Journal of Clinical & Experimental Ophthalmology

Carle et al., J Clin Exp Ophthalmol 2014, 5:6
DOI: 10.4172/2155-9570.1000373

Research Article Open Access

Tears of the Retinal Pigment Epithelium during Aflibercept Therapy: PED and Treatment Characteristics

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Received date: Oct 06, 2014, **Accepted date:** Nov 14, 2014, **Published date:** Nov 19, 2014

Abstract

Background: Tears of the Retinal Pigment Epithelium (RPE) are associated with Age-Related Macular Degeneration (AMD) in the setting of a pigment epithelial detachment (PED).

Methods: Chart review of patients treated with intravitreal (IV) Aflibercept for neovascular AMD (nvAMD). Clinical course and OCT images were analyzed to compare characteristics for patients who experienced RPE tears during treatment of symptomatic PED with IV Aflibercept.

Results: 8 eyes of 8 patients were included in the study. All cases were being treated for nvAMD with IV aflibercept. The average maximal height of PED was 475 μm (172-874 μm), and the mean linear diameter was 3426 μm, (1004-5185 μm). All eyes had associated subretinal fluid; 4 had RPE folds and irregularities, and one had subretinal hemorrhage. Four eyes experienced an RPE tear after the first injection of Aflibercept. Two eyes had received more than 10 injections of aflibercept prior to the development of RPE tear. Two patient's eyes were previously treated with other anti-VEGF agent (one bevacizumab, and one ranibizumab). The visual acuity improved by 2 or more lines in 3 eyes, and worsened by 2 or more lines in no eyes. The final BCVA was ≥ 20/40 in 2 eyes, 20/50-20/100 in 5 eyes, and </= 20/200 in 1 eye.

Conclusion: IV Aflibercept has been recommended for treatment of PED in the setting of nvAMD. In our study, 8 patients with PED experienced a tear of the RPE during the early course of treatment with Aflibercept. Aflibercept's mechanism of action is such that it binds to multiple targets with higher affinity than other anti-vascular-endothelial-growth-factors. This proposed mechanism may increase its efficacy in the setting of PED. This mechanism, however, may also augment the risk for RPE tears. Therefore, consideration for RPE tear should be given in the setting of large PED in nvAMD.

Keywords: Retinal pigment epithelium; Aflibercept; RPE tear; Age-related macular degeneration; Ant-VEGF; Pigment epithelial detachment

Introduction

Retinal Pigment Epithelium tears are associated with neovascular Age-Related Macular Degeneration (AMD). They are more commonly associated with fibro-vascularized retinal pigment epithelial detachments fv (PED) in the setting of neovascular AMD (nvAMD) [1,2]. The incidence of tear formation is about 11% in the natural history of PED, and this may be increased in the setting of anti-vascular endothelial growth factors [2-5]. Multiple reports of RPE tears have been linked with pegaptanib, bevacizumab, and ranibizumab. To date, a single case report has been associated with Aflibercept administration [4-8]. A recent review of three phase III randomized, multicenter clinical trials for the use of ranibizumab in the treatment of nvAMD showed a low incidence of RPE tears in all treatment groups (0.7%-5.1%), which was comparable to previous published rates in patients with AMD [7]. The temporal relationships and the mechanism of action of RPE tears (sudden fibrovascular contraction, strained RPE undersurface, etc.) make RPE tears in the setting of anti-VEGF treatment a risk of current treatments [6,7]. The higher affinity and broader mechanism of action against VEGF demonstrated by aflibercept in vivo could conceivably increase the risk of RPE tears [6-9].

This series represents the first case series of RPE tears in the setting of aflibercept treatment of nvAMD. An IRB ethics exemption was sought and granted for this series.

Methods

A chart review of patients treated with intravitreal (IV) Aflibercept for neovascular AMD (nvAMD) was conducted. Charts were selected by reviewing the billing and coding sheets for the practice and approximately 996 patients treated for nvAMD with Aflibercept at the time of review. Clinical course and OCT images were analyzed to compare characteristics for patients who experienced RPE tears during treatment of symptomatic PED with IV Aflibercept.

