

Comparison of Visual and Anatomical Outcomes of Anti-Vascular Endothelial Growth Factor Combined with Photodynamic Therapy Versus Solely Performing Anti-Vascular Endothelial Growth Factor Therapy in Eyes with Polypoidal Choroidal Vasculopathy

Bugra KARASU¹, Ozgur ARTUNAY²

ABSTRACT

Purpose: To compare visual and anatomical results of anti-vascular endothelial growth factor (VEGF) combined with photodynamic therapy (PDT) versus only performing anti-VEGF therapy in eyes with polypoidal choroidal vasculopathy (PCV).

Materials and Methods: Retrospective review of 60 PCV patients who underwent anti-VEGF combined with PDT (Group 1) or solely performing anti-VEGF therapy (Group 2) were enrolled. The best corrected visual acuity (BCVA), central macular thickness (CMT), presence of subretinal fluid (SF) were compared among the groups during the follow-up periods at baseline, 1st month, 3rd month, 6th month, 9th month, 12th month, 18th month, 24th month and final visit, respectively.

Results: The mean age of the patients was 71.96 ± 8.50 years (range, 52-88 years), and the mean follow-up period was 53.83 ± 14.86 (range, 20-85 months). The mean number of injections was observed as 10.56 ± 1.88 (range, 7-15) in the first group and 11.83 ± 2.61 (range, 7-17) in the second group, respectively ($p = 0.039$). In group 1, BCVA decreased from the logarithm of the minimum angle resolution (log MAR) of 0.59 ± 0.39 to 0.70 ± 0.41 log MAR in the final examination ($p = 0.016$), CMT initial 355.562 ± 95.54 μm decreased from to 296.76 ± 105.03 μm at the last examination ($p < 0.001$), the presence of SRF showed a statistically significant decrease in follow-up periods compared to the initial period ($p < 0.001$). In group 2, BCVA decreased from initial 0.65 ± 0.61 log MAR to 0.82 ± 0.56 log MAR in the final examination ($p < 0.001$), CMT decreased from baseline 372.60 ± 114.21 μm to 287.06 ± 64.32 μm at the last examination ($p = 0.001$), the presence of SF showed a statistically significant decrease in follow-up periods compared to the initial period ($p < 0.001$). In the last examination, there was no statistically significant difference between the groups in terms of presence of SF ($p = 0.305$).

Conclusion: Both full-dose PDT combined with anti-VEGF and only anti-VEGF applications are effective in the treatment of PCV. There was no significant difference in visual or anatomical results among the two groups. However, we observed that full dose PDT administration combined with anti-VEGF reduces the need for anti-VEGF usage.

Keywords: Polypoidal choroidal vasculopathy, photodynamic therapy, ranibizumab, aflibercept.

INTRODUCTION

Polypoidal choroidal vasculopathy (PCV) is a chorioretinal disorder common in Asians. It was first described by Yannuzzi in 1990 as a clinical entity different from age-related macular degeneration (AMD) which is characterized by serous and hemorrhagic pigment epithelium detachment (PED)^{1, 2}. In addition to macular involvement, it is

characterized by two distinct vascular network: multiple lesions classified by complex and branching vascular network with ill-defined margins and polypoidal lesions classified by reddish-orange perimacular or peripapillary lesions with well-defined margins².

The diagnosis of PCV is made by indocyanine green angiography (IGA) which clearly shows abnormal

1- Ophthalmologist, MD, Retina, Beyoglu Training and Research Hospital, Beyoglu, Turkey

2- Prof. MD, Retina, Beyoglu Training and Research Hospital, Beyoglu, Turkey

Received: 10.06.2020

Accepted: 20.07.2020

Ret-Vit 2021; 30: 47-54

DOI:10.37845/ret.vit.2021.30.8

Correspondence Address:

Bugra KARASU

Beyoglu Training and Research Hospital, Beyoglu, Turkey

Phone: +90 549 382 5082

E-mail: bugra_karasu@hotmail.com

vascular network^{1, 3}. Visual acuity is preserved and macular involvement is lacking in approximately one-half of patients with PCV; however, loss of vision is observed in majority of remaining patients due to frequent, recurrent hemorrhages and exudate involving macula⁴.

In PCV, treatment options include photodynamic treatment with verteporfin (PDT), intravitreal anti-vascular endothelial growth factor (VEGF) agents and thermal laser photocoagulation (TLP). In many studies, contradictory outcomes have been reported, particularly at long-term, by these treatment modalities⁵.

Some authors reported promising short-term results with intravitreal bevacizumab (IVB) plus PDT combination in the treatment of PCV⁶⁻¹⁰. In their study, Ruamviboonsuk et al. reported results of 12 eyes with PCV treated by combination therapy (PDT plus intravitreal ranibizumab (IVR)). The study showed encouraging results in visual recovery, reduction in subretinal hemorrhage incidence and polyp recurrence when compared to previous studies¹¹. However, there is no sufficient data for efficacy and safety of the combination therapy⁹. In clinical practice, clinicians dealt with eyes with recurrent PCV following first PDT or eyes with chronic PCV refractory to anti-VEGF agents; nevertheless, there is limited data regarding efficacy of the combination therapy^{6, 12-14}.

