Anatomical and Functional Outcomes Switching to Aflibercebt Injection for Polypoidal Choroidal Vasculopathy Refractory to Ranibizumab

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ABSTRACT

Purpose: To evaluated the efficacy of switching to intravitreal aflibercept (IVA) injection to treat polypoidal choroidal vasculopathy (PCV) refractory to intravitreal ranibizumab (IVR). **Materials and Methods:** In this retrospective study, medical records of 29 eyes of 29 patients with PCV treated with IVA (2 mg / 0.05 mL) followed by IVR switch were reviewed. A treatment history of 3 consecutive monthly IVR as loading dose followed by a pro re nata regimen phase over 6 months was seen for all patients and followed by the last for 3 consecutive monthly of IVR received. All patients who were refractory to IVR (defined as recalcitrant subretinal or intraretinal fluid in optical coherence tomography (OCT) and unchanged or decreased visual acuity (VA) compared with those at time of first IVR injection, despite receiving the last 3 consecutive monthly IVR injections following 12 months. The switch time to IVA was accepted as the baseline. Visual and anatomical changes were recorded at baseline and at months 1, 3 and 6, respectively.

Results: Visual acuity levels significantly improved from 0.73 ± 0.49 logarithm of the minimum angle of resolution (log MAR) at baseline to 0.58 ± 0.38 log MAR 6 months after switching to aflibercept (p = 0.037). The central macular thickness decreased significantly from 349.58 ± 101.81 at baseline to 308.68 ± 94.58 at month 6 (p= 0.001). Of 16 eyes with polypoidal lesions at baseline, the polypoidal lesions regressed completely in 6 eyes (37%) at month 6.

Conclusion: Administering intravitreal aflibercept injection for patients with polypoidal choroidal vasculopathy refractory to ranibizumab maintained or improved visual acuity and reduced or eliminated exudative lesions and occluding polypoidal lesions without adverse events with short-term follow-up.

Keywords: Polypoidal choroidal vasculopathy, Choroidal neovascular membrane, Anti-vascular endothelial growth factor.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) was first described by Yannuzzi as clinical entity characterized by subretinal polypoidal vascular lesions related to serous and hemorrhagic retinal pigment epithelium detachment, which differs from neovascular age-related macular degeneration (nAMD). Characteristically, a branching vascular network and polypoidal choroidal vascular lesions are present [1]. In newly diagnoses nAMD, PCV prevalence was reported as 23-35% in Asian descent, which is higher than Caucasians [2-4].

Currently, photodynamic treatment with verteporfin (PDT) or intravitreal anti-vascular endothelial growth factor (VEGF) agents are being used with successful outcome in the treatment [5-9]. As anti-VEGF therapy, it has been reported that intravitreal ranibizumab (IVR) or bevacizumab (IVB) have benefi cial effects in patients with nAMD. However, it was also reported that the anti-VEGF agents are less effective in occlusion of polyp lesions in PCV patients received IVB or IVR therapy [14-16, 17]. Sometimes, anti-VEGF agent fail to achieve response in eyes with PCV-related choroidal neovascular membrane (CNVM); thus, switch to another anti-VEGF agent may be required. In recent years, promising results have been reported with intravitreal aflibercept (IVA) injection as a

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novel anti-VEGF agent in nAMD. Aflibercept is a soluble, recombinant fusion protein (115 kDa in weight) containing VEGF receptors 1 and 2 fused to Fc fragment of human IgG, which is produced by recombinant DNA technology. This allows binds VEGF-A, VEGF-B and all isoforms of placental growth factor (PIGF) [18,19]. It was reported that anti-VEGF activity of aflibercept is as effective as ranibizumab: the effi cacy and safety studies, VIEW 1 and VEW2 has been available for clinical use in Japan at November, 2012 [17]. In several single-center studies, it was reported that aflibercept was effective in the treatment of eyes with PCV [20, 21]. The IVA injection administered monthly or every 2 months after first 3 monthly injections showed similar therapeutic effect when compared to IVR injections [18]. Since today, several studies have been conducted on therapeutic effect of aflibercept in PCV, reporting promising outcomes and realistic expectations in the treatment of PCV with afl ibercept monotherapy [21, 22].

