American Academy of Ophthalmology
The Eye M.D. Association

Subretinal Hyperreflective Material in the Comparison of Age-Related Macular Degeneration Treatments Trials

*Alex S. Willoughby, BS,[1] Gui-shuang Ying, PhD,[2] Cynthia A. Toth, MD,[1] Maureen G. Maguire, PhD,[2] Russell E. Burns, AAS,[3] Juan E. Grunwald, MD,[2] Ebenezer Daniel, MBBS, MD,[2] Glenn J. Jaffe, MD,[1] for the Comparison of Age-Related Macular Degeneration Treatments Trials Research Group**

Purpose: To evaluate the association of subretinal hyperreflective material (SHRM) with visual acuity (VA), geographic atrophy (GA), and scar in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Design: Prospective cohort study within a randomized clinical trial.

Participants: The 1185 CATT participants.

Methods: Masked readers graded scar and GA on fundus photography and fluorescein angiography and graded SHRM on time-domain and spectral-domain (SD) optical coherence tomography (OCT) throughout 104 weeks. Measurements of SHRM height and width in the fovea, within the center 1 mm^2, or outside the center 1mm^2 were obtained on SD OCT images at 56 (n = 76) and 104 (n = 66) weeks.

Main Outcome Measures: Presence of SHRM, as well as location and size, and associations with VA, scar, and GA.

Results: Among CATT participants, the percentage with SHRM at enrollment was 77%, decreasing to 68% at 4 weeks after treatment and to 54% at 104 weeks. At 104 weeks, scar was present more often in eyes with persistent SHRM than in eyes with SHRM that resolved (64% vs. 31%; $P < 0.0001$). Among eyes with detailed evaluation of SHRM at weeks 56 (n = 76) and 104 (n = 66), mean VA letter score was 73.5 (standard error [SE], 2.8), 73.1 (SE, 3.4), 65.3 (SE, 3.5), and 63.9 (SE, 3.7) when SHRM was absent, present outside the central 1 mm^2, present within the central 1 mm^2 but not the foveal center, or present at the foveal center ($P = 0.02$), respectively. When SHRM was present, the median maximum height under the fovea, within the central 1 mm^2 including the fovea and anywhere within the scan, was 86 μm, 120 μm, and 122 μm, respectively. Visual acuity was decreased with greater SHRM height and width ($P < 0.05$).

Conclusions: In eyes with neovascular age-related macular degeneration (AMD), SHRM is common and often persists after anti−vascular endothelial growth factor treatment. At 2 years, eyes with scar were more likely to have SHRM than other eyes. Greater SHRM dimensions were associated with worse VA. In eyes with neovascular AMD, SHRM is an important morphologic biomarker. *Ophthalmology 2015;■:1−8 © 2015 by the American Academy of Ophthalmology.*

Anti−vascular endothelial growth factor (VEGF) drugs such as ranibizumab and bevacizumab effectively prevent visual acuity (VA) loss in patients with neovascular age-related macular degeneration (AMD).[1−4] These agents induce alterations in macular morphologic features that are correlated with VA changes.

Subretinal hyperreflective material (SHRM) is a morphologic feature seen on optical coherence tomography (OCT) as hyperreflective material located external to the retina and internal to the retinal pigment epithelium (RPE). Seen in treatment-naïve eyes with neovascular AMD and eyes treated with anti-VEGF drugs, SHRM is thought to have an adverse effect on VA.[5] Participants in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) were treated and followed up for 2 years with the anti-VEGF drugs ranibizumab or bevacizumab. At 2 years, SHRM was present in 84.5% ($P < 0.001$) of eyes with sustained VA loss.[6] No long-term studies have evaluated the association over time of SHRM characteristics with VA and other morphologic features. Herein, we determined how the presence, location, and size of SHRM relates to VA and clinical and anatomic features at baseline and during follow-up in CATT.

Methods

Study Population

The design and methods used for CATT have been described elsewhere.[3,4,7] In short, between February 2008 and December 2009, 1185 patients were enrolled across 43 United States clinical

http://dx.doi.org/10.1016/j.ophtha.2015.05.042
ISSN 0161-6420/15

centers and underwent treatment for choroidal neovascularization (CNV) secondary to AMD. Inclusion criteria included age older than 50 years, active CNV that previously had been untreated, and VA between 20/25 and 20/320. The CNV or its sequela (fluid, macular edema, serous pigment epithelial detachment, hemorrhage, or blocked fluorescence) needed to involve the foveal center. Only 1 eye per subject was treated as part of the clinical trial. Eyes with active CNV had leakage or increased stippling on fluorescein angiography (FA) and fluid (intraretinal, subretinal, or sub-RPE) on time-domain (TD) OCT. Choroidal neovascularization was considered secondary to AMD if either eye had at least 1 drusen of more than 63 μm or the fellow eye had CNV or geographic atrophy (GA). At study entry, patients were assigned randomly to 1 of 4 treatment groups that comprised 1 drug (ranibizumab or bevacizumab) and 1 dosing regimen (monthly or pro re nata [PRN]). At 1 year, participants who were in monthly treatment groups continued with the same drug but were reassigned randomly to monthly or PRN treatment. The other participants who were assigned initially to PRN treatment during year 1 continued treatment with the same drug and dosing regimen throughout the second year.[8] The CATT was registered with ClinicalTrials.gov (identifier, NCT00593450). Institutional review board approval was obtained at each center, and all data handling complied with the Health Insurance Portability and Accountability Act. All participants provided written informed consent, and the research adhered to the tenets of the Declaration of Helsinki.

