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

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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

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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

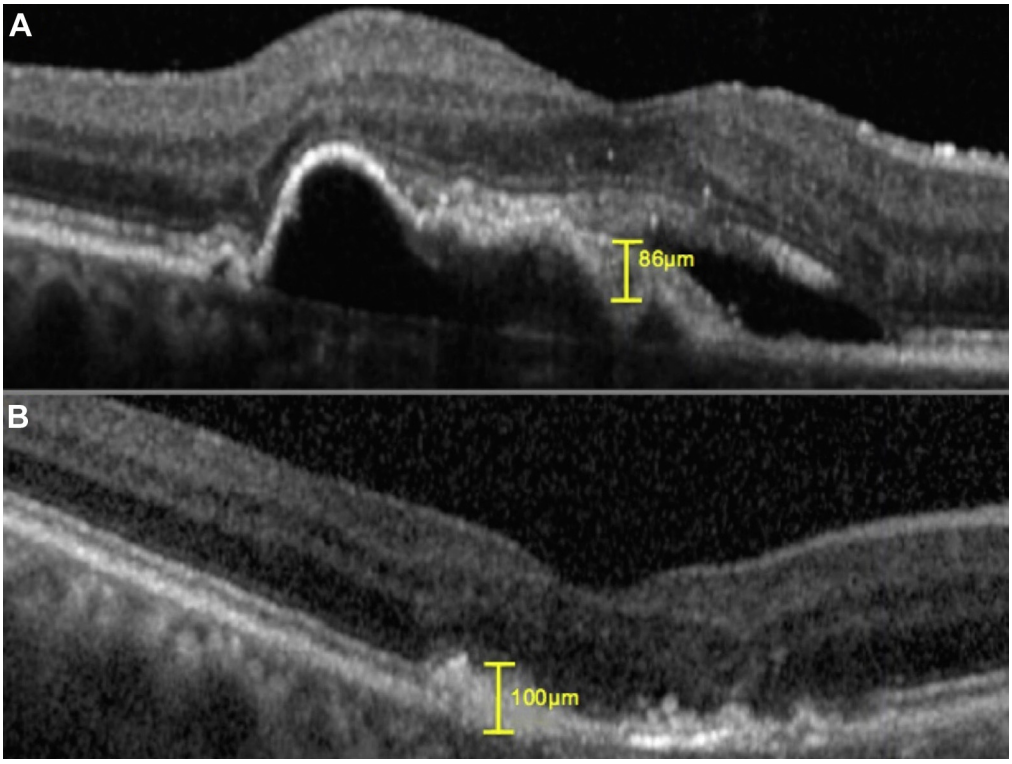

Figure 1. **A**, Optical coherence tomography scan showing average foveal subretinal hyperreflective material thickness (86 μm) that is distinguishable from the underlying retinal pigment epithelium layer. **B**, Optical coherence tomography scan showing subretinal hyperreflective material (100 μm) that is indistinguishable from underlying retinal pigment epithelium layer.

sample of 25 eyes, the intrareader agreement for presence and location of SHRM was excellent ($\kappa > 0.80$). The mean intrareader SHRM thickess agreement (95% limit of agreement) at the foveal center, within the center 1-cm cube, and the maximum height of the entire scan was −4.4 μm (−13.0 to 4.2 μm), −2.7 μm (−38 to 33 μm), and 14.7 μm (−80 to 111 μm), respectively. Among eyes with SD OCT images that were evaluated for SHRM at weeks 56 (n = 76) and 104 (n = 66), SHRM was present at the foveal center in 43 of 142 (30.3%) scans, within the central 1 mm^2 in 64 of 142 (45.1%) scans, and anywhere within the scan in 83 of 142 (58.5%)

