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Influence of the Vitreomacular Interface on Treatment Outcomes in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Objective: To assess the association of the vitreomacular interface with outcomes of eyes treated with anti–vascular endothelial growth factor 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 (CATT).

Methods: Treatment was assigned randomly as either ranibizumab or bevacizumab and as 3 different regimens for dosing over a 2-year period. Masked readers at a reading center assessed optical coherence tomography (OCT) scans at baseline and follow-up for vitreomacular traction (VMT) and vitreomacular adhesion (VMA), fluid, and central thickness. Visual acuity (VA) was measured by masked, certified examiners.

Main Outcome Measures: Anatomic features and VA at baseline and 1 and 2 years and number of treatments.

Results: At baseline, 143 patient eyes (12.8%) had VMT or VMA. Compared with those with neither (n = 972), patients with VMT or VMA were younger (mean ± standard error, 75.5±0.6 vs. 79.7±0.24 years; $P < 0.0001$) and more likely to be male (52.4% vs. 36.2%; $P = 0.0003$), to be cigarette smokers (68.5% vs. 55.3%; $P = 0.003$), and to have subretinal fluid on OCT (86.7% vs. 81.0%; P = 0.047). Vitreomacular interface status was not associated with VA at baseline or follow-up. Among eyes treated as needed (n = 598) and followed up for 2 years (n = 516), the mean number of injections 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 as needed increased from 13.0±0.3 when VMT was not observed to 13.6±1.3 when observed once and to 17±1.2 when observed 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: In eyes in the CATT, VMT and VMA were infrequent. At baseline and follow-up, VMT or VMA were not associated with VA. Eyes with VMT or VMA treated as needed required on average 2 more injections over 2 years. *Ophthalmology 2015;122:1203-1211 © 2015 by the American Academy of Ophthalmology.*

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The role of the vitreomacular interface (VMI) in the pathophysiologic features and treatment of neovascular age-related macular degeneration (AMD) has generated much recent interest. In retrospective and prospective observational case series, a higher prevalence of vitreomacular adhesion (VMA) has been reported in eyes with neovascular AMD compared with eyes with nonneovascular AMD.[1–3] In a paired eye study, VMA was observed more frequently in eyes with neovascular AMD compared with the fellow nonneovascular AMD eye that served as a control.[4] Some investigators also have observed that VMA occurs at the vitreoretinal interface overlying the choroidal neovascularization (CNV).[1,2,4] Vitreomacular adhesion also influences treatment and outcomes in neovascular AMD; the absence of VMA has been associated with slightly better visual acuity (VA),[5,6] and eyes with VMA may require more frequent dosing compared with 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 our study was to assess the relationship of the VMI to treatment frequency in neovascular AMD, as well as to VA and anatomic outcomes in the Comparison of AMD Treatments Trials (CATT),[7] one of the largest prospective treatment trials for neovascular AMD conducted to date.

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Methods

Study Participants and Inclusion and Exclusion Criteria

Between February 2008 and December 2009, CATT enrolled a total of 1185 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 older than 50 years, presence or previously untreated active CNV secondary to AMD in the study eye, and VA between 20/25 and 20/320 (letter score of 23−82 on electronic VA testing). Both leakage on fluorescein angiography and optical coherence tomography (OCT; intraretinal, subretinal, or sub−retinal pigment epithelium fluid) were required to establish the presence of active CNV. Choroidal neovascularization or its sequelae (fluid, hemorrhage, or pigment epithelial detachment) 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 μm) 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 causes other than AMD. Patients with any concurrent ocular conditions that could require medical or surgical intervention during the 2 years of the study also were excluded.

Treatment

At baseline, patients were assigned randomly 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 rerandomized 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 examination, decreased VA, or leakage on fluorescein angiography.

Optical Coherence Tomography 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 up every 4 weeks for 2 years. Optical coherence tomography 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.

Optical Coherence Tomography−Based Assessment of Vitreomacular Interface

All OCT images were evaluated for VMA, intraretinal fluid, and subretinal fluid. 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 then was 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, 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 posterior vitreous detachment (PVD) developed in eyes with VMA.

