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Authors

Muftuoglu, Ilkay Kilic
Alam, Mostafa
You, Qi Sheng
et al.

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Long-Term Remission of Neovascular Age-Related Macular Degeneration with as Needed Anti-Vascular Endothelial Growth Factor Therapy

Ilkay Kilic Muftuoglu, MD[1], **Mostafa Alam, MD**[1,2], **Qi Sheng You, MD**[1,3], **Raouf Gaber, MD**[1], **Hema L. Ramkumar, MD**[1], **Nadia Mendoza, MS**[1], **Amit Meshi, MD**[1], and **William R. Freeman, MD**[1]

[1]Jacobs Retina Center, Shiley Eye Institute, University of California San Diego, CA

Abstract

Purpose—To determine the presenting characteristics of neovascular age-related macular degeneration (AMD) patients with long-term remission (LTR), which was defined as the absence of intraretinal (IRF), subretinal fluid (SRF), or hemorrhage on spectral domain optical coherence tomography (SD-OCT) and absence of leakage on fluorescein angiography (FA) for longer than 6 months while on as needed anti-vascular endothelial growth factor treatment.

Methods—The presenting characteristics of patients with LTR was compared to a control group including 32 eyes of 28 age-, gender- and ethnicity-matched patients who did not achieve LTR.

Results—Seventy-four percent of patients in LTR group had type 1 choroidal neovascular membrane (CNV) and 18.5% had retinal angiomatous proliferation (RAP). In the control group, 28 eyes had type 1 CNV (87.5%), and none of the patients had RAP; overall, there was a significant difference in lesion types between the 2 groups (p=0.036). Eyes with LTR at presentation had significantly thinner subfoveal choroidal thickness (147 vs. 178 μm, p=0.04). There was more IRF and less SRF at the presentation in the remission group (59.3% IRF and 11.1% SRF) compared to the control group (28.1% IRF and 34.4% SRF, p=0.03).

Conclusions—The presence of RAP, thinner choroidal thickness, more IRF, and less SRF at presentation were associated with LTR in patients receiving as-needed treatment for AMD.

Keywords

age-related macular degeneration; anti-vascular endothelial growth factor; pro re nata; as needed; remission; long-term remission; optical coherence tomography

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in industrialized countries.[1,2] There have been significant advances in the

Corresponding author: William R Freeman, MD, Address: 9415 Campus Point Drive 0946, La Jolla, San Diego, CA 92093, wrfreeman@ucsd.edu.

[2]Currently affiliated with Tanta University, Department of Ophthalmology, Egypt

[3]Currently affiliated with Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, Beijing, China

management of neovascular, or wet AMD with the introduction of anti-vascular endothelial growth factor (anti-VEGF) agents. The pivotal ANCHOR and MARINA clinical trials demonstrated superior visual acuity results with monthly ranibizumab injections compared with photodynamic therapy or observation.[3,4] The Comparison of Age Related Macular Degeneration Treatment Trials (CATT) indicated that bevacizumab (Avastin, Genenetech, San Francisco, CA) had a similar treatment effect and safety profile compared with ranibizumab (Lucentis, Genentech, San Francisco, CA).[5] The VIEW 1 and VIEW 2 studies revealed that subjects in one arm exhibited similar visual outcomes when comparing aflibercept (Eylea, Regeneron Pharmaceuticals Inc, Tarrytown, N.Y., U.S.A.) 2 mg dosed every 2 months after a 3-monthly loading dose to monthly ranibizumab 0.5 mg.[6]

Although the two-year results of CATT study demonstrated that pro re nata (PRN) regimen resulted in less gain of visual acuity than monthly injections,[7] PRN or treat-and-extend (TAE) regimens are commonly used to reduce treatment burden for both patients and doctors.[8, 9] Reducing injection frequency might also reduce risk of arterial thromboembolic events, which are noted as a potential side effects of anti-VEGF agents such as ranibizumab.[10] Another reason favoring less frequent dosing stems from animal model and clinical studies suggesting progression of geographic atrophy (GA) in response to sustained exposure to anti-VEGF agents.[11] The CATT study showed that in treated wet AMD eyes, monthly dosing was associated with more GA than PRN dosing.[11] In animal studies, inhibition of retinal pigment epithelium (RPE)-derived VEGF-A and other isoforms may blunt neuroprotective and trophic effects on the choriocapillaris and photoreceptors, thereby leading to tissue loss.[12]

