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Association of Baseline Characteristics and Early Vision Response with 2-Year Vision Outcomes in the Comparison of AMD Treatments Trials (CATT)

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Purpose: To evaluate the association of baseline characteristics and early visual acuity (VA) response with visual outcomes at years 1 or 2 in the Comparison of Age-Related Macular Degeneration (AMD) Treatments Trials (CATT).

Design: Secondary analysis of CATT.

Participants: The 1185 CATT participants with baseline VA of 20/25 to 20/320.

Methods: Participants were assigned to ranibizumab or bevacizumab and to 1 of 3 dosing regimens. Associations of baseline characteristics and early VA response (week 4 or 12) with VA response at years 1 or 2 were assessed by R^2 from linear regression analyses. Patients who had a poor initial response (VA 20/40 or worse with persistent fluid and without ≥1-line VA gain) were defined as candidates for changing treatment.

Main Outcome Measures: Visual acuity change from baseline.

Results: Statistically significant ($P < 0.05$) baseline predictors for less VA gain at year 2 were older age, VA of 20/40 or better, larger choroidal neovascularization area, presence of geographic atrophy, total foveal thickness ≤325 μm or ≥425 μm, and elevation of retinal pigment epithelium. Among 176 eyes gaining ≥3 lines at week 12, 78% had a ≥3-line gain at year 2, whereas among 113 eyes losing ≥1 line at week 12, 27% improved to a ≥1-line gain at year 2. Visual acuity response at week 12 was more predictive of VA response at year 2 ($R^2 = 0.30$) than VA response at week 4 ($R^2 = 0.17$) and baseline predictors ($R^2 = 0.13$; $P < 0.0001$). Among 126 candidates for changing treatment drug at week 12, mean VA improved by 2.8 letters ($P = 0.050$), mean total retinal thickness decreased 53 μm ($P < 0.0001$), and fluid resolved in 33% ($P < 0.0001$) between week 12 and year 1 with continued use of the same drug and regimen. Similar improvements were observed among 83 candidates for changing drugs at week 24.

Conclusions: Visual acuity response at week 12 is more predictive of 2-year vision outcomes than either several baseline characteristics or week 4 response. Eyes with poor initial response may benefit from continued treatment without switching to another drug. *Ophthalmology 2015;■:1–9 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Anti–vascular endothelial growth factor (VEGF) treatments have revolutionized the treatment of choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).[1–7] Treatment with ranibizumab (Lucentis; Genentech, South San Francisco, CA), bevacizumab (Avastin; Genentech), or aflibercept (Eylea; Regeneron, Tarrytown, NY) has become standard care for the management of neovascular AMD. Despite the effectiveness of these drugs, there is large variation in response across patients, and response fluctuates over time within a patient.[8–10] In an attempt to understand better this variation, we previously investigated the baseline demographic, clinical, and genetic predictors for visual acuity (VA) response at 1 year and found that age, baseline VA, CNV lesion area, and retinal pigment epithelium (RPE) elevation on optical coherence tomography (OCT) images were predictors for VA response at 1 year,[8] whereas genetic factors (either AMD-related single nucleotide

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polymorphisms or VEGF-related single nucleotide polymorphisms) did not predict VA response.[11,12]

The purpose of this study was to evaluate how the early VA response (at weeks 4 or 12) to anti-VEGF treatment, baseline characteristics, and their combinations are associated with VA responses at years 1 or 2 by using the data collected for the Comparison of AMD Treatments Trials (CATT). This evaluation is important for several reasons. First, it may allow adjustment of expectations by ophthalmologists and patients about longer-term results from treatment after the first injections have been completed. Second, if year 1 or 2 VA gain is predicted to be unlikely with the current treatment, switching to alternative treatments (e.g., different anti-VEGF agents or combination therapy) may be considered. Third, if early VA response is associated strongly with year 1 or 2 VA response, early VA response may be considered as a surrogate outcome in future clinical trials of anti-VEGF agents or combination therapy. Finally, understanding the association of early poor vision response and VA response at years 1 or 2 provides background information when evaluating the effects of switching to another drug.

Methods

Details of the study design and methods have been reported in previous publications[5,6] and on ClinicalTrials.gov (identifier, NCT00593450). Only the major features related to this study 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. 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]), or (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 50 years or older, the study eye (1 eye per patient) having untreated active CNV resulting from AMD, and VA between 20/25 and 20/320 on electronic VA testing. Determination of active CNV required both leakage of dye on fluorescein angiography and fluid, located either within or below the retina or below the RPE, on time-domain OCT.

