



Meticulous multimodal analysis of aflibercept therapy for submacular vascularized pigment epithelial detachment associated with neovascular AMD in a prospective case series, the EVEN study

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ARTICLE INFO

Keywords:

Aflibercept therapy
Anti-vascular endothelial growth factor injection
Neovascular age-related macular degeneration
Geographic atrophy
Retinal pigment epithelial detachment
Pigment epithelial detachment height and volume
Retinal pigment epithelial tears
Subretinal fluid
Subretinal hyperreflective material
Vascularized retinal pigment epithelial detachment

ABSTRACT

Purpose: This prospective case series investigates the visual and anatomical outcomes including detailed volumetrics of eyes with vascularized pigment epithelial detachments (PED) treated with aflibercept in eyes with neovascular age-related macular degeneration (nAMD) through meticulous analysis in a reading center setting. **Methods:** We conducted a single-arm multicenter, prospective, open-labeled, interventional case series, comparing visual and anatomic outcomes at 12 months with baseline for intense aflibercept therapy. Eyes with submacular vascularized PED due to AMD received 2.0 mg of intravitreal aflibercept at baseline and then monthly for 6 months. During the subsequent 6 months, mandatory aflibercept therapy was given for every other month, while additional aflibercept injections were allowed between mandatory injections if necessary, at 4 weeks after last injection, contingent on pre-defined visual and anatomic re-treatment criteria. Standardized ETDRS vision measurement, anterior and posterior segment examination, and high-density spectral-domain optical coherence tomography scans were obtained at baseline and monthly, while fundus photography and fluorescein angiography were obtained at baseline, 3, 6, and 12 months. Indocyanine-green angiography was obtained at baseline and 3 months. Meticulous multidimensional assessment of the scanned multimodal serial images was then performed by Doheny Image Reading Center.

Results: Of 36 eyes and patients with mean age of 80, mean baseline and 12-month-ETDRS BCVA was 59 ± 8.9 letters (20/66), and 65 ± 27 letters (20/50), respectively; (6.5 letters improvement, $p = 0.02$). Significant reductions from baseline to month-12 were noted for multiple anatomic measures, including PED maximum height, entire lesion and central 1-mm subfield of PED mean thickness and volume, and mean subretinal hyperreflective material (SHRM) thickness and volume, also entire lesion of retinal thickness, retinal volume, and mean subretinal fluid (SRF) thickness (mean reductions in magnitude ranging from 37.5 to 91.7%, all $p < 0.001$). FA measurements also showed significant decrease from baseline to month-12, including area and greatest linear diameter (GLD) of fibrovascular PED, area and GLD of NV area and leakage (mean reductions in magnitude from 41.9 to 87.7%, p value from 0.002 to <0.001). This case series shows that while majority of reductions in SRF volume occurred during first month from baseline, majority of reduction in retinal, PED, and SHRM volumes occurred during first 2 months after onset of anti-VEGF injections. RPE tears developed in 5 eyes (13.9%) correlating with eyes with large PED height and volume at baseline (mean height $>800 \mu\text{m}$, mean volume $>4 \text{ mm}^3$). Geographic atrophy (GA) was noted in only 1 eye at baseline, but in 16 eyes (44.4%) by 12 months.

Conclusions and Importance: Significant improvement in vision and anatomic measures including volumetrics of vPED were noted at 12 months after aflibercept therapy. Besides substantial PED height, large PED volume at

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<https://doi.org/10.1016/j.ajoc.2020.100916>

Received 21 February 2020; Received in revised form 7 August 2020; Accepted 31 August 2020

Available online 18 September 2020

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baseline also correlated with RPE tears in 13.9% of eyes with vPED after anti-VEGF therapy. Reduction in SHRM correlated directly with decrease in PED, and more than 40% of study eyes developed GA by 12 months following intense anti-VEGF therapy.

1. Introduction

Previously, MARINA and ANCHOR established the efficacy and safety of ranibizumab for treating classic and occult neovascularization (NV) associated with neovascular age-related macular degeneration (nAMD)^{1,2}; HARBOR showed equivalent results of 0.5 and 2.0 mg doses of ranibizumab for treatment of nAMD³; VIEW 1 & 2 showed non-inferiority of bimonthly aflibercept in comparison to monthly aflibercept or monthly ranibizumab for treating nAMD.⁴ However, no pre-specified stratification of lesion subtypes for comparison was performed in these studies. Thus, the applicability of the results of these studies to vascularized pigment epithelial detachment (vPED) alone is uncertain, since it is a more difficult-to-treat subtype of nAMD. Historically, prior publications have reported that over 70% of exudative AMD can be classified as vPED,⁵ which may be further subdivided into Type-1 NV (ranging from 40 to 47% of the cases) and Type-3 NV (ranging from 24 to 34% of the cases).^{6,7} There are multiple published clinical studies on aflibercept treatment of vPED associated with AMD.⁸⁻¹¹ However, there is a paucity of published reports on an in-depth qualitative and quantitative analysis of aflibercept treatment of vPED in the setting of a reading center. We also evaluated the potential benefits and adverse events in these eyes with vPED following aflibercept treatment.

2. Methods

2.1. Objectives and outcome measures

This was a single-arm multicenter, prospective, open-labeled, interventional case series, comparing visual and anatomic outcomes at 12 months with baseline. Three centers participated in this prospective trial, including Southern California Desert Retina Consultants, Palm Desert, CA (coordinating center), Stein Eye Institute, Los Angeles, CA, and Black Hills Regional Eye Institute, Rapid City, SD. Institutional

review board approval was obtained in each center prior to the start of the study. This research trial adhered to the tenets of the Declaration of Helsinki and was conducted in accord with regulations set forth by the Health Insurance Portability and Accountability Act. All participants signed a written informed consent. The objective of the study was an in-depth qualitative and quantitative investigation of lesion components associated with submacular vPED due to AMD (Type-1 and Type-3 NV).

2.2. Inclusion and exclusion criteria

Table 1 outlines the detailed inclusion and exclusion criteria associated with this study. In brief, only subjects who were 50 years or greater in age with an active and treatment-naïve submacular vascularized PED due to AMD less than or equal to 12 disc areas in size were included in the study. For inclusion, eyes must have ETDRS BCVA of ≥ 19 letters and ≤ 73 letters (Snellen equivalent from 20/35 to 20/400).

Eyes with non-AMD vascularized PED (e.g. myopia, histoplasmosis, multifocal choroiditis, polypoidal choroidal vasculopathy [PCV]) were excluded. PCV cases were excluded due to its distinct features from traditional neovascular AMD cases. Despite recent advocacy by some retinal experts in reclassifying PCV along the spectrum of pachychoroid overlapping with AMD lesions, the optimal therapeutic profiles of PCV and AMD lesions are different. Eyes with $\geq 50\%$ hemorrhage or fibrosis of the entire PED were also excluded. In addition, eyes with any concomitant conditions that could confound the results were excluded as well (e.g. prior or current RPE tear, prior retinal surgery or vitrectomy, retinal vascular occlusion, substantial diabetic retinopathy, optic nerve problems, IOP ≥ 25 mm Hg or advanced glaucoma, etc.).

