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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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Abstract

Purpose—To compare baseline characteristics, visual acuity (VA) and morphological outcomes between eyes with baseline hard exudates (HE) and all other eyes among patients with neovascular age-related macular degeneration (NVAMD) treated with anti-vascular endothelial growth factors (anti-VEGF).

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 either ranibizumab or bevacizumab. Ophthalmologists identified HE on color images in the study eye.

Main Outcome Measures—VA; scar; geographic atrophy; retinal thickness, fluid; and number of anti-VEGF injections.

Results—HE was present in 128 of 1185 (11%) study eyes at baseline, 77% within 1 disc diameter of the foveal center. Patients with study eye HE were more likely female (81% vs 60%; $p < 0.001$) and non-smokers (53% vs 42%; $p = 0.004$). Both groups had similar proportions of hypercholesterolemia and hypertriglyceridemia. At baseline, eyes with HE had worse VA (mean

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57 vs 61 letters; $p=0.003$), larger total lesion size (3.3 vs 2.4 DA; $p<0.001$), greater total foveal thickness (522 μ m vs 452 μ m; $p<0.001$), more retinal angiomatic proliferation (18% vs 10%; $p=0.009$) and sub-RPE 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 μ m vs −158 μ m; $p<0.001$). VA at year 2 was similar but retinas of eyes with baseline HE were thinner (267 μ m vs 299 μ m; $p=0.03$) and fewer eyes had sub-retinal fluid (23% vs 36%; $p=0.008$). HE was present in 19% of eyes at 1 year and 5% of eyes at 2 years. LIPC promoter SNP rs10468017 was not associated with NVAMD HE.

Conclusion—Eyes with HE have larger CNV lesions and more RAP. Their initially thicker retina rapidly becomes thinner on anti-VEGF treatment. HE is not significantly associated with hyperlipidemia. HE at baseline does not significantly influence VA, scar and GA outcomes in eyes with NVAMD treated with anti-VEGF. Few eyes have HE at year 2.

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 co-existing 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 is also not clear whether the presence of HE is associated with any of the systemic diseases that coexist in the elderly patients with NVAMD. Furthermore, little is known in these eyes about the relationship between baseline HE and subsequent visual acuity, other retinal morphological 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 morphological outcomes after two years of treatment with anti-vascular endothelial growth factor (anti-VEGF).

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 over 50 years and the study eye, one per patient, needed to have treatment-naïve NVAMD. Study eye visual acuity 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 OCT defined active neovascularization. History of systemic diseases such as hypertension, hypercholesterolemia, diabetes mellitus and hypertriglyceridemia were obtained from patient interview. Eyes were randomly assigned to treatment with ranibizumab or bevacizumab on a monthly or 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. CATT was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT00593450).

The CATT Fundus Photograph Reading Center at the University of Pennsylvania performed grading of color and FA images at baseline and years 1 and 2. Two trained certified readers independently assessed the images and discrepant results were adjudicated. Morphological features identified on these images included active leakage of fluorescein on FA, fibrotic scar, non-fibrotic scar, type of neovascularization (classic, occult and RAP), area of total CNV lesion (consisting of CNV and contiguous sequelae other than fluid), hemorrhage, blocked fluorescence contiguous with the CNV, serous pigment epithelial detachment (SPED), non-geographic atrophy, geographic atrophy, retinal pigment epithelial tear, and the presence or absence of any of these pathology 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 (IRF), subretinal fluid (SRF), and subretinal pigment epithelium (RPE) fluid, vitreomacular adhesions (VMA) and sub-retinal hyper reflective material (SHRM). In addition, the center point retinal thickness, subretinal fluid thickness, and sub-retinal 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 while total foveal thickness at the foveal center in addition to retinal thickness also included subretinal fluid, the 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