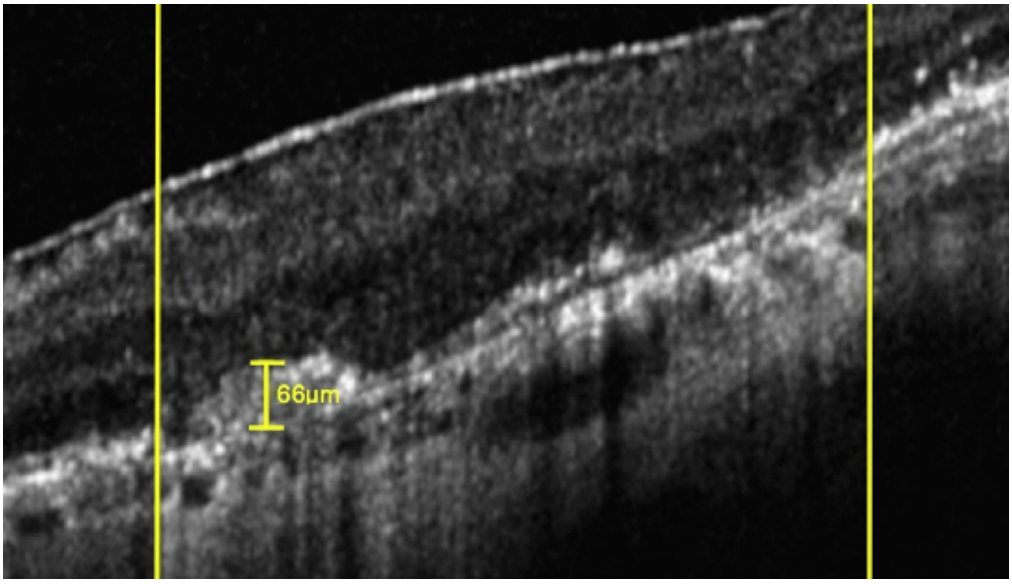

Figure 2. Optical coherence tomography scan showing subretinal hyperreflective material measurements over geographic atrophy (yellow parallel lines border area of geographic atrophy).

Table 1. Subretinal Hyperreflective Material at Baseline and during Follow-up

Follow-up Week	Among All Comparison of Age-Related Macular Degeneration Treatments Trials Study Eyes		Among Eyes with Subretinal Hyperreflective Material at Baseline	
	No. of Eyes	*No. of Eyes with Subretinal Hyperreflective Material (%)*	*No. of Eyes*	*No. of Eyes with Subretinal Hyperreflective Material at This Week (%)*
0	1184	908 (76.6)	908	908 (100)
4	1153	670 (58.1)	886	599 (67.6)
8	1128	630 (55.9)	864	571 (66.1)
12	1084	593 (54.7)	834	542 (65.0)
24	1053	533 (50.6)	802	483 (60.2)
52	1092	515 (47.2)	833	463 (55.6)
76	969	441 (45.5)	738	397 (53.8)
104	1024	468 (45.7)	774	416 (53.8)

scans. When SHRM was present, the median height (first quartile, third quartile) at the foveal center was 86 μm (49 μm, 120 μm), within the central 1 mm^2 was 120 μm (81 μm, 171 μm), and anywhere within the scan was 122 μm (84 μm, 180 μm; Table 2). The SHRM characteristics did not differ between week 56 and 104 (data not shown).

Correlation of Intact Ellipsoid Zone and External Limiting Membrane with Subretinal Hyperreflective Material

In a subset of eyes, the integrity and presence of the EZ, ELM, and SHRM were evaluated in the same location, at the foveal center. The EZ at the foveal center was absent more often in eyes with underlying foveal SHRM compared with eyes without foveal SHRM (81% vs. 38%; $P < 0.0001$). In contrast, an intact ELM at the foveal center was not significantly related to the presence or absence of underlying foveal SHRM (54% vs. 63%, respectively; $P = 0.50$).

Subretinal Hyperreflective Material Features Associated with Visual Acuity Loss

The association between SHRM location and size characteristics and VA was assessed on the subset of eyes with SD OCT scans obtained at week 56 (n = 76). The presence of SHRM was associated with worse VA, at all locations, regardless of height or width. Mean VA decreased from 73.5 letters (SE, 2.8 letters) when no SHRM was present to 63.9 letters (SE, 3.7 letters) when SHRM was at the foveal center ($P = 0.02$; Table 3). Furthermore, there was a significant correlation between both VA and SHRM height and VA and SHRM width at the foveal center, center 1 mm^2, and within the entire scan. Greater height and width were correlated with worse VA, ranging from a decrease of 10.8 to 14.4 letters, depending on the height and width at the different locations. The greatest VA difference (14.4 letters) occurred when SHRM was located at the foveal center with a width exceeding 1000 μm (57.2 letters) as compared with no SHRM at the foveal center (71.6 letters; $P = 0.04$).