To the best of our knowledge there is no study focusing on differences between these two anti-VEGF agents (ranibizumab and aflibercept) in the treatment of PCV. In this study, it was aimed to assess therapeutic effi cacy of aflibercept in patients with PCV refractory to ranibizumab..

MATERIAL AND METHOD

In this study, we retrospectively reviewed medical records for 29 eyes of 29 patients with CNVM secondary to PCV, who were refractory to ranibizumab and switched to aflibercept therapy in our clinic between January, 2013 and February, 2019. The study was approved by Ethics Committee on Clinical Research (approval#2019-07-08/08.04/2019). All patients gave written informed consent. The study was conducted in accordance to tenets of Helsinki Declaration.

The study included patients received IVR therapy (loading dose plus 3 monthly IVR injections plus PRN regimen over 6 months), who had at least 12 months of follow-up including 3 monthly injections at last 3 months [23]. All patients completed 12-months of follow-up with ranibizumab. In the study, baseline was defined at time of switch to aflibercept.

The exclusion criteria included history of previous treatment for nAMD including argon laser photocoagulation, submacular surgery or transpupillary thermotherapy; maculopathies such as retinal pigment epithelium (RPE) detachment, diabetic maculopathy, retinal vascular ocular occlusion and idiopathic macular telangiectasia; pathological myopia (spherical equivalent = -6 diopter or axial length of 26 mm); vitreomacular traction; epiretinal membrane; central serous chorioretinopathy, trauma and uveitis. We also excluded patients received PDT with verteporfin within prior 12 months.

In all patients, anterior segment examination was performed using biomicroscopy and dilated fundus examination was performed. Best-corrected visual acuity (BCVA) was assessed using Snellen charts and transformed to LogMAR for statistical analysis. Intraocular pressure (IOP) was measured using non-contact tonometry. For diagnosis of PCV, indirect ophthalmoscopy, SD-OCT, digital fundus fluorescein angiography (FFA) and indocyanine green angiography (IGA) were performed during clinical examination. The diagnosis of PCV was defined as, regardless of branching vascular network IGA, presence of one or more foci secondary to choroidal circulation within first 6 minutes following indocyanine green injection and/or polypoidal dilatation with abnormal vascular network by confocal screen laser ophthalmoscopy.

All patients received 3 consecutive IVA injections with at least 6-months of follow-up. Data regarding BCVA, central macular thickness (CMT) and other parameters of ophthalmic examination at baseline and on months 1, 3 and 6 were extracted from medical records. FFA was performed at baseline and on month 6 to determine lesion type, lesion localization and choroidal neovascularization (CNV) activity. IGA was performed at baseline and on month 6 to diagnose PCV and changes in its size. Using confocal laser ophthalmoscope, polypoidal lesions were identifi ed by early-phase IGA images. The largest linear size was measured on IGA images including polypoidal lesions and branching vascular network (IGA-guided largest linear size). In all patients, persistent subretinal or intraretinal fluid was documented at baseline by SD-OCT images. Monthly follow-up visits including SD-OCT images were scheduled. Figure 1 shows follow-up OCT, FFA and IGA images of a patient underwent IVA injection. Figure 2 shows changes in polyp diameter and size on OCT, FFA and IGA images of a patient.

All injections were performed under sterile conditions. Povidone-iodine 10% was used at eye brows and eye lashes while povidone-iodine 5% was used in conjunctival sac for preparation. Topical levofloxacin ophthalmic solution (5x1 daily) was prescribed for 5 days after intravitreal injections and patients were asked to present hospital in case of onset of new symptoms such as sudden loss of vision, ocular pain and/or redness.

