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Characteristics of Eyes With Good Visual Acuity at 5 Years After Initiation of Treatment for Age-Related Macular Degeneration but Not Receiving Treatment From Years 3 to 5

Post Hoc Analysis of the CATT Randomized Clinical Trial

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IMPORTANCE Identifying the characteristics of eyes with neovascular age-related macular degeneration (nAMD) that maintain good vision without anti–vascular endothelial growth factor treatment for at least 3 years after management, as occurred in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), may have prognostic importance and help in understanding the disease and its treatment.

OBJECTIVES To ascertain the characteristics of eyes in the CATT that retained good vision despite receiving no therapy for 3 years after release from the 2-year CATT treatment protocol.

DESIGN, SETTING AND PARTICIPANTS This case-control study analyzed the baseline and follow-up characteristics of eyes with nAMD that were enrolled in the CATT from 43 US clinical centers between February 20, 2008, and December 9, 2009. After initial randomization to 1 of 4 treatment groups (ranibizumab monthly, bevacizumab monthly, ranibizumab as needed, or bevacizumab as needed), at year 1, participants in the monthly groups were rerandomized to continue monthly treatment or to switch to as-needed treatment using the same drug as originally assigned. At year 2, participants were released from the protocol to treatment at the discretion of their ophthalmologist. At year 5, participants were recalled for examination. This present analysis, conducted from December 1, 2018, to September 30, 2019, compared the eyes of 40 participants (referred to as the cessation of treatment with good visual acuity, or CTGVA, group) with the eyes of the remainder of the CATT Follow-up Study (referred to as the other group).

MAIN OUTCOMES AND MEASURES Visual acuity, morphologic characteristics, and number of treatments over 5 years.

RESULTS Among 625 eyes with nAMD at baseline and a visual acuity measurement at year 5, 40 (6.4%; 95% CI, 4.7%-8.7%) were included in the analysis. These 40 participants, compared with the other group (n = 585), had a lower mean (SD) age of 74.7 (7.3) years (vs 77.7 [7.3] years; *P* = .01) and included 26 women (65.0%). Baseline characteristics were similar between eyes in the CTGVA and other groups, except for better visual acuity letter score in the study eye (68.8 vs 61.8; *P* = .001) and the fellow eye (78.4 vs 68.0; *P* = .01) as well as the presence of blocked fluorescence seen more often in participants in the CTGVA vs the other group (27.5% vs 13.8%; *P* = .02). Eyes in the CTGVA group with as-needed treatment received fewer mean (SD) injections in year 1 (5.8 [4.0] vs 8.1 [3.5]) and year 2 (7.7 [5.7] vs 13.8 [6.8]) than eyes in the other as-needed group. Mean (SD) visual acuity letter score at 5 years was 79.0 (5.5; Snellen 20/25) in the CTGVA group and 57.5 (24.2; Snellen 20/80) in the other group.

CONCLUSIONS AND RELEVANCE These findings suggest that a small proportion of eyes with nAMD can retain good visual acuity with no treatment for at least 3 years after the initial 2 years of treatment. Unique characteristics of eyes that could discontinue treatment while maintaining good visual acuity could not be identified at baseline, but data suggest that not all eyes with this disease may need treatment forever.

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Supplemental content

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Anti-vascular endothelial growth factor (anti-VEGF) treatment is the standard of care for neovascular age-related macular degeneration (nAMD). Multiple clinical trials have shown the efficacy of anti-VEGF therapy in improving visual acuity and decreasing retinal thickness over 1 to 2 years.[1-7] The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) enrolled and treated participants with ranibizumab or bevacizumab in either a monthly or as-needed (prn) regimen.[2] At year 1, participants in the monthly groups were rerandomized to either continued monthly or as-needed injections.[1] At year 2, the visual acuity outcomes favored the monthly treatment regimen but did not show any significant difference between anti-VEGF agents. Similarly, significantly lower retinal thickness, less retinal fluid, smaller lesions with less growth, and less fluorescein leakage were seen in participants who were treated monthly compared with those treated as needed.[1]

After year 2, participants were released from the clinical trial treatment protocol to treatment at the discretion of their ophthalmologist.[1,2] Investigators in the CATT Follow-up Study collected clinical, treatment, and outcomes data from CATT participants at year 5.[8] The CATT Follow-up Study found that 90 of 625 eyes (14.8%) received no anti-VEGF treatment after year 2 of the CATT.[8] Forty eyes (6.4%; 95% CI, 4.7%-8.7%) retained good visual acuity (Snellen 20/40 or better), despite no anti-VEGF treatment. In the present case-control study, we conducted a secondary analysis of the baseline and follow-up characteristics of these 40 eyes.