Patient 1

Patient number 1 is a 75 year old female, who had been treated for nvAMD with a fvPED in her left eye (OS) 11 times with intravitreal (IV) bevacizumab, and 26 times with IV ranibizumab maintaining a best corrected visual acuity (BCVA) of 20/50. She presented with a

new fvPED in her right eye (OD) and a decrease in BCVA from 20/25 to 20/200. (Figure 1 – Optical Coherence Tomography [OCT], Colour photo, and Fluorescein Angiography [FA] OD). She was treated with a single ranibizumab OD which brought the BCVA to 20/60, and then treated with a single aflibercept injection 4 weeks later.

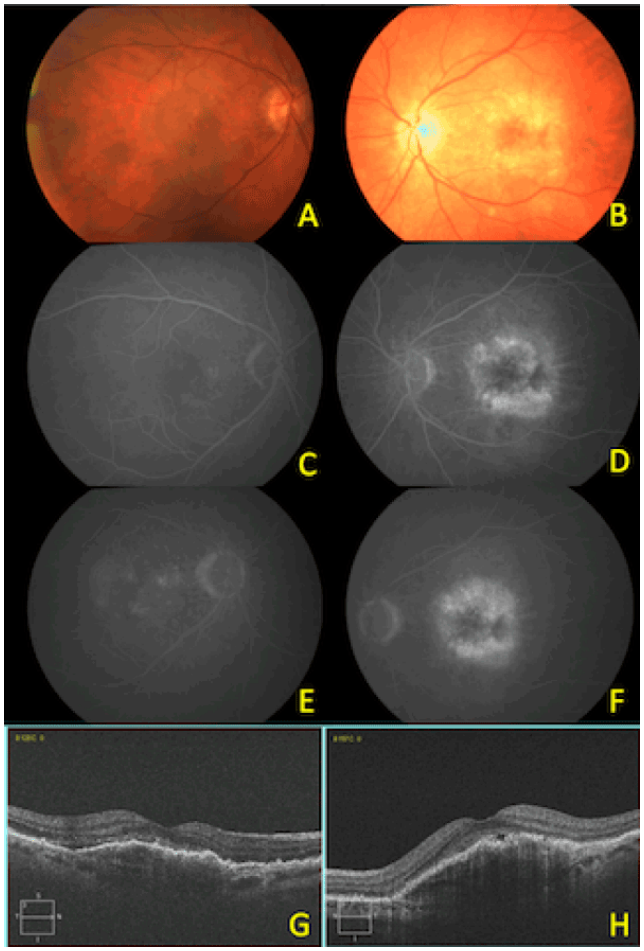

Figure 1: Patient 1: Pre-Treatment. A: Colour photo showing the PED OD, B: Colour photo showing RPE atrophy OS and the PED, C: Early FA OD showing the PED, D: Early FA OS showing window defect, E: Late FA OD showing staining in the PED, F: Late FA OS showing staining in the PED G: OCT OD showing the new PED with some associated subretinal fluid G: OCT OS showing the chronic photoreceptor changes in the retina.

Two weeks later, she was seen for treatment of her OS with IV ranibizumab as previously scheduled and reported that immediately after the OD IV aflibercept injection, the vision worsened with much distortion. BCVA was reduced to finger counting. Intraocular pressures were normal, and no addition lens changes were seen. Anterior chamber was unremarkable, and the posterior chamber had no inflammation. A large RPE tear was seen through the central macula. Additional images were obtained that day (Figure 2 – OCT, Colour photo, FA OD).

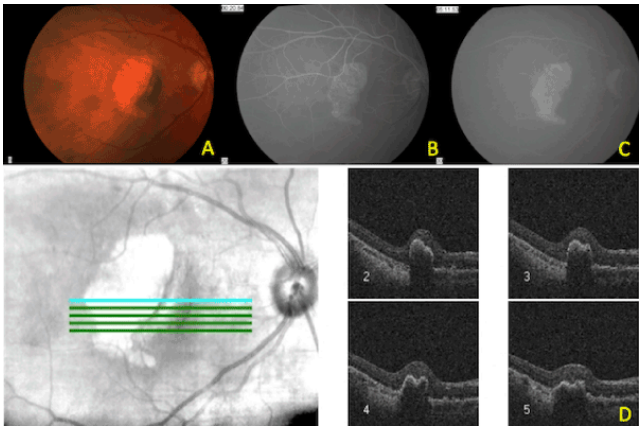

Figure 2: Patient 1: Post-Treatment OD. A: Colour photo showing the scrolled RPE and the choroid visible in the void of RPE, B: Early FA showing the choroidal circulation visible through the RPE defect, C: Late FA showing the congruous RPE defect with no staining, D: OCT images through the RPE tear: The abrupt edge of the RPE is clearly visible in the cuts labeled 2 and 3.