Photodynamic therapy is a non-invasive photochemical induction that leads localized oxidative injury in tissues following non-thermal photo-stress¹⁵. In PDT, vaso-occlusion occurs via damage on vascular endothelial membrane resulting from platelet adhesion and degranulation. Intra-luminal vaso-occlusion occurs via removal of pathological neovascularization by intravenous photo-sensitizing substance (verteporfin) administration and use of lipophilic compounds that readily fuse with lipid cell membrane of endothelial vascular wall¹⁶. It is known that PDT-induced occlusion have no effect on intact photoreceptors at choriocapillaris beneath normal retina and inhibits and treats choroidal neovascularization (CNV) by minimally damage in retina pigment epithelium (RPE) and photoreceptors at upper layers as a result of use of benzoporphyrin-derivative^{17, 18}.

In this study, it was aimed to investigate efficacy and safety of anti-VEGF treatment alone compared to anti-VEGF plus PDT combination in symptomatic patients with PCV.

MATERIALS AND METHODS

In this study, we retrospectively reviewed medical records of 60 patients with PCV including 30 patients treated with anti-VEGF agent plus full-dose PDT (group 1) and 30 patients treated with anti-VEGF therapy alone (group

2) between June, 2010 and March, 2020. 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 inclusion criteria were as follow:

- 1) Presence of symptomatic subfoveal PCV
- 2) Presence of exudative or hemorrhagic features with macular involvement
- 3) At least 24 months of follow-up.

The diagnosis of PCV was made based on presence of branching vascular network that terminated as polypoidal swelling on IGA.

The PCV was classified into 2 types according to IGA characteristics³:

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

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

In this study, there was subfoveal polypoidal lesions, a branching vascular network or type 1 and/or type 2 CNV. Eyes with additional macular disorders (AMD, pathological myopia, idiopathic CNV, angioid streaks or other secondary) CNV were excluded. In addition, eyes with history of intraocular surgery (vitrectomy) other than cataract were also excluded.

At baseline, best-corrected visual acuity (BCVA) assessment using Snellen charts, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, indirect ophthalmoscopy, split-lamp biomicroscopy with contact lens, spectral domain-optical coherence tomography (SD-OCT) were performed while OCT-angiography, fundus fluorescein angiography (FFA) and IGA were also performed as needed.

In both groups, 3 monthly anti-VEGF injections were administered initially as loading dose; followed by pro-re-nata (PRN) regimen¹⁹. In patients with impaired vision secondary to PCV, PDT in combination with either IVR (0.5 mg) injection or intravitreal aflibercept (2 mg/0.05 mL) injection (IVA) as intravitreal anti-VEGF agents or intravitreal anti-VEGF agent alone was administered. Intra-vitreous injections were administered under sterile conditions and prophylactic topical antibiotic were prescribed for one week after injection.

In group 1, regular-flow, full-dose PDT was applied using 689 nm diode laser unit one week after intravitreal anti-VEGF injection. Largest linear size of interest was selected based on previous FFA and IGA images. All polypoidal lesions (type 1 and 2) detected with IGA, all branching vascular network lesions, and all type 1 and 2 CNVs detected with FFA were included. No PDT was applied if no CNV was detected within serous PED lesion.

Modified PDT (attenuated total light energy 25 J/cm²] and laser intensity 300 mW/ cm²]) using standard verteporfin dose (6 mg/m²) and standard duration of laser emission (83 sec) was applied as full-dose PDT ²⁰.

In both groups, central macular thickness (CMT), subretinal fluid (SF) presence and BCVA were assessed at baseline (the day before anti-VEGF injection and on months 1, 3, 6, 9, 12, 18 and 24 and in final visit by SD-OCT. Mean number of injections were also recorded. If recurrent or residual polypoidal lesions were observed on IGA and exudative changes were recognized on SD-OCT, additional anti-VEGF injection plus PDT was applied in the group 1 whereas additional anti-VEGF injection alone was administered in the group 2. When residual polypoidal lesions were detected on IGA but not exudative change on SD-OCT, no additional therapy was given and the patient was re-assessed in the next visit. When only recurrent or residual exudative changes secondary to PCV were observed on SD-OCT, one additional anti-VEGF injection was administered even in the absence of polypoidal lesions or type 1 or type 2 CNV was observed on FFA or IGA. A comprehensive ophthalmological examination was performed one month after additional anti-VEGF injection.

Statistical analysis

Best corrected visual acuity was measured using Snellen charts and transformed into Log MAR units for statistical

purposes. BCVA and anatomical changes during follow-up period were compared using MANOVA test. Normal data distribution was assessed using Kolmogorov-Smirnov test. Mean number of injections was compared between groups using Student's t test. Pearson's correlation rank test was used to analyze correlations among parametric data. Data were analyzed using IBM SPSS version 22.0 (SPSS, IBM, Chicago, IL). A p value <0.05 was considered as statistically significant.

FINDINGS

The mean age was 71.96±8.50 years (range: 52-88 years) in the study population. There were 47 men (78%) and 13 women (22%). Of the eyes included, 30 (50%) were right eye while 30 (50%) were left eye. Mean follow-up was 53.83±14.86 months (range: 20-85 months).

There were no significant differences in age (p=0.529), mean follow-up (p=0.251), PCV type (p=0.545), side (p=0.306), initial BCVA (p=0.302), CMT (p=0.589) and SF (p=0.351) between groups (Student's t test).