We then determined the relationship between persistence from baseline of SHRM at weeks 52 and 104 and VA change from baseline at those time points. Visual acuity increased more when SHRM had resolved at week 52 ($P = 0.02$) and week 104 ($P < 0.0001$; Table 4). At week 52, in eyes with resolved SHRM, the mean VA increase from baseline was 9.4 letters (SE, 0.64 letter) compared with 6.9 letters (SE, 0.85 letter) in eyes with persisting SHRM. An even greater difference occurred at week 104 in which eyes with resolved SHRM gained 10.6 letters (SE, 0.68 letter) compared with a 5.5-letter gain (SE, 0.97 letter) in eyes with persistent SHRM (Table 4).

As we evaluated eyes with SHRM at weeks 56 and 104, we observed that the RPE often was disrupted. In these eyes, it was difficult to differentiate SHRM clearly from the underlying RPE layer (Fig 1). Accordingly, of these cases, in 43 of 83 (52%) of eyes we measured the SHRM–RPE complex thickness as a single unit, from the inner border of the SHRM to the inner

Table 2. The Distribution of Measurements of Subretinal Hyperreflective Material on Optical Coherence Tomography (n = 142)

Optical Coherence Tomography Measurements*	No. of Scans with Subretinal Hyperreflective Material	Among Those with Subretinal Hyperreflective Material	
		Median (First Quartile, Third Quartile)	*Minimum, Maximum*
Height at foveal center (μm)	43	86 (49, 120)	30, 463
Width at foveal center (μm)	43	917 (404, 1454)	302, 4834
Area at foveal center ($μm^2$/1000)	43	85.1 (45.6, 328.9)	18.9, 218.1
Maximum height within center 1-cm cube (μm)	64	120 (81, 171)	33, 612
Maximum width within center 1-cm cube (μm)	65	916 (471, 1276)	200, 4585
Maximum height within entire scan (μm)	83	122 (84, 180)	34, 612
Maximum width within entire scan (μm)	83	851 (445, 1276)	200, 4585

*Seventy-six eyes with spectral-domain optical coherence tomography (SD OCT) scans obtained at week 56; 66 of them underwent SD OCT imaging at week 104.

Table 3. Association of Subretinal Hyperreflective Material Characteristics with Visual Acuity

Subretinal Hyperreflective Material Characteristics	No.	Visual Acuity in Letters, Mean (Standard Error)	*P* Value*
Location			0.02
No SHRM	59	73.5 (2.78)	
SHRM under the foveal center	43	63.9 (3.68)	
SHRM within central 1 mm^2	21	65.3 (3.54)	
SHRM outside central 1 mm^2	19	73.1 (3.45)	
SHRM distinguishable from RPE			0.14
No SHRM	59	73.5 (2.78)	
Distinguishable	40	66.9 (3.41)	
Not distinguishable	43	65.8 (2.71)	
Height of at foveal center (μm)			0.04
0	99	71.6 (2.02)	
>0, ≤100	27	65.7 (3.84)	
>100	16	60.8 (5.24)	
Width at foveal center (μm)			0.04
0	99	71.6 (2.02)	
>0, ≤1000	24	69.2 (2.50)	
>1000	19	57.2 (6.97)	
Maximum height within central 1 mm^2 (μm)			0.02
0	78	73.4 (2.27)	
>0, ≤150	45	66.3 (2.65)	
>150	19	59.8 (4.98)	
Maximum width within central 1mm^2 (μm)			0.01
0	77	73.4 (2.30)	
>0, ≤1000	36	68.3 (2.72)	
>1000	29	59.7 (4.60)	
Maximum height within entire scan (μm)			0.02
0	59	73.5 (2.78)	
>0, ≤150	54	69.0 (2.50)	
>150	29	61.3 (3.54)	
Maximum width within entire scan (μm)			0.03
0	59	73.5 (2.78)	
>0, ≤1000	54	69.9 (2.42)	
>1000	29	61.0 (4.21)	