Hard exudates at baseline, 1 year, and 2 years were graded from stereo color and red-free digital images by an ophthalmologist (ED). Hard exudates were identified as white or yellowish white waxy deposits with sharp margins on color retinal images, arranged as individual dots, confluent patches, partial or complete rings surrounding zones of retinal edema and fluid. (Figure 1) The red-free image enhanced the discrete nature of the hard exudates 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 to <1.00 DA) and severe (≥ 1.00 DA). The location of HE within 1 disc diameter of the foveal center was recorded. Hard exudates categorized as "suspect" by the ophthalmologist were reviewed by two retina specialists (BK and JG) to reach a final consensus. A random sample of images containing definite HE, suspect HE and no HE was graded independently by one of the retinal specialists (BK) and the ophthalmologist (ED) to assess agreement on definitive HE.

Statistical Methods

Statistical comparison of baseline characteristics and outcomes at Year 1 and Year 2 between eyes with and without baseline HE was performed. The two group independent t-test was used to compare means of continuous variables and Fisher's exact test was used for comparison of categorical variables. Due to 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 v9.2 (SAS Institute, Inc).

Results

Baseline Characteristics

Baseline characteristics are listed in Table 1. Hard exudates were 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%, and severe in 11% of eyes. The distributions at baseline of age, 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 females (81% vs 60%, $p<0.001$) and non-smokers (53% vs 42%, $p=0.004$). Eyes with baseline HE had worse baseline mean visual acuity (VA) (57 vs 61 letters, $p=0.003$), had larger CNV area (2.2 Disc Area (DA) vs 1.7 DA, $p=0.009$) and total CNV lesion area (3.3DA vs 2.4 DA, $p<0.001$) than eyes without baseline HE. Eyes with HE were more likely to have retinal angiomatous proliferation (18% vs 10%, $p=0.009$) and SPED on FA (13% vs 4%, $p<0.001$). Although mean retinal thickness was similar between the two groups (220 μ vs 219 μ , $p=0.92$), the mean total thickness at the fovea was greater in eyes with HE (522 μ m vs 452 μ m; $p<0.001$). More eyes with HE had sub-RPE fluid than eyes without HE (65% vs 45%, $p<0.001$) while cystoid spaces within the retina⁸ (80% vs 74%, $p=0.20$) and subretinal fluid (83% vs 82%, $p=0.90$) were similar in both groups. Cystoid macular edema detected in fluorescein angiograms as a petaloid pattern was not significantly associated with HE, The LIPC promoter SNP rs10468017 was not associated with presence of HE at baseline.

Year 1 outcomes

Mean visual acuity was similar in both groups at 1 year (66 letters vs 68 letters, $p=0.21$). Although the retinal thickness was similar (152 μ m vs 158 μ m, $p=0.33$) the total thickness at the foveal center was less in eyes that had HE at baseline (263 μ m vs 295 μ m, $p=0.01$) and there was a larger change in total thickness at the foveal center from baseline (−266 μ m vs −158 μ m, $p<0.001$). 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 to eyes with no baseline HE. Intraretinal fluid (46% vs 47%, $p=0.85$) was not different between the two 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 PRN treatment, both groups required a similar mean number of injections (7 vs 7; $p=0.89$). (Table 2)

Year 2 outcomes

Mean visual acuity was similar in both groups at 2 years (65 letters vs 68 letters, $p=0.20$). Although the retinal thickness remained similar (156 μ m vs 160 μ m, $p=0.56$) the total foveal thickness at the foveal center was less in eyes that had HE at baseline (267 μ m vs 299 μ m, $p=0.03$) and there was a larger change in total foveal thickness from baseline (−265 μ m vs

–151 μ m, $p<0.001$). Absence of any fluid on OCT was similar in both groups at 2 years (29% vs 25%, $p=0.35$), and there was no significant difference in the percentages with intra-retinal fluid (60% vs 50%, $p=0.09$) or sub-RPE fluid (35% vs 36%, $p=0.92$). However, subretinal fluid at 2 years was seen less frequently in eyes that had baseline HE (23% vs 36%, $p=0.008$). RPE tears were similar in both groups (1.8% vs 1.5%, $p=0.69$). Both groups required a similar number of PRN injections in Year 2 (6.4 vs 6.4; $p=0.86$). At 2 years, HE was present in 6 eyes (5%) of 112 eyes that had HE at baseline. (Table 3)

The mean total thickness at the foveal center of eyes with and without HE from baseline through two years is shown in Figure 2. Eyes with HE start with greater retinal thickness than eyes without HE but at four weeks become slightly thinner, are thinner still at 1 year and remain thinner through two years.