Interestingly, it was reported in the CATT 5-year follow-up study that 96 patients (14.8%) received no treatments between the end of the 2-year clinical trial and the 5-year CATT follow-up study visit. Among these 96 patients, 21 of 43 patients (48.8%) in the PRN treatment arm received no treatment during year 2 of the clinical trial.[13] In a recent retrospective study, Kuroda et al,[14] looked for the predictors of recurrence of wet AMD after a loading phase of 3 monthly ranibizumab injections and found that older age and male gender predicted earlier recurrence, and polypoidal choroidal vasculopathy was associated with a shorter interval to recurrence.

In our practice, most of PRN-treated AMD patients do not get long-term remission (≥6 months) after anti-VEGF injections, but we have observed that there is a small group of patients who achieve long-term remission with PRN therapy. Despite above mentioned studies, the characteristics of the patients with long-term remission has not been previously evaluated in the literature. In this study, we wish to evaluate the characteristics of the wet AMD patients with long-term remission (LTR) during as needed therapy.

METHODS

This was a retrospective review of eyes that were treated with as needed anti-VEGF therapy for wet AMD at the Jacobs Retina Center, Shiley Eye Institute, University of California San Diego (UCSD) between 2009 and 2014. The study was conducted according to the Helsinki declaration and complied with the Health Insurance Portability and Accountability Act of

1996. Written informed consent was obtained for each patient prior to anti-VEGF intravitreal therapy. UCSD Institutional Review Board (IRB) approval was acquired for the review and analysis of patients' data.

All the patients were diagnosed with wet AMD and treated by a single experienced retinal specialist (WRF) based on clinical characteristics and multi-modal imaging including spectral domain-optical coherence tomography (SD-OCT) and fluorescein angiography (FA) at a single institution. The treatment regimen was as needed after an initial loading dose of three monthly injections with monthly evaluation and reinjection until the eye became completely dry, after which we give 1–2 bonus injections before going to an observation phase. Treatment indications included intraretinal or subretinal fluid on OCT, new or persistent hemorrhage on color fundus photography or ophthalmoscopy, decreased visual acuity as compared with the previous examination, or leakage on FA. Retinal pigment epithelial detachments were not an indication for treatment. Patients were treated with intravitreal 1.25 mg bevacizumab initially. In resistant cases, treatment was switched to aflibercept given every 8-weeks without any loading doses.[15] When there was persistent intraretinal or subretinal fluid despite a minimum of 5 injections given every 8-weeks, the interval between the injections of aflibercept was decreased to every 4-weeks. Intravitreal injection of therapeutics such as bevacizumab or aflibercept was carried out under aseptic conditions in the clinic. Preservative-free lidocaine gel[15] was instilled in the eye for at least five minutes prior to injection. A lid speculum was placed to keep the lids open and 5% povidone iodine solution was instilled on the conjunctival sac prior to injection. The intravitreal injection was performed using a 30-gauge needle in the superotemporal or superonasal quadrant, 3.5–4.0 mm posterior to the limbus depending on lens status.

All AMD patients that developed LTR after anti-VEGF therapy were identified through a search of the database of imaging records at the Jacobs Retina Center and included in the analysis as the remission group. Long-term remission was defined as absence of intraretinal, subretinal fluid or hemorrhage on OCT for longer than 6 months as well as no leakage on FA during this period. Age-and gender-matched wet AMD patients treated with as needed anti-VEGF therapy who did not achieve LTR were included as the control group. We compared the presentation features of patients with LTR with those in the control group. Patients who underwent pars plana vitrectomy for severe subretinal hemorrhage due to wet AMD, advanced glaucoma, corneal pathology, and coexisting macular disease that may influence visual acuity were excluded. The same exclusion criteria were used for both groups.