SHRM = subretinal hyperreflective material; RPE = retinal pigment epithelium.
*From generalized estimating equation linear models, accounting for correlation of repeated measures at week 56 and week 104. *P* values for ordered categories are from the test for linear trend.

border of Bruch's membrane (rather than from the inner border of SHRM to the inner border of the RPE). The VA was not different (67 vs. 66 letters; $P = 0.77$) regardless of whether it was possible to distinguish SHRM from the underling RPE. Furthermore, although larger SHRM height and width were associated with worse VA, the VA was not different regardless of whether it was possible to distinguish SHRM from underlying RPE for thicker (SHRM >150 μm) or thinner (≤150 μm) SHRM or for wider (>1000 μm) or narrower (≤1000 μm) SHRM.

Table 4. Association between the Resolution of Baseline Subretinal Hyperreflective Material with Visual Acuity Change from Baseline and the Development of Geographic Atrophy and Scar at Follow-up

Baseline Subretinal Hyperreflective Material Resolved at Follow-up	No.*	Visual Acuity Change in Letters, Mean (Standard Error)	*P* Value	No.*	Geographic Atrophy at Follow-up (%)	*P* Value	No.*	Scar at Follow-up (%)	*P* Value
Week 52									
No	412	6.9 (0.85)	0.02	385	36 (9.4)	0.04	381	200 (52.5)	<0.0001
Yes	334	9.4 (0.64)		312	45 (14.4)		315	75 (23.8)	
Week 104									
No	371	5.5 (0.97)	<0.0001	364	62 (17.0)	0.68	360	230 (63.9)	<0.0001
Yes	321	10.6 (0.86)		320	60 (15.6)		320	100 (31.3)	

*Among eyes with subretinal hyperreflective material at baseline but without baseline geographic atrophy or scar.

Relationship between Subretinal Hyperreflective Material and Geographic Atrophy or Scar

Scar, but not GA, was more frequent in eyes with SHRM compared with those without SHRM. Among the 1025 CATT participants who completed the week 52 follow-up, GA was present in 167 eyes (16%) and scar was present in 349 eyes (34%). Among those eyes, SHRM was present at week 52 in a similar proportion of eyes with GA (75/167 [45%]) and those without GA (408/858 [48%]; $P = 0.77$). In contrast, SHRM was present at week 52 in 242 of 349 eyes (69.3%) with scar and in 238 of 675 eyes (35.3%) without scar ($P < 0.0001$).

We next determined the incidence of GA and scar in the 1064 eyes without baseline GA or scar to see if GA or scar development depended on SHRM persistence from baseline. At baseline, SHRM was present in 812 of 1064 (76.3%) eyes. Geographic atrophy developed in 14% of eyes with resolved SHRM compared with 9% of eyes with persistent SHRM at week 52 ($P = 0.04$; Table 4). There was no statistically significant difference at week 104 for the development of GA with respect to SHRM persistence. Conversely, scar developed in a higher proportion of eyes with persistent SHRM compared with eyes with resolved SHRM at weeks 52 and 104 ($P < 0.0001$). When SHRM persisted from baseline, scar developed in 53% of eyes at week 52 and in 64% of eyes at week 104 compared with eyes with resolved SHRM, in which scar developed in 24% of eyes at week 52 and in 31% of eyes at week 104 ($P < 0.0001$; Table 4).

Discussion

In this study, we found that SHRM was common in treatment-naïve eyes with neovascular AMD and persisted in more than half of the eyes during anti-VEGF therapy. The presence of SHRM declined soon after therapy was initiated, and then declined further at a slower rate. Subretinal hyperreflective material was associated with more frequent scar tissue and worse VA, particularly when thicker or wider lesions involved the fovea. Eyes with persistent SHRM had worse VA and a more frequent incident of scar tissue when compared with eyes with resolved SHRM. The VA was similar regardless of whether SHRM could be distinguished clearly from the underlying RPE.