Study Procedures

The CATT methods to grade digital color fundus photographs (CFPs), FA images, and OCT images have been described previously.[3,4] Certified technicians obtained OCT images using Macular Thickness Map protocols at baseline and at follow-up visits every 4 weeks. The Stratus TD OCT device (Carl Zeiss Meditec, Jena, Germany) was used to obtain OCT images from all participants through year 1 of the trial. After this time, study sites were given the option to transition to spectral-domain (SD) OCT with the Cirrus device (Carl Zeiss Meditec) or Spectralis device (Heidelberg Engineering, Carlsbad, CA) to acquire OCT images. Bilateral CFPs and FA images were acquired at baseline, 1 year, and 2 years.

Masked readers at the Duke Reading Center evaluated SHRM on TD or SD OCT scans. A senior reader (R.E.B., G.J.J.) determined the final grade on all images in which the initial 2 readers did not agree. The presence or absence of SHRM was assessed on all CATT participant scans. A more detailed analysis of SHRM location and dimensions was performed on a subset of eyes with SD OCT at 56 weeks (n = 76). Of that subset, 10 participants were lost to follow-up at week 104, leaving 66 eyes with both week 56 and week 104 scans and 10 eyes with only week 56 scans. In the detailed analysis, all SHRM lesions were subdivided based on location: at the foveal center, within the central 1-mm^2 subfield, and outside the central 1-mm^2 subfield. Maximum height and width of SHRM was measured within each grading category location. When the RPE was discernible easily from the SHRM, regardless of whether there was an RPE detachment underlying the SHRM, height was measured from the inner border of SHRM to the inner border of the RPE layer. When the SHRM−RPE border could not be distinguished, regardless of whether there was associated RPE atrophy, height was measured from the inner SHRM border to Bruch's membrane (Figs 1 and 2).

In a subset of images with foveal SHRM (n = 43) and without foveal SHRM (n = 40), the external limiting membrane (ELM), the ellipsoid zone (EZ), and SHRM, if present, were evaluated at the same location at the foveal center. In our investigation, we specifically wanted to see if and how the ELM and EZ were affected by SHRM, which developed directly beneath the respective layers. Readers graded the integrity of the ELM and EZ as either present or absent, whereas SHRM was graded in the same way previously described.

To assess reader reliability, the primary reader (A.S.W.) regraded a random sample (n = 25) of eyes. The regrading was performed 3 months after initial grading to minimize any memory bias. Two masked readers at the Scheie Image Reading Center evaluated the CFPs and FA images for foveal involvement, dye leakage on FA, and neovascular lesion area (in square millimeters). Neovascular lesions included CNV as well as contiguous areas of pigment epithelial detachment, scar, hemorrhage, and blocked fluorescence. A senior reader (R.E.B., G.J.J.) determined the final grade on all grading discrepancies.[8,9] Certified VA examiners measured VA after refraction using an electronic VA system at baseline and follow-up weeks 4, 12, 24, 36, 52, 64, 76, 88, and 104.[4,7,10]

Statistical Analysis

A descriptive analysis was performed and included means, standard error (SE), median, and interquartiles for SHRM characteristics (height, width, area) and VA. Optical coherence tomography scans from weeks 56 and 104 were combined for analysis because the characteristics of SHRM were similar at the 2 time points. Percentages were determined for presence of SHRM, GA, and scar. An analysis of variance with a test for linear trend was performed to compare VA among groups of SHRM characteristics, and generalized estimating equations were used to account for the correlation of SHRM measurements from the same eyes at weeks 56 and 104. A chi-square test was used to compare the association between the presence or resolution of SHRM with GA or scar at year 1 or year 2. All statistical comparisons were performed with SAS software (SAS Inc, Cary, NC), and $P < 0.05$ was considered to be statistically significant.

Results

Subretinal Hyperreflective Material Prevalence

Among 1184 eyes with baseline OCT images, SHRM was present in 908 of 1184 (76.6%) at baseline (Table 1). The prevalence of SHRM decreased to 670 of 1153 (58.1%) at week 4. Throughout the remainder of the 2 years, SHRM continued to decrease gradually; by 1 year, 515 of 1092 (4 7.2%) eyes had SHRM, and at 2 years, 468 of 1024 (45.7%) eyes had SHRM. Of eyes with SHRM at baseline, it persisted in 599 of 886 (67.6%) eyes at week 4, in 463 of 833 (55.6%) eyes at week 52, and in 416 of 774 (53.8%) eyes at week 104. The persistence of baseline SHRM did not differ by treatment drug at year 1 (54.0% for ranibizumab and 57.3% for bevacizumab; $P = 0.35$) or at year 2 (52.4% for ranibizumab and 55.2% for bevacizumab; $P = 0.47$). The baseline SHRM persisted at a lower percentage in monthly treated eyes at year 1 (53.2% in monthly eyes and 57.9% in PRN eyes; $P = 0.18$), and the difference became significant at year 2 (42.9% in monthly eyes for 2 years, 55.7% in monthly year 1 PRN year 2 eyes, and 57.8% in PRN for 2 years eyes; $P = 0.003$).

For the scans associated with the 76-eye subset having SD OCT images at week 56, maximum SHRM height and width was measured at the foveal center, within the central 1-mm^2 cube, and outside the center 1-mm^2 cube. Based on the quality assurance