AMERICAN ACADEMY™ OF OPHTHALMOLOGY

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

*Neepa Shah, MD,[1] Maureen G. Maguire, PhD,[1] Daniel F. Martin, MD,[2] James Shaffer, MS,[1] Gui-Shuang Ying, PhD,[1] Juan E. Grunwald, MD,[1] Cynthia A. Toth, MD,[3] Glenn J. Jaffe, MD,[3] Ebenezer Daniel, MBBS, PhD,[1] for the Comparison of Age-related Macular Degeneration Treatments Trials Research Group**

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;123:858-864 © 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

http://dx.doi.org/10.1016/j.ophtha.2015.11.030
ISSN 0161-6420/15

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 subretinal 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

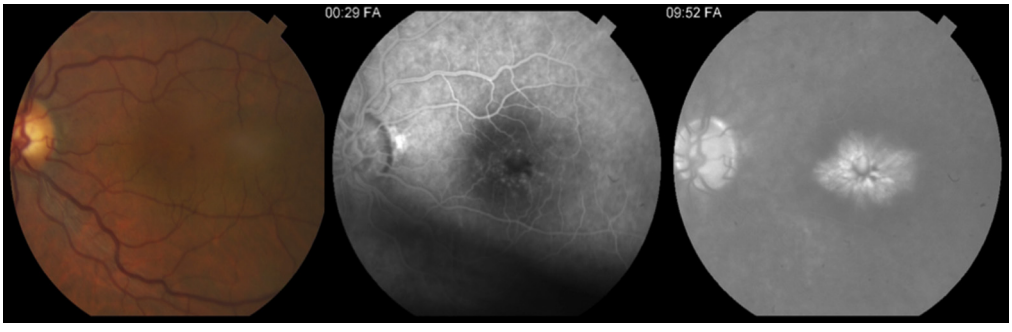

Figure 1. Example of subject with angiographic cystoid macular edema (CME). Color fundus photograph of the left eye (**left**) showing pigmentary changes along with drusen; early frame of fluorescein angiogram (**center**) showing multiple foveal and parafoveal areas of hyperfluorescence corresponding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

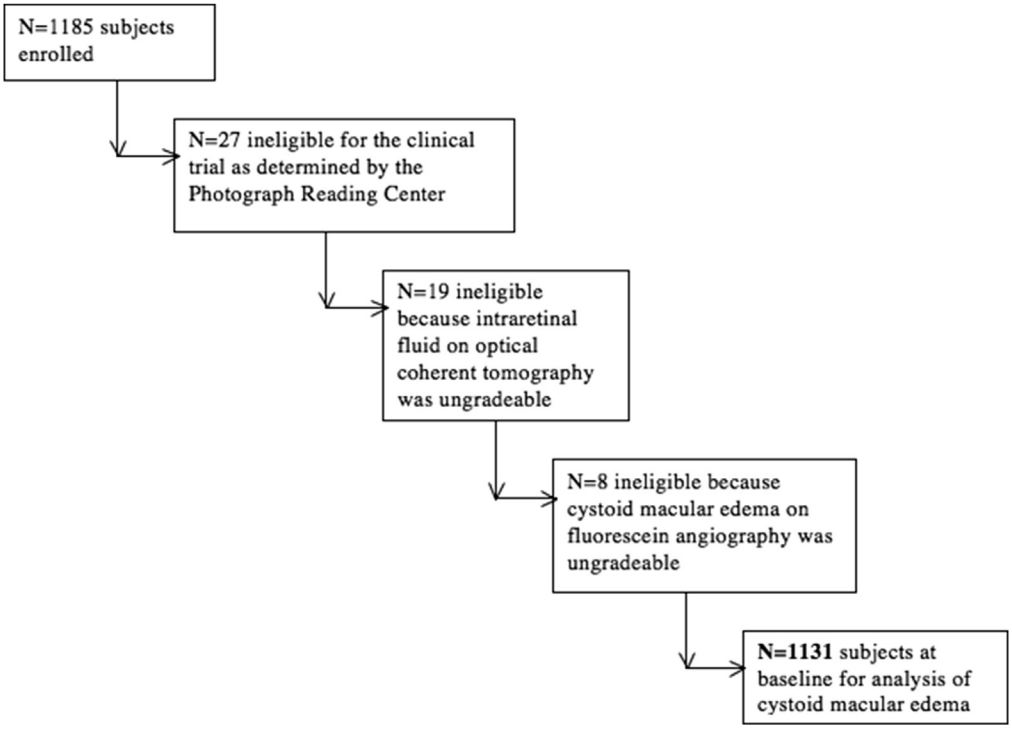

Figure 2. Eligibility flowchart for the study of cystoid macular edema (CME).