The demographic characteristics at the time of presentation, including age, gender, and ethnicity, were collected at the initial visit. The type and number of injections of anti-VEGF agents (aflibercept or bevacizumab) and the duration of remission were recorded from the clinical chart. The number of patients achieving LTR at 1 year, 2 year window and 3 year window was noted. The visual acuity was measured using a standard Early Treatment Diabetic Retinopathy Study (ETDRS) chart and noted as the closest logarithm of the minimum angle of resolution (LogMAR) line that the patient got three or more letters on.

The choroidal neovascular membrane (CNV) type, CNV size, central foveal thickness (CFT), presence of posterior vitreous detachment, presence and type of pigment epithelium detachment (PED), and subfoveal choroidal thickness were assessed using Spectral Domain Optical Coherence Tomography (SD-OCT) (Spectralis HRA+OCT, Heidelberg Engineering, Carlsbad, CA) from horizontal or vertical scans passing through the central fovea and measured using the calipers feature or thickness profile of the Spectralis device. Choroidal neovascularization was classified as type 1 (sub-retinal pigment epithelium), type 2 (subretinal), and type 3 (retinal angiomatous proliferation) based SD-OCT findings. The presence of macular atrophy and macular scar were also assessed by checking several SD-OCT scans cutting through the fovea. Macular atrophy was defined as loss of outer retinal layers and retinal pigment epithelium with increased hyperreflectivity of the choroid within 500 microns in either direction of fovea in SD-OCT scan. Macular atrophy greater than 100 microns was considered for statistical analysis. All SD-OCT images starting from the presentation visit were reviewed, and the date when macular atrophy started to occur was noted.

Statistical analyses were conducted using SAS software version 9.4 (SAS Institutes, Cary, North Carolina, USA). Descriptive statistics included mean, standard deviation (SD), median, range, and percentages. The Shapiro-Wilk test was used to test normality of the data. Chi-square test or Fisher's exact test was used to compare categorical variables, and the Wilcoxon test was used to compare continuous variables between groups. P-values represent results for 2-sided tests, with values less than 0.05 considered statistically significant. Kaplan-Meier curves were generated for the time for having long-term remission and time for having macular atrophy in all patients with wet AMD (232 eyes), and the log-Rank test was used to compare survival rates between the two groups.

RESULTS

Among the 232 eyes (205 patients) with wet AMD treated at our institution, 27 eyes (11.6%) of 25 patients achieved LTR. The mean time from presentation to last treatment to achieve LTR was 19 months (range 3–52 months). The mean remission time was 18 months (range 6–44 months). Forty-one percent of eyes (11 eyes) achieved LTR during the first year of presentation; 26% of eyes (7 eyes) had LTR at two years; and 9 eyes (33.3%) had LTR at three years. There was no significant difference in the mean follow-up duration between the two groups (42±18.4 months in LTR group versus 40.05±12.3 months in the control group, p=0.2). Figure 1 shows the Kaplan-Meier curve for time to achieve LTR.

A group of age-, gender- and ethnicity-matched wet AMD patients (32 eyes of 28 patients) without LTR were selected as the control group. The mean age of these 53 patients was 79.3±6.7 years old, and 33 (62.3%) of them were female. The demographic characteristics of the patients in both groups are summarized in Table 1.

Compared to the control group, eyes with LTR had significantly thinner mean subfoveal choroidal thickness at baseline (147.1 versus 177.7 microns, p=0.04). There was significantly more IRF and less SRF at baseline in the LTR group (59.3% IRF, 11.1% SRF and 29.6% IRF+SRF) when compared with the control group (28.1% IRF, 34.4% SRF and

37.5% IRF+SRF, p=0.03). Choroidal neovascular membranes were more often subfoveal in the remission group than in the control group (85.2% vs. 62.5% p=0.06). The mean central foveal thickness at baseline was thinner in the remission group than in the control group (275 microns vs. 315 microns, p=0.07). There was no significant difference between 2 groups in terms of baseline lens status (p=0.61), presence of retinal pigment epithelium detachment or not (p=0.55), LogMAR visual acuity p=0.55) and posterior vitreous status (detached or attached) (P=1.00) between 2 groups. There was a significant difference in CNV type between the two groups (chi square test, p=0.036). In eyes achieving long-term remission, 74% of eyes (20 eyes) had type 1 CNV, and RAP was the second most common CNV type with a rate of 18.5% (5 eyes). In the control group, 28 eyes (87.5%) had type 1 CNV; four eyes (12.5%) had type 2; and none of the patients (0%) had RAP. The clinical characteristics at presentation in the eyes achieving LTR and control eyes are summarized in Table 2.

