Comparison of switching treatment from ranibizumab to aflibercept and aflibercept to ranibizumab on serous pigment epithelial detachments due to age-related macular degeneration

Havva Kaldirim[1-2], Fatma Savur[2]

ABSTRACT

Purpose: To evaluate the effects of switching between vascular endothelial growth factor inhibitors (anti-VEGF) treatments in patients with extensive serous pigment epithelial detachment (sPED) due to neovascular age-related macular degeneration (nAMD).

Materials and Methods: This was a retrospective analysis of data where 38 patients (38 eyes) with fovea involving sPED of ≥200 µm measured manually using the caliper on the OCT due to AMD. The cases were divided into 2 groups. Group 1: included patients who were initially treated with intravitreal Ranibizumab (0.5 mg/0.05 ml) and then switched to intravitreal Aflibercept (2.0 mg/0.05ml). Group 2: included patients who were initially treated with intravitreal Aflibercept (2.0 mg/0.05ml) and then switched to intravitreal Ranibizumab (0.5 mg/0.05 ml). The outcome measures of best-corrected visual acuity (BCVA), PED height, PED width, the presence of subretinal fluid (SRF), intraretinal fluid (IRF), number of injections, and follow-up periods.

Results: At baseline, all patients in Group 1 had SRF. At switch, Group 1:22(%100) eyes, Group 2:16(%100) eyes had SRF. After the switch last visit, Group 1:11(%50) eyes, Group 2:8(%50) eyes had SRF (p=1.00). At baseline, Group 1:13(%59) eyes, Group 2:5(%31) eyes had IRF. At switch, Group 1: 1(%4.5) eyes, Group 2:1(%6) eyes had IRF. After switching the last visit, Group 1:1(%4.5) eyes, Group 2:1(%6) eyes had IRF (p= 0.816).

Conclusions: Our study found that both anti-VEGF switch treatments showed similar anatomical and functional effectiveness with a significant reduction in PED height and increases SRF, IRF absorption.

Keywords: Intraretinal fluid, Neovascular age-related macular degeneration, Pigment epithelial detachment, Subretinal fluid

INTRODUCTION

Active neovascular age-related macular degeneration (nAMD) may present with subretinal fluid (SRF), intraretinal fluid (IRF), and retinal pigment epithelial detachment (RPED). Studies have reported that RPED is seen in 63% to 80% of eyes with nAMD.[1,2] The pathophysiological mechanisms underlying the development of pigment epithelial detachment (PED) are not fully understood. PED probably represent a continuum of degenerative changes and formation of choroidal neovascularization (CNV).[3] RPED is categorized as angiographic, optical coherence tomographic (OCT), and clinically serous, drusenoid, and fibrovascular.[3] Serous PED (sPED) are thought to arise from the age-related formation of a hydrophobic barrier in Bruch's membrane preventing the free diffusion of fluid from retinal pigment epithelium (RPE) to choriocapillaris.[4]

Currently intravitreal injections of vascular endothelial growth factor inhibitors (anti-VEGF) are the gold standard for treatment in eyes with active nAMD. Current studies are aimed at evaluating the functional and anatomical response of anti-VEGF agents such as Ranibizumab,

1- MD, Istanbul Health Sciences University, Bagcilar Training and Research Hospital, Ophthalmology Department , Istanbul, Türkiye

2- MD, Istanbul Health Sciences University, Basaksehir Cam and Sakura City Hospital, Ophthalmology Department, Istanbul, Türkiye

Received: 24.05.2023
Accepted: 04.12.2023

J Ret-Vit 2024; 33: 39-50

DOİ: 10.37845/ret.vit.2024.33.7

Correspondence Adress:
Havva Kaldirim
Basaksehir Cam and Sakura City Hospital, Ophthalmology Department, P.O. Box 34200, Basaksehir, Istanbul, Türkiye
Phone: +90 212 909 6000
E-mail: drherdogan@hotmail.com

Aflibercept and Bevacizumab therapy in nAMD and the results of switching therapy between these agents.[5-7] Despite the remarkable advances made with anti-VEGF therapy, switching between existing anti-VEGF therapies is practiced in the presence of persistent fluid or recurrent exudation.[8] Neovascular age-related macular degeneration with PED is often considered a difficult subtype to treat. The resolution of PED has largely been unsatisfactory with treatments including laser, photodynamic therapy, intraocular gas, intravitreal triamcinolone, and anti-VEGF.[9-11]

There are few studies that demonstrate optimal therapy for serous PED associated with nAMD, and without treatment, significant loss of visual acuity is encountered in 40% to 50% of eyes over a mean of 9 to 10 months.[12] The purpose of this study is to compare the clinical results in patients with sPED associated with nAMD whose treatment was switched from Ranibizumab to Aflibercept (Group 1) and Aflibercept to Ranibizumab (Group 2).

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee of Health Sciences University Bagcılar Training and Research Hospital, numbered 2019.05.1.02.043/10.05.2019. All patients had given informed consent prior to inclusion in the study for the use of their data and strictly adhering to the tenets of the Declaration of Helsinki.

This retrospective, interventional case series included nAMD patients with sPED-height≥200µ who responded insufficiently to prior anti-VEGF therapy. All patients were treatment naïve before anti-VEGF therapy started and primarily received anti-VEGF therapy in three loadings and Pro-Re Nata (PRN) schedules. The decision to switch medication after insufficient response to anti-VEGF therapy was based on persisting intra- and/or subretinal fluid. Prior to the treatment switch, patients received either Ranibizumab (Lucentis ®, Novartis) (Lucentis; Genentech, Inc, South San Francisco, CA) or Aflibercept (Eylea@, Bayer) (Eylea; Regeneron, Tarrytown, NY), at least previous 12 months.

