SDC

IDENTIFICATION OF FLUID ON OPTICAL COHERENCE TOMOGRAPHY BY TREATING OPHTHALMOLOGISTS VERSUS A READING CENTER IN THE COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENTS TRIALS

CYNTHIA A. TOTH, MD,* FRANCIS CHAR DECROOS, MD,* GUI-SHUANG YING, PHD,† SANDRA S. STINNETT, DRPH,* CYNTHIA S. HEYDARY, BA,* RUSSELL BURNS, AAS,* MAUREEN MAGUIRE, PHD,† DANIEL MARTIN, MD,‡ GLENN J. JAFFE, MD*

Purpose: To examine treatment decisions by ophthalmologists versus reading center fluid identification from optical coherence tomography in Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Methods: Fluid in 6,210 optical coherence tomography scans (598 patients) in "as needed treatment" arm of CATT Year 1 was compared with ophthalmologist's treatment: positive fluid agreement (PFA, fluid+, treatment+) and positive fluid discrepancy (PFD, fluid+, treatment–), negative fluid agreement (fluid–, treatment–) and negative fluid discrepancy (fluid–, treatment+). For PFDs, fluid location and visual acuity were characterized.

Results: Treatment and reading center fluid determination agreed in 72.1% (53.0% PFA, 19.1% negative fluid agreement) and disagreed in 27.9% (25.7% PFD, 2.2% negative fluid discrepancy) of visits, with no discrepancies for 20.9% of patients. Compared with PFA, PFD occurred more commonly with lower total foveal thickness (mean ± SD: 265 ± 103 PFD, 366 ± 151 μm PFA), presence of intraretinal fluid only, smaller fluid areas (PFA areas greater than twice those of PFD, $P < 0.001$), and greater decrease in retinal and lesion thickness. Mean acuities before, at, and after PFD were 65.8, 66.9, and 66.3 letters.

Conclusion: Treatment decisions by ophthalmologists matched reading center fluid determination in the majority of visits. More pronounced response to treatment and smaller foci of fluid likely contributed to PFD. Positive fluid discrepancy did not have substantial impact on subsequent visual acuity.

RETINA 35:1303–1314, 2015

Noninvasive cross-sectional imaging of the retina and the choroid by optical coherence tomography (OCT) enables visualization of anatomical changes common to neovascular age-related macular degeneration (NVAMD) such as retinal or retinal pigment epithelium (RPE) elevation over blood or choroidal neovascularization, accumulation of intraretinal, subretinal and sub-RPE fluid, and deformation, thickening, thinning or loss of retinal layers, and choroidal thickness.[1–3] The ability of OCT to detect fluid indicative of active choroidal neovascularization leakage holds great promise to help rationally direct pharmacologic therapy for NVAMD.[4–9]

For physicians implementing as needed anti-vascular endothelial growth factor therapy, the goal is to maximize visual function while minimizing

treatment burden. Pivotal early trials were designed with once monthly intravitreal anti-vascular endothelial growth factor treatment,[10,11] but frequent dosing is highly resource-intensive. Since then, multiple studies have investigated the efficacy of less frequent, as needed treatment dosing based on various criteria.[5–7,9] The rewards of using the least injections to obtain optimal outcomes are manifold, including increased patient convenience, reduced treatment cost, and decreasing the low, but nonzero rate of injection related complications.[10–13]

Within the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), approximately half of the study patients were randomized to an as needed (pro re nata [PRN]) dosing schedule.[14] For this group, after initial therapy, treating ophthalmologists evaluated patients every 4 weeks with time domain OCT (TD-OCT) (Stratus; Carl Zeiss Meditec, Dublin, CA), and treatment was mandated with few exceptions if the ophthalmologist observed any macular fluid on OCT. During the first year of the CATT, the differences in mean change in acuity between monthly versus as needed treatment were equivalent (+1.7 letters) for ranibizumab and inconclusive (+2.1 letters) for bevacizumab.[15] Previous studies suggest that less frequent injection is associated with less visual gain[5] and that as needed dosing can result in decreased visual gain compared with monthly dosing.[9]

Because macular fluid on OCT has been the predominant reason for treatment decisions for PRN dosing during the CATT and other studies and is commonly used in PRN and treat-and-extend clinical treatment strategies, accurate identification of this fluid is important. It would be helpful to compare the clinicians' decisions to reading center (RC) determinations of macular fluid status. In the first-year report of the CATT, most discrepancies between OCT findings and treatment decisions in the PRN groups were due to detection of fluid by the RC on OCT scans of patients who were not treated, accounting for 93% of discrepancies in the ranibizumab group and 91% in the bevacizumab group.[14] In a study of the link between morphology and acuity in the first year of CATT, eyes with residual intraretinal fluid (IRF) in the fovea had worse mean visual acuity (nine letters) than those without IRF.[16] We therefore sought to characterize the frequency of discrepancies per eye and the OCT features, associated clinical factors, and subsequent visual acuity in these eyes in CATT, currently the largest study to investigate the efficacy of an as needed intravitreal NVAMD pharmacotherapy protocol based on monthly serial assessment of macular fluid.

From the *Duke University Eye Center, Department of Ophthalmology, Durham, North Carolina; †Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania; and ‡Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

None of the authors have any financial/conflicting interests to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

Reprint requests: Cynthia A. Toth, MD, Duke Reading Center, DUMC Box 3802, Durham, NC 27710; e-mail: cynthia.toth@duke.edu

Materials and Methods

The institutional review board for each center approved the study protocol, and written consent was obtained from each participant. At specified study visits, certified technicians captured two Stratus OCT scan sets in the study eye after the macular thickness map and fast macular thickness map protocols and submitted these to the RC. Protocol visual acuity was gathered by certified vision examiners at each study visit and submitted to coordinating center.[15]

The CATT treating ophthalmologists had to identify macular fluid on OCT for an eye to be enrolled in the study; the RC evaluated the OCT to confirm eligibility after enrollment. To facilitate consistent identification of macular fluid, treating ophthalmologists were provided standardized images of the minimal threshold of IRF, subretinal fluid (SRF), and sub-RPE fluid on OCT that required treatment. The RC also provided training in standardized OCT interpretation at study startup, investigator meetings and on line. Ophthalmologists were required to review all 12 images from the 2 OCT scan sets under CATT investigator training. Their certification included review of the treatment protocol and a knowledge assessment test involving interpretation of OCTs.