Patient 2

Patient number 2 is a 72-year-old female, who had been followed yearly for dry AMD with a BCVA of 20/15 and 20/20. She presented prior to her scheduled appointment with deceased BCVA and distortion OD (BCVA down to 20/40). On examination she had a very large fvPED OD with some associated thickening. She was treated with IV aflibercept 11 times over an 11-month period. The fvPED had associated subretinal and intraretinal edema over different time points over the 11-month period of treatment. Visual acuity remained stable throughout this time (Figure 3).

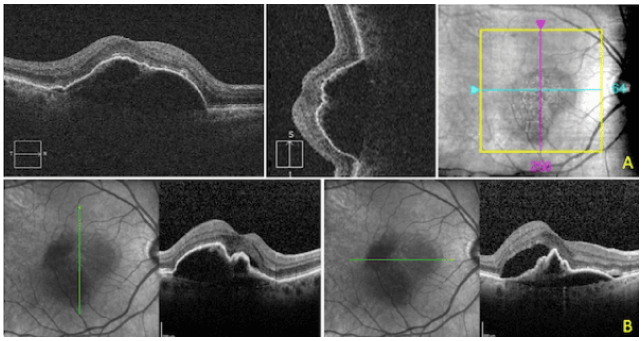

Figure 3: Patient 2: Before RPE tear. A: A large PED OD is visible two months prior to the tear. The patient was treated at this visit, B: There is increased subretinal and intraretinal fluid, and the PED takes on an irregular shape. RPE strain is visible in the horizontal cut as irregular peaking of the RPE. The patient was treated again at this visit.

Four days after the 12th injection, she presented with a sudden increase in distortion and a "grey spot" that was new in the central vision in the treated eye (OD). At that time BCVA was 20/25 and an

RPE tear was noted at the edge of the fvPED (Figure 4 – OCT, AF, and red free photo OD).

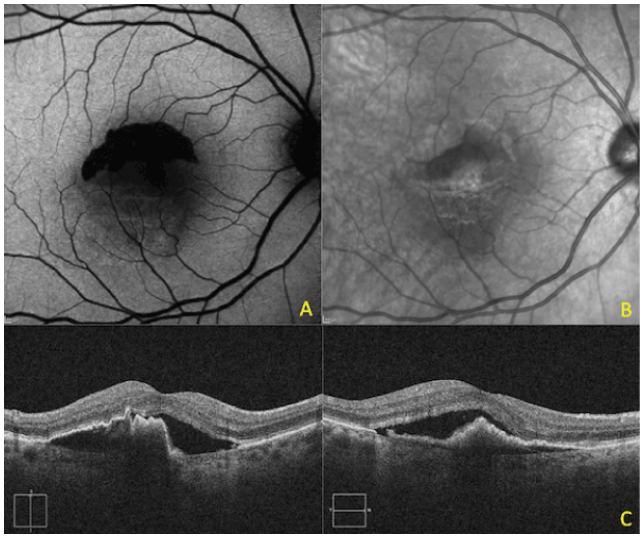

Figure 4: Patient 2: After treatment. A: Autofluorescence photo OD demonstrating the striking absence of RPE, B: Red-Free photo of the same area, the corrugated RPE is visible inferior to the torn area, C: OCT through the RPE tear showing the retracted and corrugated RPE.

