Sporadic Visual Acuity Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)

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• PURPOSE: To evaluate transient, large visual acuity (VA) decreases, termed sporadic vision loss, during anti–vascular endothelial growth factor treatment for neovascular age-related macular degeneration (AMD).

• DESIGN: Cohort within a randomized clinical trial.

• METHODS: SETTING: Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). STUDY POPULATION: Total of 1185 CATT patients. MAIN OUTCOME MEASURES: Incidence of sporadic vision loss and odds ratio (OR) for association with patient and ocular factors. Sporadic vision loss was a decline of ≥15 letters from the previous visit, followed by a return at the next visit to no more than 5 letters worse than the visit before the VA loss.

• RESULTS: There were 143 sporadic vision loss events in 122 of 1185 patients (10.3%). Mean VA at 2 years for those with and without sporadic vision loss was 58.5 (~20/63) and 68.4 (~20/40) letters, respectively ($P < .001$). Among patients treated pro re nata, no injection was given for 27.6% (27/98) of sporadic vision loss events. Multivariate analysis demonstrated that baseline predictors for sporadic vision loss included worse baseline VA (OR 2.92, 95% confidence interval [CI]:1.65–5.17 for ≤20/200 compared with ≥20/40), scar (OR 2.21, 95% CI:1.22–4.01), intraretinal foveal fluid on optical coherence tomography (OR 1.80, 95% CI:1.11–2.91), and medical history of anxiety (OR 1.90, 95% CI:1.12–3.24) and syncope (OR 2.75, 95% CI:1.45–5.22). Refraction decreased the likelihood of sporadic vision loss (OR 0.62, 95%CI: 0.42–0.91).

• CONCLUSIONS: Approximately 10% of CATT patients had sporadic vision loss. Baseline predictors included AMD-related factors and factors independent of AMD. These data are relevant for clinicians in practice and those involved in clinical trials. (Am J Ophthalmol 2014;158:128–135. © 2014 by Elsevier Inc. All rights reserved.)

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VISUAL ACUITY (VA) HAS BEEN THE PRIMARY outcome measure for every major clinical trial for neovascular age-related macular degeneration (AMD).[1–7] Previous studies have established that VA measurement administered under a standard protocol that includes refraction provides a reliable outcome measure.[8,9] Still, VA scores can be affected by multiple factors, some of which have little to do with the condition of the eye. Health issues that are not primarily ocular, such as depression and neurologic disease, can impact VA measurement or visual function.[10–17] In addition, clinicians occasionally see patients in follow-up who have a worse VA measurement without any change on clinical examination.

As part of their analysis of vision loss during the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trials, Wolf and associates identified patients that had acute loss of ≥15 letters within any 1-month period.[18] A total of 106 of 758 ranibizumab-treated patients (13.9%) experienced an acute loss of vision during the first year, and several had more than 1 episode of acute vision loss. Although they concluded that continued treatment was beneficial, there was no clear relationship between patient characteristics and acute vision loss, including an analysis of study eye adverse events (AEs) or serious adverse events (SAEs). It is possible that other factors in addition to progressive AMD disease were involved in some of these acute vision loss events.

Given that significant resources are devoted to studying a treatment's effects on VA in AMD patients, we have sought further understanding of factors that influence this outcome measurement. The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) was a 2-year study that evaluated the efficacy of ranibizumab compared with bevacizumab, as well as monthly compared with as-needed treatments.[6,19] The CATT database provides an unprecedented opportunity to investigate AMD patients as it expands on MARINA and ANCHOR data, providing treatment regimen, drug, and optical coherence tomography (OCT) correlations. We previously reported the frequency of sustained VA loss and its associated factors within CATT.[20] Here, we report similarly for sporadic VA loss within CATT. Rather than studying patients

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with only an acute loss of ≥15 letters, we were interested in patients who had a decline of ≥15 letters from the previous visit, followed by a return of vision at the next visit. Although changes of 5 and occasionally 10 letters are within test-retest variability,[9] little is known about the causes of transient VA losses of ≥15 letters for AMD patients.

METHODS

THIS STUDY WAS A SECONDARY ANALYSIS OF A COHORT within a randomized clinical trial (CATT). Previous CATT reports provide a detailed summary of the CATT study design.[6,19] CATT is registered with http://www.clinicaltrials.gov (NCT00593450). Design features relevant to this report are described here.

• **STUDY PATIENTS:** Study patients provided written informed consent to participate in CATT. The Institutional Review Board of each study site prospectively approved the CATT study protocol, and the study is in accordance with the Health Insurance Portability and Accountability Act regulations. The inclusion criteria were age ≥50 years, untreated choroidal neovascularization (CNV) from AMD in the study eye, VA of 20/25–20/320, and neovascularization or its sequelae at the foveal center. Baseline medical history was obtained from all patients.

Patients were randomized at study entry to 1 of 4 treatment arms: ranibizumab monthly, bevacizumab monthly, ranibizumab pro re nata (PRN), and bevacizumab PRN. At 1 year, study patients in the monthly groups were randomized again 1:1 to continued monthly treatment or PRN treatment. PRN treatment was given when there were signs of active neovascularization, defined as fluid on OCT, hemorrhage, decreased VA compared with the prior visit, or leakage or increased lesion size on fluorescein angiography.

All patients had monthly VA measurements using an electronic VA testing system by certified VA examiners who were masked to the patients' treatment assignment.[9] Protocol refraction before measurement of VA was required at baseline and at weeks 4, 12, 24, 36, 52, 64, 76, 88, and 104. For efficiency, refractions were not routinely performed at every visit.