No significant change was observed in IOP values during follow-up (p>0.05, MANOVA test).

Table 1 summarizes clinical data.

In group 1 (anti-VEGF plus PDT); mean number of injections was 10.56±1.88 (7-15); mean BVCA was 0.59 ± 0.39 log MAR, 0.49 ± 0.42 log MAR, 0.56 ± 0.37 log MAR, 0.52 ± 0.34 log MAR, 0.57 ± 0.38 log MAR, 0.61 ± 0.48 log MAR, 0.67 ± 0.45 log MAR and 0.71 ± 0.49 at baseline, on months 1, 3, 6, 9, 12, 18, 24 and in final visit, respectively (p=0.016; MANOVA test); mean CMT was 355.56 ± 95.54 µm, 302.10 ± 61.49 µm, 329.23 ± 95.45 µm, 312.76 ± 71.95 µm, 348.36 ± 100.26 µm, 308.46 ± 92.95 µm, 307.60 ± 102.88 µm, 317.33 ± 104.55 µm and

Table 1. Clinical and demographic data of patients.

Treatment group	Group 1	Group 2	p values
	Anti-VEGF+PDT	Anti-VEGF	
Eye	30	30	
Gender (female (f) / male (m))	8 ^f 22 ^m	5 ^f 25 ^m	
Age (mean ±SD)	71.26±7.26	72.66±9.66	0.529
Duration of follow-up (mean ±SD)	51.56±14.56	55.80±14.54	0.251
Side (right (r) / left (l))	13 ^r 17 ^l	17 ^r 13 ^l	0.306
Number of injections (mean ±SD)	10.56±1.88	11.83±2.61	0.039*
Number of injections (range)	7 to 15	7 to 17	
PCV tipi (type 1/ type2)	24/6	22/8	0.545

PDT: photodynamic therapy; SD: standard deviation; VEGF: vascular endothelial growth factor
^f female, ^m male; ^r right, ^l left; PCV, polypoidal choroidal vasculopathy
 *Student's t test

296.76 ± 105.03µm at baseline, on months 1, 3, 6, 9, 12, 18, 24 and in final visit, respectively ($p < 0.001$; MANOVA test).

In group 2 (anti-VEGF alone); mean number of injections was 10.56±1.88 (7-15); mean BVCA was 0.65 ± 0.61 log MAR, 0.57 ± 0.42 log MAR, 0.61 ± 0.46 log MAR, 0.63 ± 0.47 log MAR, 0.60 ± 0.51 log MAR, 0.63 ± 0.45 log MAR, 0.61 ± 0.45 log MAR, 0.67 ± 0.45 log MAR and 0.82 ± 0.56 log MAR at baseline, on months 1, 3, 6, 9, 12, 18, 24 and in final visit, respectively ($p < 0.001$; MANOVA test); mean CMT was 372.60 ± 114.21 µm, 353.83 ± 119.33 µm, 343.83 ± 100.53 µm, 343.96 ± 96.29 µm, 357.66 ± 118.82 µm, 319.30 ± 88.04 µm, 315.16 ± 101.96 µm, 308.16 ± 112.26 µm and 287.06 ± 64.32 µm at baseline, on months 1, 3, 6, 9, 12, 18, 24 and in final visit, respectively ($p < 0.001$; MANOVA test).

When groups were compared at assessment time points, there was significant improvement in SF in group 1 on month 6 ($p = 0.030$; Student's t test). A positive correlation was detected between BCVAs obtained at baseline and in final visit ($r = 0.383$; $p = 0.003$; Pearson's correlation rank test). It was found that final BCVA was decreased by increasing baseline CMT ($r = -0.336$; $p = 0.009$; Pearson's correlation rank test). A positive correlation was detected between CMTs obtained at baseline and in final visit ($r = 0.256$; $p = 0.048$; Pearson's correlation rank test). In the study, PDT plus anti-VEGF combination decreased need for anti-VEGF ($r = -0.272$; $p = 0.036$; Pearson's correlation rank test).

Figure 2 presents BCVA, CMT and SF count. Table 2 presents BCVA, CMT and SF values at baseline and during follow-up.

No serious ocular adverse effect such as endophthalmitis or retinal detachment was observed. Despite loading dose and PRN regimen, SF presence was found to be higher in both groups. There was SF in 25 eyes (83%) in group 1 whereas 27 eyes (90%) in group 2. In group 1, 17 eyes (56%) were treated with IVA whereas 13 eyes (44%) by IVR. In 2 eyes, anti-VEGF treatment was switched to IVA from IVR. In group 1, 15 eyes (50%) were treated with IVA whereas 15 eyes (50%) by IVR. In 3 eyes, anti-VEGF treatment was switched to IVA from IVR. There was no significant difference in injection types and switch rate ($p > 0.05$; Student's t test).