Visual Acuity Testing Procedures

A CATT-certified VA technician determined, at each visit, best-corrected VA according to an Early Treatment Diabetic Retinopathy Study protocol. Visual acuity testing was performed with the Electronic Visual Tester,[10] and VA score was calculated as the number of letters read correctly.

Statistical Analysis

We first determined the association of baseline VMA or VMT with baseline characteristics and year 1 and 2 outcomes. For this analysis, 3 hierarchical groups initially were created based on presence or absence of VMT or VMA at baseline. These groups were VMT present at baseline, VMA present at baseline, and neither VMT nor VMA present at baseline. Only 20 of 1115 patient eyes (1.8%) had baseline VMT. As a result, VMT was combined with VMA, and this combined VMT and VMA group was compared with 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 or absence of VMT or VMA at both baseline and during 2 years of 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 for 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 because these patients underwent monthly OCT. In addition, the associations of VMT frequency with change in VA 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 Vitreomacular Interface Status

Among 1185 CATT participants, baseline VMI status could not be determined in 70 participants (5.9%) because of missing OCT images or poor image quality and were excluded from the statistical analysis. Among 1115 participants with baseline VMI status known, 20 patient eyes (1.8%) had VMT at baseline and 123 eyes (11.0%) had VMA at baseline, for a total of 143 patient eyes (12.8%) with baseline VMT or VMA. The comparisons of baseline characteristics between eyes with versus those without baseline VMT or VMA are shown in Table 1. Compared with the patients with neither VMT nor VMA (n = 972), patients with VMT or VMA were younger (mean±standard error, 75.5±0.6 vs. 79.7±0.24 years, respectively; $P < 0.0001$), included a lower percentage of women (47.6% vs. 63.8%, respectively;

Table 1. Baseline Characteristics by Vitreomacular Traction or Vitreomacular Adhesion Status at Baseline among All Patients (n = 1115*)

Baseline Characteristics	Vitreomacular Traction or Vitreomacular Adhesion (n = 143)	Neither Vitreomacular Traction nor Vitreomacular Adhesion (n = 972)	P Value†
Patients			
Age (yrs), mean (SE)	75.5 (0.60)	79.7 (0.24)	<0.001
Female, no. (%)	68 (47.6)	620 (63.8)	<0.001
Former or current cigarette smoker, no. (%)	98 (68.5)	538 (55.3)	0.003
With anticoagulant use, no. (%)	82 (57.3)	503 (51.7)	0.24
Taking AREDS supplement, no. (%)	90 (62.9)	609 (62.7)	1.00
Drug, no. (%)			
Lucentis	74 (51.7)	487 (50.1)	0.72
Avastin	69 (48.3)	485 (49.9)	
Regimen, no. (%)			
Monthly always	36 (25.2)	256 (26.3)	0.78
Switched	31 (21.7)	231 (23.8)	
PRN always	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 area), mean (SE)	1.87 (0.16)	1.75 (0.06)	0.46
Total area of lesion (disc area), mean (SE)	2.53 (0.21)	2.44 (0.08)	0.68
Lesion type, no. (%)			0.16
Occult only	75 (52.4)	586 (60.3)	
Minimally classic	28 (19.6)	160 (16.5)	
Predominantly classic	38 (26.6)	207 (21.3)	
Scar in study eye, no. (%)	4 (2.80)	36 (3.70)	0.81
GA in study eye, no. (%)	7 (4.90)	65 (6.69)	0.58
OCT features in study eye, no. (%)‡			
Intraretinal fluid	99 (69.2)	738 (75.9)	0.14
Subretinal fluid	124 (86.7)	787 (81.0)	0.047
Sub-RPE fluid	64 (44.8)	477 (49.1)	0.52
Retinal thickness (μm), no. (%)			
<120	15 (10.5)	103 (10.6)	0.74
120–212	72 (50.3)	521 (53.6)	
>212	56 (39.2)	348 (35.8)	
Mean (SE)	222 (9.71)	216 (3.39)	0.56
Subretinal fluid thickness (μm), mean (SE)	32.2 (6.79)	30.9 (2.12)	0.82
Subretinal tissue complex thickness (μm), mean (SE)	226 (14.7)	205(5.50)	0.16
Total foveal thickness (μm), mean (SE)	481 (16.3)	452(5.85)	0.08

AREDS = Age-Related Eye Disease Study; GA = geographic atrophy; OCT = optical coherence tomography; PRN = pro re nata; RPE = retinal pigment epithelium; SE = standard error.
*Seventy eyes without gradable OCT results were excluded.
†One-way analysis of variance for continuous variables and Fisher exact test for categorical variables.
‡All thicknesses are at the foveal center.