• **IMAGING PROCEDURES:** Stereoscopic color fundus photography and fluorescein angiography were performed by certified photographers at baseline, 52 weeks, and 104 weeks. Stratus (version 4.0 or higher) time-domain OCT systems (Carl Zeiss Meditec, Dublin, California, USA) were used for first-year visits and most second-year visits. Spectral-domain OCT images were obtained for 23% of second-year visits. OCT images were obtained monthly in the PRN arms. Certified technicians masked to the patients' treatment assignment followed standardized procedures and performed OCT imaging with macular thickness maps and fast macular thickness maps. OCT scans were independently analyzed by 2 certified OCT readers at the CATT OCT Reading Center, and photographs were analyzed by 2 certified readers at the CATT Photography Reading Center. Details about image acquisition and analysis by the reading centers are previously described.[21–23]

• **DATA ANALYSIS:** Sporadic vision loss required VA data from 3 consecutive visits (ie, VA1, VA2, and VA3). Sporadic vision loss was defined as a decline of ≥15 letters from the previous visit (ie, VA1 − VA2 ≥ 15 letters), followed by a return at the next visit to no more than 5 letters worse than the visit before the VA loss (ie, VA3 − VA1 ≥ −5 letters). Five letters was chosen for the latter part of this definition since 89% of test-retest electronic VA measurements reportedly are within 5 letters.[9] Sporadic vision loss of 30 letters was defined as a decline of ≥30 letters from the previous visit, followed by a return at the next visit to no more than 5 letters worse than the visit before the VA loss.

The incidence of sporadic vision loss loss was calculated as the proportion of eyes with sporadic vision loss within 2 years among all CATT patients. Mean VA during the study was compared between eyes with sporadic vision loss and all other study eyes. VA, fundus photograph features, and OCT features were compared at 2 years between eyes with and without sporadic vision loss. As noted, the 2-group *t* test or the paired *t* test was used for comparison of means. Fisher exact test or McNemar test was used for comparison of proportions.

For the 27 events of sporadic vision loss that did not coincide with an injection, investigators for these events were queried about the possible cause of vision loss, whether new hemorrhage at the macula was present, and why no injection was given.

For the evaluation of baseline medical history associations with sporadic vision loss, we focused on neurologic and psychological histories because of their potential effects on visual function measurements.[10–17] Additionally, a Functional Comorbidity Index was used to determine if patients with more comorbidities in their baseline history had an increased risk for sporadic vision loss. The Functional Comorbidity Index is an established measure of comorbid disease that correlates with physical function as the outcome of interest.[24] This index contains 18 items such as visual impairment, congestive heart failure, arthritis, asthma, depression, anxiety, and neurologic disease. The Functional Comorbidity Index is scored by summing the number of specific comorbidities in a patient's medical history. A score of 0 indicates no relevant comorbidities, while a score of 18 indicates the highest number of comorbid illnesses.

The association of sporadic vision loss and nonocular SAEs was investigated using nonocular SAEs reported within 30 days (before or after) of the time of sporadic

vision loss events. These time frames were chosen as we were interested in knowing if sporadic vision loss has an association with a patient that is still recovering from a recent systemic SAE or that is becoming systemically ill and about to have an SAE. To investigate these potential associations, we matched sporadic vision loss patients (cases) with patients without sporadic vision loss (controls). The matching criteria were: drug, regimen, age (±3 years), Functional Comorbidity Index score (±2 points), and the number of visits with measured VA. To maximize the use of the controls, we allowed 1 case to have more than 1 control if available (ie, 1:n matching).

The evaluation of factors associated with sporadic vision loss was first performed by univariate analysis using repeated measures logistic regression models to accommodate patients with more than 1 event of sporadic vision loss. Multivariate analyses started with the factors with a $P < .20$ in univariate analysis, and the final multivariate analysis model was developed using a backward selection procedure by keeping only predictors with $P < .05$, with the exception of the drug and regimen groups. Adjusted odds ratios (OR) of sporadic vision loss and the 95% confidence intervals (95% CI) were calculated from the final multivariate logistic regression model for repeated measures. All data analyses were performed using SAS v9.2 (SAS Inc, Cary, North Carolina, USA). Two-sided $P < .05$ was considered statistically significant.

RESULTS

• **INCIDENCE AND VISUAL ACUITY:** Over 2 years, 122 of the 1185 patients (10.3%) had at least 1 event of sporadic vision loss. There were 143 sporadic vision loss events. One hundred and two of 122 patients (83.6%) had only 1 sporadic vision loss event; 19 (15.6%) had 2 events; and 1 patient (0.82%) had 4 events. There were 10 patients (0.8%) of the 1185 patients who developed sporadic vision loss of 30 letters, including 1 patient who had 2 events of this. The time to first sporadic vision loss event was evenly distributed across the entire duration of the study. For 59 of 143 sporadic vision loss events (41.3%), the patient had a VA of 20/40 or better at the study visit preceding the sporadic vision loss. At all time points throughout the study, the patients with sporadic vision loss had a worse mean VA than patients without sporadic vision loss (Figure).