For inclusion in study, the NV could be classic, occult, or mixed, as long as it was associated with a PED. The NV component could be under the PED (i.e. fibrovascular PED). Alternatively, the entire NV component or a portion of it could be distinctly separate from but attached to the serous component of the PED, with both components considered as

Table 1
Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
≥ 50 years of age	Any prior treatment for exudative AMD in the study eye
Study eye contains a submacular fibrovascular PED ^a ≤ 12 disc area	Non-neovascular PED (e.g. drusenoid PED, serous PED without NV)
Study eye is treatment naïve for exudative AMD ^b	Previous periorbital therapeutic radiation
Central foveal involvement by the PED or NV ^c related to AMD (NV within or attached to margin of PED)	Previous RPE ^e tear in study eye
ETDRS BCVA ^d ≥ 19 letters and ≤ 73 letters (20/400 to 20/35)	Previous ocular surgery (except laser capsulotomy) within past 90 days or anticipated surgery (except Nd:YAG ^f capsulotomy) within next 12 months
Evidence of submacular fluid outside or surrounding PED	Previous vitrectomy
Patient is not enrolled in another study and willing to follow protocol.	Presence of any causes for NV and PED other than AMD
	Presence of any substantial ocular disease (other than NV and PED) that may compromise vision and confound interpretation of data
	Surface area of any submacular hemorrhage or fibrosis $>50\%$ of the PED
	Active ocular infection during screening
	IOP ^g ≥ 25 mmHg with or without use of ocular hypotensive agents
	Prior or current systemic anti-VEGF ^h
	Prior (within 90 days) or current oral or intravenous corticosteroid treatment
	Sexually active men or women of child-bearing potential; unwilling to practice contraception
	Miscellaneous (language barrier, allergies to aflibercept or Betadine, contraindication for pupillary dilation, inability to read chart)

^a PED, pigment epithelial detachment.

^b AMD, age-related macular degeneration.

^c NV, Neovascularization.

^d ETDRS BCVA, Early Treatment of Diabetic Retinopathy Study best corrected visual acuity.

^e RPE, retinal pigment epithelium.

^f Nd:YAG, neodymium-doped yttrium aluminum garnet laser.

^g IOP, intraocular pressure.

^h VEGF, vascular endothelial growth factor.

integral parts of the PED (i.e. vascularized serous PED). The investigator must search for characteristic features of a vPED summarized here:

- a. A vascularized serous PED (an orange-yellow round, oval, or bean-shaped elevation of the RPE with a smooth, convex surface was seen on examination and fundus photography [FP]. Fluorescein angiography [FA] showed uniform staining of the PED with a well-defined margin, and more intense staining [hot-spot] for the focus of the NV) without “sharp-peak” or “thumb-like” appearance of the PED on SD-OCT (see below), or
- b. A fibrovascular PED (occult neovascularization typically showing stippled hyperfluorescence in the early phase with increasing hyperfluorescent staining and leakage in later phases of FA and a variable surrounding margin, with or without RPE folds)
- c. Regarding PED with a component of retinal angiomatous proliferation (RAP), FP frequently showed intraretinal neovascularization (IRN) with adjacent spot(s) of small retinal hemorrhage, and subsequent lateral expansion of the IRN in an irregularly stellate pattern with formation of retinal-choroidal anastomosis and associated PED. The investigator was required to perform indocyanine-green angiography (ICGA) besides FA at baseline to establish a RAP lesion and to rule-out PCV.
- d. The investigator must also search for other features associated with a PED indicating the presence of a vascular component, i.e. hemorrhage, exudates, and/or chorioretinal folds.
- e. Besides typical FP/FA features of a vPED outlined above, the investigator must confirm distinct SD-OCT features of a vPED, such as distinct elevation of the highly hyperreflective RPE layer with mild backscattering of the underlying choroidal layer in the portion of the PED without any NV. For the portion of the PED with underlying NV, typical OCT findings consisting of moderate hyperreflectivity contiguous to the overlying markedly hyperreflective detached RPE corresponding to the NV that usually extended to the choroidal layer must be present.

2.3. Sub-classification of vPED

Detailed analysis was also performed to categorize the vPED as either Type-1 or Type-3 NV according to the classification guidelines provided by Freund et al.⁶ Detailed descriptions of the FP, FA, ICGA, and SD-OCT characteristics of Type-1 versus Type-3 NV and the comparison of specific results of Type-1 versus Type-3 NV associated with the 12-month course of aflibercept treatment can be found in a separate detailed report by the same authors of this study.⁷

ICGA was performed until the late phase (>30 minutes). Through the respective phases of the ICGA, we searched for abnormal vascular network (AVN), nodular hyperfluorescent polyps, multifocal areas of patchy hyperfluorescence, and late geographic hyperfluorescence (LGH), or other features characteristic of PCV. SD-OCT images were also scrutinized for typical features characteristic of PCV, such as “sharp-

peak” PED, “thumb-like” PED, and “notch PED” to rule out PCV.

2.4. Study design and visit schedules

Table 2 outlines the study flow chart with detailed breakdown of the visit schedules of the study. A complete ocular examination, including standardized ETDRS BCVA measurement, slit-lamp biomicroscopy of the anterior and posterior segment, and indirect ophthalmoscopy of the fundus periphery was performed for enrolled patients monthly for 12 months. SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) utilizing high-density scans was performed at baseline and then monthly for 12 months in all 3 centers. FP and FA were performed at baseline, 3 months, 6 months, and 12 months. ICG was performed at baseline and 3 months. FP was performed with TOPCON TRC 50-IX/ MRP camera system (Tokyo, Japan) in one center, Zeiss Meditec camera system (Dublin, CA, USA) in a second center, and TOPCON TRC 50-EX/OIS camera system (Tokyo, Japan) in a third center. FA and ICGA were performed with Heidelberg-HRA camera system (Heidelberg Engineering, Heidelberg, Germany) in the 3 centers.

For this study, frequent aflibercept injections were performed with the goal of resolving the exudative components (fluid, hemorrhage, exudates, fibrin, and NV complex) and flattening the vPED as much as possible. Thus, mandatory intravitreal injections of 2.0 mg in 0.05 ml of aflibercept were required monthly for the first 6 months. During the second 6 months of follow-up, mandatory aflibercept injections were performed for every-other-month. However, additional aflibercept injections were allowed between mandatory injections if necessary, at 4 weeks after last injection, contingent on the following pre-defined retreatment criteria: a) a loss of 5 or more letters of the ETDRS chart due to presumed neovascular activity associated with AMD from previous visit, b) any persistent or recurrent intraretinal macular edema or subretinal fluid shown on SD-OCT, c) new-onset, persistent, or recurrent NV, d) new, persistent, or recurrent hemorrhage or hard exudates, or e) persistent vPED. Therefore, a total of up to 3 additional re-injections besides the 3 mandatory injections of aflibercept was possible during the second 6 months of follow-up (see Table 2).

2.5. Vision results

The primary visual outcome was comparison of mean standardized best corrected visual acuity (BCVA) via Early Treatment of Diabetic Retinopathy (ETDRS) measurements at 12 months with baseline for eyes with vPED treated with aflibercept.

Secondary visual outcome measures included comparison at 12 months with baseline for proportions of eyes gaining or losing 5 or more letters, 10 or more letters, and 15 or more letters, proportion of eyes with BCVA of 20/200 or better.

Table 2
Flow Chart for Examination, Treatment, and Visit Schedules.

	Screen/Baseline -14 to 0 days	Week*											
		4	8	12	16	20	24	28	32	36	40	44	48
ETDRS** Visual Acuity	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmic Exam	x	x	x	x	x	x	x	x	x	x	x	x	x
ICG ⁺	x			x									
OCT ⁺⁺	x	x	x	x	x	x	x	x	x	x	x	x	x
Fluorescein Angiography	x			x				x					x
Fundus Photos	x			x				x					x
Intravitreal Aflibercept Injection [#]	x	x	x	x	x	x	x ^o	x	x ^o	x	x ^o	x	x
Adverse Event Assessment		x	x	x	x	x	x	x	x	x	x	x	x

*window of ±7 days allowed for each visit; **ETDRS, Early Treatment of Diabetic Retinopathy Study; ⁺ICG, indo-cyanine green angiography; ⁺⁺OCT, optical coherence tomography; [#]injections every 4 weeks for 6 injections followed by treatment every 8 weeks for the remainder of the study; ^o optional injections if needed to treat, based on predefined retreatment criteria.