Inclusion and exclusion criteria

In this series, we identified eyes with active nAMD and sPED that were treated with intravitreal anti-VEGF injections between July 2014 to September 2019. The inclusion criteria were: 1) Patients older than 55 years, treatment-naïve nAMD with sPED 2) Patients initially treated with intravitreal Ranibizumab (0.5 mg/0.05 ml) and later switched to Aflibercept (2.0 mg/0.05 ml)(Group 1); 3) Patients initially treated with intravitreal Aflibercept (2.0 mg/0.05 ml) and later switched to Ranibizumab (0.5 mg/0.05 ml 2) (Group 2) 4) fovea involving serious PED; 3) minimum height of PED was 200 µm with persistent SRF and/or IRF at time of the switch, as observed on Spectral Domain OCT (SD-OCT) (Heidelberg Spectralis plus, Heidelberg Germany). Exclusion criteria were high myopia, uncontrolled glaucoma, subfoveal fibrosis, central geographic atrophy, presence of significant epiretinal membrane, vitreomacular traction, vascularized PED, drusenoid PED, retinal angiomatous proliferation, and polypoidal choroidal vasculopathy (PCV) in the study eye on SD-OCT imaging; the presence of any other ocular comorbidities such as a retinal artery or vein occlusions, uveitis, and macular edema from any other cause; and ocular surgery during the follow-up period of treatment.

Treatment protocol

In our standardized clinical protocol, all our naive patients received a serial of three monthly Ranibizumab or Aflibercept followed by a PRN schedule. The treatment protocol after the switch consisted of a fixed dosing regimen comprising of monthly injections for the first 3 months, followed by PRN injections in the last visit of treatment. Switching initial anti-VEGF was performed if: (1) there was a reduction in best-corrected visual acuity (BCVA) one Snellen line, (2) there was an increase in PED height (3) there was persistence or recurrence of SRF, IRF on SD-OCT. Topical antibiotics were administered to all patients four times a day for five days after the injection. All patients were examined monthly.

Baseline evaluation

Baseline characteristics were recorded for age, sex, initial anti-VEGF. At each visit, the patients were assessed for BCVA using the Snellen chart, intraocular pressure measurement (Goldman applanation tonometer), anterior segment assessment, and dilated fundoscopy. BCVA was converted to the minimum angle of resolution (logMAR) for statistical analysis. Patients had fundus fluorescein angiography (FFA) (Zeiss FF 450 plus, Carl Zeiss Meditec AG, Jena, Germany) at baseline and SD-OCT imaging with cube scan at each visit. (Figure 1) Patients also had indocyanine green angiography (ICG) (Zeiss FF 450 plus, Carl Zeiss Meditec AG, Jena, Germany). FFA was repeated during the follow-up period if necessary. The PED height and width were measured manually using the caliper on the SD-OCT software. (Figure 2) The PED height was

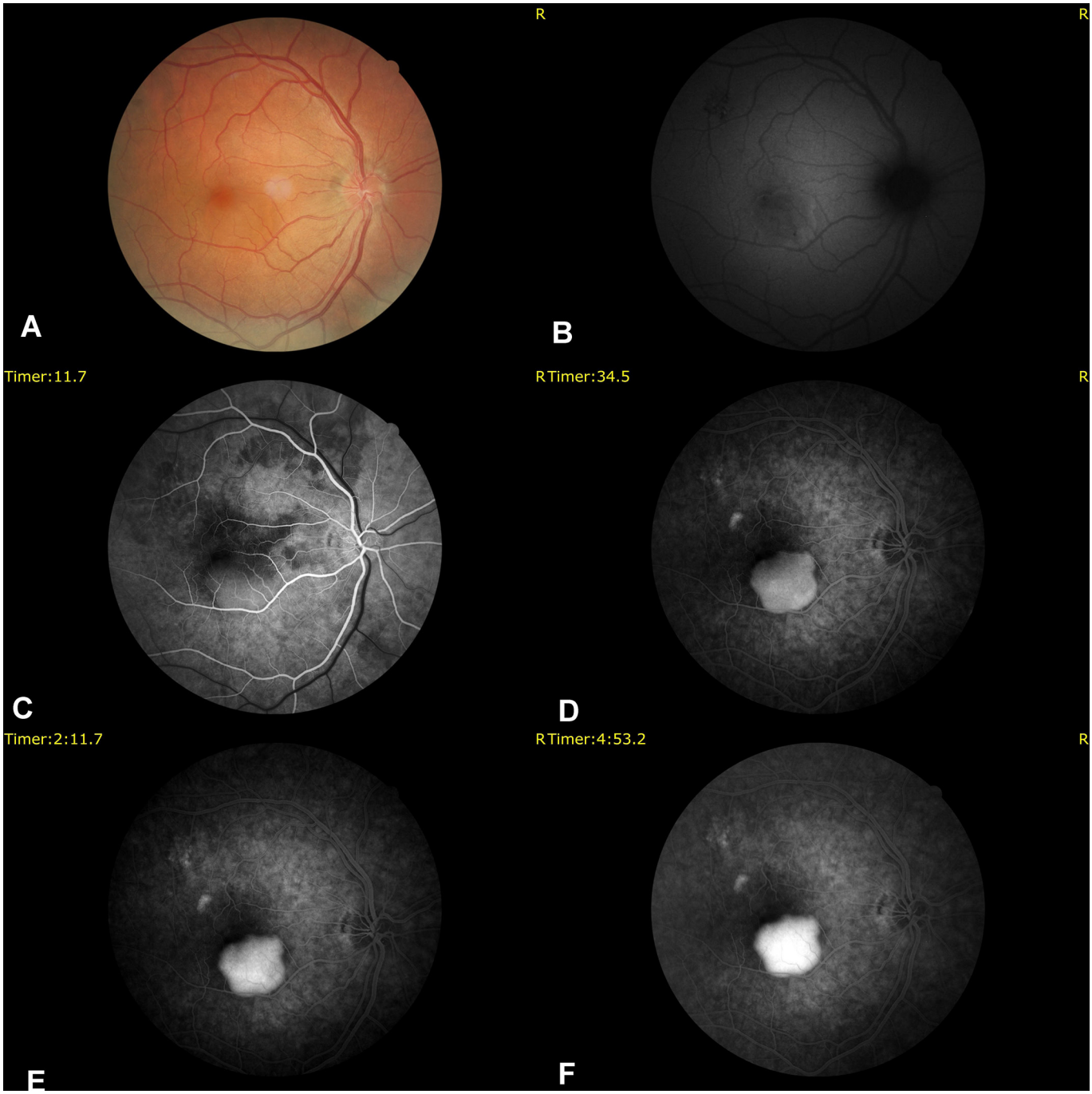

Figure 1: *Fundus fluorescein angiography (FFA) images of the right eye of a patient included in our study during the study period, (A) Color fundus image of pigment epithelial detachment (PED). (B) Autofluorescence image shows hypoautofluorescent PED surrounded by a hyperautofluorescent ring (C,D,) Early hyperfluorescent image of PED in FFA, (E-F) Increase in hyperfluorescence image in the PED region in the middle and late periods on FFA*

measured as the maximum vertical distance from the base of the RPE to Bruch's membrane. PED width was measured as the horizontal PED diameter between two points of RPE elevation at the position of greatest PED height. The variables BCVA, PED height, PED width, presence of intraretinal fluid (IRF), subretinal fluid (SRF) number of injections and follow-up periods; pre-switch, at the switch, and after switch last follow up visit were recorded.