Study Procedures

During the initial visit, patients provided information on demographic characteristics and medical history. Certified photographers obtained stereoscopic color fundus photographs and fluorescein angiograms at baseline, year 1, and year 2. Time-domain OCT images were obtained throughout the first year, whereas 22.6% of scans were obtained on spectral-domain OCT in the second year by certified OCT imagers.[6] Both photographic and OCT images were evaluated at reading centers using standardized protocols.[13,14]

At baseline and at follow-up at weeks 4, 12, 24, 36, 52 (year 1), 64, 76, 88, and 104 (year 2), 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.[15] The VA at other follow-up visits, which occurred every 4 weeks after enrollment, also was measured, but without refraction. The VA scores from the Electronic Visual Acuity Tester range from 0 to 100, corresponding to Snellen equivalents of worse than 20/800 to 20/10.

Statistical Analysis

We previously evaluated the baseline predictors for VA response at year 1 using multiple linear regression analysis.[8] Following the same analysis approach for the same candidate baseline predictors, we evaluated the baseline predictors for VA response at year 2. Early VA response at weeks 4 and 12 and VA responses at years 1 or 2 were calculated as the VA change from baseline. To facilitate the interpretation of clinical results, we also divided the VA response into 5 categories, including 3 lines or more gained (i.e., $\geq$15 letters gained from baseline), 1 to 2 lines gained (5−14 letters gained from baseline), within 1-line change (i.e., lost or gained <5 letters from baseline), 1 to 2 lines lost, or 3 lines or more lost. The agreement between VA response categories at early (week 4 or week 12) and at years 1 or 2 was calculated.

To evaluate whether the baseline characteristics, early VA response, or both predict vision outcomes at years 1 and 2, we calculated R^2 from linear regression models using various predictors, including statistically significant baseline predictors alone, early VA response (i.e., VA change from baseline at weeks 4 or 12 alone, or in combination). In these linear models, early VA response and VA response at years 1 and 2 were represented as continuous variables. The R^2 value was computed as the ratio of the variance of year 1 or 2 VA response explained by predictors and the total variance in the VA response. R^2 values range from 0 to 1, with 0 meaning no prediction beyond random variation and 1 meaning perfect prediction. The comparisons of R^2 values from various prediction models were performed by the method described by Meng et al.[16]

Patients in CATT maintained their randomly assigned drug for 2 years. In a subgroup of CATT patients who in clinical practice might have been considered candidates for switching drugs because of a poor clinical response by weeks 12 or 24, we evaluated the VA and morphologic results when the same drug and dosing regimen were continued through years 1 and 2. We surveyed a variety of past reports of switching drugs to define criteria for candidates for switching drugs among CATT patients.[17−22] Candidates had to have received all 3 initial monthly treatments (baseline and weeks 4 and 8) for switching at week 12 and had to have received 5 of 6 initial monthly treatments (baseline and weeks 4, 8, 12, 16, and 20) for switching at week 24. In addition, candidates also had to meet all 3 of the following criteria for poor clinical response at the week of switching: (1) VA 20/40 or worse, (2) 1-line or less gain from baseline, and (3) persistent OCT fluid at the foveal center. We calculated the VA change and change in OCT total retinal thickness from the switching week and percentage with OCT foveal center fluid resolved at 4 weeks after switching and at years 1 and 2 for all candidates who were eligible for switching. Statistical significance for mean changes from the switching week was assessed using the paired t test. For the analyses in this article, study participants were pooled across the ranibizumab and bevacizumab treatment groups because the treatment effects on VA were similar for both the previously reported primary analyses[5,6] and the analyses in this article. All data

analyses were performed with SAS software version 9.4 (SAS Inc, Cary, NC), and 2-sided *P* values less than 0.05 were considered to be statistically significant.

Results

Visual Acuity over Time

Among all CATT patients (n = 1185), the mean VA at baseline was 61 letters. The mean VA improved by 3.6 letters at week 4, by 5.8 letters at week 12, and by 6.4 letters at week 24; they stabilized at approximately 6 to 7 letters gained through the end of year 2 (Table 1, available at www.aaojournal.org). The percentages of eyes with VA gain or loss from baseline that were within 1 line, between 1 and 2 lines, and 3 lines or more in 2 years also are displayed in Table 1 (available at www.aaojournal.org). Over time, the percentage with a gain of 3 lines or more increased from approximately 10% at week 4 to 27% at week 36 and stabilized at approximately 30% after week 36. The percentage with a loss of 3 lines or more was 2.6% at week 4 and increased gradually to 9.2% at year 2.

