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Subretinal Hyper-Reflective Material in the Comparison of Age-related Macular Degeneration Treatments Trials

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Abstract

Objective—To evaluate the association of subretinal hyper-reflective 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 participants in CATT.

Methods—Participants were randomly assigned to ranibizumab or bevacizumab treatment monthly or as-needed. Masked readers graded scar and GA on fundus photography and fluorescein angiography images, SHRM on time domain (TD) and spectral domain (SD) optical coherence tomography (OCT) throughout 104 weeks. Measurements of SHRM height and width

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*A listing of the CATT Research Group is in the Appendix.

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Alex Willoughby: None
Gui-Shuang Ying: Janssen (Consultant)
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in the fovea, within the center 1mm^2, or outside the center 1mm^2 were obtained on SD-OCT images at 56 (n=76) and 104 (n=66) weeks. VA was measured by certified examiners.

Main Outcome Measures—SHRM presence, location and size, and associations with VA, scar, and GA.

Results—Among all CATT participants, the percentage with SHRM at enrollment was 77%, decreasing to 68% at 4 weeks after treatment and 54% at 104 weeks. At 104 weeks, scar was present more often in eyes with persistent SHRM than 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 [SE] VA letter score was 73.5 [2.8], 73.1 [3.4], 65.3 [3.5], and 63.9 [3.7] when SHRM was absent, present outside the central 1mm^2, present within the central 1mm^2 but not the foveal center, or present at the foveal center (p=0.02). SHRM was present at the foveal center in 43 (30%), within the central 1mm^2 in 21 (15%) and outside the central 1mm^2 in 19 (13%). When SHRM was present, the median maximum height in microns under the fovea, within the central 1 mm^2 including the fovea and anywhere within the scan was 86; 120; and 122, respectively. VA was decreased with greater SHRM height and width (p<0.05).

Conclusions—SHRM is common in eyes with NVAMD and often persists after anti-VEGF treatment. At 2 years, eyes with scar were more likely to have SHRM than other eyes. Greater SHRM height and width were associated with worse VA. SHRM is an important morphological biomarker in eyes with NVAMD.

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 (NVAMD).[1–4] These agents induce alterations in macular morphology that are correlated with visual acuity changes.

Subretinal hyper-reflective material (SHRM) is a morphological feature seen on optical coherence tomography (OCT) as hyper-reflective material located external to the retina, and internal to the retinal pigment epithelium. SHRM, seen in treatment-naïve eyes with NVAMD and eyes treated with anti-VEGF drugs, is thought to adversely affect VA.[5] Participants in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) were treated and followed for 2 years with anti-VEGF drugs ranibizumab or bevacizumab. At 2 years, SHRM was present in 84.5% (p<.001) of eyes with sustained visual acuity loss.[6] There are no long-term studies that evaluate the association over time of subretinal hyper-reflective material (SHRM) characteristics with visual acuity (VA) and other morphologic features. Herein, we determined how the presence, location, and size of SHRM relates to visual acuity, clinical and anatomical features, at baseline and 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 US clinical centers and underwent treatment for CNV secondary to AMD. Inclusion criteria

included subject >50 years, active CNV that had previously 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 FA and fluid (intraretinal, subretinal, or sub-RPE) on time domain (TD)-OCT. CNV was considered secondary to AMD if either eye had at least 1 drusen >63u or the fellow eye had CNV or geographic atrophy (GA). At entry into the study, patients were randomly assigned to 1 of 4 treatment groups that comprised one drug (ranibizumab or bevacizumab) and one dosing regimen (monthly or pro re nata [PRN]). At 1 year, participants who were in monthly treatment groups continued the same drug but were randomly reassigned to monthly or PRN treatment. The other participants who were initially assigned PRN treatment during year 1 continued treatment with the same drug and dosing regimen throughout the second year.[8] The CATT study was registered with ClinicalTrials.gov (NCT00593450). Institutional Review Board (IRB) approval was obtained at each center and all data remained HIPAA-compliant. All participants provided written informed consent, and the research adhered to the tenets of the Declaration of Helsinki.

