Anatomical and Functional Results of Switching to Ranibizumab for the Treatment of Aflibercept-Resistant Neovascular Age-Related Macular Degeneration

Buğra Karasu[1], Yusuf Berk Akbas[2], Aslan Aykut[3], Ali Rıza Çelebi[4]

ABSTRACT

Purpose: In this study, it was aimed to evaluate the efficacy of switching to intravitreal ranibizumab (IVR) in patients with neovascular age-related macular degeneration (nAMD) who were unresponsive or had suboptimal treatment response to intravitreal aflibercept (IVA) therapy and to determine predictive factors for switch response.

Methods: Patients were divided into 2 subgroups according to treatment resistance. Group 1 included non-responders while group 2 included those with suboptimal treatment response. Then, the patients switched to another treatment (switch from IVA to IVR) in both groups. Loading dose with monthly IVR injection (0.5 mg) (3 dose) was administered for 3 months following the switch; followed by pro re nata (PRN) IVR protocol. Main outcome measures including best-corrected visual acuity (BCVA), intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachment (PED), and central retinal thickness (CRT) were assessed at baseline (T^1), at time of switch (T^2) and 3 months (T^3) and 6 months after switch (T^4).

Results: We retrospective reviewed data regarding 40 eyes of from 36 patients with nAMD who were refractory to IVA treatment and switched to IVR. There was unresponsiveness in 2 eyes and suboptimal response in 38 eyes. A CRT increase was found from time point of T^1 to T^2 while a reduction was observed from T^2 to T^3 and T^3 to T^4 after switch. Regression analysis of alterations monthly demonstrated among time points showed significant differences in PED height (p=0.02), CRT (p=0.01), SRF (p = 0.01), and IRF (p = 0.03). However, no significant change was detected regarding BCVA (p>0.05). Predictive factors for good switch response criteria were worsening response between T^1 and T^2 time point, higher and thicker measurements at the T^2 time point, male gender, shorter therapy before switch, and smaller number of previous injections at initial therapy.

Conclusion: Eyes with IVA-resistant nAMD which had anatomical and functional deteriorated prior to switch benefited from switch to IVR. Our findings can facilitate appropriate therapy decisions and potentially improve anatomic and visual results.

Keywords: Aflibercept, anti-VEGF, neovascular age-related macular degeneration ranibizumab, switch.

INTRODUCTION

Age-related macular degeneration (AMD) is a retinal disease which is often seen above 50 years of age and it may lead loss of central vision and legal blindness[1, 2]. Neovascular AMD (nAMD) is delayed form of AMD which is characterized by choroidal neovascularization (CNV) and leads macular exudation and fibrosis with severe loss of vision eventually. It has been proven that intravitreal anti-vascular endothelia growth factor (anti-VGEF) agents improve visual acuity (VAI in nAMD)[3, 4].

The anti-VGEF agents with proven efficacy and FDA approval include ranibizumab (IVR) and aflibercept (IVA). The ranibizumab is antigen-binding fragment of humanized monoclonal antibody while aflibercept is a recombinant fusion protein of the VGEF receptor (VGEFR) 1 and VGEFR 2 extracellular domains. In

1- MD, Tuzla State Hospital, Department of Ophthalmology, Istanbul, Turkey

2- MD, University of Health Sciences, Beyoglu Eye Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey

3- MD, FEBO, FICO, Marmara University School of Medicine, Department of Ophthalmology, Istanbul, Turkey

4- Prof. MD, FEBO, FICO, FICS, FACS, MRCSEd, Acibadem University School of Medicine Department of Ophthalmology Istanbul, Turkey

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Correspondence Adress:
Buğra Karasu
Tuzla State Hospital, Department of Ophthalmology, İçmeler Mahallesi Piri Reis Caddesi No:74 Tuzla, İstanbul, Turkey
Phone: +92 549 382 5082
E-mail: bugra_karasu@hotmail.com

conclusion, unlike ranibizumab, aflibercept does not only inhibit VGEF-A but also VGEF-B and placental growth factor (PIGF), all of which are considered to play role in the pathogenesis of nAMD[5, 6, 7]. Theoretically, aflibercept has higher affinity and longer duration of action compared to ranibizumab[5,8,9]. However, both agents seems to have similar visual and anatomic effects when used in the treatment of nAMD. However, the frequency and amount of treatment required to control exudative recurrences show individual variations across patients with nAMD. In general, patients require treatment by approximately 2-months interval while intraretinal fluid (IRF) and/or subretinal fluid (SRF) is observed in patients maximum dose f monthly therapy[3]. These patients are generally defined as treatment-refractory; however, this denotes treatment failure rather than lack of efficacy[10]. Drug tolerance and/or tachyphylaxis are considered as most common potential causes for resistance[11].