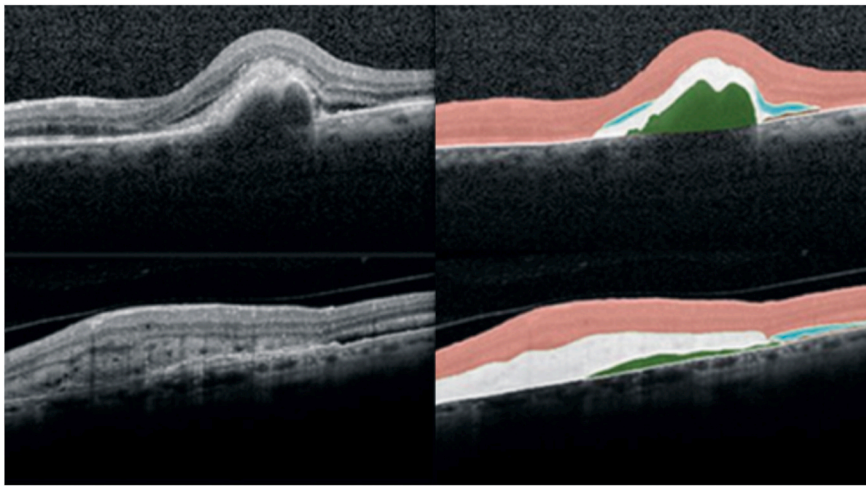


Fig. 1. Graders at Doheny Image Reading Center (DIRC) performed quantitative measurements with previously described and validated proprietary grading software, 3D-OCTOR. They meticulously drew multiple boundaries on all B-scans of the volume cube of serial SD-OCT images to segment the various structures of interest (Color code: red: retinal thickness, white: subretinal hyperreflective material [SHRM], blue: subretinal fluid [SRF], green: sub-PED space). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.6. Anatomic outcomes

All multimodal images obtained by FA, ICGA and SD-OCT were sent to a third-party reading center (Doheny Image Reading Center [DIRC] in Los Angeles, CA, USA) for qualitative and quantitative assessment. At DIRC, all quantitative measurements were performed with the previously described and validated proprietary grading software known as 3D-OCTOR.^{12,13} The grading protocol required the same graders to meticulously draw multiple boundaries on all B-scans of the volume cube of serial SD-OCT images to segment the various structures of interest (Fig. 1). A validated linear interpolation algorithm of the 3D-OCTOR software was then applied between B-scans to generate the volume and thickness maps. The foveal centers of all images were marked and ETDRS grids with nine subfields generated based on the foveal center for each SD-OCT. Additional qualitative review of the images were performed as an integral part of the data analysis.

The same graders at DIRC also performed careful segmentation on multiple pertinent lesion components on serial FA and ICGA images for assessment (Fig. 2).

The SD-OCT derived measures obtained by trained graders at DIRC included: a) PED measures (maximum height, mean thickness and volume of entire PED, and mean thickness and volume of central 1-mm subfield), b) retinal measures (mean retinal thickness and volume overlying entire PED, mean retinal thickness and volume of central 1-mm subfield), c) subretinal fluid (SRF) measures (mean SRF thickness and volume associated with entire PED, and mean SRF thickness and volume of central 1-mm subfield), d) subretinal hyperreflective material

(SHRM) measures (mean SHRM thickness and volume associated with entire PED, and mean SHRM thickness and volume of central 1-mm subfield). The FA and ICGA-derived measures were also obtained by trained graders at DIRC, including: a) surface area (SA) and greatest linear diameter (GLD) of PED, and b) area and GLD of NV leakage, and c) increase or decrease in macular staining on fluorescein angiography. Appropriate corrections were made for any incongruous measurements obtained by the different camera systems, in order to collate the adjusted measurements for proper quantitative analysis of FA and ICGA-derived lesion components.

In addition, the mean numbers of aflibercept injections were recorded.

2.7. Adverse events

Ocular complications (i.e. RPE tears, uveitis, endophthalmitis, and geographic atrophy [GA]) and systemic adverse events were tracked in this study. GA was defined as one or more discrete and well-demarcated zones of depigmentation of at least 250 μm in diameter with increased visibility of choroidal vessels on color fundus images. GA was identified on color photography, near infrared reflectance and SD-OCT. The calculation of GA area was performed with SD-OCT.

2.8. Statistical methods

Statistical analysis included the parametric method (2-tailed paired T-test) for comparing the month-12 outcome with baseline vision, and

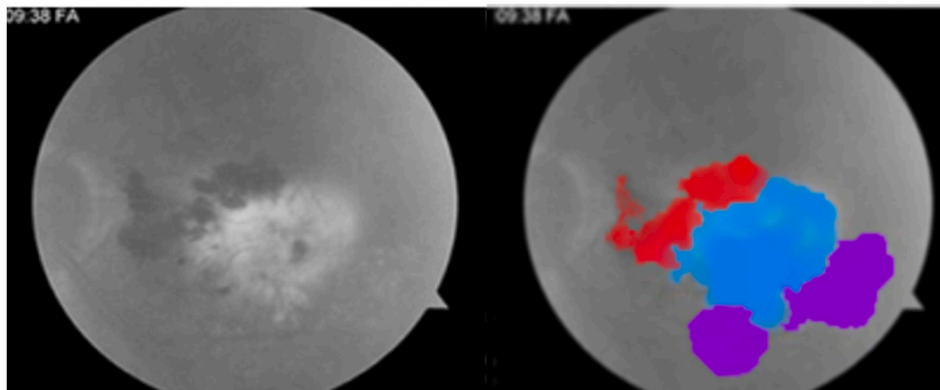


Fig. 2. The same graders at DIRC also performed careful segmentation on multiple pertinent lesion components on serial fluorescein angiography (FA) and indocyanine green angiography (ICGA) images for assessment (Color code: red: hemorrhage, blue: classic neovascular membrane, purple: late leakage of undetermined source [LLUS]). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the same was performed for comparing the month-12 measurements with baseline measurements of all of the OCT, FA, and ICGA variables. For the visual acuity data, the changes in standardized ETDRS letter scores of the month-12 visit compared with baseline letter scores were assessed. Linear discriminant analysis was employed to search for correlation between baseline factors and GA development and size. Statistical analyses were performed with Statistical Product and Service Solutions (SPSS) version 22 (IBM SPSS, Armonk, New York). Due to multiple statistical comparisons of multiple OCT, FA, and ICGA variables, Bonferroni adjustments were incorporated into the statistical calculations, so that only a p value of ≤ 0.002 was considered to be significant.

3. Results

There was enrollment of 40 eyes in 40 patients in this study from the three centers. Four eyes were excluded from analysis, since subsequent evaluation showed a vitelliform-like lesion masquerading as exudative AMD in one eye, another eye showed a pure Type-2 NV lesion with an adjacent area of irregularity on the RPE that was mistaken as a PED, one eye had significant retinal distortion associated with an epiretinal membrane confounding analysis, and one eye showed independent mixed exudative components (the NV lesion was entirely separate from and not associated with the PED), consistent with two autonomous lesions. Of the remaining 36 patients, the mean age was 80 ± 8.0 (range from 67 to 98). There were 23 women (63.9%) and 13 men (36.1%) Mean follow-up time was 11.3 months associated with variation of the visit widow at the final visit.

3.1. Vision outcome

The baseline standardized ETDRS BCVA was 59 ± 8.9 letters (20/66), and the BVCA at 12 months was 65 ± 27 letters (20/50). Thus, there was a mean of 6.5 ± 22 letters of improvement from baseline to 12 months, paired-T-test. $p = 0.02$. There were 29 of 36 eyes (80.6%) that achieved ≥ 5 letters gain, 26 of 36 eyes (72.2%) that achieved ≥ 10 letters gain, and 15 of 36 eyes (41.7%) that achieved ≥ 15 letters gain. BCVA equivalent of $\geq 20/200$ was achieved in 82.5% of study eyes. Fig. 3 shows the BCVA distribution over 12 months of the study period.