Within 4 weeks of therapy initiation, anti-VEGF therapy correlated with significantly decreased SHRM height, and the SHRM height declined more slowly after that.[3,4] Subretinal hyperreflective material is likely composed of many elements, including fluid, fibrin, blood, scar, and CNV, with the composition changing over time. Anti-VEGF therapy decreases endothelium permeability, thereby reducing vascular fluid leakage, but it is less effective at decreasing the size of the neovascular complex.[1,2,7,11,12] We hypothesize that the rapid decrease in SHRM thickness is caused by a reduction in the SHRM fluid component induced by anti-VEGF therapy. We further hypothesize that as treatment continues over time and the relative amount of SHRM fluid declines, there may be an increased fibrotic component, rendering anti-VEGF therapy less effective in reducing SHRM thickness.

We found that eyes with SHRM had worse VA than those without, and VA was most adversely affected when SHRM involved the central fovea, particularly when SHRM was thick and wide. The reasons for decreased VA in eyes with SHRM are not entirely clear, but are probably multifactorial. It is likely SHRM forms a mechanical barrier to nutrient and metabolite exchange between the RPE and photoreceptors and could interfere with the normal visual cycle. These processes, which would be exacerbated in eyes with thick SHRM, could decrease normal photoreceptor function, causing decreased VA.[13,14,15] Subretinal hyperreflective material may damage the overlying photoreceptors directly by a toxic effect. This could occur if fibrin split products were generated in eyes with a fibrin SHRM component. Furthermore, in eyes with foveal SHRM, the EZ often was absent overlying the SHRM at the foveal center. These data support the notion that SHRM disrupts overlying photoreceptors and can lead to associated decreased vision. We observed that the ELM integrity, at the late time points at which it was evaluated, did not depend specifically on the presence of SHRM. An intact ELM may predict potential photoreceptor recovery.[15,16] If true, and if SHRM causes loss of overlying photoreceptors, we speculate that treatments to resolve SHRM may allow VA to recover through photoreceptor regeneration. A detailed evaluation of changes over time in the integrity of photoreceptors overlying SHRM is beyond the scope of this study. However, we are currently evaluating in detail the morphologic features of the outer retina overlying SHRM, because SHRM changes over time.

Interestingly, foveal center SHRM width, to a greater extent than height, had the greatest adverse effect on VA. We propose that individuals with foveal SHRM, if the SHRM is not too broad, even when the central foveal SHRM is relatively thick, may be able to fixate eccentrically enough to maintain good VA. However, with increasing SHRM width, the person may not be able to fixate eccentrically enough to compensate for the adverse SHRM effect on VA.

In the beginning of our analysis, we were unsure whether the effect of SHRM on VA differed when the SHRM could be distinguished readily from underlying RPE, RPE elevation, or both versus when the RPE was disrupted or absent, thereby preventing this differentiation. To address this issue, we first attempted to use TD OCT, the OCT method used during the first year of the CATT, to identify SHRM as separate from underlying tissue. However, because of the limited TD OCT resolution, it was not always possible to do so. Accordingly, we evaluated SD OCT CATT images from a subset of eyes with either clearly distinguishable SHRM from the underlying tissue, disrupted RPE overlying an RPE detachment, or absent RPE overlying an area of atrophy. The distinguishability of SHRM from the underlying RPE had no effect on VA. Based on these data, we were able to assess the effect of SHRM presence or absence on VA during the first year of CATT with TD OCT and at later time points when SD OCT was used. However, we were unable to assess accurately the effect of SHRM location or size on VA with TD OCT because of the relatively poor resolution and large spacing of the B-scan lines with the 6-line radial scan protocol used with this method.

