Aflibercept for recurrent or recalcitrant polypoidal choroidal vasculopathy in Indian eyes: Early experience

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Treatment guidelines for symptomatic polypoidal choroidal vasculopathy (PCV) have been described, but the management of recurrent or recalcitrant PCV is a challenge. The newer anti-vascular endothelial growth factor: aflibercept has shown promise in the treatment of both treatment naive and recalcitrant PCV in studies outside India. We present the minimum 6 months results of intravitreal aflibercept in recurrent and recalcitrant PCV in Indian eyes after multiple injections of bevacizumab/ranibizumab with or without photodynamic therapy. Of 10 eyes, 7 resolved of which 4 recurred needing continued aflibercept. Three of the ten eyes did not show a response. To the best of our knowledge, this is the first report from India in this challenging situation.

Key words: Aflibercept, anti-VEGF therapy, polypoidal choroidal vasculopathy

Polypoidal choroidal vasculopathy (PCV) is a leading cause of visual morbidity in Asians. Current epidemiological data show the prevalence of 22.3%–61.6% among Asians and 8%–13% in Caucasians who present with presumed neovascular age-related macular degeneration (hospital/clinic based).[1] Treatment guidelines for symptomatic PCV do not include the role of aflibercept.[2]

Yamamoto *et al*.[3] and Hara *et al*.[4] reported effectivity of anti-vascular endothelial growth factor (VEGF) aflibercept (Eylea, Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) for treatment naïve PCV. Saito *et al*.[5] and Azuma *et al*.[6] reported that switching to aflibercept is effective for patients with PCV who develop resistance to ranibizumab. We report anatomical and functional outcomes of aflibercept for recurrent or recalcitrant PCV in Indian eyes.

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Methods

We conducted a retrospective case series of consecutive patients with recalcitrant or recurrent indocyanine green angiography (ICG) confirmed PCV treated with aflibercept and followed for a minimum 6 months at a tertiary care eye between February and November 2016. Institutional review board approved the study. All had received monthly bevacizumab or ranibizumab for 3 months followed by pro re nata (PRN) basis and/or photodynamic therapy (PDT). Recurrence was defined as an anatomical response to anti-VEGF injections with reactivation if the monthly injections were discontinued. Resistance/recalcitrance was defined as persistence or increase in the intra/subretinal fluid, pigment epithelial detachment (PED) or hemorrhage after minimum three injections on a monthly basis. Treatment-naive PCV was excluded. We followed published criteria for diagnosing active PCV.[2] All patients underwent ICG at baseline, and spectral domain optical coherence tomography (OCT) or swept-source OCT at baseline and each follow-up visit.

Treatment guidelines and technique

All patients underwent intravitreal aflibercept (2 mg/0.05 ml) on a planned monthly followed by PRN basis. Patients were examined at 1st and 3rd postinjection day then monthly thereafter. Response to treatment was defined in terms of complete resolution of intra- and sub-retinal fluid and/or decrease in the height of PED and maintenance of inactivity for minimum 8 weeks. Partial resolution was defined as a reduction in sub/intraretinal fluid and PED. Resistance/recalcitrance was defined as either persistence or increase in the intra/subretinal fluid, PED or hemorrhage after minimum 3 injections on a monthly basis. Recurrence was defined as the presence of intra/subretinal fluid/enlargement of PED/development of new PED/subretinal or subretinal pigment epithelium hemorrhage after 8 weeks of inactivity. ICG was repeated in resistant cases. In case of complete resolution at 4th week from the last injection, the patient was asked to review at 6th and 8th week, injection was repeated if activity recurred. All patients with residual fluid were retreated.

Best-corrected visual acuity (BCVA) was recorded in logMAR scale. Values of numerical characteristics were tested for normality and presented as mean value (± standard deviation). Student's paired sample *t*-test for comparing pre- and post-aflibercept BCVA and central foveal thickness (CFT). $P < 0.05$ was considered statistically significant.