Key Points

Question In the Comparison of Age-Related Macular Degeneration Treatments Trials, what was the frequency of retained good vision at 5 years when no treatment was given after 2 years from treatment initiation?

Findings In this case-control study of 625 eyes with neovascular age-related macular degeneration that were enrolled in the Comparison of Age-Related Macular Degeneration Treatments Trials, a small percentage (40 [6.4%]) retained a visual acuity letter score of 68 (Snellen 20/40) or better with no treatment for at least 3 years.

Meaning Findings of this study demonstrated that a minority of participants with neovascular age-related macular degeneration retained good vision even without treatment after 2 years of protocol management, suggesting that not all eyes with this disease will need treatment forever.

Methods

This case-control study was conducted from December 1, 2018, to September 30, 2019. Details of the designs of the CATT and CATT Follow-up Study have been published previously.[1,2,8] In summary, a total of 1185 participants were enrolled into the CATT from 43 US clinical centers between February 20, 2008, and December 9, 2009. Each institutional review board associated with a CATT clinical center approved the study. All participants provided written informed consent. The CATT was performed in compliance with the Health Insurance Portability and Accountability Act. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

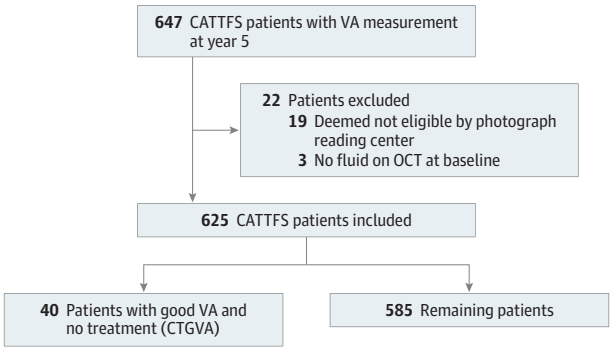
One eye (study eye) per participant was enrolled. Criteria for inclusion included treatment-naive eyes with active choroidal neovascularization (CNV) secondary to age-related macular degeneration. Participants were randomized with equal probability to 1 of 4 treatment groups, including ranibizumab monthly, bevacizumab monthly, ranibizumab as needed, or bevacizumab as needed. After the first year, participants in the monthly groups were rerandomized to continue the monthly regimen or to switch to as-needed treatments, using the same drug as originally assigned.

After 2 years, participants were released from the protocol to treatment at the discretion of their ophthalmologist. Between March 14, 2014, and March 31, 2015, participants were recalled for participation in the CATT Follow-up Study at approximately 5 years after their enrollment in the CATT. Each institutional review board associated with a participating center approved the Follow-up Study. All participants provided written informed consent. Only participants with a visual acuity measurement between 51 and 85 months after the date of initial study randomization were included. During the follow-up visits conducted at the CATT centers, an interval history, including the number of injections, was obtained, and study-certified personnel performed a full examination with ancillary testing, including fundus photography, fluorescein angiography, and optical coherence tomography in most study participants.[1,2] Some participants who did not complete a visit in a CATT clinical center completed an interview about past care, treatment, and serious medical events; signed a medical records release form; or both. Information on treatment, visual acuity, and imaging was requested from the participant's ophthalmologist outside of the CATT center.

Among the CATT Follow-up Study cohort, 90 participants were identified who had received no treatment since the completion of year 2. Fifty participants had moderate to severe visual acuity loss and received no further treatment because of 1 or more of the following: no fluid per treating ophthalmologist (71%), observation preferred per treating ophthalmologist (16%), treatment futility determined by the ophthalmologist (30%), or other reasons (20%). The remaining 40 participants had a visual acuity letter score of 68 (Snellen 20/40) or better in the study eye.[8]

This present analysis compared the eyes of these 40 participants (referred to as the cessation of treatment with good visual acuity, or CTGVA, group) with the eyes of the remainder of the CATT Follow-up Study cohort (referred to as the other group), including the 50 participants with no treatment and with visual acuity letter score worse than 68 (Snellen 20/40) (**Figure 1**). The director of the CATT Fundus Photograph Reading Center (E.D.) reviewed each case and confirmed that neovascularization secondary to age-related macular degeneration was present at baseline.

Figure 1. Eligibility for Comparison of Age-Related Macular Degeneration Treatments Trials Follow-up Study (CATTFS) and Distribution of Cessation of Treatment With Good Visual Acuity (CTGVA) Eyes vs Other Eyes



OCT indicates optical coherence tomography; VA, visual acuity.