$P = 0.0003$), included a higher percentage of former or current cigarette smokers (68.5% vs. 55.3%, respectively; $P = 0.003$), and had a higher percentage with subretinal fluid on OCT (86.7% vs. 81.0%, respectively; $P = 0.047$). There was a trend toward increased total foveal thickness in the eyes with baseline VMT or VMA compared with eyes with neither VMT nor VMA (481 vs. 452 μm), 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 VA at either year 1 or year 2 between eyes with versus without baseline VMT or VMA (all $P \geq 0.31$; Table 2). However, there were some anatomic differences. The percentage of patients who had geographic atrophy was lower in the patients with VMT or VMA at baseline compared with those with neither VMT nor VMA at baseline for both year 1 (8.82% vs. 16.7%, respectively; $P = 0.02$) and year 2 (11.7% vs. 22.5%, respectively; $P = 0.005$). The percentage with retinal thickness in the normal range (121–212 μm) was lower in patients with VMT or VMA at baseline compared with patients with neither VMT nor VMA at year 1 (55.9% vs. 68.1%, respectively; $P = 0.006$), with a similar finding in year 2 that was nearly statistically significant ($P = 0.06$). A higher percentage of patients with VMT or VMA at baseline had subretinal fluid at 1 year compared with patients with neither VMT nor VMA (39.7% vs. 27.8%, respectively; $P = 0.006$), with a similar but not statistically significant finding at year 2 (40.6% vs. 34.3%; $P = 0.13$). There was no difference in the percentage of patients within each group having intraretinal fluid or with 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. At 1 year, among 1044 patients,

Table 2. Year 1 and 2 Outcomes by Vitreomacular Traction or Vitreomacular Adhesion 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, no. (%)	39 (28.7)	268 (29.5)	0.92	41 (32.0)	247 (29.1)	0.53
VMA or VMT, no. (%)	74 (54.4)	28 (3.08)	<0.001	52 (40.6)	27 (3.18)	<0.001
Scar, no. (%)	47 (34.6)	295 (32.5)	0.62	64 (50.0)	335 (39.5)	0.03
GA, no. (%)	12 (8.82)	152 (16.7)	0.02	15 (11.7)	191 (22.5)	0.005
Retinal thickness at fovea (μm), no. (%)			0.01			0.06
<120	34 (25.0)	193 (21.3)		37 (28.9)	198 (23.3)	
120–212	76 (55.9)	618 (68.1)		68 (53.1)	544 (64.2)	
>212	23 (16.9)	83 (9.14)		20 (15.6)	95 (11.2)	
No fluid on OCT, no. (%)	33 (24.3)	262 (28.9)	0.30	23 (18.0)	204 (24.1)	0.17
Intraretinal fluid, no. (%)	63 (46.3)	422 (46.5)	0.93	64 (50.0)	427 (50.4)	1.00
Subretinal fluid, no. (%)	54 (39.7)	252 (27.8)	0.01	52 (40.6)	291 (34.3)	0.13
Sub-RPE fluid, no. (%)	43 (31.6)	275 (30.3)	0.68	49 (38.3)	302 (35.6)	0.55
Change in total foveal thickness from baseline (μm), mean (SE)	−154 (15.3)	−169 (6.01)	0.37	−152 (16.7)	−162 (6.56)	0.55
Change in retinal thickness from baseline (μm), 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 (μm), 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 (μm), 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 area), mean (SE)	0.23 (0.17)	0.20 (0.08)	0.89	0.95 (0.29)	0.73 (0.09)	0.42
No. of PRN injections, mean (SE)[†]	7.89 (0.35)	7.16 (0.16)	0.08	14.8 (0.79)	13.1 (0.34)	0.052

GA = geographic atrophy; OCT = optical coherence tomography; PRN = pro re nata; RPE = retinal pigment epithelium; SE = standard error; VMA = vitreomacular adhesion; VMT = vitreomacular traction.

