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Visual and Morphologic Outcomes in Eyes with Hard Exudate in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Purpose: To compare baseline characteristics, visual acuity (VA), and morphologic outcomes between eyes with hard exudate (HE) at baseline and all other eyes among patients with neovascular age-related macular degeneration (NVAMD) treated with anti−vascular endothelial growth factors (VEGFs).

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

Participants: Patients with NVAMD.

Methods: Readers evaluated baseline and follow-up morphology on digital color images, fluorescein angiography (FA), and optical coherence tomography (OCT) in eyes with NVAMD that were randomly assigned to treatment with ranibizumab or bevacizumab. Ophthalmologists identified HE on color images in the study eye.

Main Outcome Measures: Visual acuity, scar, geographic atrophy, retinal thickness, retinal fluid, and number of anti-VEGF injections.

Results: HE was present in 128 of 1185 study eyes (11%) at baseline, 77% within 1 disc diameter of the foveal center. Patients with study eye HE were more likely to be female (81% vs. 60%; $P < 0.001$) and nonsmokers (53% vs. 42%; $P = 0.004$). Both groups had similar proportions of hypercholesterolemia and hypertriglyceridemia. At baseline, eyes with HE had worse VA (mean 57 vs. 61 letters; $P = 0.003$), larger total lesion size (3.3 vs. 2.4 disc areas; $P < 0.001$), greater total foveal thickness (522 vs. 452 μm; $P < 0.001$), and more retinal angiomatous proliferation (RAP) (18% vs. 10%; $P = 0.009$) and sub−retinal pigment epithelium fluid (65% vs. 47%; $P < 0.001$). At 1 year, VA was similar in both groups; more eyes with baseline HE had no fluid (45% vs. 29%; $P < 0.001$) and greater reduction in total foveal thickness (−266 vs. −158 μm; $P < 0.001$). The VA at year 2 was similar, but retinas of eyes with baseline HE were thinner (267 vs. 299 μm; $P = 0.03$) and fewer eyes had subretinal fluid (23% vs. 36%; $P = 0.008$). HE was present in 19% of eyes at 1 year and 5% of eyes at 2 years. Hepatic lipase promoter single nucleotide polymorphism rs10468017 was not associated with NVAMD HE.

Conclusions: Eyes with HE have larger choroidal neovascularization lesions and more RAP. Their initially thicker retina rapidly becomes thinner with anti-VEGF treatment. HE is not significantly associated with hyperlipidemia. HE at baseline does not significantly influence VA, scar, and geographic atrophy outcomes in eyes with NVAMD treated with anti-VEGF. Few eyes have HE at year 2. *Ophthalmology Retina 2017;1:25-33 © 2016 by the American Academy of Ophthalmology*

Retinal hard exudate (HE) occurs in eyes with macular edema caused by neovascular age-related macular degeneration (NVAMD). Patients who develop NVAMD are typically elderly, and many have coexisting chronic systemic diseases, such as hyperlipidemia, hypercholesterolemia, diabetes mellitus, and hypertension. These diseases by themselves have been associated with retinal HE and are risk factors for developing more severe macular edema in diabetes.[1−5]

Unlike in diabetic macular edema (DME), HE occurring in eyes with NVAMD has not been investigated as a biomarker for more severe macular fluid. It also is not clear whether the presence of HE is associated with any of the systemic diseases that coexist in elderly patients with NVAMD. Furthermore, little is known about the relationship between baseline HE and subsequent visual acuity (VA) in these eyes, other retinal morphologic features in eyes with NVAMD, and HE changes over time. We investigated whether systemic disease associations with the presence of HE reported in DME are present in eyes with NVAMD enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT). In addition, we investigated whether eyes with HE at baseline had different functional and morphologic outcomes after 2 years of treatment with anti−vascular endothelial growth factor (VEGF).

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Methods

The methods used in CATT have been described.[6–8] Patients were recruited from 43 clinical centers in the United States between February 2008 and December 2009. Patients needed to be aged more than 50 years, and the study eye (1 per patient) needed to have treatment-naïve NVAMD. Study eye VA needed to be between 20/25 and 20/320. The neovascularization in the study eye could be subfoveal or extrafoveal, but if located in an extrafoveal area, a sequelae of neovascularization, such as fluid, serous pigment epithelial detachment (SPED), blocked fluorescence, or hemorrhage had to be under the foveal center. The presence of leakage on fluorescein angiography (FA) and any fluid on optical coherence tomography (OCT) defined active neovascularization. A history of systemic diseases, such as hypertension, hypercholesterolemia, diabetes mellitus, and hypertriglyceridemia, was obtained from patient interview. Eyes were randomly assigned to treatment with ranibizumab or bevacizumab on a monthly or an as-needed basis. Institutional review boards associated with each center approved the clinical trial protocol. All patients provided written informed consent. The study was compliant with Health Insurance Portability and Accountability Act regulations and adhered to the tenets of the Declaration of Helsinki. The CATT was registered with ClinicalTrials.gov (NCT00593450).

