Macular Morphology and Visual Acuity in the Comparison of Age-related Macular Degeneration Treatments Trials

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Objective: To describe the effects of treatment for 1 year with ranibizumab or bevacizumab on macular morphology and the association of macular morphology with visual acuity (VA) in eyes with neovascular age-related macular degeneration (AMD).

Design: Prospective cohort study within a randomized clinical trial.

Participants: Participants in the Comparison of Age-related Macular Degeneration Treatments Trials.

Methods: Participants were assigned randomly to treatment with ranibizumab or bevacizumab on a monthly or as-needed schedule. Optical coherence tomography (OCT), fluorescein angiography (FA), color fundus photography (FP), and VA testing were performed periodically throughout 52 weeks. Masked readers graded images. General linear models were applied to evaluate effects of time and treatment on outcomes.

Main Outcome Measures: Fluid type and location and thickness by OCT, size, and lesion composition on FP, FA, and VA.

Results: Intraretinal fluid (IRF), subretinal fluid (SRF), subretinal pigment epithelium fluid, and retinal, subretinal, and subretinal tissue complex thickness decreased in all treatment groups. A higher proportion of eyes treated monthly with ranibizumab had fluid resolution at 4 weeks, and the difference persisted through 52 weeks. At 52 weeks, there was little association between the presence of fluid of any type (without regard to fluid location) and the mean VA. However, at all time points, eyes with residual IRF, especially foveal IRF, had worse mean VA (9 letters) than those without IRF. Eyes with abnormally thin (<120 μm) or thick (>212 μm) retinas had worse VA than those with normal thickness (120–212 μm). At week 52, eyes with larger neovascular lesions or with foveal scar had worse VA than eyes without these features.

Conclusions: Anti–vascular endothelial growth factor (VEGF) therapy reduced lesion activity and improved VA in all treatment groups. At all time points, eyes with residual IRF had worse VA than those without. Eyes with abnormally thin or thick retinas, residual large lesions, and scar also had worse VA. Monthly ranibizumab dosing yielded more eyes with no fluid and an abnormally thin retina, although the long-term significance is unknown. These results have important treatment implications in eyes undergoing anti-VEGF therapy for neovascular AMD.

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The anti–vascular endothelial growth factor (VEGF) drugs ranibizumab (Lucentis; Genentech, South San Francisco, CA) and bevacizumab (Avastin; Genentech) are highly effective treatments to preserve visual acuity (VA) among individuals with neovascular age-related macular degeneration (AMD).[1–4] Despite the dramatic effects on VA, many of the neovascular lesions continue to leak fluid and increase in size, as seen on fluorescein angiography (FA) and optical coherence tomography (OCT).[1–4] The associations between macular morphologic features and VA after intravitreal anti-VEGF treatment are complex and not well understood. In an attempt to shed light on these associations, we now describe the effect of different anti-VEGF treatment strategies on the activity and composition of choroidal neovascularization (CNV) lesions as determined on OCT, color fundus photography (FP), and FA, as well as the association of lesion activity and composition with VA outcomes among participants of the Comparison of AMD Treatments Trials (CATT).

Materials and Methods

Study Population

Details of the design and methods for CATT have been published previously.[3] Parameters used to determine the participants'

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morphologic features at baseline and 52 weeks are summarized. A total of 1185 subjects were enrolled by 43 US clinical centers between February 2008 and December 2009. Only 1 eye per subject, the study eye, was treated as a part of the clinical trial. Inclusion criteria included subject age ≥50 years, presence of previously untreated active CNV secondary to AMD in the study eye, and VA between 20/25 and 20/320. Choroidal neovascularization was considered active when leakage or increased stippling on FA and fluid on time-domain OCT were documented through central image review. Fluid on OCT could be within or below the retina or below the retinal pigment epithelium (RPE). Choroidal neovascularization or its sequelae (i.e., pigment epithelium detachment, hemorrhage, blocked fluorescence, macular edema, or fluid) needed to involve the center of the fovea. For the CNV to be considered secondary to AMD, at least 1 druse >63 μm needed to be present in the study eye or fellow eye, or the fellow eye needed to have CNV or geographic atrophy. Participants were assigned randomly with equal probability to 1 of 4 treatment groups: (1) ranibizumab monthly, (2) bevacizumab monthly, (3) ranibizumab as needed (pro re nata [PRN]), or (4) bevacizumab PRN. The institutional review boards associated with each center approved the study. All participants provided written informed consent.

Study Procedures

All image readers and visual function examiners were masked to the subjects' treatment assignment. Certified technicians following standardized procedures performed time-domain OCT on all participants at baseline and at 4, 8, 12, 24, and 52 weeks. Technicians obtained Stratus (Carl Zeiss Meditec, Jena, Germany) OCT images in the study eye with the Macular Thickness Map and Fast Macular Thickness Map protocols.[5] Two certified readers at the CATT OCT Reading Center independently analyzed all scans for morphologic characteristics. Readers identified intraretinal fluid (IRF), subretinal fluid (SRF), and fluid below the RPE (sub-RPE fluid), and when fluid was present, they noted the location of fluid relative to the foveal center: foveal or subfoveal (within 500 μm of the foveal center) or beyond 500 μm of foveal center. Readers also measured the foveal center retinal thickness, SRF thickness, and subretinal tissue complex thickness, which included material between the inner retina or SRF, if present, and Bruch's membrane. Morphologically, the subretinal tissue complex thickness included material above the RPE, termed *subretinal highly reflective material*, which comprises CNV (and blood and fibrosis, when present), the RPE, and material under the RPE (when an RPE detachment was present). The sum of the 3 thickness measurements was termed *total thickness*.[6] A senior reader reconciled any grading disagreements between the initial reader pair.

Certified photographers obtained stereoscopic FP and FA with standardized procedures on all participants at baseline and 52 weeks.[7] Two certified readers at the CATT Photography Reading Center independently analyzed all photographic images, including FP and FA, to identify the lesion components or fluid under the foveal center, dye leakage on FA, and neovascular lesion area (mm^2). The baseline neovascular lesion, denoted total CNV lesion, included CNV and contiguous areas of serous pigment epithelium detachment, scar, hemorrhage, and blocked fluorescence. At week 52, geographic atrophy and RPE tear were also included as lesion components when they were within the baseline neovascular lesion. Two readers adjudicated any grading discrepancies; the Reading Center's principal investigator determined the final grade when the readers could not come to consensus.

Certified visual function examiners followed a standardized protocol to measure VA on all participants at baseline and at weeks 4, 12, 24, 36, and 52. Examiners performed subjective refraction and tested VA with an electronic testing system.[8]

Eyes assigned to monthly treatment received an injection of their assigned drug, 0.5 mg (0.05 ml) of ranibizumab or 1.25 mg (0.05 ml) of bevacizumab, approximately every 28 days unless they missed a scheduled visit or developed contraindications to treatment. Eyes assigned to PRN treatment were evaluated approximately every 28 days and treated with their assigned drug when there was fluid on OCT or other signs of active neovascularization.[3]

Data and Statistical Analysis

Only patients who met all eligibility criteria for the clinical trial (n=1142) were included in the analysis for this article. The numbers of patients with OCT scans available for grading was 1116, 1091, 1048, 1015, and 1053 at weeks 4, 8, 12, 24, and 52, respectively. The number of patients with FP and FA available for grading was 1033 at week 52. In addition, specific features on images could be ungradable because of insufficient image quality; the percentage of images ungradable at any particular time was approximately 2% or less each for OCT scans, FP, and FA.