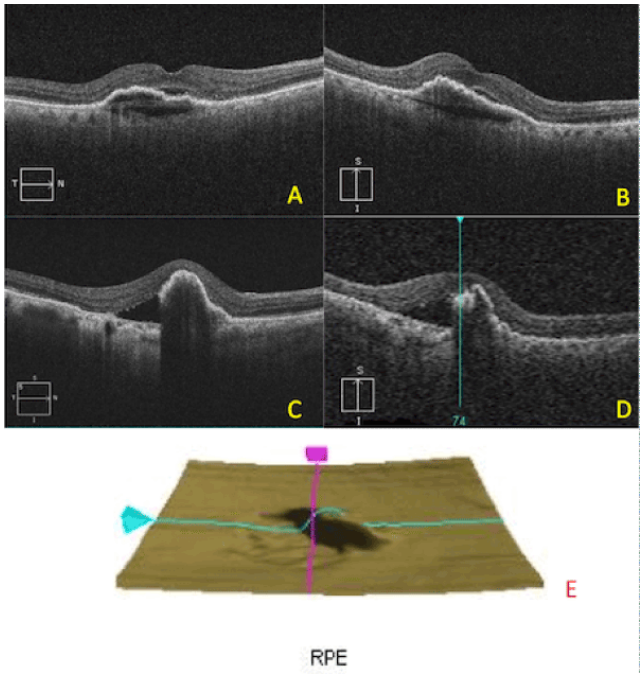

Figure 5: Patient 3: Before and after a single treatment. A& B: OCT OD demonstrating the PED and subfoveal fluid. C& D: OCT OD demonstrating the discontinuity of the RPE after the tear, E: 3D Map of the RPE demonstrating the scrolled edge, elevated RPE with choroid visible underneath.

Patient 3

Patient number 3 is an 85 year old male who had been treated in his left eye for wet macular degeneration over a period of 6 years with IV bevacizumab 11 times, and IV Aflibercept 4 times. The right eye had dry AMD during this time period and maintained a BCVA of 20/30. At a scheduled follow up visit the right eye presented with a PED with associated subfoveal fluid, and a decrease in BCVA to 20/200. (Figure 5) Intravitreal Aflibercept was administered. The patient was seen a week later for a scheduled appointment for treatment in the other eye. It was noted that although the visual acuity was improved to 20/100, there was an RPE tear temporal to the fovea (Figure 5).

Patient 4

Patient number 4 is a 67 year old female who presented with decreased vision OS to 20/60. On examination she had a large subfoveal fvPED with associated subretinal fluid and retinal thickening (Figure 6). A single dose of intravitreal Aflibercept was administered OS.The patient returned two days later stating that the morning after the injection the vision became cloudy centrally, and did not resolve. A RPE tear was seen OS (Figure 6).

Patient 5

Patient number 5 is a 69 year of female who was initially seen for dry AMD with a BCVA of 20/25 OU. She developed a PED OD and was seen at monthly intervals until OCT demonstrated some subretinal and intraretinal fluid OD and a decrease in BCVA to 20/100. Intravitreal Bevacizumab was administered and the patient returned in one month.The next month the BCVA had improved to 20/70 but there remained some subretinal fluid. Intravitreal Aflibercept was administered. One month later the patient's BCVA had fallen to 20/200 and an RPE tear was seen OD (Figure 7).

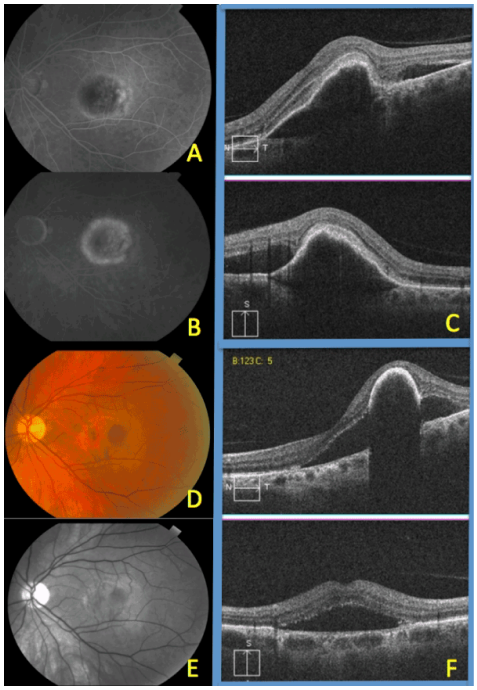

Figure 6: Patient 4: Before and after treatment with Aflibercept. A & B: Early and late FA OS, C: OCT demonstrating the PED and subretinal fluid, D: Colour Photograph of the RPE tear post injection, E: Red Free photo of the RPE tear, F: OCT demonstrating complete retraction/absence of the RPE.