Within the CATT, patients were divided into four treatment subgroups—monthly or PRN dosing, with bevacizumab or ranibizumab. For PRN dosing patients, after the first mandatory intravitreal injection, the protocol required treating ophthalmologists to examine the eye, review the study visit OCT images, and administer the designated treatment at 4-week intervals for predetermined indications. The protocol mandated treatment for macular fluid found on OCT, and the macular fluid was the principal indication of PRN dosing (98.3%) during the first year of follow-up. Other non-OCT–based criteria mandating treatment included new hemorrhage, persistent hemorrhage, or decreased visual acuity since previous study visit. Fluorescein angiography criteria requiring treatment included increased lesion size or leakage.

Treating ophthalmologists could withhold treatment for either definite or possible contraindications.

Definite contraindications included intraocular inflammation (>2+ cell), intraocular pressure >30 mmHg, vitreous hemorrhage producing a >30-letter decrease in visual acuity, ocular infection, or any anti-vascular endothelial growth factor treatment in the study eye within 23 days. Possible contraindications included recent stroke, recent myocardial infarction, new retinal break, new retinal detachment, new macular hole, RPE tear involving the macula, or patient refusal. At the treating ophthalmologist's discretion, treatment could be withheld in any eye not responding to three or more serial injections because of presumed treatment futility.

Comparison of Reading Center and Treating Ophthalmologist Assessments of Fluid

Two certified readers independently analyzed all 12 OCT images from the two scan sets in a systematic fashion for morphologic characteristics, including IRF, SRF, and sub-RPE fluid. Measurements included total thickness at the foveal center (from the internal limiting membrane to Bruch membrane). A senior reader reconciled disagreements between the initial reader pair. A reader pair and senior reader constituted an RC team, and all OCT scans from the CATT were evaluated using this team-based approach.

Reading center grading of macular fluid was compared with the treating ophthalmologist's treatment decision based on OCT-guided macular fluid identification. We excluded evaluations with no treatment because of contraindications or futility, and some OCT scans when images were not of sufficient quality to determine fluid status by the OCT RC. Definitions of corresponding visits versus RC grading events included 1) positive fluid agreement (PFA): RC identified macular fluid on OCT and the ophthalmologist administered treatment at the corresponding visit; 2) positive fluid discrepancy (PFD): RC identified macular fluid on OCT and the ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment; 3) negative fluid agreement: RC did not identify macular fluid on OCT and the ophthalmologist did not administer treatment at the corresponding visit; and 4) negative fluid discrepancy (NFD): RC did not identify macular fluid on OCT and the ophthalmologist administered treatment at the corresponding visit. Cases where an ophthalmologist treated for a reason other than fluid observed on OCT, such as decreased acuity, were specifically excluded from the NFD designation and considered as negative fluid agreement.

Random sample groups of 400 PFD (~25%), 100 PFA (100 [~3%]), and 48 NFD (~34%) were selected from Week 4 to Week 48 visits for measurement of the largest area of fluid (PFD and PFA) or for regrading for the presence of fluid (NFD). The random sample groups contained comparable numbers of patients treated with bevacizumab versus ranibizumab, with visits chosen to be representative across study visits and calendar time. For PFD and PFA, scans were intermixed, and the RC was masked to the designation of the scans. For NFD, a senior reader regraded scans for the presence of fluid with scans intermixed with other OCT scans for grading. For inconclusive or uncertain grades, scans were evaluated in a masked fashion by the RC Director of Grading or Director or at a reader meeting for consensus vote regarding the grade.

For measurement of largest cross-sectional fluid area, Stratus software-based calipers were used to quantify the maximal horizontal and vertical dimensions of the single largest cross-sectional area of IRF, SRF, and/or sub-RPE fluid, respectively for a specific scan. All 12 OCT images were reviewed to determine the largest dimensions from a single radial line image. The cross-sectional area of the single largest IRF was approximated as an ellipse (area = π [horizontal dimension / 2] $\times$ [vertical dimension / 2]) and of the single largest SRF or sub-RPE fluid, as a hemiellipse (area = $\frac{1}{2}\ \pi$ [horizontal dimension / 2] $\times$ [vertical dimension / 2]). If macular fluid was present in more than one location, the single largest area of fluid was calculated for each fluid type, and these were not required to originate from the same radial line scan. In rare cases of macular fluid extending beyond the OCT margin, the largest fluid area visible on OCT was measured.

Statistical Analysis

Descriptive statistics were used to describe the types of agreement and disagreement, the presence of fluid, location of fluid, and visual acuity in the visit subsequent to PFD. Comparison of mean fluid area, total retinal thickness, and change from baseline between eyes with PFD and PFA, were performed using generalized linear model with correlations among scans from the same eye accounted for using generalized estimating equations. Comparison of medians was performed using the Wilcoxon rank-sum test of difference in medians modified to account for correlations among scans from the same eye.[17] Statistical analyses were performed using SAS (v9.2; SAS Institute, Cary, NC), and 2-sided $P < 0.05$ was considered to be statistically significant.

To assess the effect of PFD on subsequent visual acuity, we performed a case–control analysis by 1:1 matching of PRN patients with PFD (case) with

monthly treated patients (control). The first instance of PFD for a patient was selected for analysis. Cases and controls were matched on treatment drug, OCT fluid status (IRF, SRF, sub-RPE fluid), visit (Weeks 4, 8, 12, 24), visual acuity (±2 letters), and intraretinal thickness (±50 μm). We identified 138 case–control pairs, comparing visual acuity and visual acuity change at 4 weeks after the PFD using a paired *t*-test and the Wilcoxon signed-rank test, and the mean visual acuity change from baseline at 1 year among groups defined by the total number of PFDs within 1 year (1–2, 3–4, 5+) by using 1-way analysis of variance.