DISCUSSION

In this study, mean number of injections was 10.56±1.88 (range: 7-15) in anti-VEGF plus PDT group and 11.83±2.61 (range: 7-17) in anti-VEGF alone group, indicating decreased anti-VEGF need by PDT. Baseline BCVA, CMT and SF values were comparable between groups. In the anti-VEGF plus PDT group, worsening in final BCVA was delayed or prevented. We attributed this finding to decrease in SF presence and resultant reduction in the number of activation. In anti-VEGF plus PDT group, SF tended to decrease in all time points. In anti-VEGF alone group, no improvement was observed in SF until month 9; thus, there was no improvement in final BCVA gain. Although similar results were observed regarding anatomical and visual success in both groups, less anti-VEGF injection was required to achieve same effect in combined treatment group. In the literature, several studies reported efficacy of anti-VEGF agents in the treatment of exudative PCV²¹⁻²⁹. In a recent study, Cheng et al. reported results of IVB

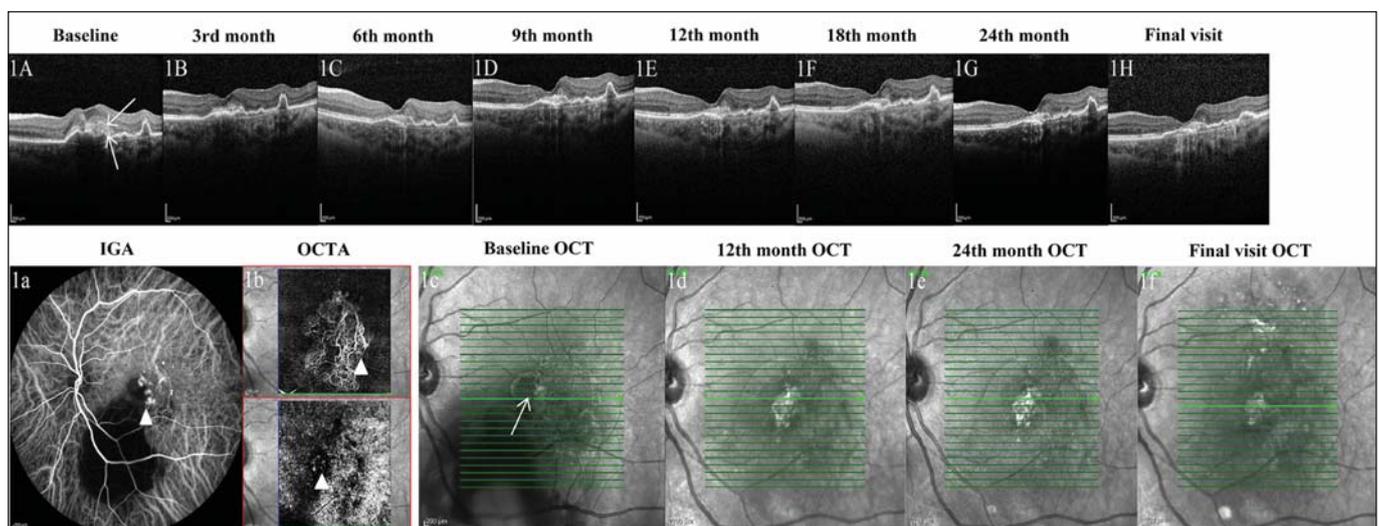


Figure 1: OCT, OCTA and IGA images during follow-up are seen in a patient received anti-VEGF + PDT treatment. Figure 1a and 1c; arrows show SF and exudation related CNV; Figure 1a and 1b; arrows show polyps and vascular network on IGA and OCTA.