Outcome measures

Outcome measures were changes in sPED dimensions (maximum PED height and maximum horizontal diameter) in micrometers, BCVA, reduction of SRF and IRF from baseline to pre-switch 3rd, 6 months, at the switch, after switch 3, 6 months and last visits. The secondary outcome measures were injection number and follow-up time during the study period treatment in each group.

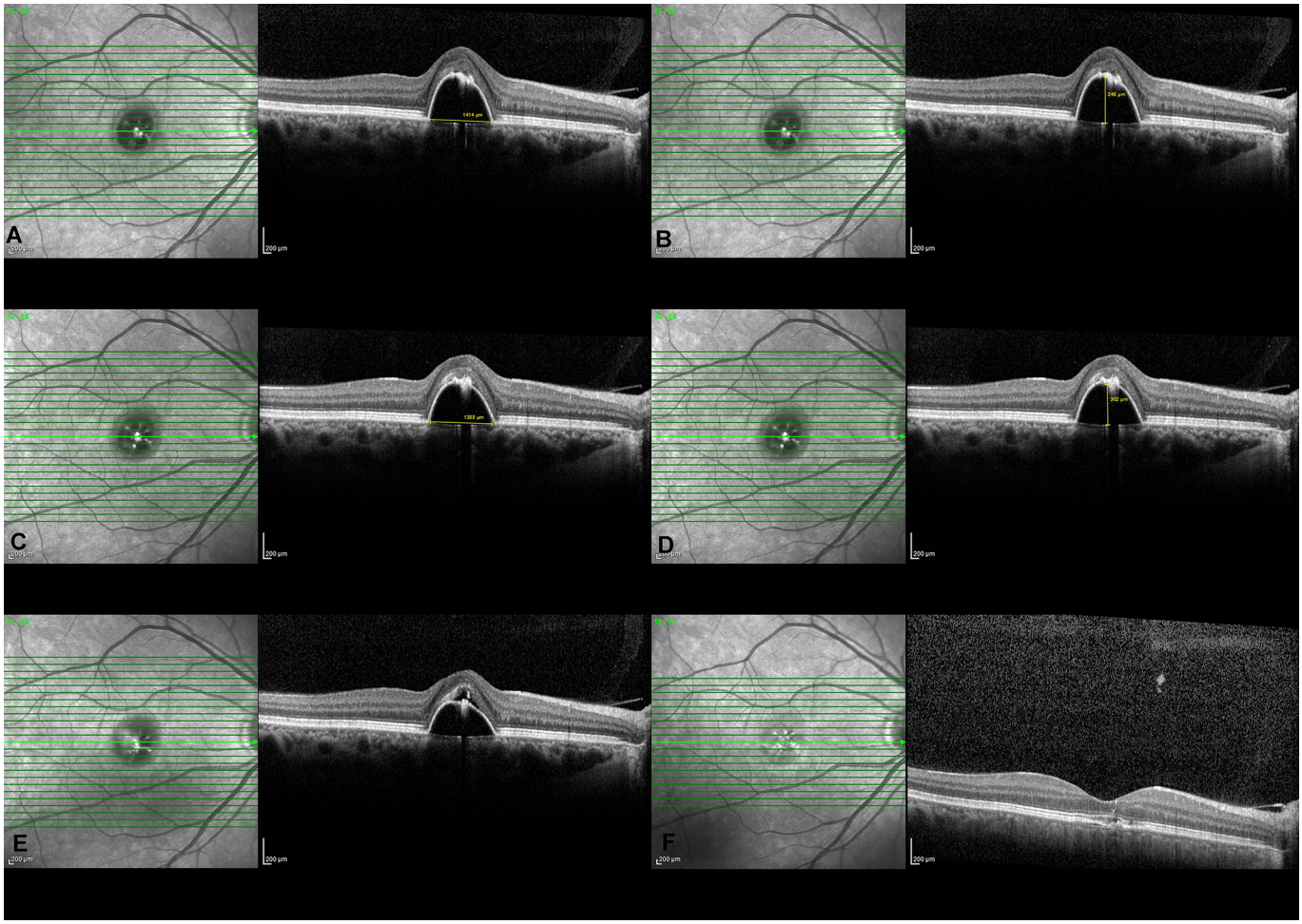

Figure 2: *Optical coherence tomography (OCT) images of a patient in our study during the study period, (A, B) pigment epithelial detachment (PED) width and height measurement in the patient's initial OCT, (C,D) PED width and height measurement in the OCT at the 6th month before the anti-VEGF switch , (E) PED and subretinal fluid (SRF) appearance during anti-VEGF change, (F) OCT image at the last examination, both PED and SRF were completely resolved*

Statistical analysis

Mean, standard deviation, median, minimum, maximum value frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. Independent Samples t-test and Mann-Whitney U test were used for the comparison of quantitative data. Wilcoxon tests were used for the repeated measurement analysis. The Chi-Square test was used for the comparison of qualitative data. SPSS 27.0 (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) was used for statistical analyses.

RESULTS

A total of 38 patients with nAMD and sPED, including 22 eyes (22) group 1 (switching from Ranibizumab to Aflibercept) and 16 eyes group 2 (switching from Aflibercept to Ranibizumab), were included. The age, median of group 1 was 61.8 ± 6 years and 61.6 ± 5.3 was group 2. Ten (45.5%) patients were female and 12 were male (54.5%) in group 1, ın group 2, 8(50%) patients were female and 8 (%50) patients were male. The patient demographic and clinical characteristics are summarized in Table 1.

Both groups were a similar baseline BCVA. In both groups, a significant increase was observed in BCVA at the 3rd month, 6th month, and at the time of switch compared to baseline. There was no statistical significance between the groups in terms of BCVA changes at the 3rd, 6th months and at the time of the switch. In group 1 and group 2, 3rd month, 6th month post-switch, the last control BCVA value increased significantly compared to the switch time. After the switch, the increase in BCVA at the 3rd, 6th months, and last follow-up visits was not significantly different between the groups. (Table 2, Figure 3).