Study Procedures

CATT methods to grade digital CFP, FA, and OCT have been previously described.[3, 4] Certified technicians obtained OCT images using Macular Thickness Map protocols at baseline and upon follow-up visits every 4 weeks. Stratus (Carl Zeiss Meditec, Jena, Germany) TD-OCT was obtained on all participants through year one of the trial. After this time, study sites were given the option to transition to spectral domain (SD) OCT with Cirrus (Carl Zeiss Meditec, Jena, Germany) or Spectralis (Heidelberg Engineering, Carlsbad, CA) to acquire OCT images. Bilateral color fundus photography (CFP) and fluorescein angiography (FA) 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 determined the final grade on all images in which the initial two 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 weeks 56 (n=76). Of that subset, 10 participants were lost to follow-up at week 104 leaving 66 eyes with both week 56 and 104 scans and 10 eyes with only week 56 scans. In the detailed analysis, all SHRM lesions were sub-divided based on location: at the foveal center, within the central $1mm^2$ subfield, and outside the central $1mm^2$ subfield. Maximum height and width of SHRM was measured within each grading category location. When the RPE was easily discernable from the SHRM, whether or not 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, whether or not there was associated RPE atrophy, height was measured from the inner SHRM border to Bruch's membrane (Figures 1, 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, while SHRM was graded in the same way previously described.

To assess reader reliability, the primary reader re-graded a random sample (n=25) of eyes. The re-grading 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 FAs for foveal involvement, dye leakage on FA, and neovascular lesion area (mm^2). Neovascular lesions included CNV as well as contiguous areas of PED, scar, hemorrhage, and blocked fluorescence. A senior reader determined the final grade on all grading discrepancies.[8, 9]

Certified visual acuity examiners measured visual acuity after refraction using an electronic visual acuity 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 inter-quartiles for SHRM characteristics (height, width, area) and visual acuity. OCT scans from weeks 56 and 104 were combined for analysis because the characteristics of SHRM were similar at the two 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 visual acuity 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-squared 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 in SAS (SAS Institute Inc, Cary, NC), and $p<0.05$ was considered to be statistically significant.

Results

SHRM Prevalence

Among 1184 eyes with baseline OCT images, SHRM was present in 908/1184 (76.6%) at baseline (Table 1). The prevalence of SHRM decreased to 670/1153 (58.1%) at week 4. Throughout the remainder of the two years, SHRM continued to decrease gradually; by one year 515/1092 (47.2%) eyes had SHRM, and at 2 years, 468/1024 (45.7%) eyes had SHRM. Of eyes with SHRM at baseline, it persisted in 599/886 (67.6%) eyes at week 4, 463/833 (55.6%) eyes at week 52, and 416/774 (53.8%) eyes at week 104. The persistence of baseline SHRM did not differ by treatment drug at year 1 (54.0% for ranbizumab and 57.3% for bevacizumab, p=0.35) or at year 2 (52.4% for ranbizumab 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, 57.9% in PRN, p=0.18), and the difference became significant at year 2 (42.9% in monthly for 2 years, 55.7% in monthly year 1 PRN year 2, 57.8% in PRN for 2 years, p=0.003).

For the scans associated with the 76-eye subset having SD-OCT at week 56, maximum SHRM height and width was measured at the foveal center, within the central 1mm^2 cube, and outside the center 1mm^2 cube. Based on the quality assurance sample of 25 eyes, the intra-reader agreement for presence and location of SHRM was excellent (kappa>0.80). The mean (microns) intra-reader SHRM thickess agreement (95% limit of agreement) at the foveal center, within the center 1cm cube, and the maximum height of the entire scan was −4.4 (−13.0, 4.2), −2.7 (−38, 33), and 14.7 (−80, 111), respectively. Among eyes with SD-OCT evaluated for SHRM at week 56 (n=76) and 104 (n=66), SHRM was present at the foveal center in 43/142 (30.3%) scans, within the central 1mm^2 in 64/142 (45.1%) scans and anywhere within the scan in 83/142 (58.5%) scans. When SHRM was present, the median height in microns (1st quartile, 3rd quartile) at the foveal center was 86 (49, 120), within the central 1 mm^2 was 120 (81, 171), and anywhere within the scan was 122 (84, 180) (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 SHRM

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 to 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).