Baseline Predictors for Visual Acuity Response at Years 1 and 2

We previously reported[8] the baseline predictors for less VA gain at year 1 (Table 2), including older age ($P = 0.003$), baseline VA of 20/40 or better in the study eye ($P < 0.0001$), larger CNV area ($P = 0.02$), absence of a retinal angiomatous proliferans lesion ($P = 0.03$), and presence of RPE elevation on OCT ($P = 0.004$). This analysis found that all the baseline predictors for less VA gain at year 1 were significant at year 2, including older age ($P = 0.02$), baseline VA of 20/40 or better in study eye ($P < 0.0001$), larger CNV area ($P = 0.02$), and presence of RPE elevation ($P = 0.001$), with the exception of a retinal angiomatous proliferans lesion. Additionally, the presence of geographic atrophy in the study eye ($P = 0.04$) and thicker (>425 μm) or thinner (≤325 μm) total foveal thickness ($P = 0.01$) were significant predictors for less VA gain at year 2, but not at year 1 (Table 2).

This analysis found that baseline predictors for less VA gain at year 2 were similar to those at year 1 and included older age ($P = 0.02$), baseline VA of 20/40 or better in the study eye ($P < 0.0001$), larger CNV area ($P = 0.02$), presence of geographic atrophy in the study eye ($P = 0.04$), thicker (>425 μm) or thinner (≤325 μm) total foveal thickness ($P = 0.01$), and presence of RPE elevation ($P = 0.001$; Table 2).

Association of Visual Acuity Response at Weeks 4 or 12 with Response at Year 1

The association between VA response at week 4 and at year 1 is shown in the top part of Table 3. Among 108 eyes with a gain of 3 lines or more at week 4, 90 eyes (83%) had a similar gain of 3 lines or more, and only 2 eyes (1.8%) had a 1-line-or-more loss at year 1. Among 147 eyes with loss of 1-line or more at week 4, 56 eyes (38%) gained 1 line or more from baseline, whereas 50 eyes (34%) had a similar loss of 1 line or more at year 1 (Fig 1A). In particular, among 27 eyes with a loss of 3 lines or more at week 4, 7 eyes (26%) gained 1 line or more from baseline at year 1 (Table 3).

The association between VA response at week 12 and at year 1 is shown in the bottom part of Table 3. Among the 187 eyes with a gain of 3 lines or more at week 12, 152 eyes (81%) had a similar gain of 3 lines or more at year 1, and only 8 eyes (4%) showed a loss of 1 line or more at year 1. In contrast, among 127 eyes with VA loss of 1 line or more at week 12, 22 eyes (17%) showed a gain of 1 line or more, whereas 58% showed a similar loss of 1 line or more at year 1 (Fig 1B).

Association of Visual Acuity Response at Week 4 or 12 with Response at Year 2

The association between VA response at week 4 and at year 2 is presented in the top part of Table 4. Among 103 eyes that showed a gain of 3 lines or more from baseline, 86 eyes (84%) showed a similar gain of 3 lines or more, and only 5 eyes (5%) showed a loss of 1 line or more, at year 2. Among 133 eyes with a loss of 1 line or more at week 4, 50 eyes (38%) showed a gain of 1 line or more, whereas 56 eyes (42%) showed a similar loss of 1 line or more, at year 2 (Fig 1C).

The association between VA response at week 12 and at year 2 is shown in the bottom part of Table 4. Among 176 eyes that showed a gain of 3 lines or more from baseline, 137 eyes (78%) showed a similar gain of 3 lines or more, whereas 9 eyes (5%) showed a loss of 1 line or more, at year 2. Among 113 eyes with a loss of 1 line or more at week 12, 30 eyes (27%) showed a gain of 1 line or more, whereas 59 eyes (52%) showed a similar loss of 1 line or more, at year 2 (Fig 1D).

Prediction of Year 1 and 2 Outcomes Using Baseline Predictors and Early Visual Acuity Response

The predictions of VA response at years 1 and 2 using baseline predictors alone, early VA response alone, and their combinations are shown in Table 5. Using the statistically significant baseline predictors for VA response at years 1 and 2, the corresponding R^2 values for predicting VA change at years 1 and 2 are 0.09 and 0.13, respectively, which are lower than those using early VA response at week 4 alone ($R^2 = 0.22$ for year 1 and 0.17 for year 2) and week 12 alone (0.47 for year 1 and 0.30 for year 2; all $P < 0.001$ for comparison with baseline predictors). Combining the baseline predictors with the week 12 VA response resulted in modest increases of R^2 to 0.49 for year 1 and 0.35 for year 2 ($P < 0.001$). Adding the VA response at week 4 to the regression models did not improve the models that already included VA response at week 12 (Table 5).

Visual Acuity and Morphologic Change over Time among Patients Eligible for Switching

Among 126 patients who were candidates for switching drugs at week 12, the mean VA at week 12 was 53 letters (Snellen equivalent, 20/80). There was a mean loss of 0.4 letters from weeks 12 to 16 ($P = 0.57$), a mean gain of 2.8 letters from week 12 at year 1 ($P = 0.050$), and a mean gain of 2.9 letters at year 2 ($P = 0.11$). The total retinal thickness decreased from week 12, with a mean decrease of 53 μm at year 1 ($P < 0.0001$) and 54 μm at year 2 ($P = 0.0004$). After week 12, fluid at the foveal center resolved in 33% of eyes at year 1 and 54% at year 2 (Table 6, top).