The CATT Fundus Photograph Reading Center at the University of Pennsylvania graded color and FA images at baseline and years 1 and 2. Two trained certified readers 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 neovascularization (classic, occult, and retinal angiomatous proliferation [RAP]), area of total choroidal neovascularization (CNV) lesion (consisting of CNV and contiguous sequelae other than fluid), hemorrhage, blocked fluorescence contiguous with the CNV, SPED, geographic atrophy (GA), non-GA, retinal pigment epithelium (RPE) tear, and the presence or absence of any of these pathologies in the foveal center. Two independent certified readers at the CATT OCT Reading Center at Duke University graded OCT scans. Discrepant data were arbitrated by an independent senior reader. Readers assessed the following parameters on OCT images: intraretinal fluid, subretinal fluid, sub-RPE fluid, vitreomacular adhesions, and subretinal hyperreflective material. In addition, the center point retinal thickness, subretinal fluid thickness, and subretinal tissue complex thickness were measured.[8] Retinal thickness was the width between the internal limiting membrane and the outer border of the photoreceptors at the foveal center, whereas total foveal thickness at the foveal center in addition to retinal thickness also included the subretinal fluid, subretinal lesion, RPE, and material or fluid below the RPE, and was the width between the internal limiting membrane and the Bruch's membrane at the foveal center irrespective of the RPE location.[8]

HE at baseline, 1 year, and 2 years was graded from stereo color and red-free digital images by an ophthalmologist (E.D.). HE was identified as white or yellowish white waxy deposits with sharp margins on color retinal images, arranged as individual dots, confluent patches, and partial or complete rings surrounding zones of retinal edema and fluid (Fig 1). The red-free image enhanced the discrete nature of the HE and corroborated the assessment from color images. Quantification of HE was based on the total area of retinal HE in relation to the disc area (DA); area was categorized as mild (<0.25 DA), intermediate (≥0.25−<1.00 DA), and severe (≥1.00 DA). The location of HE within 1 disc diameter (DD) of the foveal center was recorded. HE categorized as "suspect" by the ophthalmologist was reviewed by 2 retina specialists (B.J.K. and J.E.G.) to reach a final consensus. A random sample of images containing definite HE, suspect HE, and no HE was graded independently by 1 of the retinal specialists (B.J.K.) and the ophthalmologist (E.D.) to assess agreement on definitive HE.

Statistical Methods

Baseline characteristics and outcomes at year 1 and year 2 between eyes with and without baseline HE were statistically compared. The 2-group independent *t* test was used to compare means of continuous variables, and the Fisher exact test was used to compare categoric variables. Because of the exploratory nature of our analyses, no adjustment for multiple testing was performed, and a P value <0.05 was considered to be statistically significant. All the statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Baseline Characteristics

Baseline characteristics are listed in Table 1. HE was present in 128 of 1185 CATT patients (11%) at enrollment. The amount of HE at baseline was mild in 63.5% of eyes, intermediate in 25.5% of eyes, and severe in 11% of eyes. The distributions at baseline of age and presence of systemic hypertension, hypercholesterolemia, diabetes, and hypertriglyceridemia in patients with HE were similar to those without HE. A smaller proportion of patients with HE reported a history of myocardial infarction at baseline (6% vs. 13%; $P = 0.02$) than those without HE. A higher proportion of patients with HE were female (81% vs. 60%; $P < 0.001$) and nonsmokers (53% vs. 42%; $P = 0.004$). Eyes with baseline HE had worse baseline mean VA (57 vs. 61 letters; $P = 0.003$), larger CNV area (2.2 vs. 1.7 DAs; $P = 0.009$), and total CNV lesion area (3.3 vs. 2.4 DAs; $P < 0.001$) than eyes without baseline HE. Eyes with HE were more likely to have RAP (18% vs. 10%; $P = 0.009$) and SPED on FA (13% vs. 4%; $P < 0.001$). Although mean retinal thickness was similar between the 2 groups (220 vs. 219 μ; $P = 0.92$), the mean total thickness at the fovea was greater in eyes with HE (522 vs. 452 μm; $P < 0.001$). More eyes with HE had sub-RPE fluid than eyes without HE (65% vs. 45%; $P < 0.001$), whereas cystoid spaces within the retina[8] (80% vs. 74%; $P = 0.20$) and subretinal fluid (83% vs. 82%; $P = 0.90$) were similar in both groups. Cystoid macular edema detected on FA as a petaloid pattern was not significantly associated with HE. The hepatic lipase (LIPC) promoter single nucleotide polymorphism (SNP) rs10468017 was not associated with the presence of HE at baseline.

Year 1 Outcomes

Mean VA was similar in both groups at 1 year (66 vs. 68 letters; $P = 0.21$). Although the retinal thickness was similar (152 vs. 158 μm; $P = 0.33$), the total thickness at the foveal center was less in eyes that had HE at baseline (263 vs. 295 μm; $P = 0.01$), and there was a larger change in total thickness at the foveal center from baseline (−266 vs. −158 μm; $P < 0.001$). More eyes with HE at baseline had no retinal fluid at 1 year (45% vs. 29%; $P < 0.001$). These eyes also had less subretinal fluid (13% vs. 32%; $P < 0.001$) and sub-RPE fluid (19% vs. 33%; $P = 0.003$) when compared with eyes with no baseline HE. Intraretinal fluid (46% vs. 47%; $P = 0.85$) was not different between the 2 groups at 1 year. Although there were more RPE tears in eyes that had HE at baseline (3.5% vs. 1.5%; $P = 0.11$), this difference was not statistically significant. Among eyes assigned to pro re nata treatment, both groups required the same mean number of injections (7 vs. 7; $P = 0.89$) (Table 2).