Scar developed more often in eyes with persistent SHRM. We previously described baseline SHRM as a scar risk factor.[9] In the present report, we have extended those observations to show that when baseline SHRM persists to 1 and 2 years, there is a higher incidence of new scar formation. These data suggest that SHRM not only may be correlated with scar tissue development, but also may be a direct factor in its development. This may occur from new tissue being created or through remodeling tissue already present. Because both CFPs and FA images diagnosed scar, whereas OCT identified SHRM, we cannot definitively state that scar always developed precisely at the site of existing SHRM or that SHRM always preceded development of scar at a specific site. We are currently overlaying CFPs and FA images with SD OCT images across successive study visits to answer these questions better.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CFP** = color fundus

photographs; **CNV** = choroidal neovascularization; **ELM** = external limiting membrane; **EZ** = ellipsoid zone; **FA** = fluorescein angiography; **GA** = geographic atrophy; **HIPAA** = Health Insurance Portability and Accountability Act; **OCT** = optical coherence tomography; **PRN** = pro re nata (as needed); **RPE** = retinal pigment epithelium; **SD** = spectral domain; **SE** = standard error; **SHRM** = subretinal hyperreflective material; **TD** = time domain; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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Wills Eye Institute/ Mid Atlantic Retina (Philadelphia, PA): Richard Kaiser, MD (PI); Elizabeth Affel, MS, OCT-C (OCT); Gary Brown, MD (O); Christina Centinaro (CC); Deborah Fine, COA (OCT); Mitchell Fineman, MD (O); Michele Formoso (CC); Sunir Garg, MD (O); Lisa Grande (VA/R); Carolyn Herbert (VA/R); Allen Ho, MD (O); Jason Hsu, MD (O); Maryann Jay (OCT); Lisa Lavetsky (OCT); Elaine Liebenbaum (OP); Joseph Maguire, MD (O); Julia Monsonego (OP/OCT); Lucia O'Connor (OCT); Lisa Pierce (CC); Carl Regillo, MD (O); Maria Rosario (DE); Marc Spirn, MD (O); James Vander, MD (O); Jennifer Walsh (VA/R).

Ohio State University Eye Physicians & Surgeons-Retina Division (Dublin, OH): Frederick H. Davidorf, MD (PI); Amanda Barnett (OP/OCT); Susie Chang, MD (O); John Christoforidis, MD (O); Joy Elliott (CC); Heather Justice (VA/R); Alan Letson, MD (O); Kathryne McKinney, COMT (CC); Jeri Perry, COT (VA/R); Jill A. Salerno, COA (CC); Scott Savage (OP); Stephen Shelley (OCT).

Retina Associates of Cleveland (Beachwood, OH): Lawrence J. Singerman, MD (PI); Joseph Coney, MD (O); John DuBois (OP/OCT); Kimberly DuBois, LPN, CCRP, COA (VA/R); Gregg Greanoff, CRA (OP/OCT); Dianne Himmelman, RN, CCRC (CC); Mary Ilc, COT (VA/R); Elizabeth Mcnamara (VA/R/OP); Michael Novak, MD (O); Scott Pendergast, MD (O); Susan Rath, PA-C (CC); Sheila Smith-Brewer, CRA (OP/OCT); Vivian Tanner, COT, CCRP (VA/R); Diane E. Weiss, RN, (CC); Hernando Zegarra, MD (O).

Retina Group of Florida (Fort Lauderdale, FL): Lawrence Halperin, MD (PI); Patricia Aramayo (OCT); Mandeep Dhalla, MD (O); Brian Fernandez, MD (OP/OCT); Cindy Fernandez, MD (CC); Jaclyn Lopez (CC); Monica Lopez (OCT); Jamie Mariano, COA (VA/R); Kellie Murphy, COA (OCT); Clifford Sherley, COA (VA/R); Rita Veksler, COA (OP/OCT).

Retina-Vitreous Associates Medical Group (Beverly Hills, CA): Firas Rahhal, MD (PI); Razmig Babikian (DE); David Boyer, MD (O); Sepideh Hami (DE); Jeff Kessinger (OP/OCT); Janet Kurokouchi (CC); Saba Mukarram (VA/R); Sarah Pachman (VA/R); Eric Protacio (OCT); Julio Sierra (VA/R); Homayoun Tabandeh, MD, MS, FRCP (O); Adam Zamboni (VA/R).

Elman Retina Group, P.A. (Baltimore, MD): Michael Elman, MD (PI); Jennifer Belz (CC); Tammy Butcher (CC); Theresa Cain (OP/OCT); Teresa Coffey, COA (VA/R); Dena Firestone (VA/R); Nancy Gore (VA/R); Pamela Singletary (VA/R); Peter Sotirakos (OP/OCT); JoAnn Starr (CC).

