

# Regression in polypoidal choroidal vasculopathy treated with ziv-aflibercept monotherapy – short term study

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## Abstract:

**PURPOSE:** The aim of this study was to evaluate the effectiveness of intravitreal ziv-aflibercept (IVZ) in the treatment of polypoidal choroidal vasculopathy (PCV) and its efficacy in regard to polyp regression using optical coherence tomography (OCT) and indocyanine green angiography (ICGA).

**METHODS:** This was a retrospective study of eight eyes of eight patients with treatment-naïve PCV. Patients received IVZ on *pro re nata* protocol. OCT and ICGA parameters were assessed at baseline and subsequent visits with a minimum follow-up of 6 months. ICGA was repeated at 3–6 months to determine the disease activity and quantify the changes in branching vascular network (BVN) polyps. Quantifiable OCT parameters included central macular thickness, pigment epithelial detachment (PED) height, and subfoveal choroidal thickness.

**RESULTS:** The mean age of the study cohort was  $62.3 \pm 7.7$  years, with a mean follow-up of  $7.1 \pm 1.2$  months. The baseline best-corrected visual acuity improved from  $0.70 \pm 0.36$  logarithm of the minimum angle of resolution (Snellen's equivalent 20/100) to  $0.63 \pm 0.34$  (20/80) at last follow-up which was statistically insignificant ( $P = 0.5$ ). Post IVZ injections (mean  $\pm$  standard deviation:  $2.6 \pm 0.7$ ), the total number of polyps reduced significantly from  $3 \pm 3.5$  to  $1 \pm 1.7$  ( $P = 0.03$ ) along with a reduction in BVN size ( $3.9 \pm 4.8$  to  $2.7 \pm 3.8\text{mm}^2$ ;  $P = 0.07$ ). OCT analysis revealed a significant reduction in PED height from  $462.5 \pm 353.8 \mu$  to  $169.9 \pm 127.2 \mu$  ( $P = 0.02$ ).

**CONCLUSION:** IVZ leads to significant morphological changes on ICGA and OCT in terms of polyp regression and reduction of PED height, respectively, with a limited change in visual acuity. IVZ may serve as a cost-effective alternative to treat eyes with PCV.

## Keywords:

Branching vascular network, indocyanine green angiography, intravitreal ziv-aflibercept, optical coherence tomography, polypoidal choroidal vasculopathy

## INTRODUCTION

Yannuzzi *et al.* first described the entity “polypoidal choroidal vasculopathy” (PCV) as a pathology distinctive from neovascular age-related macular degeneration (AMD) consisting of polypoidal vascular lesions associated with serous and hemorrhagic pigment epithelial detachments (PEDs).<sup>[1]</sup> Historically, PCV is known to be less responsive to anti-vascular endothelial growth factor (anti-VEGF) therapy as compared to AMD and has a higher incidence in Asian population.<sup>[2,3]</sup>

There are several treatment strategies available for PCV including thermal laser photocoagulation, verteporfin photodynamic therapy (PDT), anti-VEGF therapy, or a combination of these.<sup>[4-7]</sup> The PLANET study showed that aflibercept monotherapy was noninferior in improving the vision in PCV patients as compared to PDT adjunctive to aflibercept. The gain of visual acuity at 52 weeks (10.7 letters) was maintained (10.7 letters) through 96 weeks in the aflibercept monotherapy arm compared to aflibercept with rescue PDT therapy (10.8 vs. 9.1 at 52 and 96 weeks, respectively).<sup>[5,8]</sup> Complete polyp regression was also comparable with 38.9% in the aflibercept monotherapy group

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as against 44.8% in the aflibercept with rescue PDT group at 52 weeks.<sup>[5]</sup>

Ziv-aflibercept (Zaltrap; Regeneron, New York, USA) is a 114 kDa recombinant protein identical to aflibercept, with an osmolarity (1000 mOsm/kg) which is 3 times that of aflibercept (300 mOsm/kg) making it hyperosmolar to the vitreous. It binds to VEGF receptor 1, VEGF receptor 2, and all the isoforms of VEGF-B and placental growth factor, which could explain its efficacy in various clinical conditions.<sup>[9-12]</sup> It has also been reported as a treatment modality for PCV in the past where there was a reduction in central macular thickness (CMT) and improvement in visual acuity.<sup>[13]</sup> A higher cost of aflibercept in many countries makes it difficult to treat patients with PCV.<sup>[14]</sup> Ziv-aflibercept appears to be effective in PCV in smaller case series with visual gain at 9 months,<sup>[13]</sup> however, its efficacy in regard to polyp regression has not been reported.