There was a higher proportion of aflibercept usage in the control group compared to the remission group (96.9% vs. 48.1%, p<0.001), as we switched treatment from bevacizumab to aflibercept in refractory cases. The mean CFT at the last visit was significantly thinner in the remission group compared to the control group (188 microns vs. 233 microns, p=0.01). Similarly, the subfoveal choroidal thickness was thinner in the LTR group than the control group (146 microns versus 171 microns, p=0.04) at the last visit. However, there was no significant difference in visual acuity and visual acuity change from baseline at the last visit between the two groups. The treatment modalities and the clinical statuses at the last visit are summarized for both groups in Table 3.

Among 232 eyes with wet AMD, 83 eyes (35.7%) had macular atrophy during a mean of 31.6±23.5 months follow-up. In the control group, 25% of eyes (8 eyes) had macular atrophy during the follow-up, and 66.6% of eyes (18 eyes) had macular atrophy in the LTR group. There was a significant different in the incidence of macular atrophy (p=0.001, chi square test). The median estimated time for all eyes (n=232) to develop macular atrophy was 66.7±7 months (95% Confidence interval: 52–79.5 months). The median estimated time to develop macular atrophy in eyes achieving LTR (n=27) was 45.7±8.01 months (95% CI: 30–61), and was 56.5±2.5 months (95% CI=53–71) in eyes not achieving LTR (N=205). There was a significant difference in the estimated time to develop macular atrophy between the LTR group (n=27) and cohort patients (n=205) (log Rank=0.008). Figure 2 shows the time to develop macular atrophy in our cohort.

At last follow-up, 4 eyes (14.8%) in the LTR group had a macular scar, while two eyes (6.3%) had scar in the control group (p=0.257).

DISCUSSION

Treat and extend and PRN regimens are commonly used to treat wet AMD in clinical practice. In our PRN regimen with monthly evaluation, we give patients as needed anti-VEGF therapy after an initial loading dose of three monthly injections until the eye has no residual intraretinal or subretinal fluid, after which we give 1–2 bonus injections then start an observation phase to reduce the burden of patient follow-up visits. In the current study,

we found that thinner choroidal thickness, more IRF, less SRF, and the presence of RAP at baseline were associated with LTR. This has not been reported previously.

Since the choroid is mainly composed of vessels and capillaries, one may assume that choroidal thickness is a marker of the choroidal circulation, which provides oxygen and nourishment to the outer retinal layers and the retinal pigment epithelium (RPE), maintaining the RPE and outer retinal integrity.[19] Previous studies have suggested that abnormalities of the choroidal circulation are involved in the development of AMD.[20,21] In wet AMD, choroidal circulation might be essential to maintain the activity of CNV. A thinner choroid may represent a damaged choroidal circulation that does not have sufficient blood flow to maintain CNV activity, allowing for LTR with anti-VEGF treatment. A similar clinical phenomenon supporting this hypothesis is that in high myopia, CNV associated with a thin choroid and usually regresses with fewer anti-VEGF injections compared to wet AMD.[22]

We found that more IRF and less SRF at presentation were associated with LTR. Interestingly, SRF has been reported to be refractory to anti-VEGF treatments, and SRF itself has a minor impact on visual acuity prognosis when compared to intraretinal fluid.[23,24,25] Joo reported that patients with SRF might be refractory to both anti-VEGF and photodynamic therapy.[23] In a recent study by Markus, SRF predicted a higher number of ranibizumab injections and a higher number of PDT treatments in the combination treatment group. However, patients with IRF presented with the lowest initial VA, and IRF had a strong negative predictive value on visual improvement.[24,25]

