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Initial experience in treating polypoidal choroidal vasculopathy with brolucizumab in Indian eyes – A multicenter retrospective study

Debdulal Chakraborty, Aniruddha Maiti[1], Sabyasachi Sengupta[2], Soumen Mondal, Krishnendu Nandi[1], Somnath Chakraborty[3]

Purpose: To report the initial experience of managing treatment-resistant and treatment-naïve eyes with polypoidal choroidal vasculopathy (PCV) by using brolucizumab 6 mg. **Methods:** This was a retrospective multicentric series of all consecutive eyes with PCV treated with brolucizumab. Treatment resistance was defined as taking at least six prior anti-VEGF injections over the past 1 year and showing persistent disease activity in the form of intra (IRF) or subretinal fluid (SRF) or both. All patients were treated on a *pro re nata* (PRN) basis and followed up monthly. Retreatment was considered when either SRF or IRF were present at any time point during the study. **Results:** We included 21 eyes of 21 patients with PCV with a mean age of 65.1 ± 9.9 years, of which 16 eyes (76%) were treatment-resistant. The mean follow-up period from receiving the first brolucizumab was 27.3 ± 3.3 weeks. Of the 21 eyes, seven eyes (33%) received three injections during follow-up, 13 eyes (62%) received two injections, and one eye received one injection. The mean injection-free interval was 12 ± 1.2 weeks. The median pretreatment vision was 0.6 logMAR (IQR = 0.47–1 logMAR) and improved to 0.3 logMAR (IQR = 0.25–0.6 logMAR), whereas the mean macular thickness improved from 443 ± 60 µm at baseline to 289 ± 25 µm ($P < 0.001$) at the last follow-up period. None of the eyes experienced any intraocular inflammation across 48 injection sessions. **Conclusion:** Brolucizumab is safe and effective in controlling PCV disease in both treatment-resistant and treatment-naïve eyes.

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Polypoidal choroidal vasculopathy (PCV) is now recognized as a subtype of neovascular age-related macular degeneration (nAMD) with specific and distinct characteristics on indocyanine angiography (ICGA) and optical coherence tomography (OCT).[1-3] Though treatment of PCV and nAMD involves the use of intravitreal anti-vascular growth factor (anti-VEGF) agents for disease control, it is still important to distinguish between these due to differences in response to anti-VEGF, with PCV eyes showing a suboptimal response[3] and higher risk of recurrence in the same and other eye in PCV as opposed to nAMD.[4] Additionally, the higher predilection of PCV to cause massive and blinding subretinal hemorrhages is another cause of concern. Lastly, regression of polypoidal lesions and flattening of pigment epithelial detachments (PED), considered to be a major endpoint in most clinical trials,[5] requires a combination of anti-VEGF with photodynamic therapy (PDT), whereas PDT is no longer considered a treatment option in nAMD.

The management of PCV has evolved over the past decade with the availability of more potent anti-VEGF agents that have better penetration through the retinal pigment epithelium (RPE) and higher affinity to inhibit the action of VEGF.[1,2] After the recommendations of the PLANET clinical trial,[6] which showed excellent outcomes in PCV eyes receiving intravitreal aflibercept monotherapy, and with nonavailability of the Visudyne dye in many parts of the world, the trend in management is gravitating toward anti-VEGF monotherapy for PCV. However, the treatment burden remains significantly high, and until recently, aflibercept was considered to be the drug of choice for management of eyes with PCV in view of its higher efficacy in polyp regression compared to ranibizumab.[2]

Brolucizumab has recently received FDA approval for management of nAMD and its subtypes and is now commercially available globally. The pivotal HAWK and HARRIER clinical trials[7,8] showed excellent efficacy of brolucizumab in management of nAMD compared to aflibercept with equivalent visual outcomes and significantly better drying capacity with respect to intraretinal (IRF), subretinal (SRF), and sub-RPE fluid. A subgroup analysis of the HAWK cohort with treatment-naïve PCV in Japanese patients showed robust and consistent visual gains with q8w/q12w brolucizumab that were comparable to q8w aflibercept dosing.[9] Another study has shown the good efficacy of brolucizumab in management of treatment naïve PCV eyes.[10]

