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Outcomes in Eyes with Retinal Angiomatous Proliferation in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)

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Purpose: To compare baseline characteristics, visual acuity (VA), and morphologic outcomes between eyes with retinal angiomatous proliferation (RAP) and all other eyes among patients with neovascular age-related macular degeneration (NVAMD) treated with anti–vascular endothelial growth factor (VEGF) drugs.

Design: Prospective cohort study within the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Participants: Patients with NVAMD.

Methods: Reading center staff evaluated digital color fundus photographs, fluorescein angiography (FA) images, and optical coherence tomography (OCT) scans of eyes with NVAMD treated with either ranibizumab or bevacizumab over a 2-year period. Retinal angiomatous proliferation was identified by the intense intra-retinal leakage of fluorescein in combination with other associated features.

Main Outcome Measures: Visual acuity; fluorescein leakage; scar; geographic atrophy (GA) on FA; retinal thickness, fluid, and subretinal hyperreflective material (SHRM) on OCT; and the number of intravitreal anti-VEGF injections at 1 and 2 years.

Results: Retinal angiomatous proliferation was present in 126 of 1183 (10.7%) study eyes at baseline. Mean VA improvement from baseline was greater (10.6 vs. 6.9 letters; $P = 0.01$) at 1 year, but similar at 2 years (7.8 vs. 6.2 letters; $P = 0.34$). At 1 year, eyes with RAP were more likely to have no fluid (46% vs. 26%; $P < 0.001$) on OCT, no leakage on FA (61% vs. 50%; $P = 0.03$), and greater reduction in foveal thickness (−240 μm vs. −161 μm; $P < 0.001$). They were more likely to demonstrate GA (24% vs. 15%; $P = 0.01$) and less likely to have scarring (17% vs. 36%; $P < 0.001$) or SHRM (36% vs. 48%; $P = 0.01$). These results were similar at 2 years. The mean change in lesion size at 1 year differed (−0.27 DA vs. 0.27 DA; $P = 0.02$), but was similar at 2 years (0.49 DA vs. 0.79 DA; $P = 0.26$). Among eyes treated PRN, eyes with RAP received a lower mean number of injections in year 1 (6.1 vs. 7.4; $P = 0.003$) and year 2 (5.4 vs. 6.6; $P = 0.025$).

Conclusions: At both 1 and 2 years after initiation of anti-VEGF treatment in CATT, eyes with RAP were less likely to have fluid, FA leakage, scar, and SHRM and more likely to have GA than eyes without RAP. Mean improvement in VA was similar at 2 years. *Ophthalmology 2016;123:609-616 © 2016 by the American Academy of Ophthalmology.*

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

Retinal angiomatous proliferation (RAP), also termed type 3 choroidal neovascularization (CNV), is a distinct form of neovascular age-related macular degeneration (NVAMD) whose intraretinal pathologic features differentiate it from classic and occult CNV. Depending to a large extent on imaging methods used (fluorescein angiography [FA], indocyanine green angiography, and optical coherence tomography [OCT]), the prevalence of RAP among eyes with treatment-naïve NVAMD is between 10% and 40%, with most cases occurring among white persons.[1–5] Untreated, eyes with RAP often have poor visual acuity (VA). For example, one study showed that more than one third of patients with RAP followed up for 20 months became legally blind.[6] Before the introduction of intravitreal anti-VEGF for RAP, several methods of treatment that included direct laser photocoagulation of the vascular lesion, laser photocoagulation of the feeder retinal arteriole, scatter grid-like laser photocoagulation, photodynamic therapy, transpupillary thermotherapy, and intravitreal triamcinolone acetonide were used, yielding only marginally better VA, short-term VA improvement, or both.[7–9] In contrast, better visual outcomes can be achieved by treating

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RAP with intravitreal anti-VEGF injections.[10–14] However, no prospective studies have described visual and anatomic outcomes at 1 and 2 years in eyes with RAP treated with anti-VEGF therapy.

The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study followed up a large cohort of patients with treatment-naïve NVAMD eyes who received randomly assigned ranibizumab or bevacizumab through 2 years. The cohort included eyes with classic and occult CNV and RAP, occurring alone or in varying combinations. We compared the baseline characteristics and 2-year visual and morphologic outcomes between eyes having RAP and eyes without RAP.

