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

Gui-shuang Ying, PhD, Maureen G. Maguire, PhD, Wei Pan, MS, Juan E. Grunwald, MD, Ebenezer Daniel, MBBS, PhD, Glenn J. Jaffe, MD, Cynthia A. Toth, MD, Stephanie A. Hagstrom, PhD, Daniel F. Martin, MD, for the Comparison of AMD Treatments Trials Research Group*

**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, 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

Supplemental material available at www.ophthalmologyretina.org.

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. 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. 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. 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. 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).
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 due to AMD, and baseline study eye VA were excluded.

Only the major features related to this article are described.

Methods

Details on the study design and methods of the CATT have been reported in previous publications 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 choroidal 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.

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.

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 (rs10499024), 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.

Statistical Analysis

We previously evaluated the baseline predictors for VA response at year 1 and year 2 using univariate and multivariate regression models. 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 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 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 models.

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

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

CNV = choroidal neovascularization; SE = standard error; VA = visual acuity.

*Seven eyes with ungradable subretinal fluid were excluded.
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.\(^2\) The univariate analysis results for baseline predictors of each 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 (\( P = 0.002 \)), and absence of subretinal fluid (\( P = 0.03 \)). 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, 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. 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. Early detection of CNV and timely treatment before substantial loss of VA and lesion growth are important to maximize the patient’s VA.

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 2 years (28.8% vs. 30.6%, \( P = 0.53 \)). 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. 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 mm², \( P = 0.06 \)) and a higher rate of geographic atrophy growth (0.38 vs. 0.28 mm/year, \( P = 0.009 \)).

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%, 7.5%, 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. The Macular Photocoagulation Study found that cigarette smoking was associated with a higher recurrence rate of CNV after laser photocoagulation.

Cigarette smoking also may 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 compared with nonsmokers. Piermarocchi et al 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. 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. 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). 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.

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. 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. 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. 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. 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 CVN 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.

**References**

29. Hagstrom SA, Ying GS, Pauer GJ, et al. Pharmacogenetics for genes associated with age-related macular degeneration in the

Footnotes and Financial Disclosures

Originally received: June 16, 2017.
Final revision: September 26, 2017.
Accepted: October 2, 2017.
1 Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.
2 Duke Eye Center, Duke University, Durham, North Carolina.
3 Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.
*A listing of the Comparison of Age-Related Macular Degeneration Treatments Trials Research Group is available at www.ophthalmology-retina.org.

Supported by cooperative agreements U10 EY017823, U10 EY017825, U10 EY017826, and U10 EY017828 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): M.G.M.: Data and Safety Monitoring Committee — Genentech/Roche. G.Y.: Consultant — Chengdu Kanghong Biotech Company.

Human Subjects: This study includes human subject/tissues. No animal subjects were used in this study. Study protocol was approved by IRB/ethics committee of Perelman School of Medicine, University of Duke Eye Center, Duke University, Cleveland Clinic, and the other participating centers. Written consent was obtained prior to subject enrollment.

Author Contributions:
Research design: Maguire, Jaffe, Toth
Data acquisition and/or research execution: Ying, Maguire, Pan, Grunwald, Daniel, Jaffe, Toth, Hagstrom, Martin
Data analysis and/or interpretation: Ying, Maguire, Pan
Obtained funding: Martin, Maguire, Jaffe and Grunwald

Manuscript preparation: Ying, Maguire, Grunwald, Daniel, Jaffe, Toth, Hagstrom, Martin

Abbreviations and Acronyms:
AMRD = 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.

Correspondence:
Gui-shuang Ying, PhD. 3535 Market Street, Suite 700, Philadelphia, PA 19104. E-mail: gysing@mail.med.upenn.edu.