SHRM 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 (SE) VA letters decreased from 73.5 (2.8) when no SHRM was present to 63.9 (3.7) 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 1mm^2, and within the entire scan. Greater height and width was correlated with worse visual acuity, ranging from a decrease of 10.8–14.4 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 (microns) exceeding 1000 (57.2 letters) as compared to 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 visual acuity change from baseline at those time points. VA 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 (SE) was 9.4 (0.64) letters compared to 6.9 (0.85) letters in eyes with persisting SHRM. An even greater difference occurred at week 104 in which eyes with resolved SHRM gained 10.6 (0.68) letters compared to a 5.5 (0.97) letter gain in eyes with persistent SHRM (Table 4).

As we evaluated eyes with SHRM at weeks 56 and 104, we observed that the RPE was often disrupted. In these eyes, it was difficult to clearly differentiate SHRM from the underlying RPE layer (Figure 1). Accordingly, in these cases 43/83 (52%) of eyes we measured the

SHRM-RPE complex thickness as a single unit, from the inner border of the SHRM to the inner border of Bruch's membrane (rather than from the inner border of SHRM to the inner border of the RPE). The visual acuity was not different (67 letters vs. 66 letters, p=0.77) whether or not it was possible to distinguish SHRM from the underling RPE. Furthermore, although larger SHRM height and width (microns) was associated with worse VA, the VA was not different whether or not it was possible to distinguish SHRM from underlying RPE for thicker (SHRM >150) or thinner SHRM (≤150), or for wider (>1000) or narrower (≤1000) SHRM.

Relationship between SHRM and GA or scar

Scar, but not GA, was more frequent in eyes with SHRM compared to those without SHRM. Among the 1,025 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 242/349 eyes (69.3%) with scar and in 238/675 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 812/1064 (76.3%) eyes. GA developed in 14% of eyes with resolved SHRM compared to 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 to 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 64% of eyes at week 104 compared to eyes with resolved SHRM, which developed scar in 24% of eyes at week 52 and 31% of eyes at week 104 (p<0.0001, Table 4).

Discussion

In the present study, we found that SHRM is common in treatment naïve eyes with NVAMD and persists 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. SHRM 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 to eyes with resolved SHRM. The VA was similar regardless of whether SHRM could be clearly distinguished form the underlying RPE.

Anti-VEGF therapy correlated with significantly decreased SHRM height within 4 weeks of therapy initiation, and the SHRM height declined more slowly after that.[3, 4] SHRM 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, 14,16] SHRM 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 ellipsoid zone was often 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 might allow VA to recover through photoreceptor regeneration. A detailed evaluation of changes over time in the integrity of photoreceptors overlying SHRM is beyond the current study scope. However, we are currently evaluating in detail, the morphology of the outer retina overlying SHRM, as 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 in individuals with foveal SHRM, if the SHRM is not too broad, even when the central foveal SHRM is relatively thick, that person 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 might differ when the SHRM could be readily distinguished from underlying RPE and/or RPE elevation vs. 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 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 accurately assess 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 modality.

Scar developed more often in eyes with persistent SHRM. We have previously described baseline SHRM as a scar risk factor.[9] In the present report, we have extended these observations to show that when baseline SHRM persists to one and two years, there is a higher incidence of new scar formation. These data suggest that SHRM might not only be correlated with scar tissue development, but may also be a direct factor in its development. This may occur from new tissue being created or through remodeling already present tissue. Because both color fundus photography and FA diagnosed scar, while 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 CFP and FA images with SD-OCT images across successive study visits to better answer these questions.