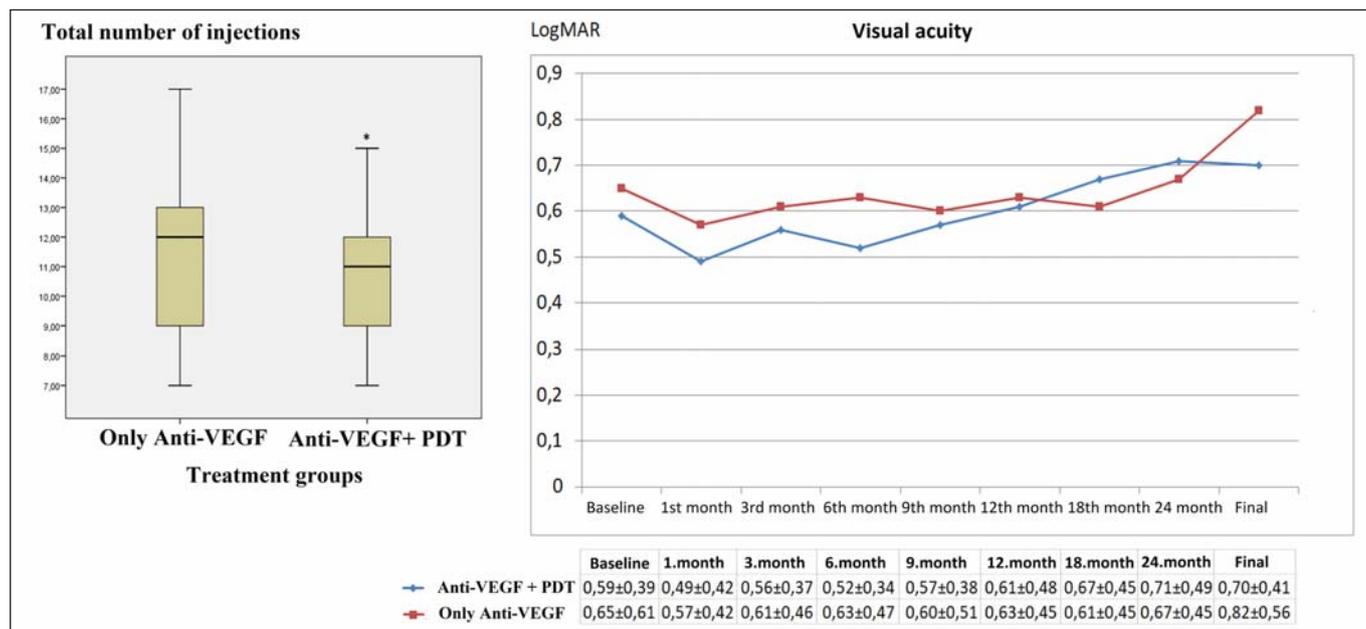


Figure 2: Results of visual acuity and number of injections in the groups.

Table 2: Man BCVA, CMT and SF values at baseline and during follow-up.

Groups	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	Final Visit	p value
<i>Anti-VEGF + PDT combination</i>										
BCVA	0.59±0.39	0.49±0.42	0.56±0.37	0.52±0.34	0.57±0.38	0.61±0.48	0.67±0.45	0.71±0.49	0.70±0.41	0.016
CMT	355.562±95.54	302.10±61.49	329.23±95.45	312.76±71.95	348.36±100.26	308.46±92.95	307.60±102.88	317.33±104.55	296.76±105.03	<0.001
SF (+/-)	(22/8)	(24/6)	(21/9)	(16/14)	(25/5)	(16/14)	(13/17)	(17/13)	(12/18)	<0.001
<i>Anti-VEGF alone</i>										
BCVA	0.65±0.61	0.57±0.42	0.61±0.46	0.63±0.47	0.60±0.51	0.63±0.45	0.61±0.45	0.67±0.45	0.82±0.56	<0.001
CMT	372.60±114.21	353.83±119.33	343.83±100.53	343.96±96.29	357.66±118.82	319.30±88.04	315.16±101.96	308.16±112.26	287.06±64.32	0.001
SF (+/-)	(25/5)	(25/5)	(26/4)	(24/6)	(27/3)	(17/13)	(18/12)	(18/12)	(16/14)	<0.001
MANOVA test										
BCVA: best corrected visual acuity; CMT: central macular thickness; SF: subretinal fluid; VEGF: vascular endothelia growth factor; PDT: photodynamic treatment										

injections at year 1 in PCV treatment. Authors reported that mean BCVA (Log MAR was improved to 0.67 ± 0.51 from 0.79 ± 0.42 by mean injection number of 3.3 over 12 months; however, complete regression in polypoidal lesions was confirmed in only 16.1% of eyes ²⁹.

Kokame et al. showed that monthly ranibizumab injections successfully decreased exudative changes in PCV. However, regression was achieved in only 33% polypoidal lesions even with month injections and branching vascular network persisted in all eyes ²⁷. Although anti-VEGF agents can lead BCVA gain with reduction in exudative changes secondary anti-VEGF agents, their effect on regression of vascular lesion seemed to be limited in PCV ²⁶⁻³⁰. On contrary, in a series of studies, promising results were shown in vascular lesions of PCV and a few PDT could generally achieve complete regression of polypoidal lesions ³¹⁻³⁵.

In a study by Chan et al., it was shown that complete regression was achieved in 95% of PCV eyes underwent PDT ²⁷. Although all polypoidal lesions regressed following PDT, effects on branching vascular network were limited and polypoidal lesions can recur ≥ 1 years after PDT ^{12-14, 33, 34, 36}.

It is anticipated that anti-VEGF agents which lead rapid recovery of exudative changes in combination therapy (anti-VEGF plus PDT) would contribute permanent recovery in visual improvement together with regression polypoidal lesions due to PDT ^{21-29, 31-35}. In addition, it was reported that visual improvement was more favorable in eyes with PCV than those with AMD after PDT; Gomi et al. showed that median change in BCVA was 7.0 letters in AMD and 8.0 letters in PCV ³⁴.

Moreover, it seems reasonable to administer anti-VEGF agent before PDT since VEGF expression is increased