Thickness measurements based on OCT were divided into categories as follows: total thickness: 0−325, 326−425, 426−550, and >550 μm; retinal thickness: 0−119, 120−212, and >212 μm; SRF thickness: 0, 1−25, and >25 μm; and subretinal tissue complex: 0−75, 76−160, 161−275, and >275 μm. Categories were based on the baseline quartiles except for retinal thickness, which was determined on the basis of the mean of healthy eyes on Stratus OCT measured manually ±2 standard deviations.[9]

General linear models were used to compare the retinal morphology responses or VA responses among 4 treatment groups, between 2 drug groups, or between 2 treatment regimens. Time was treated as a continuous variable to assess the retinal morphology responses (presence of OCT fluid and OCT thickness) or VA responses over time. The interactions of morphologic responses and VA with treatment groups, drug groups, and regimens also were determined. The relationships between retinal thickness and VA were explored using locally weighted scatterplot smoothing (LOWESS) plots.[10] The association of retinal morphology findings from FP, FA, or OCT with VA at 1 year was analyzed by multiple regression models, which went through backward elimination processes by retaining in the model only the statistically significant morphology findings. All statistical analyses were performed in SAS version 9.2 (SAS Inc., Cary, NC), and 2-sided P values <0.05 were considered to be statistically significant.

Results

Optical Coherence Tomography Morphologic Characteristics Over Time by Treatment Group

Presence and Type of Fluid on Optical Coherence Tomography Over Time

At baseline, all eligible eyes had at least 1 type of fluid, reflecting active CNV. The distribution of each fluid type at baseline was similar among the 4 treatment groups (Fig 1A−D). A high proportion of eyes had both SRF (83.8%) and IRF (76.7%). Sub-RPE fluid was present in approximately half (53.7%) of the eyes.

After anti-VEGF therapy, in all treatment groups, the proportion of eyes with fluid of any type (intraretinal, subretinal, or sub-RPE fluid) decreased markedly (Fig 1A). The largest decrease in the proportion with fluid of any type was observed between baseline

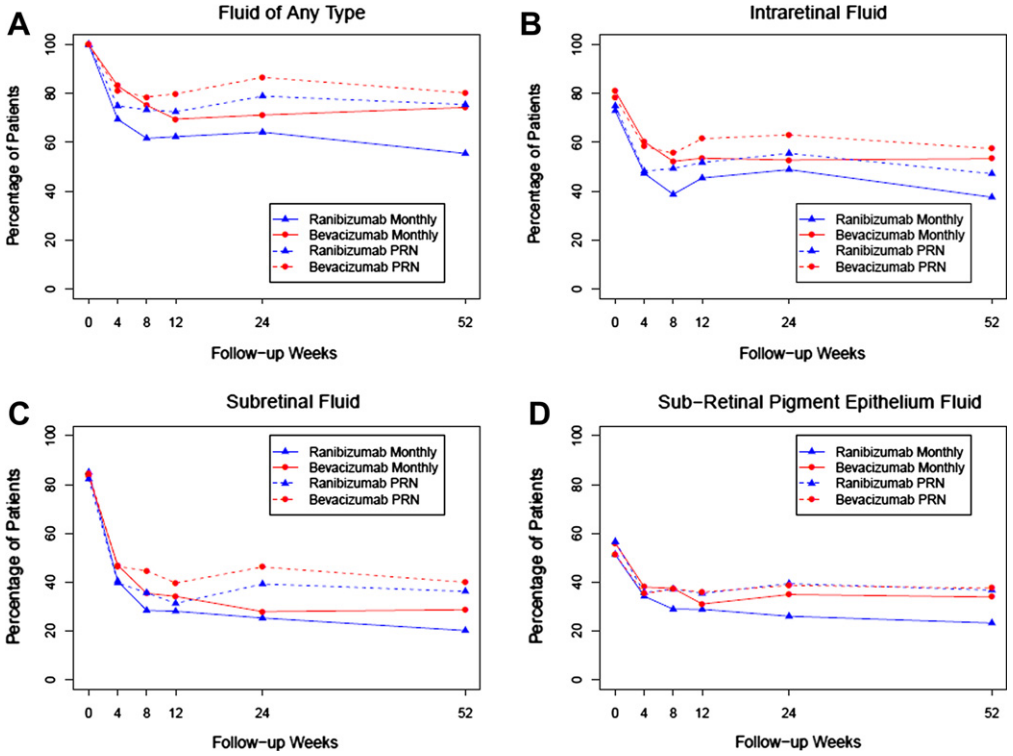

Figure 1. Percentage in each treatment group over time with fluid of any type **(A)**, intraretinal fluid **(B)**, subretinal fluid **(C)**, and subretinal pigment epithelium fluid **(D)**. PRN = pro re nata (as needed).

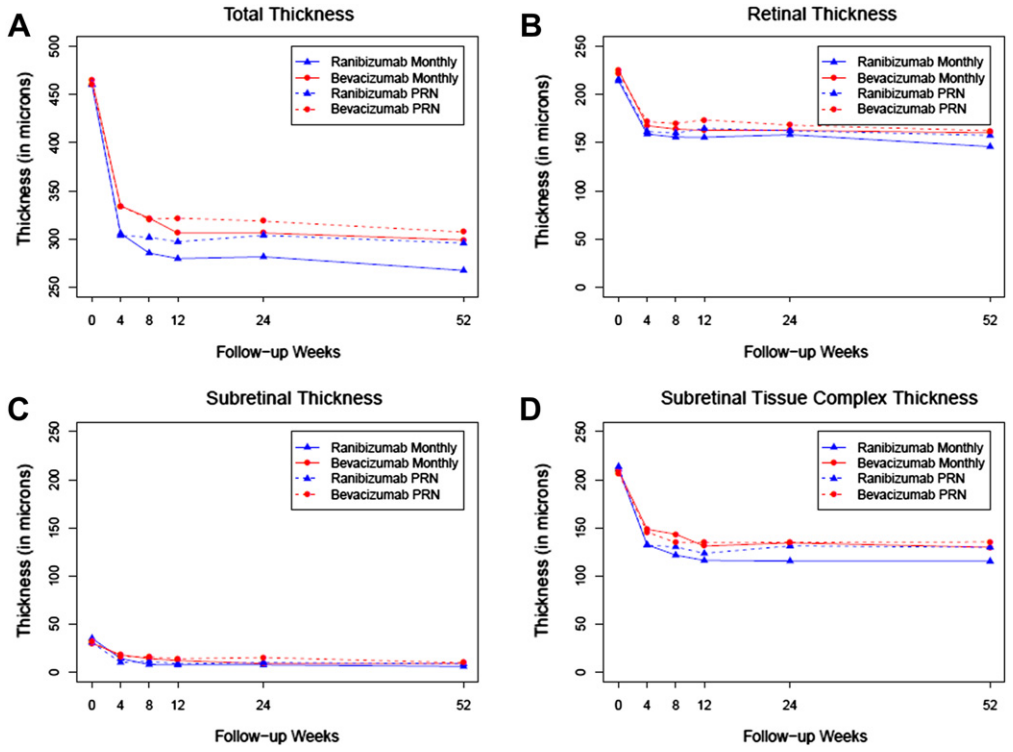

Figure 2. The optical coherence tomography thickness over time by treatment group for total thickness **(A)**, retinal thickness **(B)**, subretinal thickness **(C)**, and subretinal tissue complex thickness **(D)**. PRN = pro re nata (as needed).