Methods

The methods used to grade CATT study images have been described previously.[15,16] Briefly, the CATT cohort consisted of patients with treatment-naïve NVAMD who were assigned randomly for treatment with ranibizumab or bevacizumab on a monthly or as-needed basis. Patients were recruited from 43 clinical centers in the United States between February 2008 and December 2009 and needed to be older than 50 years. Institutional review boards associated with each center approved the clinical trial protocol. All patients provided written informed consent. The study complied with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. The CATT study is registered with ClinicalTrials.gov (identifier, NCT00593450). Study eyes had to have active neovascularization associated with age-related macular degeneration and VA between 20/25 and 20/320. The neovascularization could be subfoveal or extrafoveal, but if extrafoveal, a sequelae of neovascularization, such as fluid, serous pigment epithelial detachment, blocked fluorescence, or hemorrhage, had to be located under the foveal center. Active neovascularization was defined by the presence of leakage on FA and fluid on OCT.

Grading of color and FA images at baseline and years 1 and 2 was performed at the CATT Fundus Photograph Reading Center of the University of Pennsylvania. Two trained certified graders independently assessed the images, and discrepant results were adjudicated. Morphologic features identified on these images included active leakage of fluorescein on FA, fibrotic scar, nonfibrotic scar, type of CNV (classic, occult, and RAP), type of total CNV lesion, hemorrhage, blocked fluorescence contiguous with the CNV, serous pigment epithelial detachment, nongeographic atrophy, geographic atrophy (GA), retinal pigment epithelial tear, and pathologic features in the foveal center. The OCT scans were graded at the CATT OCT Reading Center of Duke University by 2 independent certified readers. Discrepant data were arbitrated by an independent senior reader. Readers assessed the following parameters on OCT images: intraretinal fluid, subretinal fluid, fluid beneath the retinal pigment epithelium (RPE), vitreomacular adhesion, and subretinal hyperreflective material (SHRM). In addition, the center point retinal thickness, subretinal fluid thickness, and subretinal tissue complex thickness were measured.[17]

Retinal angiomatous proliferation lesions were identified by FA and color fundus photography findings (Fig 1). To be considered a RAP lesion, a focal area of intense intraretinal hyperfluorescence (hot spot) in the early phase of the FA was required, along with 1 or more of the following signs on FA: focal intraretinal superficial hemorrhages; lipid; serous or fibrovascular pigment epithelial detachment; and retinal vascular abnormality, such as an anastomosis between retinal vessels or between retinal and choroidal vessels or retinal vessels with the underlying CNV complex.[1,2]

Statistical Methods

We performed the statistical comparison of baseline characteristics and outcomes at years 1 and 2 between eyes with baseline RAP and eyes without baseline RAP. The 2-group independent t test was used to compare means of continuous variables and the Fisher exact test was used for comparison of proportions of categorical variables. A P value less than 0.05 was considered to be statistically significant. All the statistical comparisons were made using SAS software version 9.2 (SAS Inc., Cary, NC).

Results

Baseline Characteristics

At enrollment, RAP was present in 126 of 1183 (10.7%) CATT patients who had images of sufficient quality. The frequencies of specific RAP features are listed in Table 1. Superficial hemorrhage was present in 91% of RAP eyes, 12% had serous pigment epithelial detachment, 14% had fibrovascular pigment epithelial detachment, 22% had hard exudates, 20% had retina vessel–CNV lesion anastomosis, and 1% had retinal vessel–retinal vessel anastomosis.

Comparison of baseline characteristics between patients with and without RAP is shown in Table 2. Patients who had RAP were older (mean age, 81.7 years) than patients without RAP lesions (mean age, 79 years; $P < 0.001$). There was a lower percentage of past or current cigarette smokers in the RAP group (45% vs. 59%; $P = 0.004$). Systemic diseases such as hypertension and diabetes mellitus were similar in the 2 groups. The baseline VA was similar in eyes with and without RAP (60.1 letters vs. 60.6 letters; $P = 0.47$). The CNV lesion size in disc area (DA) was smaller in eyes with RAP (1.22 DA vs. 1.85 DA; $P < 0.001$), and the total CNV lesion area showed a similar difference (1.59 DA vs. 2.59 DA; $P < 0.001$) between the 2 groups. The RAP eyes had CNV that was located more commonly away from the foveal center in comparison with eyes with no RAP (40% vs. 60%; $P < 0.001$). Retinal angiomatous proliferation lesions were almost always associated with occult-only CNV (93% vs. 56%; $P < 0.001$); classic-only CNV was uncommon when RAP was present (4% vs. 25%; $P < 0.001$). Choroidal neovascularization-associated hemorrhages were more frequent in eyes with RAP (93% vs. 59%), but tended to be smaller (91% with <1 DA vs. 47% with <1 DA; $P < 0.001$). Serous pigment epithelial detachments identified on FA were more common in eyes with RAP than in eyes that had no RAP (13% vs. 4%; $P < 0.001$). The mean retinal thickness did not differ between the 2 groups (191 vs. 211 μm; $P = 0.23$), but there was more intraretinal fluid (93% vs. 73%; $P < 0.001$) and sub-RPE fluid (60% vs. 47%; $P = 0.08$) and less subretinal fluid (67% vs. 84%; $P < 0.001$) in eyes with RAP when compared with eyes without RAP. Subretinal hyperreflective material was similar between the 2 groups (71% vs. 77%; $P = 0.14$).