The purpose of this study was to evaluate the morphological outcomes using indocyanine green angiography (ICGA) and optical coherence tomography (OCT) features in treatment-naïve eyes with PCV undergoing intravitreal ziv-aflibercept (IVZ) monotherapy.

## METHODS

We retrospectively studied eight consecutive eyes of eight patients aged 50 years or older who were diagnosed with PCV. All patients were treatment naïve and underwent treatment with IVZ monotherapy between March 2017 and February 2018. The study was conducted with the approval of the Institutional Review Board and adhered to the principles of the Declaration of Helsinki. All patients signed a written consent form before treatment explaining the off-label use of IVZ and the potential risks and benefits.

Inclusion criteria comprised the eyes with PCV diagnosed based on the presence of clinical, OCT, and ICGA findings showing polyp-like structures along with branching vascular network (BVN). Patients who were previously treated for PCV (i.e., thermal laser photocoagulation, PDT, submacular surgery, or intravitreal injection of other anti-VEGF agents) and had unavailability of imaging details during follow-up were excluded from this study.

OCT measurements included CMT, PED height, and subfoveal choroidal thickness (SFCT) along with the presence or absence of intra- or subretinal fluid (IRF/SRF). OCT scans were performed at baseline, then every month till the complete resolution of the disease on OCT as well as on ICGA. CMT, PED height, and SFCT were calculated manually using in-built calipers in swept-source OCT (SS-OCT) machine. CMT was measured at the center of the fovea from the internal limiting membrane to the retinal pigment epithelium (RPE). PED height was calculated at the site of maximum separation of RPE from underlying Bruch's membrane measured as the distance between inner surface of Bruch's membrane and RPE.

SFCT was defined as choroidal thickness under the fovea from the outer portion of the hyperreflective line corresponding to RPE and the inner surface of the sclerochoroidal junction. OCT characteristics including the presence of tall, multiple, notched PED, intraretinal hard exudates, and sub-RPE hyporeflectivity with hyper-reflective ring suggestive of polyps were also analyzed.<sup>[15]</sup>

Fluorescein angiography (FA) and ICGA (HRA-II; Heidelberg Engineering, Dossenheim, Germany) and OCT (SS-OCT; Topcon DRI OCT Triton® plus, Japan) were performed at baseline to diagnose PCV and evaluate the morphological changes. ICGA features included the presence or absence of BVN, polyps, and feeder vessels. The area of BVN and the number of polyps were calculated in mid or late phase of ICGA after at least 60 s of dye injection as per the criteria set by the EVEREST study.<sup>[4]</sup> OCT imaging was performed at every visit while ICGA being an invasive modality was repeated based on clinical discretion in cases with suboptimal response or recurrence of disease activity in terms of best-corrected visual acuity (BCVA) drop  $\geq 0.1$  logarithm of the minimum angle of resolution (logMAR) units, fresh subretinal or sub-RPE hemorrhage, and/or persistence or recurrence of IRF/SRF.

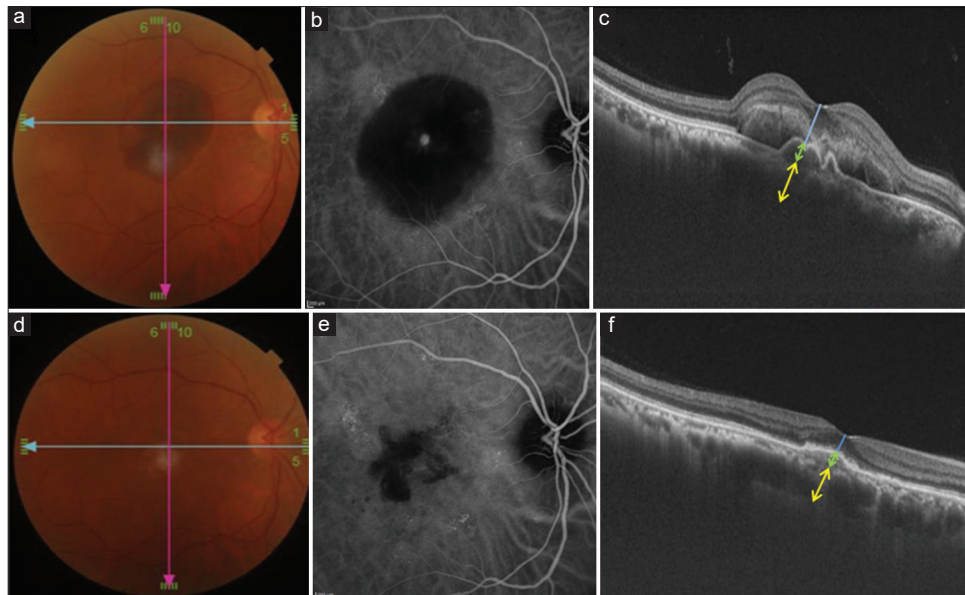
Polyp regression was defined as no IRF/SRF on OCT and no detectable leak on FA/ICGA with the absence of polyps on ICGA.