Among 83 patients who were candidates for switching drugs at week 24, the mean VA at week 24 was 50 letters (Snellen

Table 2. Multivariate Analysis for Association of Baseline Characteristics with Visual Acuity Change from Baseline at Years 1 and 2

Baseline Characteristics	Visual Acuity Score Change (Letters) from Baseline at Year 1 (n = 1069)*			Visual Acuity Score Change (Letters) from Baseline at Year 2 (n = 1014)*		
	No.	*Adjusted Mean (Standard Error)*	*P Value*	*No.*	*Adjusted Mean (Standard Error)*	*P Value*
Age (yrs)						
50–69	125	10.8 (1.3)	0.003	127	9.3 (1.4)	0.02
70–79	374	8.2 (0.8)		357	7.1 (0.8)	
80–89	500	5.8 (0.6)		465	5.0 (0.7)	
≥90	70	6.2 (1.7)		65	4.7 (1.9)	
Visual acuity in study eye in letters (Snellen equivalent)						
68–82 (20/25–20/40)	382	3.3 (0.7)	<0.0001	378	0.7 (0.8)	<0.0001
53–67 (20/50–20/80)	401	8.4 (0.7)		373	6.9 (0.8)	
38–52 (20/100–20/160)	218	11.9 (1.0)		201	14.3 (1.1)	
23–37 (20/200–20/320)	68	7.9 (1.7)		62	10.5 (2.0)	
Area of CNV (mm^2)						
≤2.54	435	8.7 (0.7)	0.02	411	7.5 (0.8)	0.004
>2.54–≤5.08	214	7.5 (1.0)		199	7.8 (1.1)	
>5.08–≤10.2	207	6.7 (1.0)		191	6.0 (1.1)	
>10.2	102	4.2 (1.4)		99	2.1 (1.6)	
Can't measure	111	4.8 (1.4)		114	3.4 (1.5)	
Geographic atrophy						
None/questionable				948	6.5 (0.5)	0.04
Present				66	2.4 (1.9)	
RAP lesion						
No	951	6.9 (0.5)	0.03			
Yes	118	10.1 (1.3)				
Total foveal thickness (μm)						
First quartile (≤325)				261	5.4 (1.0)	0.01
Second quartile (>325–≤425)				259	8.9 (1.0)	
Third quartile (>425–≤550)				232	6.0 (1.0)	
Fourth quartile (>550)				262	4.7 (1.0)	
RPE elevation						
No	139	10.5 (1.2)	0.004	136	10.3 (1.4)	0.001
Yes	930	6.8 (0.5)		878	5.6 (0.5)	
Treatment group in year 1						
Ranibizumab monthly	280	8.6 (0.9)	0.07			
Bevacizumab monthly	251	7.9 (0.9)				
Ranibizumab PRN	276	6.9 (0.9)				
Bevacizumab PRN	262	5.5 (0.9)				
Treatment group in year 2						
Ranibizumab monthly for 2 yrs				135	8.0 (1.3)	0.21
Bevacizumab monthly for 2 yrs				124	7.7 (1.4)	
Ranibizumab monthly year 1, PRN year 2				130	7.2 (1.4)	
Bevacizumab monthly year 1, PRN year 2				122	4.4 (1.4)	
Ranibizumab PRN for 2 yrs				256	6.5 (1.0)	
Bevacizumab PRN for 2 yrs				247	4.8 (1.0)	

CNV = choroidal neovascularization; PRN = pro re nata; RAP = retinal angiomatous proliferans; RPE = retinal pigment epithelium.
*Number of subjects included in the multivariate model. Thirty-seven patients were excluded because of a missing value in 1 or more predictors for the multivariate model of year 1 visual acuity (VA) outcome, and 20 patients were excluded because of missing value in 1 or more predictors for the multivariate model of year 2 VA outcome.

equivalent, 20/100). There was a mean gain of 1.9 letters from week 24 at week 28 ($P = 0.03$), 3.3 letters at year 1 ($P = 0.03$), and 4.9 letters at year 2 ($P = 0.008$). The total retinal thickness decreased from week 24, with a mean decrease of 26 μm at year 1 ($P = 0.04$) and 36 μm at year 2 ($P = 0.02$). After week 24, fluid at the foveal center resolved in 32% of eyes at year 1 and in 51% at year 2 (Table 6, bottom).