The PCV was classified into 2 types according to IGA characteristics [3]:

Type 1 PCV: Polyp or polyps having vascular network with marked branching (vascular network from both supplying and draining vessels).

Type 2 PCV: Poly or polyps having no vascular network with branching (no supplying vessel)

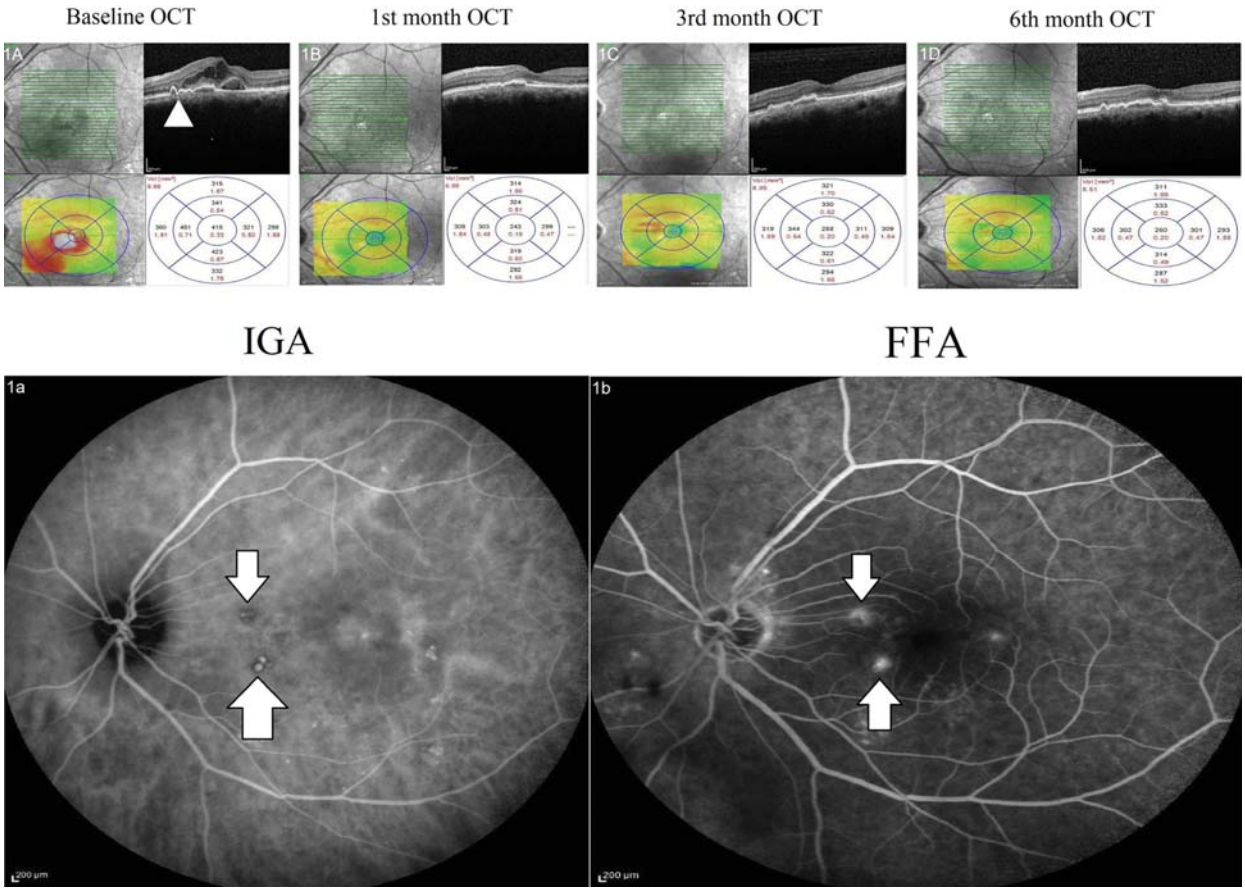

Figure 1: *Optical coherence tomography (OCT), fundus fluorescein angiography (FFA) and indocyanine green angiography (IGA) images of patients received intravitreal aflibercept during follow-up; A) PED is seen; a) and b) shows IGA and FFA images of polyp.*