In the CATT study, 10.7% of patients had RAP lesion at baseline. At 1 year, eyes with RAP were more likely to have no fluid on OCT, no leakage on FA, and geographic atrophy at both 1 and 2 years. These eyes also required fewer anti-VEGF injections compared to eyes that did not have RAP lesions at 2 years (5.36 versus 6.57, p=0.018). The CATT study suggested that the increased geographic atrophy development may be related to baseline subfoveal choroidal thinning, reticular pseudodrusen, and atrophy in the fellow eye. In this study, among 59 control and LTR eyes, 8.4% of patients had a RAP lesion at presentation, and the RAP lesion was related to achieving LTR. Unlike the CATT study, in which atrophy evaluated using fluorescein angiography and color fundus photography was reported to be 18.3%, 44.1% of patients had some atrophy during the follow-up in this study. Patients with macular atrophy were most likely to get LTR during the follow-up. The variation in the rate of macular atrophy may be explained by the difference in method used for the evaluation of macular atrophy. Although the characteristics of the patients with RAP lesion have been well elucidated in the literature, our study is the first study reporting the features of patients with LTR.

Achieving LTR may also be related with the anti-VEGF agent used. Although in VIEW trails, ranibizumab dosed monthly was found to be non-inferior to aflibercept injections. In our study, there was a higher proportion of aflibercept usage in the control group compared to the LTR group (96.9% vs. 48.1%), which may be explained by our practice of routinely switching from bevacizumab to aflibercept in refractory cases.

This study has several limitations, including its retrospective nature and relatively small study population. In our study, there is a significant proportion of patients who achieved LTR using PRN treatment. However, our results are limited to the PRN regimen and do not allow us to compare rates of LTR with a treat and extend regimen. Further studies are needed to address this issue. Although we used Kaplan-Meier analyses which take censoring into account, it would be interesting to study the characteristics of all patients presenting with wet AMD. On the other hand, since our institution is a referral center, it is highly likely that patients who present to our clinic may have more severe disease. However, only multicenter prospective clinical trials can address this issue by avoiding bias. A strength of the study is that it is the first study looking for the baseline features of wet AMD patient achieving LTR while on as needed anti-VEGF treatment. In this study, the same experienced retina specialist used an identical treatment algorithm for all patients. This study is also void of any bias from pharmaceutical sponsorship and compares remission with therapy with both aflibercept and bevacizumab, so the data is generalizable to the typical retina practice patient.

In conclusion, in wet AMD patients treated with as needed anti-VEGF therapy, a thinner choroidal thickness, presence of RAP, and more IRF and less SRF at baseline are associated with a higher likelihood of achieving LTR in a PRN treatment regimen. Patients who have macular atrophy during follow-up are most likely to get LTR.

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Summary statement

This retrospective study demonstrated that 11.6% of wet AMD patients treated with as needed anti-VEGF agents achieved long-term remission. Thinner choroidal thickness, presence of RAP, more intraretinal fluid, and less subretinal fluid at baseline were associated with long-term remission.

