HHS Public Access

Author manuscript

Ophthalmology. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Ophthalmology. 2015 June ; 122(6): 1203–1211. doi:10.1016/j.ophtha.2015.02.031.

Influence of the Vitreomacular Interface on Treatment Outcomes in the Comparison of AMD Treatments Trials (CATT)

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Abstract

Objective—To assess the association of the vitreomacular interface (VMI) with outcomes of eyes treated with anti-VEGF drugs for neovascular age-related macular degeneration (AMD).

Design—Prospective cohort study within a multicenter randomized clinical trial.

Participants—Patients enrolled in the Comparison of AMD Treatments Trials.

Methods—Treatment was assigned randomly to either ranibizumab or bevacizumab and to 3 different regimens for dosing over a two-year period. Masked readers at a reading center assessed optical coherence tomography (OCT) scans at baseline and follow-up for vitreomacular traction (VMT) and adhesion (VMA), fluid and central thickness. Visual acuity (VA) was measured by masked, certified examiners.

Main Outcome Measures—VA and anatomical features at baseline, 1 and 2 years and number of treatments.

Results—At baseline, 143 (12.8%) patient eyes had VMT or VMA. Compared to those with neither (N=972), patients with VMT or VMA were younger (mean (SE): 75.5 ±0.6 versus 79.7 ± 0.24 years, p<0.0001), more likely to be male (52.4% versus 36.2%, p=0.0003), cigarette smokers (68.5% versus 55.3%, p=0.003), and to have subretinal fluid on OCT (86.7% versus 81.0%, p=0.047). VMI status was not associated with VA at baseline or follow-up. Among eyes treated as needed (PRN, n=598) and followed for 2 years (n=516), the mean number of injections over 2

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

ClinicalTrials.gov number, NCT00593450

years was 15.4 ±0.9 for eyes having VMT at baseline or during follow-up (n=60), 13.8 ±0.7 for eyes with VMA at baseline or follow-up (n=79), and 12.9 ±0.4 (p=0.02) for eyes without VMT or VMA (n=377). In addition, the mean number of injections in eyes treated PRN increased from 13.0 ±0.3 when VMT was not observed, to 13.6 ±1.3 when observed once, to 17 ±1.2 when observe more than once during follow-up. At 2 years, geographic atrophy developed in a lower percentage of eyes with VMT or VMA at baseline (11.7%) than with neither condition (22.5%, p=0.005).

Conclusions—VMT and VMA were infrequent in eyes in the CATT. At baseline and follow-up, VMT or VMA were not associated with VA. Eyes with VMT or VMA treated PRN required on average 2 more injections over 2 years.

The role of the vitreomacular interface (VMI) in the pathophysiology and treatment of neovascular age-related macular degeneration (AMD) has generated much recent interest. In retrospective and prospective observational case series, a higher incidence of vitreomacular adhesion (VMA) has been reported in eyes with neovascular AMD compared to eyes with non-neovascular AMD.[1-3] In a paired eye study, VMA was observed more frequently in eyes with neovascular AMD as compared to the fellow non-neovascular AMD eye that served as a control.[4] Some investigators have also observed that VMA occurs at the vitreoretinal interface overlying the choroidal neovascularization (CNV).[1, 2, 4] VMA also influences treatment and outcomes in neovascular AMD; the absence of VMA has been associated with slightly better VA, [5, 6] and eyes with VMA may require more frequent dosing compared to neovascular AMD eyes without VMA.[5, 6] This combined body of evidence suggests that VMA may have a role in the pathogenesis and management of CNV.

The purpose of the our study was to assess the relationship of the VMI to treatment frequency in neovascular AMD, as well as to visual acuity and anatomical outcomes in the Comparison of Age related Macular Degeneration Treatments Trials (CATT),[7] one of the largest prospective treatment trials for neovascular AMD conducted to date.

Methods and Materials

Study Participants, Inclusion and Exclusion Criteria

Between February 2008 and December 2009, CATT enrolled a total of 1,185 patients through 43 clinical centers in the United States.[7] Institutional Review Board approval was obtained at each site and written informed consent was obtained from each patient. The study adhered to the tenets of the Declaration of Helsinki and was performed in compliance with the Health Insurance Portability and Accountability Act.