The improvement in anatomic response has been reported comprehensively after switch from IVR to IVA[12-15]. It has been speculated that whether the effect of switch may be attributed to surmounting drug tolerance or different pharmacological behaviors of drugs. However, there is limited evidence regarding efficacy of switch from IVA to IVR[16-18]. Such evidence can help to elucidate role of drug tolerance against pharmacological differences. In addition, this will help individualized decision-making in clinical practice.

The aim of this study was to assess effects of switch to IVR from IVA in patients with nAMD and to identify potential predictive factors.

MATERIAL AND METHOD

In this study, we retrospectively reviewed data from 40 eyes of 36 patients with nAMD who switched to IVR due to resistance to IVA in a tertiary academic center between January, 2013 and February, 2019.

The study was approved by Ethics Committee on Clinical Research (approval date: 28.01.2021-02/08). The study was conducted in accordance to tenets of Helsinki Declaration. All patients gave informed consent before participation. The electronic database was screened for patients with nAMD who were unresponsive to monthly anti-VGEF therapy with IVA and switched to IVR.

The exclusion criteria were presence of retinal pathology other than nAMD, poor quality of optical coherence tomography (OCT) image and discontinuation of treatment. The response to aflibercept was divided into 2 groups according to modified criteria described in SAFARI trial[16]:

1- Unresponsiveness

- No history of previous anti-VGEF therapy (treatment-naïve)
- Maximum 3 monthly loading doses of aflibercept at time of screening.
- Available spectral-domain optical coherence tomography (SD-OCT) scan within 30 days prior to screening,
- Duration of aflibercept therapy <120 days before screening
- The last aflibercept injection within ≤40 days before initial visit
- No improvement in best-corrected visual acuity (BCVA) since initiation of aflibercept therapy (0.1 decimal)
- Persistent and/or increased IRF and SRF throughout aflibercept therapy

2. Suboptimal treatment response

- No history of previous anti-VGEF therapy (treatment-naïve)
- ≥6 months of aflibercept therapy before screening
- Aflibercept injection in addition to 3 monthly loading doses at time of screening
- Available spectral-domain optical coherence tomography (SD-OCT) scan within 30 days prior to screening,
- Reduction in disease activity (≥50 µm reduction in central retinal thickness on OCT) in the study eye during aflibercept therapy
- The PRN aflibercept injections following 3 monthly loading doses in the study eye
- 30-days interval between last aflibercept injection and previous injection and last injection ≤40 days before initial visit
- Relative reduction and/or lack of reduction in IRF and SRF throughout treatment

When unresponsiveness or suboptimal response was observed in nAMD despite aflibercept therapy, anti-VGEF switch was planned. The first-line anti-VGEF was selected based on discretion of clinician and no clinical marker was taken into account. At the end of the study, the treatment was typically switched to IVR. After switch to IVR, 3 loading doses (monthly) was given to patients over 6 months; followed by PRN regimen.

The data below were collected in each patient and eye included:

** Best-corrected visual acuity was measured using decimal visual scheme according to Snellen chart and transformed to logMAR units for statistical purposes,

** Presence or absence of IRF and SRF with height, presence or absence of pigment epithelium detachment (PED) on SD-OCT and central retinal thickness as measured by OCT Spectralis device (Heidelberg Engineering, Dossenheim, Germany) (Figure 1),

The presence of intraretinal fluid was defined as presence of cystoid or diffuse intra-retinal hypo-reflective fluid on two linear SD-OCT scans. The SRF height was measured as vertical length of fluid between retinal pigment epithelium (RPE) and external limiting membrane (ELM) on vertical axis.

The choroidal neovascularization activation was based on leakage beyond CNV margins at delayed phase of angiogram and detection of novel choroidal vascular network on early phase of fundus fluorescein angiography (FFA). In addition, indocyanine green angiography (ICGA) was performed to exclude polypoidal choroidal vasculopathy in CNV.

