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Angiographic Cystoid Macular Edema and Outcomes in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Purpose: To describe morphologic and visual outcomes in eyes with angiographic cystoid macular edema (CME) treated with ranibizumab or bevacizumab for neovascular age-related macular degeneration (nAMD).

Design: Prospective cohort study within a randomized clinical trial.

Participants: A total of 1185 CATT study subjects.

Methods: Baseline fluorescein angiography (FA) images of all CATT study eyes were evaluated for CME. Grading of other characteristics on optical coherence tomography (OCT) and photographic images at baseline and during 2-year follow-up was completed by readers at the CATT Reading Centers. Three groups were created on the basis of baseline CME and intraretinal fluid (IRF) status: (1) CME, (2) IRF without CME, (3) neither CME nor IRF.

Main Outcome Measures: Visual acuity (VA) and total central retinal thickness (CRT) on OCT at baseline, year 1, and year 2.

Results: Among 1131 participants with images of sufficient quality for determining CME and IRF at baseline, 92 (8.1%) had CME, 766 (67.7%) had IRF without CME, and 273 (24.1%) had neither. At baseline, eyes with CME had worse mean VA (letters) than eyes with IRF without CME and eyes with neither CME nor IRF (52 vs. 60 vs. 66 letters, $P < 0.001$); higher mean total CRT (μm) on OCT (514 vs. 472 vs. 404, $P < 0.001$); and greater hemorrhage, retinal angiomatous proliferation (RAP) lesions, and classic choroidal neovascularization (CNV). All groups showed improvement in VA at follow-up; however, the CME group started and ended with the worst VA among the 3 groups. Central retinal thickness, although higher at baseline for the CME group, was similar at 1 and 2 years follow-up for all groups. More eyes with CME (65.3%) developed scarring during 2 years of follow-up compared with eyes with IRF without CME (43.8%) and eyes with neither CME nor IRF (32.5%; $P < 0.001$).

Conclusions: In CATT, eyes with CME had worse baseline and follow-up VA, although all groups showed similar rates of improvement in VA during 2 years of follow-up. Cystoid macular edema seems to be a marker for poorer visual outcomes in nAMD because of underlying baseline retinal dysfunction and subsequent scarring. *Ophthalmology 2016;■:1—7 © 2016 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Cystoid macular edema (CME) is a pathologic condition associated with breakdown of the blood—retinal barrier and is characterized by cystic accumulation of extracellular intraretinal fluid (IRF) in the outer plexiform and inner nuclear layers of the retina.[1] On fluorescein angiography (FA), extensive CME takes on a characteristic "petaloid" appearance as cysts extending radially along the Henle nerve fiber layer fill with fluorescein and appear to resemble flower petals.[2,3] Some common causes for CME include postsurgical edema (Irvine—Gass syndrome), inflammatory uveitis, diabetic retinopathy, vein occlusions, and certain medications.[2,4] It is not common for this pattern of leakage, particularly on

FA, to be associated with neovascular age-related macular degeneration (nAMD).

The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) was a multicenter clinical trial of the efficacy of ranibizumab and bevacizumab to treat nAMD.[5,6] In patients receiving anti—vascular endothelial growth factor (VEGF) therapy, there was improvement in macular swelling demonstrated by improvement in vision and reduced thickness on macular ocular coherence tomography (OCT).[5,6] Further study into the morphology of fluid and visual outcomes from the CATT patients showed that, although all types of fluid improved with anti-VEGF administration, patients with IRF on OCT in particular had

poorer visual acuity (VA) outcomes compared with those with subretinal fluid or sub−retinal pigment epithelium (RPE) fluid.[7] This finding has been substantiated by other work showing IRF to have a strong negative predictive value for functional improvement to anti-VEGF therapy and combinations of anti-VEGF therapy and photodynamic therapy.[8]

The purpose of our study was to examine the presence of angiographic CME on FA, as a subtype of IRF, and its association with visual and morphologic outcomes within patients enrolled in CATT.