Inclusion criteria included: age > 50 years, presence or previously untreated active CNV secondary to AMD in the study eye, and visual acuity between 20/25 and 20/320 (letter score of 23 to 82 on electronic visual acuity testing, EVA). Both leakage on fluorescein angiography and OCT (intraretinal, subretinal, or subRPE fluid) were required to establish the presence of active FCNV. CNV or its sequelae (fluid, hemorrhage, or pigment epithelial detachment [PED]) were required to be under the center of the macula. The total area of fibrosis could not exceed 50% of the total lesion. One or more drusen (>63 microns) had to be present in either eye or evidence of late AMD had to be present in the fellow eye.

Exclusion criteria included prior treatment for CNV in the study eye, retinal pigment epithelial tear, fibrosis or geographic atrophy in the center of the macula, or CNV deemed related to etiologies other than AMD. Patients with any concurrent ocular conditions that could require medical or surgical intervention during the 2 years of the study were also excluded.

Treatment

At baseline, patients were randomly assigned to monthly ranibizumab, monthly bevacizumab, as-needed ranibizumab, or as-needed bevacizumab. Ranibizumab was dosed at 0.5 mg and bevacizumab was dosed at 1.25 mg, both in volumes of 0.05 ml. At the end of year 1, patients in the monthly dosing regimen retained their original medication assignment, but were re-randomized to monthly or as-needed dosing for year 2. All patients randomized to the as-needed dosing regimen were treated whenever the investigator noted fluid on OCT, new or persistent hemorrhage on exam, decreased visual acuity, or leakage on fluorescein angiography.

OCT Scan Acquisition

All OCT scans were acquired by CATT-certified OCT technicians, using Stratus OCT systems (Carl Zeiss Meditec, Dublin, CA) throughout year 1 and Stratus or spectral domain OCT systems (Cirrus, Carl Zeiss Meditec, Dublin, CA or Spectralis, Heidelberg Engineering, Carlsbad, CA) in year 2 following study-specific imaging protocols.[8, 9] Patients were followed every four weeks for 2 years. OCT scans were obtained every 4 weeks and assessed to determine whether patients assigned to the variable dosing schedule required retreatment. For those patients assigned to the monthly dosing regimen, OCT scans were obtained at baseline, and at visits occurring on weeks 4, 8, 12, 24, 52, 76, and 104.

OCT-Based Assessment of VMI

All OCT images were evaluated for VMA, intraretinal fluid (IRF) and subretinal fluid (SRF). Vitreomacular attachment was defined as vitreous attachment and focal separation from the inner retina within a 3 mm diameter centered at the middle of the fovea. If a VMA was identified, the scan was then screened for the presence of any associated deformation of the central 1 mm of the macula, which signified the presence of vitreomacular traction (VMT). Henceforth, in this paper, the term “VMA” means vitreomacular attachment without traction. Because the CATT OCT image acquisition protocol did not include an optic nerve scan, it was not possible to assess whether eyes with VMA developed a PVD.

Visual Acuity Testing Procedures

A CATT-certified visual acuity technician determined, at each visit, best-corrected visual acuity (BCVA) according to an ETDRS protocol. Visual acuity testing was performed with the Electronic Visual Tester (EVA)[10] and VA score was calculated as number of letters read correctly.

Statistical Analysis

We first determined the association of baseline VMA or VMT with baseline characteristics, year 1 and year 2 outcomes. For this analysis, 3 hierarchical groups were initially created based on presence/absence of VMT or VMA at baseline. These groups were baseline VMT present, baseline VMA present, and neither VMT nor VMA present at baseline. Only 20 (1.8%) of 1115 patient eyes had baseline VMT. As a result, VMT was combined with VMA and this combined VMT/VMA group was compared to patient eyes with neither VMT nor VMA at baseline for differences in baseline characteristics, year 1 outcomes, year 2 outcomes, and the number of treatments using analysis of variance for continuous measures, and Fisher exact test for categorical measures.

We also determined the association of change in VMI status with 2 year outcome among patients treated “as-needed” throughout the 2 year follow-up period. Based on the presence/absence of VMT or VMA at both baseline and during 2 years follow-up, 3 hierarchical groups were created to capture VMI status. These groups were VMT at any time, VMA at any time, and neither VMT nor VMA at any time. Comparisons of baseline characteristics and year 2 outcomes among these 3 groups were performed on patients receiving as-needed treatment throughout the 2 years of the study. The as-needed treatment groups allowed for more direct assessment of the effect of VMI on required dosing frequency over time as these patients underwent monthly OCT. In addition, the associations of VMT frequency with change in visual acuity from baseline, change in OCT central thickness from baseline, and the number of treatments in 2 years were evaluated in patients receiving as-needed treatment using Spearman correlation coefficients.