The above-mentioned parameters were assessed at 3 different time points including baseline (T^1), time of switch (T^2) and 3 months (T^3) and 6 months after switch (T^4). Figure 2 summarizes treatment algorithm.

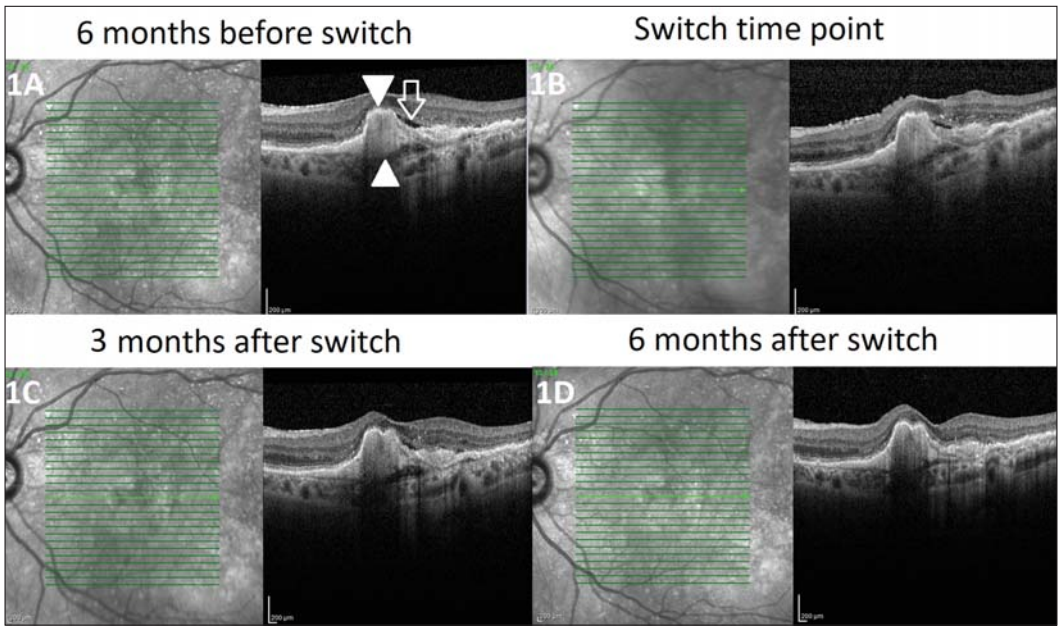

Figure 1: *Optical coherence tomography images of a patient switched to ranibizumab from aflibercept. Subretinal fluid (SRF) and pigment epithelial detachment (PED) are seen in Figure 1A (white arrow).*

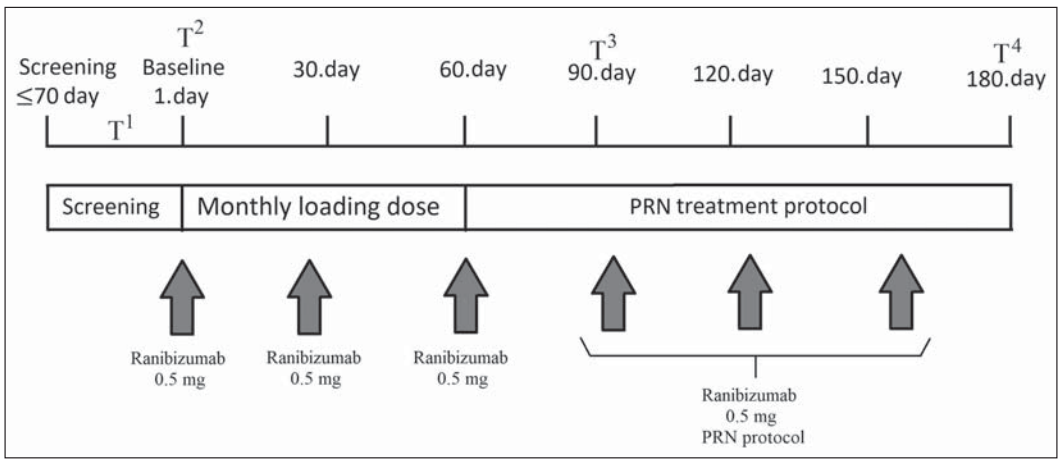

Figure 2: *Treatment scheme.*

In addition, data regarding number of injections, age and gender were also collected. The outcome measures were changes in BCVA, CRT, macular dryness, SRF height and PED height.