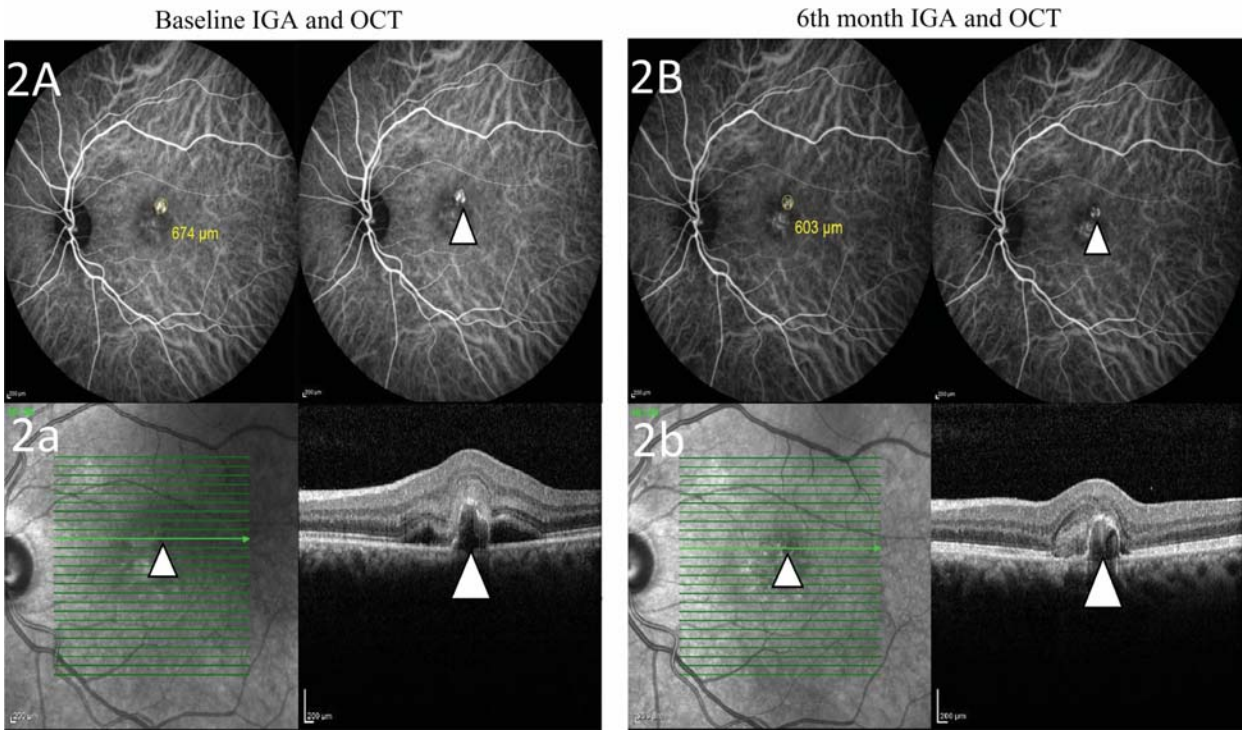

Figure 2: *Optical coherence tomography (OCT), fundus fluorescein angiography (FFA) and indocyanine green angiography (IGA) images of patients received intravitreal aflibercept during follow-up; A) and a) shows poly diameter and PED image on IGA and OCT; B) and b) shows poly diameter and PED image on IGA and OCT after IVA injections.*

A typical supplying vascular network originates from on vessels and radiated outwards, which is generally localized around polyps. Abnormal vascular network is visualized within 30 seconds using IGA and it is difficult to identify these vessels after 1 minute when normal choroidal vessels are filling.