*One-way analysis of variance for continuous variables and Fisher 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); for year 2 outcome, 484 patients were in PRN groups (69 baseline VMT or VMA, 415 neither VMT nor VMA at baseline).

Table 3. Baseline Characteristics by Vitreomacular Traction or Vitreomacular Adhesion Status among Patients Treated as Needed through 2 Years (n = 598)

Baseline Characteristics	Vitreomacular Traction (n = 63)	Vitreomacular Adhesion (n = 90)	Neither Vitreomacular Traction nor Vitreomacular Adhesion (n = 445)	*P* Value*
Patients				
Age (yrs), mean (SE)	75.2 (0.96)	76.1 (0.85)	80.0 (0.35)	<0.001
Female, no. (%)	31 (49.2)	43 (47.8)	295 (66.3)	0.001
Former or current cigarette smoker, no. (%)	47 (74.6)	53 (58.9)	238 (53.5)	0.01
With anticoagulant use, no. (%)	30 (47.6)	48 (53.3)	247 (55.5)	0.47
Taking AREDS supplement, no. (%)	42 (66.7)	49 (54.4)	281 (63.1)	0.21
Drug, no. (%)				
Lucentis	32 (50.8)	47 (52.2)	219 (49.2)	0.86
Avastin	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, no. (%)				
Occult only	34 (54.0)	49 (54.4)	263 (59.1)	0.54
Minimally classic	13 (20.6)	14 (15.6)	72 (16.2)	
Predominantly classic	13 (20.6)	27 (30.0)	100 (22.5)	
Scar in study eye, no. (%)	4 (6.35)	4 (4.44)	17 (3.82)	0.52
GA in study eye, no. (%)	5 (7.94)	5 (5.56)	36 (8.09)	0.76
Intraretinal fluid, no. (%)	43 (68.3)	70 (77.8)	334 (75.1)	0.39
Subretinal fluid, no. (%)	54 (85.7)	77 (85.6)	359 (80.7)	0.34
Sub-RPE fluid, no. (%)	34 (54.0)	41 (45.6)	217 (48.8)	0.48
Retinal thickness (μm), no. (%)				
<120	4 (6.35)	11 (12.2)	48 (10.8)	0.71
120–212	34 (54.0)	42 (46.7)	229 (51.5)	
>212	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 (μm), mean (SE)	20.5 (6.40)	27.7 (6.06)	33.0 (3.47)	0.35
Subretinal tissue complex thickness (μm), mean (SE)	260 (25.2)	203 (15.9)	204 (8.24)	0.053
Total foveal thickness (μm), mean (SE)	513 (26.1)	455 (17.8)	453 (8.71)	0.051

AREDS = Age-Related Eye Disease Study; GA = geographic atrophy; RPE = retinal pigment epithelium; SE = standard error.
*One-way analysis of variance for continuous variables and Fisher exact test for categorical variables.

1.15% had VMT and 8.62% had VMA. At 2 years, among 976 patients, 1.24% had VMT and 7.33% had VMA.

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 ± standard error, 7.89±0.35 vs. 7.16±0.16, respectively; $P = 0.08$) and in 2 years (14.8±0.79 vs. 13.1±0.34, respectively; $P = 0.052$) than eyes with neither VMT nor VMA at baseline.

Analysis by Dynamic Vitreomacular Interface Status in As-Needed Treatment Patients

Among the 598 patients in the as-needed treatment groups whose VMI statuses were evaluated at baseline and monthly during 2 years of follow-up, there were 63 patient eyes (10.5%) with VMT at any time (could also have VMA at other visits), 90 patient eyes (15.1%) 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 had greater total foveal thickness ($P = 0.051$) when compared with 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 VA 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 group and VMA at any time group compared with 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 anatomic outcomes based on OCT or fluorescein angiography. During 2 years, there were a greater number of injections in the VMT at any time group and VMA at any time group compared with the neither VMT nor VMA at any time group (15.4±0.87, 13.8±0.73, and 12.9±0.35, respectively; $P = 0.02$).