One-Year Outcomes

Greater VA improvement from baseline was seen in eyes with RAP (10.6 letters vs. 6.9 letters; $P = 0.01$) than in eyes without RAP, and more eyes with RAP had a 15-letter or more increase from baseline (41% vs. 28%; $P = 0.005$). Foveal total thickness decreased to a greater extent in eyes with RAP (−240 μm vs. −161 μm; $P < 0.001$) than those without RAP. On OCT, more eyes with RAP had complete fluid resolution (46% vs. 26%; $P < 0.001$) than eyes without RAP. The proportion of eyes with no active fluorescein leakage on FA was higher in the RAP group than in the non-RAP group (61% vs. 50%; $P = 0.03$). Total CNV lesion size decreased in eyes with RAP, whereas it increased in those with CNV but no RAP

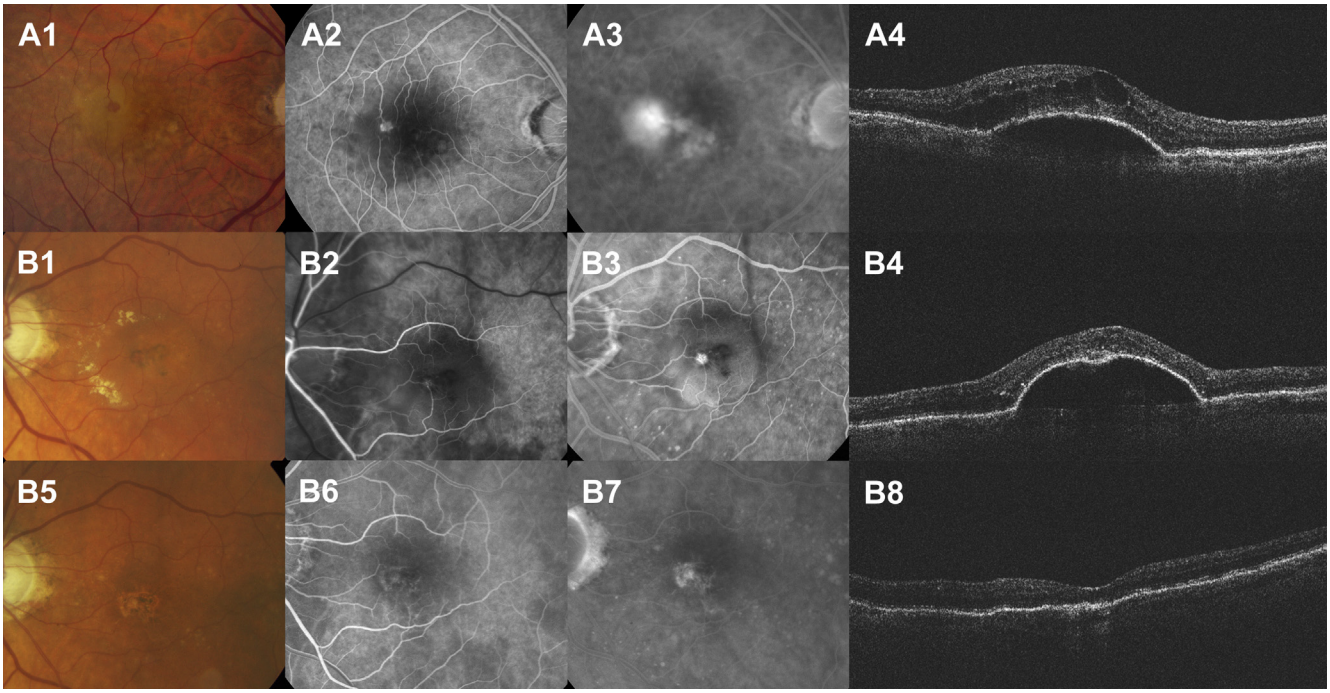

Figure 1. **A1**, Color image of the study eye at baseline. **A2**, Late-phase-angiogram showing intraretinal hyperfluorescence (hot spot) that leaks intensely. Petaloid hyperfluorescence can be observed (**A3**) in the fovea corresponding to (**A4**) the large intraretinal cysts noted on optical coherence tomography (OCT). Sub-retinal pigment epithelium (RPE) fluid (serous pigment epithelial detachment) also can be seen on OCT. **B1**, Color image of another patient at baseline showing intraretinal lipid. **B2**, **B3**, Angiograms showing (**B2**) an intense hyperfluorescent spot surrounded by (**B3**) hyperfluorescence in the sub-RPE space consistent with a serous pigment epithelial detachment. **B4**, Optical coherence tomography showing sub-RPE fluid (serous pigment epithelial detachment). **B5**, **B6**, **B7**, Images obtained at 2 years showing atrophic areas with (**B8**) corresponding signal penetration into the choroid on OCT.

(−0.27 DA vs. 0.27 DA; $P = 0.02$). A greater proportion of eyes demonstrated GA (24% vs. 15%; $P = 0.01$) in the RAP group, whereas a lesser proportion demonstrated scarring (17% vs. 36%; $P < 0.001$) and SHRM (36% vs. 48%; $P = 0.01$) at 1 year. Among PRN-treated eyes (60 eyes with RAP, 497 without RAP), fewer injections were required in eyes that had RAP (mean, 6.1 injections vs. 7.4 injections; $P = 0.003$) than in eyes that did not have RAP (Table 3). Within the RAP group, more eyes treated monthly had complete fluid resolution (63% vs. 31%; $P < 0.001$) and no leakage on FA (73% vs. 56%; $P = 0.08$) than eyes treated PRN.