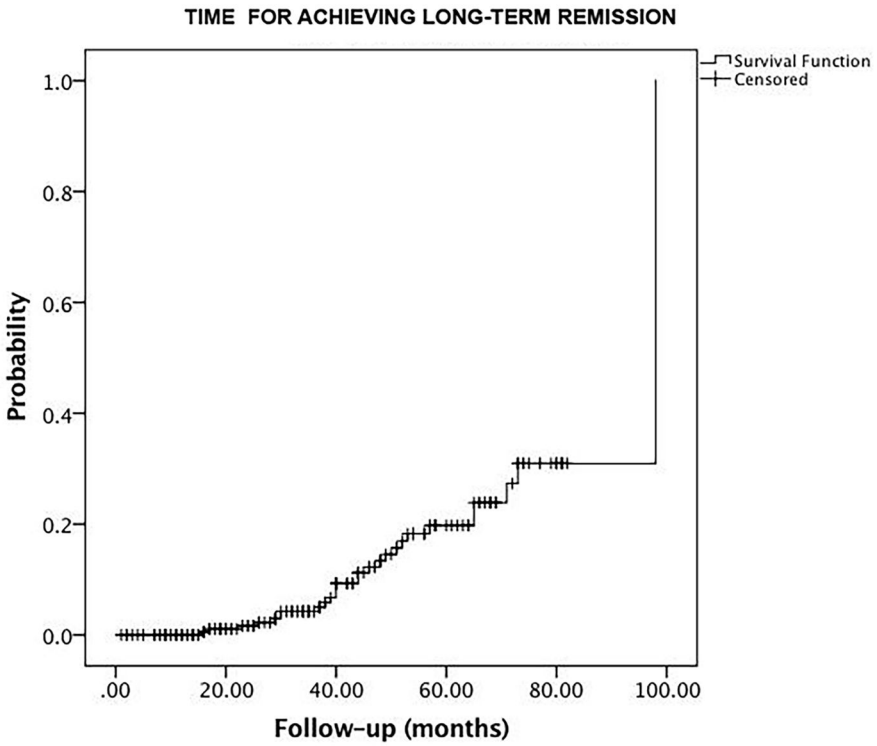

Figure 1.

Kaplan-Meier curve of the survival time to achieve long-term remission in eyes with neovascular age-related macular degeneration treated with as needed anti-VEGF therapy.

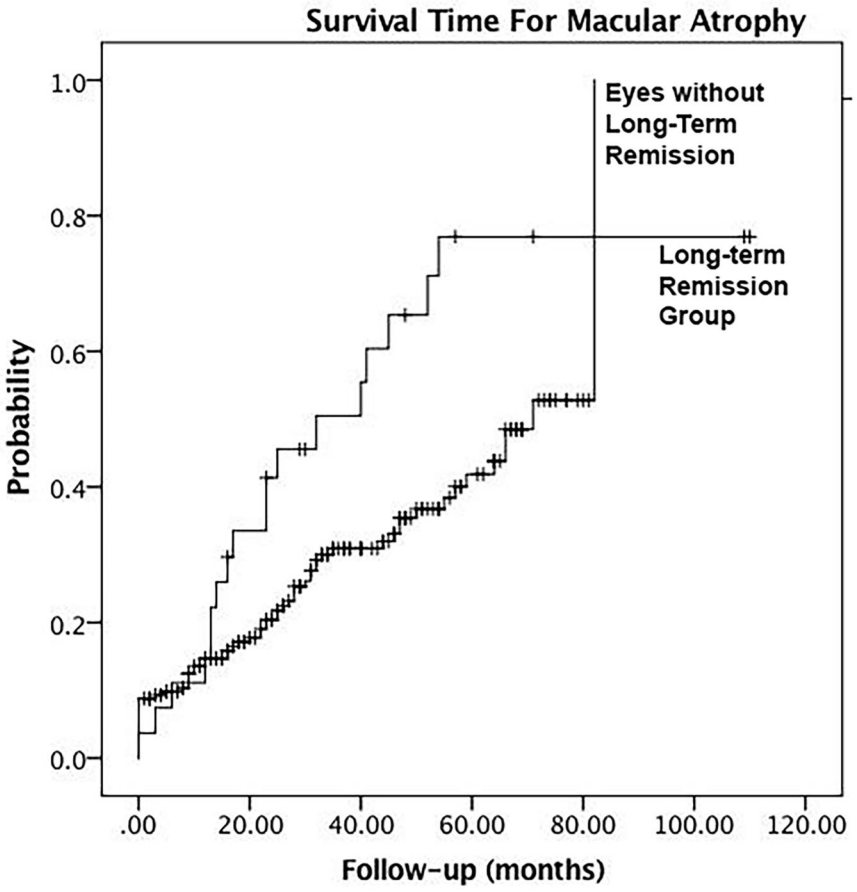

Figure 2.

Kaplan-Meier curve of the survival time for macular atrophy in eyes with long-term remission (n=27 eyes) and eyes with neovacular AMD without long-term remission (205 eyes) (control group+other neovascular AMD patiens) treated with as needed anti-VEGF therapy.

