Original Article

Comparison of intravitreal ziv-aflibercept and bevacizumab monotherapy in treatment-naive polypoidal choroidal vasculopathy

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Purpose: To report the visual and anatomical outcomes of intravitreal ziv-aflibercept (IVZ) and bevacizumab (BVZ) monotherapy in treatment-naive polypoidal choroidal vasculopathy (PCV). **Methods:** This was a retrospective case series of 16 eyes (8 eyes each in IVZ and BVZ groups). The study period was from January 2016 to March 2018. The inclusion criteria were treatment-naive PCV patients who were treated with either IVZ or BVZ monotherapy on *pro re nata* protocol and followed up monthly for 6 months. The change in best-corrected visual acuity (BCVA), central macular thickness (CMT), and pigment epithelial detachment (PED) height was measured at baseline and 6 months. **Results:** A total of 16 eyes were studied. IVZ group had an improvement in BCVA by 0.15 logarithm of minimum angle of resolution (logMAR; approximately 1.5 lines) at 6 months, whereas BVZ group had a reduction in BCVA by 0.21 logMAR (approximately 2 lines) (P = 0.027). Five patients and one patient in IVZ and BVZ groups, respectively, had ≥5 letters gain of BCVA. IVZ group had significant reduction in PED height (P = 0.048), whereas the change in CMT was not significant at 6 months (P = 0.681). The mean number of injections (2.87 ± 0.83 in IVZ and 2.25 ± 0.89 BVZ group; P = 0.168) and longest treatment-free interval (3.00 ± 2.20 months in IVZ and 2.12 ± 1.96 months in BVZ group; P = 0.41) were not significantly different. **Conclusion:** The visual and anatomical outcomes in terms of PED reduction in treatment-naive PCV patients were better in IVZ group compared with BVZ. IVZ monotherapy is a viable, cost-effective alternative in these patients with good safety profile.

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Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (n-AMD) and characterized by the presence of hemorrhagic pigment epithelial detachment (PED), subretinal fluid (SRF), and branching vascular network (BVN) along with the presence of polyps.[1,2] Currently, among the various treatment options available, the anti-vascular endothelial growth factor (VEGF) agents with or without photodynamic therapy using verteporfin (vPDT) form the first line of therapy.[3-7] The major randomized controlled trials (RCTs) including EVEREST, EVEREST II, and PLANET have evaluated the role of photodynamic therapy and anti-VEGFs in patients with PCV and showed variable results on superiority.[3,4,6] Considering the availability, cost, and long-term side effects of PDT, anti-VEGF monotherapy is now being considered as first line of therapy.

The 12-month results of PLANET study have shown that gain in visual acuity (10.7 letters) with aflibercept (AFL) monotherapy was comparable to AFL + vPDT combination therapy (10.8 letters; P = 0.54).[6] Few authors have reported a favorable outcome on switching over to AFL from other anti-VEGF agents.[8,9] AFL monotherapy has been shown to have better polyp regression when compared with RBZ, although there are no RCTs with direct comparison showing this favorable effect.[3,4,6,7,10] Higher binding affinity of AFL to VEGF A, B, and placental growth factor may play a role in these apparently superior outcomes.[11] Ziv-aflibercept, a molecule similar to AFL with different osmolarity, has been used in other chorioretinal pathologies and in treatment-naive PCV patients with considerable success.[12-16]

On the other hand, BVZ has been used in the treatment of PCV in a limited number of studies showing improvement in best-corrected visual acuity (BCVA), reduction in central macular thickness (CMT), and PED height.[17-19] In the absence of head-to-head comparison of anti-VEGF agents, the superiority of bevacizumab (BVZ), ranibizumab (RBZ), AFL, or intravitreal ziv-aflibercept (IVZ) over one another is not known in the management of PCV. The effect of ziv-aflibercept and the comparison to other anti-VEGF agents particularly BVZ in PCV have not been studied in greater detail in the past.[16]

In this case series, we compared the treatment outcomes of two off-label cheaper alternatives, intravitreal BVZ and ziv-aflibercept monotherapy, in eyes with treatment-naive PCV at 6 months' follow-up.