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Abbreviations and Acronyms

SHRM	subretinal hyper-reflective material
VA	visual acuity
GA	geographic atrophy
CATT	Comparison of Age related Macular Degeneration Treatments Trials
TD	time domain
SD	spectral domain
OCT	optical coherence tomography
SE	standard error
NVAMD	neovascular age-related macular degeneration
VEGF	Anti-vascular endothelial growth factor
US	United States
AMD	age-related macular degeneration
CNV	choroidal neovascularization
RPE	retinal pigment epithelium
FA	fluorescein angiography
PRN	pro re nata (as needed)
IRB	Institutional Review Board
HIPAA	Health Insurance Portability and Accountability Act

CFP	color fundus photographs
ELM	external limiting membrane
EZ	ellipsoid zone
PED	pigment epithelial detachment

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Credit Roster for the Comparison of AMD Treatments Trials Clinical Centers (Ordered by Number of Patients Enrolled)

Certified Roles at Clinical Centers: Clinic Coordinator (CC), Data Entry Staff (DE), Participating Ophthalmologist (O), Ophthalmic Photographer (OP); Optical Coherent Tomography Technician (OCT), Principal Investigator (PI), Refractionist (R), Visual Acuity Examiner (VA)

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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).

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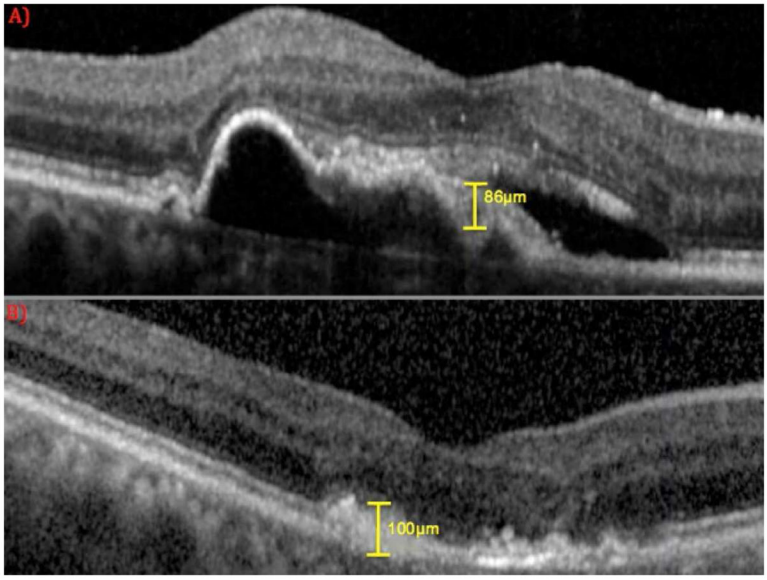

Figure 1.

A Average foveal subretinal hyper-reflective material thickness (86u) that is distinguishable from the underlying retinal pigment epithelium layer **B** Subretinal hyper-reflective material (100u) that is indistinguishable from underlying retinal pigment epithelium layer

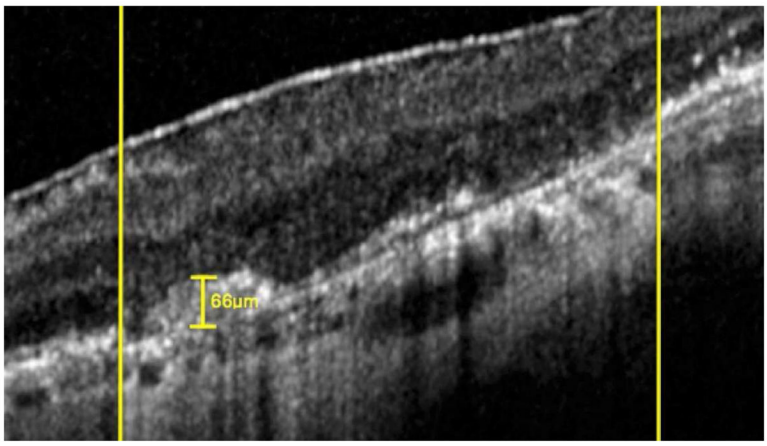

Figure 2.
Subretinal hyper-reflective material measurements over geographic atrophy (yellow parallel lines border area of geographic atrophy)