HE within 1 DD of foveal center vs HE outside 1 DD of foveal center at baseline

Among eyes that had HE at baseline, 99 eyes (77%) had HE within 1 DD of the foveal center while the remaining 29 (23%) had HE located only outside this area. Baseline characteristics and year 1 outcomes were similar between the two groups. Year 2 outcomes were similar except that eyes having HE located with 1DD of the foveal center gained fewer letters (5.6 vs 13.8 letters, $p=0.04$).

Presence or Absence of HE at 1 year

Among 128 eyes that had HE at baseline, 23 eyes (18%) had HE at Year 1. Baseline characteristics were similar among eyes with or without HE at Year 1, except that eyes with HE at 1 year had a reduced total foveal thickness at the foveal center at baseline (178 μ m vs 230 μ m, $p=0.04$). At year 1 eyes with HE at 1 year had a greater retinal thickness (181 μ m vs 145 μ m, $p=0.03$), a greater proportion with sub-RPE fluid (39% vs 15%, $p=0.02$) and a greater proportion with fluorescein leakage (70% vs 39%, $p=0.01$). At year 2, eyes with HE at 1 year continued to have greater retinal thickness than eyes without HE at 1 year (208 μ m vs 145 μ m, $p=0.007$), and a greater proportion had intraretinal fluid (84% vs 54%, $p=0.02$), sub-RPE fluid (58% vs 30%, $p=0.03$), and fluorescein leakage (50% vs 18%, $p=0.01$). Eyes with HE at 1 year had more anti-VEGF intravitreal injections (7.8 vs 5.6, $p=0.04$) during Year 2

Discussion

Our findings demonstrate that the presence of hard exudate in eyes with treatment naïve NVAMD is associated with greater total foveal thickness (retina+SRF+SHRM+RPE+sub-RPE material and fluid) but is not associated with sensory retinal thickness. HE within one disc diameter of the foveal center is used as a surrogate marker for clinically significant macular edema (CSME) in diabetic retinopathy screening projects.^{1,2} In diabetic maculopathy HE within one disc diameter of the macular center detects CSME with 94% sensitivity and HE anywhere in the macular region predicted CSME with 89% sensitivity.³ Although our study was not designed to evaluate the prediction of HE for CSME, the presence of HE anywhere in the macular area of eyes with naïve NVAMD correlated well with pronounced sub-RPE thickening but not with thickening of the sensory retina making it

useful for detecting fluid and material under the RPE in NVAMD. The appearance of HE in the fundus of patients with early or intermediate AMD being followed up by a primary physician using only a hand held direct ophthalmoscope should dictate a quick referral to the retina specialist for a more extensive examination with indirect ophthalmoscopy and OCT, leading up to appropriate treatments.

The macular edema in CATT study eyes with HE at enrolment was comprised predominantly of both intraretinal and subretinal fluid even though the primary source of the fluid was likely from choroidal neovascularization with only around 11% of the CATT cohort having RAP lesions.⁹ However unlike these two types of fluid sub-RPE fluid was not distributed similarly between the two groups (with and without HE) with more eyes that had HE having sub-RPE fluid suggesting that leakage from occult lesions was the primary source of fluid in eyes with HE. Unlike the CSME in diabetes which is usually associated with large cystic accumulations of intra-retinal fluid, presumably because the vascular pathology is located within the sensory retina, the CATT cohort patient study eyes with HE were not associated with petaloid patterns in fluorescein angiography (angiographic cystoid macular edema).¹⁰ HE related to diabetic macular edema is derived from retinal vasculature and is located in the inner layers of the retina down to the outer plexiform layer at its deepest level. This is in contrast to exudates from AMD that arise from subretinal or sub RPE lesions or RAP and thus may develop preferentially in different locations compared to DME.