Two-Year Outcomes

At 2 years, the mean VA improvement from baseline (7.8 letters vs. 6.2 letters; $P = 0.34$) and a 15-letter or more increase from baseline (33% vs. 29%; $P = 0.51$) were not significantly different between eyes with and without RAP lesions. The change in mean VA from baseline through 2 years of follow-up is shown in Figure 2. The total foveal thickness reduction from baseline continued to be greater in eyes with RAP (−223 μm vs. −156 μm; $P < 0.001$). A greater proportion of eyes with RAP had no fluid on OCT (36% vs. 22%; $P = 0.002$) and no leakage on FA (78% vs. 68%; $P = 0.02$). The mean change in area of the total CNV lesion from baseline did not differ significantly between the groups (0.49 DA vs. 0.79 DA; $P = 0.26$) at 2 years. Eyes with RAP continued to demonstrate a greater rate of GA (32% vs. 19%; $P = 0.004$), less scarring (31% vs. 44%; $P = 0.01$), and less SHRM (35% vs. 44%; $P = 0.001$). In the PRN treatment group, fewer injections in year 2 were required in eyes with RAP (5.4 injections vs. 6.6 injections; $P = 0.025$; Table 4). Within the RAP group, more eyes treated monthly for 2 years had complete fluid resolution (55%) than eyes treated PRN for 2 years (29%) or eyes switched from monthly treatment in year 1 to PRN treatment in year 2 (33%; $P = 0.06$).

Table 1. Features of Retinal Angiomatous Proliferation

Retinal Angiomatous Proliferation Components	No. (%)
Area of intense intraretinal hyperfluorescence (hot spot)	126 (100.0)
Superficial intraretinal hemorrhages	114 (90.5)
Associated serous pigment epithelial detachment	15 (11.9)
Associated lipid (hard exudates)	28 (22.2)
Associated fibrovascular pigment epithelial detachment	18 (14.3)
Associated retinal anastomosis	
None	100 (79.4)
Retina−retina	1 (0.8)
Retina−lesion	25 (19.8)

Discussion

This study reports the VA and morphologic outcomes from anti-VEGF treatment in eyes with RAP compared with eyes with CNV but no RAP. There are few reports of VA in eyes with RAP treated for more than 1 year with anti-VEGF drugs. The studies that do exist are difficult to compare with the CATT because most had a small number of patients (<25) and did not have a comparison group of treated eyes without RAP.[13,18–22] The few retrospective studies that had

Table 2. Baseline Characteristics of Groups Based on the Presence of Retinal Angiomatous Proliferation