Results

Treating Ophthalmologist and Reading Center Agreement

A total of 6,401 OCT scans were obtained from 598 patients in the PRN groups in Year 1 (Week 4–48). After excluding 62 scans (25 ranibizumab and 37 bevacizumab) with treatment contraindications, 12 scans (3 ranibizumab and 9 bevacizumab) with treatment futility, and 117 scans (69 ranibizumab and 48 bevacizumab) with image quality insufficient to determine OCT fluid status, 6,210 OCT scans (97%, 3,171 ranibizumab and 3,039 bevacizumab) from 594 patients were used to compare the RC grading of macular fluid to the ophthalmologist's treatment decision based on identification of macular fluid on OCT. The treatment decision and RC determination of macular fluid status agreed in 4,473 visits (72.1%) during the first year of CATT follow-up (Table 1). Agreement was comprised of PFA in 3,290 visits (53.0%) and negative fluid agreement in 1,183 (19.1%), and ranibizumab had a lower rate (48.3%) of PFA than did bevacizumab (57.9%). Discrepancies occurred in 1,737 visits (27.9%) with PFD in 1,598 (25.7%) and NFD in 139 visits (2.2%). Among the 594 patients, 124 (20.9%) had no PFD, 93 (15.7%) patients had 1 PFD, and 255 (42.9%) had 2 to 4 PFD (Table 2).

Localization, Distribution, and Persistence of Fluid for Positive Fluid Discrepancies

Types of macular fluid, combinations of fluid present, and treatment status at each visit are detailed in Table 3A and in **Supplemental Digital Content 1** (see **Table 3B**, ranibizumab; http://links.lww.com/IAE/A322) and **Supplemental Digital Content 2** (see **Table 3C**, bevacizumab; http://links.lww.com/IAE/A323). The most common pattern of fluid identified by the RC was IRF alone, present at 1,548 of the 4,888 visits (31.7%) when some type of fluid was present. Subretinal fluid alone was more likely to be treated (71.1%) than either IRF alone (49.0%) or sub-RPE fluid (46.4%) alone. When SRF was present in any combination, treatment was more likely than at a visit without SRF. The proportion treated with IRF alone or sub-RPE fluid alone was comparable (49.0% vs. 46.4%). When two or three types of fluid were present, the proportion treated was higher than when only one type of fluid was present. These relationships generally held in subgroup analysis by assigned drug (see **Tables 3B and 3C, Supplemental Digital Content 1 and 2**, http://links.lww.com/IAE/A322, http://links.lww.com/IAE/A323).

At the visit after a PFD, fluid persisted in 1,409 of 1,443 visits (97.6%). Fluid at the subsequent visit to PFD was still most likely to be IRF alone (405 of 1,443, 28.1%) or in any combination (897 of 1,443, 62.2%) (Table 4A). At the subsequent visit to a PFD event, ophthalmologists often did not administer treatment (779 of 1,443, 54.0% of visits) (Table 5A). Fluid and subsequent treatment status at the visits after a PFD event are detailed by assigned drug in **Supplemental Digital Content 3 and 4** (see **Tables 4B and 5B**, http://links.lww.com/IAE/A324, http://links.lww.com/IAE/A325).

Table 1. Agreement Between RC Identification of Macular Fluid on OCT and Ophthalmologist's Treatment Decision in the As Needed Dosing Groups During the First Year of CATT

As Needed Dosing Treatment Group	No. Scans Evaluated by Both Ophthalmologist and RC	PFA, n (%)	NFA, n (%)	PFD, n (%)	NFD, n (%)
Ranibizumab	3,171	1,531 (48.3)	708 (22.3)	865 (27.3)	67 (2.1)
Bevacizumab	3,039	1,759 (57.9)	475 (15.6)	733 (24.1)	72 (2.4)
All treatment	6,210	3,290 (53.0)	1,183 (19.1)	1,598 (25.7)	139 (2.2)

Macular fluid: the presence of one or more of the following on OCT: IRF, SRF, or sub-RPE fluid. Positive fluid agreement: RC identified macular fluid on OCT and an ophthalmologist administered treatment at the corresponding visit. NFA, negative fluid agreement: RC did not identify macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit. Positive fluid discrepancy: RC identified macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment. NFD: RC did not identify macular fluid on OCT and an ophthalmologist administered treatment at the corresponding visit.

Table 2. Frequency of PFDs Per Eye During the First Year of CATT

No. PFDs	Ranibizumab, n (%) Eyes		Bevacizumab, n (%) Eyes		All Treatment, n (%) Eyes	
0	42	14.1	82	27.7	124	20.9
1	49	16.4	44	14.9	93	15.7
2	50	16.8	48	16.2	98	16.5
3	47	15.8	34	11.5	81	13.6
4	47	15.8	29	9.8	76	12.8
5	26	8.7	24	8.1	50	8.4
6	18	6.0	13	4.4	31	5.2
7	9	3.0	8	2.7	17	2.9
8	6	2.0	8	2.7	14	2.4
9	2	0.7	3	1.0	5	0.8
10	2	0.7	3	1.0	5	0.8
Any	298	100.0	296	100.0	594	100.0

Positive fluid discrepancy: RC identified macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment.

Cross-sectional Area of Fluid and Total Foveal Thickness in Positive Fluid Agreement Versus Disagreement

The median of the single largest cross-sectional area of fluid of each type was greater for cases of PFA than for cases of PFD (Table 6; Figures 1–3). For both PFD and PFA groups, the largest median cross-sectional area of fluid on OCT was for sub-RPE fluid, whereas the smallest median area was for IRF. The median cross-sectional area for PFA scans relative to PFD scans was twice as large for IRF ($P < 0.001$; Figure 1, C and D) and over 4 times as large for SRF ($P < 0.001$; Figure 2, C and D), and for sub-RPE fluid ($P < 0.001$; Figure 3, C and D).

Total foveal center point thickness (internal limiting membrane to Bruch membrane) reflected the presence and amount of fluid and neovascular complex at the foveal center. Mean total foveal center point thickness (366 ± 151 μm) was greater for the 3,290 study visits with PFA than for the 1,598 study visits with PFD (265 ± 103; $P < 0.0001$). The mean decrease in total foveal thickness from baseline to the study visit was less for visits with PFA (−120 ± 172 μm) compared with those with PFD (−170 ± 164 μm, $P < 0.0001$). At the subsequent visit, the mean thickness decreased (−27 ± 83) for PFA (treatment administered), whereas the mean thickness increased (+34 ± 76) for PFD (treatment not given; $P < 0.001$).