VA and morphological outcomes did not differ with the location of HE at baseline other than VA gain at year 2 was much less in eyes that had HE located within 1 DD of the foveal center when compared to HE being present external to this area.

Our study results show that many of the associations of HE with serum lipids, comorbidities, and outcomes after treatment observed in patients with DME do not hold for patients with NVAMD. In observational, but not interventional studies, it has been reported that patients whose eyes have HE and DME have high levels of serum cholesterol, low density lipoproteins, total cholesterol: HDL ratio and triglycerides and low levels of HDL, when compared to those with DME without HE.^{11–14,15–17} In contrast to these observations we found no association between hypercholesterolemia or hypertriglyceridemia and HE in the eyes of patients enrolled in CATT.

Other researchers have suggested that the causal pathways for cardiovascular disease and AMD could share similar risk factors.^{18,19} Both diabetes and hypertension have been reported to be strong risk factors for NVAMD.^{20–23} Although the presence of HE might indicate a severe form of diabetic and hypertensive retinopathy, the proportion of patients with diabetes or hypertension in the group with HE was similar to the proportion without HE. However, the CATT study eligibility criteria excluded patients who had any concurrent intraocular condition such as diabetic retinopathy that might require medical or surgical intervention during the two years of the study or, that could likely contribute to loss of vision over the two year follow-up period. Therefore, patients with other signs of non-proliferative retinopathy who might be more likely to have HE generally were not enrolled, which could obscure any true association of these diseases with HE. We did however find that the presence of HE was significantly associated with not having a history of myocardial

infarction (MI). A large retrospective cohort study reported that subjects with NVAMD have lower rates of MI and another study reported that the history of coronary artery disease was a risk factor for PCV (polypoidal choroidal vasculopathy) but was a protective factor for NVAMD. However, the presence of HE was not assessed in these two studies.^{24,25}

Our study shows that fluid resolved more quickly with a larger reduction in retinal thickness after anti-VEGF therapy in the eyes that had baseline HE compared to eyes that did not have baseline HE. These findings are consistent with the results of a randomized interventional ranibizumab DME trial in which eyes with macular HE at baseline had a 31 μ m (95% CI, 8–53 μ m) greater reduction in thickness than eyes without any HE.²⁶ DME develops when macromolecules such as lipoproteins and ions leak from retinal capillaries into the extravascular space of the retina causing an oncotic influx of water into this space resulting in retinal edema. As this edematous fluid is resorbed by relatively normal capillaries, the concentration of lipoproteins increases, leading to their precipitation and the formation of hard exudates. The deposition of these HE often occur at the border between abnormal and more normal retinal capillaries.^{27,28} In NVAMD, in eyes without early retinal angiomatous proliferation, fluid leakage would be derived mostly from choroidal neovascularization and HE associated NVAMD eyes, apart from having large amounts of intra and subretinal fluid, are also observed to have more sub-RPE fluid when compared to eyes without HE. It is also possible that the process of fluid absorption had already begun in the eyes that had baseline HE and the treatment with anti-VEGF drugs accelerated this process resulting in larger proportion of these eyes having complete resolution of all fluid and a more rapid decrease in retinal thickness.