3.2. Anatomic outcome

As reported in a prior publication, Type-1 lesions were noted in 28 of 36 eyes (77.8%), while Type-3 lesions were detected in 8 of 36 eyes (22.2%) with vPED.⁷

The mean number of aflibercept injections in this study was 9.8 with a range from 9 to 12 injections over 12 months.

Regarding the OCT measurements, there were significant reductions

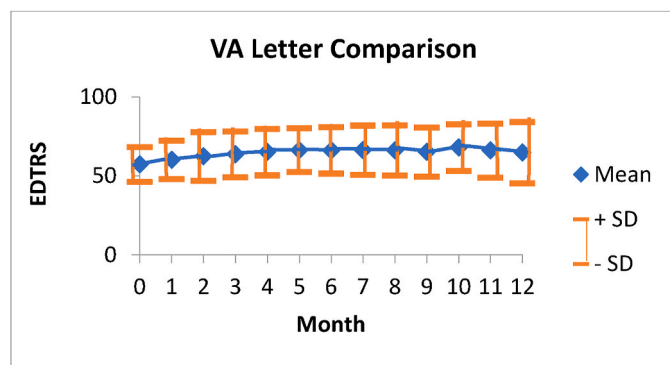


Fig. 3. A plot depicting the distribution of mean ETDRS BCVA over 12 months of the study period (□: + or - one standard deviation).

in month-12 measurements compared with baseline measurements for the following variables: Maximum height of PED, mean thickness of entire PED, mean PED thickness of central 1-mm subfield, volume of entire PED, PED volume of central 1-mm subfield, mean retinal thickness overlying entire PED, retinal volume overlying entire PED, mean SRF thickness associated with entire PED, subretinal fluid volume associated with entire PED, mean SHRM thickness associated with entire PED, mean SHRM thickness of central-1mm subfield, mean SHRM volume associated with entire PED, and mean SHRM volume of central 1-mm subfield (mean reductions in magnitude ranged from 6.0% to 95.3%, all $p < 0.001$) (Table 3). Regarding FA measurements, there were significant reductions in month-12 measurements compared with baseline measurements for the following variables: area of fibrovascular PED, GLD of fibrovascular PED, total area of leaking active NV, area of NV lesion, GLD of NV leakage (mean reductions in magnitude ranged from 41.9% to 87.7%, and p value ranged from 0.002 to < 0.001) (Table 4 top). Regarding the ICGA measurements, there was significant reduction in the month-12 measurement compared with baseline measurement for GLD of NV ($p = 0.001$) (Table 4 bottom). For the rest of the OCT, FA, and ICGA variables, 8 of the 9 variables showed p values of ≤ 0.05 , but they did not reach the more stringent threshold of $p \leq 0.002$ associated with the Bonferroni adjustment for multiplicities, when comparing month-12 with baseline measurements.

3.3. Time course of changes of retinal, SRF, PED, and SHRM volumes

Fig. 4A and B shows the time course of changes of SRF volume and retinal volume from baseline to month-12. It shows that most reduction of SRF volume occurred during the first month, while most decrease in retinal volume developed during the first two months following onset of treatment. Fig. 5A and B shows the time course of changes of PED volume and SHRM volume from baseline to month-12. It shows that most of the reduction of PED volume and SHRM volume occurred during the first two months after onset of treatment.

3.4. Adverse events

Retinal pigment epithelial tears developed in 5 eyes (13.9%) (all with Type-1 NV), as confirmed by multi-modal imaging of FP, FA, and SD-OCT (Table 5). GA was detected and assessed by FP, FAF, and infrared reflectance on SD-OCT. While only one eye (with Type-3 NV) had GA at baseline, 21 eyes (58.3%) were noted with GA by 12 months. However, after excluding the 5 eyes that developed GA due to RPE tears, 16 eyes with GA (10 eyes [38.5%] with Type-1 NV and 6 eyes [75%] with Type-3 NV) remained at 12 months, consistent with a prevalence of 44.4% (Table 6). Table 6 outlines the timing of GA onset and the corresponding accumulated number of aflibercept injections for each of the 16 eyes without RPE tears. The mean timing of GA onset was 35.2 ± 12.4 weeks (8.8 ± 3.1 months) with the range from 16 to 48 weeks. The mean timing of GA onset corresponded to a mean of 7.5 ± 1.9 injections of aflibercept (range: 4 to 10 injections). Utilizing the GA definition of at least $250 \mu\text{m}$ in diameter of atrophy, the mean size of GA at the end of study was $0.33 \pm 0.35 \text{ mm}^2$ (range: 0.02–1.2 mm^2).

Of the 5 eyes that developed RPE tears, 3 eyes developed the tears after the 1st aflibercept injection (4 weeks), 1 eye after the 4th aflibercept injection (16 weeks), and 1 eye after the 5th aflibercept injection (20 weeks) (Table 5). For these 5 eyes, mean baseline BCVA was 60.4 ± 7.7 letters (20/66), mean BCVA at the protocol visit immediately following development of RPE tear was 70.2 ± 14.4 letters (20/42) ($p = 0.13$, paired -T-Test), and mean BCVA at last protocol visit was 52.6 ± 29.7 letters (20/91) ($p = 0.33$, paired T-Test). Utilizing the GA definition of at least $250 \mu\text{m}$ in diameter of atrophy, 3 of these eyes developed GA at 4 weeks after the onset of RPE tears, 1 developed GA at 20 weeks after onset of RPE tear, and 1 eye developed GA at 32 weeks after onset of RPE tear.

Linear discriminant analysis showed no correlation of baseline PED

Table 3
Optical Coherence Tomography Results.

Variable	Baseline Mean	Baseline Standard Deviation (SD) ^a	Last Visit Mean	Last Visit SD	% mean Change	p-value ^b
PED ^c Max Height (μm^d)	403.7	274.5	177.1	183.5	56.1	<0.001
PED Mean Thickness Entire (μm)	47.6	62.9	12.5	18.2	73.7	<0.001
PED Mean Thickness-central 1mm (μm)	229.7	239.8	74.6	112.9	67.5	<0.001
PED Volume Entire (mm^3e)	1.5	2.0	0.41	0.61	72.9	<0.001
PED Volume-central 1mm (mm^3)	0.18	0.19	0.06	0.09	68.0	<0.001
Mean Retinal Thickness Entire (μm)	283.5	39.7	266.6	23.5	6.0	<0.001
Mean Retinal Thickness-central 1mm (μm)	269.0	90.5	236.7	75.4	12.0	0.062
Retinal Volume Entire (mm^3)	9.8	2.9	8.0	1.5	18.4	<0.001
Retinal Volume-central 1mm (mm^3)	0.21	0.07	0.18	0.04	14.7	0.004
Mean SRF ^f Thickness Entire (μm)	16.6	25.7	0.79	2.9	95.3	<0.001
Mean SRF Thickness-central 1mm (μm)	14.2	34.7	2.4	7.8	83.1	0.045
SRF Volume Entire (mm^3)	0.57	0.89	0.03	0.1	94.7	<0.001
SRF Volume-central 1mm (mm^3)	0.01	0.03	0.002	0.01	81.8	0.055
Mean SHRM ^g Thickness Entire (μm)	14.6	15.1	3.6	8.6	75.3	<0.001
Mean SHRMThickness-central 1mm (μm)	85.7	81.4	16.9	35.3	80.3	<0.001
Mean SHRMVolume Entire (mm^3)	0.47	0.51	0.1	0.22	79.4	<0.001
Mean SHRMVolume-central 1mm (mm^3)	0.07	0.06	0.01	0.03	81.2	<0.001

^a SD, standard deviation.

^b paired T-test.

^c PED, pigment epithelial detachment.

^d μm , microns.

^e mm^3 , millimeter cube.

^f SRF, subretinal fluid.