Statistical Analysis

We used 2-sample *t* tests for comparing continuous measures and Fisher exact test for comparing categorical measures. We used univariable and multivariable logistic regression models for determining the factors associated with cessation of treatment with good visual acuity (yes or no). The initial multivariable model included variables with $P < .20$ in univariable analyses. The factors included in the final multivariable model were identified by backward variable selection. For the evaluation of associations between continuous measures at baseline and cessation of treatment with good visual acuity at year 5, continuous measures were categorized into groups for calculating odds ratio (OR), and the linear-trend *P* value was used to test their statistical significance. All statistical analyses were performed in SAS, version 9.4 (SAS Institute Inc), and 2-sided $P < .05$ was used to indicate statistical significance. Data analyses were performed from December 1, 2018, to September 30, 2019.

Results

Baseline Characteristics of the CTGVA Group

Of the 625 eyes that had nAMD at baseline and a visual acuity measurement at year 5, 40 (6.4%; 95% CI, 4.7%-8.7%) were in the CTGVA group. Participants in the CTGVA group, compared with the other group (n = 585), had a lower mean (SD) age of 74.7 (7.3) years (vs 77.7 [7.3] years; $P = .01$) and included 26 women (65.0%) (vs 382 women [65.3%] in the other group). Mean (SD) baseline visual acuity letter score in the study eye was better in the CTGVA group compared with the other group (68.8 [9.7] vs 61.8 [13.1]; $P = .001$). Mean (SD) baseline visual acuity letter score in the fellow eye was also better in the CTGVA group than in the other group (78.4 [16.1] vs 68.0 [26.0]; $P = .01$). No difference in baseline medical comorbidities was observed between the 2 groups. No difference in baseline characteristics was observed between the assigned drug group and regimen group (ie, as needed, monthly, or switched) (eTable 1 in the Supplement).

The associations between baseline anatomical characteristics and cessation of treatment with good visual acuity are included in eTables 2 and 3 in the Supplement. Univariable comparison of baseline morphologic and optical coherence tomography characteristics revealed that blocked fluorescence was present more often (27.5% vs 13.8%; $P = .02$) and that intraretinal fluid (IRF) was present less often (55% vs 74.2%; $P = .02$) in CTGVA eyes compared with other eyes. The 2 groups were similar in size of CNV, CNV lesion type, retinal angiomatous proliferation lesion, hemorrhage associated with lesion, geographic atrophy (GA), or presence of pseudodrusen in the fellow eye. They were similar in retinal thickness, subretinal tissue complex, subretinal fluid (SRF), sub-retinal pigment epithelial (sub-RPE) fluid, vitreomacular attachment, and subretinal hyperreflective material (SHRM).

The initial multivariable analysis started with the following factors: age, baseline visual acuity in the study eye, baseline visual acuity in the fellow eye, blocked fluorescence, CNV in the fellow eye, hard exudates in the study eye, subretinal tissue complex thickness at foveal center, IRF, RPE elevation, and regimen and treatment drug. In the final multivariable model, worse visual acuity in the study eye (52-23 [Snellen 20/100-20/320]; OR, 0.17; 95% CI, 0.05-0.59; $P = .001$) and worse visual acuity in the fellow eye (≤67 [Snellen 20/50 or worse]; OR, 0.15; 95% CI, 0.03-0.67; $P = .02$) were associated with lower likelihood of cessation of treatment with good visual acuity, whereas presence of blocked fluorescence (OR, 2.29; 95% CI, 1.08-4.87; $P = .03$) was associated with higher likelihood of cessation of treatment with good visual acuity (**Table 1**).

Visual Acuity Progression

Visual acuity over time in the CTGVA group and other group is shown in **Table 2** and **Figure 2**. The mean (SD) change in visual acuity letter score from baseline at week 12 (or month 3) was similar in the CTGVA group and other group (net gain, 7.7 [8.9] vs 6.4 [10.8]), whereas the mean visual acuity letter score at week 12 was better in the CTGVA group compared with the other group (76.6 [7.8] vs 68.2 [14.7]).

At year 1, both groups continued to have vision improvement from baseline. Eyes in the CTGVA group, compared with the other group, had better mean (SD) visual acuity letter score (80.3 [6.4] vs 70.0 [16.4]) and gained more (11.8 [9.1] vs 8.2 [13.9]). At year 2, the difference widened for both mean (SD) visual acuity letter score between the CTGVA and other groups (80.8 [6.6] vs 69.0 [16.9]) and mean (SD) change from baseline (net gain, 12.0 [8.9] vs 7.2 [16.3]). At year 5, the mean (SD) visual acuity letter score was 79.0 (5.5; Snellen 20/25) in the CTGVA group and 57.5 (24.2; Snellen 20/80) in the other group, with a net gain from baseline of 10.2 (10.5) in the CTGVA group and a loss of 4.2 (22.4) in the other group.

