Commentary: Managing treatment-resistant polypoidal choroidal vasculopathy – Evolving concepts

Understanding polypoidal choroidal vasculopathy (PCV) as a variant of neovascular age-related macular degeneration (AMD) has enormous clinical and prognostic implications in the long term.[1] The pathophysiology of PCV is complex, involving dilation of large choroidal vessels (Haller's layer) and choroidal venous stasis. Thus, PCV shows different characteristics when compared to exudative AMD. These can have multiple tall retinal pigment epithelium detachments (PEDs), more of exudation, and a high risk of recurrent subretinal hemorrhages which may involve multiple levels (sub- retinal pigment epithelium [RPE]/subretinal).[2] The prevalence of PCV depends on the ethnicity – more in Asians than Caucasians. However, it is underreported due to the limited use of indocyanine green (ICG) angiography. Role of ICG angiography has re-emerged in the diagnosis and monitoring of non-responding patients of AMD and pachychoroid disorders. It has become the gold standard to detect polyps in PCV. Video ICG angiography reveals the presence of distinct focal hypercyanescent lesions appearing before 6 min, which are pulsatile and associated with hypocyanescent halo. A branched vascular network (BVN) may also be present. In the absence of ICG angiography, optical coherence tomography (OCT) shows distinct findings in PCV, which include thumb-like PEDs, notched PEDs, and "double-layer sign" due to the presence of BVN, subretinal fluid, and thickened choroid. Enface imaging using OCT angiography (OCTA) has an immense role in providing details about retinal and choroidal microcirculation like BVN. Slow-flowing lesions like polyps of PCV can be missed on OCTA.[1]

The standard of care for the management of PCV is anti-vascular endothelial growth factor (anti-VEGF) therapy alone or in combination with verteporfin photodynamic therapy (PDT).[3,4] PLANET trial has shown that intravitreal aflibercept monotherapy can provide good visual/functional outcomes without the need for PDT.[3] There are no definitive genetic markers to predict anti-VEGF resistance. Various phenotypic biomarkers can predict response to anti-VEGF therapy to some extent. Some authors have identified PCV (subretinal neovascularization with aneurysmal dilations) as a strong biomarker for anti-VEGF resistance, more in Caucasian ethnicity than Asians.[5]

For symptomatic juxtafoveal or subfoveal polyps not responding to anti-VEGF, full-fluence or reduced-fluence PDT with or without intravitreal anti-VEGF injection should be considered as the second-line management. PDT alone has some limitations like the risk of choroidal ischemia, subretinal haemorrhage, and upregulation of VEGF which causes secondary neovascular membrane formation and PCV recurrence. Anti-VEGF agents used alone have low polyp regression rates and negligible effect on BVN. However, if used along with PDT, these can probably suppress the proangiogenic activity and result in lesser complications than those caused by PDT monotherapy alone.[1] For regression of extrafoveal polyps and residual BVN (away from the fovea), ICG angiography-guided focal thermal laser can be another alternative.[6]

There is an increasing role of inflammation in the pathogenesis of neovascular age related macular degeneration (nAMD) and PCV. Oxidative stress leads to aggregation of inflammasomes in RPE and activation of complement pathway components like C3a and C5a. Some authors have tried the addition of dexamethasone implants in refractory PCV eyes to lengthen the injection-free interval.[7]

With the advent of newer and potent anti-VEGF therapies, switching over to newer anti-VEGFs might be helpful.

Brolucizumab is a newer 26-kDa single-chain antibody fragment that has a high affinity for VEGF and has currently been US Food and Drug Administration (FDA) approved for the treatment of nAMD. It allows the delivery of more drug per injection compared with other anti-VEGFs and offers more effective tissue penetration and increased duration of action.[8] The present retrospective study by Chakraborty *et al*. has shown promising initial results of *pro re nata* Brolucizumab therapy in recalcitrant PCV eyes in Indian settings.[9] It helped in reducing subretinal/intraretinal fluid, PED height and in maintaining visual acuity gains. HAWK Phase III trial subanalysis also reported that visual outcomes achieved with brolucizumab q12w/q8w treatment over 96 weeks were comparable with aflibercept treatment on a fixed q8w dosing.[8] Moreover, fluid resorption (subretinal/intraretinal/sub-RPE) was greater in the Brolucizumab arm than aflibercept arm. However, there is a need to conduct prospective randomized clinical trials with large sample size, longer follow-up, and proper comparison arm to comment upon the actual efficacy and safety of Brolucizumab in the long run. More importantly, trials should also aim to find the appropriate injection regimen – *pro re nata*, treat and extend, or every 12 weekly. Treat-and-extend intervals could be increased from the conventional 12-weeks gap to incorporate for long duration of action of Brolucizumab. In trials, clinical response should also be documented using ICG angiography on follow-ups to comment upon polyp regression, as persistent polyps can lead to recurrence of clinical activity in the long run. In one retrospective study, complete polyp regression was noted in 79% of eyes after three monthly loading doses of Brolucizumab.[10]

The safety of Brolucizumab is still an evolving area of consensus with intraocular inflammation and occlusive retinal vasculitis reported in clinical trials.[8,10] A higher incidence of intraocular inflammation was reported in PCV eyes of the Brolucizumab arm (15.4%, six eyes) when compared to aflibercept therapy in HAWK Phase III trial subanalysis.[8] In these six patients, the investigators identified signs of retinal vasculitis in five out of six eyes. Thus, in the event of a suspected intraocular inflammation, they have recommended wide-field imaging to rule out retinal vasculitis and occlusion. Brolucizumab therapy should be withheld and inflammation should be treated accordingly. In another study by Matsumoto *et al*.,[10] up to 19% of intraocular inflammation events were noted in PCV eyes, requiring urgent steroid therapy. In the study conducted by Chakraborty *et al*., no such events were found.[9] This could be due to the differential racial response and *pro re nata* dosing regimen usage which might have reduced the antigenic load caused due to frequent repeated injections. Novartis has also communicated that Brolucizumab should not be administered at intervals of less than 2 months after three monthly loading doses. Thus, dosing intervals should be extensively researched for optimal outcomes and patients should be made aware of the risk of intraocular inflammation and the need for strict follow-ups.

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