In case of bilateral PCV, only one eye was included to the analysis in order to exclude potential effects resulting from activity of agent given to the eye.

Criteria for switching anti-vascular endothelial growth factor:

1- During 12 months of IVR therapy, lack of ≥ 5 letters improvement or worsening in visual acuity as determined by Snellen charts,

2- Presence of persistent subretinal fl uid (SF) on SD-OCT despite consecutive or monthly IVR injections,

3- Following consecutive or monthly IVR injections, gradual prolongation of SR-free time or tachyphylaxis on SD-OCT,

4- During 12-months of IVR therapy, lack of complete (no polyp) or partial regression (10% reduction in poly site) on IGA in response to IVR,

5- During 12-months IVR therapy, lack of at least 10% reduction in CMT at monthly visits or stable CMT,

6- In addition to above-mentioned criteria, clinician judgment on benefit of anti-VGEF agent switch,

7- Persistence of above-mentioned criteria despite 3 consecutive IVR injections at last months.

Statistical analysis

Visual acuity was measured using Snellen charts and transformed into LogMAR units for statistical purposes. Data are expressed mean ± standard deviation. Normal data distribution was assessed using Kolmogorov-Smirnov test. BCVA changes and anatomic differences during follow-up were compared using Friedman test. Data were analyzed using IBMM SPSS version 22.0 (SPSS, IBM, Chicago, IL). A p value < 0.05 was considered as statistically significant.

FINDINGS

There were 13 women and 16 women in the study. Mean age was 72.51±9.79 years (range 52-88 years). Table 1 summarizes demographic data of the patients.

The best-corrected visual acuity was 0.73 ± 0.49 log MAR at baseline, 0.67 ± 0.45 log MAR at month 1, 0.64 ± 0.45 log MAR at month 3 and 0.58 ± 0.38 log MAR at month 6 (p=0.037, Friedman test). Figure 3 presents BCVA change during follow-up.

Table 1: *Clinical and demographic characteristics of patients.*

Clinical characteristics	Study group
Eyes	29
Gender	$13^{1}16^{2}$
Side	$16^{a}13^{b}$
BCVA (log MAR), baseline	0.73±0.49
Age (mean ±SD)	72.51±9.79
Duration of follow-up	6 ay
PCV type(type 1/2)	(22/7)
Lesion type, non-classical occult CNV	29
SF, count (%)	24(%82)
PED, count (%)	20(%68)
Number of previous IVR injections	11.93±2.60

PCV: polypoidal choroidal vasculopathy, **SD:** standard deviation; **IVR:** intravitreal ranibizumab; **PED:** pigment epithelium detachment; **BCVA:** best-corrected visual acuity; **Log MAR:** logarithm of the minimum angle of resolution; [1]female, [2]male; [a] right, [b]left; **CNV:** choroidal neovascularization

Central macular thickness (CMT) was 349.58 ± 101.81 µm at baseline, 318.82 ± 106.07 µm at month 1,307.89 ± 104.69 µm at month 3 and 308.68 ± 94.58 µm at month 6 (p=0.001, Friedman test). The CMT was decreased by 12% at month 6 when compared to baseline. The complete SF regression (+/-) was found as follows: 24/5 at baseline, 15/14 at month 1, 12/17 ay month 3 and 16/13 at month 6, indicating significant difference (p<0.001, Friedman test). At baseline, SF was observed in 82% of eyes whereas in 45% of eyes at month 6. No significant change was detected in PED regression at any time point compared to baseline (p=0.468, Friedman test). Table 2 presents summarizes in parameters during follow-up.

In all 29 eyes, lesions were classified as occult CNV with no classical CNV on FFA. There was polypoidal lesion in 16 eyes at baseline. In remaining 13 eyes, IGA showed that polypoidal lesions were completely regressed due to previous PDT (8 eyes) or IVR injections (5 eyes); however, lesions with recurrent or residual leakage resulting from vascular network was found to be persistent on FFA and OCT images. In 13 eyes, PED larger than 1 disc diameter was observed on FFA and OCT images. During 6-months follow-up, polypoidal lesions were completely regressedin 6 of 16 eyes (37%) while they were shrunk in 6 eyes (37%) and remained stable in 4 eyes (26%).