In both groups, PED height decreased significantly at the 3rd month, 6th month, and transition time compared to baseline, but this decrease did not differ significantly

Table 1: *Demographic and clinical characteristics of patients between groups, duration of disease before and after switch, number of injections, subretinal fluid (SRF), intraretinal fluid (IRF), statistical results of change.*

		Group I			Group II			
		Mean±sd	/n-%	Median	Mean±sd	/n-%	Median	p
Age		61.8±6.0		61.0	61.6±5.3		61.5	0.938[t]
Gender	Female	10	45.5%		8	50.0%		0.782[X²]
	Male	12	54.5%		8	50.0%		
Eye-Side	Right	11	50.0%		8	50.0%		1.000[X²]
	Left	11	50.0%		8	50.0%		
Lens Status	Phakic	15	68.2%		11	68.8%		0.970[X²]
	Pseudophakic	7	31.8%		5	31.3%		
Other Eye	CNV	6	27.3%		4	25.0%		0.962 [X²]
	D-AMD	10	45.5%		8	50.0%		
	GA	6	27.3%		4	25.0%		
Duration of Treatment								
Before Switch		18.7 ±5.6		18.0	20.1 ± 4.6		20.0	0.229[m]
After Switch		18.7 ±4.9		18.0	18.5 ± 4.5		17.0	0.917[m]
Number of Injection								
Before Switch		10.8 ± 3.1		10.0	10.8 ±2.3		11.0	0.765[m]
After Switch		11.0 ± 2.1		11.0	11.7 ±2.7		12.0	0.241m
SRF								
Baseline	(+)	22	100.0%		16	100.0%		1.000[X²]
At Switch	(+)	22	100.0%		16	100.0%		1.000[X²]
Last-Visit	(-)	11	50.0%		8	50.0%		1.000[X²]
	(+)	11	50.0%		8	50.0%		
IRF								
Baseline	(-)	9	40.9%		11	68.8%		0.090[X²]
	(+)	13	59.1%		5	31.3%		
At Switch	(-)	21	95.5%		15	93.8%		1.000[X²]
	(+)	1	4.5%		1	6.3%		
Last Visit	(-)	21	95.5%		15	93.8%		1.000[X²]
	(+)	1	4.5%		1	6.3%		
T.Protocol Pre-Switch 3+PRN		22	100.0%		16	100.0%		1.000[X²]
T.Protocol Post-Switch 3+PRN		22	100.0%		16	100.0%		1.000[X²]

[m] Mann-whitney u test / [t] Independent Samples t test / [X²] Chi-square (Fischer test)

between the groups. In Group 2, PED height at the 3rd month after the transition did not show a significant change according to the transition time, while a significant decrease was observed in the PED height at the 6th month and at the last control compared to the transition time. PED height drop was significantly higher in group 1 than in group 2 at 3 months post-transition. The decrease in PED height at 6 months post-transition and at the final follow-up was not significant between the groups. (Table 3, Figure 4)

While there was no significant difference in PED width at the 3rd month post-transition in both groups according to the transition time, a significant decrease was observed in the PED width at the 6th month after the transition and at the last follow-up. The change in PED width between group 1 and group 2 did not differ significantly between groups at 3rd, 6th months before switching, at the time of transition, and at 3rd months and 6th months after switching. (Table 4, Figure 5).

Table 2: *Statistical comparison results of best-corrected visual acuity (BCVA) change in both groups.*

	Group I		Group II		
	Mean±sd	Median	Mean±sd	Median	p
Baseline	0.41 ± 0.21	0.40	0.42 ± 0.23	0.45	0.881[m]
3 Month	0.32 ± 0.18	0.30	0.31 ± 0.18	0.35	0.892[m]
6 Month	0.32 ± 0.19	0.30	0.31 ± 0.19	0.30	0.881[m]
At Switch	0.38 ± 0.18	0.40	0.36 ± 0.20	0.40	0.833[m]
Difference With Baseline					
3 Month	-0.10 ± 0.07	-0.10	-0.11 ± 0.10	-0.10	0.743[m]
Intra Group Difference p Value	***0.000***	[w]	***0.002***	[w]	
6 Month	-0.09 ± 0.06	-0.10	-0.11 ± 0.09	-0.10	0.826[m]
Intra Group Difference p Value	***0.000***	[w]	***0.001***	[w]	
At Switch	-0.04 ± 0.07	0.00	-0.06 ± 0.07	0.00	0.460[m]
Intra Group Difference p Value	***0.021***	[w]	***0.014***	[w]	
BCVA After Switch					
At Switch	0.38 ± 0.18	0.40	0.36 ± 0.20	0.40	0.833[m]
3 Month	0.33 ± 0.19	0.35	0.31 ± 0.20	0.35	0.869[m]
6 Month	0.33 ± 0.19	0.35	0.32 ± 0.19	0.35	0.904[m]
Last Visit	0.32 ± 0.19	0.35	0.32 ± 0.19	0.35	0.988[m]
Difference With At Switch					
3 Month	-0.05 ± 0.05	-0.05	-0.05 ± 0.05	-0.05	1.000[m]
Intra Group Difference p Value	***0.001***	[w]	***0.005***	[w]	
6 Month	-0.05 ± 0.05	-0.05	-0.04 ± 0.05	0.00	0.707[m]
Intra Group Difference p Value	***0.001***	[w]	***0.008***	[w]	
Last Visit	-0.06 ± 0.07	-0.05	-0.04 ± 0.05	0.00	0.547[m]
Intra Group Difference p Value	***0.002***	[w]	***0.008***	[w]	

[m] Mann-whitney u test / [w]Wilcoxon test

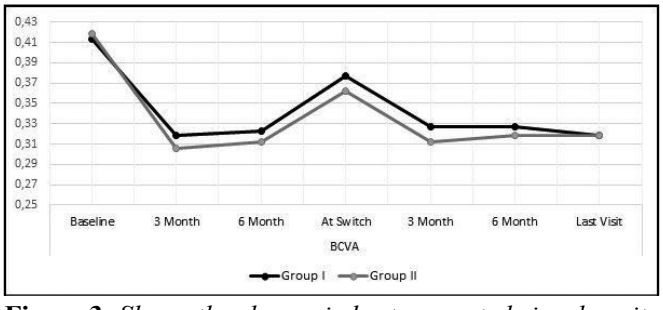

Figure 3: *Shows the change in best-corrected visual acuity (BCVA) in the two groups during the study period.*