• **OPTICAL COHERENCE TOMOGRAPHY FEATURES AND INJECTIONS AROUND THE TIME OF SPORADIC VISION LOSS AMONG EYES TREATED PRO RE NATA:** Sporadic vision loss events occurred 98 times in 83 eyes treated according to the PRN dosing regimen. OCT analysis of the 98 events showed that the mean retinal thickness was 169 μm at the visit before the sporadic vision loss, 183 μm at the time of sporadic vision loss, and 151 μm at the visit afterwards (Table 1). Among all CATT patients, a change in OCT retinal thickness had a weak correlation with a change in VA (data not shown), and only 13 of these 98 sporadic vision loss events (13.3%) among eyes treated PRN coincided with an increase of retinal thickness of 50 μm or more. Foveal fluid was seen in 25 of the 98 events (25.5%) before the sporadic vision loss, in 37 (37.8%) at the time of sporadic vision loss, and in 17 (17.4%) afterwards. Subretinal fluid at the fovea was seen in 12 events (12.2%) before the sporadic vision loss, in 14 (14.3%) at the time of sporadic vision loss, and in 5 (5.1%) afterwards.

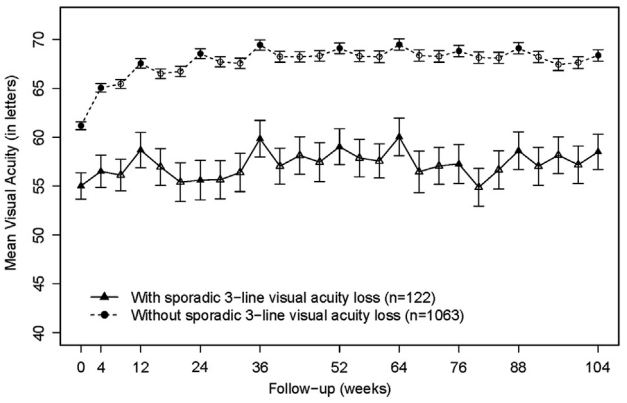

FIGURE. Mean (±standard error) visual acuity over 2 years among patients with and without sporadic vision loss in the Comparison of Age-Related Macular Degeneration Treatments Trials. Study visits with refraction are represented by solid symbols.

Of the 98 events among eyes treated PRN, 43 (43.9%) had a study injection at the prior visit and 71 (72.4%) had an injection at the visit when sporadic vision loss was noted. Among the 27 patients that were not treated at the time of sporadic vision loss, 6 (22.2%) had intraretinal or subretinal fluid at the fovea. Investigators were queried about these 27 events, and responses for 21 of these events were received. No identifiable cause for vision loss was found for 11 of these 21 events. For the remaining events, the cause of sporadic vision loss was thought to be related to a change in systemic health (3/21), progression of non-neovascular AMD (3/21), dry eyes (2/21), cataract (1/21), and increased subretinal fluid from neovascular AMD (1/21). The 1 patient that that had increased subretinal fluid refused treatment on that day, and the other patients were not treated because the investigator did not think there were signs of neovascular AMD activity. None of the responding investigators indicated that there was new hemorrhage at the macula.

• **TWO-YEAR VISUAL ACUITY AND MORPHOLOGIC FEATURES ASSOCIATED WITH SPORADIC VISION LOSS:** A total of 113 patients that had sporadic vision loss were available for data analysis of 2-year VA and morphology.

TABLE 1. Comparison of Treatment Status and Optical Coherence Tomography Features Before, At, and After Sporadic Vision Loss Among Eyes Treated Pro Re Nata in the Comparison of Age-Related Macular Degeneration Treatments Trials (83 Eyes, 98 Events)[a]—Patients in Pro Re Nata Arm for 2 Years or Switchers in the Second Year

	4 Weeks Before Sporadic Vision Loss	At Sporadic Vision Loss	4 Weeks After Sporadic Vision Loss	*P* Value[b] (At vs Before Sporadic Vision Loss)	*P* Value[b] (At vs After Sporadic Vision Loss)	*P* Value[b] (Before vs After Sporadic Vision Loss)
Events with injections in pro re nata groups, n (%)	43 (43.9%)	71 (72.4%)	38 (38.8%)	<.001	<.001	.45
Retinal thickness at foveal center (μm)						
<120	24 (24.5%)	21 (21.4%)	28 (28.6%)	.28	.006	.43
120–212	55 (56.1%)	50 (51.0%)	58 (59.2%)			
>212	17 (17.4%)	25 (25.5%)	12 (12.2%)			
Mean (SE)	169 (8)	183 (10)	151 (6)	.15	<.001	.007
Retinal fluid at foveal center						
No	69 (70.4%)	59 (60.2%)	79 (80.6%)	.08	<.001	.07
Yes	25 (25.5%)	37 (37.8%)	17 (17.4%)			
Subretinal fluid at foveal center						
No	82 (83.7%)	80 (81.6%)	90 (91.8%)	.78	.007	.01
Yes	12 (12.2%)	14 (14.3%)	5 (5.1%)			

SE = standard error.

[a]The totals may not add to 98 because of missing values in less than 5%.

[b]McNemar test for comparing proportions, paired *t* test for comparing means.