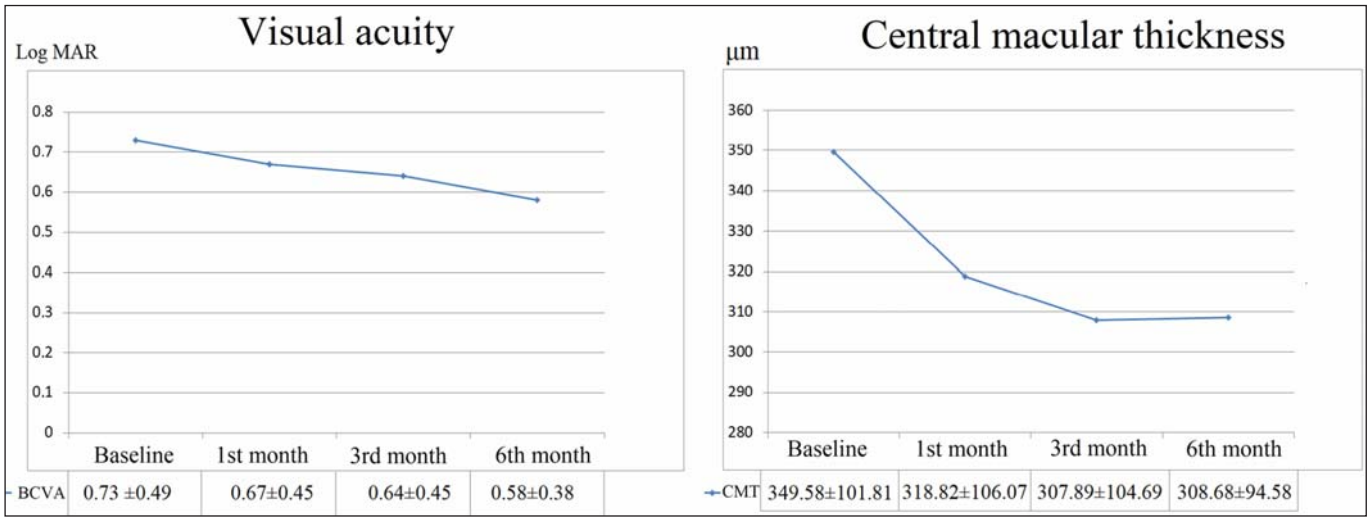

Figure 3: *Changes in BCVA and CMT according to follow-up period.*

Table 2: *Changes in parameters during follow-up*

	Baseline	Mont 1	Month 3	Month 6	p value*
BCVA	0.73±0.49	0.67±0.45	0.64±0.45	0.58±0.38	0.037
CMT	349.58±101.81	318.82±106.07	307.89±104.69	308.68±94.58	0.001
SF (+/-)	(24/5)	(15/14)	(12/17)	(16/13)	<0.001
PED (+/-)	(20/9)	(21/8)	(19/10)	(21/8)	0.468
Friedman test					

BCVA: best-corrected visual acuity; **CMT:** central macular thickness; **SF:** subretinal fluid; **PED:** pigment epithelium detachment

Table 3: *Changes in time points compared to baseline.*

	Baseline-Month 1	Baseline-Month 3	Baseline-Month 6
BCVA	p=0.074	p=0.011*	p<0.001*
CMT	p=0.039*	p=0.002*	p=0.005*
SF (+/-)	p=0.003*	p=0.001*	p=0.005*
PED (+/-)	p=0.317	p=0.564	p=0.564
Wilcoxon signed test*			

DISCUSSION

This study included 29 eyes of 29 PCV patients who received 3 monthly IVR injections at first and last 3 months (loading doses) during 12-months of follow-up and PRN regimen in remaining 6 months. After switch to IVA therapy, polypoidal lesion regression was achieved in 75% of eyes included. IVA therapy was found to be effective regarding anatomic recovery and visual acuity improvement.