Results

Ten eyes of 10 patients with recurrent or recalcitrant PCV were included. Five males and five females, aged 53–83 years (mean 66 ± 9.2 years). All patients had received multiple

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Table 1: Baseline characteristics and treatment outcomes

Cases	History			Anatomical outcomes					
	Anti-VEGF: Avastin/ Accentrix	PDT	Recurrent or recalcitrant	Number of aflibercept	Follow-up postaflibercept	Complete resolution after treatment	Recurrence after resolution	Management of recurrence	Management of recalcitrance
1	24	3	Recalcitrant	3	6	No	NA	NA	Switched
2	22	2	Recurrent	2	9	Yes	Yes	Aflibercept	NA
3	15	2	Recalcitrant	6	8	No	NA	NA	Switched
4	17	0	Recalcitrant	3	9	No	NA	NA	Switched
5	16	3	Recalcitrant	2	6	Yes	Yes	Aflibercept	NA
6	16	1	Recurrent	2	6	Yes	No	NA	NA
7	7	0	Recalcitrant	2	6	Yes	No	NA	NA
8	4	0	Recalcitrant	3	6	Yes	Yes	Aflibercept	NA
9	5	1	Recalcitrant	5	6	Yes	No	NA	NA
10	5	0	Recalcitrant	2	6	Yes	Yes	Aflibercept	NA

VEGF: Vascular endothelial growth factor, PDT: Photodynamic therapy, NA: Not applicable

Table 2: Spectral domain optical coherence tomography characteristics before and after aflibercept

	Before				After			
	PED (multiple/peaked/ notched)	SRF	Intraretinal fluid	CFT	PED (increased/decreased/resolved/ new)	SRF	Intraretinal fluid	CFT
1	Yes	Yes	Yes	490	Decreased, new	Yes	Yes	648
2	Yes	Yes	Yes	189	Decreased	No	No	94
3	Yes	Yes	Yes	256	Decreased, new	Yes	Yes	198
4	Yes	Yes	No	191	Decreased	Yes	Yes	160
5	Yes	Yes	No	320	Decreased	No	No	105
6	Yes	Yes	Yes	215	Decreased	No	No	70
7	Yes	Yes	Yes	160	Decreased	No	No	147
8	Yes	Yes	No	180	Decreased	No	No	140
9	Yes	Yes	No	310	Decreased	No	No	129
10	Yes	No	No	126	Decreased	No	No	126

PED: Pigment epithelial detachment, SRF: Subretinal fluid, CFT: Central foveal thickness

intravitreal anti-VEGF injections (bevacizumab/ranibizumab) with median of 15.5 ± 7.3 (range 4–24) with/without PDT. One eye had vitrectomy for PCV-related vitreous hemorrhage.

Baseline mean logMAR BCVA was 0.39 ± 0.37 (range 0–1). All patients had branching vascular network (BVN) on ICG. Baseline characteristic, OCT features and treatment outcomes are tabulated in Tables 1 and 2. Mean baseline CFT was 243.7 ± 106.7 microns. Mean number of aflibercept injections were 3 ± 1.4 (range 2–6). Patients had a mean follow-up of 6.8 ± 1.31 months (range 6–9) after the first aflibercept, whereas median of total follow-up was 53 ± 44.8 (range 16–130 months). Mean final logMAR BCVA was 0.37 ± 0.35 (P = 0.49). Mean CFT reduced to181.7 ± 167.6 microns (P = 0.049). No ocular or systemic complications were noted.

Complete resolution was seen in seven eyes [Figs. 1 and 2 - Case no. 2]. Three eyes had a reduction in PED and partial resolution of sub- and intra-retinal fluid even after minimum three injections. ICG in all these showed the persistence of BVN in one eye and enlargement in two. Two eyes switched back to maintenance with ranibizumab, and one eye underwent PDT with ranibizumab. Four of the seven eyes that showed initial resolution developed recurrence after a period of quiescence of which all were re-treated with aflibercept and responded satisfactorily to the same.