At 2 years, the mean VA of sporadic vision loss patients was 58.5 letters (~20/63), as compared with 68.4 letters (~20/40) for those patients without sporadic vision loss ($P < .001$) (Table 2). The mean VA change from baseline was 3.1 letters for patients with sporadic vision loss, compared with 6.7 letters for patients without sporadic vision loss ($P = .03$). Forty-four of 113 patients (38.9%) with sporadic vision loss were 20/40 or better, as compared with 610 of 921 patients (66.2%) without sporadic vision loss ($P < .001$). Fifty-six of 113 sporadic vision loss patients (49.6%) had a scar, as compared with 371 of 921 patients (40.3%) without sporadic vision loss ($P = .04$). Sixteen of 113 sporadic vision loss patients (14.2%) had no pathology at the foveal center, compared with 188 of 921 patients (20.4%) without sporadic vision loss ($P = .02$). Also, patients with sporadic vision loss had a larger total area of CNV lesion (9.97 mm^2 vs 8.04 mm^2, $P = .02$). The presence of geographic atrophy was not significantly associated with sporadic vision loss ($P = .27$). OCT analysis showed that the percent with fluid and the mean retinal thickness were not associated with sporadic vision loss ($P > .05$).

• **ASSOCIATION OF SERIOUS ADVERSE EVENTS WITH SPORADIC VISION LOSS:** There were 11 events (10 patients) of sporadic vision loss of 30 letters, which met criteria for an ocular SAE. The causes reported by the investigator were related to AMD (5/11), related to central retinal vein occlusion (1/11), and possibly related to systemic health condition (3/11). There was no clear cause stated for the vision loss in 2 of these 11 events. Furthermore, an evaluation of ocular and systemic AEs did not show any significant associations (data not shown).

Using a matched case-control approach, we also evaluated whether a nonocular SAE within 30 days (before or after) was associated with sporadic vision loss. Among 94 matched case-control pairs that met criteria for analysis, 6 of 94 patients (6.4%) with sporadic vision loss had a nonocular SAE within 30 days compared with 9 of 199 matched controls (4.5%) without sporadic vision loss ($P = .48$). Similarly, 47 of 122 patients (38.5%) with sporadic vision loss had a nonocular SAE during the 2 years of the trial, compared with 377 of 1063 patients (35.5%) without sporadic vision loss ($P = .55$).

• **BASELINE MEDICAL HISTORY AND OCULAR PREDICTORS OF SPORADIC VISION LOSS:** The univariate analysis (Supplemental Table 1, available at AJO.com) showed that a baseline neurologic history and a baseline psychological history were risk factors for sporadic vision loss. Sixty-five of 546 patients (11.9%) with a neurologic history had sporadic vision loss, compared with 57 of 639 patients (8.9%) without a neurologic history ($P = .04$). Thirty-two of 232 patients (13.8%) with a psychological history had sporadic vision loss, compared with 90 of 953 patients (9.4%) without a psychological history ($P = .02$). Within the broad category of psychological disorders, subcategory analysis showed an "anxiety" history for 12 of 122 (9.8%) sporadic vision loss patients and only 43 of 1063 patients (4.1%) without sporadic vision loss ($P = .01$) (Supplemental Table 2, available at AJO.com). Additionally, the neurologic history subcategory of "syncope" was present for 10 of 122 patients (8.2%) with sporadic vision loss, compared with 28 of 1063 patients (2.6%) without

TABLE 2. Comparison of Visual Acuity and Morphology Features at Year 2 Between Eyes With and Without Sporadic Visual Acuity Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (N = 1034)

Visual Acuity and Morphology Features at Year 2	With Sporadic Vision Loss (N = 113)	Without Sporadic Vision Loss (N = 921)	*P* Value[a]
Visual acuity at year 2, n (%)			
20/40 or better	44 (38.9%)	610 (66.2%)	<.001
Worse than 20/40	69 (61.1%)	311 (33.8%)	
Mean (SE)	58.5 (1.8)	68.4 (0.6)	<.001
Mean (SE) change from baseline	3.05 (1.88)	6.74 (0.53)	.03
Features of fundus photographs/fluorescein angiogram, n (%)			
Scar anywhere	56 (49.6%)	371 (40.3%)	.04
Geographic atrophy anywhere	28 (24.8%)	188 (20.4%)	.27
Pathology in foveal center, n (%)			
No pathology	16 (14.2%)	188 (20.4%)	.02
Fluid	3 (2.6%)	30 (3.3%)	
CNV/SPED	15 (13.3%)	166 (18.0%)	
Scar	38 (33.6%)	191 (20.7%)	
Geographic atrophy	11 (9.7%)	52 (5.7%)	
RPE tear	1 (0.9%)	8 (0.9%)	
Other	29 (25.7%)	286 (31.1%)	
Total area of CNV lesion (mm^2)			
Mean (SE)	9.97 (0.85)	8.04 (0.27)	.02
Mean (SE) change from baseline	2.46 (0.84)	1.86 (0.22)	.39
OCT features			
Intraretinal fluid: Yes (%)	66 (60.6%)	460 (51.8%)	.10
Subretinal fluid: Yes (%)	29 (27.9%)	325 (36.9%)	.08
Sub-RPE fluid: Yes (%)	32 (32.3%)	332 (38.2%)	.27
Retinal thickness at foveal center (μm)			<.001
<120	43 (38.7%)	203 (22.4%)	
120–212	50 (45.1%)	593 (65.5%)	
>212	18 (16.2%)	110 (12.1%)	
Mean (SE)	147 (8)	162 (3)	.06
Mean (SE) change from baseline	−92 (13)	−53 (4)	.004
Subretinal tissue complex thickness at foveal center (μm):			
Mean (SE)	124 (9)	128 (4)	.77
Mean (SE) change from baseline	−100 (15)	−80 (5)	.21

CNV = choroidal neovascularization; OCT = optical coherence tomography; RPE = retinal pigment epithelium; SE = standard error; SPED = serous retinal pigment epithelial detachment.