ischemic attack. Patients with CME and IRF had lower rates of diabetes mellitus (16.3% and 15.7%, respectively) than patients with neither CME nor IRF (22.7%) ($P = 0.04$). The mean [standard error] VA score (letters) at baseline was worst for those with CME (52.3 [1.52]) compared with those with IRF without CME (59.9 [0.48]) and those with neither CME nor IRF (65.8 [0.66]) ($P < 0.001$).

The CNV and OCT characteristics at baseline were also compared by CME and IRF status (Table 2). The proportion with subfoveal CNV was higher in the group with CME (81.5%) than in the other 2 groups (70.5% and 74%, respectively), although the differences were not statistically significant ($P = 0.06$). Eyes with neither CME nor IRF were less likely to have hemorrhage associated with the neovascular lesion and less likely to have RAP lesions than the other groups ($P < 0.001$). Eyes with CME had a higher percentage of classic CNV on FA (52.2%) compared with eyes with IRF without CME (21.1%) and eyes with neither CME nor IRF (16.5%; $P < 0.001$). The mean total

Table 1. Baseline Characteristics by Status of Baseline Cystoid Macular Edema and Intraretinal Fluid (n = 1131)

Characteristic	Category	CME (n = 92)	IRF without CME (n = 766)	No IRF or CME (n = 273)	P Value*
Age, yrs	Mean (SE)	79.5 (0.86)	79.8 (0.27)	77.5 (0.46)	<0.001
Sex	Female, n (%)	61 (66.3)	490 (64.0)	154 (56.4)	0.06
Diabetes	Yes, n (%)	15 (16.3)	120 (15.7)	62 (22.7)	0.04
Hypertension	Yes, n (%)	64 (69.6)	538 (70.2)	179 (65.6)	0.35
History of myocardial infarction	Yes, n (%)	8 (8.7)	90 (11.7)	37 (13.6)	0.46
History of congestive heart failure	Yes, n (%)	4 (4.3)	50 (6.5)	18 (6.6)	0.80
History of stroke	Yes, n (%)	6 (6.5)	45 (5.9)	18 (6.6)	0.86
History of transient ischemic attack	Yes, n (%)	4 (4.3)	48 (6.3)	12 (4.4)	0.49
Smoking status	Never, n (%)	33 (35.9)	340 (44.4)	115 (42.1)	0.24
	Current, n (%)	13 (14.1)	59 (7.7)	25 (9.2)	
	Quit, n (%)	46 (50.0)	367 (47.9)	133 (48.7)	
BMI	Age-Adjusted Mean (SE)	27.2 (0.5)	26.9 (0.2)	27.5 (0.3)	<0.001
AREDS supplement use	Yes, n (%)	49 (53.3)	492 (64.2)	175 (64.1)	0.11
Lens status, study eye	Phakic, n (%)	34 (37.0)	328 (42.8)	135 (49.5)	0.06
VA score, study eye (letters)	Mean (SE)	52.3 (1.5)	59.9 (0.5)	65.8 (0.7)	<0.001

AREDS = Age-Related Eye Disease Study; BMI = body mass index; CME = cystoid macular edema; IRF = intraretinal fluid; SE = standard error; VA = visual acuity.
*P values are from a 1-way analysis of variance for continuous variables and Monte Carlo exact test for categoric variables.