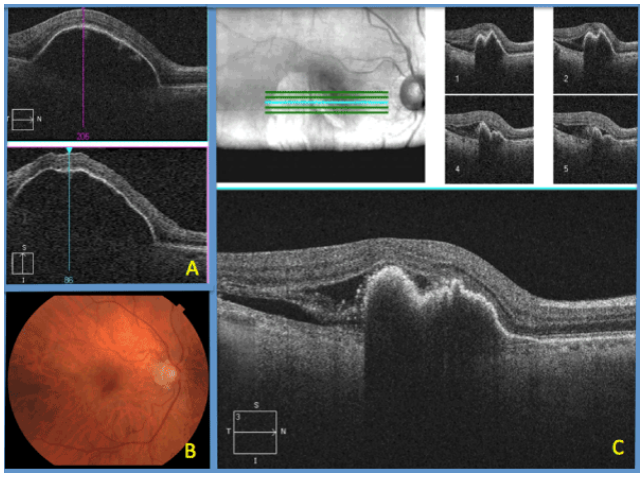

Figure 7: Patient 5: Before and after treatment with Aflibercept. A: Large PED, B: Colour Photograph, C: Post injection OCT demonstrating the tear.

Patient 6

Patient number 6 is an 80 year old female who presented with decreased vision OS for a few weeks. She was pseudophakic with a BCVA of 20/25 OD and finger counting OS. She demonstrated high risk characteristics of dry AMD OD and a subretinal hemorrhage with retinal edema and a fvPED OS. She was given an IV Aflibercept injection OS and her vision improved to 20/200. Following her second dose her vision improved to 20/100 but she had developed an RPE tear (Figure 8).

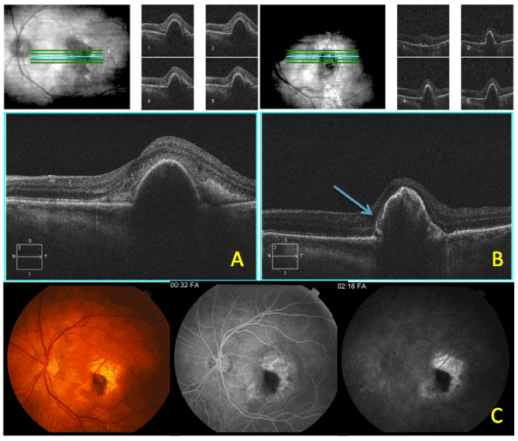

Figure 8: Patient 6: Before and after treatment with Aflibercept. A: OCT image of PED with associated subretinal hemorrhage. B: OCT image of the torn and irregular PED after two injections. C: Colour photo and FA demonstrating the tear after hemorrhage resolved.

Patient 7

Patient number 7 is an 83 year old male who had been seen for 22 months prior for treatment NVAMD OD and had been started on IV Aflibercept OD with a q2 monthly injection regiment. BCVA was 20/60 OU and treatment OD was initiated. After 13 months of treatment OD (7 IV Aflibercept treatments) OS developed an active CNVM and was treated with IV Aflibercept twice and PDT once. BCVA OU was 20/40. After the 12th injection of IV Aflibercept OD an RPE tear developed. BCVA remained at 20/40 (Figure 9).

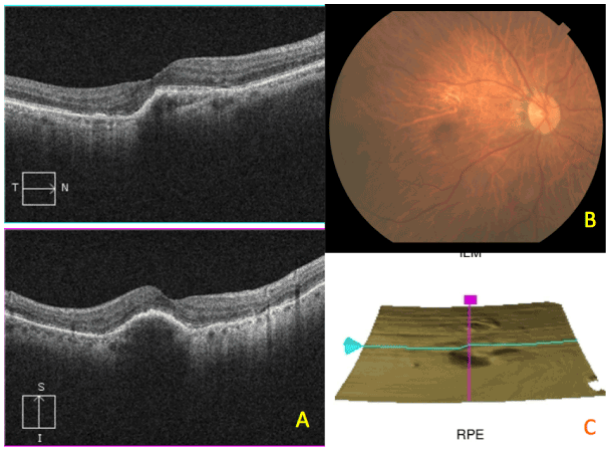

Figure 9: Patient 7: Before and After treatment, A: PED prior to rip, B: Colour photo showing rolled RPE, C: RPE map showing scrolled RPE.

Patient 8

Patient number 8 is a 74 year old female who had been follow for a large fibrotic sub-retinal scar OS, and a large PED OD. The PED demonstrated subretinal fluid and treatment with Aflibercept was begun at and she was treated every two months for 4 iterations. BCVA was 20/50. Treatment was switched to monthly and after 2 injections she developed a RPE tear superior to the fovea, but not involving the fovea and the BCVA remained 20/50. After the next dose the patient returned with a second RPE tear in the same eye, with the tear inferior to the fovea (Figure 10). BCVA remained 20/60 (Figure 10).