The totals may not add to 113 or 921 due to missing values in less than 5%.

[a]Fisher exact test for comparing proportions; 2-groups *t* test for comparing means.

sporadic vision loss ($P = .004$). Of note, the 1 patient that had 2 events of sporadic vision loss of 30 letters had a baseline history including early Alzheimer disease and anxiety with hallucinations; for both of these events, the investigator did not find an ocular cause and thought that the medical history played a role. To further analyze whether patients with more comorbidities in their medical history had an increased risk for sporadic vision loss events, we applied a Functional Comorbidity Index to the data.[24] However, there was no significant association between the Functional Comorbidity Index values and sporadic vision loss.

Univariate analysis of baseline ocular and OCT features are provided in the online supplement (Supplemental Tables 3 and 4, available at AJO.com).

In multivariate analysis, history of a psychological disorder (OR 1.52, 95% CI: 1.03–2.25) was an independent predictor (Table 3). Further analysis of psychological subcategories demonstrated that an anxiety history was the driving force for this association (OR 1.90, 95% CI: 1.12–3.24). Although a neurologic history was not a significant independent predictor, further subcategory analysis showed that a syncope history was an independent predictor (OR 2.75, 95% CI: 1.45–5.22). Other independent baseline predictors for sporadic vision loss included worse baseline VA (OR 2.92, 95% CI: 1.65–5.17 for baseline VA of 20/200–20/320 compared with 20/25–20/40), baseline scar (OR 2.21; 95% CI: 1.22–4.01), and OCT presence of foveal intraretinal fluid (OR 1.80; 95% CI: 1.11–2.91)

TABLE 3. Multivariate Analysis For Baseline Predictors of Sporadic Vision Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (N = 1152)

Baseline Characteristics	Patients at Baseline, N	Sporadic Vision Loss in 2 Years, n (%)	Odds Ratio (95% CI)	*P* Value[a]
Baseline visual acuity in study eye				
20/25–40	410	29 (7.1%)	1.00	.002
20/50–80	431	41 (9.5%)	1.43 (0.89, 2.27)	
20/100–160	233	32 (13.7%)	1.88 (1.15, 3.08)	
20/200–320	78	18 (23.1%)	2.92 (1.65, 5.17)	
Refraction when visual acuity measured (by visit)				
No	17 877	107 (0.6%)	1.00	.01
Yes	9153	34 (0.4%)	0.62 (0.42, 0.91)	
Psychological disorder				
No	922	88 (9.5%)	1.00	.03
Yes	230	32 (13.9%)	1.52 (1.03, 2.25)	
Baseline fibrotic or atrophic scar				
No	1108	109 (9.8%)	1.00	.009
Yes	44	11 (25.0%)	2.21 (1.22, 4.01)	
Intraretinal fluid				
No fluid	275	20 (7.3%)	1.00	.04
Fluid not in foveal center	315	28 (8.9%)	1.33 (0.76, 2.34)	
Fluid in foveal center	562	72 (12.8%)	1.80 (1.11, 2.91)	
Drug				
Ranibizumab	584	64 (11.0%)	1.00	.41
Bevacizumab	568	56 (9.9%)	0.86 (0.61, 1.23)	
Regimen				
Monthly	303	32 (10.6%)	1.00	.14
Switched	266	22 (8.3%)	–	
Pro re nata	583	66 (11.3%)	1.32 (0.91, 1.92)	

CI = confidence interval.

Patients (n = 33) with missing data in any of variables in the final multivariate model were excluded from analysis.

[a]From generalized linear model using generalized estimating equation to account for correlation from multiple events of sporadic visual acuity loss in some eyes. Initial model includes baseline visual acuity of study eye, lesion type, fibrotic or atrophic scar, retinal fluid, psychological disorder, neurologic disorder, refraction status, drug, and regimen.

(Table 3). Drug or treatment regimen was not associated with sporadic vision loss ($P > .10$).

• **ASSOCIATION OF REFRACTION STATUS WITH SPORADIC VISION LOSS:** Refractions were performed approximately every 3 months, and multivariate analysis showed that refraction decreased the likelihood of sporadic vision loss (OR 0.62; 95% CI: 0.42–0.91) (Table 3). As seen in the Figure, refractions generally gave a small but consistent VA boost for all patients. After anti-VEGF therapy stabilized the vision (after 12 weeks), refractions were associated with a mean VA score 1.21 letters (95% CI: 1.00–1.42) better than visits without refraction.

DISCUSSION

OVER 2 YEARS OF MONTHLY VISITS, 122 OF 1185 CATT PATIENTS (10.3%) had sporadic vision loss, and these patients had less VA gains at 2 years compared with patients without sporadic vision loss. There were significant associations of sporadic vision loss with worse baseline vision, and this is consistent with the increased variability of vision measurements with lower acuities.[9] Furthermore, there were some AMD-related associations, such as the presence of a scar or other pathology at the fovea. These findings can explain the lower mean VA gains of this subgroup. Still, for those patients who did have OCTs around the time of sporadic vision loss, the average increase in mean retinal thickness was only 14 μm more compared with the visit prior to the sporadic vision loss event. While some patients may have had acute worsening of the disease, many others did not, and this caused the average change in mean retinal thickness to be modest. We attempted to further correlate sporadic vision loss events with changes in OCT morphology. However, only 13 of 98 sporadic vision loss events among eyes treated PRN correlated with a ≥50 μm change in retina thickness. Thus, it should be emphasized that there were many cases in which the cause of sporadic vision loss was not clearly linked to AMD.