Association of Vitreomacular Traction Frequency and Outcomes Among As-Needed Treatment Patients

Vitreomacular traction frequency during 2 years was not significantly associated with VA change from baseline to year 2

Table 4. Year 2 Outcomes by Vitreomacular Traction or Vitreomacular Adhesion Status among Patients Treated as Needed through 2 Years (n = 516*)

Year 2 Outcomes	Vitreomacular Traction (n = 60)	Vitreomacular Adhesion (n = 79)	No Vitreomacular Traction or Vitreomacular Adhesion (n = 377)	P Value†
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-Letter increase from baseline, no. (%)	18 (30.0)	24 (30.4)	110 (29.2)	0.96
Scar in study eye, no. (%)	29 (48.3)	39 (49.4)	149 (39.5)	0.16
GA in study eye, no. (%)	8 (13.3)	8 (10.1)	84 (22.3)	0.02
Retinal thickness at fovea, microns, no. (%)				
<120	15 (25.0)	15 (19.0)	94 (24.9)	0.32
120–212	32 (53.3)	51 (64.6)	237 (62.9)	
>212	12 (20.0)	11 (13.9)	44 (11.7)	
No fluid on OCT, no. (%)	6 (10.0)	16 (20.3)	72 (19.1)	0.20
Intraretinal fluid, no. (%)	35 (58.3)	42 (53.2)	198 (52.5)	0.46
Subretinal fluid, no. (%)	29 (48.3)	29 (36.7)	139 (36.9)	0.20
Sub-RPE fluid, no. (%)	28 (46.7)	31 (39.2)	146 (38.7)	0.50
Change in total foveal thickness from baseline (μm), mean (SE)	−163 (23.6)	−163 (21.5)	−159 (9.92)	0.98
Change in retinal thickness from baseline (μm), mean (SE)	−47 (17.0)	−70 (14.5)	−56 (6.23)	0.53
Change in subretinal fluid thickness from baseline (μm), mean (SE)	−7.9 (7.49)	−23 (7.27)	−27 (3.95)	0.16
Change in subretinal tissue complex thickness from baseline (μm), mean (SE)	−109 (22.4)	−70 (17.1)	−75 (8.02)	0.27
Change in lesion size from baseline (disc area), mean (SE)	0.51 (0.40)	1.17 (0.27)	1.00 (0.15)	0.37
No. of PRN injections, mean (SE)	15.4 (0.87)	13.8 (0.73)	12.9 (0.35)	0.02

GA = geographic atrophy; OCT = optical coherence tomography; PRN = pro re nata; RPE = retinal pigment epithelium; SE = standard error.
*Number of patients with year 2 visual acuity outcome.
†One-way analysis of variance for continuous variables and Fisher exact test for categorical variables.

(Spearman correlation coefficient, $r = 0.03$; $P = 0.55$) or change in OCT total thickness from baseline to year 2 ($r = -0.04$; $P = 0.40$), but it was associated significantly with the number of treatments during 2 years ($r = 0.12$; $P = 0.0007$). At 2 years, the mean number of injections (±standard error) 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 ($P = 0.03$, linear trend; Fig 1).

Discussion

In this report, we determined the baseline prevalence of VMA and VMT in eyes with neovascular AMD and the association of these vitreoretinal interface changes with the number of anti-vascular endothelial growth factor (VEGF) injections and VA. In addition, we determined the relationship between baseline nonophthalmic 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 were not likely to be affected by the selection of spectral-domain OCT or time-domain OCT for imaging. In a recent study,[8] there was no significant difference in the ability of spectral-domain OCT to detect VMA and VMT when compared with time-domain OCT.

