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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 2015;■:1−8 © 2015 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