Baseline Characteristics	With Retinal Angiomatous Proliferation (n = 126)	Without Retinal Angiomatous Proliferation Lesion (n = 1057)	P Value*
Patients (n = 1183)†			
Mean age (SE), yrs	81.7 (0.65)	79.0 (0.23)	<0.001
Female gender, no. (%)	87 (69.1)	644 (60.9)	0.08
Former or current cigarette smoker, no. (%)	57 (45.2)	620 (58.7)	0.004
Presence of hypertension, no. (%)	80 (63.5)	742 (70.2)	0.13
Presence of diabetes mellitus, no. (%)	22 (17.5)	184 (17.4)	1.00
Geographic atrophy in fellow eye, no. (%)	21 (16.7)	122 (11.5)	0.11
CNV or scar in fellow eye, no. (%)	40 (31.8)	308 (29.1)	0.47
Study eye, mean (SE)			
Mean visual acuity, letters	60.1 (1.09)	60.6 (.042)	0.70
Mean area of choroidal neovascularization, disc areas	1.22 (0.13)	1.85 (0.06)	<0.001
Baseline total area of lesion, disc areas	1.59 (0.15)	2.59 (0.08)	<0.001
Pathologic features in foveal center, no. (%)			<0.001
Fluid only	60 (47.6)	254 (24.0)	
Choroidal neovascularization	50 (39.7)	637 (60.3)	
Hemorrhage	5 (3.97)	88 (8.33)	
Other (pigment, drusen, etc.)	11 (8.73)	69 (6.53)	
Location of lesion (does not include fluid), no. (%)			<0.001
Subfoveal	65 (51.6)	777 (73.5)	
Not subfoveal	61 (48.4)	261 (24.7)	
CNV, no. (%)			<0.001
Occult only	117 (92.86)	577 (55.91)	
Classic only	4 (3.97)	258 (25.0)	
Occult and classic	5 (3.97)	197 (19.1)	
None/cannot grade/cannot decide	0 (0.00)	25 (2.37)	
Hemorrhage (associated with the lesion), no. (%)			<0.001
None	9 (7.14)	432 (40.87)	
≤1 disc area	114 (90.5)	495 (46.8)	
≤2 disc areas	1 (0.79)	58 (5.49)	
>2 disc areas	2 (1.59)	52 (4.92)	
Geographic atrophy, no. (%)	5 (3.97)	77 (7.28)	0.20
Scar, no. (%)	1 (0.79)	45 (4.26)	0.05
Serous pigment epithelial detachment, no. (%)	16 (12.7)	46 (4.35)	<0.001
Cystoid macular edema on fluorescein angiogram, no. (%)	11 (8.73)	88 (8.33)	0.86
OCT features			
Retinal thickness (μm), mean (SE)	191 (14.2)	211 (5.40)	0.23
Total thickness (μm), mean (SE)	476 (16.4)	458 (5.78)	0.30
Intraretinal fluid, no. (%)	117 (92.9)	768 (72.7)	<0.001
Subretinal fluid, no. (%)	84 (66.7)	885 (83.7)	<0.001
Subretinal pigment epithelium fluid, no. (%)	76 (60.3)	495 (46.8)	0.08
Vitreomacular adhesion/traction, no. (%)	10 (7.94)	133 (12.6)	0.15
Subretinal hyperreflective material, no. (%)	90 (71.4)	817 (77.3)	0.14

CNV = choroidal neovascularization; OCT = optical coherence tomography; SE = standard error.
*Independent *t* test for continuous variables and Fisher exact test for categorical variables.
†Two subjects excluded because of poor image quality.

follow-up periods extending up to 3 years showed there was improvement and stabilization of VA in the anti-VEGF-treated eyes with RAP. However, one small retrospective study showed that although all 20 study eyes had improved or stable VA at months 1 and 3, only 63% had similar stability or improvement at 2 years of follow-up.[22] Similar to these studies, our study showed a rapid improvement in VA within the first 3 months of intravitreal anti-VEGF therapy that continued to improve and then stabilize during the first year (Tables 3 and 4; Fig 2). However, in the second year, VA began to decline modestly such that there was no statistically significant difference between eyes with or without RAP in overall VA gain at the end of 2 years of treatment. When eyes in which GA developed by 2 years were excluded from the analysis, the pattern of a modest decline in VA gain during year 2 among eyes with RAP and of stable VA in eyes without RAP persisted (Fig 3, available at www.aaojournal.org), indicating that the decline was not solely the result of the higher incidence of GA among eyes with RAP.