All patients received an initial dose of IVZ (1.25 mg/0.05 ml), and then, further treatment was based on *pro re nata* (PRN) protocol. Retreatment criteria were the presence of new, clinically detectable subretinal or sub-RPE hemorrhages, and/or persistence or recurrence of IRF/SRF on OCT. Patients were followed up for a minimum of 6 months.

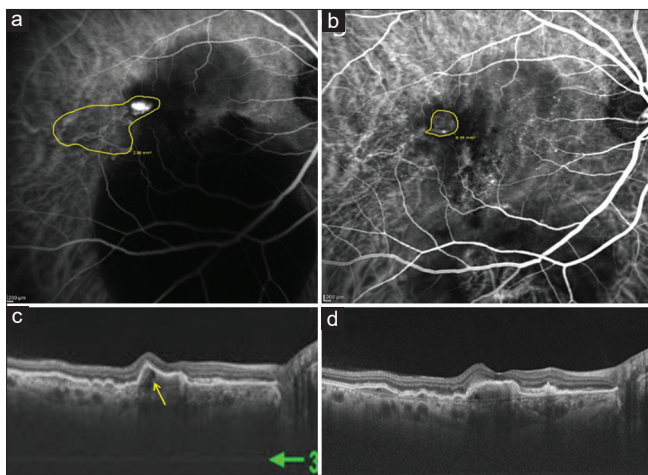
Statistical analyses were performed using the Statistical Package for the Social Sciences version 23 (IBM, Armonk, NY).  $P = 0.05$  was considered to denote statistical significance. Normality distribution of data was confirmed using Shapiro–Wilk test. Paired *t*-test (parametric test) and Wilcoxon signed-rank test (nonparametric test) were done based on normality distribution pattern to compare the parameters at the baseline and at the last follow-up.

## RESULTS

We excluded 13 eyes during our retrospective chart review due to the history of previous treatment for PCV (8 eyes) and unavailability of treatment details during follow-up (5 eyes). We analyzed the OCT and ICGA characteristics of eight eyes of eight patients with PCV treated with monotherapy of IVZ on a PRN basis. The mean age was  $62.3 \pm 7.7$  years with 7 males and 1 female. All patients were phakic at baseline. The mean ( $\pm$ standard deviation) BCVA at baseline was  $0.70 \pm 0.36$  logMAR (Snellen's equivalent 20/97) which improved to  $0.63 \pm 0.34$  logMAR (20/85) at last follow visit [Table 1]. The change in BCVA using paired *t*-test was statistically insignificant ( $P = 0.5$ ). Four patients had an improvement



**Figure 1:** (a) Fundus photo (case 8) showing subretinal pigment epithelium heme involving macula with indocyanine green angiography; (b) Blocked fluorescence and focal hyperfluorescence suggestive of polyp. Optical coherence tomography (c) showing subretinal hyper-reflectivity and notched pigment epithelial detachment. Post 2 ziv-aflibercept injections, fundus showed resolved heme (d). Indocyanine green angiography (e) showing the absence of polyp with optical coherence tomography (f) showing reduction in pigment epithelial detachment height. Note the reduction in central macular thickness (blue line), pigment epithelial detachment height (green arrow), and subfoveal choroidal thickness (yellow arrow) in (c and f)



**Figure 2:** Indocyanine green angiography, late phase; (a) Blocked fluorescence due to subretinal heme and indocyanine green angiography showing branching vascular network (area, 2.88 mm<sup>2</sup>) with localized hyperfluorescence suggestive of polyp. Optical coherence tomography scan (c) showing tall, peaked pigment epithelial detachment hyporefectivity beneath pigment epithelial detachment suggestive of polyp (arrow). After four intravitreal ziv-aflibercept injections through 8 months, there was a reduction in branching vascular network size (0.44 mm<sup>2</sup>) with regressed polyp (b) and optical coherence tomography showed a reduction in pigment epithelial detachment height with flattening of pigment epithelial detachment and reduction in hyporefectivity beneath retinal pigment epithelium (d)

of visual acuity, with three patients showing  $\geq 2$ -line improvement. Among the remaining four patients, two patients lost (2 lines and 3 lines) while the other two maintained the same vision. One patient with a drop in BCVA received focal

laser as a rescue therapy to the extrafoveal polyps. Another patient developed a scar involving the macula leading to drop in BCVA.