Morphologic Characteristics Over Time

As stated previously, the mean baseline retinal thicknesses in the 2 groups were similar. With treatment, the mean change in thickness at month 3 and year 1 was not different between groups, nor was the absolute retinal thickness at either time point (Table 2). At year 2, the total mean (SD) retinal thickness

Table 1. Results of Multivariable Analysis for Baseline Characteristics Associated With Cessation of Treatment With Good Visual Acuity

Baseline Characteristic	No. (%)		Odds Ratio (95% CI)	*P* Value
	CTGVA Eyes (n = 40)	Other Eyes (n = 585)		
Visual acuity letter score in the study eye (Snellen equivalent)				
82-68 (20/25-20/40)	27 (67.5)	231 (39.5)	1 [Reference]	.001
67-53 (20/50-20/80)	10 (25.0)	214 (36.6)	0.41 (0.19-0.88)	
52-23 (20/100-20/320)	3 (7.5)	140 (23.9)	0.17 (0.05-0.59)	
Visual acuity letter score in the fellow eye (Snellen equivalent)				
>83 (20/20 or better)	19 (47.5)	204 (34.9)	1 [Reference]	.02
68-82 (20/25-20/40)	19 (47.5)	220 (37.6)	1.05 (0.53-2.07)	
≤67 (20/50 or worse)	2 (5.0)	161 (27.5)	0.15 (0.03-0.67)	
Blocked fluorescence				
No	29 (72.5)	504 (86.2)	1 [Reference]	.03
Yes	11 (27.5)	81 (13.8)	2.29 (1.08-4.87)	

Abbreviation: CTGVA, cessation of treatment with good visual acuity.

Table 2. Comparisons of Visual Acuity and Morphologic Outcomes at 3 Months and Years 1, 2, and 5[a]

Outcome Measure	Month 3		Year 1		Year 2		Year 5	
	CTGVA Group (n = 40)	Other Group (n = 585)	CTGVA Group (n = 40)	Other Group (n = 585)	CTGVA Group (n = 40)	Other Group (n = 585)	CTGVA Group (n = 40)	Other Group (n = 585)
VA letter score, mean (SD)	76.6 (7.8)	68.2 (14.7)	80.3 (6.4)	70.0 (16.4)	80.8 (6.6)	69.0 (16.9)	79.0 (5.5)	57.5 (24.2)
Change from baseline	7.7 (8.9)	6.4 (10.8)	11.8 (9.1)	8.2 (13.9)	12.0 (8.9)	7.2 (16.3)	10.2 (10.5)	−4.2 (22.4)
OCT outcomes								
Total retinal thickness, mean (SD), μm	279.4 (142.4)	312.0 (144.2)	271.3 (126.7)	302.0 (138.9)	250.0 (66.8)	300.9 (134.9)	252.8 (106.2)	278.6 (159.0)
Change in total retinal thickness, mean (SD), μm	−119.2 (98.3)	−154.6 (164.5)	−130.1 (115.6)	−168.6 (185.0)	−150.8 (155.5)	−161.3 (188.4)	−136.0 (115.3)	−186.9 (210.6)
Intraretinal fluid	13/37 (35.1)	288/540 (53.3)	8/34 (23.5)	270/552 (48.9)	10/29 (34.5)	214/409 (52.3)	13/36 (36.1)	280/496 (56.5)
Subretinal fluid	10/38 (26.3)	206/540 (38.1)	5/33 (15.2)	190/546 (34.8)	3/29 (10.3)	155/401 (38.7)	6/36 (16.7)	195/493 (39.6)
Sub-RPE fluid	8/36 (22.2)	190/516 (36.8)	10/33 (30.3)	175/532 (32.9)	9/29 (31.0)	148/394 (37.6)	8/36 (22.2)	188/495 (38.0)
SHRM	13/38 (34.2)	299/547 (54.7)	11/34 (32.4)	270/558 (48.4)	5/29 (17.2)	192/414 (46.4)	15/36 (41.7)	337/498 (67.7)
Outcomes from fundus photographs/FA[b]								
Geographic atrophy	NA	NA	4/37 (10.8)	94/561 (16.8)	6/39 (15.4)	115/578 (19.9)	13/33 (39.4)	194/465 (41.7)
Scarring	NA	NA	13/37 (35.1)	198/562 (35.2)	16/39 (41.0)	255/574 (44.4)	9/33 (27.3)	199/466 (42.7)
Pathological condition in foveal center (yes vs no)	9/12 (75.0)	147/165 (89.1)	24/35 (68.6)	449/556 (80.8)	24/37 (64.9)	458/568 (80.6)	18/28 (64.3)	357/429 (83.2)
Pathological condition in foveal center								
None	NA	NA	11/35 (31.4)	107/556 (19.2)	13/37 (35.1)	110/568 (19.4)	10/28 (35.7)	72/429 (16.8)
Geographic atrophy	NA	NA	1/35 (2.9)	12/556 (2.2)	1/37 (2.7)	36/568 (6.3)	3/28 (10.7)	76/429 (17.7)
Scarring	NA	NA	3/35 (8.6)	116/556 (20.9)	5/37 (13.5)	136/568 (23.9)	5/28 (17.9)	109/429 (25.4)
CNV	NA	NA	8/35 (22.9)	143/556 (25.7)	5/37 (13.5)	114/568 (20.1)	1/28 (3.6)	39/429 (9.1)
Other	NA	NA	12/35 (34.3)	178/556 (32.0)	13/37 (35.1)	172/568 (30.3)	9/28 (32.1)	133/429 (31.0)
Cumulative No. of injections in as-needed treated participants, mean (SD)[c]	2.6 (1.1)	3.0 (0.9)	5.8 (4.0)	8.1 (3.5)	7.7 (5.7)	13.8 (6.8)	7.7 (5.7)	30.4 (16.9)