Our study also showed that among eyes assigned to the PRN treatment, the eyes with RAP needed fewer anti-VEGF injections than eyes without RAP in year 1. In a smaller study, which included 11 eyes with RAP given anti-VEGF therapy, the mean number of injections required for eyes with RAP was 7 in the first year, 6 in the second year, and 7

Table 3. Year 1 Outcomes of Groups Based on Presence of Baseline Retinal Angiomatous Proliferation (n = 1104*)

Year 1 Outcomes	With Retinal Angiomatous Proliferation Lesion (n = 116)	Without Retinal Angiomatous Proliferation Lesion (n = 988)	*P* Value†
Visual acuity (letters), mean (SE)	70.9 (1.19)	67.7 (0.58)	0.07
Visual acuity change from baseline (letters), mean (SE)	10.6 (1.00)	6.93 (0.48)	0.011
≥15-Letter increase from baseline, no. (%)	48 (41.4)	279 (28.2)	0.005
Hemorrhage contiguous with lesion, no. (%)	2 (1.72)	19 (1.92)	1.00
Retinal thickness at fovea (μm), no. (%)			0.20
<120	27 (23.3)	208 (21.1)	
120–212	82 (70.7)	651 (65.9)	
>212	7 (6.03)	112 (11.3)	
Change in total foveal thickness from baseline (μm), mean (SE)	−240 (17.8)	−161 (5.7)	<0.001
No fluid on OCT, no. (%)	53 (45.7)	260 (26.3)	<0.001
No leakage on FA, no. (%)	71 (61.2)	491 (49.7)	0.027
Change in lesion size from baseline (disc areas), mean (SE)	−0.27 (0.14)	0.27 (0.08)	0.019
Pathologic features in fovea center, no. (%)			<0.001
None	51 (44.0)	161 (16.3)	
Fluid only	19 (16.4)	66 (6.68)	
Choroidal neovascularization	8 (6.90)	251 (25.4)	
Scar	5 (4.31)	197 (19.9)	
Geographic atrophy	2 (1.72)	20 (2.02)	
Nongeographic atrophy	13 (11.2)	138 (14.0)	
Other	18 (15.5)	155 (15.7)	
RPE tear involving macula, no. (%)	1 (0.86)	17 (1.79)	0.71
Mean no. of injections (PRN‡ only), mean (SE)	6.07 (0.38)	7.42 (0.15)	0.003
Geographic atrophy, no. (%)	28 (24.1)	144 (14.6)	0.014
Scar, no. (%)	20 (17.2)	359 (36.3)	<0.001
Subretinal hyperreflective material, no. (%)	42 (36.2)	472 (47.8)	0.013

FA = fluorescein angiography; OCT = optical coherence tomography; PRN = pro re nata; RPE = retinal pigment epithelium; SE = standard error.
*No. of patients with year 1 visual acuity outcome.
†Independent *t* test for continuous variables and Fisher exact test for categorical variables.
‡Sixty patients with retinal angiomatous proliferation lesions and 497 patients without retinal angiomatous proliferation lesions were in the PRN groups.

in the third year.[19] In another slightly larger study, ranibizumab was given monthly for 3 months, and then PRN thereafter to treat eyes with RAP. The mean number of injections in this study was 5.5 and 7.7 at 12 and 24 months, respectively.[21] In the CATT cohort, the mean reduction in total foveal thickness at both 1 and 2 years and the proportion of eyes without intraretinal, subretinal, or sub-RPE fluid was significantly greater in eyes with RAP than in treatment-naïve NVAMD eyes without RAP. These data from our clinical trial suggest that the response of RAP lesions to anti-VEGF treatment is more rapid at the start of therapy and is similar to that of other types of NVAMD at the end of 2 years. The rapid response of RAP lesions to anti-VEGF therapy could be attributed to the smaller baseline NVAMD lesion that is known to have a more favorable prognostic outcome in exudative AMD with anti-VEGF treatment. Other baseline features such as the preponderance of RAP associated occult CNV, as well as the non-subfoveal location of CNV in almost half of the eyes with RAP also could have contributed to a more favorable morphologic outcome. Within the RAP group, more eyes with RAP became fluid free and had less fluorescein leakage during follow-up years 1 and 2 with the monthly regimen when compared with eyes receiving the PRN regimen; these differences among dosing regimens are consistent with the overall results of the CATT.[15]