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

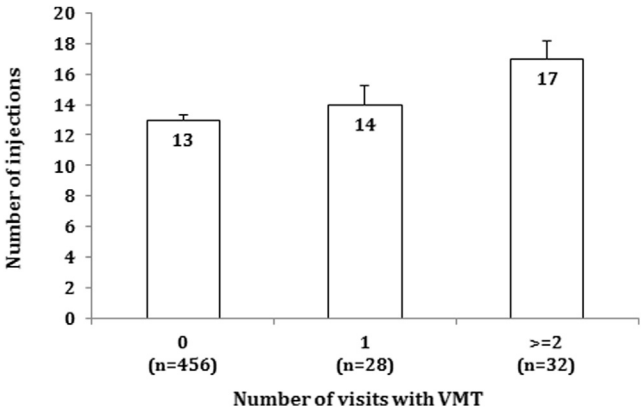

Figure 1. Bar graph showing the mean (standard error) number of treatments by total number of follow-up visits with vitreomacular traction (VMT) through 2 years among patients treated as needed for 2 years.

was 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 VA between the groups based on VMI status, a result that differed from the findings of 2 smaller studies of shorter duration[5,6] and was comparable with the findings of a third 1-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 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, specifically to treat VMT and VMA.

The VMI changes over time, with the seminal event being the development of a PVD. During the course of a 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 VA among eyes treated with anti-VEGF therapy. In this study, VA did not depend on VMI status either at baseline or follow-up. By contrast, other investigators have observed slightly better VA outcomes in eyes with neovascular AMD without VMA compared with those with VMA.[5,6] For example, Lee and Koh[5] 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.[6] Mean best-corrected VA decreased in the group with VMA at baseline (n = 38; 25.7%) compared with 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 et al[6] performed a secondary analysis of 252 eyes with sufficient OCT images from the study. A Randomized, Double-masked, Active-controlled, Multi-center Study Comparing the Efficacy and Safety of Ranibizumab Administered as Two Dosing Regimens in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration (EXCITE), a prospective, multicenter, 12-month clinical trial involving 353 eyes of 353 patients with treatment-naïve neovascular AMD. The study protocol excluded eyes with VMT and 4 eyes with persistent vitreous attachment. At baseline, 162 eyes (64.3%) had PVD and 85 eyes (33.7%) had VMA. Over the 1-year observation period, the VMA persisted in 37 (14.7%) and released in 48 (19%). Patients were randomized to monthly 0.3 mg versus 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 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 data from a 255-subject multicenter clinical trial involving as-needed ranibizumab monotherapy and verteporfin photodynamic therapy combination therapy in neovascular AMD.[13]

We identified baseline demographic characteristics, 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 have a greater chance of a complete PVD developing after the VMA develops, 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 reported previously. Other well-known VMI conditions such as macular hole and epiretinal membrane also have been shown to occur more commonly with aging[16–18] and in women,[19–22] whereas there are inconsistent findings with regard 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 compared with eyes with nonneovascular 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 or that VMA can function as a diffusion barrier for oxygen or VEGF or both. However, the association between VMI and CNV does not necessarily imply that VMI causes CNV. One study suggested that CNV may cause VMA.[12] Waldstein et al[12] performed a prospective study of 49 eyes with nonneovascular AMD in 49 patients who had neovascular AMD in the fellow eye; these patients were examined every 3 months for 4 years. 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 lead 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 geographic atrophy in patients with VMA.[26] In the entire CATT population, the percentage of patients with geographic atrophy at 2 years

was lower in the patients with VMT or VMA at baseline compared with those with neither VMT nor VMA at baseline (11.7% vs. 22.5%, respectively; $P = 0.005$). In this report, when eyes in the group of patients assigned to as-needed treatment were followed up longitudinally, a similar relationship was observed: The percentage of patients with geographic atrophy was lower in the VMT at any time group and VMA at any time group compared with 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 geographic atrophy; however, the mechanism by which VMT or VMA relates to geographic atrophy remains to be determined.

In conclusion, our study suggested that neovascular AMD patients with VMT or VMA compared with those with neither VMT nor VMA were younger, less likely to be female, more likely to be former or current cigarette smokers, and had greater total foveal thickness. It also demonstrated a statistically significantly greater number of required injections in eyes with neovascular AMD that 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.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CATT** = Comparison of AMD Treatments Trials; **CNV** = choroidal neovascularization; **OCT** = optical coherence tomography; **PVD** = posterior vitreous detachment; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor; **VMA** = vitreomacular adhesion; **VMI** = vitreomacular interface; **VMT** = vitreomacular traction.

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