Polyps were identified in 7 of 8 eyes at baseline, and at last follow-up, 4 of 8 eyes had persistence of polyps. The mean number of polyps reduced from  $3 \pm 3.5$  to  $1 \pm 17.0$  ( $P = 0.03$ ) after treatment. There was presence of BVN in 4 eyes before and after treatment. Interestingly, the area of BVN reduced in size in all 4 eyes. The mean BVN area (in mm sq) reduced from  $3.9 \pm 4.8$  to  $2.7 \pm 3.8$  ( $P = 0.07$ ), and the change in BVN size compared using Wilcoxon signed-rank test was not significantly different. Feeder vessel was noted in 3 eyes in pre- and posttreatment imaging. The mean number of injections based on PRN protocol was  $2.6 \pm 0.7$  during the follow-up period (mean follow-up:  $7.1 \pm 1.2$  months). Representative cases are shown in Figures 1 and 2.

OCT analysis revealed a CMT reduction in 6 of 8 eyes (75%). The mean CMT reduced from  $372.0 \pm 104.3 \mu$  to  $291.9 \pm 141.5 \mu$  ( $P = 0.31$ ). PED height reduced significantly from  $462.5 \pm 353.8 \mu$  to  $169.9 \pm 127.2 \mu$  ( $P = 0.02$ ). The mean SFCT (in microns) reduced from  $264.4 \pm 72.5 \mu$  to  $214.5 \pm 97.3 \mu$  ( $P = 0.12$ ). SFCT reduced in 5 eyes, increased in 1 eye, and remained unchanged in 2 eyes, as shown in Table 1. Polyps defined as hyporefective lesions with a hyperreflective ring on the undersurface of RPE were demonstrable only in 3 out of 8 (37.5%) eyes. Moreover, baseline OCT analysis showed that among the rest of OCT markers, tall PED (2 eyes), notched PED (5 eyes), multiple PED (4 eyes), and intraretinal hyper-reflectivity suggestive of hard exudates (1 eye) were present in a limited number of study patients.

**Table 1: The baseline and final parameters in eyes treated with monotherapy of intravitreal ziv-aflibercept**

Age/sex	BCVA		BVN area		Polyp number		CMT		PED height		SFCT		Number of IVZ	Follow-up (months)
	logMAR		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
	Pre	Post												
76/male	1	0.8	8.88	7.06	4	1	289	204	51	40	210	194	3	8
59/male	0.4	0.4	2.88	0.43	1	1	330	477	1218	295	351	408	4	8
57/female	0.4	0.7	11.67	9.46	11	5	220	510	320	74	150	146	2	6
54/male	1	0.48	0	0	2	1	394	371	627	419	278	211	3	6
62/male	0.48	0.48	0	0	3	0	488	221	568	85	291	210	2	9
59/male	0.7	0.9	0	0	0	0	374	175	329	131	334	116	2	6
72/male	1.3	1.2	7.67	4.86	2	0	338	142	258	173	191	132	3	8
59/male	0.3	0.1	0	0	1	0	543	235	329	142	310	299	2	6

BCVA=Best-corrected visual acuity; logMAR=Logarithm of the minimum angle of resolution; BVN=Branching vascular network (area in sq. mm); CMT=Central macular thickness; PED=Pigment epithelial detachment; SFCT=Subfoveal choroidal thickness; IVZ=Intravitreal ziv-aflibercept

## DISCUSSION

In this study, we found that monotherapy of IVZ leads to significant reduction in number of polyps ( $3 \pm 3.5$  to  $1 \pm 17.0$ ;  $P = 0.03$ ) in eyes with PCV, though change in BCVA was not significantly different. Polyps are terminal protuberances at the end of BVN which have a tendency to exude and/or bleed. The importance of polyp regression on disease activity has been highlighted in previous studies.<sup>[5,8,16]</sup>