Vitreo-Retina Services, Disha Eye Hospitals, Kolkata, West Bengal, [1]Netralayam Super Speciality Eye Care Centre, Kolkata, West Bengal, [2]Vitreo-Retina Services, Consultant Vitreoretinal Surgeon, Future Vision Eye Care and Research Centre, Mumbai, Maharashtra, [3]Retina Institute of Bengal, Siliguri, West Bengal, India

Correspondence to: Dr. Debdulal Chakraborty, Department of Vitreo-Retinal Services, Disha Eye Hospitals, 88 Ghosh Para Road Barrackpore, Kolkata - 700 120, West Bengal, India. E-mail: devdc@rediffmail.com

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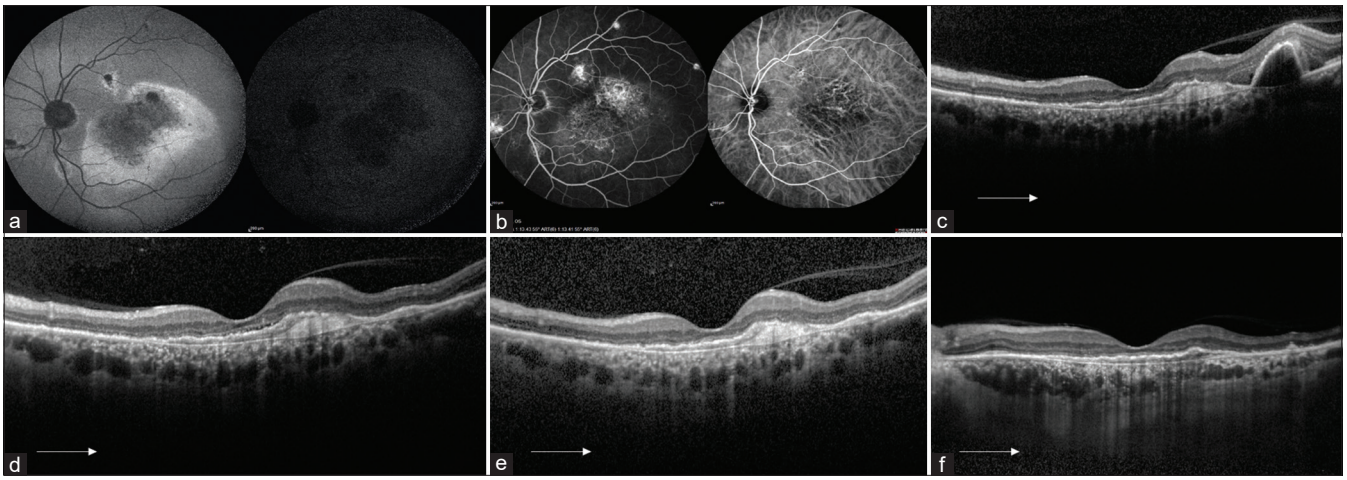

Figure 1: Mutimodal imaging of left eye of a patient with Polypoidal Choroidal Vasculopathy. Blue Autofluorescence and infrared image showing the extent of the lesion (a). Fundus fluorescein angiography (right) shows stippled hyperfluorescence at macula with window defects superior to macula and nasal to disc. Indocyanin Green Angiography shows presence of a string of polyps with branching vascular network in the macula (b). Optical coherence tomography showed a submacular fibrovascular PED with presence of a double layer sign along with the presence of a thumb-like PED and pachychoroid (c). Gradual resolution of neurosensory detachment with decrease in size of thumb - like PED was seen in OCT after 1st injection (d), 2nd injection (e), and 3rd injection (f) of brolucizumab

The early enthusiasm related to the brolucizumab has been slightly marred due to recent reports of intraocular inflammation (IOI) in about 5% of eyes that receive this drug.[11,12] In view of this, a lot of physicians, including our group, have resorted to using brolucizumab for refractory cases that have persistent IRF or SRF despite multiple previous anti-VEGF injections. We believe that PCV eyes constitute a considerable proportion of such treatment-resistant eyes that are extremely difficult to manage. To the best of our knowledge, there are no studies showing the efficacy of brolucizumab in treatment-resistant PCV eyes. In this study, we present early results from such eyes as well as treatment-naïve eyes managed using brolucizumab.