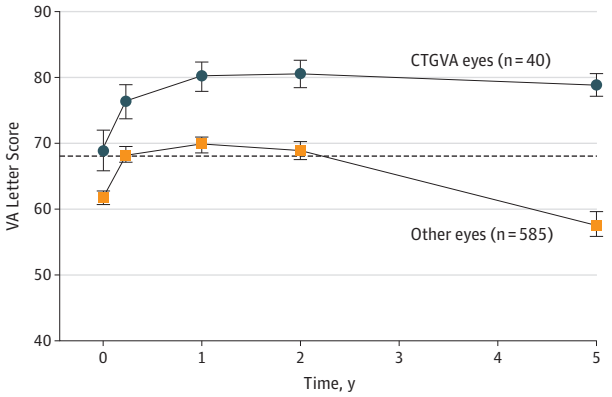
Abbreviations: CNV, choroidal neovascularization; CTGVA, cessation of treatment with good visual acuity; FA, fluorescein angiography; NA, not applicable; OCT, optical coherence tomography; RPE, retinal pigment epithelium; SHRM, subretinal hyperreflective material; VA, visual acuity.

[a] Unless otherwise specified, data are presented as No./No. of eyes evaluated (percentage).

[b] Only assessed at years 1, 2, and 5.

[c] A total of 313 participants received treatment as needed, with 18 in the CTGVA group and 295 in the other group.

Figure 2. Mean Visual Acuity in Cessation of Treatment With Good Visual Acuity (CTGVA) Eyes and Other Eyes During the Comparison of Age-Related Macular Degeneration Treatments Trials



Dashed line indicates visual acuity letter score of 68 (Snellen 20/40); error bars, 95% CIs; and VA, visual acuity.

in the CTGVA group was less than in the other group (250.0 [66.8] µm vs 300.9 [134.9] µm). At year 5, the retinal thickness in both groups became more similar, but the eyes in the other group had more decrease in mean (SD) retinal thickness compared with baseline (-136 [115.3] µm for CTGVA vs -186.9 [210.6] µm for other).

The presence of retinal fluid and SHRM in each group over time is graphically depicted in **Figure 3** and listed in Table 2. After 3 months of treatment, the CTGVA cohort continued to have proportionally less IRF (35.1% [13 of 37] vs 53.3% [288 of 540]) but similar SRF (26.3% [10 of 38] vs 38.1% [206 of 540]) and sub-RPE fluid (22.2% [8 of 36] vs 36.8% [190 of 516]) compared with the other group. Less SHRM was found in the CTGVA group than in the other group at month 3 compared with baseline (34.2% [13 of 38] vs 54.7% [299 of 547]).

At year 1, less IRF was found in the CTGVA group compared with the other group (23.5% [8 of 34] vs 48.9% [270 of 552]). New at year 1, reduced SRF in the CTGVA cohort was observed (15.2% [5 of 33] vs 34.8% [190 of 546]). The proportions with sub-RPE fluid and SHRM were similar among the CTGVA and the other groups. At year 2, the prevalence of IRF and sub-RPE fluid were not different between groups, but less SRF (10.3% [3 of 29] vs 38.7% [155 of 401]) and less SHRM (17.2% [5 of 29] vs 46.4% [192 of 414]) were seen in CTGVA eyes.