and 4 weeks, the time of the first OCT after the initial treatment. There was a further small decrease in the proportion with fluid of any type between 4 and 8 weeks, followed by relatively little change through week 52. Also, for each of the 3 types of fluid, the largest decrease in the proportion with fluid was observed between baseline and 4 weeks (Fig 1B–D). At 4 weeks, the decline in the proportion of eyes with each type of fluid for all treatment groups combined was largest for SRF (40.5%), followed by IRF (23.3%), and then sub-RPE fluid (18.0%). There was further decrease over time through week 52, mainly between weeks 4 and 8 for SRF ($P < 0.0001$), sub-RPE fluid ($P=0.0009$), and IRF ($P=0.06$).

Although SRF was the fluid type most commonly seen in all groups at baseline, because of the marked reduction in SRF at 4 weeks, by week 52, the proportion of eyes with IRF (48.7%) was greater than the proportions with SRF (31.2%) or sub-RPE fluid (32.8%; all $P < 0.0001$).

Impact Over Time of Drug and Dosing Regimen on Optical Coherence Tomography–Determined Fluid

The drug and dosing regimen administered during the first year of the study influenced the changes in the proportion of eyes with fluid of any type (Fig 1A). Ranibizumab resolved fluid of any type more effectively than bevacizumab over the first 4 weeks ($P < 0.0001$); thereafter, the difference between drugs persisted but did not change significantly over the next 48 weeks. Furthermore, monthly treatment eliminated fluid of any type during the first year more effectively than PRN treatment ($P=0.002$). The joint effects of the drug and regimen used during the first year yielded considerable variation in the percentage of eyes at week 52 with complete fluid resolution. Complete resolution was observed in 44.6% of eyes treated monthly with ranibizumab, 25.7% of eyes treated monthly with bevacizumab, 24.5% of eyes treated PRN with ranibizumab, and 19.8% of eyes treated PRN with bevacizumab.

When the proportions of eyes with each of the 3 fluid types were considered, modest differences in the effects of drug and dosing regimen again emerged (Fig 1B–D). Ranibizumab better eliminated IRF than bevacizumab ($P=0.001$); the difference between drugs was less marked for SRF ($P=0.052$) and sub-RPE fluid ($P=0.11$). The difference in IRF resolution between drugs was apparent by week 4 and then persisted with little change over the next 48 weeks (Fig 1B). In contrast, the difference in the proportion with fluid between eyes treated monthly and eyes treated PRN increased over time during the first year for SRF ($P < 0.0001$) and sub-RPE fluid ($P < 0.006$). The difference between dosing regimens on IRF did not increase with time ($P=0.24$).

Impact Over Time of Drug and Dosing Regimen on Optical Coherence Tomography–Determined Thickness Measurements

In all treatment groups, anti-VEGF therapy substantially reduced total thickness (Fig 2A). After a sharp decrease from a mean (standard error [SE]) at baseline of 462 (5.5) μm to 319 (4.5) μm at 4 weeks, there was additional decrease in total thickness, mainly between weeks 4 and 8. The pattern of decrease over time was similar for retinal, SRF, and subretinal tissue complex thicknesses (Fig 2B–D).

Eyes treated with ranibizumab had a larger decrease between baseline and week 4 in mean total thickness than eyes treated with bevacizumab (Fig 2A; $P=0.002$); this initial difference between drugs persisted through week 52. After week 4, the difference in mean total thickness between eyes treated monthly and eyes treated PRN increased over time ($P=0.03$, Fig 2A). Most of the differences in total thickness among treatment groups were attributable to the effects on the subretinal tissue complex. The mean subretinal tissue complex thickness decreased more between baseline and 4 weeks in eyes treated with ranibizumab ($P=0.008$), and the difference persisted through week 52. Also, decrease in mean thickness of the subretinal tissue complex between weeks 4 and 52 was greater for eyes treated monthly than for eyes treated PRN ($P=0.04$; Fig 2D).

As one would expect, the proportion of eyes with thinner than normal retinas (<120 μm, which is >2 standard deviations from the mean Stratus measurement among normal subjects[9]) was small at baseline and increased progressively in all treatment groups by week 52 (Fig 3). This effect was more pronounced among the eyes treated with ranibizumab on a monthly basis. In this treatment group, there was a higher proportion of eyes with thinner than normal retinas by week 52 when compared with the other treatment groups (26.4% vs. 20.2%, respectively; $P=0.05$). At the same time, the number of eyes with thicker than normal retinas, >212 μm, decreased markedly between the baseline and week 52 visits, and the lowest proportion of eyes with thicker than normal retinas was observed in the ranibizumab monthly treatment group (Table 1; Fig 3).

Given the higher proportion of thinner than normal retinas in eyes treated monthly with ranibizumab, we determined whether the difference in retinal thickness depended on residual IRF. When one considers only eyes without residual IRF at the foveal center, eyes treated with ranibizumab monthly still had a higher proportion of abnormally thin retinas (28.4%) compared with the other 3 treatment groups combined (22.3%), but not to a statistically significant degree ($P=0.06$; Table 1).

Lesion Components Under the Foveal Center by Drug and Dosing Regimen

On baseline FA and FP, the majority of eyes (59.2%) had CNV under the foveal center, 26.8% had fluid only, and an additional 8.0% had hemorrhage under the foveal center (Fig 4A). After 52 weeks of anti-VEGF therapy, the percentages with CNV under the foveal center decreased substantially to 24.8% (Fig 4B). Only 3 eyes (0.3%) had hemorrhage in the foveal center, and the percentage with only fluid decreased to 8.2%. Nongeographic atrophy (depigmented RPE without clearly defined boundaries) developed in the foveal center in 14.6% of eyes, and scar developed in 18.6% of eyes. There was no foveal center pathology in 19.6% of eyes, the majority of which had fluid only (60.1%) or hemorrhage (7.4%) in the foveal center at baseline.

Among the 4 treatment groups, foveal involvement at baseline was similar (data not shown). At 52 weeks, the distribution of foveal center CNV and CNV sequelae was generally similar across all treatment groups, with no significant drug or dosing regimen effects ($P > 0.07$; Fig 5A–D).

Correlation of Morphology with Visual Acuity

To assess the functional impact of observed morphologic changes induced by anti-VEGF therapy, we determined the correlation of VA with OCT and photographic (color fundus photographic and angiographic) morphologic parameters stratified by drug and regimen.