Table 1

SHRM at Baseline and During Follow-up

	Among all CATT Study Eyes		Among Eyes with SHRM at Baseline	
Follow-up Week	**Number of eyes**	**Number of eyes with SHRM (%)**	**Number of eyes**	**Number of eyes with SHRM at this Week (%)**
000	1184	908 (76.6%)	908	908 (100%)
004	1153	670 (58.1%)	886	599 (67.6%)
008	1128	630 (55.9%)	864	571 (66.1%)
012	1084	593 (54.7%)	834	542 (65.0%)
024	1053	533 (50.6%)	802	483 (60.2%)
052	1092	515 (47.2%)	833	463 (55.6%)
076	969	441 (45.5%)	738	397 (53.8%)
104	1024	468 (45.7%)	774	416 (53.8%)

SHRM = subretinal hyper-reflective material; CATT = Comparison of Age related Macular Degeneration Treatments Trials

Table 2

The Distribution of Measurements of SHRM on OCT (N=142)

		Among those with SHRM	
OCT measurements	**Scans with SHRM n**	**Median (1st quartile, 3rd quartile)**	**(Min, Max)**
Height at foveal center (microns)	43	86 (49, 120)	(30, 463)
Width at foveal center (microns)	43	917 (404, 1454)	(302, 4834)
Area at foveal center, (microns^2/1000)	43	85.1 (45.6, 328.9)	(18.9, 218.1)
Maximum height within center 1cm cube (microns)	64	120 (81, 171)	(33, 612)
Maximum width within center 1cm cube (microns)	65	916 (471, 1276)	(200, 4585)
Maximum height within entire scan (microns)	83	122 (84, 180)	(34, 612)
Maximum width within entire scan (microns)	83	851 (445, 1276)	(200, 4585)

*76 eyes with SD-OCT scans taken from week 56, and 66 of them had SD-OCT scans taken from week 104.

SHRM = subretinal hyper-reflective material; OCT = optical coherence tomography; SD-OCT = spectral domain optical coherence tomography

Table 3

The Association of SHRM Characteristics with Visual Acuity

SHRM Characteristics	N	Mean VA (SE), letters	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 1mm^2	21	65.3 (3.54)	
SHRM outside central 1mm^2	19	73.1 (3.45)	
SHRM distinguishable from RPE			0.14
No SHRM	59	73.5 (2.78)	
Yes distinguishable	40	66.9 (3.41)	
Not distinguishable	43	65.8 (2.71)	
Height of at foveal center (microns)			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 (microns)			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 1mm^2			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			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 (microns)			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 (microns)			0.03
0	59	73.5 (2.78)	
>0, ≤1000	54	69.9 (2.42)	
>1000	29	61.0 (4.21)	

[§]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.

SHRM = subretinal hyper-reflective material; VA = visual acuity; SE = standard error; RPE = retinal pigment epithelium

Table 4

The Association Between the Resolution of Baseline SHRM with VA Change from Baseline and the Development of Geographic Atrophy and Scar at Follow-up

Baseline SHRM resolved at	N[§]	Mean (SE) VA change, letters	P-value	N[§]	Geographic atrophy at follow-up (%)	P-value	N[§]	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 SHRM at baseline but without baseline geographic atrophy or scar

SHRM = subretinal hyper-reflective material; VA = visual acuity; SE = standard error