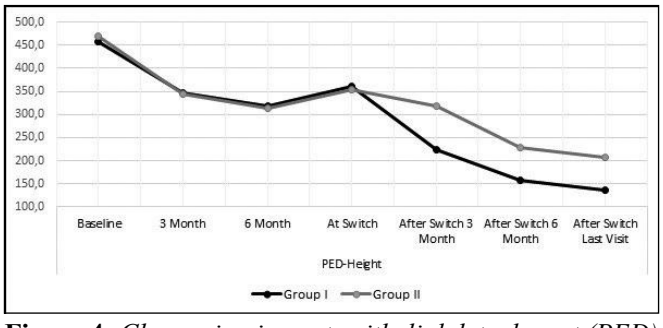

Figure 4: *Change in pigment epithelial detachment (PED) height in the two groups over time.*

At the last follow-up after the switch which PED height was below 350 microns completely regressed in 8 (36.4%) eyes in group 1 and 5 (31.3%) eyes in group 2.

After the last control, 11 (50%) eyes in group 1 had SRF and 1 (4.5%) eye had IRF. Group 2 had SRF in 8 (50%) eyes and IRF in 1 (6.3%) eye. There is no statistically significant difference between the two groups in terms of SRF and IRF changes at baseline, at the switch, and after-switch last visits. (Table 1).

The median number of intravitreal injections and follow-up times before and after the transition in Group 1 and Group 2 are given in Table 1. After the switch in group 1, the

Table 3: *Statistical comparison results of pigment epithelial detachment (PED) height change in both groups.*

	Group I		Group II		
	Mean±sd	Median	Mean±sd	Median	p
Baseline	457.8 ± 114.6	429.0	468.7 ± 158.8	416.5	0.859[m]
3 Month	346.6 ± 103.6	330.0	344.1 ± 93.8	313.5	0.734[m]
6 Month	317.9 ± 124.4	315.5	313.6 ± 147.6	267.0	0.615[m]
At Switch	361.2 ± 112.4	343.5	352.9 ± 156.7	306.5	0.515[m]
Difference With Baseline					
3 Month	-111.2 ± 122.2	-57.0	-124.6 ± 96.1	-108.5	0.249[m]
Intra Group Difference p Value	***0.000***	[w]	***0.000***	[w]	
6 Month	-140.0 ± 159.3	-60.0	-155.1 ± 129.0	-159.0	0.515[m]
Intra Group Difference p Value	***0.000***	[w]	***0.001***	[w]	
At Switch	-96.6 ± 122.2	-60.5	-115.8 ± 151.1	-97.0	0.657[m]
Intra Group Difference p Value	***0.003***	[w]	***0.003***	[w]	
PED-Height-After Switch					
At Switch	361.2 ± 112.4	343.5	352.9 ± 156.7	306.5	0.515[m]
3 Month	224.0 ± 101.0	224.0	319.1 ± 192.9	244.0	0.307[m]
6 Month	158.5 ± 118.6	201.0	229.8 ± 218.2	182.0	0.485[m]
Last Visit	135.7 ± 122.4	163.5	206.9 ± 232.6	121.5	0.450[m]
Difference With At Switch					
3 Month	-137.2 ± 89.3	-135.5	-33.8 ± 116.8	-18.0	***0.005***[m]
Intra Group Difference p Value	***0.000*** [w]		0.156 [w]		
6 Month	-202.7 ± 114.2	-171.5	-123.1 ± 165.0	-118.5	0.069[m]
Intra Group Difference p Value	***0.000***	[w]	***0.006***	[w]	
Last Visit	-225.5 ± 118.4	-219.5	-145.9 ± 184.3	-159.0	0.174[m]
Intra Group Difference p Value	***0.000***	[w]	***0.013***	[w]	

[m] Mann-whitney u test / [w] Wilcoxon test

median number of intravitreal injections was 11 (11±2.1). The median follow-up time after the first Aflibercept injection after switching to Aflibercept was 18 months (18.7 ± 4.9). After the switch in group 2, the median number of intravitreal injections was 12 (11.7 ± 2.7). The median follow-up time after the first Ranibizumab injection after switching to Ranibizumab was 17 months (18.5±4.5). There was no significant difference between the groups in terms of mean number of injections, pre- and post-transition follow-up times. (Table 1).

None of the study eyes experienced any serious adverse events following anti-VEGF therapy.

DISCUSSION

Intraretinal edema and subretinal fluid are the main causes of decreased vision in neovascular age-related macular degeneration. These factors can be effectively reduced by anti-VEGF therapy. Conversely, serous PED patients have intra- and subretinal as well as sub-RPE fluid. It is known that the presence of sPED complicates the response to standard treatment in patients. Currently, sPED is generally considered to require long-term anti-VEGF therapy for optimal response.

Many studies have reported reductions in PED height, SRF and IRF resolution, and anatomical improvement nAMD-related PED with Bevacizumab, Ranibizumab, and Aflibercept.[13-19] Freeman et al. He reported no statistically significant change in SRF and IRF resorption or improvement in visual acuity in the PED and non-PED groups administered Bevacizumab.[14] Chevreaud et al. reported that Ranibizumab improved anatomical and functional outcomes in patients with nAMD-related

Table 4: *Statistical comparison results of pigment epithelial detachment (PED) width change in both groups.*