Methods

This was a retrospective multicentric series conducted across several centers in India. The study was approved by the institute's ethics committees of all participating centers and followed the tenets of the declaration of Helsinki where all patient identifiers were kept confidential during analysis. All patients gave informed consent before taking brolucizumab injections.

All consecutive patients with a diagnosis of PCV at baseline and treated with intravitreal brolucizumab 6 mg (Pagenax, Novartis, India) were included in this analysis. A diagnosis of PCV was considered if OCT showed multiple, tall, and tented PEDs with a notch and intralesional hyporeflective oval spaces within the PED indicative of the PCV lumen or clear evidence of a hot spot and branching vascular network on ICGA.[13] Eyes with prior history of intraocular inflammation (IOI) such as uveitis or inflammation after prior anti-VEGF injections, eyes with cataract surgery within the previous 1 month, and one-eyed patients were not considered for brolucizumab injections by the treating physicians. The pretreated cases were managed with a loading dose of monthly ranibizumab injections for at least 3 months and then a treat and extend (T&E) protocol was employed when fluid-free status was achieved such that the duration between injections was prolonged by 2 additional weeks at a time from the previous injection. Treatment resistance was defined as taking at least six prior anti-VEGF injections over the past 1 year and showing persistent disease activity in the form of IRF or SRF or both despite strict adherence to T&E protocols. All patients were treated on a *pro re nata* (PRN) basis and followed up monthly. At each visit, patients underwent a comprehensive ophthalmic evaluation, including best-corrected visual acuity (BCVA), dilated retinal evaluation, and OCT. Measurements obtained using the Spectralis OCT (Heidelberg, Germany) and an automated CMT display were recorded at each visit from scans with a minimum image quality of 50%. Fundus fluorescein angiography and ICGA findings were also recorded from case files when available. Retreatment was considered in case of presence or recurrence of either SRF or IRF at any time point or signs of recurrent disease activity such as fresh subretinal or sub-RPE hemorrhage.

Table 1: Number of injections based on switch vs. treatment-naïve PCV

Number of injections	Switch	Treatment-naïve	Total
1	1 (6%)	0	1 (5%)
2	10 (63%)	3 (60%)	13 (62%)
3	5 (31%)	2 (40%)	7 (33%)
Total	16 (100%)	5 (100%)	21 (100%)

All case files of eligible patients were drawn from the computerized database of each participating center and basic demographics, BCVA, CMT, and presence of IRF, SRF, and PEDs was noted. The total duration of follow-up, interval between injections, indication of reinjections, and the BCVA and CMT at the final follow-up visit were extracted from the electronic case files for analysis. Any evidence of IOI at any visit was also recorded if available. All case files mentioned about IOI even if there was none seen at every visit. Any systemic adverse events if found in the case files were also recorded.

Statistical analysis

All continuous variables were presented as mean with standard deviation or median with interquartile range, and group