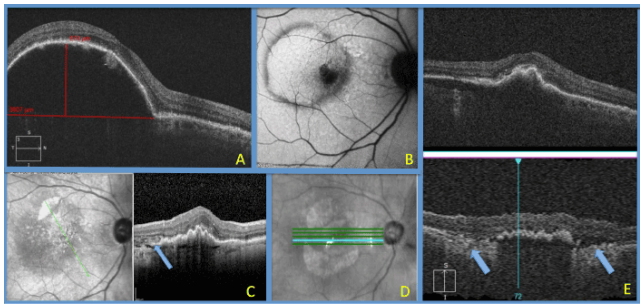

Figure 10: Patient 8: Before Treatment and After two tears, A: OCT demonstrating height of PED prior to RPE tear, B: FAF of PED; C: First small superior tear of PED as seen on infrared image after the 11th injection. Arrow indicates torn RPE, D: Two RPE tears seen on infrared image after the 12th injection, E: OCT images at 90 and 180 degree of the RPE tears seen in image D. The tears are seen in the inferior image with arrows indicating the absent RPE and increased transmission. The superior image shows the contracted RPE and flattened PED.

Results

Herein are described the clinical course of 8 patients (7 female and 1 male, age 67-85 years) (Table 1) who developed an RPE tear while being treated with IV Aflibercept. A review of the billing and coding sheets for the large retinal practice at which this review was conducted revealed approximately 996 patients treated for nvAMD by Aflibercept at the time of writing, with approximate 3196 injections performed on these patients. RPE tear was identified in 8 patients attributable to the IV Aflibercept injection by temporal relationship.

Patient Number	Age	Gender	Eye
1	75	Female	OS
2	72	Female	OD
3	85	Male	OS
4	67	Male	OS
5	69	Female	OD
6	80	Female	OS
7	83	Male	OD
8	74	Female	OD

Table 1: Patient Characteristics.

All patients had PEDs with an average maximal height of 475 um (172-874 μm). All PEDs were large, with a greatest linear diameter averaged at 3426 μm, ranging from 1004-5185 μm (Table 2).

Previously reported association of RPE tears are characteristics including associated Sub-Retinal Fluid, RPE folds, and Sub-Retinal Hemorrhage: all our patients had associated subretinal fluid; 4 of 8 had RPE folds and irregularities, and one had subretinal hemorrhage (Table 2).

	PED characteristics					
Patient No.	Maximal Height (um)	Largest Diameter (um)	Perpendicular Measurement (um)	Associated Sub-retinal Fluid	RPE folds	Sub-Retinal Hemorrhage
1	216	3290	3040	Yes	Yes	No
2	569	4390	4178	Yes	Yes	No
3	172	2721	2318	Yes	Yes	No
4	583	3142	2722	Yes	Yes	No
5	737	4252	3974	Yes	No	No
6	420	5185	3452	Yes	No	Yes
7	233	1004	996	Yes	No	No
8	874	>3670	>3500	Yes	No	No

Table 2: PED characteristics.

Four of the 8 patients treated experienced an RPE tear after the first injection of Aflibercept. Two of the 8 patients experienced an RPE tear after their very first intravitreal treatment with any anti-VEGF. Two patients had had more than 11 injections of Aflibercept prior to the RPE tear. Two patients had been previously treated with other anti-VEGF agent (one treated with bevacizumab, and one treated with ranibizumab) and tore on their second injection (Table 3).

Patient Number	Number of Aflibercept Doses Prior to Tear	Other AntiVEGF Agent (#)
1	1	Ranibizumab (1)
2	12	None
3	1	None
4	1	None
5	1	Bevacizumab (1)
6	2	None
7	12	None
8	7	None

Table 3: Patient treatment characteristics.

Discussion

The treatment of nvAMD in the setting of fvPED is a difficult therapuetic dilemma. Some patients have persistent fvPED, but maintain a good BCVA. Others have PED with chronic subretinal exudation and loss of BCVA. Fibro-vascular PED has been demonstrated to be more difficult to treat with current modalities (anti-VEGF) and with a worse visual outcome than serous PED [10].

