One year outcomes of eyes with polypoidal choroidal vasculopathy with ≥20/40 visual acuity treated with anti-vascular endothelial growth factor agents

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Abstract:

PURPOSE: To report the 12 months outcomes of treatment naïve polypoidal choroidal vasculopathy (PCV) in patients with ≥20/40 Snellen's best-corrected visual acuity (BCVA).

METHODS: This was a retrospective study including eyes treated with monotherapy of anti-vascular endothelial growth factors (VEGF) agents (bevacizumab, ranibizumab, aflibercept, and ziv-aflibercept) on a pro-re-nata (PRN) protocol. Photodynamic therapy using verteporfin (vPDT) was used as rescue therapy. The primary study objective was change in BCVA at 12 months. Secondary objectives included change in optical coherence tomography parameters: central macular thickness (CMT) and pigment epithelial detachment (PED) height, the mean number of injections, and treatment-free interval at 12 months.

RESULTS: A total of 18 eyes of 18 patients (7 males, 11 females) were included. The mean age was 58.0 ± 12.0 years. BCVA at baseline and 12 months were 0.16 ± 0.08 (Snellen equivalent 20/30) and 0.15 ± 0.15 logarithm of the minimum angle of resolution (20/30), respectively. Twelve (66.6%) eyes either improved or maintained BCVA. Mean (±standard deviation [SD]) CMT at baseline and 12 months were 188.2 ± 61.1 μ and 161.7 ± 47.4 μ ($P = 0.15$), respectively. PED height improved to 236.4 ± 208.7 μ at 12 months ($P = 0.05$). The mean (±SD) number of injections was 3.28 ± 1.96 with a treatment-free period of 6.83 ± 3.63 months. Three eyes required vPDT (4 treatment sessions; mean: 1.33) as a rescue therapy through 12 months.

CONCLUSION: PRN anti-VEGF monotherapy in real-life situations for the treatment of naïve PCV eyes with good visual acuity (≥20/40) achieves maintenance or improvement of visual acuity through 12 months follow-up.

Keywords:
Anti-vascular endothelial growth factor, fluorescein angiography, indocyanine angiography, optical coherence tomography, polypoidal choroidal vasculopathy

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INTRODUCTION

Polypoidal choroidal vasculopathy (PCV), a disease entity in the spectrum of pachychoroid disease, could be considered one of the subtypes of neovascular age-related macular degeneration.[1-4] It is characterized by the presence of serous or serosanguinous retinal pigment epithelial detachments (PED) along with subretinal fluid or heme, polyps, and branching vascular network.[1-3] More commonly seen in the Asian population, the disease has been underdiagnosed due to the limited use of indocyanine green angiography (ICG) by retinal physicians.[5]

The treatment options currently used (including the major landmark trials FUJISAN, EVEREST, EVEREST II, and PLANET study) have been various anti-vascular endothelial growth factors (VEGF) including ranibizumab (RBZ), aflibercept (AFL) along with or without the combination of photodynamic therapy using verteporfin (vPDT).[6-9] Other anti-VEGF agents including bevacizumab (IVB) and ziv-aflibercept (IVZ) have also been used in

smaller case series with good outcomes.[10,11] Direct focal laser photocoagulation remains a viable option in patients with extrafoveal leaking polyps.[12,13] Despite multiple treatment strategies, visual prognosis remains variable with poor outcomes in 50% of the patients.[14] One of the reasons for the poor outcomes could be the delay in diagnosis with irreversible damage to retinal architecture. Initiating treatment early in the course of the disease remains one of the feasible options.

The inclusion criteria in pivotal trials (EVEREST, PLANET) has been the patients with best-corrected visual acuity (BCVA) of 20/320–20/40 while FUJISAN and EVEREST II enrolled patients with BCVA of 20/200 to 20/28 and 20/320 to 20/32, respectively. The percentage of patients with 20/32 (≥74 early treatment of diabetic retinopathy study letters) in EVEREST II were 17.70% (57 eyes) which formed a small subset of 322 eyes studied. There is the paucity of literature describing patients of PCV with good visual acuity (≥20/40 or logarithm of the minimum angle of resolution [logMAR] ≤0.3 units) – their disease characteristics, response to treatment, and visual prognosis. The aim of the study is to analyze the anatomical and visual outcomes in this subset of better vision PCV patients at 12 months.