Correlation of Fluid on Optical Coherence Tomography with Visual Acuity

Among all participants, at 52 weeks there was little association between the presence of fluid of any type (without regard to fluid location) and the mean VA. Furthermore, the mean (SE) VA was similar whether fluid was absent (69.7 [1.0] letters), foveal (67.5 [0.8] letters), or extrafoveal (68.4 [1.0] letters); $P=0.25$; Fig 6A).

In contrast to results obtained without regard to fluid location, when each fluid location was considered individually, eyes with

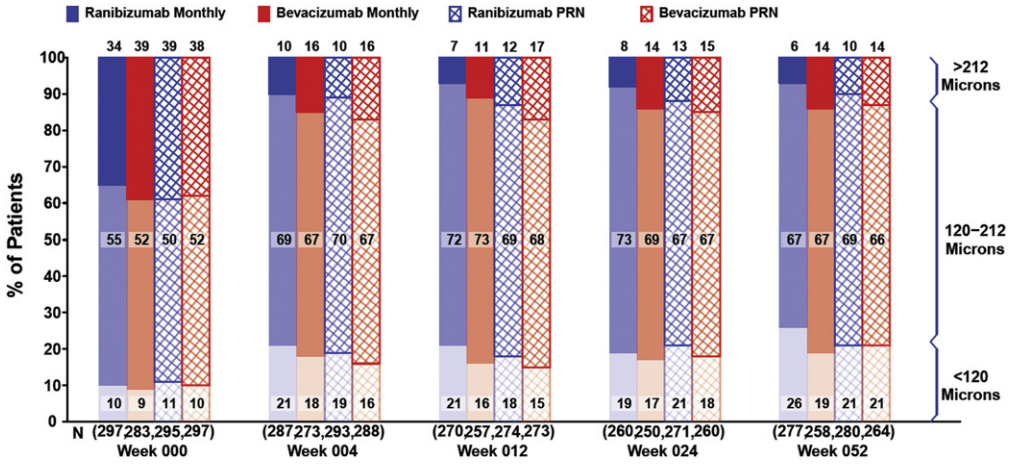

Figure 3. Retinal thickness category over time by treatment group. PRN = pro re nata (as needed).

IRF had worse VA than eyes without IRF, and eyes with foveal IRF had worse VA than eyes with extrafoveal IRF. The adverse effect of foveal IRF was apparent by 4 weeks and persisted over time; VA in eyes with foveal IRF was approximately 2 lines worse than in eyes without fluid and was 1 line worse than in eyes with extrafoveal IRF at all time points evaluated ($P < 0.0001$; Fig 6). At 52 weeks, mean (SE) VA of eyes with foveal, extrafoveal, and no IRF was 62.4 (1.3), 67.2 (1.0), and 71.2 (0.7) letters, respectively ($P < 0.0001$; Fig 6B). In contrast, at 52 weeks, presence and foveal involvement of sub-RPE fluid and SRF had little effect on mean VA (P=0.40 and 0.051, respectively; Fig 6C–D).

In a longitudinal model of VA between 4 and 52 weeks that included presence and foveal involvement of each type of fluid, as well as total thickness and follow-up time, the strong effect of IRF persisted ($P < 0.0001$). In contrast, VA was not significantly affected by the presence of subretinal and sub-RPE fluid or total thickness when all of these factors were considered simultaneously.

When the impact of the presence and foveal involvement of IRF on VA was assessed over time and among treatment groups, we found no significant interactions between IRF and treatment group or with time ($P > 0.05$ for interactions). Taken together, the results indicate that across treatment groups, over time, residual IRF, particularly intraretinal foveal fluid, had a significant effect on VA, whereas subretinal or sub-RPE fluid did not.

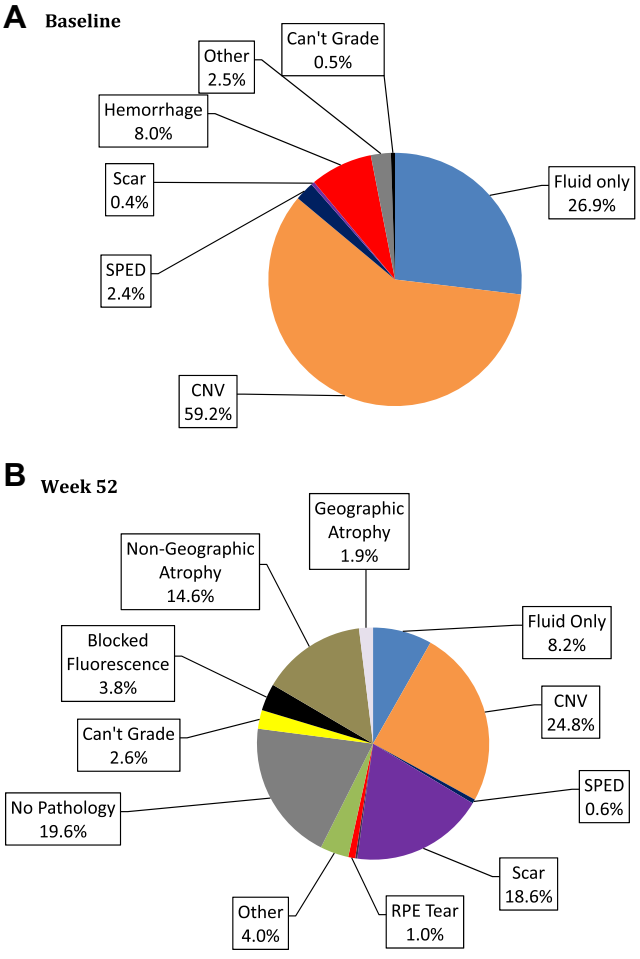

Figure 4. Involvement of the foveal center by choroidal neovascularization (CNV) or sequelae of CNV at baseline **(A)** and week 52 **(B)**. RPE = retinal pigment epithelium; SPED = serous pigment epithelial detachment.

Correlation of Optical Coherence Tomography–Determined Thickness Measurements with Visual Acuity

The correlation of VA with thickness at the foveal center depended on the tissue layer (retina, SRF, and subretinal tissue complex) and time in follow-up. At baseline, when substantial fluid was present, greater total thickness was associated with worse VA ($P < 0.0001$; Fig 7A). When total thickness was <325 μm, mean (SE) VA was 65.4 (0.7) letters, and when total thickness was >550 μm, mean VA was 53.8 (0.8) letters. Thicker subretinal tissue complex at baseline also was associated with worse VA, as was retinal thickness >212 μm ($P < 0.0001$; Fig 7B, D). However, the mean VA among eyes with no SRF (59.2 [0.5] letters) or SRF ≤25 μm (62.4 [1.4] letters) was worse than among eyes with >25 μm SRF (63.7 [0.7] letters; $P < 0.0001$).

The overall relation of VA to thickness during the 52 weeks after initiation of treatment was explored by combining data from weeks 4, 12, and 24, which were summarized with LOWESS curves (Fig 8). The relation differed by retinal layer. For the retina (Fig 8B), eyes with low or high retinal thickness had worse VA. Within the range of 120 to 212 μm (mean of healthy eyes on Stratus OCT measured manually ±2 standard deviations), the LOWESS curve was relatively flat, whereas progressively worse

VA was associated with both lower retinal thickness and higher retinal thickness. For SRF thickness, acuity was lower when there was no fluid present or a relatively thick layer of fluid present (Fig 8C). Visual acuity was highest when there was no or only a thin subretinal tissue complex under the fovea (Fig 8D).