	Group I		Group II		
	Mean±sd	Median	Mean±sd	Median	p
PED-Width					
Baseline	747.7± 233.6	778.0	745.8± 194.3	768.0	0.801[m]
3 Month	770.4± 253.3	788.5	751.1± 188.8	783.5	0.711[m]
6 Month	774.5± 248.8	794.5	756.9± 181.7	783.5	0.756[m]
At Switch	761.1± 257.0	794.5	754.6± 180.6	789.5	0.976[m]
Difference With Baseline					
3 Month	22.7± 38.3	2.5	5.4± 35.1	1.0	0.281[m]
Intra Group Difference p Value	***0.001*** [w]		0.182 [w]		
6 Month	26.8± 39.3	11.0	11.1± 38.0	11.0	0.847[m]
Intra Group Difference p Value	***0.001*** [w]		***0.016*** [w]		
At Switch	13.4± 69.5	10.5	8.8± 51.8	11.0	0.636[m]
Intra Group Difference p Value	***0.027*** [w]		0.301 [w]		
PED-Width-After Switch					
At Switch	761.1± 257.0	794.5	754.6± 180.6	789.5	0.976[m]
3 Month	727.6± 288.0	737.5	749.7± 195.1	779.0	0.779[m]
6 Month	588.6± 443.1	689.0	501.7± 447.8	621.5	0.602[m]
Last Visit	517.7± 478.1	582.0	496.9± 451.9	621.5	0.916[m]
Difference With At Switch					
3 Month	-33.5± 119.6	0.0	-4.9± 60.7	0.5	0.834[m]
Intra Group Difference p Value	0.910 [w]		0.814 [w]		
6 Month	-172.5± 276.6	-2.0	-252.9± 336.8	-31.0	0.391[m]
Intra Group Difference p Value	***0.043*** [w]		***0.025*** [w]		
Last Visit	-243.4± 288.7	-121.0	-257.7± 339.3	-41.0	0.941[m]
Intra Group Difference p Value	***0.003*** [w]		***0.026*** [w]		

[m] Mann-whitney u test / [w] Wilcoxon test

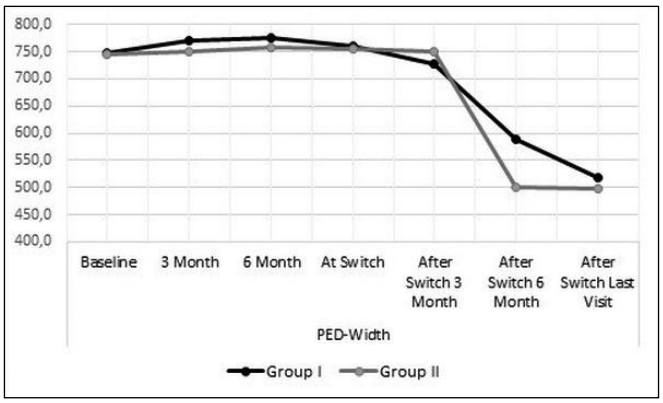

Figure 5: *Change in pigment epithelial detachment (PED) widht in the two groups over time*

PED.[20] Arora et al. reported 12-month results of intravitreal Ranibizumab therapy for large, sPED associated with age-related macular degeneration and occupying more than 50% of the total lesion area.[21]

Although the PED elevation in the study tended to decrease with treatment, it did not completely resolve in any case.[22] Inoue et al. reported that Ranibizumab was effective in stabilizing vision in their study in which they evaluated the prognosis of neovascular age-related macular degeneration according to pigment epithelial detachment type and the response to intravitreal Ranibizumab.[22] Regarding PED elevation, a decrease in maximum PED height was observed in all eyes (%100) in the serous and mixed PED group, 17 eyes (60.7%) in the fibrovascular PED group, and 9 eyes (90.0%) in the hemorrhagic PED group 100 µm or more.

PED response to IVR was not correlated with final BCVA. Although it is important to consider the type of PED to predict visual acuity in patients treated with intravitreal ranibizumab, the anatomical response of the PED may not be directly related to visual outcome.[22] According to Panos et al. reported that Ranibizumab is an effective and safe treatment for improving vision in patients with serous PED, but anatomical response is not directly related to visual outcome.[23]

There is limited evidence in both the retrospective and prospective literature supporting the concept that higher dosages of various anti-VEGF agents, delivered either as more frequent dosing or as a greater dosage, may lead to a more rapid or more improved anatomical response. However, there is no evidence that this correlates with an improvement in vision. As with the administration of higher dosages of antiVEGF agents, switching anti-VEGF agents may result in additional anatomical improvement, but vision typically remains stable in eyes with treatmentresistant PEDs. Lesions defined as fibrovascular PEDs may be a more difficult subtype to treat, but even these difficult-to-treat eyes can have significant vision improvements with anti-VEGF therapy. Chan et al. the results of 0.5 mg and 2.0 mg intravitreal injections of Ranibizumab in patients with AMD-related vascularized PED were compared. Intravitreal high-dose (2 mg) Ranibizumab resulted in faster resolution of choroidal neovascularization and associated retinal pigment epithelial detachment in eyes with exudative age-related macular degeneration.[24] However, at the end of the study, both doses had similar visual and anatomical results. RPE tears developed more frequently in the intravitreal high dose (2 mg) Ranibizumab group.[24] According to Sarraf et al. reported visual and anatomical results at 24 months for the presence and height of pigment epithelial detachments (PEDs) at baseline in neovascular age-related macular degeneration (AMD) patients treated with 0.5 g and 2 mg Ranibizumab. In neovascular AMD patients, regardless of PED status and height, significant initial visual gains were achieved with Ranibizumab 0.5 mg monthly, but no additional visual benefit with higher dose Ranibizumab (2.0 mg).[25] In addition, complete resolution of PED has been associated with macular atrophy and a worse overall visual acuity outcome, suggesting that curative therapy may not be beneficial for all patients.[24,26,27] Treatment for PED due to nAMD is constantly evolving, with additional evidence emerging from both clinical and real-world settings. Based on the findings of the current comprehensive review of anti-VEGF therapies for PED in eyes with nAMD, the authors recommend the treatment of PED cases in which IRF and/or SRF are detected simultaneously as biomarkers of exudative activity. In addition, cases in which visual acuity and PED stabilize in the absence of fluid can be followed or continued without additional treatment. In some cases, PED treatment without SRF and/or IRF may be considered, as with a documented increase in PED size or volume or associated vision loss.

Some studies comparing Aflibercept and Ranibizumab treatments reported a greater reduction in PED height at 1 year in the Aflibrcept group compared with Ranibizumab.[17,19] It has been reported that Aflibercept showed greater reduction in PED height but no difference in visual acuity compared to both Ranibizumab and Bevacizumab.[13,23] In our study, we found that untreated eyes with large sPED and nAMD showed similar anatomical and functional responses to both groups before and during the transition period.