We found that among eyes that had HE at baseline only a small percentage of eyes have HE at the end of the 2 year anti-VEGF treatment period. In contrast, in a short term study with a 6 month follow up, there were increasing amounts of HE in eyes with DME that were treated with anti-VEGF therapy suggesting that the non-lipid fluid components resolve first followed by resolution of the HE.²⁹ A longer follow up study however found that after 6 months, the percentage of eyes without HE increased from around 20% to 60% at the end of 2 years.³⁰

A retrospective study done before the era of anti-VEGF treatment for NVAMD that specifically compared eyes with and without HE in NVAMD reported that ill-defined neovascular lesions were significantly associated with the presence of HE.³¹ This association, although not statistically significant, was also observed in another study that suggested that the presence of HE in NVAMD was related to large lesion size and occult leakage.³² CNV and the total CNV lesion areas (comprising the CNV and confluent hemorrhage, blocked fluorescence, serous pigment epithelial detachments SPED) in CATT were larger in eyes that had hard exudates. Occult type of CNV was also more common in eyes having HE although this was not statistically significant. Eyes with HE had more angiographically observed SPED, a finding corroborated by the other study. Retinal angiomatous proliferation is known to be a risk factor in the development of geographic atrophy (GA) and, although eyes with HE had more RAP lesions and more SPED, the development of GA was similar in eyes with and without HE. This is probably because a

RAP lesion as a whole appears to be a risk factor for the development of GA while individual components of RAP such as HE or SPED do not seem to carry that risk.

Categorization of eyes with and without HE at year 1 from among those eyes that had HE at baseline did not show any significant difference in visual outcomes at 2 years. In our study visual acuity outcomes in eyes that had HE at baseline were similar to a DME ranibizumab treated study which did not find the presence of baseline HE to be a prognostic indicator of a poor VA outcome.³⁰ Though eyes with HE had thicker retinas, more fluid and larger CNV lesions than eyes that did not have HE, the VA outcome after anti-VEGF treatment was not much different between the two groups. The ETDRS reported that severe hard exudates are the strongest risk factor for the development of subretinal fibrosis.³³ HE in NVAMD did not appear to influence the outcome of scar or GA.

Several studies have reported that lipids may play an important role in AMD.^{34,35} A genome-wide association study found a significant association between advanced AMD and hepatic lipase (*LIPC*), the gene encoding hepatic triglyceride lipase.^{36,37} A meta-analysis showed that *LIPC* rs10468017 variant is associated with a reduced risk of advanced AMD.³⁸ Since hard exudates are composed primarily of lipid material, we investigated whether there could be an association between the *LIPC* promoter SNP rs10468017 and HE in eyes with NVAMD; our results show that there was no significant association. There are no comparable studies in the current literature on studies investigating SNPs and HE in diabetes.

A limitation of our study is that we performed many statistical comparisons between eyes with and without HE for various outcomes without consideration for multiple testing and other possible confounders. The findings from these exploratory secondary data analyses need to be validated in future studies. The sample size in the HE group may also limit our statistical power to detect small difference between eyes with and without HE.

In summary, the presence of retinal HE in eyes with treatment naïve NVAMD is a sign of retinal thickening and sub-RPE macular fluid. Anti-VEGF treatment resolves subretinal and sub-RPE fluid better and faster in eyes that had HE at baseline when compared with eyes that did not have HE at baseline. Only a small number of eyes have HE at the end of 2 years. HE is not significantly associated with VA outcomes or the development of scar or GA. Unlike HE in DME, they do not appear to be significantly associated with hypercholesterolemia or hypertriglyceridemia. There is no significant association between HE and *LIPC* promoter SNP rs10468017.

Anti-VEGF treatment resolves . . . fluid better and faster in eyes that had HE at baseline when compared with eyes that did not have HE at baseline

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Figure 1.

[A] Baseline images. A1=Color image with a small amount of hard exudates (yellow arrow), A2 Fluorescein angiogram showing leakage and A3 Time domain OCT with sub-retinal and sub-RPE fluid (red arrows). [B] Year 1 images. B1 = Color image with increased amounts of hard exudates and B2 Fluorescein angiogram showing leakage. [C] Year 2 images. C1 Color image showing increased amounts of hard exudates and C2 Fluorescein angiogram showing leakage. The top green line in C1 corresponds to the spectralis OCT scan in C3 showing the hard exudates on OCT (red arrows) occupying the lower portion of the inner retina and some hard exudates in the sub-retinal space. The bottom blue line in C1 corresponds to C4 where the spectralis OCT shows sub-RPE lesion and fluid (fibrovascular PED) (red arrow) and intraretinal cystoid spaces (green arrow).