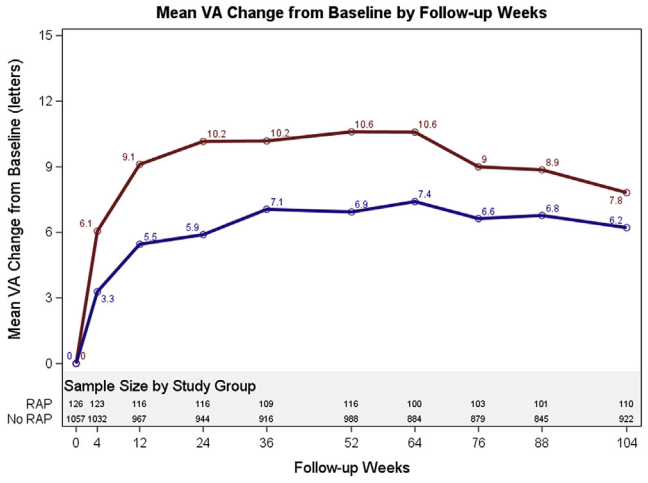

Figure 2. Graph showing mean visual acuity (VA) change from baseline through 2 years. Red line = eyes with retinal angiomatous proliferation (RAP); blue line = eyes without RAP.

Our study corroborated many of the findings from previous studies of treatment-naïve eyes with RAP. For example, patients with untreated RAP and NVAMD tend to be older than patients with NVAMD without RAP.[23,24] However, patients who were past or present cigarette smokers tended to have a lower risk of RAP, a finding that

Table 4. Year 2 Outcomes of Groups Based on Presence of Baseline Retinal Angiomatous Proliferation (n = 1032*)

Year 2 Outcomes	With Retinal Angiomatous Proliferation Lesion (n = 110)	Without Retinal Angiomatous Proliferation Lesion (n = 922)	P Value†
Visual acuity (letters), mean (SE)	68.0 (1.57)	67.3 (0.61)	0.72
Visual acuity change from baseline (letters), mean (SE)	7.82 (1.60)	6.21 (0.54)	0.34
≥15-Letter increase from baseline, no. (%)	36 (32.7)	271 (29.4)	0.51
Hemorrhage contiguous with lesion, no. (%)	2 (1.82)	28 (3.04)	0.76
Retinal thickness at fovea (μm), no. (%)			0.83
<120	25 (22.7)	220 (23.9)	
120–212	72 (65.5)	570 (61.8)	
>212	12 (10.9)	116 (12.6)	
Change in total foveal thickness from baseline (μm), mean (SE)	−223 (20.5)	−156 (6.22)	<0.001
No fluid on OCT, no. (%)	40 (36.4)	200 (21.7)	0.002
No Leakage on FA, no. (%)	86 (78.2)	624 (67.7)	0.023
Change in lesion size from baseline (disc areas), mean (SE)	0.49 (0.19)	0.79 (0.09)	0.26
Pathologic features in fovea center, no. (%)			<0.001
None	41 (37.3)	162 (17.6)	
Fluid only	5 (4.55)	28 (3.04)	
Choroidal neovascularization	13 (11.82)	164 (17.8)	
Scar	7 (6.36)	222 (24.1)	
Geographic atrophy	7 (6.36)	56 (6.07)	
Nongeographic atrophy	20 (19.2)	168 (18.2)	
Other	17 (15.5)	122 (13.2)	
Mean no. of injections (PRN only‡), mean (SE)	5.36 (0.43)	6.57 (0.18)	0.025
Geographic atrophy, no. (%)	35 (31.8)	179 (19.4)	0.004
Scar, no. (%)	34 (30.9)	405 (43.9)	0.010
Subretinal hyper reflective material, no. (%)	38 (34.5)	428 (43.8)	0.014

FA = fluorescein angiography; OCT = optical coherence tomography; PRN = pro re nata; RPE = retinal pigment epithelium; SE = standard error.
*No. of patients with year 2 visual acuity outcome.
†Independent *t* test for continuous variables and Fisher exact test for categorical variables.
‡Fifty-six patients with retinal angiomatous proliferation lesions and 460 patients without retinal angiomatous proliferation lesions were in the PRN groups.

has was not identified in the one other study that evaluated smoking.[24] As reported in other anti-VEGF studies, in our study a relatively high proportion of eyes with RAP lesions demonstrated GA by 2 years. The increased GA development may be related to baseline subfoveal choroidal thinning, reticular pseudodrusen, and GA in the fellow eye.[25–27] However, a lower proportion of eyes with RAP demonstrated scarring. This finding may be related to the strong association of RAP lesions with occult CNV, which is known to produce fewer scars than classic or mixed CNV lesions, and also to fewer number of eyes with RAP having SHRM during the 2 years of follow-up. Subretinal hyperreflective material, a morphologic feature seen on OCT as hyperreflective material located external to the retina and internal to the RPE, is associated with reduced VA and increased scar formation.[28,29] The CATT cohort had either CNV or its sequelae in the foveal center, and eyes with RAP tended to have CNV that was predominantly extrafoveal. As a result, deleterious morphologic outcomes such as GA and scar tended to occur in an extrafoveal location.