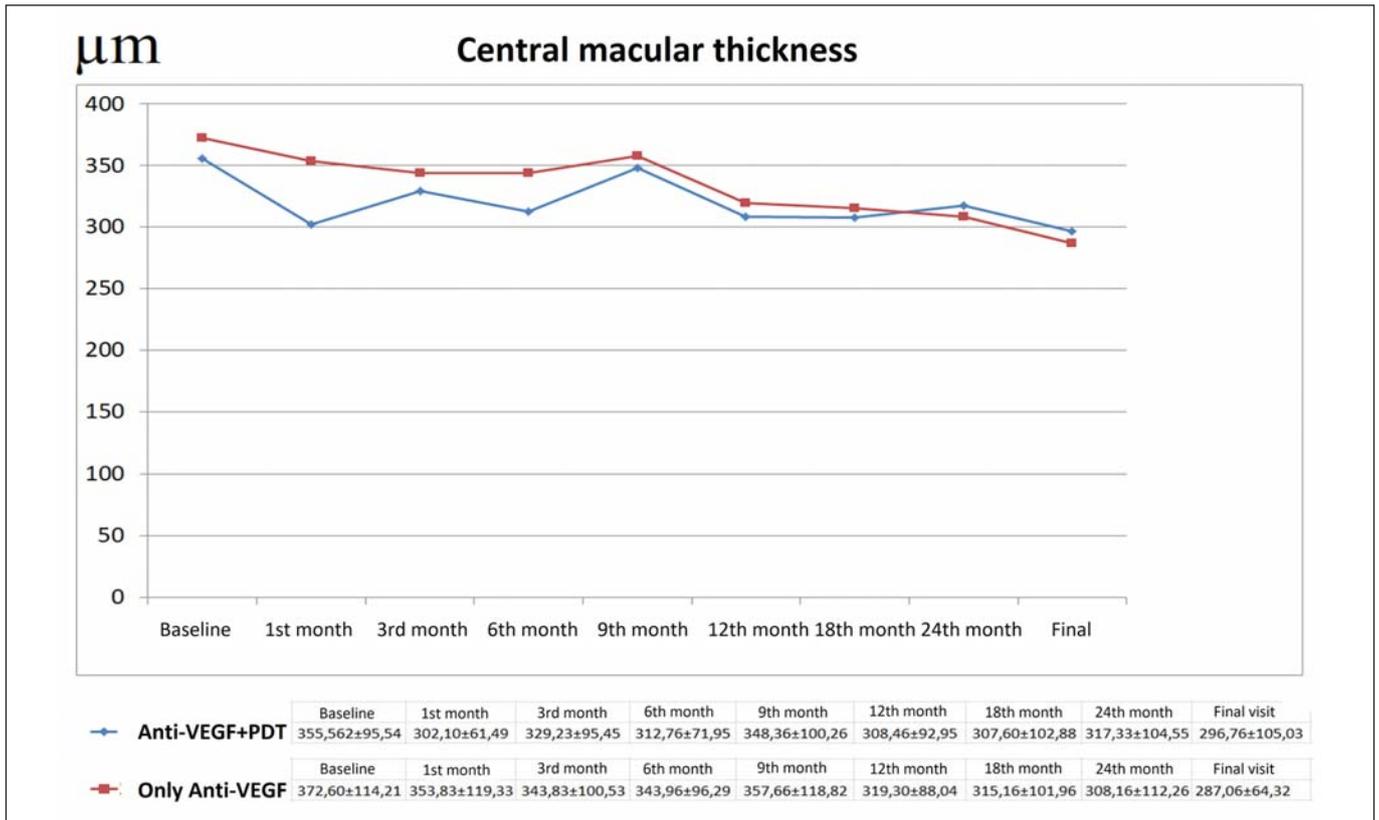


Figure 3: Central macular thickness values during follow-up.

immediately after PDT^{6-8, 11, 28, 37}. In a study using bevacizumab plus PDT for PCV, Sato et al. reported that mean BCVA gain was 2.69 lines and that there was ≥3 lines improvement in 51.7% of patients. In addition, in a study using ranibizumab plus PDT combination in 12 eyes with PCV, Ruamviboonsuk et al. reported ≥15 letters improvement in 58.3% of eyes on month 12^{7, 11}.

The EVEREST study is randomized, controlled trial designed to compare PDT alone, IVR alone and PDT plus IVR combination in 3 groups of PCV eyes. PDT alone or PDT plus ranibizumab (0.5 mg) was found to be superior to ranibizumab monotherapy in regression of polyps in patients with symptomatic macular PCV on month 6³⁸.

Fujisan study is a prospective, randomized study designed to assess PDT timing by comparing IVR plus PDT at baseline and delayed PDT. When PDT alone and PDT plus IVR were compared with IVR alone, it was seen that regression rate for polypoidal lesions was higher but did not reach statistical significance and there was no significant difference in BCVA improvement among 3 groups. Although there was no significant difference in BCVA improvement and polyp regression rate among groups, number of ranibizumab injections was significantly lower in PDT group compared to IVR group at year 1⁴⁰. We also found similar results together with favorable effect of PDT on long-term follow-up.

In a study by Hikichi et al. it was reported that, in PCV treatment, 3 monthly IVR injections and extended injection program was effective in preserving BCVA but polypoidal lesions regression was lower when compared to PDT (40%)⁴¹.

In the VIEW studies, it was shown that aflibercept is effective in all subgroups of neovascular AMD including PCV. Although many studies showed that aflibercept treatment in PCV resulted in favorable visual gain and polyp regression, these studies are limited with retrospective design^{42, 43}.

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 PDT⁴⁴. There is limited data about combination therapy in PCV refractory to anti-VEGF therapy. This study showed that when PDT was combined either ranibizumab or aflibercept as anti-VEGF agents, somewhat visual improvement was achieved in PCV eyes even in those previously treated with anti-VEGF agents. Since anti-VEGF agents have limited

effect on polypoidal lesions, combination therapy can be treatment option when recurrent or persistent exudative changes are seen after anti-VEGF therapies²¹⁻²⁹.