At the year 5 visit, the proportion of eyes with retinal fluid had increased in both groups, but eyes in the CTGVA group had less IRF (36.1% [13 of 36] vs 56.5% [280 of 496]) and SRF (16.7% [6 of 36] vs 39.6% [195 of 493]) as well as less SHRM (41.7% [15 of 36] vs 67.7% [337 of 498]). The percentage of participants in each cohort with sub-RPE fluid was similar.

At year 5, 34 (85.0%) of the 40 participants had color photography and 28 (70.0%) had fluorescein angiography. No difference was seen between groups in prevalence of GA, scarring, or pathological condition in the foveal center (including GA, scarring, CNV, or other) at baseline, month 3, or year 1. More pathological conditions in the foveal center were found in year 2 (458 [80.6%] of 568 vs 24 [64.9%] of 37) and year 5 (357 [83.2%] of 429 vs 18 [64.3%] of 28) in the other group compared with CTGVA group (Table 2).

Treatment and Treatment Cessation in the CTGVA Group

Among 625 total participants, 313 (50.1%) were assigned to the as-needed group for the duration of CATT, with 18 in the CTGVA group and 295 in the other group. After 3 months, as-needed participants in each cohort had received similar numbers of injections. Afterward, however, participants in the CTGVA group, compared with those in the other cohort, received fewer mean (SD) cumulative injections in the study eye by year 1 (5.8 [4.0] vs 8.1 [3.5]), year 2 (7.7 [5.7] vs 13.8 [6.8]), and year 5 (7.7 [5.7] vs 30.4 [16.9]) (Table 2). No injections were administered for CTGVA participants between years 2 and 5 by definition. Within the CTGVA group, the median (interquartile [IQR]) number of visits between year 2 and year 5 was 11 (8-17), whereas in the other group, the median (IQR) number of visits between year 2 and year 5 was 25 (18-34).

At year 5, the CATT center clinicians who were responsible for the participants completed surveys that indicated the reasons (1 or more) for treatment cessation after exit from the CATT. In the CTGVA group, no further treatment was given owing to (1) the absence of fluid in 37 participants (92.5%), (2) physician preference to observe in 17 participants (42.5%), (3) participant preference to observe in 5 participants (12.5%), (4) treatment futility as judged by the ophthalmologist in 1 participant (2.5%), and (5) good visual acuity and stable CNV in 1 participant (2.5%).

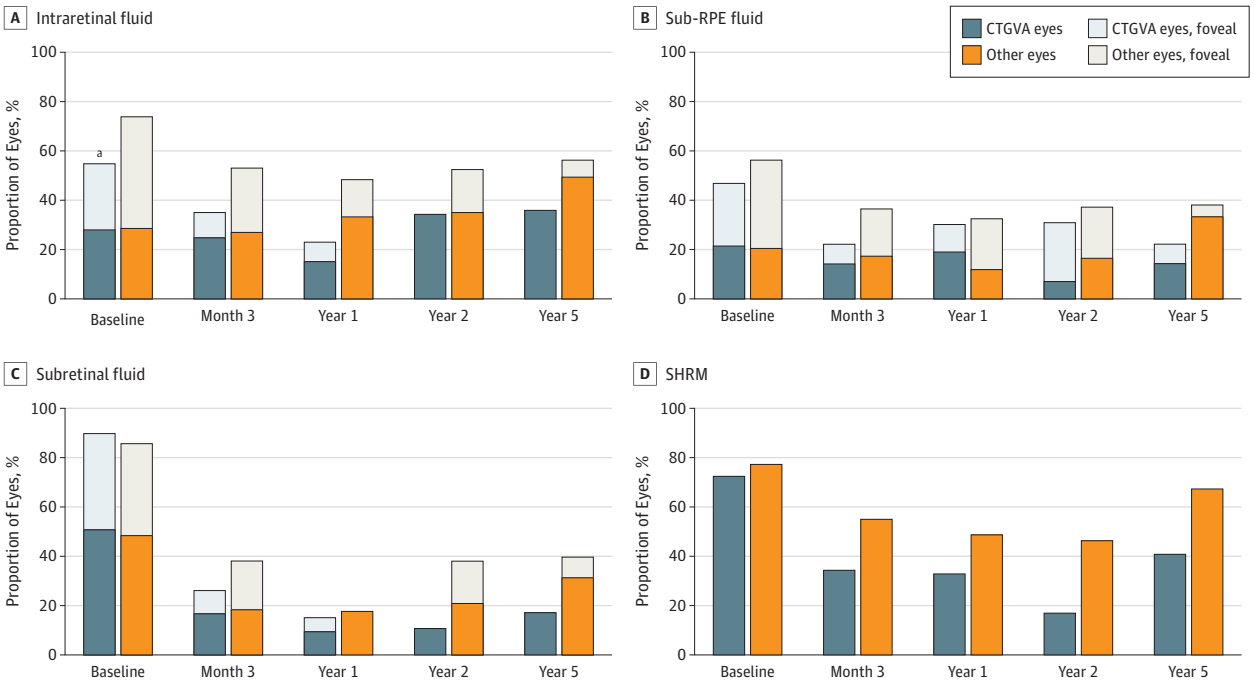
At year 5, mean (SD) fellow eye visual acuity letter score was 72.3 (18.3) in CTGVA group and 59.3 (28.3) in the other group. Fellow eye treatment during the 5-year follow-up occurred in 12 participants (30.0%) in the CTGVA group and in 266 participants (45.5%) in the other group, with the corresponding median (IQR) number of injections of 10 (6-18) for the CTGVA group and 12 (5-19) for the other group.