Positive Fluid Discrepancy Visual Outcomes

The visual acuities at the visit before, at visit of, and at the next visit after the PFD were similar (mean visual acuity: 66.4, 67.6, and 66.9 letters [≈20/50], respectively), and this pattern was consistent in ranibizumab and bevacizumab PRN-treated patients (Table 7). The case–control analysis showed that

Table 3. Frequency of Treatment Compared With RC Determined Macular Fluid Location on OCT in Year 1 of CATT

RC Determined Fluid Location	No. Scans With Fluid Subtype (%)	No. of PFA: Treatment at Corresponding Study Visit (%)		No. of PFD: No Treatment at Corresponding Study Visit (%)	
IRF only	1,548 (31.7)	759	49.0	789	51.0
SRF only	519 (10.6)	369	71.1	150	28.9
Sub-RPE fluid only	401 (8.20)	186	46.4	215	53.6
IRF and SRF	704 (14.4)	565	80.3	139	19.7
IRF and sub-RPE fluid	509 (10.4)	345	67.8	164	32.2
SRF and sub-RPE fluid	434 (8.88)	380	87.6	54	12.4
IRF and SRF and sub-RPE fluid	773 (15.8)	686	88.8	87	11.3
Any IRF	3,534 (72.3)	2,355	66.6	1,179	33.4
Any SRF	2,430 (49.7)	2,000	82.3	430	17.7
Any sub-RPE fluid	2,117 (43.3)	1,597	75.4	520	24.6
Total	4,888	3,290	67.3	1,598	32.7

RC performed grading of OCT scans from as needed dosing patients evaluated during the CATT Year 1 visits (Week 4–48). Positive fluid agreement: RC identified macular fluid on OCT and an ophthalmologist administered treatment at the corresponding visit. Positive fluid Discrepancy: RC identified macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment. Macular fluid: presence of any one or more of IRF, SRF, or sub-RPE fluid on OCT.

Table 4. Macular fluid Status at Visit Subsequent to PFD Event

Macular Fluid Status at Subsequent Visit to PFD Event	All Treatment PFD Events, n (%)	
No fluid	189	13.1
IRF only	405	28.1
SRF only	135	9.4
Sub-RPE fluid only	105	7.3
IRF and SRF	191	13.2
IRF and sub-RPE fluid	98	6.8
SRF and sub-RPE fluid	89	6.2
IRF and SRF and sub-RPE fluid	203	14.1
Unknown	28	1.9
Any IRF	897	62.2
Any SRF	618	42.8
Any Sub-RPE fluid	495	34.3
Total	1,443*	100.0

Positive fluid discrepancy: RC identified macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment. Macular fluid: presence of one or more of the following on OCT: IRF, SRF, and sub-RPE fluid.

*One hundred and fifty-five eyes that did not have subsequent visit after PFD were excluded.

visual acuity at 4 weeks after the first PFD was similar to the matched monthly treated patients (mean visual acuity: 68.1 vs. 69.4 letters, $P = 0.16$). The visual acuity change at 4 weeks after the first PFD visits was also similar to matched controls (−1.0 letters vs. 0.22 letters, $P = 0.15$) (Table 8).

When change in visual acuity at Year 1 was stratified by frequency of PFD, the 191 eyes (41%) with 1 to 2 PFD had mean visual acuity gain of 7.7 letters versus mean gain of 7.2 letters for 157 eyes (33%) with 3 to 4 PFD and mean gain of 6.1 letters in 122 eyes (26%) with ≥5 PFD. These small differences were not statistically significant ($P = 0.58$) (Table 9) and remained nonsignificant when analyzed by drug group.

Table 5. Treatment Status After PFD Event

Treatment Status at Subsequent Visit After PFD Event	All Treatment PFD Events, n (%)	
Not treated	779	54.0
Treated for macular fluid on OCT only	520	36.0
Treated for macular fluid on OCT and another reason	99	6.9
Treated for persistent subretinal hemorrhage or new hemorrhage	14	1.0
Treated for leakage on fluorescein angiography	3	0.2
Treated for decreased visual acuity only	17	1.2
Multiple non-OCT reasons	5	0.3
Other	6	0.4
Total	1,443*	100.0

Positive fluid discrepancy: RC identified macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment. Macular fluid: presence of one or more of the following on OCT: IRF, SRF, and sub-RPE fluid.

*One hundred and fifty-five eyes that did not have subsequent visit after PFD were excluded.

Discussion

In this study of OCT image review for anti-vascular endothelial growth factor treatment decisions in the PRN groups at Year 1 of the CATT, the treatment decisions of ophthalmologists matched RC determination of macular fluid status in the majority (72.1%) of the 6,210 examinations. Disagreement on macular fluid status was most commonly PFD in which the ophthalmologist did not treat and the RC detected macular fluid. This occurred more commonly for IRF than for any other fluid (SRF and sub-RPE fluid). Relative to eyes with PFA, PFD occurred in visits with thinner retinas, smaller cross-sectional fluid areas, and greater decrease in total retinal thickness at the foveal center, suggesting that eyes with smaller sites of fluid and greater improvement from baseline were less likely to have fluid identified for treatment. At visits after a PFD event, the fluid often persisted, and often was not treated. The PFD did not have substantial impact on the early subsequent visual acuity (4 weeks later). At 1 year, eyes with repeated PFD had no significant difference in visual acuity change compared with eyes with rare PFD. Repeat evaluation of NFD scans rarely revealed fluid not reported during original grading.

Every OCT was independently graded by at least two readers at the RC using a standardized protocol, therefore it is not surprising that macular fluid, subtle or otherwise, was more often noted by the RC than by individual treating ophthalmologists. Supporting this assertion, of the 6,210 OCT scans evaluated by both treating ophthalmologists and the RC, 1,598 discrepancies (25.7%) were noted where the RC graded macular fluid present on OCT and treating ophthalmologists did not administer treatment presumably because of not observing the same fluid on OCT, whereas treating ophthalmologists administered treatment in only 139 events (2.2%) when the RC graded macular fluid as absent. Diffuse thickening without cystoid spaces may have influenced the observing ophthalmologist in some of the 139 cases, because IRF was positive at the RC only if cystoid spaces were observed. Repeat RC evaluation of a randomized selection of 48 of these NFD scans revealed only 1 scan (2.1%) with macular fluid.