Results

Analysis by Baseline VMI Status

Among 1185 CATT participants, baseline VMI status could not be determined in 70 (5.9%) participants due to missing OCT images or poor image quality and were excluded from the statistical analysis. Among 1115 participants with baseline VMI status known, 20(1.8%) patient eyes had VMT at baseline, and 123 (11.0%) eyes had VMA at baseline for a total of 143 (12.8%) patient eyes with baseline VMT or VMA. The comparison of baseline characteristics between eyes with versus those without baseline VMT or VMA are shown in Table 1. Compared to the patients with neither VMT nor VMA (N=972), patients with VMT or VMA were younger (mean ± SE: 75.5±0.6 versus 79.7 ± 0.24 years respectively, $p<0.0001$), included a lower percentage of women (47.6% versus 63.8% respectively, $p=0.0003$), included a higher percentage of former or current cigarette smokers (68.5% versus 55.3% respectively, $p=0.003$), and showed a higher percentage of having subretinal fluid on OCT (86.7% versus 81.0% respectively, $p=0.047$). There was a trend towards increased total foveal thickness in the eyes with baseline VMT or VMA, compared to eyes with neither VMT nor VMA (481μ vs. 452μ), but this difference did not reach statistical significance ($p=0.08$).

The comparisons of year 1 and year 2 outcomes between the baseline VMI groups are shown in Table 2. There was no difference in visual acuity at either year 1 or year 2 between

eyes with vs. without baseline VMT or VMA (all p≥0.31, Table 2). However, there were some anatomical differences. The percentage of patients who developed geographic atrophy was lower in the patients with VMT or VMA at baseline compared to those with neither VMT nor VMA at baseline for both year 1 (8.82% versus 16.7% respectively, p=0.02) and year 2 (11.7% versus 22.5% respectively, p=0.005). The percentage with retinal thickness in normal range (121-212 u) was lower in patients with VMT or VMA at baseline compared to patients with neither VMT nor VMA at year 1 (55.9% versus 68.1% respectively, p=0.006), with a similar finding in year 2 that is nearly statistically significant (p=0.06). A higher percentage of patients with VMT or VMA at baseline had subretinal fluid at 1 year compared to patients with neither VMT nor VMA (39.7% versus 27.8% respectively, p=0.006) with a similar but non-statistically significant finding at year 2 (40.6% versus 34.3%, p=0.13). There was no difference in the percentage of patients within each group having intraretinal fluid, or no fluid on OCT at year 1. Similarly, there was no difference in the change in total foveal thickness or subretinal fluid thickness from baseline between the groups. The percentage with VMT or VMA was 1.24% and 8.75% at year 1 and 1.24% and 7.33% at year 2.

At both years 1 and 2, in those patients randomized to as-needed dosing, eyes with baseline VMA or VMT tended to have a greater number of required injections in 1 year (mean± SE: 7.89 ± 0.35 versus 7.16 ± 0.16 respectively, p=0.08) and in 2 years (14.8 ± 0.79 versus 13.1 ± 0.34 respectively, p=0.052) than eyes with neither VMT nor VMA at baseline.

Analysis by Dynamic VMI Status in As-Needed Treatment Patients

Among the 598 patients in the as-needed treatment groups whose VMI status were evaluated at baseline and monthly during 2 years follow-up, there were 63 (10.5%) patient eyes with VMT at any time (could also have VMA at other visits), 90 (15.1%) patient eyes with VMA at any time (could not have VMT at other visits), and 445 patient eyes with neither VMT nor VMA at any time. Similar to the analysis of baseline VMI status, patients with VMT or VMA at any time were younger (p<0.0001), less likely to be female (p=0.001), more likely to be former or current cigarette smokers (p=0.006), and showed greater total foveal thickness (p=0.051) when compared to those with neither VMT nor VMA at any time (Table 3).

In the as-needed treatment population, comparisons of year 2 outcomes among eyes with VMT at any time, VMA at any time, and neither VMT nor VMA at any time are shown in Table 4. There were no differences in visual acuity outcomes across the VMI groups (p=0.70, Table 4). However, the percentage of eyes with geographic atrophy was lower in the VMT at any time and VMA at any time groups compared to the neither VMT nor VMA at any time group (13.3%, 10.1%, and 22.3% respectively, p=0.02). At year 2, there were no differences in other anatomical outcomes based on OCT or fluorescein angiography. During 2 years, there were a greater number of injections in the VMT at any time and VMA at any time groups compared to the neither VMT nor VMA at any time group (15.4 ±0.87, 13.8 ±0.73, 12.9 ± 0.35 respectively, p=0.02).