There have been several large case series of patients with fvPED in the setting of AMD with suboptimal response to bevacizumab and/or ranibizumab, who were subsequently treated with aflibercept with better anatomic and visual outcomes [11,12]. In fact, it has been proposed that aflibercept may be a useful and effective treatment option in patients with persistent fluid and PEDs, despite IV ranibizumab treatment, due to its higher binding affinity and additional binding capacity to placental growth factor [11,12].

Nagiel et al. have well summarized the know risk factors for RPE tears, including: maximal height, surface area, greatest linear diameter, associated subretinal fluid, and RPE folds [6]. The summarized proposed mechanisms for tearing include: leakage from the CNV increasing the hydrostatic pressure, contraction of the CNV and fibrosis, sudden vitreomacular tractional forces, or rapid intraocular pressure shifts [6]. Early statistical work by Chiang et al. demonstrated that pre-injection basal diameter and height of the PED highly correlated with RPE tears and proposed that patients with highly vascularized PEDs (by FA or OCT analysis) should be alerted of this increased risk [14]. Most our patients' PEDs were large (average 516 μm), but there were ones that would not have been considered at risk for tears based on previous published data (at 236 and 276 μm). All of our patients had associated sub-retinal fluid. Four of 8 patients who developed an RPE tear had associated RPE folds; one patient had sub-retinal hemorrhage. These characteristics are generally in keeping with the known risk factors for developing an RPE tear.

Having a macular hemorrhage (MH), as Patient 6 did, has been demonstrated to be associated with RPE tear, but even patients who develop RPE tears demonstrate visual benefit from treatment with anti-VEGF agents [13]. While many patients with (MH) demonstrate an existing RPE tear, our patient did not initially have a tear, but did develop one following her second dose of Aflibercept. The final VA, however, was improved over her initial VA (20/100 from 20/200) after a short course of therapy with aflibercept.

Recent work by Sarraf et al. looking at the prospective risk factors for RPE tear after ranibizumab therapy demonstrated that these patients were older, average 78.8 years, and have large PEDs with an average height of 657 μm and greatest linear diameter of 5077 μm [15]. Our patients were also older, averaging 75 years. In contrast, our series found that RPE tears occurred with a lower maximal height and lesser greatest linear diameter (GLD) than the recent reported series for Ranibizumab (average height of 420 vs 657 μm, and GLD 3426 vs 5077 μm) [15]. Nevertheless, all reported patients in both series had associated sub-retinal fluid [15].

The problem of fvPED presents a clinical dilemma for both treating physician and patient. The incidence of RPE tear in fvPED is low (in the range of about 2%) but the effects are devastating [7]. In our clinical setting there were 8 patients who experienced an RPE tear out of approximately 996 patients (less than 1%) treated with a total of 3196 injections. The numbers of patients reflects an approximation as the data was pulled from billing sheet and coding, and may not reflect the total utilization of Aflibercept.

Fibrovascular PEDs are more greatly associated with worse visual outcomes and resistance to treatment, and carry with them a risk of tearing with any conventional treatment, or even spontaneously [1-8, 10-12]. It has been shown that aflibercept is effective at reducing fvPED volume and symptoms, including sub-foveal fluid, when other anti-VEGF agents have failed to do so [11,12]. Perhaps due to Aflibercept's biochemical characteristics it is more efficacious in treating resistant nvAMD lesions, such as PED. That increased efficaciousness, however, may result in a more robust response; 4 of 8 of our patients were treatment naïve and had the RPE tear after the first 1-2 doses of Aflibercept. Three of the patients who developed an RPE tear, had smaller (<300 μm) PEDs. The greater response evoked by Aflibercept may produce a tear in PEDs that we would have previously considered not high risk.

The greater binding affinity and additional binding mechanisms that the aflibercept compound possesses may be critical in its ability to decrease or even flatted fvPEDs; however, this could also potentially carry a greater risk of RPE tears as sudden fluid shifts (sudden fibrovascular contraction have been repeatedly proposed as risk factors) [6-9]. The deterioration of BVCA in suboptimally treated fvPED must be considered against the risk of RPE tear from a theoretically stronger treatment agent. Aflibercept has been shown to be effective in case series at reducing the fvPED volume and symptoms [11,12]. Our series shows that Aflibercept may also produce tears in the RPE in patients previously not considered at risk for RPE tears. More work is needed in elucidating the risk to benefit ratio for which agents concerning risk of tear, weighted out against more efficacious treatment of fvPED.

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