Data from the eyes treated PRN further support the conclusion that many cases of sporadic vision loss were not directly linked to worsening of AMD. Of particular interest is the finding that investigators did not give an injection for 27 of 98 (27.6%) sporadic vision loss events in eyes treated PRN, even though vision loss was an indication for PRN treatment. Six of these 27 patients (22.2%) had fluid at the fovea based on OCT reading center evaluation, and this also was a treatment indication. It was previously reported that approximately 30% of patients in PRN groups did not receive an injection even though the reading center found fluid on the OCT.[6] For these untreated sporadic vision loss cases with fluid, the investigator may not have noticed a small amount of fluid or, less likely, thought that the fluid was not significant enough to warrant treatment. When investigators for these 27 events were queried, 11 of the 21 responses indicated that there was no identifiable cause and 3 indicated that the event may be related to a change in systemic health. Only 1 of 21 responses indicated that there was a worsening of neovascular AMD. Our data suggest that there were other causes for sporadic vision loss, including a low baseline VA, syncope history, anxiety history, or absence of refraction.

Previous reports have highlighted the role that depression plays on visual function in AMD patients.[10–13] While we did not find that a baseline history of depression specifically is associated with sporadic vision loss, our multivariate analysis showed that a psychiatric history generally increases the odds of sporadic vision loss. Further analysis showed that a history of anxiety, rather than depression, was the driving force behind the significance of a psychiatric history. Additionally, the neurologic subcategory of syncope was a significant predictor of sporadic vision loss. Among the elderly population, the most common causes of syncope are orthostatic hypotension, volume depletion, cardiovascular events, vasovagal reflex, and idiopathic.[25,26] These data suggest that acute changes in mental health as well as those factors that lead to syncope may lead to sporadic vision loss. One may wonder if patients who are "sicker" overall at baseline are more likely to have sporadic vision loss, but we could not find a clear association of this through our use of a Functional Comorbidity Index. We also could not find any associations between SAEs or AEs with sporadic vision loss. This is consistent with Wolf and associates' analysis of acute vision loss in the MARINA and ANCHOR studies,[18] although they looked at ocular adverse events and did not specifically focus on transient vision loss. Given the paramount importance of vision measurements, it may be worthwhile for investigators to consider these findings when enrolling patients for clinical trials. This is emphasized by a study patient with a history of anxiety and hallucinations who had 2 events of sporadic vision loss of 30 letters.

In an effort to increase efficiency, some clinical trials do not perform refracted VA at every study visit. These data from CATT showed that refraction slightly boosted the mean VA measurements, and absence of refraction was associated with sporadic vision loss. Although the vision difference on average was small, the data demonstrate the important role of study visit refractions. Some studies have defined visits with refractions and a protocol stipulation for the visits without routine refractions. If the VA has changed by 10 or more letters since the last visit, then a refraction should be performed.[27]

There are several limitations of this secondary analysis. In the CATT, OCT was not required at every visit for the monthly treatment patients. Thus, we had OCT data from the time of all sporadic vision loss events for PRN-treated patients but not for monthly-treated patients. Fundus photos were performed only at the baseline, 1-year, and 2-year visits. Although we recognize that an image characteristic at the last study visit may not have been present at the time of the sporadic vision loss event, we did investigate the differences to understand why sporadic vision loss patients had a lower mean VA at 2 years. It should be noted that we cannot exclude the possibility of hemorrhage at the macula at the time of sporadic vision loss in some patients, since photographs were not available at every visit. However, investigators for the 27 events in PRN eyes that were not treated were queried about the sporadic vision loss and the decision not to treat. None of the responses indicated that there was new hemorrhage at the macula. Although hemorrhage at the macula could explain some of the 143 events of sporadic vision loss, the data suggest that there were several other factors involved in sporadic vision loss as well.

In summary, approximately 10% of CATT patients had a sporadic vision loss event during the trial, and 27.6% of sporadic vision loss events in PRN groups did not coincide with an injection. Although there is some expected relationship between acute worsening of AMD and sporadic vision loss, there certainly were other associations with these aberrant VA measurements, including worse baseline vision, psychiatric history, syncope history, and lack of refraction. We believe that these data are valuable for clinicians, those planning clinical trials, and trial investigators.

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The members of the CATT Research Group are listed in the Appendix (Supplemental material, available at AJO.com).

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APPENDIX. CREDIT ROSTER FOR THE COMPARISON OF AMD TREATMENTS TRIALS

Clinical Centers (Ordered by Number of Patients Enrolled)

Certified Roles at Clinical Centers: Clinic Coordinator (CC), Data Entry Staff (DE), Participating Ophthalmologist (O), Ophthalmic Photographer (OP); Optical Coherence Tomography Technician (OCT); Principal Investigator (PI); Refractionist (R); Visual Acuity Examiner (VA).