Table 2. Baseline Choroidal Neovascularization and Optical Coherence Tomography Characteristics by Baseline Cystoid Macular Edema and Intraretinal Fluid Status

Characteristic	Category	CME (n=92)	IRF without CME (n=766)	No IRF or CME (n=273)	*P* Value*
CNV location	Subfoveal	75 (81.5)	537 (70.5)	202 (74.0)	0.06
	Not subfoveal	17 (18.5)	225 (29.5)	71 (26.0)	
	CD or CG	0	4	0	
Presence of hemorrhage associated with lesion	Yes	62 (67.4)	502 (65.7)	134 (49.4)	<0.001
	No	30 (32.6)	262 (34.3)	137 (50.6)	
	CD or CG	0	2	2	
Presence of SPED	Yes	5 (5.4)	43 (5.6)	13 (4.8)	0.87
	No	87 (94.6)	723 (94.4)	260 (95.2)	
	CD or CG	0	0	0	
Presence of blocked fluorescence	Yes	21 (22.8)	116 (15.1)	31 (11.4)	0.03
	No	71 (77.2)	650 (84.9)	242 (88.6)	
	CD or CG	0	0	0	
RAP lesions	Yes	11 (12.0)	108 (14.2)	7 (2.6)	<0.001
	No	81 (88.0)	652 (85.8)	266 (97.4)	
	CD or CG	0	6	0	
CNV type	Classic	48 (52.2)	167 (22.1)	45 (16.5)	<0.001
	Minimally classic	15 (16.3)	129 (17.0)	45 (16.5)	
	Occult	29 (31.5)	461 (60.9)	182 (66.9)	
	CD or CG	0	9	1	
Area of CNV, mm^2	Mean (SE)	1.43 (0.14)	1.87 (0.07)	1.65 (0.10)	0.35
	CD or CG	4	89	23	
Total area of CNV lesion, mm^2	Mean (SE)	1.90 (0.17)	2.57 (0.10)	2.26 (0.14)	0.11
	CD or CG	1	23	6	
Central subretinal tissue complex thickness	Mean (SE)	205 (14.1)	209 (6.2)	206 (11.0)	0.95
	CD or CG	0	1	1	
Central subretinal fluid thickness	Mean (SE)	8.6 (3.3)	31.8 (2.6)	39.2 (4.5)	0.001
	CD or CG	0	1	1	
CRT	Mean (SE)	300 (12.5)	231 (4.01)	158 (2.86)	<0.001
	CD or CG	0	1	1	
Total CRT	Mean (SE)	514 (15.8)	472 (6.82)	404 (10.4)	<0.001
	CD or CG	0	1	1	
IRF	Present	91 (98.9)	766 (100)	0 (0.00)	N/A
	Absent	1 (1.09)	0 (0.00)	273 (100)	
	CD or CG	0	0	0	
Subretinal fluid	Present	67 (74.4)	611 (80.4)	250 (91.9)	<0.001
	Absent	23 (25.6)	149 (19.6)	22 (8.09)	
	CD or CG	2	6	1	
Sub-RPE fluid	Present	30 (35.3)	395 (55.8)	129 (49.8)	0.001
	Absent	55 (64.7)	313 (44.2)	130 (50.2)	
	CD or CG	7	58	14	

CD = cannot determine; CG = cannot grade; CME = cystoid macular edema; CNV = choroidal neovascularization; CRT = central retinal thickness; IRF = intraretinal fluid; N/A = not available; RAP = retinal angiomatous proliferans; RPE = retinal pigment epithelium; SE = standard error; SPED = serous pigment epithelium detachment.
*For continuous variables, *P* values are from a 2-way analysis of variance except that the Kruskal–Wallis test was used for area of CNV and total area of CNV lesion. For categoric variables, *P* values are from the Monte Carlo exact test. CD and CG are not included in statistical tests.

central retinal thickness (CRT) was highest for the CME group (514 [15.8] μm) compared with those with IRF without CME (472 [6.68] μm) and those with neither IRF nor CME (404 [10.4] μm, $P < 0.001$). Eyes with CME were less likely to have subretinal or sub-RPE fluid than eyes in the other groups ($P < 0.05$ for all comparisons).