^g SHRM, subretinal hyperreflective material.

Table 4
Fluorescein Angiography and Indo-cyanine Green Angiography Outcomes.

Variable	Baseline Mean	Baseline SD ^a	Last Visit Mean	Last Visit SD	%mean Change	p-value ^b
FLUORESCIN ANGIOGRAPHY						
Area of Fibrovascular PED ^c (mm^2d)	5.85	4.91	2.08	5.12	64.4	0.002
GLD ^e of Fibrovascular PED (mm^f)	3.07	1.61	0.95	1.75	69.1	<0.001
Total Area of Leaking/Active NV ^g (mm^2)	6.96	4.99	2.15	5.15	69.1	<0.001
LLUS ^h	0.6	1.4	0.03	1.2	95.0	0.02
Area of Other Lesion Components (mm^2)	1.74	3.62	3.74	4.41	-53.5	0.043
Area of NV Lesion (mm^2)	8.73	5.16	5.7	5.70	34.7	0.002
GLD of NV Leakage (mm)	3.88	1.3	2.90	1.66	25.3	<0.001
INDO-CYANINE GREEN ANGIOGRAPHY						
Area of PED (mm^2)	4.06	5.7	1.47	3.3	63.8	0.023
GLD of PED (mm)	1.77	2.1	0.86	1.6	51.4	0.018
Area of NV Leakage (mm^2)	3.09	3.9	1.64	3.7	46.9	0.009
GLD of NV Leakage (mm)	2.37	1.3	1.24	1.4	47.7	0.001

^a SD, standard deviation.

^b T-test.

^c PED, pigment epithelial detachment.

^d mm^2 , millimeters squared.

^e GLD, greatest linear diameter.

^f mm , millimeters.

^g NV, neovascularization.

^h LLUS, late leakage of undetermined source.

size, SRF volume, and SHRM volume to the development or size of GA, with the exception of Type-3 lesions; for the Type-3 lesions, there was a correlation between baseline SHRM volume with GA development ($p = 0.026$). There were no systemic complications encountered in this study.

3.5. Selected case reports

3.5.1. Case 1. Flattening of a small vPED without complications after anti-VEGF therapy (Fig. 6A–H)

An 83-year-old woman presented with a small vascularized PED, consistent with a Type-1 NV in her left eye that measured 205.5 μm at its maximum height at baseline. Baseline BCVA measured 56 letters on the ETDRS chart. Treatment with aflibercept was performed per protocol. At 24 weeks after treatment, there was complete flattening of the PED and the BCVA was improved to 70 letters without complications. Fig. 6A–D.

(top row) shows multimodal color, FA, ICG, and OCT images, respectively at baseline, while Fig. 6E–H (bottom row) shows corresponding post-treatment images. All post-treatment images were obtained at 24 weeks with the exception of post-treatment ICG image, which was obtained at 12 weeks from baseline per protocol.

3.5.2. Case 2. Treatment of a large vPED without complications (Fig. 7A–H)

A 94-year-old woman presented with a large fibrovascular PED with multiple features characteristic of a Type-3 NV (retinal dot hemorrhage, exudates, and retinochoroidal anastomoses [RAP]) in her left eye that measured 859 μm at its maximum height at baseline. Baseline BCVA measured 60 letters on ETDRS chart. Anti-VEGF treatment with aflibercept was performed per protocol. At 24 weeks after repeated aflibercept treatment, PED height was reduced to 122.3 μm and ETDRS VA

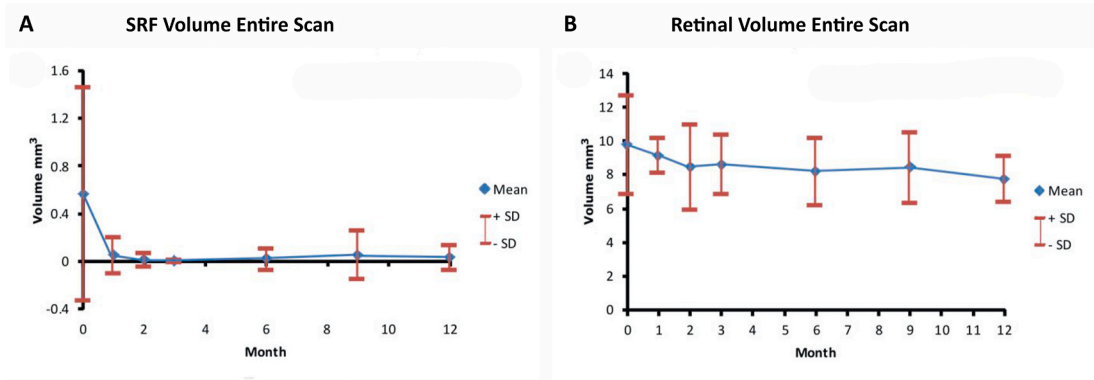


Fig. 4. A, B shows the time course of changes of SRF volume and retinal volume, respectively, from baseline to 12 months. Most reduction of SRF volume occurred during the first month while most decrease of retinal volume developed during the first two months after onset of aflibercept treatment.

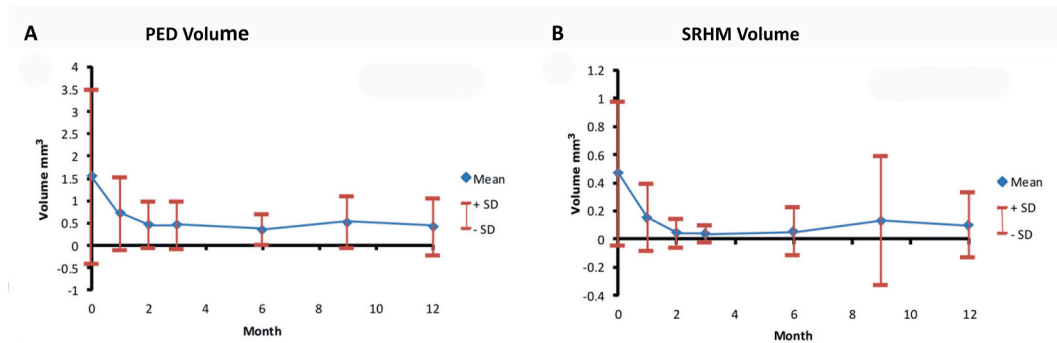


Fig. 5. A, B shows the time course of changes of PED volume and SRHM volume, respectively, from baseline to 12 months. Most reduction of PED volume and SRHM volume occurred during the first two months after start of aflibercept treatment.