Figure 7 displays the mean VA at different times during follow-up in subgroups of eyes classified by the total central foveal thickness and by thickness of the retinal tissue layers. The trends described earlier for the combined data generally held for each time point. At all follow-up time points, eyes with retinal thickness between 120 and 212 μm had better VA than eyes with thickness <120 μm and eyes with thickness >212 μm. By week 52, the mean VA in eyes with retinal thickness between 120 and 212 μm was 12.4 letters better than in eyes with retinal thickness <120 μm. Eyes with a relatively thin layer of SRF had a mean VA at 52 weeks that was 5.3 letters better than eyes without any SRF. Eyes with a subretinal tissue complex thickness of 0 to 75 μm had a mean VA at 52 weeks that was 5.1 to 7.1 letters better than the 3 subretinal tissue complex subgroups with greater thickness.

Because thinner than normal retinas (thickness <120 μm) tended to have worse VA than their thicker counterparts, we examined in more detail the relationship between the time to onset of retinal thickness <120 μm and the VA at 52 weeks. Of note, the week 52 VA depended on the time at which the retina became thinner than normal. Among eyes that ever had a retina thickness <120 μm, the best average week 52 VA (69 letters) was in eyes that were thinner than normal at baseline. When the onset of a thinner retina was later in follow-up, the week 52 VA was worse, with week 52 VA of 65, 65, 60, and 62 letters thinner retinas first observed at week 4, 12, 24, and 52 respectively (P=0.01, for time).

Correlation of Fundus Features Determined on Fluorescein Angiograms and Color Fundus Photographs with Visual Acuity at 52 Weeks

At week 52, larger neovascular lesion area was associated with worse VA ($P < 0.0001$; Table 2). The eyes with lesion area in the smallest quartile had a mean (SE) VA of 74.3 (1.1) letters, whereas the mean VA among eyes with lesion area in the largest quartile was 61.9 (1.1) letters. The pathology in the foveal center determined by FA and FP also strongly influenced VA ($P < 0.0001$; Table 2). Eyes with no apparent pathology in the foveal center and eyes with fluid under the foveal center had a mean VA of approximately 75 letters, whereas mean (SE) VA was lowest among eyes with scar (59.5 [1.3] letters) in the foveal center.

Table 1. Retinal Thickness by Presence of Intraretinal Fluid and Treatment Group Over Time

Week	Foveal IRF Present	Retinal Thickness Category (μm)	Ranibizumab Monthly	Bevacizumab Monthly	Ranibizumab PRN	Bevacizumab PRN
0	Yes	<120	3 (2.0%)	3 (2.1%)	7 (5.3%)	5 (3.4%)
		120–212	56 (38.1%)	47 (33.1%)	35 (26.7%)	50 (33.6%)
		>212	88 (59.9%)	92 (64.8%)	89 (67.9%)	94 (63.1%)
	No	<120	28 (19.2%)	22 (16.4%)	24 (15.3%)	25 (17.5%)
		120–212	105 (71.9%)	95 (70.9%)	110 (70.1%)	100 (69.9%)
		>212	13 (8.9%)	17 (12.7%)	23 (14.6%)	18 (12.6%)
4	Yes	<120	5 (7.4%)	3 (4.1%)	4 (6.1%)	5 (6.6%)
		120–212	47 (69.1%)	43 (58.9%)	48 (72.7%)	48 (63.2%)
		>212	16 (23.5%)	27 (37.0%)	14 (21.2%)	23 (30.3%)
	No	<120	55 (25.7%)	45 (22.6%)	51 (23.4%)	41 (20.4%)
		120–212	148 (69.2%)	139 (69.8%)	153 (70.2%)	139 (69.2%)
		>212	11 (5.1%)	15 (7.5%)	14 (6.4%)	21 (10.4%)
12	Yes	<120	6 (10.2%)	6 (10.0%)	5 (7.7%)	8 (8.2%)
		120–212	41 (69.5%)	35 (58.3%)	33 (50.8%)	57 (58.2%)
		>212	12 (20.3%)	19 (31.7%)	27 (41.5%)	33 (33.7%)
	No	<120	50 (24.4%)	34 (17.8%)	44 (21.5%)	32 (18.7%)
		120–212	148 (72.2%)	148 (77.5%)	154 (75.1%)	127 (74.3%)
		>212	7 (3.4%)	9 (4.7%)	7 (3.4%)	12 (7.0%)
24	Yes	<120	3 (6.5%)	6 (9.5%)	3 (5.3%)	8 (10.1%)
		120–212	30 (65.2%)	34 (54.0%)	34 (59.6%)	43 (54.4%)
		>212	13 (28.3%)	23 (36.5%)	20 (35.1%)	28 (35.4%)
	No	<120	46 (21.7%)	36 (20.0%)	53 (25.6%)	36 (20.8%)
		120–212	159 (75.0%)	134 (74.4%)	142 (68.6%)	128 (74.0%)
		>212	7 (3.3%)	10 (5.6%)	12 (5.8%)	9 (5.2%)
52	Yes	<120	2 (7.7%)	6 (11.8%)	4 (8.7%)	4 (7.0%)
		120–212	17 (65.4%)	23 (45.1%)	27 (58.7%)	33 (57.9%)
		>212	7 (26.9%)	22 (43.1%)	15 (32.6%)	20 (35.1%)
	No	<120	69 (28.4%)	42 (20.8%)	49 (22.0%)	49 (24.0%)
		120–212	163 (67.1%)	146 (72.3%)	161 (72.2%)	139 (68.1%)
		>212	11 (4.5%)	14 (6.9%)	13 (5.8%)	16 (7.8%)

IRF = intraretinal fluid; PRN = pro re nata.