Polypoidal choroid vasculopathy is prevalent among Asians. IVR and IVA as anti-VEGF therapy are considered as evidence-based treatment for nAMD worldwide [10-12, 19]. However, there are insufficient data regarding effectiveness of IVR and IVA in patients with PCV as IGA is lacking in majority of studies. It is though that IVR has lower efficacy in vaso-occlusion of polypoidal lesions in PCV patients, which may result in persistent subretinal or intraretinal fluid at long-term during monthly IVR injections [15, 16]. In the literature, there is limited number of study about switching to IVA from IVR in patients with PCV. However, therapeutic efficacy was attempted to be assessed by choroidal thickness measurement in most studies [20, 24].

In a study by Saito et al., 66 eyes of 65 patients with PCV refractory to IVR (mean age: 75.7 years) were retrospectively reviewed. In the study, IVA regimen

including 3 consecutive monthly injections (2 mg/0.05 mL) as loading dose followed by bimonthly injections was employed. Mean subfoveal choroidal thickness (SFCT) was decreased to 171 µm on month 6 from 203 µm at baseline (p<0.0001). Mean BCVA was improved to 0.33 LogMAR on month 6 from 0.40 LogMAR at baseline (p<0.001). The CMT was decreased to 161 µm from 149 µm at baseline (p<0.0001). Regression in polypoidal lesions was achieved in 26 (56.5%) of 46 eyes with polypoidal lesion at baseline. Authors proposed that afl ibercept prevented CNV adjacent to or beneath RPE in eyes with PCV and that may induce more vaso-occlusion in polypoidal lesions when compared to ranibizumab [24]. However, major drawbacks were that there was no data regarding systemic disease and medication history in the study given elder study population (mean age 75.7±5.8 years; range: 60-88 years) and potential significant effects of several systemic and local disorders as well as drugs [25]. In a study by Tan et al., significant differences were detected at all time points in SFCT and choroidal thickness measured by 2-hours interval between 09:00 AM and 17:00 PM. In that study, mean diurnal SFCT amplitude was found as 33.7±21.5 µm (range: 3-67 µm) [26]. In the study on healthy individuals, Usui et al. measured SFCT by 3-hours interval over 24 hours. In that study, it was shown that daily SFCT may vary up to 65 µm (range: 8-65 µm) [27]. These factors may have somewhat influence on outcomes and statistical analysis in the study by Saito et al. Thus, lack of choroidal measurements in our study may exclude limitation in ourstudy. Despite results similar to those reported by Saito et al., complete polyp regression was observed in 37% of patients and complete or partial regression was observed in 74% of eyes under IVA therapy.

In a retrospective observational study, Kim et al. reviewed medical records in 240 eyes of 240 patients with naïve nAMD treated with 3 consecutive month injections of IVR or IVA. The duration of disease and change in choroidal thickness were compared between two groups. Authors, then, classified eyes into 3 groups: typical nAMD, PCV and retinal angiomatous proliferation (RAP). The change in choroidal thickness was also compared in 3 subgroups between treatment groups. The extent of decrease was higher in PCV group received IVA therapy (p=0.001) while no significant difference was detected in nAMD and RAP groups. They found that SFCT was significantly decreased following 3 monthly injections regardless of agent used. The extent of SFCT reduction was higher in eyes treated with IVA when compared to those treated with IVR. The difference was greater in PCV subgroup when compared to remaining subgroups [28]. Despite limitations including shorter follow-up (3-months) and evaluation of choroidal thickness alone, our study has advantages including 6-months of follow-up, polyp diameter measurement and changes in PED and SF during follow-up.