Change in Visual Acuity and Central Retinal Thickness over Time by Cystoid Macular Edema and Intraretinal Fluid Status

The graph in Figure 3A shows the mean change in VA for each group over the 2-year time period of study. All groups showed considerable improvement in VA after treatment. At week 52, the mean change in VA (letters) was 8.82 in the group with CME, 7.23 in the group with IRF without CME, and 6.91 in the group with neither CME nor IRF ($P = 0.59$). At week 104, the corresponding mean changes were 10.0, 5.89, and 6.31 letters, respectively ($P = 0.13$). After adjustment for previously identified risk factors for worse VA (including baseline VA and age), the mean changes in VA for the 3 groups were 7.7, 7.3, and 7.2, respectively ($P = 0.97$), at week 52; and 7.8, 6.0, and 6.8, respectively ($P = 0.59$), at week 104. Those with CME started off with the worst VA and continued to have the worst VA at each time point through 2 years (Fig 3B) ($P < 0.001$ at each point). At week 52, the mean VA (letters) was 61.2 in the

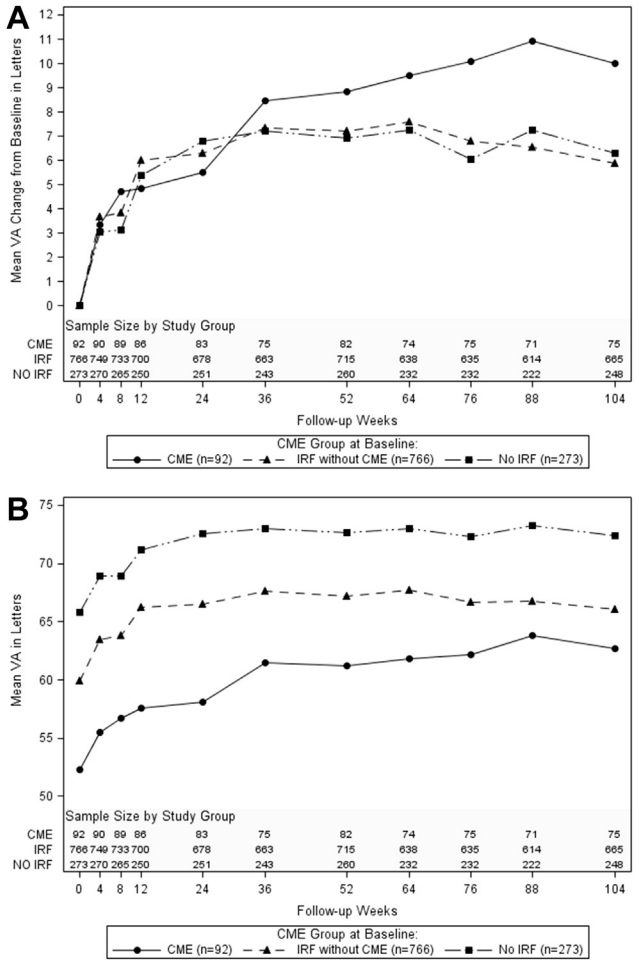

Figure 3. **A**, Change in visual acuity (VA) from baseline by cystoid macular edema (CME) and intraretinal fluid (IRF) status. **B**, Mean VA over time by CME and IRF status.