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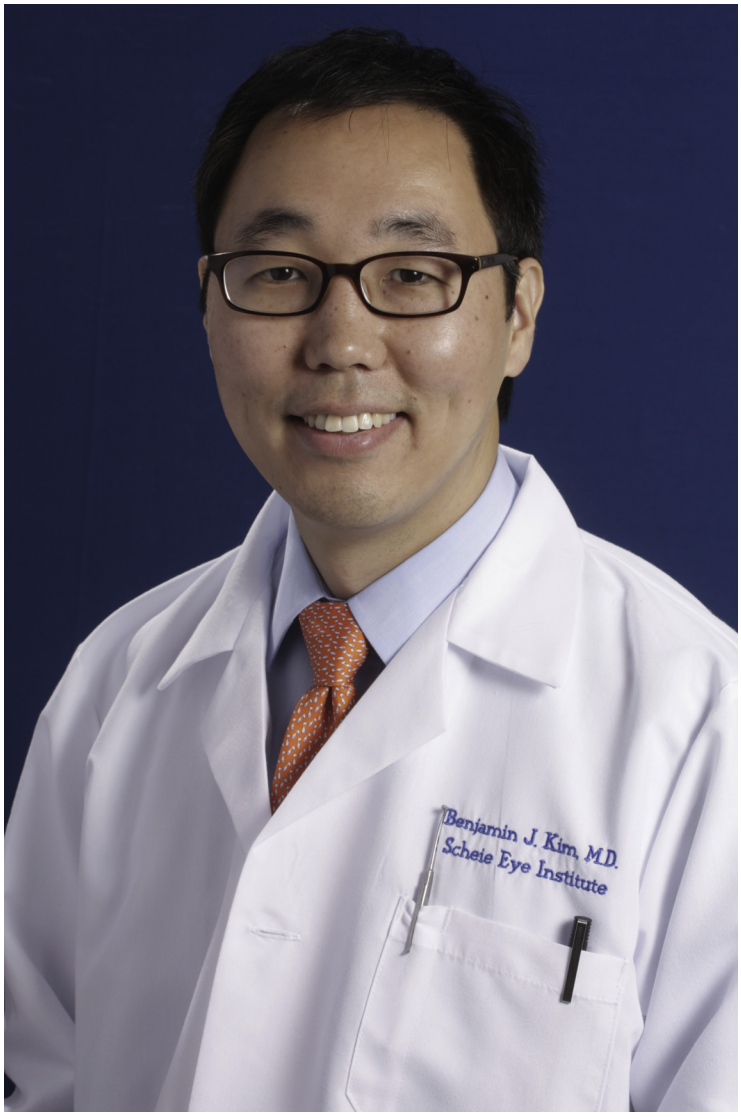

Biosketch

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SUPPLEMENTAL TABLE 1. Univariate Analysis for Baseline Patient Characteristics With Sporadic Vision Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (N = 1185)

Baseline Characteristics	Patients at Baseline, N	Ever Sporadic Vision Loss in 2 Years, n (%)	Odds Ratio (95% CI)	*P* Value[a]
Age				
50–69	137	15 (10.9%)	1.00	.14
70–79	404	33 (8.2%)	0.66 (0.35, 1.24)	
80–89	560	63 (11.3%)	0.99 (0.55, 1.78)	
≥90	84	11 (13.1%)	1.30 (0.59, 2.88)	
Sex				
Female	732	75 (10.2%)	1.00	.91
Male	453	47 (10.4%)	0.98 (0.68, 1.41)	
Cigarette smoking				
Never	507	54 (10.7%)	1.00	.46
Quit	577	56 (9.7%)	0.94 (0.65, 1.37)	
Current	101	12 (11.9%)	1.43 (0.75, 2.73)	
Hypertension				
No	362	35 (9.7%)	1.00	.28
Yes	823	87 (10.6%)	1.24 (0.84, 1.84)	
Diabetes				
No	978	105 (10.7%)	1.00	.33
Yes	207	17 (8.2%)	0.77 (0.46, 1.30)	
Neurologic disorder				
No	639	57 (8.9%)	1.00	.04
Yes	546	65 (11.9%)	1.44 (1.01, 2.07)	
Psychological disorder				
No	953	90 (9.4%)	1.00	.02
Yes	232	32 (13.8%)	1.64 (1.09, 2.46)	
Drug				
Ranibizumab	599	66 (11.0%)	1.00	.46
Bevacizumab	586	56 (9.6%)	0.87 (0.61, 1.25)	
Regimen				
Monthly	318	32 (10.1%)	1.00	.17
Switched	269	22 (8.2%)	–	
Pro re nata	598	68 (11.4%)	1.30 (0.89, 1.90)	

CI = confidence interval.

[a]From generalized linear model using generalized estimating equation to account for correlation from multiple events of sporadic visual acuity loss in some eyes.

SUPPLEMENTAL TABLE 2. Comparison of Baseline Neurologic and Psychological Medical History Between Patients With and Without Sporadic Vision Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (N = 1185)

Baseline Medical History	With Sporadic Vision Loss (N = 122) n (%)	Without Sporadic Vision Loss (N = 1063) n (%)	*P* Value[a]
Neurologic disorder			
Memory loss	18 (14.8%)	146 (13.7)	.78
Headache	26 (21.3%)	167 (15.7%)	.12
Sensory/motor disturbance	9 (7.4%)	72 (6.8%)	.85
Sleep disturbance	33 (27.1%)	222 (20.9%)	.13
Syncope	10 (8.2%)	28 (2.6%)	.004
Seizures	2 (1.6%)	10 (0.9%)	.35
Other	15 (12.3%)	95 (8.9%)	.25
Psychological disorder			
Depression	26 (21.3%)	165 (15.5%)	.12
Bipolar	0 (0%)	4 (0.4%)	1.00
Anxiety	12 (9.8%)	43 (4.1%)	.01

[a]From Fisher exact test for comparison of proportions.