University of North Carolina at Chapel Hill (Chapel Hill, NC): Travis A. Meredith, MD (PI); Cassandra J. Barnhart, MPH (CC/VA/R); Debra Cantrell, COA (VA/R/OP/OCT); RonaLyn Esquejo-Leon (OP/OCT); Odette Houghton, MD (O); Harpreet Kaur (VA/R); Fatoumatta NDure, COA (CC).

Ophthalmologists Enrolling Patients but No Longer Affiliated with a CATT Center: Ronald Glatzer, MD (O); Leonard Joffe, MD (O); Reid Schindler, MD (O).

Resource Centers

Chairman's Office (Cleveland Clinic, Cleveland, OH): Daniel F. Martin, MD (Chair); Stuart L. Fine, MD (Vice-Chair; University of Colorado, Denver, CO); Marilyn Katz (Executive Assistant).

Coordinating Center (University of Pennsylvania, Philadelphia, PA): Maureen G. Maguire, PhD (PI); Mary Brightwell-Arnold, SCP (Systems Analyst); Ruchira Glaser, MD (Medical Monitor); Judith Hall (Protocol Monitor); Sandra Harkins (Staff Assistant); Jiayan Huang, MS (Biostatistician); Alexander Khvatov, MS (Systems Analyst); Kathy McWilliams, CCRP (Protocol Monitor); Susan K. Nolte (Protocol Monitor); Ellen Peskin, MA, CCRP (Project Director); Maxwell Pistilli, MS, MEd (Biostatistician); Susan Ryan (Financial Administrator); Allison Schnader (Administrative Coordinator); Gui-Shuang Ying, PhD (Senior Biostatistician).

OCT Reading Center (Duke University, Durham, NC): Glenn Jaffe, MD (PI); Jennifer Afrani-Sakyi (CATT PowerPoint Presentations); Brannon Balsley (OCT Technician Certifications); Linda S. Bennett (Project Manager); Adam Brooks (Reader/SD-Reader); Adrienne Brower-Lingsch (Reader); Lori Bruce (Data Verification); Russell Burns (Senior Technical Analyst/Senior Reader/SD Reader/OCT Technician Certifications); Dee Busian (Reader); John Choong (Reader); Lindsey Cloaninger (Reader Reliability Studies/Document Creation/CATT PPT Files); Francis Char DeCroos (Research Associate); Emily DuBois (Data Entry); Mays El-Dairi (Reader/SD-Reader); Sarah Gach (Reader); Katelyn Hall (Project Manager/Reader Reliability Studies/Data Verification/Document Creation); Terry Hawks (Reader); ChengChenh Huang (Reader); Cindy Heydary (Senior Reader/Quality Assurance Coordinator/SD Reader/Data Verification); Alexander Ho (Reader, Transcription); Shashi Kini (Data Entry/Transcription); Michelle McCall (Data Verification); Daaimah Muhammad (Reader Feedback); Jayne Nicholson (Data Verification); Jeanne Queen (Reader/SD-Reader); Pamela Rieves (Transcription); Kelly Shields (Senior Reader); Cindy Skalak (Reader); Adam Specker (Reader); Sandra Stinnett (Biostatistician); Sujatha Subramaniam (Reader); Patrick Tenbrink (Reader); Cynthia Toth, MD (Director of Grading); Aaron Towe (Reader); Kimberly Welch (Data Verification); Natasha Williams (Data Verification); Katrina Winter (Senior Reader); Ellen Young (Senior Project Manager).

Fundus Photograph Reading Center (University of Pennsylvania, Philadelphia, PA): Juan E. Grunwald, MD (PI); Judith Alexander (Director); Ebenezer Daniel, MBBS, MS, MPH, PhD (Director); Elisabeth Flannagan (Administrative Coordinator); E. Revell Martin (Reader); Candace Parker (Reader); Krista Sepielli (Reader); Tom Shannon (Systems Analyst); Claressa Whearry (Data Coordinator).

National Eye Institute, National Institutes of Health: Maryann Redford, DDS, MPH (Program Officer).

Committees

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