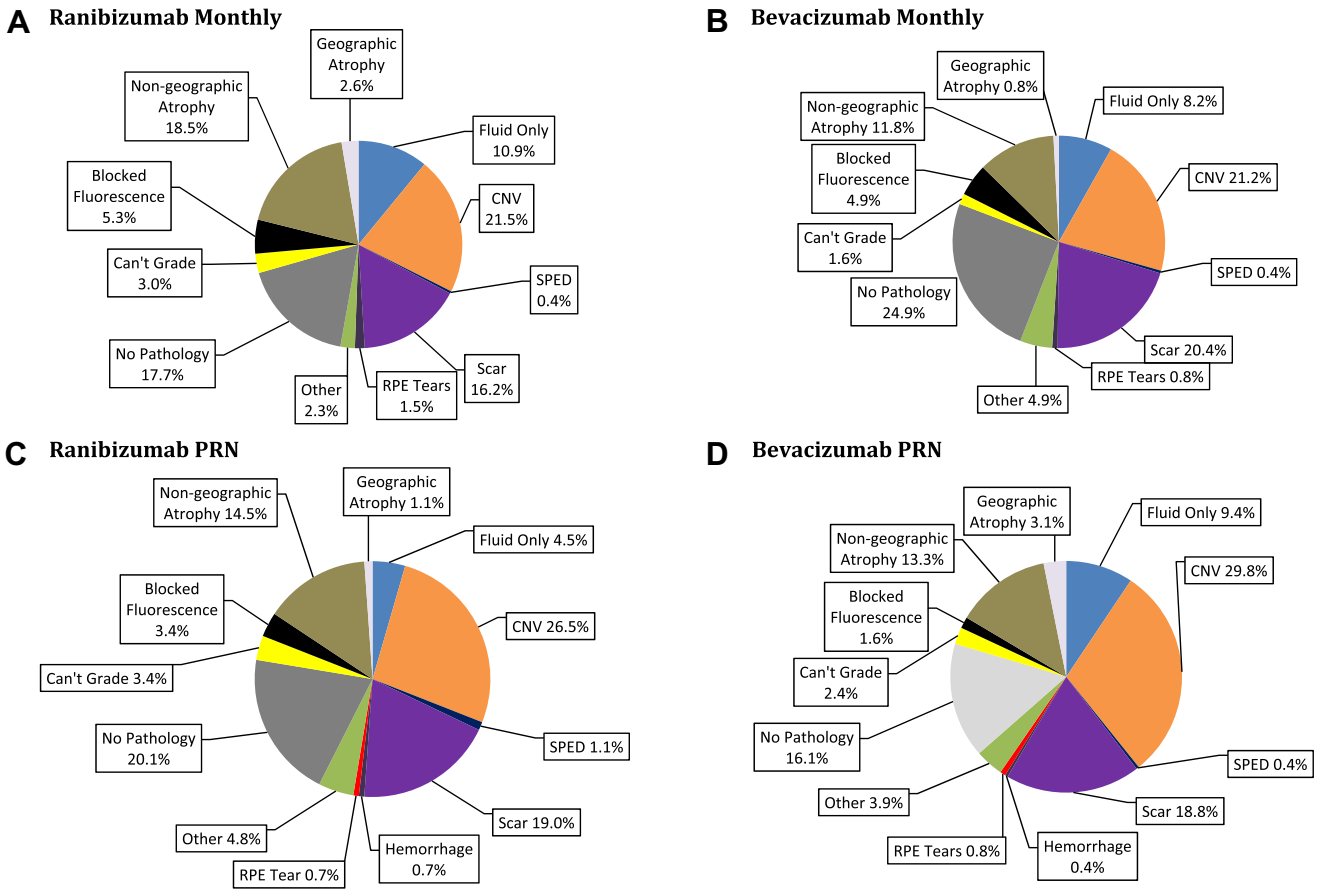

Figure 5. Involvement of the foveal center by choroidal neovascularization (CNV) or sequelae of CNV at week 52 for ranibizumab monthly **(A)**, bevacizumab monthly **(B)**, ranibizumab pro re nata (PRN; as needed) **(C)**, and bevacizumab PRN **(D)**. RPE = retinal pigment epithelium; SPED = serous pigment epithelial detachment.

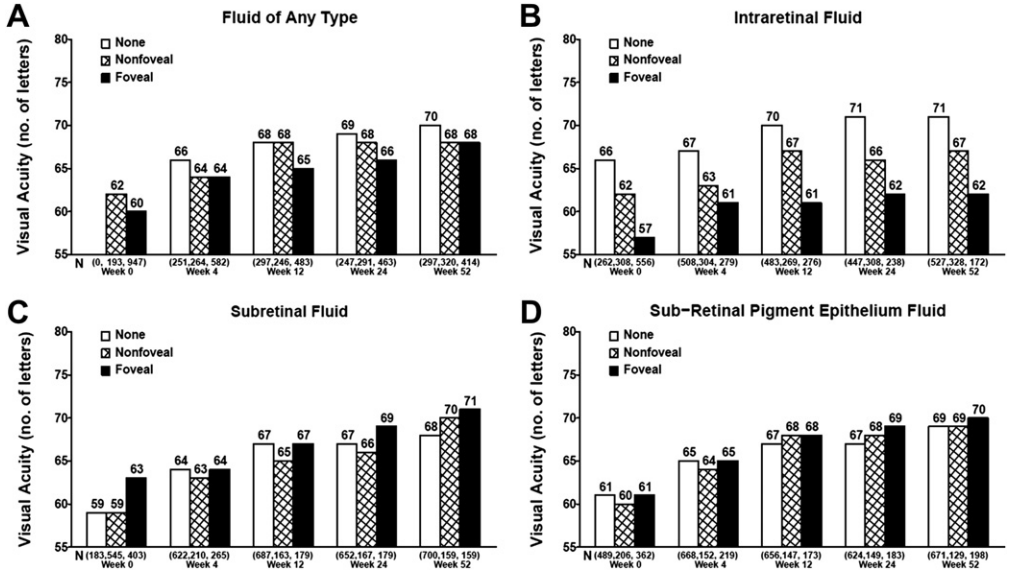

Figure 6. Mean visual acuity by status of fluid by time for fluid of any type **(A)**, intraretinal fluid **(B)**, subretinal fluid **(C)**, and subretinal pigment epithelium fluid **(D)**.

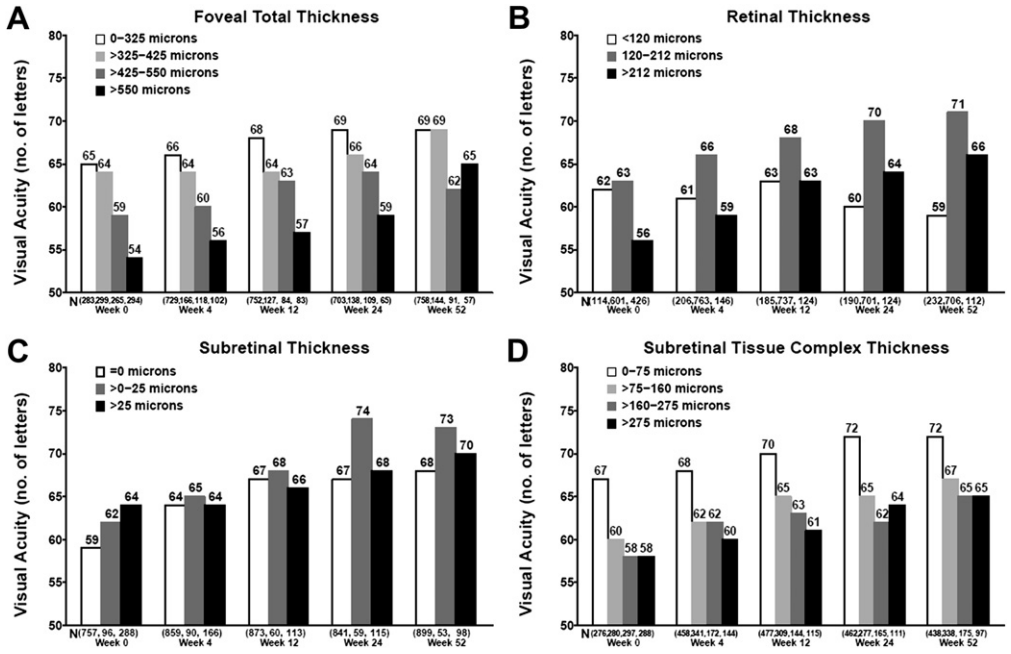

Figure 7. Relationship between retinal thickness and visual acuity at baseline and follow-up: foveal total thickness **(A)**, retinal thickness **(B)**, subretinal thickness **(C)**, and subretinal tissue complex thickness **(D)**.