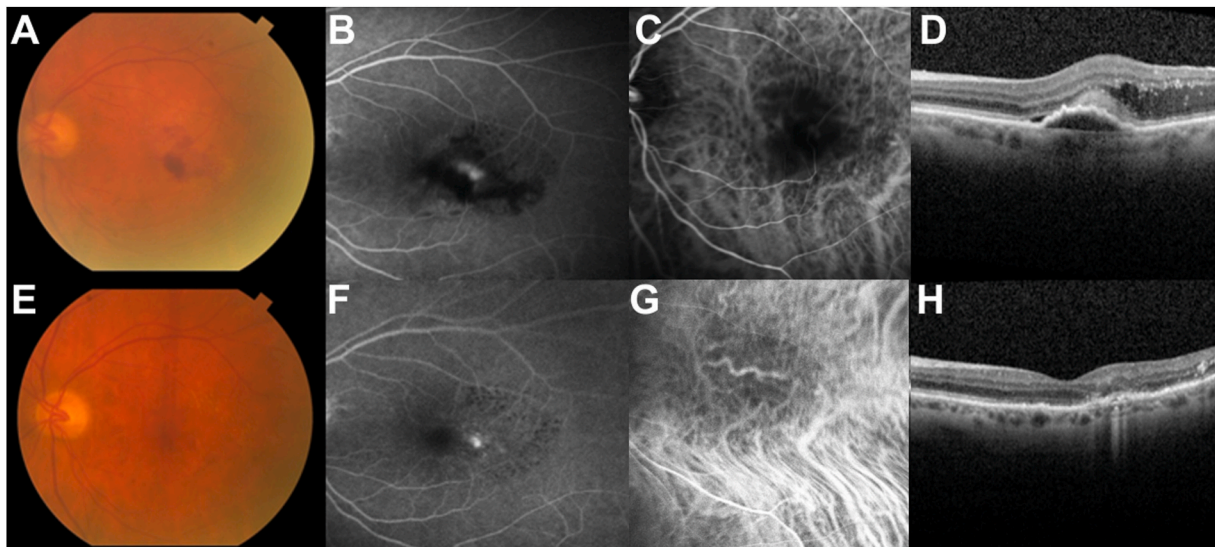


Fig. 6. A to H (Treatment of small vPED without complications): Multimodal color FP, FA, ICG and SD-OCT images show a small vascularized PED (Type-1 NV) in an 83-year-old woman's left eye that measured 205.5 μm at its maximum height with an ETDRS BCVA of 56 letters at baseline (top row). At 24 weeks after treatment, there was complete flattening of the PED and the BCVA was improved to 70 letters without complications (bottom row). All post-treatment images (bottom row) were obtained at 24 weeks with the exception of post-treatment ICG image, which was obtained at 12 weeks from baseline per protocol schedule. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

measured 57 letters with almost complete flattening of the PED. Fig. 7A–D (top row) shows multimodal color, FA, ICG, and OCT images, respectively, at baseline, while Fig. 7E–H (bottom row) shows corresponding post-treatment images. All post-treatment images were

obtained at 24 weeks with the exception of post-treatment ICG image, which was obtained at 12 weeks from baseline per protocol. Careful scrolling through the cross-sectional OCT B-scan images of this large, smooth, dome-shaped PED confirmed Type-3 intraretinal NV inferior to

Table 5
Eyes with Retinal Pigment Epithelial Tears.

Age	F*/M**	Eye	Baseline Maximum PED ⁺ height (microns)	Count of aflibercept injections before RPE ⁺⁺ tears (weeks)	Timing of GA [#] onset (weeks)	BCVA ^{##} Baseline		BCVA immediately after RPE tears		BCVA at 48 weeks		GA area at 48 weeks (mm ²)
						letter score	LogMar (Snellen)	letter score	LogMar (Snellen)	letter score	LogMar (Snellen)	
76	M	left	736.8	5 (20)	24	62	0.498 (20/63)	73	0.301 (20/40)	63	0.397 (20/50)	0.1
75	F	right	1142.1	1 (4)	8	72	0.301 (20/40)	69	0.301 (20/40)	14	1.5 (20/633)	0.09
87	F	right	468.7	1 (4)	8	61	0.498 (20/63)	53	0.602 (20/80)	29	1.09 (20/246)	1.7
79	F	left	954	1 (4)	24	52	0.698 (20/100)	68	0.397 (20/50)	74	0.204 (20/32)	2.18
73	F	right	941.1	4 (16)	48	55	0.602 (20/80)	88	0 (20/20)	83	0.096 (20/25)	0.1

*F, females; **M, males; ⁺PED, retinal pigment epithelial detachment; ⁺⁺RPE, retinal pigment epithelial; [#]GA, geographic atrophy; ^{##}BCVA, best-corrected visual acuity.

Table 6
Geographic Atrophy in Eyes without Retinal Pigment Epithelial Tears.

Age	F*/M**	Eye	Baseline Maximum PED ⁺ height (microns)	Count of aflibercept injections before GA ⁺⁺ onset	Timing of GA onset (weeks)	BCVA [#] Baseline		BCVA Last Visit		GA area last visit mm ²
						letter score	LogMar (Snellen)	letter score	LogMar (Snellen)	
91	F	left	167.2	0 [#]	0 [#]	55	0.602 (20/80)	55	0.602 (20/80)	0.34
82	M	left	353.1	6	24	50	0.698 (20/100)	64	0.397 (20/50)	0.92
86	F	left	91.5	8	40	72	0.301 (20/40)	85	0 (20/20)	0.17
70	F	right	456.9	9	48	66	0.397 (20/50)	83	0.096 (20/25)	0.09
67	F	left	284.1	6	24	44	0.795 (20/125)	76	0.204 (20/32)	0.63
94	F	left	859.9	6	24	60	0.498 (20/63)	65	0.301 (20/40)	0.24
73	M	right	339.2	9	48	71	0.301 (20/40)	84	0 (20/20)	0.42
86	F	right	259.3	6	24	54	0.602 (20/80)	44	0.795 (20/125)	0.57
83	F	right	322.6	10	48	65	0.397 (20/50)	16	1.39 (20/491)	0.02
73	M	left	309.9	10	48	62	0.498 (20/63)	72	0.301 (20/40)	0.07
76	F	left	222.4	6	24	39	0.903 (20/160)	49	0.698 (20/100)	0.17
80	M	left	158.6	4	16	65	0.397 (20/50)	78	0.204 (20/32)	1.2
70	M	right	557.7	9	48	69	0.301 (20/40)	84	0 (20/20)	0.2
78	F	left	758.7	9	48	59	1.3 (20/399)	20	1.3 (20/399)	0.06
83	M	left	300.6	8	40	44	0.795 (20/125)	69	0.301 (20/40)	0.16
69	M	left	192.7	6	24	63	0.397 (20/50)	78	0.204 (20/32)	0.09

*F, females; **M, males; ⁺PED, retinal pigment epithelial detachment; ⁺⁺GA, geographic atrophy; [#]BCVA, best-corrected visual acuity; ^{##}single eye with GA at baseline.

the fovea associated with marked macular thickening and prominent cystoid macular edema but only mild SRF extending through an RPE defect into the sub-RPE space. There was no evidence of underlying polyps and branching vascular networks (Figure 7D Supplement).

3.5.3. Case 3. A large vPED with RPE Tear after treatment (Fig. 8A–H)

A 75-year-old woman showed a large vascularized PED consistent with a Type-1 NV in her right eye that measured 1142.1 μ m at its maximum height at baseline. Baseline BCVA measured 72 letters on the ETDRS chart. Aflibercept injection was started according to protocol. However, an RPE tear developed at temporal margin of PED within 4

weeks after initial aflibercept injection, corresponding to the basal angle diametrically opposed to the location of NV. At week-24, maximum PED height measured 578.8 μ m, corresponding to BCVA of 28 ETDRS letters. Fig. 8A–D (top row) shows multimodal color, FA, ICG, and OCT images, respectively at baseline, while Fig. 8E–H (bottom row) shows corresponding post-treatment images. All post-treatment images were obtained at 24 weeks with the exception of post-treatment ICG image, which was obtained at 12 weeks from baseline per protocol.