METHODS

This was a retrospective study involving treatment naïve patients of PCV having BCVA of ≥20/40 (or logMAR ≤0.3 units) with a follow-up of at least 12 months. The study was conducted at a tertiary eye care center from the period of Jan 2015 to March 2017. Institutional Review Board approval was obtained and the procedures conformed to the tenets of the Declaration of Helsinki. All the participants signed a written consent form.

All the patients underwent a complete ophthalmic examination, which included BCVA, refraction, slit-lamp biomicroscopy, dilated fundus examination using indirect ophthalmoscopy and +90D lens. Swept-source optical coherence tomography (SS-OCT) scans were done using DRI OCT-plus (*Triton*®, Topcon, Tokyo, Japan) while fundus fluorescein angiography (FFA) and ICG were performed using Heidelberg HRA (Heidelberg Engineering, Inc., Vista, CA) and Zeiss Visupac (FF4 and FF450-plus, Carl Zeiss, Dublin, CA).

The diagnosis of PCV was made based on well-laid out criteria.[8] The patients were treated with anti-VEGF agents including BVZ, IVZ, RBZ or AFL. The switch between anti-VEGF agents was made in cases with inadequate response in terms of loss of BCVA or intra/subretinal (IRF/SRF) on OCT. vPDT as a rescue therapy was used as per the discretion of the treating physician when certain criteria were met. These included inadequate treatment response, presence of new or persistent fluid on OCT, and presence of active polyps based on FFA/ICG. Additional therapy in the form of the focal laser was done in cases with extrafoveal leaking polyps. The patients were followed up every month with a repeat OCT scan every visit, however, the treatment was given as per pro-re-nata (PRN) protocol. The minimal duration between repeat anti-VEGF injections was 4 weeks while the same interval for PDT retreatment was 3 months.

The baseline characteristics included were BCVA, central macular thickness (CMT), PED height, and the predominant subtype of disease whether exudative or hemorrhagic. The total number of anti-VEGF injections, PDT treatment sessions, CMT, and PED height were calculated along with the duration of treatment-free interval at 6 and 12 months.

Statistical analysis
Mean and standard deviation (SD) for baseline and final parameters were calculated and tabulated. The outcome data including BCVA, CMT, and PED reduction were analyzed using paired *t*-test in SPSS software (version 23.0, New York: IBM Corp.). $P ≥ 0.05$ was considered statistically significant.

RESULTS

The study included 18 eyes of 18 patients of Indian origin including 7 males and 11 females. The mean (±SD) age of the study group was 58.0 ± 12.0 years. Fourteen patients had the predominantly hemorrhagic type of PCV, while the other 4 patients had the exudative type of PCV.

The mean baseline BCVA in logMAR was 0.16 ± 0.08 (Snellen equivalent 20/30, with range 20/40–20/20). At 6 months and 12 months, mean (±SD) BCVA were 0.16 ± 0.16 logMAR (approximately 20/30) and 0.15 ± 0.15 logMAR (approximately 20/30), respectively. BCVA improved to 20/20 in 6 eyes at 12 months [Table 1]. Among the 18 eyes, a total of 10 eyes gained BCVA and 2 eyes maintained the same BCVA. Six eyes had gain of ≥1 line. Through 12 months follow-up, the remaining 6 eyes had a loss of visual acuity including 2 patients with loss of ≥3 lines [Table 1].

The (mean ± SD) CMT at baseline, 6 months and 12 months were 188.2 ± 61.1 μ, 175.6 ± 52.6 μ ($P = 0.51$), and 161.7 ± 47.4 μ ($P = 0.15$), respectively. PED height at baseline was 393.2 ± 217.6 μ which improved to 259.3 ± 225.6 μ and 236.4 ± 208.7 μ at 6 months ($P = 0.07$) and 12 months, respectively ($P = 0.05$) which was statistically significant. A representative case is shown as Figure 1.