Table 6. Comparison of Single Largest Cross-sectional Fluid Area Found on OCT Scans From Random Samples of PFAs Versus PFDs in Year 1 of CATT

	PFA				PFD				
	n	Median (Q1, Q3)	Min	Max	n	Median (Q1, Q3)	Min	Max	*P**
IRF area ($\times 10^{-3}$ mm^2)	74	12.8 (8.67, 21.8)	2.59	129	290	6.28 (3.78, 10.1)	0.60	60.7	<0.0001
SRF area ($\times 10^{-3}$ mm^2)	44	24.9 (10.7, 45.2)	1.26	354	102	5.43 (2.71, 10.9)	1.06	213	<0.0001
Sub-RPE fluid area ($\times 10^{-3}$ mm^2)	36	45.0 (14.9, 121)	1.87	806	126	10.0 (4.15, 33.6)	0.66	1,370	<0.0004

**P* is based on a modified version of the Wilcoxon rank-sum test to compare median areas of fluid between groups.[17] Positive fluid agreement: RC identified macular fluid on OCT and an ophthalmologist administered treatment at the corresponding visit. Positive fluid discrepancy: RC identified macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment. Single largest cross-sectional area of IRF was approximated as an ellipse using the following formula: area = $\pi \times$ ([horizontal dimension / 2] $\times$ [vertical dimension / 2]). Single largest cross-sectional area of SRF and sub-RPE fluid was approximated as a hemiellipse using the following formula: area = π / 2 $\times$ ([horizontal dimension / 2] $\times$ [vertical dimension / 2]).

Several additional reasons may account for the treating ophthalmologist—RC discrepancies, such as varied interpretation of fluid across ophthalmologists in CATT, impact of other clinical data on treating ophthalmologist interpretation of OCT or interpretation of lesion activity, and other circumstances such as patient reticence. Readers were provided OCT scans in a batch format through a standard computer interface and followed a standardized grading protocol reviewing all 12 radial line images (6 macular thickness map and 6 fast macular thickness map). Treating ophthalmologists were trained in OCT review, provided with reference OCT images and instructed to review all 12 radial line OCT images. Although treating ophthalmologists were able to use analysis tools such as the retinal mapping function, they also reviewed OCT images on a variety of sources, ranging from printed images to digital images on an assortment

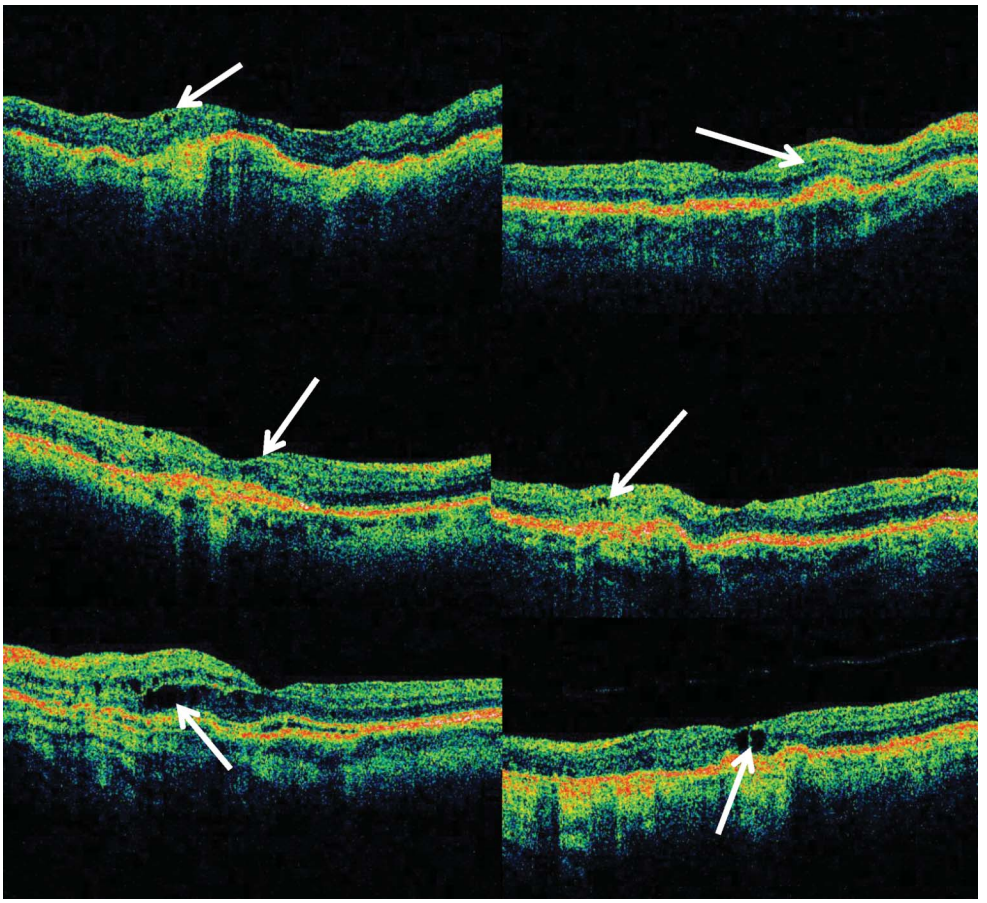

Fig. 1. Representative OCT images comparing the areas of single largest IRF between cases where RC identified OCT macular fluid and treatment was administered by an ophthalmologist (PFA), and cases where RC identified OCT macular fluid and treatment was not administered by the ophthalmologist at the corresponding visit (PFD): PFA IRF fifth percentile area (upper left), PFD IRF fifth percentile area (upper right), PFA IRF median area (center left), PFD IRF median area (center right), PFA IRF 95th percentile area (lower left), and PFD IRF 95th percentile area (lower right).