Association of VMT Frequency and Outcomes Among As-Needed Treatment Patients

VMT frequency during 2 years was not significantly associated with visual acuity change from baseline to year 2 (Spearman correlation coefficient r=0.03, p=0.55), change in OCT total thickness from baseline to year 2 (r=−0.04, p=0.40), but was significantly associated with number of treatments during 2 years (r=0.12, p=0.0007). At 2 years, the mean number of injections (±SE) was 13.0±0.32 for patients with no visits with VMT (n=456), 13.6±1.28 for patients with 1 visit with VMT (n=28), and 17.0±1.19 for patients with 2 or more visits with VMT (n=32), and this difference was statistically significant (linear trend p=0.03, Figure 1).

Discussion

In the present report, we determined the baseline prevalence of VMA and VMT in eyes with NVAMD, and the association of these vitreoretinal interface changes with the number of anti-VEGF injections and visual acuity. In addition, we determined the relationship between baseline non-ophthalmic patient characteristics, and various ocular anatomic features.

The baseline prevalence of VMT or VMA was relatively low, 1.8% and 10.4%, respectively. These values are less than those reported in other smaller studies (25.7%, 33.7% or 35.8%).[5, 6, 11] The reason for the difference is not clear. However, identification of VMA and VMT, and changes over time was not likely to be impacted by the selection of SDOCT or TDOCT for imaging. In a recent study,[8] there was no significant difference in the ability of SDOCT to detect VMA and VMT when compared to TDOCT.

We found that a greater number of anti-VEGF injections were required in eyes with VMA or VMT, and a linear relationship between the number of visits with VMA observed on OCT and the number of injections. Although this relationship is statistically significant, the differences, approximately 1 injection over 1 year, and 2 injections over 2 years, are modest. Our study did not show any difference in visual acuity between the groups based on VMI status, a result that differed from the findings of two smaller studies of shorter duration,[5, 6] and was comparable to the findings of a third one-year study.[12] Nevertheless, this information may be useful for clinicians who encounter neovascular AMD patients with VMT or VMA. In particular, clinicians may be more cautious when extending time intervals between visits or treatments in these patients. This information also provides some justification for clinical trials currently underway to investigate the potential benefit of targeted treatment of VMA in neovascular AMD using ocriplasmin, an intravitreally-injected proteolytic enzyme, to specifically treat VMT and VMA.

The VMI changes over time with the seminal event being the development of a posterior vitreous detachment. During the course of a posterior vitreous detachment (PVD), the posterior hyaloid usually separates first from the perifovea, then the fovea, and later the optic nerve head and mid-peripheral retina. Several studies have investigated the relationship between vitreoretinal interface changes and visual acuity among eyes treated with anti-VEGF therapy. In the present study, visual acuity did not depend on vitreomacular interface status, either at baseline, or followup. In contrast, other investigators have observed slightly better visual acuity outcomes in eyes with neovascular AMD without VMA

compared to those with VMA.[5, 6] For example, Lee and others performed a retrospective comparative series of 148 eyes of 148 consecutive patients with newly diagnosed neovascular AMD treated with ranibizumab or bevacizumab for 12 months or longer, as an initial series of 3 monthly injections followed by as-needed treatment based on decreased vision, persistent fluid on OCT, or new macular hemorrhage.[5, 6] Mean best-corrected visual acuity (BCVA) decreased in the group with VMA at baseline (n=38, 25.7%) compared to the group without VMA (n=110, p=0.04). There was no statistically significant difference in OCT central retinal thickness between the groups.

More recently, Mayr-Sponer and others performed a secondary analysis of 252 eyes with sufficient OCT images from the EXCITE study, a prospective, multicenter12 month clinical trial involving 353 eyes of 353 patients with treatment-naïve neovascular AMD.[6] The study protocol excluded eyes with VMT and the 4 eyes with persistent vitreous attachment. At baseline 162 eyes (64.3%) had PVD, and 85 eyes (33.7%) had VMA. Over the one-year observation period, the VMA persisted in 37 (14.7%) and released in 48 (19%). Patients were randomized to monthly 0.3 mg vs quarterly 0.3 mg versus quarterly 0.5 mg ranibizumab after receiving 3 consecutive monthly loading dose treatments. Visual acuity in eyes given quarterly treatment was non-inferior to monthly treatment in the PVD group, but not in the groups of eyes with persistent VMA (quarterly vs. monthly, n= 25 vs. 12, −0.2 vs. +7.5 letters, p=0.043) or released VMA (n=29 vs. 19, +3.2 vs. +12.7 letters, p=0.008), suggesting that the VMI influences treatment efficacy. These same investigators similarly noted an effect of the VMI on treatment outcomes in another post hoc analysis of a prospective randomized 12-month multicenter clinical trial data from a 255 subject clinical trial involving as-needed ranibizumab monotherapy and verteporfin photodynamic therapy (PDT) combination therapy in neovascular AMD.[13]