Figure 2. Mean total foveal thickness in μm (retinal thickness plus subretinal fluid and lesion plus RPE and sub RPE fluid and lesion thickness) on OCT through 2 years between the two groups.

Table 1

Baseline Characteristics by presence of hard exudates

		Hard Exudate at Baseline		
Characteristic	Value	Present (n=128)	Absent (n=1057)	P-Value
Age (Years)	Mean (SD)	78.2 (8.4)	79.4 (7.4)	0.09
Sex	Female	103 (80.5%)	629 (59.5%)	<0.001
Myocardial Infarction	Yes	7 (5.5%)	133 (12.6%)	0.02
Congestive Heart Failure	Yes	4 (3.1%)	69 (6.5%)	0.17
Hypertension	Yes	87 (68.0%)	736 (69.6%)	0.69
Diabetes Mellitus	Yes	16 (12.5%)	191 (18.1%)	0.14
Hypercholesterolemia	Yes	64 (50.0%)	612 (57.9%)	0.09
Hypertriglyceridemia	Yes	10 (7.8%)	146 (13.8%)	0.07
Cigarette Smoking	Never	68 (53.1%)	439 (41.5%)	0.004
	Current	15 (11.7%)	86 (8.1%)	
	Former	45 (35.2%)	532 (50.3%)	
Drug	Ranbizumab	70 (54.7%)	529 (50.0%)	0.35
	Bevacizumab	58 (45.3%)	528 (50.0%)	
Regimen	Monthly for 2 yrs	36 (28.1%)	282 (26.7%)	0.88
	Monthly Yr 1, PRN Yr 2	27 (21.1%)	242 (22.9%)	
	PRN for 2 yrs	65 (50.8%)	533 (50.4%)	
Visual Acuity in Study Eye	<20/320	18 (14.1%)	85 (8.0%)	0.02
	20/200–20/320	36 (28.1%)	220 (20.8%)	
	20/100–20/160	43 (33.6%)	424 (40.1%)	
	20/50–20/80	31 (24.2%)	328 (31.0%)	
	Mean (SD)	57.2 (14.8)	60.9 (13.3)	0.003
Type of choroidal neovascularization	Classic	21 (16.4%)	241 (23.4%)	0.09
	Occult	88 (68.8%)	608 (58.9%)	
	Mixed	19 (14.8%)	183 (17.7%)	
Choroidal neovascularization (CNV) Area	Mean (SD)	2.2 (2.0)	1.7 (1.7)	0.009
Total choroidal neovascularization Area *	Mean (SD)	3.3 (3.3)	2.4 (2.4)	<0.001
Retinal Angiomatous Proliferation	Yes	23 (18.1%)	103 (9.8%)	0.009
Hemorrhage (Associated with the Lesion)	< 1 DA	73 (57.0%)	538 (51.9%)	0.22
	< 2 DA	9 (7.0%)	50 (4.8%)	
	> 2 DA	7 (5.5%)	47 (4.5%)	
Geographic Atrophy (GA)	Yes	6 (4.7%)	76 (7.2%)	0.36
Scar	Yes	4 (3.1%)	42 (4.0%)	0.81
Pathology in Fovea Center	No Pathology	1 (0.8%)	0 (0.0%)	0.09
	Fluid Only	32 (25.0%)	283 (26.8%)	
	CNV	75 (58.6%)	613 (58.0%)	