Among 10 patients who had progressive loss of vision (n = 8) or progressive increase of total retinal thickness over the first 3 visits (n = 2), a mean of 3.2 letters was gained from week 12 at year 1 ($P = 0.68$) and 7 letters was gained at year 2 ($P = 0.41$). The total retinal thickness decreased from week 12, with a mean decrease of 83 μm ($P = 0.03$) at year 1 and 100 μm at year 2 ($P = 0.01$).

Table 3. Association of Visual Acuity Response at Weeks 4 or 12 with Visual Acuity Response at Year 1

Visual Acuity Change	No.	Visual Acuity Change from Baseline at Year 1, No. (%)				
		≥3 Lines Gained	*1–2 Lines Gained*	*Within 1-Line Change*	*1–2 Lines Lost*	*≥3 Lines Lost*
From baseline at week 4						
≥3 lines gained	108	90 (83.3)	13 (12.0)	3 (2.8)	1 (0.9)	1 (0.9)
1–2 lines gained	354	143 (40.4)	141 (39.8)	44 (12.4)	12 (3.4)	14 (4.0)
Within 1-line change	480	65 (13.5)	190 (39.6)	157 (32.7)	42 (8.8)	26 (5.4)
1–2 lines lost	120	19 (15.8)	30 (25.0)	34 (28.3)	19 (15.8)	18 (15.0)
≥3 lines lost	27	6 (22.2)	1 (3.7)	7 (25.9)	7 (25.9)	6 (22.2)
Total	1089	323 (29.7)	375 (34.4)	245 (22.5)	81 (7.4)	65 (6.0)
From baseline at week 12						
≥3 lines gained	187	152 (81.3)	27 (14.4)	7 (3.7)	1 (0.5)	0 (0.0)
1–2 lines gained	399	120 (30.1)	202 (50.6)	62 (15.5)	11 (2.8)	4 (1.0)
Within 1-line change	312	25 (8.0)	115 (36.9)	127 (40.7)	32 (10.3)	13 (4.2)
1–2 lines lost	88	6 (6.8)	14 (15.9)	26 (29.6)	22 (25.0)	20 (22.7)
≥3 lines lost	39	1 (2.6)	1 (2.6)	5 (12.8)	8 (20.5)	24 (61.5)
Total	1025	304 (29.7)	359 (35.0)	227 (22.1)	74 (7.2)	61 (6.0)

Discussion

We evaluated the association of baseline predictors and early VA response on year 1 and year 2 vision outcomes among CATT patients treated with ranibizumab or bevacizumab on a monthly or PRN basis for neovascular AMD. Baseline predictors for year 2 vision response were nearly identical to those that we previously reported for year 1.[8] Age, baseline VA, and CNV lesion size remain significant predictors, consistent with year 1 and also consistent with findings of other treatment trials for neovascular AMD.[23] Although a number of these baseline variables were highly significant in their association with year 1 and 2 vision response, these predictors explain only a small portion of the variation in VA response, with R^2 values of 0.09 for year 1 and 0.13 for year 2, indicating that their actual ability to predict vision outcome was quite modest.

The strongest predictor of vision outcome at years 1 or 2 in our study was VA response at week 12. Other studies that evaluated anti-VEGF drugs for neovascular AMD also demonstrated a rapid rise in VA in the first 12 weeks, followed by a plateau that remains relatively flat throughout the remaining 1 or 2 years of the study.[1,2,4,7,24,25] With only a small change in VA improvement between 12 weeks and 2