Discussion

This case-control study reviewed outcomes of CATT participants treated per clinical trial protocol for 2 years and then followed up by unsupervised physician management. We identified 40 participants at year 5 in the CATT Follow-up Study who maintained stable good visual acuity despite no treatment for at least 3 years.

Several studies, including the CATT, have identified characteristics before treatment and during follow-up that have been associated with poor visual outcome in nAMD.[9-13] Worse baseline acuity, larger CNV lesion, type 2 or 3 CNV, nonuse of clopidogrel bisulfate, IRF, SHRM, foveal GA, fibrotic scarring, abnormally thin or thick retina, and increasing sub-RPE tissue complex thickness have been associated with worse visual acuity at baseline and at later time points.[9-12] When evaluating these baseline characteristics in the CTGVA cohort, multivariable analysis showed that only better visual acuity in the study and fellow eyes and the presence of blocked fluorescence were associated with higher likelihood of cessation of treatment with good visual acuity.

Figure 3. Breakdown of Retinal Fluid and Subretinal Hyperreflective Material (SHRM) Visualized by Optical Coherence Tomography During the Comparison of Age-Related Macular Degeneration Treatments Trials in Cessation of Treatment With Good Visual Acuity (CTGVA) Eyes and Other Eyes



Determination of foveal vs nonfoveal SHRM was not available at all time points. RPE indicates retinal pigment epithelium.

[a] Statistical significance (sum of foveal and nonfoveal) between groups at baseline ($P < .05$).

Throughout the 5 years of the CATT, the eyes in the CTGVA group had better mean visual acuity than the eyes in the other group, but morphologic differences were present as well. Less IRF in the CTGVA eyes was observed at all time points except year 2. Less SRF in the CTGVA eyes at years 1, 2, and 5 was also found, and so was less SHRM in the CTGVA eyes at month 3, year 2, and year 5. No difference in sub-RPE fluid was observed at any time point. No difference emerged in anatomical outcomes, such as the development of GA or scarring at any time, but a pathological condition in the foveal center (including GA, scarring, CNV, or other) was less common in the CTGVA group than the other group at years 2 and 5. However, besides baseline characteristics, this post hoc analysis with multiple subgroup analyses did not perform formal statistical comparisons between eyes in the CTGVA and other groups to ascertain whether these differences were statistically significant. Such analyses would likely be heavily influenced by the choice to include only excellent visual outcomes in the CTGVA group.

As reported previously, the presence of SRF was associated with better visual acuity in nAMD, and sub-RPE fluid had no association with visual acuity.[10,11] In the present study, residual fluid in the CTGVA group, as identified by the CATT Fundus Photograph Reading Center, was common at the 5-year follow-up, with 22.2% of these participants having sub-RPE fluid, 16.7% with SRF, and 36.1% with IRF. However, these findings on Reading Center review differed substantially from the reports of clinicians who stated on surveys that 93% of CTGVA participants had no fluid. Discrepancies between clinician reports and Reading Center review were examined in participants treated as needed previously in the first[14] and second[2] years of the CATT and were found to occur in approximately 30% of eyes, with IRF most commonly in conflict.[2] Most disagreements (95%) were regarding cases in which fluid was identified by the Reading Center but no treatment was given.[2] At year 1, no difference in visual acuity was seen between participants, with or without Reading Center or clinician consensus.[14] Small amounts of fluid may have not been recognized by the ophthalmologist or may have been tolerated because the participants maintained good visual acuity.