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Methods

The study was a retrospective case series including patients with treatment-naive PCV who were treated at a tertiary care institute in South India during January 2016 to March 2018 with anti-VEGF monotherapy either BVZ or IVZ with at least 6 months follow up. The approval for the study was obtained from the Institute Review Board and the study conformed to the tenets of the Declaration of Helsinki. An informed consent was taken from all the participants in the study.

Inclusion and exclusion criteria

The symptomatic treatment-naive cases of PCV who were ≥18 years of age were included in the study. Comprehensive examination included clinical examination, fundus photography using Zeiss Visupac® FF4 and FF450-plus (Carl Zeiss, Dublin, CA, USA), fluorescein angiography (FFA), and indocyanine green angiography (ICGA) using HRA-2 (Heidelberg Engineering Inc., Dossenheim, Germany) and swept-source optical coherence tomography (OCT) (DRI OCT; Topcon, Tokyo, Japan). The presence of localized hyperfluorescence within the first 6 min suggestive of polyps in ICGA with or without the presence of BVN was taken as the diagnostic criterion of PCV for the study.[4] The activity of the disease was confirmed on OCT by the presence of SRF, intraretinal fluid (IRF), hemorrhagic PED, or increase of ≥100 µm in CMT from the last visit. The confirmed cases were treated with either monotherapy of BVZ (1.25 mg/0.05 mL) or ziv-aflibercept (1.25 mg/0.05 mL) based on the discretion of the treating physician. Although the injections were given on a *pro re nata* (PRN) protocol, the patients were evaluated monthly.

The exclusion criteria included cases of choroidal neovascular membrane, previously treated cases of PCV, or patients with <6 months of follow-up. Eyes with significant cataract precluding fundus view or other vision disabling ocular pathology were also excluded from the study.

Data collected included baseline demographic details including age, gender, duration of ocular complaints, clinical findings, systemic complaints, affected eye, and fellow eye status. Slit lamp biomicroscopy along with BCVA in Snellen and logarithm of minimum angle of resolution (logMAR) units, CMT, and PED height were recorded at baseline and at final follow-up visit of 6 months. The mean number of injections and mean treatment-free interval were calculated. During the follow-up visit, BCVA was recorded and an OCT scan was performed. The patients were retreated when there was a decrease in BCVA by more than 0.1 logMAR and/or presence of SRF/IRF or CMT measuring >250 µm.

Primary outcome measure was change in BCVA at month 6 from baseline. Secondary outcome measures were changes in CMT and PED height at month 6 from baseline, mean number of injections through 6 months, and longest treatment-free interval.

Statistical analysis

Statistical analysis was done using SPSS version 23 (IBM, Chicago, IL, USA). The visual acuities (recorded in Snellen chart) were converted to logMAR units for analysis. Improvement or worsening was defined as difference of 0.1 logMAR units from the initial visit while stable vision was within 0.1 logMAR units from baseline visit. The continuous variables were analyzed using Wilcoxon rank-sum test. A P value of <0.05 was considered as statistically significant.

Results

Baseline characteristics

A total of 16 treatment-naive eyes of 16 patients (8 each in IVZ and BVZ groups) were included in the analysis. The mean [± standard deviation (SD)] age of the IVZ and BVZ groups was 60.25 ± 7.1 and 59.28 ± 8.65 years, respectively. The baseline characteristics were not statistically different in the two study groups. The gender distribution in the two groups was four males and four females in the IVZ group and four males and four females in the BVZ group. The mean (±SD) duration of the disease was 5.37 ± 7.92 and 4.99 ± 8.14 months in the IVZ and BVZ groups, respectively (P = 0.92) [Table 1].

