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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;■:1–9 © 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;