Baseline comparisons identified a higher prevalence of blocked fluorescence in eyes in the CTGVA group compared with the other group in univariable (27.5% vs 13.8%) and multivariable analyses (Table 1). Blocked fluorescence was previously defined as localized hypofluorescence on fluorescein angiography that was contiguous with CNV and not generally due to visible hemorrhage, pigmentation, or other conditions observed on color photography that may decrease fluorescence transmission. The blocked fluorescence was believed to represent the advancing edge of a fibrovascular CNV and has been associated with worse baseline vision.[15,16] In previous analyses of CATT data, increased blocked fluorescence was negatively associated with the development of GA[15] and positively associated with the development of scarring at year 2[17] but not at year 5.[18] The good long-term visual acuity in these eyes may be associated with less GA,[15] less scarring at the foveal center at year 5,[18] or chance.

The concept of cessation of treatment in nAMD has been previously discussed. Nguyen et al[19] described 434 eyes that received no treatment for at least 3 months and received subsequent injections only when reactivation, defined as new fluid or hemorrhage, occurred. At year 1, 41% of eyes had reactivated, and by year 5, 79% had reactivated.[19] Eyes with good vision were twice as likely to reactivate than eyes with poor vision (letter score <35). Arendt et al[20] described eyes managed under a treat-extend-stop regimen and had significantly lower recurrence rates than those in the study by Nguyen et al.[19] Treatment could be stopped after three 16-week stable treatment intervals had been achieved. Among 598 eyes, 17% had cessation of treatment and only 13% of these eyes had recurrent disease that required the restart of therapy after a mean follow-up of 41 weeks.[20] Haddad et al[21] found that 63% of 132 participants achieved remission, defined as cessation of treatment for 1 full year. Worse baseline visual acuity was associated with cessation of treatment, and 51% of these eyes eventually had recurrence after achieving cessation of treatment in the 8-year study.[21] Muftuoglu et al[22] defined long-term remission as a cessation of treatment by the ophthalmologist for at least 6 months and found that 11.6% of eyes that received as-needed treatment achieved cessation of treatment. The mean time to cessation of treatment was 19 months, and the length of cessation of treatment was 18 months.[22] Cessation of treatment was considerably more common in eyes with baseline findings of retinal angiomatous proliferation lesions, more IRF, less SRF, and thinner subfoveal choroid as well as in eyes that developed macular atrophy in follow-up.[22] Eyes that reached cessation of treatment had a good mean final visual acuity (approximately Snellen 20/50) with a wide distribution.[22]

Overall, these findings, especially that cessation of treatment was more common in eyes with bad vision, differed substantially from the results of the present study. The association of macular atrophy with cessation of treatment may be due to the fact that these eyes often do not have active exudation or that ophthalmologists may be reluctant to treat eyes with macular atrophy. Overall, retinal angiomatous proliferation lesions were uncommon in the CATT (10.7%) and the CTGVA cohort (7.5%).[23] The association of more baseline IRF and less baseline SRF with cessation of treatment in other studies is not surprising given the known poor prognosis of IRF and the protective nature of SRF in nAMD.[11]

Limitations

This study has limitations. Because only 71% of CATT participants who were alive at the time of the CATT Follow-up Study returned, the proportion with good visual acuity may be overestimated.[8] Participants in the follow-up study had a mean baseline visual acuity score that was 3 letters better than the score for nonparticipants, and participants with better baseline visual acuity were more likely to be in the CTGVA group.[8] Some participants in the follow-up study did not have imaging results, decreasing the accuracy and precision of the description of morphologic features present at year 5.

Conclusions

Cessation of anti-VEGF treatment after 2 years with maintenance of good visual acuity was successful in a small percentage of participants with nAMD enrolled in the CATT. Baseline characteristics of these participants included good visual acuity in the study eyes and fellow eyes as well as blocked fluorescence. Eyes in the CTGVA group that received as-needed treatment received fewer injections in years 1 and 2. Most participants in the CTGVA group were followed up closely by an ophthalmologist, and 30% received injections in their fellow eyes. Thus, treatment of these participants likely was deemed unnecessary during follow-up. Other baseline characteristics had no association with which eyes could have treatment discontinued while maintaining good visual acuity, but the CTGVA group demonstrated that not all eyes with nAMD will need treatment forever. However, long-term monitoring is necessary for both eyes, given that the fellow eyes may need treatment, and it is unknown how many of the eyes in the CTGVA group will need treatment with longer follow-up.

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