The large number of treatment-naïve eyes with RAP was a major study strength. The method used to identify RAP was a relative study limitation. The diagnosis of RAP lesions in this study was based on the fluorescein angiographic appearance supported by color fundus photographic features and correlated well with the fluid observed on OCT. Indocyanine green angiography is useful to diagnose RAP, particularly in the later stages, but was not available in this study. Accordingly, RAP may have been underdiagnosed, and therefore, the actual number of eyes with RAP may have been higher than what we have reported.[5,30,31]

In summary, approximately 10% of treatment-naïve eyes in our cohort had RAP. Eyes with RAP treated with anti-VEGF drugs in CATT were less likely to have fluid, FA leakage, scarring, or SHRM and were more likely to have GA at 1 or 2 years than other types of CNV. Although VA gain was greater and lesion growth was less in eyes with RAP at 1 year, by 2 years, they were similar to eyes without RAP. Fewer injections were needed to treat RAP than the other types of CNV.

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Abbreviations and Acronyms:
CATT = Comparison of Age-Related Macular Degeneration Treatments Trials; **CNV** = choroidal neovascularization; **DA** = disc area; **FA** = fluorescein angiography; **GA** = geographic atrophy; **NVAMD** = neovascular age-related macular degeneration; **OCT** = optical coherence tomography; **RAP** = retinal angiomatous proliferation; **RPE** = retinal pigment epithelium; **SHRM** = subretinal hyperreflective material; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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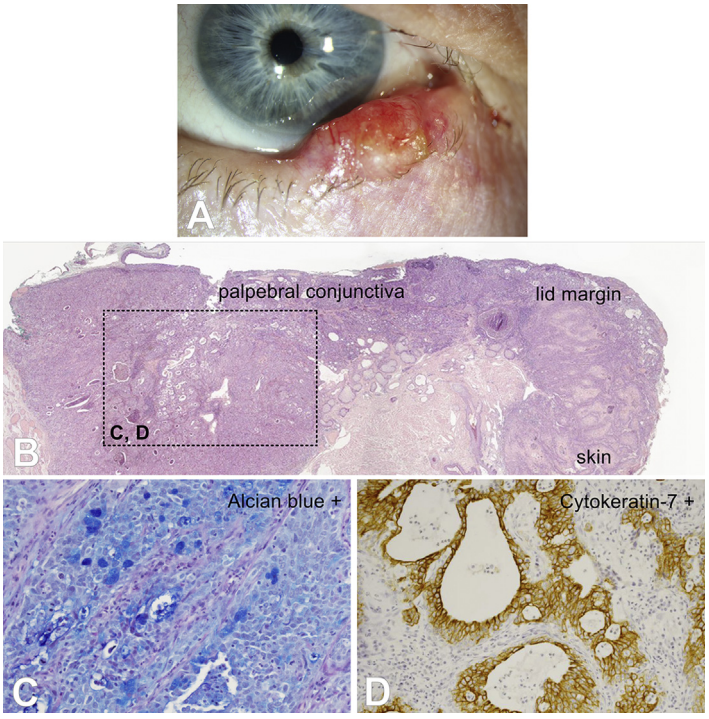
Pictures & Perspectives



Conjunctival Mucoepidermoid Carcinoma

A nodular tumor had grown from the palpebral conjunctiva over the lower lid margin of the left eye in a 62-year-old man during 5 months (Fig 1**A**). Histopathologically, a smaller portion around the lid margin resembled squamous cell carcinoma (Fig 1**B**, *right*). It merged into a major undifferentiated portion replacing the palpebral conjunctiva, with high mitotic activity (Fig 1**B**, *left*), focal glandular differentiation including mucin production (Fig 1**C**, Acian blue positive), and immunopositivity for cytokeratin-7 (Fig 1**D**) and carcinoembryonic antigen (CEA). This was consistent with conjunctival mucoepidermoid carcinoma – a rare, highly recurrent and prognostically unfavorable epithelial malignancy.

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