In a study on eyes with neovascular AMD, Astam et al. assessed outcomes of PDT alone and combination therapy in cases diagnosed as retinal angiomatous proliferation (RAP) and PCV. In that study, PDT alone or PDT plus IVB therapy was used in 8 eyes of 7 cases with RAP and 3 eyes of 3 cases with PCV. When all eyes with RAP was assessed, visual acuity was improved in 4 of 8 eyes (50%); remained stable in one eye (12.5%) and decreased in 3 eyes (37.5%). Anatomical success was achieved in 75% of eyes with foveal contour formation in 6 eyes on SD-OCT. PDT or combination treatment was given to 3 eyes of 3 cases with PCV. Visual acuity was improved in 2 eyes (66%) while remained stable in one eye (33%). Anatomical success was achieved in 66% of eyes with foveal contour formation in 2 eyes on SD-OCT. In most studies, effects of PDT on anatomical and visual success as well as need for anti-VEGF need were observed³⁹.

Rates of RPE tear, subretinal hemorrhage, fibrosis or atrophy were higher in patients treated with verteporfin³⁶. In our study, no intraocular complication or adverse effect secondary to PDT was observed in two groups. Significant reduction was observed in CMT and SF in both groups in all time points other than month 9 while significant improvement was observed in BCVA in both groups. However, to achieve similar effect, number of injections was lower in anti-VEGF plus PDT group when compared to anti-VEGF group.

The advantages of our study included long-term follow-up and being one of the rare studies in this field in our country; thus, it can provide important data regarding treatment response in PCV in Turkey. And also has some limitations including small sample size, lack of pre- and post-treatment measurements of polyp size and retrospective design. There is a need for larger, prospective studies in the management of PCV. In conclusion, no significant difference was detected between groups regarding anatomical and visual outcomes in our study. Significant differences were detected in anti-VEGF plus PDT when compared to anti-VEGF alone. Based on these results, anti-VEGF plus PDT combination decreases need for injections and aids achievement of visual and anatomical success.

REFERENCES

- Spaide RF, Yannuzzi LA, Slakter JS, et al. Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. *Retina* 15:100-10, 1995.
- Yannuzzi LA, Sorenson J, Spaide RF, et al. Idiopathic polypoidal choroidal vasculopathy (IPCV). *Retina* 32 ;1:1-8, 2012.
- Yannuzzi LA, Ciardella A, Spaide RF, et al. The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. *Arch Ophthalmol* 115:478-85, 1997.
- Uyama M, Wada M, Nagai Y, et al. Polypoidal choroidal vasculopathy: natural history. *Am J Ophthalmol* 133: 639-648, 2002.
- Koh AH; Expert PCV Panel, Chen LJ, Chen SJ, et al. Polypoidal choroidal vasculopathy: Evidence-based guidelines for clinical diagnosis and treatment. *Retina* 2013;33:686-716.
- Romano MR, Cipollone U, Semeraro F, et al. Combined photodynamic therapy and intravitreal bevacizumab for idiopathic polypoidal choroidal vasculopathy: oneyear follow-up. *Clin Ophthalmol* 2010; 4:1237-1241.
- Sato T, Kishi S, Matsumoto H, et al. Combined photodynamic therapy with verteporfin and intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010;149(6):947-954.
- Gomi F, Sawa M, Wakabayashi T, et al. Efficacy of intravitreal bevacizumab combined with photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010;150(1):48-54.
- ZuoC, WenF, LiJ, et al. Transitions of multifocal electroretinography following combined intravitreal bevacizumab and photodynamic therapy for polypoidal choroidal vasculopathy. *Doc Ophthalmol* 2009;119(1):29-36.
- Moon SW, Kim MS, Kim ES, et al. Photodynamic therapy combined with intravitreal injection of vascular endothelial growth factor antibody for polypoidal choroidal vasculopathy. *Ophthalmologica* 2011;225(3):169-175.
- Ruamviboonsuk P, Tadarati M, Vanichvaranont S, et al. Photodynamic therapy combined with ranibizumab for polypoidal choroidal vasculopathy: results of a 1-year preliminary study. *Br J Ophthalmol* 2010;94(8):1045- 1051.
- Kurashige Y, Otani A, Sasahara M, et al. Two-year results of photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2008;146(4):513-519.
- Tsuchiya D, Yamamoto T, Kawasaki R, et al. Twoyear visual outcomes after photodynamic therapy in age-related macular degeneration patients with or without polypoidal choroidal vasculopathy lesions. *Retina* 2009; 29(7):960-965.
- Akaza E, Mori R, Yuzawa M. Long-term results of photodynamic therapy of polypoidal choroidal vasculopathy. *Retina* 2008;28(5):717-722.
- Milanesi C, Biolo R, Reddi E, et al. Ultrastructural studies on the mechanisms of photodynamic therapy of tumors. *Photochem. Photobiol* 1987;46: 675-81.
- Henderson BW, Dougherty TJ. How does PDT work? *Photochem Photobiol* 1992;55: 145-57.
- Miller JW, Walsh AW, Kramer M, et al. Photodynamic therapy of experimental choroidal neovascularization. *Arch Ophthalmol* 1995; 113:8 10-8 18.
- Schmidt-Erfurth U, Hasan T, Gragoudas E, et al. Vascular targeting in photodynamic occlusion of subretinal vessels. *Ophthalmology* 1994; 101: 1953-61.

