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Pseudodrusen and Incidence of Late Age-Related Macular Degeneration in Fellow Eyes in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Purpose: To evaluate the association between pseudodrusen and incidence of late age-related macular degeneration (AMD) in fellow eyes of patients with unilateral neovascular AMD (nAMD).

Design: Cohort study within the Comparison of AMD Treatments Trials (CATT).

Participants: Patients with neither nAMD nor geographic atrophy (GA) in the fellow eye at baseline.

Methods: Presence and type (dot, reticular, or confluent) of baseline pseudodrusen were assessed using digital color fundus photography (CFP) viewed under full color, green channel, and blue channel; red-free images; and fluorescein angiography (FA). Incidence of nAMD was based on monthly clinical examination and reading center evaluation of images at years 1 and 2. Incidence of GA was based on reading center evaluation of CFP and FA images at years 1 and 2. Associations of baseline pseudodrusen with incident nAMD and GA were summarized with adjusted risk ratios (aRRs) and their 95% confidence intervals (CIs) from multivariate Cox models, with adjustment of covariates identified through backward stepwise selection.

Main Outcome Measures: Incident nAMD and GA.

Results: Among 620 fellow eyes, 176 (28.4%) had baseline pseudodrusen (55% dot, 82% reticular, 35% confluent). Within 2 years, nAMD occurred in 54 eyes (30.7%) with pseudodrusen and in 72 eyes (16.2%) without pseudodrusen (aRR, 2.05; 95% CI, 1.43−2.93); GA occurred in 27 eyes (15.3%) with pseudodrusen and in 37 eyes (8.3%) without pseudodrusen (aRR, 1.89; 95% CI, 1.13−3.17); late AMD occurred in 73 eyes (41.5%) with pseudodrusen and in 101 eyes (22.8%) without pseudodrusen (aRR, 2.07; 95% CI, 1.51−2.83). Dot pseudodrusen were associated independently with nAMD (aRR, 2.53; 95% CI, 1.60−4.00), whereas confluent pseudodrusen were associated independently with GA (aRR, 4.35; 95% CI, 1.69−11.2). Eyes with pseudodrusen had increased incidence of late AMD regardless of whether the Age-Related Eye Diseases Study (AREDS) severity score was 2 (28.7% vs. 10.3%), 3 (34.9% vs. 13.7%), or 4 (50.5% vs. 32.0%).

Conclusions: In fellow eyes of CATT participants, pseudodrusen were associated independently with a higher incidence of both nAMD and GA. Dot pseudodrusen were associated with nAMD, whereas confluent pseudodrusen were associated with GA. Pseudodrusen should be considered along with the AREDS severity score for predicting late AMD. *Ophthalmology 2016;■:1−11 © 2016 by the American Academy of Ophthalmology.*

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Pseudodrusen were reported first by Mimoun et al[1] in 1990 as a special type of drusen in the macula of patients with age-related macular degeneration (AMD). Later, the terms *reticular drusen*, *reticular pseudodrusen*, *reticular macular disease* or *reticular macular lesions*, and *subretinal drusenoid deposits* were used to describe this type of drusen.[2−8] Population-based studies, such as the Beaver Dam Eye Study and the Blue Mountains Eye Study, found that eyes with early AMD features and pseudodrusen demonstrated on color fundus photography (CFP) were 4 to 6 times more likely to progress to late AMD within 5 years when matched to eyes without pseudodrusen but with otherwise similar early AMD features.[9−11] Several clinical studies also have demonstrated a strong association between pseudodrusen and the development of late AMD.[3,7,8,12−14] However, the specific association of pseudodrusen with neovascular AMD (nAMD) or with geographic atrophy (GA) is not clear because these studies were limited by a small number of incident cases.

It is well known that when nAMD is present in one eye, the fellow eye is at high risk of demonstrating late AMD.[15−17] A meta-analysis provided incidence estimates for nAMD in the fellow eye of 12.2% by 1 year after nAMD detection in the first eye and of 26.8% by 4 years.[18] These estimates are much higher than the estimates of the annual incidence of 0.57% to 1.13% in white Americans 75 to 84

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years of age.[19] This elevated risk is independent of treatment with ranibizumab or bevacizumab for nAMD.[20] A few clinical studies with sample sizes ranging from 20 to 271 patients have evaluated the association of pseudodrusen with development of nAMD and GA in the fellow eye of patients with unilateral nAMD.[21–25] However, the conclusions from these studies were inconsistent, most likely because of small numbers of incident cases of nAMD and GA and differences in the imaging methods used to detect pseudodrusen.

The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) provided a large cohort of patients with nAMD in the study eye treated with randomly assigned ranibizumab or bevacizumab through 2 years.[26,27] This well-characterized cohort provided a unique opportunity to evaluate the association of pseudodrusen with incidence of nAMD and GA in the fellow eye of patients with unilateral nAMD.

Methods

Details on the CATT study design and methods have been reported in our previous publications[20,26,27] and at ClinicalTrials.gov (identifier, NCT00593450). Only features relevant to the evaluation of pseudodrusen at baseline and assessment of nAMD and GA in the fellow eye are noted here.