We identified baseline demographic characteristic, age and gender that were associated with VMI abnormalities. Younger patients were more likely to have VMA or VMT, an observation that corroborated the previously reported relationship between age and changes at the VMI.[6] We also found that patients with VMT or VMA were less likely to be female. Older age and female gender are associated with complete, but not partial PVD.[11, 14, 15] Together, our data, and those of others suggest that in older patients and women, the vitreoretinal adhesion is not as tight as in younger patients or men, and, accordingly, these individuals would have a greater chance to develop a complete PVD once they developed VMA, an intermediate step in the evolution to complete PVD. Interestingly, we found that current or former cigarette smokers were more likely to have VMA or VMT, a finding that has not been previously reported. Other well-known VMI diseases such as macular hole and ERM have also been shown to occur more commonly with aging[16-18] and in women,[19-22] whereas there are inconsistent findings with regards to smoking as a risk factor. [11, 15, 23, 24] The reason that smoking is associated with VMA and VMT in AMD remains to be determined.

The relationship between VMI and AMD pathophysiology has been well studied. Using OCT imaging, a higher incidence of VMA in eyes with neovascular AMD has been noted as compared to eyes with non-neovascular AMD or controls. Furthermore, VMA has been noted to localize to the area of CNV.[1-4, 25] A proposed pathophysiologic mechanism for

this association is that VMA-associated traction causes localized inflammation that facilitates CNV development, and/or that VMA can function as a diffusion barrier for oxygen or vascular endothelial growth factor. However, the association between VMI and CNV does not necessarily imply that VMI causes CNV. One study has suggested that CNV might cause VMA.[12] Waldstein, et al performed a prospective study of 49 eyes with non-neovascular AMD in 49 patients who had neovascular AMD in the fellow eye; these patients were examined every 3 months for four years. [12] They found no significant difference between eyes with and without VMA regarding rate of CNV development or time to disease progression. In contrast to other investigators, they postulated that CNV fosters inflammatory and neovascular processes that leads to an abnormally strong adhesion between the hyaloid and the area of the CNV. They postulate that this would account for the localization of VMA over CNV.

Geographic atrophy occurred less frequently in our study in eyes with VMA. This finding supports the previous report from the CATT that noted a lower rate of GA in patients with VMA.[26] In the entire CATT population, the percentage of patients who developed geographic atrophy at 2 years was lower in the patients with VMT or VMA at baseline compared to those with neither VMT nor VMA at baseline (11.7% versus 22.5% respectively, p=0.005). In the current report, when eyes in the group of patients assigned to as-needed treatment were followed longitudinally, a similar relationship was observed; the percentage of patients with geographic atrophy was lower in the VMT at any time and VMA at any time groups compared to the neither VMT nor VMA at any time group (13.3%, 10.1%, and 22.3% respectively, p=0.02). Our data suggest a protective effect of VMA and VMT on GA, however, the mechanism by which VMT or VMA relates to geographic atrophy remains to be determined.

In conclusion, our study suggests that neovascular AMD patients with VMT or VMA compared to those with neither VMT nor VMA were younger, less likely to be female, more likely to be former or current cigarette smokers, and showed greater total foveal thickness. It also demonstrates a statistically significant greater number of required injections in eyes with neovascular AMD who have concurrent VMA or VMT. Furthermore, there was a statistically significant linear relationship between the number of visits with VMA noted on OCT and the number of injections. This may have clinically useful implications in the care of neovascular AMD patients. Further study of the relationship between the VMI, AMD and CNV is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Ciulla has received research support from Genentech and serves on a data safety monitoring committee for Thrombogenics.

Dr. Toth receives research support through her Institution from Bioptigen and Genentech, and royalties through her Institution from Alcon.

Supported by cooperative agreements U10 EY017823, U10 EY017825, U10 EY017826, U10 EY017828 and R21EY023689 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services.