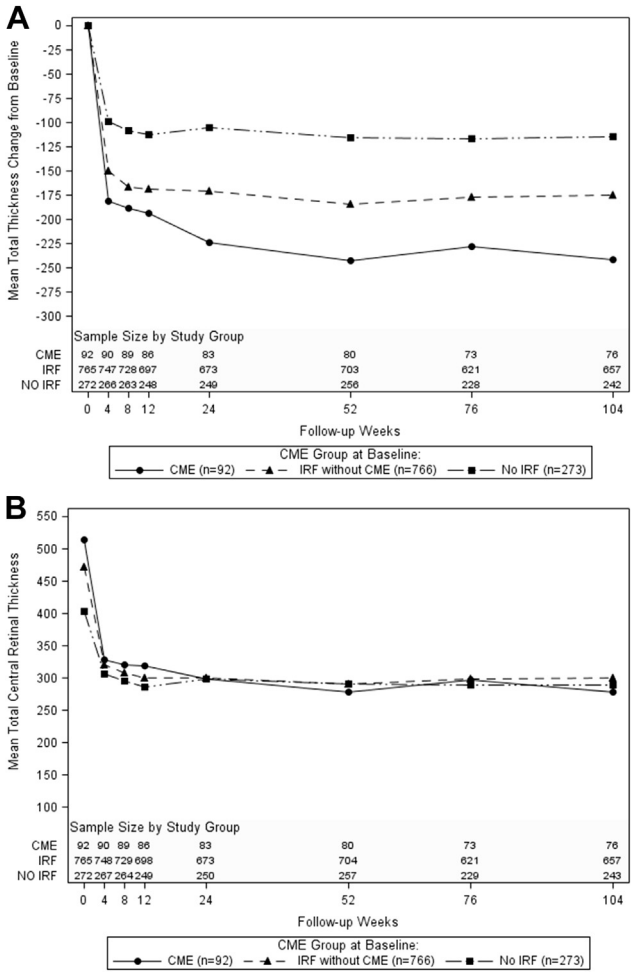

Figure 4. **A**, Change in total central retinal thickness (CRT) from baseline by cystoid macular edema (CME) and intraretinal fluid (IRF) status. **B**, Total CRT over time by CME and IRF status.

group with CME, 67.2 letters in the group with IRF without CME, and 72.7 in the group with neither CME nor IRF ($P < 0.001$). At week 104, the corresponding means were 62.7, 66.1, and 72.4 letters, respectively ($P < 0.001$). After adjustment for previously identified risk factors for worse VA, the mean visual acuities for the 3 groups were 67.7, 68.2, and 68.4, respectively ($P = 0.94$), at week 52 and 67.9, 67.2, and 68.3, respectively ($P = 0.67$), at week 104.

Figure 4A shows the mean change in total CRT after treatment for each group. The group with CME had the largest decrease in mean CRT at all points during follow-up. At week 104, the mean decrease in CRT thickness was 241 μm in the group with CME, 175 μm in the group with IRF without CME, and 114 μm in the group with neither CME nor IRF ($P < 0.001$). By 24 weeks and beyond, all groups had similar mean total CRT (Fig 4B).

Study Eye Features over Time by Cystoid Macular Edema and Intraretinal Fluid Status

Table 3 summarizes the morphologic findings over the follow-up period in eyes with CME compared with eyes without CME at baseline. At both 52 and 104 weeks follow-up, eyes with CME or IRF at baseline had lower percentages of active CNV. At 104 weeks, 24.0% of those with CME had active CNV compared with 26.2% with IRF without CME and 36.0% without IRF or CME ($P = 0.01$). Those with IRF (both CME and non-CME eyes) had the highest rates of geographic atrophy at baseline and 1 and 2 years follow-up ($P < 0.001$ for all time points). Although all groups had similar rates of scarring at baseline ($P = 0.41$), 17.3% of CME eyes had a scar at the foveal center at 2 years follow-up compared with 6.7% of IRF eyes and 6.9% of eyes with neither CME nor IRF ($P < 0.001$). Among patients treated PRN for 2 years, the total number of injections was similar among the 3 groups with an adjusted mean of 12.2 in the group with CME, 12.3 in the group with IRF without CME, and 12.5 in the group with neither CME nor IRF ($P = 0.95$).

Discussion

Previously published results from CATT and other large-scale studies have shown that the presence of IRF during follow-up is associated with worse VA, whereas the presence of sub-RPE fluid has relatively little impact on vision and the presence of subretinal fluid is associated with better VA.[7,8] Our study examined a specific type of IRF—angiographically present CME—and assessed its impact on visual

Table 3. Presence of Study Eye Features over Time by Cystoid Edema and Intraretinal Fluid Status