Pharmacological differences in drugs and their ability to bind to different receptors in the retina led to monitoring the effectiveness of the recently introduced Aflibercept in resistant patients. Treating patients effectively and preventing permanent vision loss are among the most important reasons for switching treatment. The effect of switching treatment from Ranibizumab or Bevacizumab to Aflibercept is currently being reported in recent studies.[28-34] Most studies showed reduction in PED size and reduction in SRF and IRF but the effect of the switch on visual acuity proved to be variable. Some studies reported improvement in vision.[28,29] Whereas others reported no change or worsening of vision.[30-32] These patients usually had persistent SRF, IRF, PED and some degree of RPE atrophy to retina due to long term anti-VEGF use and disease process itself. Some patients had shown good earlier response but later reached a plateau due to tachyphylaxis or tolerance. Simader et al. it has been reported that although the transition from Ranibizumab to Aflibercept was morphologically successful, it was not functionally successful.[35] They thought that this was due to previous irreversible retinal damage.

These observations contribute to early outcomes however it's difficult to draw parallels and uniform conclusion. Often, protocol-mandated treatment regimens in clinical trials differ from those used in the real-world setting. As such, clinical trial findings may not be truly representative of the treating physician experience; however, it is important to gain knowledge and insight from clinical trial results. Because Aflibercept is licensed after Ranibizumab,

there has been a substantial number of studies switching from Ranibizumab to Aflibercept, but not many studies evaluating the transition from Aflibrcept to Ranibizumab. Marquis et al.[36] reported that PED, IRF, and SRF showed significantly different positive changes at 3th months after switching to ranibizumab in patients with aflibercept-resistant nAMD. Rouvas et al.[37] reported that six months of ranibizumab treatment resulted in a statistically significant improvement in visual acuity and baseline diameter of PED, with no change in central macular thickness, in patients with inadequate response to Aflibercept.

In our study, patients with nAMD accompanied by sPED were switched to patients whose SRF and IRF continued for at least 1 year after the start of the first treatment. In our study, SRF was present in 100% of the cases in both groups at the time of transition. We found complete resolution of sPED in 36.4% eyes in group 1 and %31.3 in group 2. There was no statistical difference in both groups in terms of pre- and post-switching BCVA, PED height, PED width, mean follow-up times and injection numbers. Our paper adds strength to outcomes in switching treatment to different anti-VEGF drug in recalcitrant CNV with PED with substantial follow-up before and after switch.

In conclusion, patients presenting with sPED today remain a diagnostic and therapeutic challenge, and unfortunately there is no generally accepted treatment protocol. Treatment should focus on achieving improvements in visual acuity, reduction SRF and IRF, not necessarily complete resolution of PED because there is no apparent correlation between anatomical and functional improvement in most eyes with PED and nAMD. Our study also adds that recalcitrant PEDs which remain high after ranibizumab treatment may be less likely to respond to further Aflibercept injections. We detected increased visual acuity in cases with ongoing sPED but decreased or completely resorbed SRF and IRF. Further, When BCVA and sPED size are stable, with no IRF or SRF, observation seems to be a reasonable approach. Moreover, cases in which visual acuity and PED stabilize in the absence of fluid may be observed without additional treatment. In special circumstances, as with a documented increase in size or volume of the PED, or associated vision loss, treatment of a PED without clear SRF and/or IRF can be considered.

Our study is a study comparing the results of switching from Aflibercept to Ranibizumab and from Ranibizumab to Aflibercept. There are not many studies on this subject in the literature. To objectively assess the variation between anti-VEGF therapies, it would be helpful to have longer-term and more patient studies reporting the results of switching from Aflibercept to Ranibizumab and from Ranibizumab to Aflibercept.

Acknowledgements

Not applicable.

Funding: None

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Coscas F, Coscas G, Souied E, et al. Optical coherence tomography identification of occult choroidal neovascularization in age-related macular degeneration. Am J Ophthalmol 2007;144:592-529. https://doi.org/10.1016/j.ajo.2007.06.014
2. Schmidt-Erfurth U, Waldstein SM, Deak GG, et al. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. Ophthalmology 2015;122:822-32. https://doi.org/10.1016/j.ophtha.2014.11.017
3. Zayit-Soudry S, Moroz I, Loewenstein A. Retinal pigment epithelial detachment. Surv Ophthalmol 2007;52:227-43. https://doi.org/10.1016/j.survophthal.2007.02.008
4. Bird AC. Doyne Lecture. Pathogenesis of retinal pigment epithelial detachment in the elderly; the relevance of Bruch's membrane change. Eye (Lond) 1991;5(Pt 1):1-12. https://doi.org/10.1038/eye.1991.2
5. Mitchell P, Korobelnik JF, Lanzetta P, et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol 2010;94:2-13. https://doi.org/10.1136/bjo.2009.159160
6. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537-48. https://doi.org/10.1016/j.ophtha.2012.09.006
7. Bashshur ZF, Haddad ZA, Schakal AR, et al. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: the second year of a prospective study. Am J Ophthalmol 2009;148:59-65.e1. https://doi.org/10.1016/j.ajo.2009.02.006
8. Gasperini JL, Fawzi AA, Khondkaryan A, et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol 2012;96:14-20. https://doi.org/10.1136/bjo.2011.204685
9. Gross-Jendroska M, Flaxel CJ, Schwartz SD, et al. Treatment of pigment epithelial detachments due to age-related macular degeneration with intra-ocular C3F8 injection. Aust N Z J Ophthalmol 1998;26:311-7. https://doi.org/10.1111/j.1442-9071.1998.tb01335.x
10. Axer-Siegel R, Ehrlich R, Rosenblatt I, et al. Photodynamic therapy for occult choroidal neovascularization with pigment epithelium detachment in age-related macular degeneration.