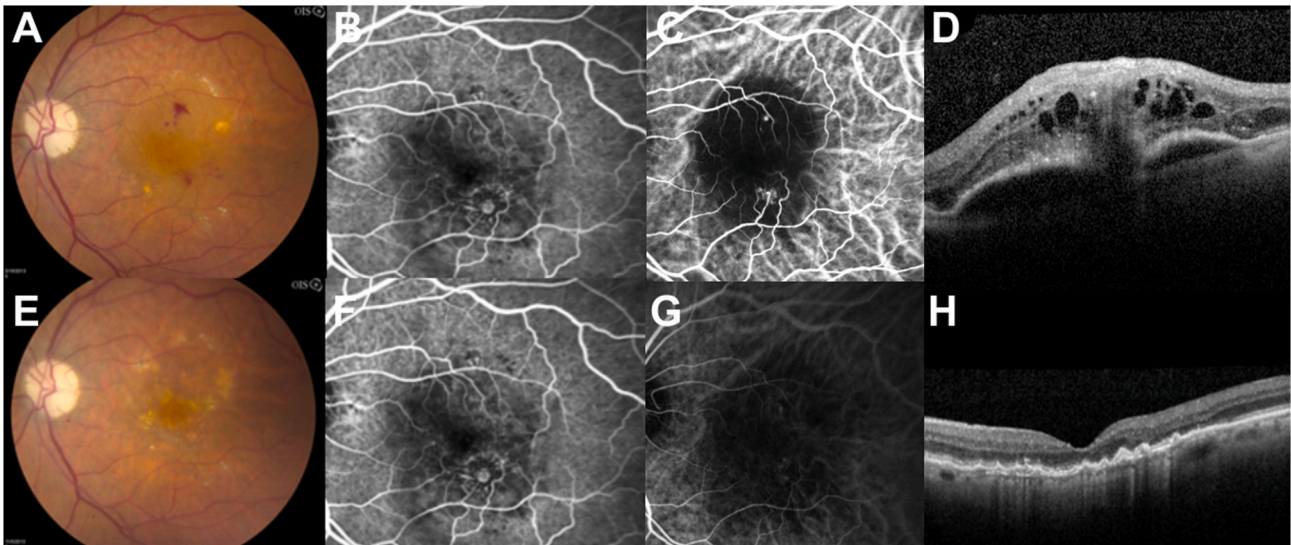


Fig. 7. A to H (Treatment of large vPED without complications): Multimodal color FP, FA, ICG and SD-OCT images of a 94-year-old woman show a large fibrovascular PED, characteristic of a Type-3 NV with retinal dot hemorrhage, mild exudates, and retinochoroidal anastomoses (RAP) in her left eye (top row). This vPED measured 859 μm at its maximum height and the ETDRS BCVA was 60 letters at baseline. At 24 weeks after repeated aflibercept treatment per protocol, PED height was reduced to 122.3 μm and ETDRS VA measured 57 letters with almost complete flattening of the PED (bottom row). Careful scrolling through the cross-sectional OCT B-scan images of this large, smooth, dome-shaped PED confirmed intraretinal Type 3 NV inferior to the fovea associated with marked macular thickening and prominent cystoid macular edema, but only mild SRF extending through an RPE defect into the sub-RPE space. 7D Supplement: SD-OCT EDI cross-sectional B-scan image at the point of RAP lesion explores the anatomic features underlying the RPE breach at baseline in the left eye of this 94-year-old woman (Case Report 2), (<https://doi.org/10.1016/j.ajoc.2020.100916>) 7D Supplement. There was no evidence of polyps or branching vascular networks. All post-treatment images (bottom row) were obtained at 24 weeks with the exception of post-treatment ^{14}C image, which was obtained at 12 weeks from baseline per protocol schedule. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

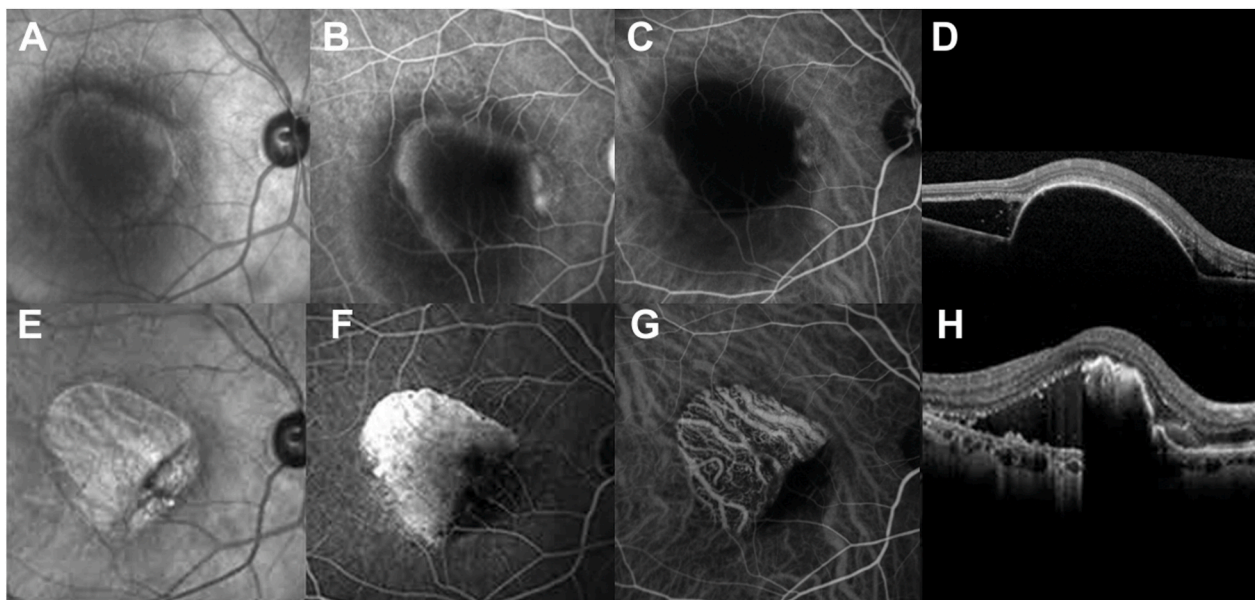


Fig. 8. A to H (Treatment of large vPED with complications): Multimodal red-free, FA, ICG and SD-OCT images reveal the right eye of a 75-year-old woman with a large vascularized PED (Type-1 NV) measuring 1142.1 μm at its maximum height and ETDRS BCVA of 72 letters at baseline (top row). At 4 weeks after onset of aflibercept injection according to protocol, an RPE tear developed at temporal margin of PED, corresponding to the basal angle diametrically opposed to the location of the NV. Maximum PED height measured 578.8 μm corresponding to BCVA of 28 ETDRS letters at 24 weeks. All post-treatment images (bottom row) were obtained at 24 weeks with the exception of post-treatment ICG image, which was obtained at 12 weeks from baseline per protocol schedule.

4. Discussion

This study providing meticulous qualitative and quantitative assessment in a reading center setting shows notable visual recovery corresponding to concomitant substantial anatomic improvements for essentially all of the study variables. EVEN Study shows a significant

mean standardized BCVA improvement of 6.5 ± 22 letters at 12 months compared with baseline. In addition, more than 80% of treated eyes achieved a BCVA gain of greater than or equal to 5 letters, and also BCVA of greater than or equal to 20/200. As many as 72% of treated eyes attained greater than or equal to 10 letters gain, and 41.7% attained greater than or equal to 15 letters gain. These results compare favorably

with publications in the literature regarding aflibercept treatment for eyes with vascularized PED.^{8,9,14}

Regarding the anatomic outcomes, there were marked reductions in measurements for the majority of the anatomic lesion components (18) shown by multi-modal imaging, reaching the adjusted statistically significant threshold of $p \leq 0.002$. They included PED height, SA and volume, retinal thickness and volume, SRF thickness and volume, SHRM thickness and volume, GLD of PED, SA of NV lesion, GLD of NV lesion, and SA and GLD of NV leakage. For the anatomic reductions of the remaining 9 SD-OCT, FA, and ICGA variables, all except one showed a p value of ≤ 0.05 ; but they failed to reach the more stringent threshold of $p \leq 0.002$, likely due to a lack of sufficient sample sizes for those subcategories.

Regarding SHRM corresponding to subretinal lesion components of NV tissue, hemorrhage, lipid and fibrin, and pigmentary debris, Liakopoulos et al. showed in 2008 that its reduction correlates directly with reduction in Type-2 NV subtype of exudative AMD.¹⁵ Our EVEN Study shows that reduction in SHRM also correlates directly with reduction in Type-1 and Type-3 neovascular AMD.

In addition, EVEN Study shows that most reduction in subretinal fluid volume occurs primarily during the first month after onset of aflibercept injections, whereas majority of decrease in retinal thickness and volume and SHRM height and volume mirror decrease in vPED height and volume during the first two months after start of aflibercept injections.