Multivariate Analysis of the Association between Visual Acuity and Optical Coherence Tomography and Fundus Features at 52 Weeks

When the presence and foveal involvement of each of the 3 types of fluid on OCT, the thickness of each of the 3 retinal layers, the lesion size, and the foveal pathology were considered simultaneously in a linear regression model of VA (Table 3), the presence and foveal involvement of IRF and SRF, retinal thickness <120 μm, larger CNV lesion area, and the type of foveal pathology were independent predictors of VA. In an alternative model with the categories of thickness of subretinal tissue complex at the fovea

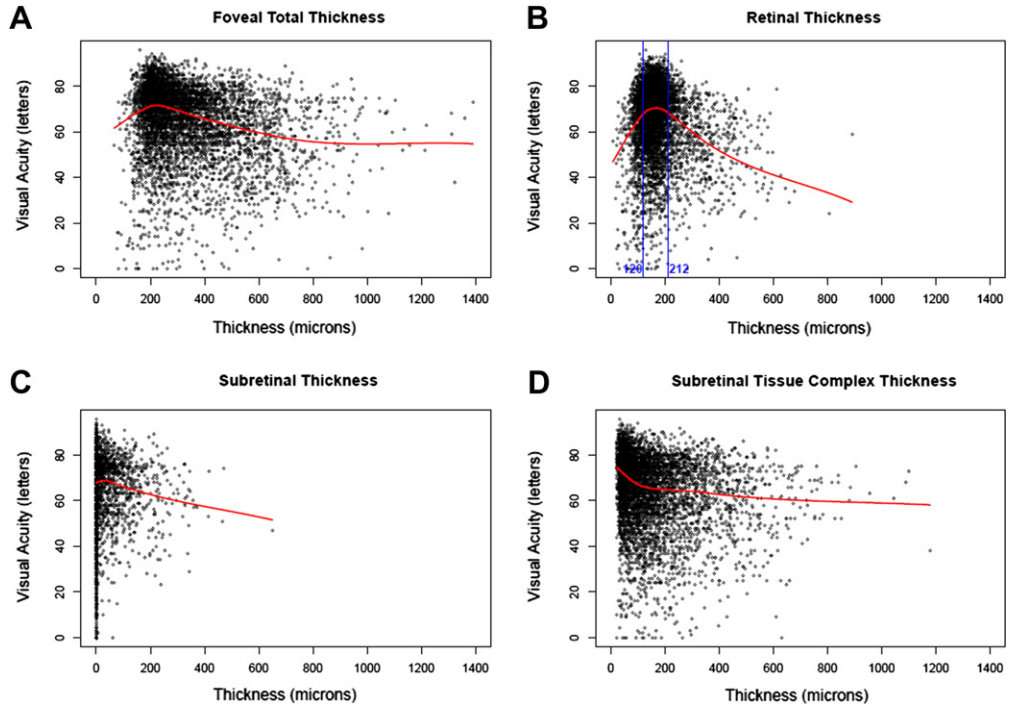

Figure 8. Nonlinear relationship during follow-up of visual acuity with foveal total thickness **(A)**, retinal thickness **(B)**, subretinal thickness **(C)**, and subretinal tissue complex thickness **(D)**.

Table 2. Mean Visual Acuity at Week 52 by Neovascular Lesion Area and Pathology in the Foveal Center at Week 52 (N=1053)

Fundus Feature at Week 52	N	Unadjusted Mean VA Score (SE)	*P* Value*
Neovascular lesion area (mm^2)			<0.0001
≥0 to ≤1.92	244	74.3 (1.11)	
>1.92 to ≤4.96	246	70.4 (1.10)	
>4.96 to ≤9.62	245	67.1 (1.10)	
>9.62	242	61.9 (1.11)	
Missing	76	63.1 (1.98)	
Pathology in foveal center			<0.0001
None	202	73.9 (1.20)	
Fluid only	85	75.3 (1.85)	
CNV or serous pigment epithelium detachment	259	69.7 (1.06)	
Nongeographic atrophy	151	66.5 (1.39)	
Geographic atrophy, hemorrhage, RPE tear, blocked fluorescence	72	64.8 (2.01)	
Scar	188	59.5 (1.25)	
Other† or missing	96	66.8 (1.75)	

CNV = choroidal neovascularization; RPE = retinal pigment epithelium; SE = standard error; VA = visual acuity.
*One-way analysis of variance.
†Other includes pigment, drusenoid pigment epithelial detachment, and nonleaking CNV.

Table 3. Adjusted Mean Visual Acuity for Optical Coherence Tomography and Fundus Features at Week 52 (n=1004)*

Optical Coherence Tomography and Fundus Features at Week 52	N	Adjusted Mean (SE) VA Score at Week 52	*P* Value
Intraretinal fluid			<0.0001
No fluid	527	70.9 (0.68)	
Fluid not in fovea center	311	68.7 (0.88)	
Fluid in fovea center	166	62.3 (1.27)	
Subretinal fluid			0.02
No fluid	693	67.8 (0.61)	
Fluid not in fovea center	156	71.7 (1.29)	
Fluid in fovea center	155	70.4 (1.29)	
Retinal thickness (μm)			<0.0001
<120	216	60.9 (1.10)	
120–212	680	71.1 (0.60)	
>212	108	70.2 (1.59)	
CNV lesion area (mm^2)			<0.0001
≥0 to ≤1.92	239	72.4 (1.12)	
>1.92 to ≤4.96	235	71.5 (1.02)	
>4.96 to ≤9.62	234	69.1 (1.04)	
>9.62	226	64.4 (1.08)	
Missing	70	61.0 (2.21)	
Pathology in the fovea center			<0.0001
None	198	71.6 (1.20)	
Fluid only	84	72.7 (1.74)	
CNV or serous pigment epithelial detachment	250	69.2 (1.07)	
Nongeographic atrophy	142	69.1 (1.34)	
Geographic atrophy, hemorrhage, RPE tear, blocked fluorescence	67	66.4 (1.90)	
Scar	176	62.2 (1.18)	
Other or missing	87	72.6 (1.98)	

CNV = choroidal neovascularization; RPE = retinal pigment epithelium; SE = standard error; VA = visual acuity.
*Subjects (n=49) with missing data for fluid or retinal thickness were excluded.

derived from OCT included and the type of foveal pathology derived from FA and FP excluded, the categories of thickness of subretinal tissue complex were a significant predictor of VA (P=0.01). There was no strong association with either drug or dosing regimen (P=0.24 and P=0.13, respectively), nor did drug or dosing regimen affect the association of these factors with VA.