		Hard Exudate at Baseline		
Characteristic	Value	Present (n=128)	Absent (n=1057)	P-Value
	Scar	0 (0.0%)	7 (0.7%)	
	GA	1 (0.8%)	0 (0.0%)	
	Hemorrhage	12 (9.4%)	81 (7.7%)	
	Other	7 (5.5%)	73 (6.9%)	
Angiographic cystoid macular edema (CME) (Petaloid Pattern)	CME	15 (11.8%)	77 (7.7%)	0.21
	IRF without CME	86 (67.7%)	680 (67.7%)	
	No IRF	26 (20.5%)	247 (24.6%)	
Serous pigment epithelial detachment	Yes	16 (12.5%)	46 (4.4%)	<0.001
Retinal Thickness (µm)	Mean (SD)	220.3 (107.7)	219.3 (107.7)	0.92
Total foveal thickness (µm) **	Mean (SD)	521.6 (224.1)	452.3 (180.5)	<0.001
Intra-retinal fluid	Yes	102 (79.7%)	785 (74.3%)	0.20
Sub-retinal fluid	Yes	106 (82.8%)	864 (81.8%)	0.90
Sub-RPE fluid	Yes	82 (65.1%)	491 (47.3%)	<0.001
Vitreo-macular adhesion/traction	Yes	17 (13.7%)	126 (12.7%)	0.78
Sub-retinal hyper-reflective material	Yes	102 (81.0%)	806 (77.4%)	0.43
LIPC Genotype	CC	52 (61.9%)	388 (51.9%)	0.22
	CT	29 (34.5%)	315 (42.1%)	
	TT	3 (3.6%)	45 (6.0%)	

* Total CNV Area includes CNV and its sequelae such as hemorrhage, blocked fluorescence, serous pigment epithelial detachment,

** Total foveal Thickness = (Retina + Sub-retinal fluid + Sub-retinal Hyperreflective material + retinal pigment epithelium (RPE) + Sub-RPE fluid and material).

Table 2

Year 1 Outcomes by Presence of Hard Exudate

		Hard Exudate at Baseline		
Year 1 Outcomes		Present (n=120)	Absent (n=986)	p-value
Visual acuity, letters	Mean (SD)	66.3 (19.2)	68.2 (17.6)	0.27
Visual acuity change from baseline, letters	Mean (SD)	9.1 (14.6)	7.1 (14.7)	0.15
Hemorrhage contiguous with lesion	Yes	4 (3.5%)	17 (1.8%)	0.27
Serous pigment epithelial detachment	Yes	1 (0.8%)	21 (2.1%)	0.72
Total area of CNV lesion, DA	Mean (SD)	3.11 (3.12)	2.65 (2.64)	0.14
Change of total area of CNV lesion from baseline, DA	Mean (SD)	-0.17 (2.11)	0.26 (2.30)	0.07
Retinal thickness(μm)	Mean (SD)	152.2 (69.8)	157.8 (58.5)	0.33
Total foveal Thickness (μm) *	Mean (SD)	262.6 (139.9)	295.4 (135.2)	0.01
Change in total foveal thickness from baseline. (μm)	Mean (SD)	-265.7 (235.4)	-158.2 (169.2)	<0.001
Intra-retinal fluid	Yes	55 (46.2%)	461 (47.4%)	0.85
Sub-retinal fluid	Yes	16 (13.4%)	308 (31.7%)	<0.001
Sub-RPE fluid	Yes	23 (19.3%)	311 (32.5%)	0.003
No fluid on OCT	Yes	53 (44.5%)	275 (28.5%)	<0.001
Leakage on FA	Yes	50 (45.0%)	429 (46.0%)	0.92
Pathology in fovea center	No pathology	31 (25.8%)	182 (18.5%)	0.28
	Fluid Only	8 (6.7%)	78 (7.9%)	
	CNV	22 (18.3%)	237 (24.0%)	
	Scar	16 (13.3%)	186 (18.9%)	
	GA	2 (1.7%)	20 (2.0%)	
	Non-GA	21 (17.5%)	130 (13.2%)	
	Hemorrhage	0 (0.0%)	3 (0.3%)	
	RPE tear	2 (1.7%)	8 (0.8%)	
	Other	18 (15.0%)	142 (14.4%)	
RPE tear	Yes	4 (3.5%)	14 (1.5%)	0.11
Geographic atrophy	Yes	21 (18.6%)	153 (16.1%)	0.50
Scar	Yes	37 (32.7%)	342 (35.7%)	0.60
Sub-retinal hyper reflective material	Yes	55 (46.2%)	460 (47.8%)	0.77
Mean number of injections, PRN only	Mean (SD)	7.2 (3.1)	7.3 (3.3)	0.89