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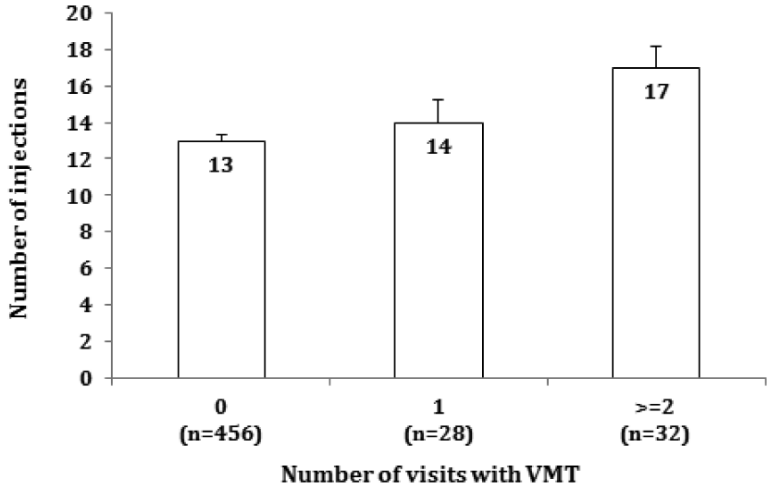

Figure 1.

Bar plot for mean (standard error) of number of treatments by total number of follow-up visits with vitreomacular traction through 2 years among patients treated as-needed for 2 years.

Table 1

Baseline characteristics by VMT/VMA status at baseline among all patients (n=1115[§])

Baseline Characteristics	VMT or VMA (n=143)	Neither VMT nor VMA (n=972)	P Value[*]
Patients			
Age, years: Mean (SE[†])	75.5(0.60)	79.7(0.24)	<0.001
Female (n, %)	68(47.6)	620(63.8)	<0.001
Former or current cigarette smoker (n, %)	98(68.5)	538(55.3)	0.003
With anticoagulant use (n, %)	82(57.3)	503(51.7)	0.24
Taking AREDS supplement (n, %)	90(62.9)	609(62.7)	1.00
Drug			
Lucentis (n, %)	74(51.7)	487(50.1)	0.72
Avastin (n, %)	69(48.3)	485(49.9)	
Regimen			
Monthly Always (n, %)	36(25.2)	256(26.3)	0.78
Switched (n, %)	31(21.7)	231(23.8)	
PRN Always (n, %)	76(53.1)	485(49.9)	
Study eye			
Visual acuity, letters: Mean (SE[†])	59.6(1.16)	61.2(0.42)	0.18
Area of choroidal neovascularization, disc areas: Mean (SE[†])	1.87(0.16)	1.75(0.06)	0.46
Total area of lesion, disc areas: Mean (SE[†])	2.53(0.21)	2.44(0.08)	0.68
Lesion type			0.16
Occult only (n, %)	75(52.4)	586(60.3)	
Minimally classic (n, %)	28(19.6)	160(16.5)	
Predominantly classic (n, %)	38(26.6)	207(21.3)	
Scar in study eye (n, %)	4(2.80)	36(3.70)	0.81
GA in study eye (n, %)	7(4.90)	65(6.69)	0.58
OCT Features in Study eye[#]			
Intraretinal fluid (n, %)	99(69.2)	738(75.9)	0.14
Subretinal fluid (n, %)	124(86.7)	787(81.0)	0.047
Sub-RPE fluid (n, %)	64(44.8)	477(49.1)	0.52
Retinal thickness (n, %)			
<120 microns	15(10.5)	103(10.6)	0.74
120-212 microns	72(50.3)	521(53.6)	
>212 microns	56(39.2)	348(35.8)	
Mean, microns (SE[†])	222(9.71)	216(3.39)	0.56
Subretinal fluid thickness, microns: Mean (SE[†])	32.2(6.79)	30.9(2.12)	0.82
Subretinal tissue complex thickness,	226(14.7)	205(5.50)	0.16

Baseline Characteristics	VMT or VMA (n=143)	Neither VMT nor VMA (n=972)	P Value*
microns: Mean (SE†)			
Total foveal thickness, microns: Mean (SE†)	481(16.3)	452(5.85)	0.08

*From one way ANOVA for continuous variables and Fisher's exact test for categorical variables.

†SE is standard error.

§70 eyes without gradable OCT were excluded.