The variables influencing on these parameters included absolute value at T^2, age, gender and number of previous injections.

Statistical analysis

The statistical analyses included descriptive statistics and binary comparisons of continuous analysis to define significant variables over time. A correlation analysis was performed to define factors associated with structural outcome measures after switch using Pearson's correlation coefficient for continuous variables and MANOVA for categorical variables. Data are presented as mean ± standard deviation (SD). Data were analyzed using IBM SPSS version 22.0 (SPSS, IBM, Chicago, IL). A p value<0.05 was considered as statistically significant. Bonferroni Holmes correction was performed to adjust repeated measures.

RESULTS

Mean age was 70.51±10.79 years (range: 53-76 years). There were 24 women (60%) and 16 men (40%) in the study population. There was occult type in 37 of 40 eyes (92.5%). There was classical neovascularization in 2 eyes and angiomatous proliferation one eye. Mean number of intravitreal aflibercept injection was 8.1±3.2 given over 305±115 days.

Comparisons across time points

The central retinal thickness, SRF and PED height measurements were increased from T^1 to T^2 while they were decreased from T^2 to T^3 and T^3 to T^4.

The differences across time points reached partial statistical significance (Table 1). However, there was no marked difference in the comparison from T^1 to T^4. Although BCVA was decreased from T^1 to T^2, it was slightly improved from T^2 to T^3 but not changed from T^3 to T^4. The presence of IRF showed slight variation across time points (novel IRF was increased in only 1 eye from T^1 to T^2, decreased in 2 eyes from T^2 to T^3 and in 1 eye from T^3 to T^4) (Table 1) while SRF showed more fluctuation with clear increase from T^1 to T^2 (19 eyes to 24 eyes) and a slight reduction from T^2 to T^3 (to 18 eyes)and between T^3 to T^4 (17 eyes). Complete dryness was achieved in 4 eyes (13%) at T^3 and in 6 eyes (15%) T^4; in other words, absence of IRF and SRF was achieved. Table 1 summarizes mean values of BCVA, CRT, PED and SRF and number of eyes with and without IRF at different time points (T^1 T^2 T^3 T^4). Figure 3 presents PED, CRT and SRF measurements.

Regression analysis of changes before and after switch

Since there was a clear effect on development of exudative signs before and after switch, we not only compared individual time points but also individual regression coefficients (slopes) before and after switch.

Binary analyses revealed significant statistical changes. The slope of pigment epithelium detachment height (regression coefficient) was significantly increased from T^1 to T^2 while