19. Wang F, Yuan Y, Wang L, et al. One-Year Outcomes of 1 Dose versus 3 Loading Doses Followed by Pro Re Nata Regimen Using Ranibizumab for Neovascular Age-Related Macular Degeneration: The ARTIS Trial. *J Ophthalmol* 2019 Oct 10;2019: 7530458.
20. Nowak-Sliwinska P, van den Bergh H, Sickenberg M, Koh AH. Photodynamic therapy for polypoidal choroidal vasculopathy. *Prog Retin Eye Res* 2013; 37:182-99.
21. Lai TY, Chan WM, Liu DT, et al. Intravitreal bevacizumab (Avastin) with or without photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2008;92:661-6.
22. Gomi F, Sawa M, Sakaguchi H, et al. Efficacy of intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2008;92:70-3.
23. Song JH, Byeon SH, Lee SC, et al. Short term safety and efficacy of a single intravitreal bevacizumab injection for the management of polypoidal choroidal vasculopathy. *Ophthalmologica* 2009;223:85-92.
24. Pai SA, Shetty R. Sequential therapy with intravitreal bevacizumab and photodynamic therapy for idiopathic polypoidal choroidal vasculopathy. *Acta Ophthalmol* 2009; 87:806-7.
25. Lee SY, Kim JG, Joe SG, et al. The therapeutic effects of bevacizumab in patients with polypoidal choroidal vasculopathy. *Korean J Ophthalmol* 2008; 22:92-9.
26. Tsujikawa A, Ooto S, Yamashiro K, et al. Treatment of polypoidal choroidal vasculopathy by intravitreal injection of bevacizumab. *Jpn J Ophthalmol* 2010;54:310-9.
27. Kokame GT, Yeung L, Lai JC. Continuous anti-VEGF treatment with ranibizumab for polypoidal choroidal vasculopathy: 6-month results. *Br J Ophthalmol* 2010;94:297-301.
28. Rouvas AA, Papakostas TD, Ntouraki A, et al. Photodynamic therapy, ranibizumab, and ranibizumab with photodynamic therapy for the treatment of polypoidal choroidal vasculopathy. *Retina* 2011;31:464-74.
29. Cheng CK, Peng CH, Chang CK, et al. One-year outcomes of intravitreal bevacizumab (Avastin) therapy for polypoidal choroidal vasculopathy. *Retina* 2011; 31:846-56.
30. Cho M, Barbazetto IA, Freund KB. Refractory neovascular age-related macular degeneration secondary to polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2009;148: 70-8.
31. Spaide RF, Donsoff I, Lam DL, et al. Treatment of polypoidal choroidal vasculopathy with photodynamic therapy. *Retina* 2002; 22:529-35.
32. Chan WM, Lam DS, Lai TY, et al. Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy: one-year results of a prospective case series. *Ophthalmology* 2004;111:1576-84.
33. Otani A, Sasahara M, Yodoi Y, et al. Indocyanine green angiography: guided photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2007;144: 7-14
34. Gomi F, Ohji M, Sayanagi K, et al. One-year outcomes of photodynamic therapy in age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese patients. *Ophthalmology* 2008;115:141-6.
35. Silva RM, Figueira J, Cachulo ML, et al. Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. *Graefes Arch Clin Exp Ophthalmol* 2005;243:973-9.
36. Yamashiro K, Tsujikawa A, Nishida A, et al. Recurrence of polypoidal choroidal vasculopathy after photodynamic therapy. *Jpn J Ophthalmol* 2008;52:457-62.
37. Schmidt-Erfurth U, Schlötzer-Schrehard U, Cursiefen C, et al. Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor. *Invest Ophthalmol Vis Sci* 2003; 44:4473-80.
38. Koh A, Lee WK, Chen LJ, et al. EVEREST study: Efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina* 2012; 32: 1453-64.
39. Neslihan Astam, Emin Özmert, Figen Batioğlu. Results of Photodynamic Therapy/Combination Therapy for Retinal Angiomatous Proliferation and Polypoidal Choroidal Vasculopathy in Age-Related Macular Degeneration. *Journal of Retina- Vitreous* 2007;15:2.
40. Gomi F, Oshima Y, Mori R, et al. Fujisan Study Group: Initial versus delayed photodynamic therapy in combination with ranibizumab for treatment of polypoidal choroidal vasculopathy: the Fujisan Study. *Retina* 2015; 35: 1569-76.
41. Hikichi T, Higuchi M, Matsushita T, et al. One-year results of three monthly ranibizumab injections and as-needed reinjections for polypoidal choroidal vasculopathy in Japanese patients. *Am J Ophthalmol* 2012; 154: 117-24.
42. Saito M, Kano M, Itagaki K, et al. Switching to intravitreal aflibercept injection for polypoidal choroidal vasculopathy refractory to ranibizumab. *Retina* 2014; 34: 2192-201.
43. Yamamoto A, Okada AA, Kano M, et al. One year results of intravitreal aflibercept for polypoidal choroidal vasculopathy. *Ophthalmology* 2015; 122: 1866-72.
44. Lee WK, Iida T, Ogura Y, et al. PLANET Investigators. Efficacy and Safety of Intravitreal Aflibercept for Polypoidal Choroidal Vasculopathy in the PLANET Study: A Randomized Clinical Trial. *JAMA Ophthalmol* 2018;1;136:786-93.