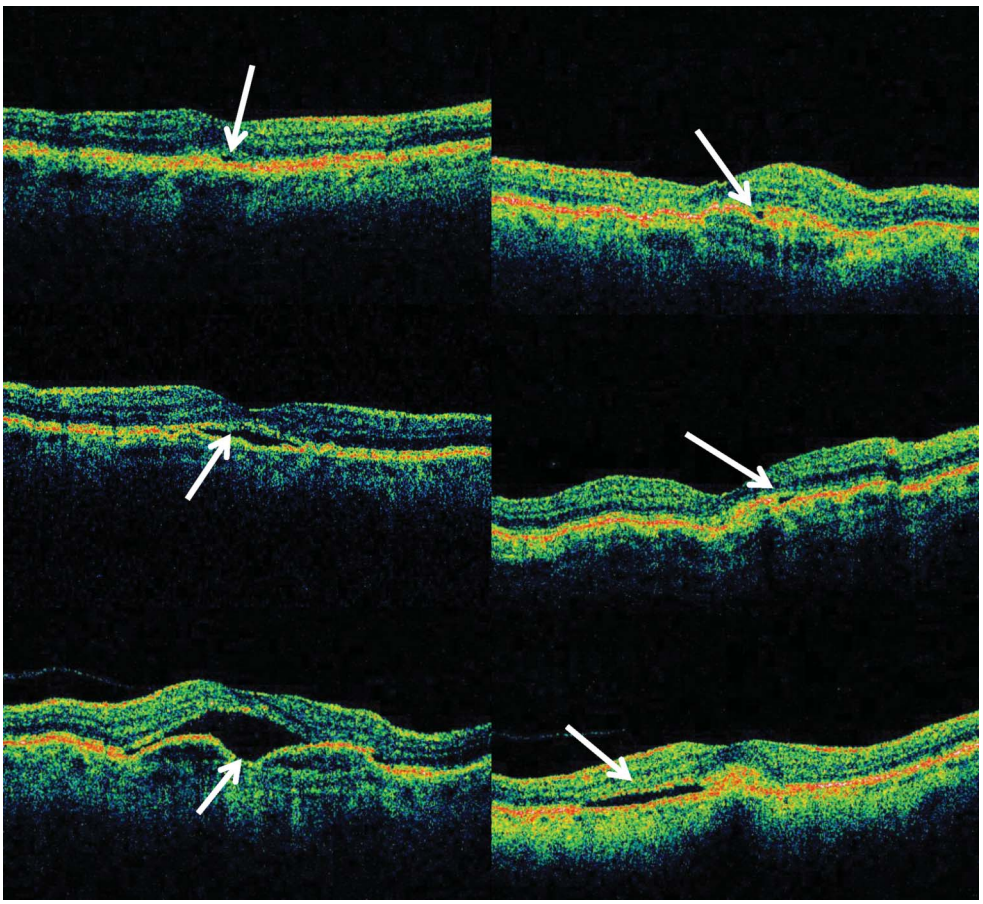

Fig. 2. Representative OCT images comparing the areas of single largest SRF between cases where RC identified OCT macular fluid and treatment was administered by a treating ophthalmologist (PFA), and cases where RC identified OCT macular fluid and treatment was not administered by the treating ophthalmologist at the corresponding visit (PFD): PFA SRF fifth percentile area (upper left), PFD SRF fifth percentile area (upper right), PFA SRF median area (center left), PFD SRF median area (center right), PFA SRF 95th percentile area (lower left), and PFD SRF 95th percentile area (lower right).

of monitors. These may have increased variability of their evaluation and may have presented obstacles to reviewing all of the OCT scans. For all fluid types, in some cases, very large areas of IRF, SRF, and sub-RPE fluid were present at a PFD (Figures 1, 2, and 3). Many of these scans with larger areas of fluid were not on the horizontal or vertical axis, and thus some perhaps were missed if select scans, rather than the entire set, were reviewed at a particular visit. Although treatment in the PRN groups, with exceptions noted in methods, per protocol was based on OCT finding of fluid, the clinician had access to interval change information, visual acuity, angiography, and symptoms that all may impact the decision-making process. A more pronounced improvement in these multiple factors may have made subsequent OCT-based treatment administration more challenging. Reading center OCT interpretation was not provided to the treating ophthalmologist as feedback, in part so as not to bias treatment decisions that would then not reflect clinical practice. Treating ophthalmologists most commonly agreed with RC determination of fluid in CATT, and the small size of most PFD suggests that review of the full OCT scan set was performed. One must recognize the careful review of the OCT scan set by the treating ophthalmologist at monthly visits when generalizing from the outcomes of the PRN treatment in CATT.

There were differences in PFD by location of fluid. Intraretinal fluid only was the most common (789 of 1,598 total discrepancies, 49.3%) cause of treatment discrepancy. Treating ophthalmologists may have less frequently identified IRF on OCT for several reasons. Although IRF was frequently present on OCT images, it was small in cross-sectional area and thus more difficult to detect or distinguish from normal pixel variation (Figure 2, A–D). Hyporeflectivity of the OCT scan at the foveal center can add to difficulty in delineating subtle IRF from pixel void artifact, and discrepancies in identifying the small areas of IRF may reflect the resolution limits of TD-OCT. In some cases, treating ophthalmologists may have been more prone to interpret subtle IRF as noise or artifact and not administer treatment, whereas conversely, RC teams may have graded artifact as subtle IRF, again leading to discrepancy. In contrast to the other fluid types, when SRF was present, whether alone or in combination, the treating ophthalmologist was most