Consistent with previous reports by Chiang et al.,¹⁶ Chan et al.,^{17,18} Sarraf et al.,¹⁹ and Clemens et al.²⁰ EVEN Study demonstrates the association of substantial PED height (e.g. $>400 \mu\text{m}$) at baseline with increased tendency for RPE tears following anti-VEGF therapy. In fact, the mean PED height of all five eyes that developed RPE tears in EVEN was $>800 \mu\text{m}$. Moreover, our study also has documented clearly that large PED volume was correlated with increased trend for RPE tears, as all five eyes that developed RPE tears had a mean PED volume of greater than 4.0 mm^3 in contrast to mean PED volume of less than 1.0 mm^3 ($p = 0.004$) in eyes without RPE tears at baseline. It is noteworthy that despite RPE tears, our study shows that continued aflibercept therapy resulted in a trend of substantial reduction in mean PED maximum height and volume ($p = 0.032$ and $p = 0.013$, respectively), while limiting the amount of mean BCVA loss (60.4 ± 7.7 letters at baseline, 52.6 ± 29.7 letters at 12 months, $p = 0.33$, Table 5) at 12 months when compared with baseline for these eyes with RPE tears. As expected, poor vision outcome was noted in those eyes with grade-3 or 4 RPE tears.

Also regarding RPE tears, all 5 eyes (13.9%) had Type-1 NV, while none of the eyes with Type-3 NV developed RPE tears. The association of Type-1 NV with RPE tears is not surprising, since the entire tractional force induced by Type 1 NV is directed narrowly in a tangential fashion at the opposing acute basal angle within the limited confine of the PED, leading to an eventual rupture of the RPE at that location. In contrast, the tractional force associated with Type 3 NV is distributed diffusely throughout a broad area, as the Type-3 NV descends from the sensory retina at the level of the deep capillary plexus above the PED through a gap in the crest of the PED into the sub-RPE space, allowing dissipation of the tension generated by the tractional force.

The early breach of the integrity of the RPE in eyes with Type-3 NV may also explain their high association with GA formation. As noted above, while GA was found in only one study eye at baseline, more than 40% of study eyes (38.5% of Type-1 NV eyes versus 75% of Type-3 NV eyes) developed GA by 12 months, independent of another 5 eyes that developed substantial RPE atrophy due to RPE tears. Our data revealed the mean timing for the onset of GA to be 8.8 months (range: 4–12 months) from baseline, following a mean of 7.5 in (range: 4–10) aflibercept injections. With the exception of Type-3 lesions, our study did not find any correlation of RPE size, SRF volume, and SHRM volume with the formation or size of GA. For the Type-3 lesions, GA was correlated with baseline SHRM volume. Given the GA data, the direct role of anti-VEGF therapy in aggravating GA progression is suggestive

but not proven. This finding of GA formation is consistent with previous publications associated with anti-VEGF therapy for eyes with nAMD enrolled in clinical trials.^{21–23} However, there is a possibility that other mechanisms may contribute to GA formation. For example, 2 of the 3 eyes that developed total collapse of vPED with complete resolution of SHRM at 12 months in this study also showed marked GA formation, consistent with the intriguing hypothesis that sparing of a neovascular remnant of vPED or presence of an inactive sub-RPE NV lesion is more beneficial than complete resolution or flattening of a vPED, because the former condition retards GA progression by recapitulating the morphology of native choriocapillaris for maintenance of overlying RPE and photoreceptor metabolism, while the latter condition does the opposite.^{24,25} Grossniklaus et al. first proposed that Type-1 NV under the RPE layer may form as a compensatory mechanism to provide nutrients and oxygen to the RPE and outer retinal layer.²⁴ Subsequently, Freund and colleagues²⁶ as well as Xu and coauthors²⁷ and Chae and associates²⁸ also showed that eyes with Type-1 NV treated with anti-VEGF therapy had more favorable vision outcome and less GA formation, respectively, compared with eyes with other lesion types. The trend of more complete resolution of SHRM and flattening of the PED associated with less sparing of sub-RPE NV remnants and subsequent more prevalent GA formation in Type-3 NV eyes in comparison to Type-1 NV eyes without RPE tears in our study is consistent with this hypothesis. This finding in our study is also consistent with the conclusion of Grunwald et al., who found that eyes with retinchoroidal proliferation (Type-3 NV) had a higher risk for GA formation in their retrospective review of the 2-year CATT data.²²

The deficiencies of this study include a limited sample size and lack of a comparison group. Also, to avoid obscuration of pertinent features associated with PED that could interfere with their accurate assessment, we excluded eyes with large hemorrhage occupying more than 50% of the PED. It is possible that exclusion of such eyes precluded us from investigating relevant findings associated with certain large vascularized PED with extensive hemorrhage. However, these shortcomings are outweighed by its strengths, which include its prospective design, meticulous analysis at a reading center setting, close follow-up, periodic high-quality and standardized multimodal imaging on a consistent basis, and standardized BCVA measurements. More studies are needed to elucidate factors increasing the tendency for GA progression beyond the natural history of this process for eyes with vPED associated with AMD.

CRedit authorship contribution statement

Clement K. Chan: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **David Sarraf:** Conceptualization, Methodology, Validation, Investigation, Writing - review & editing. **Prema Abraham:** Investigation, Resources, Data curation. **Maziar Lalezary:** Investigation. **Steven G. Lin:** Investigation, Data curation. **Xuejing Chen:** Data curation, Formal analysis, Writing - review & editing. **Muneeswar Gupta Nittala:** Methodology, Software, Data curation, Formal analysis. **SriniVas Satta:** Methodology, Software, Formal analysis, Resources, Writing - review & editing.

Declaration of competing interest

None of the authors hold proprietary or financial interests in any products mentioned in this study.

Clement K Chan has received research support from Allergan, Chengdu Kanghong Biotechnology, NEI, Regeneron, Roche-Genentech, and Regenerative Patch Technologies.

David Sarraf has received research support from Regeneron, and has also received research support, equipment, or served as consultant or speaker for Amgen, Bayer, Roche-Genentech, Heidelberg, Novartis, Topcon, and Optovue.

Prema Abraham has received research support from Roche-Genentech, Appellis, Allergan, Stealth Biotherapeutics, Regeneron, Santen Pharmaceuticals, and Chengdu Kanghong Biotechnology.

Steven G Lin has received research support from Roche-Genentech, NEI, Allergan, Regeneron, Regenerative Patch Technologies, and Chengdu Kanghong Biotechnology.

Maziar Lalezary has no conflicts of interest to disclose.

Xuejing Chen has no conflicts of interest to disclose.

Muneeswar Gupta Nittala has served as consultant for Eyenuk Inc.

Srinivas Sadda has served as consultant for and received honoraria from Allergan, Amgen, CenterVue, Heidelberg, Novartis, Optos, Oxurion, Roche-Genentech, Samsung Bioepis, 4DMT; research instruments from Carl Zeiss Meditec, Heidelberg, Nidek, Optos, Topcon; research support from Carl Zeiss Meditec.

Acknowledgements

Aileen Arakaki-Chan DDS prepared all figures and tablets for this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajoc.2020.100916>.

Disclosure

The Even Study was registered with ClinicalTrials.gov: Identifier: NCT01722656.

Patient consent

Institutional review board approval was obtained in each center prior to the start of the study.

All participants signed a written informed consent for enrollment in the study, after they were provided with detailed verbal discussion and written information for their review.

The report does not contain any personal information that could lead to the identification of any of the patients, who participated in this study.

This research trial adhered to the tenets of the Declaration of Helsinki and was conducted in accord with regulations set forth by the Health Insurance Portability and Accountability Act.

Funding

Regeneron Pharmaceuticals, Tarrytown, New York, USA provided a grant for this study. The authors have maintained complete control of all aspects of this study.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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