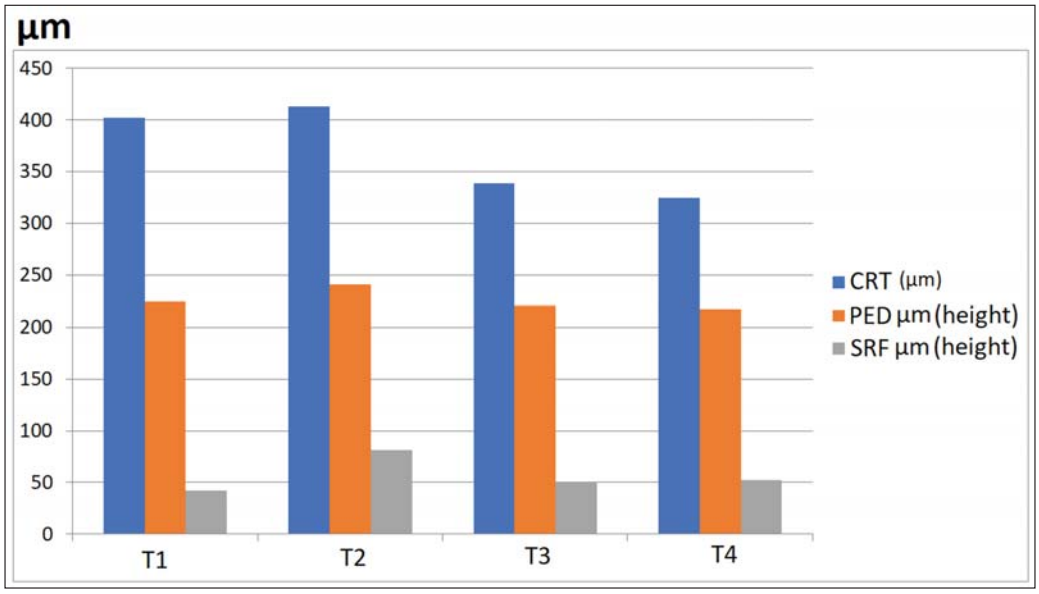

Figure 3: *Central retinal thickness, PED and SRF results.*

Table 1: *Visual and anatomic outcomes at different time points.*

Results	**T1**		**T2**	**T3**			**T4**			
		p value			**p value**	**p value**		**p value**	**p value**	**p value**
	Mean ± SD	Comparison with T2	Mean ± SD	Mean ± SD	Comparison with T2	Comparison with T1	Mean ± SD	Comparison with T1	Comparison with T2	Comparison with T3
BCVA (log MAR)	0,75±0,48	0.076	0,85±0,55	0,83±0,53	0.820	0.090	0,83±0,55	0.117	0.775	0.478
CRT (µm)	402,30±227,75	0.634	413.10±235,81	339,12±209,91	0.028	0.015	324,37±179,42	0.083	0.001	0.400
PED µm (height)	224,47 ± 104,51	0.194	240,74 ± 109,79	220,84±94,92	0.041	0.200	217,34 ± 98,81	0.467	0.031	0.689
SRF µm (height)	42 ± 46	0.021	81 ± 80	51±67	0.048	0.671	52 ± 71	0.653	0.070	0.746
	T1 number of eyes (%)		T2 number of eyes (%)	T3 number of eyes (%)			T4 number of eyes (%)			
IRF positive	18 (45%)		19 (47%)	17 (42%)			16 (40%)			
SRF positive	19 (47%)		24 (60%)	18 (45%)			17 (42%)			

paired t test
BCVA: best-corrected visual acuity; **CRT**: central retinal thickness; **PED**: pigment epithelium detachment; **SRF**: subretinal fluid; **IRF**: intraretinal fluid; Mean ± SD, mean ± standard deviation; T1, 6 months before switch;
Z2, time eof switch; Z3, 3 months after switch; Z4, 6 months after switch; log MAR, logarithm of the Mminimum angle of resolution

it was significantly decreased from T^2 to T^3 and from T^3 to T^4 (p=0.02). This was also observed in CRT (p=0.01), SRF height slope (p=0.01) and IRF presence (p=0.03). No significant change was observed in regression coefficients of BCVA (p>0.05).

Analysis of relevant factors after switch

We analyzed factors identified to have potential association with extent of changes after switch by multivariate analysis. We found significant correlation in 4 outcome measures (CRT, IRF, SRF and PED) among changes observed before (T^1 to T^2) and after switch (T^2 to T^3 and T^3 to T^4).

This finding was confirmed for CRT, SRF and PED by multivariate analysis, indicating that greater increase before switch predicts greater reduction after switch.

Similarly, changes in IRF and SRF after switch were correlated with absolute measurements at T^2, suggesting that there is a better response to switch by higher amounts of pathological fluid. In addition, changes in PED response was linked to gender with stronger treatment response in male patients than female patients.

It was found that shorter treatment duration before switch was correlated with better response in SRF and CRT changes, which was confirmed with multivariate analysis.

However, it was found that remaining factors such as age or number of injections before switch had no predictive value for switch to IVR from IVA, as CRT change being exception. Table 2 presents results of multivariate analysis.

DISCUSSION

In the present study, we observed a promising response after switch to ranibizumab therapy in eyes with nAMD unresponsive to aflibercept. In addition, we found that this favorable response was associated with some specific factors before switch.

As similar to previous studies involving switch to IVA from

Table 2: *Multifactorial analysis after switch.*

	CRT		**IRF**		**SRF**		**PED**	
	rho	***p***	***rho***	***p***	***rho***	***p***	***rho***	***p***
T1-T2	-0.54	<0.0001*	-0.41	0.042*	-0.48	0.048*	-0.37	0.082
Absolute value at T2	-0.19	0.47	-0.51	0.028*	-0.39	0.031*	-0.34	0.09
Age	-0.29	0.18	0.02	0.91	0.14	0.58	0.03	0.96
Gender		0.21		0.09		0.61		0.02*
Number of injections	0.22	0.41	0.10	0.67	0.57	0.003*	0.09	0.83
Duration of aflibercept therapy	0.33	0.08	0.04	0.89	0.69	0.002*	− 0.06	0.82

Continuous variables are analyzed using Pearson's correlation analysis while categorical variables using MANOVA test
CRT: central retinal thickness; **IRF**: intraretinal fluid; **SRF**: subretinal fluid; **PED**: pigment epithelium detachment;
rho, corrrelation coefficient.