Arch Ophthalmol 2004;122:453-9. https://doi.org/10.1001/archopht.122.4.453

11. Nicolò M, Ghiglione D, Lai S, et al. Intravitreal triamcinolone in the treatment of serous pigment epithelial detachment and occult choroidal neovascularization secondary to age-related macular degeneration. Eur J Ophthalmol 2005;15:415-9. https://doi.org/10.5301/EJO.2008.3735
12. Pauleikhoff D, Löffert D, Spital G, et al. Pigment epithelial detachment in the elderly. Clinical differentiation, natural course and pathogenetic implications. Graefes Arch Clin Exp Ophthalmol 2002;240:533-8. https://doi.org/10.1007/s00417-002-0505-8
13. Au A, Parikh VS, Singh RP, et al. Comparison of anti-VEGF therapies on fibrovascular pigment epithelial detachments in age-related macular degeneration. Br J Ophthalmol 2017;101:970-5. https://doi.org/10.1136/bjophthalmol-2016-309434
14. Freeman WR, Kozak I, Yuson RM, et al. Prognosti implications of pigment epithelial detachment in bevacizumab (avastin)-treated eyes with age-related macular degeneration and choroidal neovascularization. Retina 2011;31:1812-8. https://doi.org/10.1097/IAE.0b013e31821987a4
15. Giansanti F, Bacherini D, Giacomelli G, et al. Intravitreal anti-VEGF therapy for vascularized pigment epithelium detachment in age-related macular degeneration. Eur J Ophthalmol 2014;24:402-8. https://doi.org/10.5301/ejo.5000388
16. Baba T, Kitahashi M, Kubota-Taniai M, et al. Two-year course of subfoveal pigment epithelial detachment in eyes with age-related macular degeneration and visual acuity better than 20/40. Ophthalmologica 2012;228:102-9. https://doi.org/10.1159/000337251
17. Cho HJ, Kim KM, Kim HS, et al. Response of Pigment Epithelial Detachment to Anti-Vascular Endothelial Growth Factor Treatment in Age-Related Macular Degeneration. Am J Ophthalmol 2016;166:112-9. https://doi.org/10.1016/j.ajo.2016.03.039
18. Dirani A, Ambresin A, Marchionno L, et al. Factors Influencing the Treatment Response of Pigment Epithelium Detachment in Age-Related Macular Degeneration. Am J Ophthalmol 2015;160:732-8.e2. https://doi.org/10.1016/j.ajo.2015.06.025
19. Balaskas K, Karampelas M, Horani M, et al. Quantitative analysis of pigment epithelial detachment response to different anti-vascular endothelial growth factor agents in wet age-related macular degeneration. Retina 2017;37:1297-304. https://doi.org/10.1097/IAE.0000000000001342
20. Chevreaud O, Oubraham H, Cohen SY, et al. Ranibizumab for vascularized pigment epithelial detachment: 1-year anatomic and functional results. Graefes Arch Clin Exp Ophthalmol 2017;255:743-51. https://doi.org/10.1007/s00417-016-3564-y
21. Arora S, McKibbin M. One-year outcome after intravitreal ranibizumab for large, serous pigment epithelial detachment secondary to age-related macular degeneration. Eye (Lond) 2011;25:1034-8. https://doi.org/10.1038/eye.2011.115
22. Inoue M, Arakawa A, Yamane S, et al. Variable response of vascularized pigment epithelial detachments to ranibizumab based on lesion subtypes, including polypoidal choroidal vasculopathy. Retina 2013;33:990-7. https://doi.org/10.1097/IAE.0b013e3182755793
23. Panos GD, Gatzioufas Z, Petropoulos IK, et al. Effect of ranibizumab on serous and vascular pigment epithelial detachments associated with exudative age-related macular degeneration. Drug Des Devel Ther 2013;7:565-9. https://doi.org/10.2147/DDDT.S46610
24. Chan CK, Abraham P, Sarraf D, et al. Earlier therapeutic effects associated with high dose (2.0 mg) Ranibizumab for treatment of vascularized pigment epithelial detachments in age-related macular degeneration. Eye (Lond) 2015;29:80-7. https://doi.org/10.1038/eye.2014.233
25. Sarraf D, London NJ, Khurana RN, et al. Ranibizumab Treatment for Pigment Epithelial Detachment Secondary to Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of the HARBOR Study. Ophthalmology 2016;123:2213-24. https://doi.org/10.1016/j.ophtha.2016.07.007
26. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2014;121:2181-92. https://doi.org/10.1016/j.ophtha.2014.05.009
27. Sarraf D, Chan C, Rahimy E, et al. Prospective evaluation of the incidence and risk factors for the development of RPE tears after high- and low-dose ranibizumab therapy. Retina 2013;33:1551-7. https://doi.org/10.1097/IAE.0b013e31828992f5
28. Kumar N, Marsiglia M, Mrejen S, et al. Visual and anatomical outcomes of intravitreal aflibercept in eyes with persistent subfoveal fluid despite previous treatments with ranibizumab in patients with neovascular age-related macular degeneration. Retina 2013;33:1605-12. https://doi.org/10.1097/IAE.0b013e31828e8551
29. Patel KH, Chow CC, Rathod R, et al. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. Eye (Lond) 2013;27:663-667. https://doi.org/10.1038/eye.2013.31
30. Gharbiya M, Iannetti L, Parisi F, et al. Visual and anatomical outcomes of intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. Biomed Res Int 2014;2014:273754. https://doi.org/10.1155/2014/273754
31. Grewal DS, Gill MK, Sarezky D, et al. Visual and anatomical outcomes following intravitreal aflibercept in eyes with recalcitrant neovascular age-related macular degeneration: 12-month results. Eye (Lond) 2014;28:895-9. https://doi.org/10.1038/eye.2014.101
32. He L, Silva RA, Moshfeghi DM, Blumenkranz MS, Leng T. Aflibercept for the treatment of retinal pigment epithelial

detachments. Retina 2016;36:492-8. https://doi.org/10.1097/IAE.0000000000000749

33. Broadhead GK, Hong T, Zhu M, et al. Response of pigment epithelial detachments to intravitreal aflibercept among patients with treatment-resistant neovascular age-related macular degeneration. Retina 2015;35:975-81. https://doi.org/10.1097/IAE.0000000000000409
34. de Massougnes S, Dirani A, Ambresin A, et al. Pigment epithelial detachment response to aflibercept in neovascular age-related macular degeneration refractory to ranibizumab: time course and drug effects. Retina 2016;36:881-8. https://doi.org/10.1097/IAE.0000000000000813
35. Simader C, Ritter M, Bolz M, et al. Morphologic parameters relevant for visual outcome during anti-angiogenic therapy of neovascular age-related macular degeneration. Ophthalmology 2014;121:1237-45. https://doi.org/10.1016/j.ophtha.2013.12.029
36. Marquis LM, Mantel I. Beneficial switch from aflibercept to ranibizumab for the treatment of refractory neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2020;258:1591-6. https://doi.org/10.1007/s00417-020-04730-8
37. Rouvas A, Datseris I, Androudi S, et al. A Real-World, Multicenter, 6-Month Prospective Study in Greece of the Effectiveness and Safety of Ranibizumab in Patients with Age-Related Macular Degeneration Who Have Inadequately Responded to Aflibercept: The "ELEVATE" Study. Clin Ophthalmol 2022;16:2579-93. https://doi.org/10.2147/OPTH.S371036