During 12 months, the cohort received different anti-VEGF agents (BVZ [6], RBZ [17], AFL [13], IVZ[23]) on PRN protocol as per the re-treatment criteria and patient consent in view of the off-label use. The switch of anti-VEGF agents (RBZ to IVZ in 3 eyes and RBZ to AFL in 2 eyes) was done in a total of five eyes in view of unsatisfactory response. Two patients received one treatment session of PDT while one patient received two sessions of PDT through 12 months. vPDT was administered using the retreatment criteria based on treatment response, FFA/ICGA findings and as per the discretion of the treating physician. Another two patients received one session of focal laser for extrafoveal polyps in combination with anti-VEGF injections.

The mean number of intravitreal injections during the first 6 months and last 6 months were 1.89 ± 0.9 and 1.39 ± 1.38, respectively. The cumulative mean (±SD) at 12 months was 3.28 ± 1.96 injections. The treatment-free period during the follow-up period of 12 months was 6.83 ± 3.63 months.
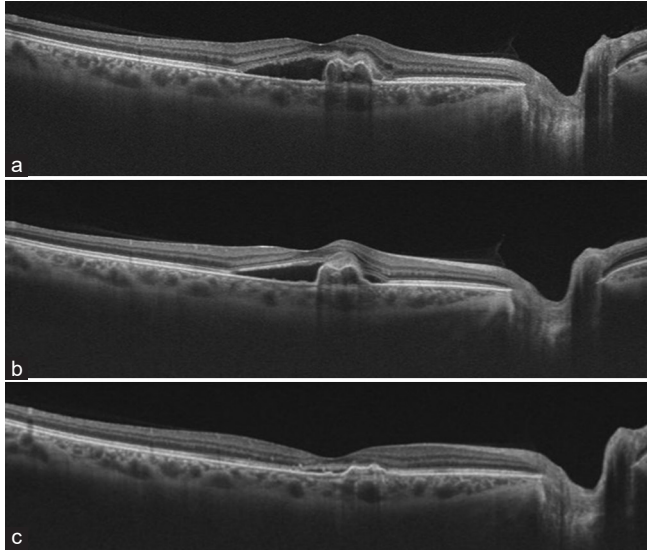

Figure 1: Optical coherence tomography of right eye of a 44 year male showing subretinal fluid and notched pigment epithelial detachment (a). Through 12 months, the patient received 2 ranibizumab, 3 aflibercept intravitreal injection along with two sessions of photodynamic therapy using verteporfin. Optical coherence tomography showed reduction in both pigment epithelial detachment height and SRF (b and c). The visual acuity at final visit was maintained at 20/20

No ocular (RPE rip, glaucoma, endophthalmitis, vitreous hemorrhage, cataract) or systemic (acute coronary events, stroke, hypertensive crisis) complications were noted during the entirety of follow-up period.

Discussion

We analyzed the subset of PCV patients who presented with ≤0.3 logMAR (≥20/40 Snellen equivalent) BCVA which has not been evaluated in pivotal trials. The percentage of patients with at least 20/40 BCVA in EVEREST II was 32.7% (RBZ + vPDT) and 40.8% (RBZ) respectively.[7] This forms a small subset within the study population. Other studies excluded this subset with BCVA≥20/40.[6,8] Therefore, the long-term treatment results in these eyes are not available in much details. Our study focuses on this subset and tries to analyze whether the early treatment plays a role in maintaining acceptable BCVA with the minimum number of injections.

As PCV in advanced stages is associated with poor long-term visual prognosis,[14] we sought to understand the disease-specific changes and treatment outcomes in the PCV cases when treatment was initiated early. Although the treatment protocol was PRN, the reduced number of injections (mean ± SD: 3.28 ± 1.96) at 12 months proves the utility of the regimen with minimal cost implications. The duration of fluid-free retina (mean: 6.83 months) also adds utility to the approach of initiating early treatment. In our study, the gain in visual acuity was not significant though the PED reduction was statistically significant at 12 months. Among

Table 1: Comparison of baseline and final best-corrected visual acuity, central macular thickness, and pigment epithelial detachment