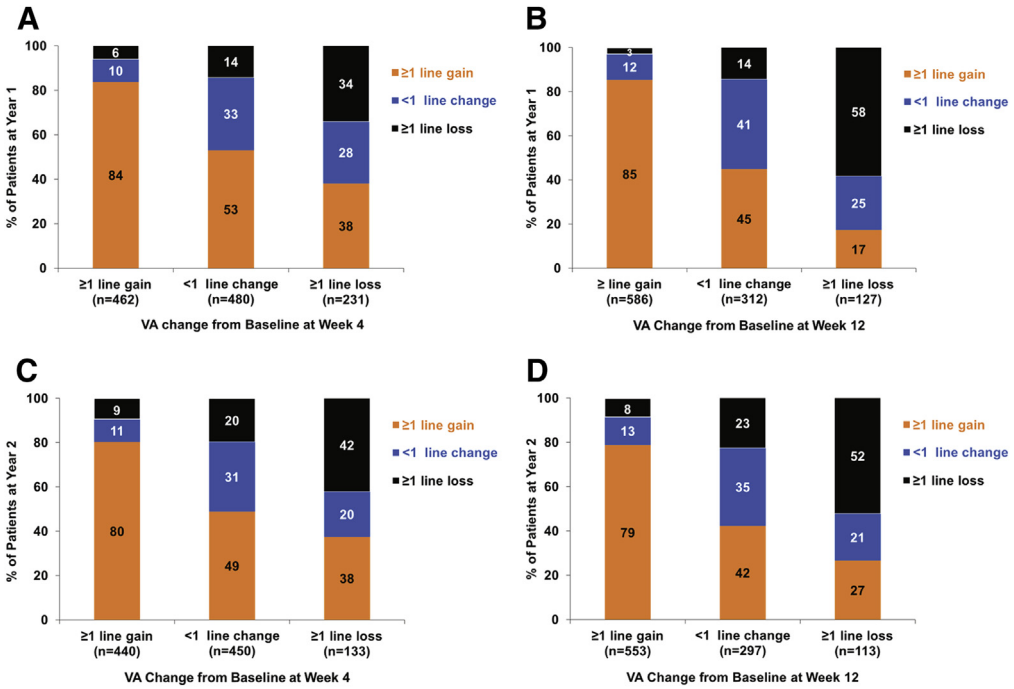

Figure 1. Bar graphs showing the visual acuity (VA) response category (≥1-line gain, <1-line change, ≥1-line loss) at years 1 or 2 by the early VA response category at weeks 4 or 12: (**A**) VA response category at year 1 by VA response at week 4, (**B**) VA response category at year 1 by VA response at week 12, (**C**) VA response category at year 2 by VA response at week 4, and (**D**) VA response category at year 2 by VA response at week 12.

Table 4. Association of Visual Acuity Response at Weeks 4 or 12 with Visual Acuity Response at Year 2

Visual Acuity Change	No.	Visual Acuity Change from Baseline at Year 2, No. (%)				
		≥3 Lines Gained	1–2 Lines Gained	Within 1-Line Change	1–2 Lines Lost	≥3 Lines Lost
From baseline at week 4						
≥3 lines gained	103	86 (83.5)	10 (9.7)	2 (1.9)	3 (2.9)	2 (1.9)
1–2 lines gained	337	124 (36.8)	133 (39.5)	44 (13.1)	16 (4.8)	20 (5.9)
Within 1-line change	450	72 (16.0)	148 (32.9)	142 (31.6)	50 (11.1)	38 (8.4)
1–2 lines lost	107	16 (15.0)	26 (24.3)	21 (19.6)	17 (15.9)	27 (25.2)
≥3 lines lost	26	6 (23.1)	2 (7.7)	6 (23.1)	6 (23.1)	6 (23.1)
Total	1023	304 (29.7)	319 (31.2)	215 (21.0)	92 (9.0)	93 (9.1)
From baseline at week 12						
≥3 lines gained	176	137 (77.8)	25 (14.2)	5 (2.8)	3 (1.7)	6 (3.4)
1–2 lines gained	377	101 (26.8)	173 (45.9)	66 (17.5)	22 (5.8)	15 (4.0)
Within 1-line change	297	40 (13.5)	86 (30.0)	104 (35.0)	37 (12.5)	30 (10.1)
1–2 lines lost	79	6 (7.6)	18 (22.8)	19 (24.1)	16 (20.3)	20 (25.3)
≥3 lines lost	34	3 (8.8)	3 (8.8)	5 (14.7)	7 (20.6)	16 (47.1)
Total	963	287 (29.8)	305 (31.7)	199 (20.7)	85 (8.8)	87 (9.0)

years, one might expect that the VA response at week 12 would be highly predictive of VA response at year 1 or 2. Instead, it was surprising to learn that the VA response at 12 weeks predicted only less than 50% of the variation in the VA responses at years 1 or 2, with R^2 values of 0.47 for year 1 and 0.30 for year 2 VA outcomes. Combining all baseline predictors with the week 12 VA response only increased the R^2 value (from 0.47 to 0.49 for year 1 and 0.30 to 0.35 for year 2). This fluctuation of VA during the course of anti-VEGF treatment makes it challenging to determine the beneficial effect on VA from switching to another treatment. Eyes that had a VA gain of at least 1 line at 12 weeks generally had a similar gain at years 1 and 2. However, some eyes that initially showed a loss of 1 line or more at 12 weeks were able to gain 1 line or more at year 1 (17%) or at year 2 (27%). This shift from early VA loss to later VA gain contributes to the lower than expected association between early VA response and later VA response at years 1 or 2. Although forecasting treatment response at years 1 or 2 may not be exact, the response at 12 weeks does provide valuable information on the likely response at years 1 or 2, as illustrated in Figure 1B, D. In addition, the fact that a meaningful percentage of eyes eventually had VA gain despite early loss is encouraging and should prompt ophthalmologists and patients not to give up anti-VEGF treatment, even if early VA response is not optimal, or at the very least to be careful about the attribution of improvement in VA or retinal thickness after switching treatment.