Visual acuity gain

The mean BCVA improved from 0.48 ± 0.36 (Snellen equivalent 20/60) to 0.34 ± 0.40 (Snellen equivalent 20/40) (Δ −0.15 ± 0.16) logMAR units at 6 months in IVZ group. Five patients had an improvement of ≥0.1 logMAR (approximately 5 letters) units, while three patients maintained BCVA. None of the patients had a loss of BCVA in IVZ group. On the other hand, in the BVZ group, the mean BCVA reduced from 0.46 ± 0.39 (Snellen equivalent 20/60) to 0.66 ± 0.65 (approximate Snellen

Table 1: Mean baseline parameters (BCVA in logMAR, CMT, PED height) along with clinical and anatomical outcomes in IVZ and BVZ monotherapy groups at 6 months

	IVZ (n=8)	BVZ (n=8)	P
Age (years, mean±SD)	60.25±7.1	59.28±8.65	0.80
Gender	Four males, four females	Four males, four females	
Duration of disease (months, mean±SD)	5.37±7.92	4.99±8.14	0.92
Baseline BCVA logMAR	0.48±0.36 (20/60)†	0.46±0.39 (20/60)	0.91
Final BCVA (at 6 months) logMAR	0.34±0.40 (20/40)	0.66±0.65 (20/90)	
Change in BCVA logMAR	−0.15±0.16	+0.21±0.37	**0.027**
Change in CMT (µm)	17.62±115.67	2.5±71.16	0.681
Change in PED height (µm)	122±135.85	34.12±152.13	**0.048**
Mean (±SD) number of injections	2.87±0.83	2.25±0.89	0.168
Longest treatment-free interval (months)	3.00±2.20	2.12±1.96	0.41

BCVA: best-corrected visual acuity; logMAR: logarithm of minimum angle of resolution; CMT: central macular thickness; PED: pigment epithelial detachment; IVZ: intravitreal ziv-aflibercept; BVZ: bevacizumab; SD: standard deviation. †Bracketed values represent approximate Snellen equivalent visual acuity

equivalent 20/100) (Δ +0.21 ± 0.37; approximate 10 letters loss) logMAR units at 6 months. Three patients maintained the same visual acuity, while one patient had an improvement of >0.2 logMAR (more than 10 letters). Four patients had reduction in BCVA in BVZ group and three patients among them lost more than three lines or 15 letters (>0.3 logMAR units) [Table 2]. The difference in BCVA between IVZ and BVZ at month 6 was statistically significant (P = 0.027). Representative cases are shown in Figs. 1–3.

OCT parameters

The OCT parameters including CMT and PED height were compared in the two groups [Table 2]. The difference in CMT in the two groups was not statistically significant (P = 0.681) [Table 1]. PED height increased by a mean of 34.12 µm in the group treated with BVZ, whereas IVZ group had a mean reduction of 122 ± 135.85 µm, which was statistically significant (P = 0.048). Three patients had persistence or increase in SRF or subretinal hemorrhage in BVZ group, whereas all patients in IVZ group had resolution of SRF at 6 months.

Number of injections

The mean (±SD) number of injections at 6 months was 2.87 ± 0.83 and 2.25 ± 0.89 in the IVZ and BVZ groups, respectively (P = 0.168).

Treatment-free interval

The mean (±SD) treatment-free interval in the IVZ and BVZ groups was 3.00 ± 2.20 and 2.12 ± 1.96 months, respectively (P = 0.41).

Complications

Overall, there were no injection-related ocular (endophthalmitis, retinal detachment, vitreous hemorrhage) or systemic complications (cerebrovascular accident, myocardial infarction, hypertensive crisis) during the follow-up period of 6 months.