Study Eye Feature	Week	N	CME (n = 92)	IRF without CME (n = 766)	No IRF or CME (n = 273)	*P* Value*
Visual acuity, letters, mean (SE)	000	(92, 766, 273)	52.3 (1.5)	59.9 (0.5)	65.8 (0.7)	<0.001
	052	(82, 715, 260)	61.2 (2.3)	67.2 (0.7)	72.7 (1.0)	<0.001
	104	(75, 665, 248)	62.7 (1.9)	66.1 (0.7)	72.4 (1.0)	<0.001
Presence of active CNV leakage, n (%)	000	(92, 766, 273)	92 (100)	766 (100)	273 (100)	1.00
	052	(78, 673, 251)	31 (39.7)	301 (44.7)	132 (52.6)	0.048
	104	(75, 637, 242)	18 (24.0)	167 (26.2)	87 (36.0)	0.014
Presence of GA at fovea center, n (%)	000	(92, 766, 273)	0 (0.0)	1 (0.1)	0 (0.)	1.00
	052	(79, 690, 254)	0 (0.0)	20 (2.9)	4 (1.6)	0.22
	104	(75, 655, 245)	5 (6.7)	46 (7.0)	7 (2.9)	0.048
Presence of atrophic scar/fibrosis at fovea center, n (%)	000	(87, 742, 265)	1 (1.1)	3 (0.4)	1 (0.4)	0.41
	052	(79, 690, 254)	10 (12.7)	41 (5.9)	22 (8.7)	<0.001
	104	(75, 655, 245)	13 (17.3)	44 (6.7)	17 (6.9)	<0.001

CME = cystoid macular edema; CNV = choroidal neovascularization; GA = geographic atrophy; IRF = intraretinal fluid; SE = standard error.
**P* values are from a 1-way analysis of variance for continuous variables and the Monte Carlo exact test for categoric variables.

outcomes in the CATT study patients. We found an association between angiographic CME and VA, but not with change in VA after treatment. After adjustment for other risk factors for VA during follow-up, the VA at 1 and 2 years of follow-up was similar whether IRF or CME was present, so having CME does not portend posttreatment VA worse than would be expected on the basis of the pretreatment level of VA. In addition, although total CRT for eyes with CME was greater at baseline than in eyes with IRF without CME and in eyes with neither CME nor IRF, this equalized in all groups at 1 and 2 years follow-up. Despite these findings, eyes with CME had the worst VA both at baseline and at 2 years follow-up.

At baseline, the patients with CME, as well as those with IRF were slightly older with lower mean BMI. This raises the possibility that IRF and CME may develop in patients with more fragile health. However, diabetes was less common in patients with CME or IRF. Pseudophakic eyes were more common in the CME group, but not to a statistically significant degree ($P = 0.06$). It is not surprising that CME with IRF had an association with RAP lesions because there is disruption of the inner retina during this process.[13] The CME group had a higher proportion of classic CNV, known to be associated with worse VA at presentation.

The reason that the CME group had worse VA at study entry and during follow-up is likely multifactorial. First, our study showed that a high proportion of CME is associated with subfoveal CNV, which has a greater negative impact on vision than occult or nonfoveal lesions.[14] Second, as mentioned previously, associations with hemorrhage and RAP lesions also may lead to further retinal damage and poor visual recovery because these entities are thought to be associated with more "aggressive" nAMD.[13] Third, despite there being less active CNV leakage at week 104 in the CME group compared with the others with anti-VEGF therapy, there were higher rates of geographic atrophy and scarring in this group. The proportion with foveal geographic atrophy was similar in eyes with CME and eyes with IRF without CME, but higher than in the eyes with neither CME nor IRF. Formation of a scar occurred more often in eyes with CME, especially near the fovea. The higher incidence of scarring with CME may be related to the fact that more of these patients have classic CNV, which histopathologically corresponds to type 2 CNV located between the RPE and the neurosensory retina; thus, contraction of this type of CNV leads to RPE loss or hyperplasia. Last, CME is a marker for fluid persistence in nAMD and signifies patients with worse disease at baseline. With the exception of RAP-associated exudation, the exudative process in nAMD typically begins in the outer retina with collection of fluid here first and pervades the inner retina only when the external limiting membrane is broken down, which is related to the amount and time the fluid is present. The damage incurred to the retinal microstructure from this process creates an effect of poor VA that persists despite resolution of the fluid on OCT at 52 and 104 weeks.

In conclusion, CME is associated with worse VA in patients with nAMD. Patients with CME have an improvement in VA after anti-VEGF treatment similar in magnitude to the improvement in other treated eyes, but not enough to compensate for their initially poor VA. Although CME is not commonly seen with nAMD, its presence should alert the clinician of poorer visual outcomes and higher rates for eventual atrophy and scarring.