Table 1

Demographic characteristics of study participants

Demographic characteristics	Remission group (n=25)	Control group (n=28)	P value
Mean age (standard deviation)	79.6 (8.6)	79 (4.6)	0.49
Gender (male/female)	11/14	9/19	0.41
Ethnic (Caucasian %)	96%	92%	0.73

Table 2

Clinical characteristics of the study participants at the presentation

Variables	Classification	Remission group (n=27)	Control group (n=32)	Combined (n=59)	p-Value
CNV type	Sub-RPE	20 (74%)	28 (87.5%)	48 (81.3%)	0.036
	Sub-Retinal	2 (7.4%)	4 (12.5%)	6 (10.1%)	
	RAP	5 (18.5%)	0 (0%)	5 (8.5%)	
CNV location	Subfoveal	23 (85.2%)	20 (62.5%)	43 (72.9%)	0.06
	Juxta-foveal	3 (11.1%)	4 (12.5%)	7 (11.9%)	
	Extra-foveal	1 (3.7%)	8 (25.0%)	9 (15.3%)	
Intraretinal fluid (IRF) or subretinal fluid (SRF)	IRF only	16 (59.3%)	9 (28.1%)	25 (42.4%)	0.03
	SRF only	3 (11.1%)	11 (34.4%)	14 (23.7%)	
	IRF+SRF	8 (29.6%)	12 (37.5%)	20 (33.9%)	
Lens status at baseline	Phakic	12 (44.4%)	12 (37.5%)	24 (40.7%)	0.61
	Pseudophakic	15 (55.6%)	20 (62.5%)	35 (59.3%)	
Posterior vitreous detachment (yes=present, no=not present)	Yes	27 (100%)	32 (100%)	59 (100%)	1.00
	No	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Retinal pigment epithelium detachment (PED) at baseline	Fibro vascular	22 (81.5%)	29 (90.6%)	51 (86.4%)	0.55
	Serous	1 (3.7%)	0 (0.0%)	1 (1.7%)	
	No PED	4 (14.8%)	3 (9.4%)	7 (11.9%)	
LogMAR baseline visual acuity (Snellen equivalent)	Mean	0.42 (≈20/50)	0.37 (≈20/50)	0.39 (≈20/50)	0.55
	SD	0.28	0.17	0.23	
Subfoveal choroidal thickness, microns	Mean	147	178	164	0.04
	SD	49.9	62.1	58.4	
Central foveal thickness, microns	Mean	275	315	297	0.07
	SD	113	97.7	106	

CNV=choroidal neovascularization, RAP=retinitis angiomatous proliferans, RPE=retinal pigment epithelium. SD=standard deviation.

Table 3

Treatment modality and clinical characteristics at the final visit of the study participants

Variables	Classification	Remission group (n=27)	Control group (n=32)	Combined (n=59)	p-Value
Duration of remission (months)	Mean	18.33	2.97	10.00	0.00
	SD	10.13	1.71	10.35	
Anti-vascular endothelial growth factor agent	bevacizumab	14 (51.9%)	1 (3.1%)	15 (25.4%)	0.00
	aflibercept	1 (3.7%)	6 (18.8%)	7 (11.9%)	
	Both	12 (44.4%)	25 (78.1%)	37 (62.7%)	
Number of injections of bevacizumab	Mean	7.37	5.91	6.58	0.41
	SD	5.32	4.67	4.99	
Number of injections of aflibercept	Mean	2.67	12.00	7.73	0.00
	SD	3.48	6.63	7.14	
Central foveal thickness at the last visit, microns	Mean	188	233	213	0.01
	SD	48.7	72.99	66.5	
Subfoveal choroidal thickness at the last visit, microns	Mean	145.7	171	159	0.07
	SD	61.9	66.3	65.0	
Lens status at last visit	Phakic	10 (37.0%)	11 (34.4%)	21 (35.6%)	1.00
	Pseudophakic	17 (63.0%)	21 (65.6%)	38 (64.4%)	
Vision improvement (lines)	Mean	0.56	0.47	0.51	0.79
	SD	1.58	1.81	1.70	
Visual acuity at the last visit, LogMAR (Snellen equivalent)	Mean	0.36 (20/50)	0.31(20/40)	0.33 (20/40)	0.37
	SD	0.21	0.16	0.19	

SD=standard deviation, LogMAR= logarithm of the minimum angle of resolution