Discussion

Aflibercept, a fusion protein with binding sequences from VEGF receptors 1 and 2 possesses high binding affinity for isomers of VEGF-A, VEGF-B and placental growth factor (PGF), and prevents VEGF from initiating proliferation and migration of vascular endothelial cells.[7] Other members of the VEGF family, including PGF[8] and VEGF-B[9] have critical roles for angiogenesis and hyperpermeability. Because of wider spectrum pharmacological targets, aflibercept might have greater effectiveness for suppression of PCV vascular lesions.

Till date, there are no treatment guidelines for aflibercept in PCV. Most studies have used 3 monthly followed by PRN injections. We analyzed eyes with recurrent and recalcitrant PCV who had already received multiple (median: 15.5 ± 7.3) intravitreal anti-VEGF injections (bevacizumab/ranibizumab) with/without PDT. We treated these patients with intravitreal

Figure 1: (a-c) Color fundus, indocyanine green angiography and swept source optical coherence tomography images of the right eye of a patient with active macular polypoidal choroidal vasculopathy 8 years after treatment with multiple sessions of anti-vascular endothelial growth factor monotherapy, two sessions of combination photodynamic therapy and anti-vascular endothelial growth factor. The fundus image shows exudation at the macula with a partly fibrotic lesion. Indocyanine green angiography shows a large branching vascular network. Swept source optical coherence tomography image shows the polypoidal network involving the fovea, pigment epithelial detachment and intraretinal cystic spaces

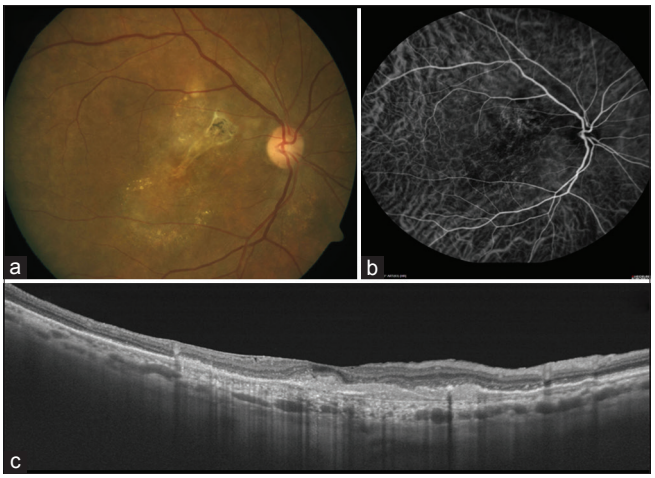

Figure 2: (a-c) Fundus image, indocyanine green angiography and swept source optical coherence tomography images after 2 monthly aflibercept injections shows a decrease in exudation, reduction in the branching vascular network on indocyanine green angiography. The swept source optical coherence tomography image shows resolution of the intraretinal cystic spaces as well as the pigment epithelial detachment

aflibercept on planned monthly followed by PRN basis in contrast to Saito *et al*.[5] and Azuma *et al*.[6] who gave minimum three injections on a monthly basis.

In our cohort, BCVA improved in two eyes, maintained in seven and deteriorated in one. Mean BCVA (logMAR) improved to 0.37 from 0.39, but the difference was statistically not significant. Mean CFT improved to 181.7 from 243.7 microns, and difference was statistically significant. Hirakata *et al*.[10] found no significant gain in vision or CFT at 6 months but gain was significant at 1 year. Saito *et al*.[5] and Azuma *et al*.[6] reported significant CFT reduction and visual gain at month 3 and 12, respectively. No ocular or systemic adverse events were seen.

Limitations were small sample size, short follow-up which could explain the limited visual improvement. To the best of our knowledge, this is the first series from India reporting the results of aflibercept in recurrent or recalcitrant PCV.

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Conflicts of interest

There are no conflicts of interest.

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