Discussion

In this study, several morphologic features determined on OCT, FA, and FP were significantly affected by intravitreal anti-VEGF therapy and had a significant relationship with VA. In particular, anti-VEGF treatment, regardless of drug and regimen, generally caused rapid and sustained reduction in macular fluid and thickness, stabilized lesion growth, reduced vascular leakage, and normalized retinal anatomy. Furthermore, presence of IRF, abnormally thin or thick retinas, larger CNV area, and foveal scar were associated with the largest decreases in VA at week 52 when compared with other features evaluated.

A key study finding was that IRF (cysts) as determined by OCT had a greater negative impact on VA than SRF or sub-RPE fluid at all time points analyzed. In a previous report, eyes with cystoid macular edema, as observed on OCT, associated with subfoveal CNV had worse VA than those with subfoveal CNV but no cystoid macular edema.[11] We found that IRF was associated independently with worse VA over the entire study duration when controlling for other potentially confounding variables, even in eyes with subfoveal CNV. Indeed, subfoveal CNV did not worsen the adverse effect of IRF on VA. The reason for the specific negative impact on VA of IRF, but not SRF or sub-RPE fluid, is not entirely clear. In the beginning of the study, the majority of eyes had cysts, whereas the proportion of eyes with residual IRF at week 52 was less, and the cysts tended to be small. We hypothesize that early in the study, when the proportion of eyes with IRF decreased markedly, the IRF was largely driven by VEGF-mediated vascular permeability. However, toward the end of the first year, when IRF was eliminated at a lower rate, we speculate that non–VEGF-mediated mechanisms, such as apoptotic or necrotic cell death, accounted for some of the small hyporeflective cystoid structures.

What are the clinical implications of the adverse relationship between IRF, particularly foveal IRF, and VA? This relationship held at all times during the study, was independent of other morphologic features, and was insensitive to the specific anti-VEGF drug and regimen. On the basis of these data, if one chooses a PRN treatment strategy, we believe that it would be reasonable to aggressively treat IRF, particularly when located in the fovea, during the first few months after initiation of therapy in treatment-naïve participants, when IRF responds dramatically to therapy, and to continue to treat as long as there is continued IRF improvement. In addition, given the favorable outcomes of most participants in whom OCT drove treatment of

subretinal and sub-RPE fluid, even when IRF is absent, one should also consider treatment of subretinal and sub-RPE fluid, at least early during the course of therapy. In contrast, toward the end of the first year of therapy, aggressive treatment of small amounts of SRF or sub-RPE fluid, and possibly even IRF that does not change significantly from 1 examination to the next, may not be warranted. The CATT was not designed to address this point, and further studies are needed to determine whether there is an adverse effect on VA when small amounts of fluid that persist after several months of therapy are not treated.

There was a bimodal effect of retinal thickness on VA. As expected, abnormally thick retinas had decreased VAs. Furthermore, abnormally thin retinas also had worse VA. Because both geographic and nongeographic atrophy also developed after anti-VEGF therapy, geographic atrophy could be one of the causes of retinal thinning and associated decreased VA. However, it is unknown whether the observed pathologic retinal thinning occurred specifically in regions of underlying RPE and choriocapillaris atrophy. Although it is beyond the scope of this article, we are currently exploring the relationship between retinal thinning, geographic and nongeographic atrophy, and VA. This investigation will be facilitated by a recently completed spectral-domain CATT substudy, in which many more cross-sectional images are available to correlate with fundus photographic and fluorescein angiographic features than are available with the 6 radial cross-sectional images from the Stratus OCT machine.

A higher proportion of eyes treated with ranibizumab monthly had abnormally thin retinas (<120 μm). However, the precise relationship among drug, dosing, and retinal thinning remains unclear. It is possible that retinal thinning due to loss of neural tissue may occur in all eyes treated with anti-VEGF therapy independent of specific drug and dosing regimen. The differences in retinal thinning could be due in part to the differences in the amount of residual fluid between treatment groups, with greater retinal thickness masking the loss of neural tissue. However, when analysis was restricted to only eyes that had no residual fluid on OCT (as determined in masked fashion by the OCT Reading Center), there was still a higher proportion of eyes with abnormal retinal thinning among those treated with ranibizumab monthly compared with other treatment groups. Additional studies are clearly required to confirm whether ranibizumab monthly is truly associated with a higher rate of neural tissue loss.

Thicker subfoveal subretinal tissue complex, which may include CNV, hemorrhage, fibrosis, and fibrovascular or serous pigment epithelium detachment, was significantly and independently correlated with worse VA. This material is not always given attention in analyses of anti-VEGF effects.[12,13] However, our data clearly show that in many eyes, anti-VEGF therapy reduces this tissue height, as measured by OCT, and decreases components of this tissue, such as subretinal hemorrhage and CNV, as observed on FA and FP. Indeed, in a substantial proportion of eyes, this tissue was completely eliminated by week 52. These data, which demonstrate reduction of tissue, in addition to fluid, and the observed slowing of lesion growth, suggest an anti-VEGF therapeutic effect on VA that includes not only reduced vascular permeability but also regression of pathologic tissue. The data further indicate that when anti-VEGF therapy is not fully effective in this regard, VA is negatively affected.

In conclusion, foveal lesion composition changed dramatically during the first year of anti-VEGF treatment, and the effect was independent of drug and dosing regimen. In general, the observed effects were desired, with decreased retinal fluid, hemorrhage, and CNV. However, there were some treatment-emergent adverse effects, including atrophy and fibrosis. The latter was associated with the greatest reduction in VA. Ideally, it would be possible to achieve favorable effects on macular anatomy without generating subretinal fibrosis. It would be beneficial in this regard to develop treatments that have an antifibrotic effect that might be used in combination with anti-VEGF therapy.

References

1. Brown DM, Kaiser PK, Michels M, et al, ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
2. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–98.
3. CATT Research Group, Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.
4. Rosenfeld PJ, Brown DM, Heier JS, et al, MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
5. Decroos FC, Toth CA, Stinnett SS, et al. Optical coherence tomography grading reproducibility during the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology 2012;119:2549–57.
6. Ying GS, Huang J, Maguire MG, et al, Comparison of Age-related Macular Degeneration Treatments Trials Research Group. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2013;120:122–9.
7. 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.
8. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the Early Treatment of Diabetic Retinopathy Study testing protocol. Am J Ophthalmol 2003;135:194–205.
9. Chan A, Duker JS, Ko TH, et al. Normal macular thickness measurements in healthy eyes using Stratus optical coherence tomography. Arch Ophthalmol 2006;124:193–8.
10. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 1979;74:829–36.
11. Ting TD, Oh M, Cox TA, et al. Decreased visual acuity associated with cystoid macular edema in neovascular age-related macular degeneration. Arch Ophthalmol 2002;120:731–7.

12. Gamulescu MA, Radeck V, Lustinger B, et al. Bevacizumab versus ranibizumab in the treatment of exudative age-related macular degeneration. Int Ophthalmol 2010;30: 261–6.

13. Kaiser PK, Blodi BA, Shapiro H, Acharya NR, MARINA Study Group. Angiographic and optical coherence tomographic results of the MARINA Study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114:1868–75.

Footnotes and Financial Disclosures

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*The credit roster for the CATT Research Group is provided in Appendix 1, available at http://aaojournal.org.

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This article contains online-only material. The following should appear online-only: Appendix 1.