#All thicknesses are at the foveal center

Table 2

Year 1 and 2 outcomes by VMTA/MA status at baseline among all patients

Outcomes in study eye	Outcomes at Year 1 (N=1044)			Outcomes at Year 2(N=976)		
	VMT or VMA (n=136)	No VMT or VMA (n=908)	P Value*	VMT or VMA (n=128)	No VMT or VMA (n=848)	P Value*
Visual acuity, letters: Mean (SE°)	67.9(1.49)	68.5(0.59)	0.75	67.6(1.48)	67.7(0.63)	0.97
Visual acuity change from baseline, letters: Mean (SE°)	7.95(1.19)	7.15(0.49)	0.55	7.70(1.49)	6.10(0.57)	0.31
≥ 15 letters increase from baseline (n, %) VMA or VMT (n, %)	39(28.7)	268(29.5)	0.92	41(32.0)	247(29.1)	0.53
	74 (54.4)	28 (3.08)	<0.001	52 (40.6)	27(3.18)	<0.001
Scar (n,%)	47(34.6)	295(32.5)	0.62	64(50.0)	335(39.5)	0.03
GA (n,%)	12(8.82)	152(16.7)	0.02	15(11.7)	191(22.5)	0.005
Retinal thickness at fovea, microns			0.01			0.06
<120 (n, %)	34(25.0)	193(21.3)		37(28.9)	198(23.3)	
120-212 (n, %)	76(55.9)	618(68.1)		68(53.1)	544(64.2)	
>212 (n, %)	23(16.9)	83(9.14)		20(15.6)	95(11.2)	
No fluid on OCT (n, %)	33(24.3)	262(28.9)	0.30	23(18.0)	204(24.1)	0.17
Intraretinal fluid (n, %)	63(46.3)	422(46.5)	0.93	64(50.0)	427(50.4)	1.00
Subretinal fluid (n, %)	54(39.7)	252(27.8)	0.01	52(40.6)	291(34.3)	0.13
Sub-RPE fluid (n, %)	43(31.6)	275(30.3)	0.68	49(38.3)	302(35.6)	0.55
Change in total foveal thickness from baseline, microns: Mean (SE°)	−154(15.3)	−169(6.01)	0.37	−152(16.7)	−162(6.56)	0.55
Change in Retinal thickness from baseline, microns: Mean (SE°)	−52(10.3)	−61(3.74)	0.38	−54(12.0)	−56(4.28)	0.86
Change in Subretinal fluid thickness from baseline, microns: Mean (SE°)	−14(7.35)	−24(2.38)	0.15	−20(7.79)	−23(2.56)	0.63
Change in Subretinal tissue complex thickness from baseline, microns: Mean (SE°)	−88(13.8)	−84(5.05)	0.74	−78(15.7)	−83(5.18)	0.74
Change in lesion size from baseline, disc areas: Mean (SE°)	0.23(0.17)	0.20(0.08)	0.89	0.95(0.29)	0.73(0.09)	0.42
Number of injections in PRN†: Mean (SE°)	7.89(0.35)	7.16(0.16)	0.08	14.8(0.79)	13.1(0.34)	0.052

For year 2 outcome, 484 patients were in PRN groups (69 Baseline VMT or VMA, 415 Neither VMT nor VMA at baseline).

*From one way ANOVA for continuous variables and Fisher's exact test for categorical variables.

†For year 1 outcome, 523 patients were in PRN groups (74 Baseline VMT or VMA, 449 Neither VMT nor VMA at baseline);

°SE is standard error

Table 3

Baseline characteristics by VMT/VMA status through 2 years among patients treated as needed through 2 years (n=598)