Table 5. Proportion of Variance R^2 in Visual Acuity Response at Years 1 and 2 Explained by Baseline Predictors and Early Visual Acuity Response at Weeks 4 or 12

Predictors	R^2 for Visual Acuity Change from Baseline at Year 1 (n = 982)*	R^2 for Visual Acuity Change from Baseline at Year 2 (n = 937)*
Baseline predictors†	0.09	0.13
Visual acuity change at week 4	0.22	0.17
Visual acuity change at week 12	0.47	0.30
Visual acuity change at both weeks 4 and 12	0.47	0.31
Baseline predictors + visual acuity change at week 4	0.26	0.25
Baseline predictors + visual acuity change at week 12	0.49	0.35
Baseline predictors + visual acuity change at weeks 4 and 12	0.49	0.36

*Among those with complete data for baseline predictors, visual acuity at weeks 4 and 12.
†Baseline predictors: age, visual acuity in study eye, area of choroidal neovascularization, lesion of retinal angiomatous proliferans, elevation of retinal pigment epithelium, and treatment group for year 1; age, visual acuity in study eye, area of choroidal neovascularization, geographic atrophy, total foveal thickness, elevation of retinal pigment epithelium, and treatment group in year 2.

Although the week 4 VA response was a better predictor than other baseline variables of year 1 and 2 VA outcomes, it was considerably worse than the week 12 VA response for predicting the VA response at year 1 or 2. The most likely explanation comes from consideration of the VA response curve, where there is continued improvement in many eyes through the first 3 monthly injections; that is, some eyes do not reach their optimal treatment benefit after a single injection and need additional injections to do so. Combining week 4 response with week 12 response did not improve the predictions beyond what was predicted by VA response at week 12, regardless of whether baseline predictors were considered.

When a patient does not respond to treatment after a few injections, ophthalmologists may consider switching to another anti-VEGF drug. Several uncontrolled studies have investigated the effect of switching from one anti-VEGF drug to another on vision and morphologic outcomes.[17–22] Although different switching criteria were used among the studies, most found some improvement in morphologic outcomes (decrease in retinal thickness, resolution of fluid in the retina) and stabilization or slight improvement in VA

Table 6. Visual Acuity and Optical Coherence Tomography Morphologic Outcomes for Eyes Meeting Criteria for Hypothetical Switching of Drug Outside of the Clinical Trial

Switching at Week 12 (n = 126)	Week 12 (n = 126)	Week 16 (n = 116)*,†	Year 1 (n = 117)	Year 2 (n = 108)
Mean VA (SD), letters	52.5 (16.3)	52.0 (18.6)	55.5 (20.9)	55.5 (23.0)
Mean VA change (SD) from week 12, letters		−0.4 (7.12)	2.8 (15.5)	2.9 (18.3)
P value for VA comparison with week 12		0.57	0.050	0.11
Fluid at foveal center, no. (%)	126 (100)	—	77 (67.0)	49 (46.2)
Mean total thickness (SD), μm	401 (163)	—	357 (163)	360 (176)
Mean change in total thickness (SD) from week 12, μm		—	−53 (137)	−54 (153)
P value for total thickness comparison with week 12			<0.0001	0.0004
Switching at Week 24 (n = 83)	**Week 24 (n = 83)**	**Week 28 (n = 77)*,†**	**Year 1 (n = 82)**	**Year 2 (n = 81)**
Mean VA (SD), letters	50.0 (17.5)	51.7 (18.3)	53.6 (20.8)	55.0 (20.3)
Mean VA change (SD) from week 24, letters		1.9 (7.8)	3.3 (13.8)	4.9 (16.1)
P value for VA comparison with week 24		0.03	0.03	0.008
Fluid at foveal center, no. (%)	83 (100)	—	54 (68.4)	38 (48.7)
Mean total thickness (SD), μm	427 (169)	—	399 (177)	384 (188)
Mean change in total thickness (SD) from week 24, μm		—	−26 (108)	−36 (137)
P value for total thickness comparison with week 12			0.04	0.02

SD = standard deviation; VA = visual acuity; — = not calculated because optical coherence tomography images were not evaluated in reading center in patients randomized to monthly treatment.
*Only pro re nata–treated subjects had optical coherence tomography measurements.
†Visual acuity was measured without refraction.

after switching.[17,18,21,22] In the largest of these studies, Yonekawa et al[17] evaluated 132 eyes that switched from ranibizumab or bevacizumab to aflibercept because of refractory or recurrent neovascular AMD and found that central retinal thickness decreased by 30 μm ($P < 0.0001$) and VA improved by approximately 3 letters ($P = 0.25$) after an average of 4 aflibercept injections. The primary limitations in all of these studies are the absence of a group of similar patients who were not switched and the implicit assumption that vision and retinal thickness would not change with continued use of the same drug. These studies do not provide convincing evidence that switching from one anti-VEGF drug to another anti-VEGF drug has any long-term benefit.