The PLANET study which compared aflibercept monotherapy with combination of aflibercept and rescue PDT reported a complete polyp regression of 38.9% in the aflibercept monotherapy group as compared to 44.8% in the combination arm at 52 weeks. During the same time, the number of patients with no active polyps was 81.7% and 88.9% in the monotherapy and combination therapy arms, respectively.<sup>[5]</sup> A 96-week analysis of the PLANET study revealed a polyp regression of 33.1% and 29.1% in the monotherapy and combination groups, whereas 82.1% and 85.6% of the patients had no evidence of polyp activity in the respective groups.<sup>[8]</sup> Studies such as EVEREST and EVEREST II which compared ranibizumab, PDT, and/or combination of ranibizumab with PDT have reported variable results with regard to polyp regression. The EVEREST study showed that PDT alone (71.4%) or in combination with ranibizumab (77.8%) was superior to IVR monotherapy (28.6%) in achieving regression of polyps during the 6-month follow-up period.<sup>[4]</sup> EVEREST II showed a significant difference of polyp regression between the ranibizumab (34.7%) and combination therapy groups (69.3%) at month 12 ( $P < 0.001$ ).<sup>[6]</sup>

Treatment with anti-VEGF agents leads to reduction in IRF/SRF due to reduced exudation from BVN and polyps. Successful anatomical outcomes, therefore, are linked to polyp inactivation and in a small subset to polyp regression. Therefore, the studies consider polyp regression as an important marker to assess disease activity. However, anatomical success may not be directly linked to successful functional outcomes. There is ample literature evidence to suggest that polyp regression is not directly linked to visual acuity gain which is evident in our study as well.<sup>[4-6,8,16]</sup> Lee *et al.* have shown that disease activity may be present without the presence of active polyps. This

may be due to active exudation from BVN which necessitates further treatment.<sup>[16]</sup> This suggests that polyp regression may not be treatment endpoint in eyes with PCV.

OCT being a noninvasive modality shows a high sensitivity and specificity in the diagnosis of PCV and identification of disease activity in terms of the presence of subretinal or IRF.<sup>[15,17]</sup> The presence of different types of PED (tall, notched, and/or multiple), intraretinal hard exudates, and hyporeflective lesion with a hyperreflective ring on undersurface of RPE (polyps) suggest a diagnosis of PCV (sensitivity, 94.6%; specificity, 92.9%).<sup>[15]</sup> These findings are, however, not consistent and could be confirmed in a limited number of patients in our cohort.

In our study, we used the standard dose of IVZ (1.25 mg/0.05 ml) which is less than the dose of aflibercept (2 mg) used in clinical practice. We found a significant decrease in PED height following treatment with IVZ, whereas change in CMT and SFCT was not significant at last follow-up. The mean reduction in BVN area though was notable, the difference was not significant. Previous reports have shown a short-term, significant reduction of PED height after instituting aflibercept therapy in eyes with neovascular AMD refractory to ranibizumab manifesting in the form of persistent SRF/IRF and PED height ( $>100-150 \mu$ ). However, despite the anatomical improvement, there was no significant change in visual function.<sup>[18,19]</sup> Hypothetically, a higher penetration of aflibercept (or ziv-aflibercept in this series) in sub-RPE space is a possibility, however, this has not been proven conclusively in the past.

Even though aflibercept may have superior outcomes compared to other anti-VEGF drugs and PDT in the treatment of PCV, the biggest concern is the economic burden of treatment.<sup>[14]</sup> Ziv-aflibercept which contains the same molecule but a higher osmolarity has also been reported to be used to treat various retinal pathologies including PCV.<sup>[13,20]</sup> Its major concern was its higher osmolarity and the risk of retinal toxicity which has been studied in the past. IVZ has been found to be safe in both short-term and long-term studies at different doses (1.25, 2, and 2.5 mg) with electroretinogram testing.<sup>[21]</sup> A recent multicenter study has established the safety profile of IVZ and supported its intraocular use.<sup>[20]</sup>

The main limitations of this study were its small sample size, short follow-up, and the use of data from only a single center. We did not have advanced OCTA devices; therefore, quantitative measurements could not be done. We did not have any comparison arm with aflibercept or other anti-VEGF agents or combination therapy group. Moreover, we did not study the effects of other effective modalities for regression of polyps in macular PCV such as stereotactic radiotherapy.<sup>[22]</sup>

## CONCLUSION

This series suggests a cost-effective alternative treatment with ziv-aflibercept over aflibercept with comparable polyp regression rate and reduction in CMT for use in countries with lower gross domestic product and poor insurance coverage. Further studies on long-term anatomical and visual outcome with ziv-aflibercept in PCV in a head-to-head comparison with aflibercept may establish ziv-aflibercept as an effective treatment option for PCV.

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## Conflicts of interest

There are no conflicts of interest.

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