Case number	Age/gender	BCVA logMAR		CMT (μm)		PED (μm)		Anti-VEGF
		Baseline	Final	Baseline	Final	Baseline	Final	injections
1	82/male	0.10	0.40	322	245	423	514	6
2	62/male	0.30	0.18	136	96	176	113	5
3	53/female	0.18	0.00	187	124	548	136	2
4	78/female	0.18	0.40	240	234	674	541	5*
5	69/female	0.18	0.10	201	238	179	94	1*
6	59/female	0.10	0.18	180	164	456	238	5
7	65/female	0.10	0.18	126	104	73	0	2
8	57/male	0.18	0.30	178	184	473	576	1
9	36/male	0.18	0.00	156	165	347	0	1
10	45/female	0.10	0.00	163	145	716	157	1
11	54/female	0.18	0.00	118	147	422	269	1
12	67/female	0.18	0.48	190	184	74	12	2
13	41/female	0.30	0.10	265	125	473	84	4
14	44/male	0.00	0.00	283	156	377	16	5*
15	59/female	0.30	0.18	252	225	224	173	5
16	57/female	0.10	0.10	134	115	754	451	2
17	52/male	0.10	0.00	137	135	585	572	6
18	71/male	0.18	0.10	119	125	103	310	5
Average±SD	58±12	0.16±0.08	0.15±0.15	188.2±61.1	161.7±47.4	393.2±217.6	236.4±208.7	3.28±1.96

*Eyes treated with rescue photodynamic therapy (vPDT). SD=Standard deviation; logMAR=Logarithm of the minimum angle of resolution; VEGF=Vascular endothelial growth factor; BCVA=Best-corrected visual acuity; CMT=Central macular thickness; PED=Pigment epithelial detachment; vPDT=Verteporfin photodynamic therapy

18 eyes, 10 eyes gained BCVA with 6 eyes gaining ≥1 line while 2 eyes maintained the baseline BCVA. The discrepancy between the anatomical and functional outcomes could be explained by the ceiling effect due to better baseline visual acuity in this cohort.

The receding role of vPDT needs particular attention in view of the side effect profile and higher cost, especially in the developing world scenario. Moreover, the probability of loss of BCVA with vPDT, especially with good vision always remains a concern.[15] The proposed practice pattern could be either baseline (combination group of EVEREST II) or PRN (PLANET study) vPDT. Although the different nature, drugs, and treatment regimens of the study (EVEREST II and PLANET) prevent any direct comparison, the role of monotherapy has been proven in PLANET study. In our study, using monotherapy (total of 59, mean ± SD: 3.28 ± 1.96 injections), 12/18 (66.6%) patients maintained or gained BCVA while 4 patients lost ≥1 line of BCVA. Our results bear resemblance with PLANET study where vPDT was used as a rescue therapy and <15% required rescue PDT at 12 months.[7] These results show that PRN monotherapy could be an acceptable alternative in real life with the role of vPDT only in few select cases. Furthermore, anti-VEGF agents were injected on a PRN protocol in our study. It is difficult to determine whether vPDT was actually needed in few of the nonresponding eyes or increased administration of anti-VEGF agents on a monthly basis would have led to an equivalent outcome.

Though our study did not provide information about the superiority of any anti-VEGF, the other studies (EVEREST II, PLANET) have shown better results with AFL as compared to RBZ monotherapy.[6] However, these trials have the inclusion of vPDT as a rescue therapy with differing retreatment criteria.[6-9] Therefore, in the absence of trials with direct comparison of RBZ, AFL, BVZ or IVZ, a definite conclusion remains elusive.

The strengths of the study include the inclusion of the subset of patients with better than ≥20/40 BCVA with a follow-up period of 12 months. The study also focuses on the real-life practice patterns as compared to the strict trial-based protocols; therefore, the results are more applicable for clinical practice. This study has certain inherent limitations due to its retrospective nature, small sample size and limited follow-up period. The inclusion of different anti-VEGF injections and administration of PDT on PRN protocol also adds to the ambiguity. In view of cost-constraints and variable affordability in different patients, different anti-VEGF injections were given based on the discretion of the treating physician. The analysis of polyps patterns based on ICG and their regression with treatment was not assessed in this study. However, ICG was used to determine the treatment response and administration of vPDT.

Conclusion

Our study reports good visual outcome with intravitreal anti-VEGF monotherapy in eyes with PCV with visual acuity equal or better than 20/40 using PRN protocol in real-life situations through 1 year. PDT as rescue therapy was required in very few eyes with maintenance or improvement of vision in almost 2/3rd of our study participants. However, larger prospective trials evaluating the role of anti-VEGF, PDT in PCV patients with good vision could pave the way for optimal management and reducing the disease burden.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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