Study Participants

Participants were enrolled from 43 clinical centers in the United States between February 2008 and December 2009. The study enrollment criteria included age of 50 years or older, untreated active neovascularization resulting from AMD in the study eye (1 eye per participant), and visual acuity between 20/25 and 20/320 on electronic visual acuity testing. Active neovascularization was defined by the presence of leakage on fluorescein angiography (FA) and fluid on time-domain optical coherence tomography (OCT). The study was approved by an institutional review board associated with each center. All patients provided written informed consent.

At enrollment, participants provided information on demographic characteristics and medical history, including a history of cardiovascular diseases and hypertension. Participants were randomized to 1 of the 4 treatment groups: (1) ranibizumab monthly, (2) bevacizumab monthly, (3) ranibizumab as needed (pro re nata [PRN]), and (4) bevacizumab PRN. At 1 year, participants initially assigned to monthly treatment retained their drug assignment, but were reassigned randomly to either monthly or PRN treatment. Participants initially assigned to PRN treatment retained both their drug and regimen for year 2.

Study Procedures

At enrollment, patients were examined by study-certified retina specialists. The retina specialist indicated whether there was a history of nAMD or active nAMD in the fellow eye. Patients underwent bilateral stereoscopic CFP, red-free (RF) imaging, and FA that included stereo images of the macula of the fellow eye at 2 and 10 minutes after dye injection. Follow-up examinations for both the study eye and the fellow eye were scheduled every 28 days for 2 years. During each examination, the study retina specialist completed case report forms with specific questions regarding whether there had been any treatment for nAMD in the fellow eye since the last CATT examination or whether treatment was scheduled on the day of the examination. At years 1 and 2, CFP and FA also were performed in both study eyes and fellow eyes. Certified graders at the CATT Fundus Photograph Reading Center reviewed images acquired at baseline and years 1 and 2 for nAMD morphologic features in the study eye and the presence of nAMD, GA, and scar in the fellow eye.[28] The presence of large drusen (>125 μm) and pigment abnormalities (hyperpigmentation or depigmentation) at baseline in the fellow eye also were graded.

Patients were included in this study if the fellow eye did not have any evidence of neovascularization, scar, or GA at baseline on either clinical examination or image evaluation by the reading center using CFP and FA. Incident nAMD in the fellow eye was considered present at the earliest follow-up visit when the examining retina specialist indicated that treatment for nAMD in the fellow eye had occurred since the last study examination or would occur on the day of the study visit. In addition, eyes confirmed to have leakage on FA or a new scar on CFP at years 1 or 2 by the Director of the Fundus Photograph Reading Center (E.D.) were classified as having nAMD. Incident GA was identified from reading center evaluation of images from year 1 or 2. The diagnosis of GA required the presence within the macular vascular arcades of 1 or more patch of 250 μm or more in longest linear dimension of partial or complete depigmentation on the CFP that had 1 or more of these additional characteristics: sharply demarcated borders seen on CFP, FA, or both; visibility of underlying choroidal vessels; excavated or punched out appearance on stereoscopy of CFP or FA; or uniform hyperfluorescence bounded by sharp borders on late-phase angiography.[29]

Pseudodrusen Evaluation

Baseline digital CFP images from fellow eyes of CATT participants were evaluated for the presence and type of pseudodrusen by one of the authors (Q.Z.), who was masked to the status of late AMD during follow-up. To enhance the visibility of pseudodrusen, CFP images were reviewed with full color, only the green channel, or only the blue channel in Photoshop (Photoshop CS6, version 13.0; Adobe System, Inc., San Jose, CA). Pseudodrusen usually are more visible when viewing CFP images with the green or blue channel than in full color.[2,8] In Photoshop, the command "Channels" was used to display channels for each color (red, green, and blue) plus a composite channel (i.e., original image) of the RGB (full-color) image. If needed, adjustment of brightness and contrast was made to improve the view of pseudodrusen. Besides the CFP, digital RF fundus photographs also were used to aid in the detection of pseudodrusen that were not clearly apparent when viewing CFPs. In addition, FA images were used to distinguish pseudodrusen from other drusen (soft, hard, or cuticular drusen). We graded the presence of pseudodrusen (none, questionable, yes) and the type of pseudodrusen (dot, reticular, and confluent; Figs 1, 2, and 3). When the presence of pseudodrusen was questionable, the consensus results after review with the Director of the Fundus Photograph Reading Center (E.D.) and a senior certified grader (R.M.) were used for data analysis.

Our definition of pseudodrusen on CFP was based primarily on 2 previous studies.[30,31] In full-color and green- or blue-channel viewing of CFP images, pseudodrusen were considered to be present if 5 or more drusen were brighter in the green or blue channel than in full color (Figs 1A, 2A, and 3A).[2,13,32] The method to determine the presence of pseudodrusen on RF images was similar to that on green- or blue-channel images (Figs 1B, 2B, and 3B). On FA, pseudodrusen are different from regular drusen in that pseudodrusen are not visible in the early phase and generally are not visible in the middle and late phases (Figs 1E, F; 2E, F; and 3E, F)[1,7,8,12,33–35] or show only faint fluorescence in the late phase.[3,36] In contrast, regular drusen usually are hyperfluorescent in the early phase and stain in the late phase (Fig 1E, F).