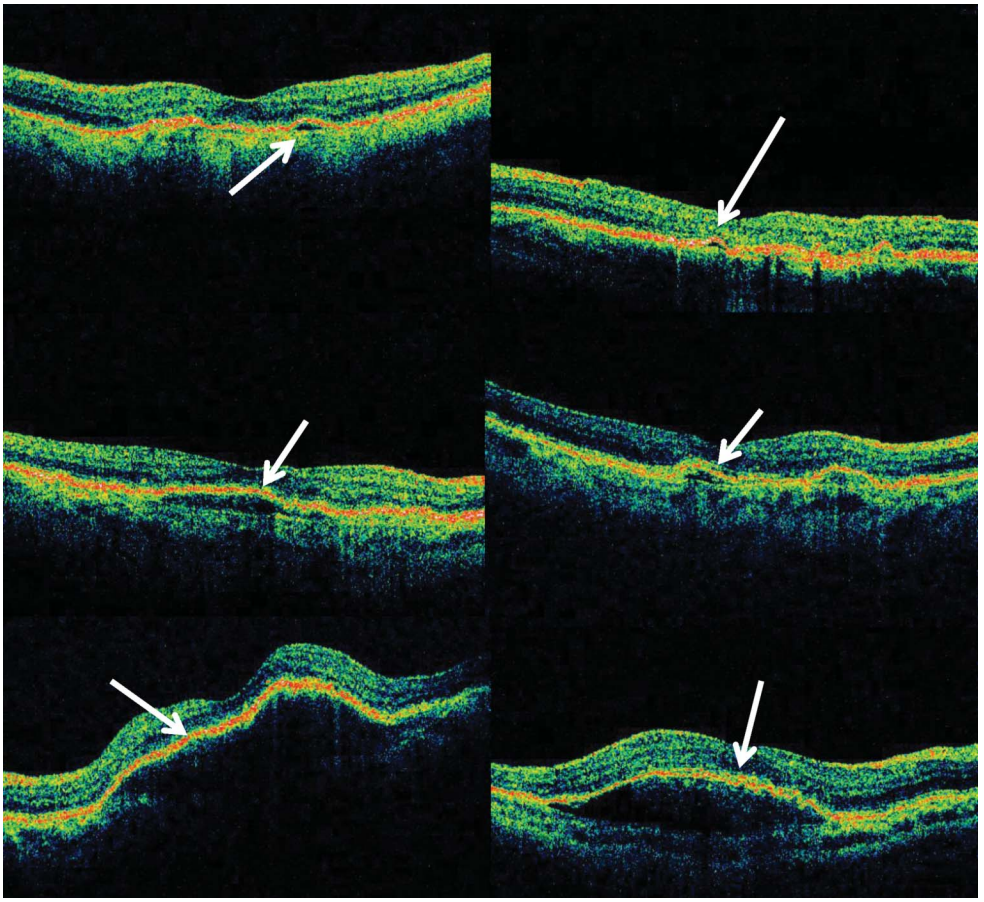

Fig. 3. Representative OCT images comparing the areas of single largest sub-RPE fluid between cases where RC identified OCT macular fluid and treatment was administered by a treating ophthalmologist (PFA), and cases where RC identified OCT macular fluid and treatment was not administered by the treating ophthalmologist at the corresponding visit (PFD): PFA sub-RPE fluid fifth percentile area (upper left), PFD sub-RPE fluid fifth percentile area (upper right), PFA sub-RPE fluid median area (center left), PFD sub-RPE fluid median area (center right), PFA sub-RPE fluid 95th percentile area (lower left), and PFD sub-RPE fluid 95th percentile area (lower right).

likely to agree with RC regarding treatment of fluid. Both SRF and sub-RPE fluid seemed to match RC findings except when the area of fluid was relatively small. The median largest cross-sectional area for PFD was less than one fourth that for PDA for both SRF and sub-RPE fluid. For all three types of fluid, the cross-sectional fluid area was consistently smaller, total thickness at the foveal center point was smaller, and foveal center point decreased more from baseline for PFD compared with PFA.

Discrepant fluid from PFD events frequently persisted in study eyes, which often had PFD at the visit after a PFD event. This prevalence of macular fluid was high compared with the prevalence of persistent fluid in monthly treatment patients. At 1 year of follow-up, 53.2% and 70.9% of patients dosed monthly with ranibizumab and bevacizumab, respectively, demonstrated persistent fluid on RC OCT review. In comparison, macular fluid was observed by the RC in 97.6% of eyes during the subsequent visit after a PFD event occurred, although these were throughout rather than at the end of 1 year of treatment. Minimizing subsequent discrepant fluid after PFD would diminish overall rates of macular fluid during PRN treatment.

Secondary analysis did not reveal pronounced disparities between patients in the ranibizumab and bevacizumab PRN dosing groups. For both drug

Table 7. Visual Acuity Before, at, and After the PFD Events

	All Treatments PFD Events		Ranibizumab PFD Events		Bevacizumab PFD Events	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
VA before PFD	1,597	66.4 (16.3)	865	67.0 (15.3)	733	65.8 (17.3)
At PFD	1,597	67.6 (16.1)	865	68.1 (15.0)	733	66.9 (17.3)
After PFD	1,597	66.9 (16.7)	865	67.4 (15.6)	733	66.3 (17.9)

Positive fluid discrepancy: RC identified macular fluid on OCT and an ophthalmologist did not administer treatment at the corresponding visit when there were no contraindications to treatment.

Table 8. Comparison of Visual Acuity at 4 Weeks After the First PFD in PRN Groups and Their Matched Controls in Monthly Treated Group

	PFD Case	Monthly Treated Control	*P*
VA at 4 weeks after the first PFD			
N	138	138	
Mean (SE)	68.1 (1.00)	69.4 (0.95)	0.16*
Median (min, max)	70 (33, 88)	72 (27, 88)	0.08†
VA change at 4 weeks after the first PFD			
Mean (SE)	–1.0 (0.70)	0.22 (0.59)	0.15*
Median (min, max)	–1.0 (–43, 22)	1 (–25, 32)	0.08†

*P is from paired *t*-test.
†P is from signed-rank test.
Positive Fluid Discrepancy: RC identified OCT macular fluid and treatment not administered by a treating ophthalmologist at the corresponding visit; SE, standard error; VA, visual acuity.

groups, the frequency and distribution of discrepant treatment were comparable. After PFD events, fluid persisted at comparable rates for both groups, although rate of treatment was slightly higher at subsequent visit to PFD events for eyes in the ranibizumab group. Cases in the PRN ranibizumab group demonstrated a larger reduction in total thickness at the foveal center point from baseline to PFD than cases in the bevacizumab group; however, total foveal thicknesses at 1 year were comparable (294 ± 139 for bevacizumab PRN and 308 ± 127 for ranibizumab PRN).[14]

Although we have shown that generally smaller areas of discrepant fluid are widespread and persistent, the ultimate impact of discrepant macular fluid on visual outcomes is currently not well understood. Multiple studies have investigated variable-dosing regimens based in part on OCT assessment of fluid as an alternative protocol to maximize visual gain while minimizing treatment burden.[6,7] Across these studies, criteria for treatment differed across the variable-dosing regimens,[6,7] and assessment of fluid through detailed morphologic analysis involved as few as two cross-hair scans.[6] None of the studies compared decisions to treat to RC interpretations of fluid on OCT.

For CATT study patients at 1 year, the differences in mean change in acuity were +1.7 letters between ranibizumab monthly and PRN groups and +2.1 letters between the bevacizumab monthly and PRN groups. These outcomes were obtained with a mean 6.9 ± 3.0 ranibizumab and 7.7 ± 3.5 bevacizumab injections, respectively.[14] The overall visual and anatomical impact of treatment discrepancies was not notable at the 4-week visit after PFD. Moreover, when we compared the 1 year visual acuity between eyes with >5 PFD and eyes with minimal PFD, there was no significant difference in acuity. Thus from this study, we could not identify a difference in acuity in the PRN groups that could be based on PFD.