Discussion

PCV, currently considered a subtype of n-AMD, has been treated with monotherapy of anti-VEGF agents in the past

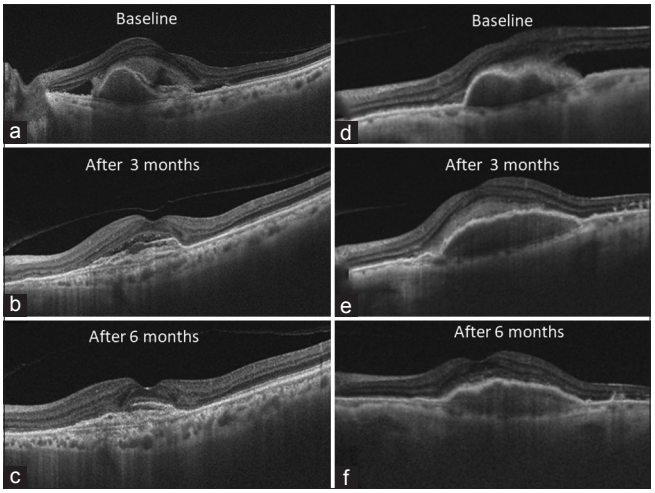

Figure 1: (a) Baseline swept-source optical coherence tomography (SS-OCT) with subretinal fluid (SRF), subretinal hyperreflectivity (SHRM), and pigment epithelial detachment (PED). At 3 (b) and 6 months (c), after three intravitreal ziv-aflibercept (IVZ) injections on *pro re nata* (PRN) protocol, PED height reduction was noted with subretinal scarring. (d) SRF, SHRM, and notched PED. After three intravitreal bevacizumab (BVZ) injections (at baseline, 2nd and 4th month), SS-OCT showed resolution of SRF with persistent PED at 3 (e) and 6 months (f)

Table 2: Baseline and final parameters through 6 months of all 16 eyes including BCVA in logMAR, CMT, and PED height in microns (µm)

	Age	Sex	Duration (months)	BCVA (logMAR)			CMT (µm)			PED height (µm)		
				1st*	Final	Diff†	1st	Final	Diff	1st	Final	Diff
IVZ												
1	63	F‡	4	0.6	0.6	0	244	206	38	178	72	106
2	59	F	5	0.3	0.1	0.2	325	265	60	178	109	69
3	75	M§	2	1	0.8	0.2	319	298	21	35	56	−21
4	51	M	0.3	0.1	0.1	0	264	517	−253	531	387	144
5	58	M	0.2	0.48	0	0.48	262	225	37	480	177	303
6	63	F	0.5	0.3	0.1	0.2	412	398	14	258	189	69
7	57	M	24	0.1	0	0.1	329	217	112	128	159	−31
8	56	F	7	1	1	0	188	76	112	902	565	337
Intravitreal BVZ												
1	55	F	1	1	1.35	−0.3	364	321	43	213	422	−209
2	50	F	24	0.48	1	−0.5	321	348	−27	62	223	−161
3	50	F	0.2	0.18	0.1	0.08	293	356	−63	812	549	263
4	70	M	7	0.4	0.4	0	403	337	66	189	211	−22
5	63	M	1	0.7	0.48	0.22	312	267	45	178	166	12
6	53	F	0.2	0	0.18	−0.2	267	233	34	28	18	10
7	53	M	0.5	0	0	0	247	221	26	67	55	12
8	71	M	6	0.9	1.82	−0.9	289	433	−144	211	389	−178

BCVA: best-corrected visual acuity; logMAR: logarithm of minimum angle of resolution; CMT: central macular thickness; PED: pigment epithelial detachment; IVZ: intravitreal ziv-aflibercept; BVZ: bevacizumab. *1st=baseline visit; †diff=difference between 1st and final visit; ‡F=female; §M=male