In a retrospective, interventional case series, Cho et al. compared efficacy of IVA and IVR injections in patients diagnosed as PCV. Overall, 98 treatment-naïve eyes with PCV were treated with 3 monthly injections (loading dose) followed by PRN regimen using either IVA or IVR. The anatomic and visual outcomes were assessed at the end of 12-months follow-up period. In IVA treatment group (n=38), mean BCVA was improved to 0.44±0.37 LogMAR from 0.63±0.49 LogMAR (p=0.012). Similarly, mean BCVA was improved to 0.49±0.36 LogMAR from 0.66±0.43 LogMAR in IVR treatment group (n=60) (p=0.018). Mean central foveal thickness was decreased to 212 ± 144 µm from 396 ± 167 µm in IVA group and to 240 ± 183 µm from 402 ± 198 µm in IVR group (p<0.001 in both groups). Polyp regression was significantly more in IVA treatment group (39.5% of eyes) when compared to IVR treatment group (p=0.007). Authors observed no significant difference in visual acuity improvement after 12-months between IVA and IVR but IVA treatment resulted in more poly regression compared to IVR [29]. In our study, although favorable outcomes were obtained in poly regression, CMT reduction and visual acuity at 6-months follow-up, long-term results are unknown.

In most patients with PCV, persistent leakage or recurrent hemorrhage and poor visual outcomes are found in the history. The IGA is essential in the diagnosis of PCV since it clearly delineates abnormal vascularity. The FFA shows polypoidal lesions or branching choroidal vessels ad occult or minimal classical CNV [5, 6].

The PLANET study is a randomized, clinical trial conducted to assess efficacy and safety of IVA in PCV. In the PLANET study, improvement was achieved in visual and/or functional outcomes >85% and no finding of leakage was observed in polypoidal lesions in >80% of patients treated with IVA monotherapy. Since less than 15% of patient fulfilled minimal response criteria for PDT, no conclusion was drawn on effects of adding PDT. Based on results at year 1, it was shown that IVA monotherapy can be an appropriate treatment option to prevent worsening to a level requiring salvage therapy in majority of patients with PCV; however, it is unclear how to compare IVA monotherapy to combination with PDT at baseline as adjunctive therapy. Given potential risk following PDT such as normal choroidal vascularity and cumulative damage in RPE, it seemed reasonable to delay PDT in patients with favorable visual acuity and fluid detected on OCT [30]. Since patients underwent PDT within prior 12 months were excluded in our study, it is not possible to compare our results with PLANET study but

it can be suggested that IVA can be an effective treatment option in reducing need for PDT based on its duration of action and efficacy.

In the VIEW studies, it was shown that aflibercept is effective in all subgroups of nAMD including PCV [18]. Although many studies showed that aflibercept treatment in PCV resulted in favorable visual gain and polyp regression, these studies are limited with retrospective design.

The EVEREST study showed that IVR plus PDT or PDT monotherapy is superior to IVR monotherapy regarding polyp regression at 6-months follow-up in PCV patients (77.8%, 71.4% and 28.6%) [7].

Based on above-mentioned results, it could be predicted that aflibercept may prevent CNV adjacent to or beneath RPE and that this may be achieved by more occlusion of polypoidal lesions.

Our study has some limitation including small sample size, shorter follow-up and retrospective design. However, strengths of this study include limited number of studies on this issue in the literature. In this study, it was shown that aflibercept injection has significant efficacy in protecting and improving visual acuity and achieving anatomic recovery in patients with IVR-refractory PCV. On month 6, it was observed that polypoidal lesions completely regressed in 37% of eyes and shrunk in another 37% of eyes.

In conclusion, IVA injections preserved or improved visual acuity and reduced or completely healed exudative lesions in patients with IVR-refractory PCV and polypoidal lesions were regressed with adverse events in short-term follow-up. There is a need for larger, prospective, randomized studies with longer follow-up in order to determine safety and efficacy of anti-VEGF agents in PCV patients.

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