References

1. Quinn CJ. Cystoid macular edema. Optom Clin 1996;5: 111–30.
2. Jaffe G, Cahill MT. Cystoid macular edema. In: Huang D, ed. Retinal Imaging. 18. Philadelphia, PA: Mosby Elsevier; 2006: 206–18.
3. Gass JDM. Current concepts concerning cystoid macular edema. In: Franklin RM, ed. Retina and Vitreous: Proceedings of the Symposium on Retina and Vitreous. Amsterdam: Kugler; 1993:295–7.
4. Jampol LM, Stephanie MP. Macular edema. In: Ryan S, ed. Retina. 2nd ed. 2. St. Louis, MO: Mosby; 1994. 61:999-1008.

5. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.
6. CATT Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–98.
7. Jaffe GJ, Martin DF, Toth CA, et al; CATT Research Group. Macular morphology and visual acuity in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2013;120:1860–70.
8. Ritter M, Simader C, Bolz M, et al. Intraretinal cysts are the most relevant prognostic biomarker in neovascular age-related macular degeneration independent of the therapeutic strategy. Br J Ophthalmol 2014;0:1–7.
9. Grunwald JE, Daniel E, Ying GS, et al; CATT Research Group. Photographic assessment of baseline fundus morphologic features in the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology 2012;119:1634–41.
10. DeCroos FC, Toth CA, Stinnett SS, et al; CATT Research Group. Optical coherence tomography grading reproducibility during the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology 2012;119:2549–57.
11. Williams TD, Wilkinson JM. Position of the fovea centralis with respect to the optic nerve head. Optom Vis Sci 1992;69:369–77.
12. Ying GS, Huang J, Maguire MG, et al; CATT Research Group. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2013;120:122–9.
13. Yannuzzi LA, Freund KB, Takahashi BS. Review of retinal angiomatous proliferation or type 3 neovascularization. Retina 2008;28:375–84.
14. Bressler SB, Bressler NM, Fine SL, et al. Subfoveal neovascular membranes in senile macular degeneration: relationship between membrane size and visual prognosis. Retina 1983;3:7–11.

Footnotes and Financial Disclosures

Originally received: July 2, 2015.
Final revision: November 28, 2015.
Accepted: November 30, 2015.
Available online: January 8, 2016. Manuscript no. 2015-1116.

[1] Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

[3] Department of Ophthalmology, Duke University, Durham, North Carolina.

*A complete list of participating members of the CATT Research Group can be found in the Appendix (available at www.aaojournal.org).

Financial Disclosure(s):
The author(s) have made the following disclosure(s): M.G.M.: Consultant – Genentech.

G.-S.Y.: Consultant – Janssen.

C.A.T.: Funding – Genentech, Bioptigen; Patents – Alcon; Consultant –Thrombogenics.

G.J.J.: Consultant – Heidelberg Engineering, Roche/Genentech, Novartis/Alcon, Neurotech.

Supported by grants R21EY023689, U10EY017823, U10EY017825, U10EY017826, and U10EY017828 from the National Eye Institute, National Institutes of Health, Department of Health and Human Services. ClinicalTrials.gov number, NCT00593450. The sponsor or funding organization had no role in the design or conduct of this research.

Author Contributions:

Conception and design: Shah, Maguire, Ying, Daniel

Data collection: Shah, Maguire, Martin, Shaffer, Ying, Grunwald, Toth, Jaffe, Daniel

Analysis and interpretation: Shah, Maguire, Martin, Shaffer, Ying, Grunwald, Toth, Jaffe, Daniel

Obtained funding: Not applicable

Overall responsibility: Shah, Maguire, Martin, Ying, Toth, Jaffe, Daniel

Abbreviations and Acronyms:
CATT = Comparison of Age-related Macular Degeneration Treatments Trials; **CME** = cystoid macular edema; **CNV** = choroidal neovascularization; **CRT** = central retinal thickness; **FA** = fluorescein angiography; **IRF** = intraretinal fluid; **nAMD** = neovascular age-related macular degeneration; **OCT** = optical coherence tomography; **PRN** = pro re nata; **RAP** = retinal angiomatous proliferation; **RPE** = retinal pigment epithelium; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

Correspondence:
Neepa Shah, MD, Scheie Eye Institute, Presbyterian Medical Center, 51 N. 39th St., Philadelphia, PA 19104. E-mail: neepa.shah@uphs.upenn.edu.