IVR[12-15], we found that reverse switch can be effective in the treatment of nAMD. Thus, a part of the switch effect can be attributed to factors such as drug tolerance rather than differences in the drugs[10, 11, 19]. The tolerance is reduction in treatment response (aflibercept in our study) and it may occur when a reduction was observed in treatment response after repeated intravitreal injections. These changes may include increased expression of VGEF or VGEF receptors, release of other growth factors, interaction of specific antibodies or alteration in signal transduction[20]. Typically, it may be needed to escalate anti-VGEF dose or shorten treatment interval to maintain effect achieved at the beginning of treatment. An alternative explanation seems to be not applicable in nAMD due to tachyphylaxis since this corresponds to a rapid reduction in treatment efficacy that cannot be improved by drug dose, suspension of treatment or increasing dose interval. This mechanisms can occur typically in drugs releasing neurotransmitters[10].

In our study, no improvement was observed in visual acuity after switch to IVR; this finding is in agreement with many studies showing a beneficial response in only morphologic parameters by anti-VGEF agent switch[12-14, 16, 17]. However, an improvement was observed in visual acuity after switch in other studies[15-17, 18].

Although the ultimate goal of clinical trials is limited to improvement in visual function, recovery in structural aspects of retina is also beneficial despite lack of acute effects on vision. In fact, visual gain will increasingly irreversible as a result of long-term persistence of structural abnormalities in retinal anatomy. Thus, the retinal changes closest to normal anatomy can lead improvement in visual acuity at long-term even in the absence of short-term visual gain. The lack of acute changes in BCVA despite presence of molecular and structural changes can be associated with irreversible retinal injury [21]. In our study, no ocular adverse event that may impair functional results were observed.

We found that switch to IVR from IVA led favorable, short-term results in retinal structure in agreement with previous studies about switch from IVR to IVA[17, 18].

In our study, the novel findings included prognostic and predictive factors that may be important in clinical practice after switch. The anatomic changes under IVA before switch were negatively correlated to anatomic gains after IVR therapy. This was also true for all structural outcomes including CRT, IRF, SRF and PED. This finding was in agreement with studies evaluated effect of switch to IVA from IVR[11-13]. Thus, regardless of anti-VGEF agent used, duration of unresponsiveness before switch may be helpful to identify eyes which may benefit from switch to another anti-VGEF agent. In addition, absolute IRF and SRF values at time of switch predicted degree of response to switch from IVA to IVR. Another predictive factor was duration of IVA therapy before switch to IVR. It was an independent predictor for SRF and CRT; thus, eyes with shorter duration of IVA therapy showed better treatment response to new agent. Although reasons underlying this observation are unclear, it can be predicted that long-term treatment reduces structural reactivity, presumably due to protein-enriched fluids. Thus, a novel strategy may be alternate short-term anti-VGEF therapies with switch to another anti-VGEF agent. Interestingly, it was found that male gender predicted changes in PED and that gender was a predictive factor.

To best of our knowledge, no study has defined gender as a factor that affects the response to switching from one anti-VGEF agent to another. It is possible that development of tolerance against aflibercept can be associated with gender, presumably due to anti-PIGF component of the drug; thus, women may be less immunogenic to this component[22]. This study has some limitations including retrospective design and shorter follow-up. There is a need for longer follow-up to assess potential long-term effects. Higher percent of occult neovascularization may limit our result to this subtype. In addition, sample size was small and no manual correction was performed in CRT measurements for segmentation errors.

In conclusion, our study revealed encouraging results about structural aspects of refractory nAMD following switch to IVR from IVA. We identified several factors to predict which eyes will benefit from such switch.

In a retrospective case series including 21 eyes of 19 patients, Slean et al. showed that recurrent exudation may develop with aflibercept in some patients and that it may be improved by switch to bevacizumab or ranibizumab although aflibercept therapy appeared as effective initially[17]. In our study, in addition to changes in CRT, short-term worsening of exudation immediately before switch was a strong predictive factor; increasing likelihood favorable outcome in treatment response. Ideally, further studies with prospective design and larger cohort are needed to confirm these results.

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