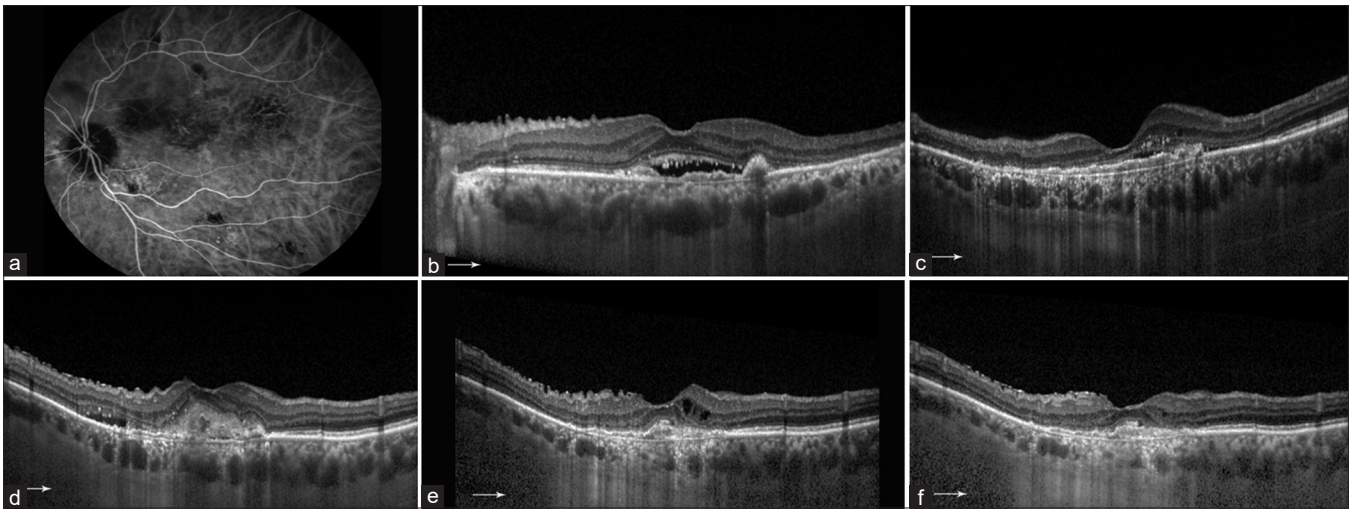

Figure 2: Imaging of left eye of a patient with Polypoidal Choroidal Vasculopathy. Indocyanin Green Angiography shows dilated choroidal vessels with cluster polyps at macula (a). Optical coherence tomography showed fibrovascular PED with neurosensory detachment and presence of double layer sign in the macular region along with a peaked PED and presence of pachychoroid (b). After an injection of ranibizumab, the neurosensory detachment decreased but there was presence of hyperreflective foci in the outer retina above the fibrovascular PED (c). One month later, there was a recurrence of polypoidal choroidal vasculopathy with increase in height of PED (d). A switch-over to brolucizumab showed prompt response with decrease in size of PED but presence of intraretinal fluid (e) a second injection of brolucizumab, six weeks later, demonstrated resolution of most of the intraretinal fluid (f)

differences between these were assessed using student *t* test or Wilcoxon's rank-sum test for nonparametric distributions. Categorical variables were presented as proportions (n, %), and group differences were analyzed using Chi-square or Fischer's exact test. Comparison between continuous variables before and after treatment were assessed using the paired *t* test. Linear regression analysis was used to determine the association between change in BCVA and CMT at the last follow-up.

All data were collected using Microsoft Excel and analyzed using STATA 12.1 I/c (Stata Corp, Fort Worth, Texas, USA), and $P < 0.05$ was considered statistically significant.

Results

We included 21 eyes of 21 patients with PCV with a mean age of 65.1 ± 9.9 years (range: 45–79 years), of which 17 (81%) were men and 11 (52%) had right-eye involvement. Sixteen eyes (76%) had received prior anti-VEGF injections, while the remaining five (24%) eyes were treatment-naïve at the time of receiving brolucizumab. All 16 eyes (100%) that were switched to receive brolucizumab were resistant to previous treatments and had either SRF (n = 12, 75%) or IRF (n = 14, 88%) at the time of receiving the first brolucizumab.

The mean follow-up period from receiving the first brolucizumab was 27.3 ± 3.3 weeks (median = 28 weeks, range = 20–32 weeks). Of the 21 eyes, seven eyes (33%) received three injections during the follow-up period, 13 eyes (62%) received two injections, and one eye received one injection. The distribution of the number of injections received based on history or prior treatment (i.e., switch vs. naïve) is shown in Table 1. The mean injection-free interval was 12 ± 1.2 weeks in this cohort. Fig. 1 shows a distribution of the injection free interval. The injection free interval did not differ between eyes that were switched versus those that were treatment-naïve.