To date, there are no widely accepted prospectively defined criteria for switching anti-VEGF drugs. When we surveyed a variety of past reports of results after switching drugs, it was clear that the decision to switch anti-VEGF treatments was highly subjective, but always involved failure to achieve a desired result for vision or macular morphologic features. We therefore attempted to define prospectively the criteria by which switching would be considered at either 12 or 24 weeks. Variables considered were VA, macular morphologic features (mostly persistence of fluid on OCT), changes in vision over time, and the number of injections already given. We arrived at the following definition for hypothetical patients eligible for switching in CATT. First, patients had to have a VA of 20/40 or worse. Second, patients had to have gained less than 1 line of vision. Third, patients had to have persistent fluid at the center of the fovea on OCT. Finally, patients had to have received all 3 initial monthly treatments of ranibizumab or bevacizumab up to the time of hypothetical switching (at baseline, week 4, and week 8) for switching at week 12 and had to have received 5 of 6 monthly treatments (baseline and weeks 4, 8, 12, 16, and 20) for switching at week 24. Because there is no consensus on the number of injections that need to be received before considering switching a drug, we considered 2 possible switching time points, one at week 12 and another at week 24 after initiating treatments. Patients who met our hypothetical drug-switching criteria at week 12 achieved on average an additional 3 letters of VA improvement and a 53-μm reduction in retinal thickness at 1 year. There was almost no additional VA gain or reduction in thickening between years 1 and 2. Patients who met our hypothetical drug-switching criteria at week 24 achieved on average an additional 3 letters of VA improvement at year 1 and 5 letters of VA improvement at year 2, whereas retinal thickness decreased by 26 and 36 μm at years 1 and 2, respectively. This degree of VA gain and anatomic improvement is strikingly similar to the degree of improvement that has been reported when patients actually did switch drugs, such as the 3-letter and 30-μm improvements reported by Yonekawa et al.[17] Caution must be exercised when comparing our cohort, who continued taking the same drug, with patients who actually switched in other studies because of differences in patient populations and the exact criteria for switching. However, the results of switching at week 12 or 24 from our study establish that outcomes can be improved when the same drug is continued and underscore the need for a control group when interpreting the changes observed after switching drugs in other studies.

In conclusion, we found that baseline predictors are similar for VA response at years 1 and 2. The more powerful predictor of VA outcomes was the VA response at week 12; most eyes with early VA gain had a similar VA gain at years 1 or 2. However, some eyes with an initial decline in VA

had VA gains late, even without switching to another drug, supporting the continuation of anti-VEGF therapy.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CNV** = choroidal neovascularization; **OCT** = optical coherence tomography; **PRN** = pro re nata; **RPE** = retinal pigment epithelium; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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Table 1. (online) Visual Acuity Change Over Time

Week	No. of Patients	Mean Visual Acuity in Letters (SD)	Mean Change in Visual Acuity from Baseline (SD)	Visual Acuity Change from Baseline, no. (%)				
				≥3-line gain	*1- to 2-line gain*	*Within 1-line change*	*1- to 2-line loss*	*≥3-line loss*
000	1185	60.6 (13.5)						
004	1157	64.1 (14.5)	3.6 (9.0)	114 (9.9)	378 (32.7)	509 (44.0)	126 (10.9)	30 (2.6)
012	1085	66.6 (15.6)	5.8 (11.3)	198 (18.3)	415 (38.3)	336 (31.0)	95 (8.8)	41 (3.8)
024	1061	67.2 (16.9)	6.4 (12.9)	235 (22.2)	405 (38.2)	287 (27.1)	82 (7.7)	52 (4.9)
036	1026	68.4 (16.6)	7.4 (13.7)	277 (27.0)	383 (37.3)	236 (23.0)	72 (7.0)	58 (5.7)
052	1106	68.0 (17.8)	7.3 (14.7)	327 (29.6)	381 (34.5)	246 (22.2)	84 (7.6)	68 (6.2)
064	986	68.5 (17.6)	7.7 (14.9)	293 (29.7)	330 (33.5)	223 (22.6)	79 (8.0)	61 (6.2)
076	984	67.5 (18.1)	6.9 (15.7)	284 (28.9)	349 (35.5)	193 (19.6)	84 (8.5)	74 (7.5)
088	948	68.0 (17.5)	7.0 (15.0)	268 (28.3)	321 (33.9)	200 (21.1)	85 (9.0)	74 (7.8)
104	1034	67.3 (18.3)	6.3 (16.6)	307 (29.7)	322 (31.1)	218 (21.1)	92 (8.9)	95 (9.2)