OCT: Optical coherence tomography, FA: Fluorescein Angiogram, PRN: Pro re nata, CNV: Choroidal neovascularization, GA: Geographic Atrophy, RPE: Retinal pigment epithelium.

* Total foveal Thickness = (Retina + Sub-retinal fluid + Sub-retinal Hyperreflective material + retinal pigment epithelium (RPE) + Sub-RPE fluid and material).

Table 3

Year 2 Outcomes by Presence of Hard Exudates

		Hard Exudates at Baseline		
Year 2 Outcomes		Present (n=112)	Absent (n=922)	p-value
Visual acuity, letters	Mean (SD)	65.2 (20.3)	67.5 (18.1)	0.20
Visual acuity change from baseline, letters	Mean (SD)	7.6 (17.8)	6.2 (16.4)	0.40
Hemorrhage contiguous with lesion	Yes	1 (0.9%)	29 (3.2%)	0.36
Serous pigment epithelial detachment	Yes	3 (2.7%)	22 (2.4%)	0.74
Total area of CNV lesion, DA	Mean (SD)	3.70 (3.49)	3.19 (3.08)	0.16
Change of total area of CNV lesion from baseline, DA	Mean (SD)	0.27 (1.98)	0.82 (2.68)	0.01
Retinal thickness(μm)	Mean (SD)	156.0 (92.0)	160.5 (73.7)	0.56
Total foveal thickness(μm) *	Mean (SD)	267.3 (141.9)	299.2 (142.7)	0.03
Change in total foveal thickness from baseline.(μm)	Mean (SD)	-265.3 (243.2)	-151.4 (180.0)	<0.001
Intra-retinal fluid	Yes	66 (59.5%)	460 (50.4%)	0.09
Sub-retinal fluid	Yes	26 (23.4%)	328 (36.0%)	0.008
Sub-RPE fluid	Yes	39 (35.1%)	325 (36.1%)	0.92
No fluid on OCT	Yes	32 (28.8%)	225 (24.7%)	0.35
Leakage on FA	Yes	25 (23.6%)	255 (28.8%)	0.30
Pathology in fovea center	No pathology	26 (23.2%)	178 (19.3%)	0.39
	Fluid Only	5 (4.5%)	28 (3.0%)	
	CNV	12 (10.7%)	165 (17.9%)	
	Scar	22 (19.6%)	207 (22.5%)	
	GA	6 (5.4%)	57 (6.2%)	
	Non-GA	24 (21.4%)	165 (17.9%)	
	Other	17 (15.2%)	122 (13.2%)	
RPE tear	Yes	2 (1.8%)	14 (1.5%)	0.69
Geographic atrophy	Yes	29 (26.6%)	187 (20.7%)	0.17
Scar	Yes	45 (41.3%)	394 (43.3%)	0.76
Sub-retinal hyper reflective material	Yes	55 (49.5%)	412 (46.1%)	0.55
Mean number of injections, PRN only	Mean (SD)	6.4 (3.6)	6.4 (3.8)	0.86

OCT: Optical coherence tomography, FA: Fluorescein Angiogram, PRN: Pro re nata, CNV: Choroidal neovascularization, GA: Geographic Atrophy, RPE: Retinal pigment epithelium.

* Total foveal Thickness = (Retina + Sub-retinal fluid + Sub-retinal Hyperreflective material + retinal pigment epithelium (RPE) + Sub-RPE fluid and material).