This work must be interpreted in the context of several limitations. Because treating ophthalmologists did not report OCT grading like RC teams, agreement was approximated by comparing treating ophthalmologist treatment decisions with RC team OCT grading. If the rationale for treatment was not reported correctly, then agreement rates may be inaccurate. Agreement may have been overestimated if eyes were treated for other factors, but macular fluid was reported as the indication for treatment. Conversely, although the protocol mandated treatment for any macular fluid on OCT, a treating ophthalmologist may have withheld treatment despite residual fluid because of excellent visual acuity, marked treatment response to the previous injection, or patient reticence. Another

Table 9. Change in Visual Acuity From Baseline at Year 1 Stratified by Number of Discrepant Treatments in the CATT as Needed Dosing Group Patients

No. Missed Treatment in Year 1	Overall		Ranibizumab		Bevacizumab	
	n	Mean VA Change From Baseline at 1 Year (SD)	n	Mean VA Change From Baseline at 1 Year (SD)	n	Mean VA Change From Baseline at 1 Year (SD)
1–2	191	7.7 (12.5)	99	8.0 (12.8)	92	7.3 (12.2)
3–4	157	7.2 (13.4)	94	6.6 (12.7)	63	8.0 (14.4)
5+	122	6.1 (13.4)	63	5.8 (12.7)	59	6.3 (14.3)
P		0.58		0.57		0.78

VA, visual acuity.

limitation is that the total cross-sectional areas of all IRF, SRF, and sub-RPE fluid on a radial line image were not calculated. Rather the single largest area for each type of macular fluid present on an OCT scan was approximated. Because this method was consistently applied, relative comparisons could be made with reasonable certainty across groups. This work is the first to characterize treatment discrepancies from a large cohort of patients prospectively undergoing OCT-guided PRN treatment of NVAMD. By examining the treatment decision, this study is instructive regarding the nuances in implementing an OCT-guided PRN treatment protocol in real-world practice.

Spectral domain OCT (SD-OCT) technology offers many promises for future clinical trials, some of which may facilitate OCT-based PRN dosing. Compared with conventional TD-OCT, SD-OCT offers increased image resolution and more rapid data acquisition leading to subsequent decreased motion artifact.[18,19] Thus, SD-OCT may facilitate recognition of macular fluid, although, as with TD-OCT, a review of the full scan set would likely be important. Sayanagi et al[20] reported that various SD-OCT platforms compared with TD-OCT were superior in detection of IRF, SRF, and sub-RPE fluid in eyes with NVAMD. Folgar et al,[21] in a review of over 1,200 pairs of SD-OCT and TD-OCT scans from study visits in Year 2 of the CATT, found 6% greater frequency of IRF detected on TD-OCT possibly because of lower resolution with interpretation of dark pixels as cystoid edema, although fluid overall was detected with 5% greater frequency with SD-OCT. Improved fluid detection may result in increased treatment frequency, improved outcomes, and decreased intertreating ophthalmologist variability.

The CATT treating ophthalmologist decisions suggest that ophthalmologists less frequently identified OCT macular fluid than the RC; however, clinical decisions were also likely to be impacted by other factors (acuity, presence of blood, patient reticence to treatment) that would not be considered by an RC. The areas of discrepant fluid were most commonly located within the retina and were smaller than the corresponding areas in eyes undergoing protocol treatment. A more pronounced anatomical response to treatment including larger decrease in total thickness at the foveal center and smaller macular fluid may have contributed to increased discrepancy rates. Fluid tended to persist after a PFD, and often it was not treated. The visual impact for missed fluid was minimal at the subsequent examination. Although repeated PFD might affect visual acuity, this was not evident in the 1-year study. There were infrequent large areas of fluid in OCTs at PFD, which is an alert to the importance of review of all scans for a clinical visit in which a treatment decision is made for NVAMD.

Key words: OCT, age-related macular degeneration, bevacizumab, ranibizumab, optical coherence tomography, subretinal fluid, intraretinal fluid, pigment epithelial detachment, CATT, choroidal neovascularization.

References

1. Hee MR, Baumal CR, Puliafito CA, et al. Optical coherence tomography of age-related macular degeneration and choroidal neovascularization. Ophthalmology 1996;103:1260–1270.
2. 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;120:731–737.
3. Rahman W, Chen FK, Yeoh J, da Cruz L. Enhanced depth imaging of the choroid in patients with neovascular age-related macular degeneration treated with anti-VEGF therapy versus untreated patients. Graefes Arch Clin Exp Ophthalmol 2013;251:1483–1488.
4. Gupta OP, Shienbaum G, Patel AH, et al. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. Ophthalmology 2010;117:2134–2140.
5. Dadgostar H, Ventura AA, Chung JY, et al. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. Ophthalmology 2009;116:1740–1747.
6. Rothenbuehler SP, Waeber D, Brinkmann CK, et al. Effects of ranibizumab in patients with subfoveal choroidal neovascularization attributable to age-related macular degeneration. Am J Ophthalmol 2009;147:831–837.
7. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143:566–583.
8. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 2009;148:43–58 e1.
9. Holz FG, Amoaku W, Donate J, et al. Safety and efficacy of a Flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. Ophthalmology 2011;118:663–671.
10. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–1431.
11. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–1444.
12. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008;246:81–87.
13. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. Br J Ophthalmol 2006;90:1344–1349.
14. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–1908.

15. CATT. Comparison of age-related macular degeneration treatments trials manual of procedures. Available at: http://www.med.upenn.edu/cpob/studies/documents/CATTManualofProceduresJan2011.pdf. Accessed April 4, 2013.
16. Ying GS, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2013;120:122–129.
17. Rosner B, Glynn RJ, Lee ML. Incorporation of clustering effects for the Wilcoxon rank sum test: a large-sample approach. Biometrics 2003;59:1089–1098.
18. Srinivasan VJ, Wojtkowski M, Witkin AJ, et al. High-definition and 3-dimensional imaging of macular pathologies with high-speed ultrahigh-resolution optical coherence tomography. Ophthalmology 2006;113:2054 e1–14.
19. Wojtkowski M, Bajraszewski T, Gorczynska I, et al. Ophthalmic imaging by spectral optical coherence tomography. Am J Ophthalmol 2004;138:412–419.
20. Sayanagi K, Sharma S, Yamamoto T, et al. Comparison of spectral-domain versus time-domain optical coherence tomography in management of age-related macular degeneration with ranibizumab. Ophthalmology 2009;116:947–955.
21. Folgar FA, Jaffe GJ, Ying GS, et al. Comparison of optical coherence tomography assessments in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2014;121:1956–1965.