SUPPLEMENTAL TABLE 3. Univariate Analysis for Baseline Ocular Characteristics With Sporadic Vision Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (N = 1185)

Baseline Ocular Characteristics	Patients at Baseline, N	Ever Sporadic Vision Loss in 2 Years, n (%)	Odds Ratio (95% CI)	*P* Value[a]
Baseline visual acuity in study eye				
20/25–40	424	30 (7.1%)	1.00	<.001
20/50–80	443	41 (9.3%)	1.50 (0.93, 2.39)	
20/100–160	236	32 (13.6%)	2.16 (1.32, 3.55)	
20/200–320	82	19 (23.2%)	4.29 (2.44, 7.54)	
Baseline visual acuity in fellow eye				
20/20 or better	346	41 (11.8%)	1.00	.81
20/25–20/40	469	42 (9.0%)	0.88 (0.57, 1.36)	
20/50 or worse	370	39 (10.5%)	0.89 (0.58, 1.38)	
Baseline total area of CNV lesion (DA)				
1st quartile (≤1)	376	36 (9.6%)	1.00	.38
2nd quartile (>1 to ≤2)	260	25 (9.6%)	1.14 (0.69, 1.89)	
3rd quartile (>2 to ≤4)	287	31 (10.8%)	1.47 (0.91, 2.38)	
4th quartile (>4)	215	25 (11.6%)	1.39 (0.84, 2.30)	
Missing[b]	47	5 (10.6%)		
Location of lesion				
Not subfoveal	323	35 (10.8%)	1.00	.66
Subfoveal	843	86 (10.2%)	1.09 (0.74, 1.60)	
Missing[b]	19	1 (5.3%)		
Lesion type				
Predominantly classic	267	37 (13.9%)	1.00	.23
Minimally classic	197	23 (11.7%)	0.82 (0.49, 1.38)	
Occult only	696	61 (8.8%)	0.65 (0.43, 0.99)	
CG/no lesion	25	1 (4.0%)		
Hemorrhage (associated with the lesion)				
None	441	40 (9.1%)	1.00	.21
≤1 DA	611	68 (11.1%)	1.42 (0.96, 2.10)	
≤2 DA	59	5 (8.5%)	1.08 (0.42, 2.75)	
>2 DA	54	8 (14.8%)	1.88 (0.88, 4.01)	
CD or CG or missing[b]	20	1 (5.0%)		
Fibrotic or atrophic scar				
No	1125	110 (9.8%)	1.00	.001
Yes	46	11 (23.9%)	2.93 (1.58, 5.43)	
Missing[b]	14	1 (7.1%)		
Geographic atrophy				
None/questionable	1101	114 (10.4%)	1.00	.95
Present	82	8 (9.8%)	1.02 (0.50, 2.12)	
Missing[b]	2	0 (0.0%)		

CD = cannot determine; CG = cannot grade; CI = confidence interval; CNV = choroidal neovascularization; DA = disc areas.

[a]From generalized linear model using generalized estimating equation to account for correlation from multiple events of sporadic visual acuity loss in some eyes.

[b]Missing category was not included in the *P* value calculation.

SUPPLEMENTAL TABLE 4. Univariate Analysis for Baseline Optical Coherence Tomography Features With Sporadic Vision Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (N = 1185)

Baseline Characteristics	Patients at Baseline, N	Ever Sporadic Vision Loss in 2 Years, n (%)	Odds Ratio (95% CI)	*P* Value[a]
Retinal thickness at foveal center (μm)				
<120	120	13 (10.8%)	1.00	.08
120–212	622	55 (8.8%)	0.86 (0.48, 1.56)	
>212	437	53 (12.1%)	1.32 (0.73, 2.41)	
Missing[b]	6	1 (16.7%)		
Subretinal tissue complex thickness at foveal center (μm)				
1st quartile (>0 to ≤75)	290	26 (9.0%)	1.00	.15
2nd quartile (>75 to ≤160)	291	24 (8.2%)	1.01 (0.58, 1.76)	
3rd quartile (>160 to ≤275)	304	41 (13.5%)	1.63 (1.00, 2.66)	
4th quartile (>275)	294	30 (10.2%)	1.16 (0.69, 1.96)	
Missing[b]	6	1 (16.7%)		
Intraretinal fluid				
No fluid	277	20 (7.2%)	1.00	.003
Fluid not in foveal center	318	28 (8.8%)	1.51 (0.86, 2.67)	
Fluid in foveal center	569	73 (12.8%)	2.23 (1.38, 3.61)	
Missing[b]	21	1 (4.8%)		
Subretinal fluid				
No fluid	202	21 (10.4%)	1.00	.28
Fluid not in foveal center	556	63 (11.3%)	1.03 (0.63, 1.69)	
Fluid in foveal center	414	37 (8.9%)	0.75 (0.44, 1.28)	
Missing[b]	13	1 (7.7%)		
Sub-RPE fluid				
No fluid	518	56 (10.8%)	1.00	.39
Fluid not in foveal center	210	19 (9.0%)	0.74 (0.44, 1.23)	
Fluid in foveal center	363	31 (8.5%)	0.79 (0.51, 1.23)	
Missing[b]	94	16 (17.0%)		

CI = confidence interval; RPE = retinal pigment epithelium.

[a]From generalized linear model using generalized estimating equation to account for correlation from multiple events of sporadic visual acuity loss in some eyes.

[b]Missing category was not included in the *P* value calculation.