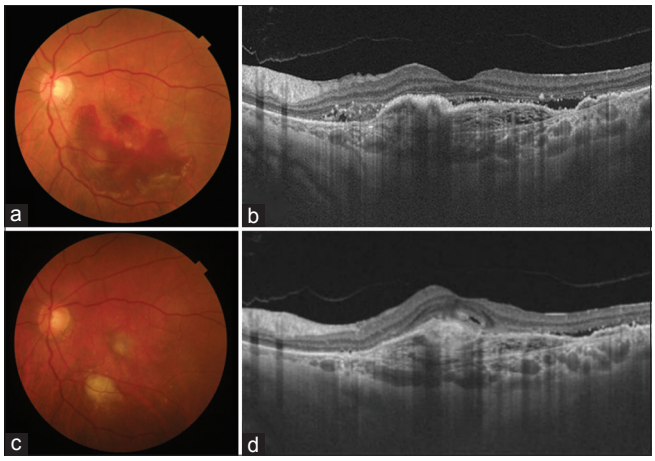

Figure 2: Fundus photograph of a 50-year-old female with best-corrected visual acuity of 20/30 (a) showing presence of subretinal hemorrhage (SRH), fluid (SRF) at and inferior to fovea with swept-source optical coherence tomography (b) showing SRH, SRF, and fibrovascular pigment epithelial detachment (fv-PED). After four intravitreal bevacizumab injections in 6 months, BCVA improved to 20/25 with presence of shallow SRF and subretinal scarring (c) on SS-OCT (d)

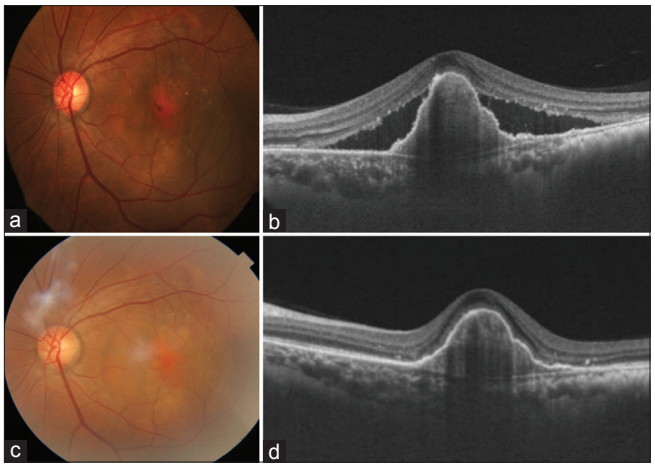

Figure 3: Fundus photograph of a 51-year-old male with best-corrected visual acuity (BCVA) of 20/25 along with presence of subretinal reddish nodule with subretinal fluid (SRF), min subretinal hemorrhage (SRH) (a). swept-source optical coherence tomography (SS-OCT) (b) shows presence of SRF and pigment epithelial detachment (PED). After three intravitreal ziv-aflibercept injections on *pro re nata* (PRN) protocol, BCVA remained 20/25 with fundus and SS-OCT showing resolution of subretinal hemorrhage and SRF and persisting PED (c, d)

with successful results.[3,4,7,16,20,21] We previously reported a significant improvement in BCVA by 0.16 logMAR ($P < 0.001$) at 9 months in 23 eyes with PCV, treated with IVZ monotherapy on PRN protocol.[16] We compared the effects of IVZ and BVZ monotherapy in treatment-naive PCV patients with a follow-up period of 6 months. While there was an improvement in BCVA in the IVZ group (mean ± SD = 0.15 ± 0.16 logMAR units), the BVZ group had a vision drop of 0.2 logMAR units ($P = 0.027$).

In our study, the mean number of injections required in the IVZ group was 2.87 ± 0.83 as compared with 2.25 ± 0.87 injections in the BVZ group ($P = 0.168$) through 6 months of follow-up using PRN protocol. The longest treatment-free interval was not statistically significant between the two groups. IVZ group had a significantly more reduction in PED height compared with BVZ ($P = 0.048$). However, the difference in CMT reduction was not significant across the two groups ($P = 0.681$). This suggests some benefits of IVZ over IVA monotherapy through a short interval of 6 months.