Methods

Study Population and Procedures

The methodology of CATT has been described.[5,6] Briefly, CATT enrolled 1185 subjects, aged 50 years or more, from 43 clinical centers across the United States who had evidence of previously untreated active nAMD in the study eye. Only 1 eye per subject, the study eye, was randomized to intravitreal ranibizumab or bevacizumab on a monthly or as needed (pro re nata [PRN]) basis; at week 52, patients treated monthly were re-randomized to continued monthly therapy or PRN therapy with the same drug. Visual acuity was tested using an electronic VA tester. Color fundus photography, FA, and OCT were performed at baseline and during 2 years of follow-up by certified technicians and photographers following standardized protocols.[9,10]

Grading of characteristics on optical coherence tomography (OCT) at baseline or during 2-year follow-up was completed by readers at the CATT OCT Reading Center at Duke University. The OCT readers independently analyzed the scans for morphologic characteristics including, but not limited to, the presence of IRF, subretinal fluid, and sub-RPE fluid; the thickness at the foveal center of the retina; the thickness of the subretinal fluid and sub-retinal tissue complex; and the location of fluid in relation to the foveal center.[10] Readers at the CATT Photograph Reading Center at the University of Pennsylvania independently examined stereoscopic color fundus photographs and FAs for components of the neovascular lesion, size of choroidal neovascularization (CNV), presence of scar or hemorrhage, and retinal angiomatous proliferation (RAP) lesions.[9]

Baseline FA images of all CATT study eyes were evaluated for CME by 1 of 2 physician readers at the CATT Photograph Reading Center. Cystoid macular edema was defined as honeycombed patterns of hyperfluorescence surrounding the foveal center, with features of pooling in well-defined foveal and parafoveal spaces. Only CME cases that were well defined angiographically, with at least 3 or more "petals" apparent on FA imaging in late frames, confirmed by both readers were included as CME cases in our analyses (Fig 1). Our criteria for angiographic inclusion were fairly strict, and images with <3 petals or leakage that was not at the foveal center (defined as 2.75 disc diameters from the optic nerve[11]) were excluded from our study. It should be noted that for the purpose of our study, the term "CME" defines the angiographic presence of cysts, whereas "IRF" describes their presence on OCT alone.

An institutional review board 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. The CATT was registered with ClinicalTrials.gov (NCT00593450).

Statistical Analysis

Subjects who were ineligible for the clinical trial or had ungradable images at baseline were excluded, leaving a total of 1131 patients available for data analysis (Fig 2). Three groups were formed on the basis of baseline CME and IRF status: those with (1) CME; (2) IRF without CME; or (3) neither CME nor IRF. The comparison of baseline characteristics, visual outcomes, and morphologic outcomes was performed using analysis of variance for most continuous measures and Monte Carlo exact tests for categoric measures. When the distribution of continuous measures was highly skewed, the nonparametric Kruskal−Wallis test was used. Linear regression models were used to adjust for the effects of previously identified risk factors for VA and change from baseline in VA at 1 year.[12] All the statistical analyses were performed in SAS v9.4 (SAS Inc, Cary, NC), and a 2-sided P value <0.05 was considered to be statistically significant.

Results

Baseline Characteristics by Cystoid Macular Edema and Intraretinal Fluid Status

Among the 1131 participants in the data analysis at baseline, 92 (8.1%) had CME, 766 (67.7%) had IRF without CME, and 273 (24.1%) had neither. Baseline demographic features and baseline VA were compared among groups (Table 1). Those with CME or IRF without CME were approximately 2 years older than those with neither CME nor IRF ($P < 0.001$). There was no difference among groups in prevalence of hypertension, myocardial infarction, congestive heart failure, and history of stroke/transient

Figure 1. Example of subject with angiographic cystoid macular edema (CME). Color fundus photograph of the left eye (**left**) showing pigmentary changes along with drusen; early frame of fluorescein angiogram (**center**) showing multiple foveal and parafoveal areas of hyperfluorescence corresponding to drusen and choroidal neovascularization (CNV); late frame of angiogram (**right**) showing petaloid leakage around the fovea.