The median pretreatment BCVA was 0.6 logMAR (IQR = 0.47–1 logMAR) and improved to 0.3 logMAR (IQR = 0.25–0.6 logMAR) at the last follow up period ($P = 0.01$) [Fig. 2]. Seven eyes (33%) in the cohort experienced at least 3 lines of visual improvement, while an additional six eyes (29%) had 2 lines of improvement; another six eyes (29%) had maintained vision, and the remaining two eyes (10%) lost vision of 2 lines. Similarly, the mean CMT improved from 443 ± 60 µm at baseline to 289 ± 25 µm ($P < 0.001$). Prior to treatment, SRF was present in 17 eyes, of which nine (53%) had reduced SRF while eight (47%) had complete SRF resolution at the last follow-up. Similarly, IRF was present in 17 eyes at baseline, of which 10 (59%) had complete resolution while seven (41%) had reduced IRF at the last follow-up. Nine eyes (43%) had no disease activity, that is, no SRF and IRF at the last follow-up, while the remaining 12 (57%) had persistent disease in the form of either IRF (n = 3, 25%) or SRF (n = 5, 42%)) or both (n = 4, 33%). All 21 eyes had PED at baseline, of which five (24%) experienced complete resolution while the remaining 16 (76%) had persistent PED but with appreciably reduced PED height.

A comparison between eyes that received three injections versus those that received fewer injections is shown in Table 2. Eyes that had received three injections had a longer follow-up duration. There were no differences in terms of vision and CMT across groups. Similarly, the injection-free interval did not differ, and the number of eyes with active disease at the last follow-up were statistically similar between groups [Table 2]. The improvement in vision was slightly greater in the treatment-naïve group (ΔBCVA = 0.32 ± 0.42) compared to the switched group (ΔBCVA = 0.16 ± 0.16), though this was not statistically significant ($P = 0.22$). We also found a linear relationship between reduction in CMT and improvement in BCVA [Fig. 2] with every 50-micron reduction in CMT leading to a 1-line improvement in vision (β coefficient = 0.11, 95%CI = 0.01–0.20, $P = 0.049$).

With a total of 48 treatment sessions, none of the eyes experienced any intraocular inflammation involving the anterior or posterior segments and none of the patients experienced any systemic adverse events such and cerebrovascular accidents and ischemic cardiac events.

Table 2: Comparison of eyes that received three injections vs. those that had fewer injections

Variable	±2 injections (*n*=14)	3 injections (*n*=7)	*P*
Age (years)	65.6±9.5	64.1±11.4	0.76
Gender (% men)	11 (79%)	6 (86%)	0.69
Prior treatment (% switched)	11 (78%)	5 (71%)	0.71
Injection free interval	12±1.4	11.8±1.5	0.83
Follow up	25.7±2.5	29.4±3.0	0.01
Pre injection vision (logMAR)	0.78±0.46	0.51±0.30	0.17
Post injection vision (logMAR)	0.57±0.45	0.32±0.25	0.25
Change in vision (logMAR)	0.21±0.26	0.18±0.22	0.80
Pre injection CMT (μ)	444±69	439±41	0.84
Post injection CMT (μ)	291±28	284±15	0.12
Change in CMT (μ)	153±61	155±29	0.85
% with Active PCV	7 (50%)	5 (71%)	0.35

Discussion

In this retrospective series, we found brolucizumab to be effective in controlling PCV in both treatment-resistant and treatment-naïve eyes with reduced disease activity in all eyes and improvement in vision in most eyes despite adopting a PRN protocol from baseline. As none of the recalcitrant eyes experienced poor response to brolucizumab, that is, no effect on SRF, IRF, and PED size and continued visual loss, it may be indicative that brolucizumab is perhaps more efficacious in drying the retinal layers and improving vision compared to previous molecules. Eyes that were switched appeared to have slightly lower vision at the last follow-up, with treatment-naïve eyes experiencing more than 3-line gain compared to 1.5 lines in switched eyes. Most eyes needed retreatment at the 12th week time point; however, 24% (5 eyes) needed reinjection starting at 9 weeks. About half of the treated eyes continued to harbor active disease and looked likely to need more injections in the future, while the rest appeared to have quiescent disease (i.e., no SRF and IRF) at the last time point. None of the treated eyes experienced any IOI.