Several authors have studied the combination of anti-VEGF with vPDT against the monotherapy of anti-VEGF. However, the lack of studies comparing the anti-VEGF agents has led to difficulty in identifying the anti-VEGF agent with best outcomes. EVEREST II group reported the superior outcomes of combination therapy (vPDT + RBZ) when compared with monotherapy of RBZ. The gain of visual acuity was significantly higher in the combination group when compared with monotherapy (8.3 and 5.1 letters). Yamamoto *et al.* have reported significant improvement of BCVA from 0.31 to 0.17 logMAR (difference of 0.14 logMAR) at 12 months with monotherapy of AFL.[7] Similarly, PLANET study results showed that AFL monotherapy was noninferior to combination of vPDT + AFL. The gain of visual acuity was 10.7 versus 10.8 letters, and polyp regression was noted in 39% versus 45% of patients in AFL monotherapy arm compared with combination arm.[6] Previous reports have shown that switching over to AFL from RBZ may be helpful in resistant cases. Saito *et al.* in their study of 43 eyes have reported that AFL therapy led to significant improvement in BCVA (Δ 0.04 logMAR units) with OCT and FFA showing no exudation at 3 months in 37 of 43 patients.[8] The plausible explanation may be high-affinity binding (140×) of AFL to VEGF A along with VEGF B and placental growth factor compared with RBZ and BVZ.[11] The superior effect of IVZ can also be extrapolated based on the previous findings considering the fact that IVZ and AFL share similar molecule except for osmolarity.[12] However, clinical dose of IVZ (1.25 mg/0.05 mL) is only 62.5% of AFL (2 mg/0.05 mL). This significant difference in dosing may lead to different clinical outcomes with the two drugs.

Our results in BVZ group are in contrast to previously published studies,[17,19,21] which have shown either improved or stable visual acuity in BVZ-treated patients with PCV. This could be due to increased PED height in our cases as BVZ being a larger molecule has been shown to have worse visual acuity outcomes in patients with n-AMD and PCV with PED due to limited penetration in subretinal pigment epithelium space.[18,22] Cheng *et al.* in their study of PCV eyes treated with BVZ monotherapy reported that in 59.3% and 51.6% of patients, polyps remained either similar in size or increased at 6 and 12 months of follow-up, respectively.[19] This suggests that even though intra- or SRF, BCVA, or CMT may show a significant response, the underlying pathology of BVN and polyps were not affected significantly leading to only a transient effect. Moreover, three eyes in the BVZ group showed presence of rebleeding leading to a drop in BCVA. On the other hand, de Massougnes *et al.* have shown that switching over to AFL from RBZ in eyes refractory to RBZ led to reduction in PED height without significant improvement in visual acuity.[23]

Compared with the higher cost of approved anti-VEGF therapy (1950 USD per injection for RBZ and AFL each), these off-label drugs, such as BVZ (50 USD per injection and IVZ (30 USD per injection), provide a much cheaper alternative.[15] Considering the long-term treatment of this disease, these

drugs certainly reduce the treatment burden and appear to be cost-effective alternative with acceptable treatment outcomes.

The study has limitations due to its retrospective nature, small sample size, and short follow-up duration. As mentioned before, ziv-aflibercept dose was lesser than approved AFL (1.25 mg vs. 2 mg), which may affect the efficacy. Differentiation from n-AMD, nonusage of ICGA in routine clinical practice, and non-Food and Drug Administration–approved status of BVZ and IVZ for PCV are some of the issues which need to be kept in mind before planning any comparative trials involving IVZ and BVZ. Though there was an insignificant difference in the number of injections and treatment-free interval between the groups, a trend in favor of IVZ monotherapy was noted. Significant reduction in BCVA in BVZ group compared with IVZ could also be due to smaller sample size and limited follow-up, a limitation of the study. This study did not include patients who were switched to other anti-VEGF or received PDT as rescue therapy during 6 months.

Conclusion

In conclusion, IVZ is another addition in the available anti-VEGF armamentarium in the treatment for PCV with superior visual outcomes and better PED reduction compared with BVZ. Considering the similarity to AFL and lesser cost make IVZ therapy a good alternative for third-world countries. However, adequately powered RCT with larger sample size and longer follow-up is warranted.

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Conflicts of interest

There are no conflicts of interest.

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