Baseline Characteristics	VMT (n=63)	VMA (n=90)	Neither VMT nor VMA (n=445)	P values*
Patients				
Age, years: Mean (SE†)	75.2(0.96)	76.1(0.85)	80.0(0.35)	<0.001
Female (n, %)	31(49.2)	43(47.8)	295(66.3)	0.001
Former or current cigarette smoker (n, %)	47(74.6)	53(58.9)	238(53.5)	0.01
With anticoagulant use (n, %)	30(47.6)	48(53.3)	247(55.5)	0.47
Taking AREDS supplement (n, %)	42(66.7)	49(54.4)	281(63.1)	0.21
Drug				
Lucentis (n, %)	32(50.8)	47(52.2)	219(49.2)	0.86
Avastin (n, %)	31(49.2)	43(47.8)	226(50.8)	
Study eye				
Visual acuity, letters: Mean (SE†)	61.0(1.69)	60.6(1.47)	61.0(0.63)	0.97
Area of choroidal neovascularization, disc areas: Mean (SE†)	2.11(0.25)	1.81(0.17)	1.70(0.09)	0.26
Total area of lesion, disc areas: Mean (SE†)	2.76(0.29)	2.42(0.24)	2.34(0.11)	0.42
Lesion type				
Occult only (n, %)	34(54.0)	49(54.4)	263(59.1)	0.54
Minimally classic (n, %)	13(20.6)	14(15.6)	72(16.2)	
Predominantly classic (n, %)	13(20.6)	27(30.0)	100(22.5)	
Scar in study eye (n, %)	4(6.35)	4(4.44)	17(3.82)	0.52
GA in study eye (n, %)	5(7.94)	5(5.56)	36(8.09)	0.76
Intraretinal fluid (n, %)	43(68.3)	70(77.8)	334(75.1)	0.39
Subretinal fluid (n, %)	54(85.7)	77(85.6)	359(80.7)	0.34
Sub-RPE fluid (n, %)	34(54.0)	41(45.6)	217(48.8)	0.48
Retinal thickness (n, %)				
<120 microns	4(6.35)	11(12.2)	48(10.8)	0.71
120-212 microns	34(54.0)	42(46.7)	229(51.5)	
>212 microns	25(39.7)	37(41.1)	164(36.9)	
Mean (SE†)	233(17.3)	224(11.5)	216(4.82)	0.44
Subretinal fluid thickness: Mean (SE†)	20.5(6.40)	27.7(6.06)	33.0(3.47)	0.35
Subretinal tissue complex thickness: Mean (SE†)	260(25.2)	203(15.9)	204(8.24)	0.053
Total foveal thickness, microns: Mean (SE†)	513(26.1)	455(17.8)	453(8.71)	0.051

*From one way ANOVA for continuous variables and Fisher's exact test for categorical variables.

† SE is standard error

Table 4

Year 2 outcomes by VMT/VMA status through 2 years among patients treated as needed through 2 years (N=516[§])

Year 2 Outcomes	VMT (n=60)	VMA (n=79)	No VMT or VMA (n=377)	P values[*]
Visual acuity, letters: Mean (SE[°])	67.3(2.30)	67.3(1.88)	67.1(0.93)	0.99
Visual acuity change from baseline, letters: Mean (SE[°])	6.53(2.46)	7.04(1.50)	5.47(0.84)	0.70
≥ 15 letters increase from baseline (n, %)	18(30.0)	24(30.4)	110(29.2)	0.96
Scar in study eye (n,%)	29(48.3)	39(49.4)	149(39.5)	0.16
GA in study eye (n,%)	8(13.3)	8(10.1)	84(22.3)	0.02
Retinal thickness at fovea, microns				
<120 (n, %)	15(25.0)	15(19.0)	94(24.9)	0.32
120-212 (n, %)	32(53.3)	51(64.6)	237(62.9)	
>212 (n, %)	12(20.0)	11(13.9)	44(11.7)	
No fluid on OCT (n, %)	6(10.0)	16(20.3)	72(19.1)	0.20
Intraretinal fluid (n, %)	35(58.3)	42(53.2)	198(52.5)	0.46
Subretinal fluid (n, %)	29(48.3)	29(36.7)	139(36.9)	0.20
Sub-RPE fluid (n, %)	28(46.7)	31(39.2)	146(38.7)	0.50
Change in total foveal thickness from baseline, microns: Mean (SE[°])	−163(23.6)	−163(21.5)	−159(9.92)	0.98
Change in Retinal thickness from baseline, microns: Mean (SE[°])	−47(17.0)	−70(14.5)	−56(6.23)	0.53
Change in Subretinal fluid thickness from baseline, microns: Mean (SE[°])	−7.9(7.49)	−23(7.27)	−27(3.95)	0.16
Change in Subretinal tissue complex thickness from baseline, microns: Mean (SE[°])	−109(22.4)	−70(17.1)	−75(8.02)	0.27
Change in lesion size from baseline, disc areas: Mean (SE[°])	0.51(0.40)	1.17(0.27)	1.00(0.15)	0.37
Number of injections in PRN: Mean (SE[°])	15.4(0.87)	13.8(0.73)	12.9(0.35)	0.02

[§] Number of patients with Year 2 visual acuity outcome.

[*] From one way ANOVA for continuous variables and Fisher's exact test for categorical variables.

[°] SE is standard error.