)		23 (19.5%)	
rs833069			0.23		0.20				0.14
TT	237	58.0 (1.7)		-4.5 (1.6)		36 (15.2%)		51 (21.5%)	
TC	231	59.9 (1.5)		-2.5 (1.4)		38 (16.5%)		42 (18.2%)	
CC	71	61.4 (2.5)		-1.1 (2.3)		16 (22.5%)		10 (14.1%)	
rs833070			0.95		0.84				0.82
TT	122	59.7 (2.2)		-3.6 (1.9)		16 (13.1%)		23 (18.9%)	
CT	261	59.0 (1.5)		-3.1 (1.4)		50 (19.2%)		52 (19.9%)	
CC	156	59.4 (1.8)		-3.1 (1.6)		24 (15.4%)		28 (17.9%)	
rs1413711			0.91		0.91				0.82
TT	124	59.8 (2.2)		-3.4 (1.9)		17 (13.7%)		23 (18.5%)	
CT	257	58.9 (1.5)		-3.2 (1.5)		49 (19.1%)		52 (20.2%)	
CC	158	59.4 (1.8)		-3.1 (1.6)		24 (15.2%)		28 (17.7%)	
rs2010963			0.22		0.19				0.17
CC	68	61.3 (2.6)		-1.1 (2.4)		16 (23.5%)		10 (14.7%)	
CG	233	60.1 (1.5)		-2.5 (1.3)		38 (16.3%)		42 (18.0%)	
GG	238	57.9 (1.7)		-4.5 (1.6)		36 (15.1%)		51 (21.4%)	
rs2071559			0.78		0.72				0.71
GG	143	60.5 (1.8)		-2.2 (1.7)		19 (13.3%)		22 (15.4%)	
AG	281	57.6 (1.5)		-4.7 (1.3)		47 (16.7%)		62 (22.1%)	
AA	115	61.7 (2.1)		-0.9 (2.1)		24 (20.9%)		19 (16.5%)	
3 SNPs in VEGFR2									
rs2146323			0.52		0.66				0.92
CC	240	58.4 (1.5)		-4.0 (1.4)		38 (15.8%)		46 (19.2%)	
AC	240	59.9 (1.6)		-2.3 (1.4)		45 (18.8%)		45 (18.8%)	
AA	59	59.9 (3.2)		-3.7 (2.7)		7 (11.9%)		12 (20.3%)	
rs4576072			0.21		0.41				0.42

SNP and genotype	# of Subjects at Year 5 (N=539)	VA score (letters) at year 5		Change in VA score (letters) from baseline at year 5		>= 3-line gain from baseline at year 5		VA 20/200 or worse at year 5		
		n	Mean (SE)	P-value	Mean (SE)	P-value	n (%)	P-Value	n (%)	P-value
TT	376		58.7 (1.3)		-3.6 (1.1)		65 (17.3%)		74 (19.7%)	
CT	149		59.7 (1.8)		-2.8 (1.7)		22 (14.8%)		28 (18.8%)	
CC	14		69.9 (3.7)		2.4 (5.4)		3 (21.4%)		1 (7.1%)	
rs6828477				0.70		0.37		0.31		0.45
TT	155		58.9 (1.9)		-4.3 (1.7)		22 (14.2%)		30 (19.4%)	
CT	294		59.2 (1.4)		-3.1 (1.3)		51 (17.3%)		60 (20.4%)	
CC	90		60.1 (2.5)		-1.7 (2.5)		17 (18.9%)		13 (14.4%)	

SNP = Single-nucleotide polymorphism, AMD=age-related macular degeneration, VA=visual acuity, SE= standard error. P-value is for the test of linear trend.