Management of PCV disease has undergone paradigm shifts, with aflibercept monotherapy showing equal visual and anatomical gains compared to its combined therapy with PDT. About 80% of eyes in the recently concluded PLANET trial fared well with aflibercept monotherapy, making it the drug of choice for initiation of anti-VEGF monotherapy in PCV.[6] However, a recent subgroup analysis of Japanese eyes with treatment-naïve PCV that were part of the HAWK trial showed that brolucizumab 6 mg (n = 39) was as good as aflibercept (n = 30) in improving vision. The anatomical parameters favored brolucizumab, with 92% eyes having no IRF and SRF at 48 weeks compared to 70% in the aflibercept 2 mg group, and this advantage was maintained at the 96th week time point. Additionally, about 76% in the brolucizumab group maintained a q12w injection schedule after an initial 3-monthly loading dose, which was significantly higher than in nAMD eyes, where only about half the eyes maintained q12w dosing. Though there were considerable differences between our cohort and the HAWK trial subgroup with PCV receiving brolucizumab 6 mg, the most notable being ours were predominantly recalcitrant PCV while the HAWK was in treatment-naïve eyes. We report similar outcomes with a near similar visual gain and CMT values at 28 weeks mean follow-up. Matsumoto *et al*.[10] showed similar results from 23 treatment-naïve PCV eyes treated with a loading dose of 3× monthly brolucizumab monotherapy.

Eyes that were switched appeared to have slightly lower vision after therapy, with treatment-naïve eyes experiencing more than a 3-line gain compared to 1.5 lines in switched eyes. Thus, it may be prudent to start treatment with brolucizumab in PCV rather than consider it in resistant eyes alone. Most eyes needed retreatment at the 12th week time point, very similar to the PCV sub-analysis from the HAWK trial,[9] suggesting that the duration of action of brolucizumab is about 12 weeks *in vivo*, same as that promised by the manufacturer. This has the potential to significantly reduce the retreatment burden in patients with PCV. In our series, 24% (five eyes) needed reinjection starting at 9 weeks despite following a PRN protocol from baseline. This appears to be an improvement over the HAWK and HARRIER outcomes where treatment-naïve eyes with nAMD receiving a loading dose of 3× monthly injections had about a 50% chance of requiring injections every 8 weeks. Given these results of the majority requiring 12 weekly injections and excellent drying capacity, it is possible that brolucizumab may be more potent against PCV than nAMD. As the anatomical results were better with brolucizumab and it is more durable than aflibercept, it should be considered as a viable alternative for initiating monotherapy in eyes with PCV.

None of the treated eyes experienced any IOI in our series. With a 4%–5% expected incidence of IOI,[11] we should have seen 2–3 eyes with IOI, but this did not happen, hinting at careful patient selection by the treating physicians and a possibility of racial differences in inflammatory response to brolucizumab, with the Indian population being more immune to such occurrences. Results from the Japanese studies report a higher incidence of IOI with brolucizumab for PCV.[9,10] Physicians should take the risk of potential IOI into consideration before choosing brolucizumab as the molecule of choice in eyes with PCV.

This study has some drawbacks, including a relatively small sample size, a PRN regimen from baseline due to patient unaffordability, and relatively short follow-up, making it difficult to generalize our results for global application.

Conclusion

This is perhaps the first real world study evaluating efficacy of brolucizumab in recalcitrant PCV and shows that it is safe and effective in managing these difficult cases. Further studies are required with longer follow up and an appropriate comparison group to enable us to understand the long term efficacy of brolucizumab in PCV eyes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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