Commentary: Long-term efficacy and safety of verteporfin photodynamic therapy in combination with anti-vascular endothelial growth factor for polypoidal choroidal vasculopathy

Polypoidal choroidal vasculopathy (PCV) is characterized by multiple nodular recurrent sero-sanguineous retinal pigment epithelial detachments (PEDs). Yannuzzi *et al.* first described characteristic choroidal abnormalities such as dilated and branching choroidal vessels with terminal aneurysmal dilatation.[1] On histopathological examination, it was found that these abnormal vessels are lined by a thin endothelium with occasional pericytes associated with surrounding lymphocytic infiltration and have a tendency to bulge and cause aneurysmal polyp-like protrusion.[2]

The landmark EVEREST study has outlined the diagnostic criteria of PCV on indocyanine green (ICG) angiography as early hyperfluorescence (appearing within the first 5 min of ICG dye injection) and at least one out of nodular appearance of the polyp on stereoscopic viewing, hypofluorescent halo around the nodule, abnormal vascular channel(s) supplying the polyps, pulsatile filling of polyps, orange subretinal nodules corresponding to the hyperfluorescent area on ICG angiography, and massive submacular hemorrhage of more than four disc diameters.[3]

Optical coherence tomography (OCT) and OCT angiography are also very important investigations in the diagnosis of PCV. OCT shows characteristic thumb-like polyps, double-layer sign, tall-peaked PEDs, and tomographic notch sign.[3] OCT angiography is highly sensitive for diagnosing branching vascular network (BVN), whereas the polyp detection rate is comparatively lesser (50–90%).[4] However, ICG angiography is the gold standard for diagnosing and managing PCV.[3]

Recently, combination therapies are gaining popularity for the treatment of PCV. Herein, the thrombotic property of photodynamic therapy (PDT) and antipermeability property of antivascular endothelial growth factor (VEGF) agents is combined to cause regression of polypoidal lesions and reduce subretinal exudation, respectively. PDT alone has some limitations such as subretinal hemorrhage and upregulation of VEGF, which causes secondary choroidal neovascularization (CNV) 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 PDT monotherapy alone.

The EVEREST study concluded that PDT is more effective than intravitreal ranibizumab in achieving polyp regression. The visual outcome was not significantly different in the two groups; however, it was better in the ranibizumab monotherapy group than in the PDT monotherapy group.[3] LAPTOP study was subsequently undertaken to address this issue. Intravitreal ranibizumab was significantly superior to PDT monotherapy in achieving visual gain. Both the treatment options reduced the retinal thickness significantly.[5] Few authors have evaluated the role of intravitreal or subtenon triamcinolone acetonide (TA) in PCV. It is hypothesized that TA reduces the size of polyps and exudation. Nakata *et al.* compared PDT monotherapy with a combination therapy of PDT, intravitreal bevacizumab and intravitreal TA (triple therapy), and found that the visual gain is significantly higher in triple therapy arm at 24 months.[6] Triple therapy arm also had reduced retreatment rates and posttreatment vitreous hemorrhage than PDT monotherapy arm. On the contrary, Lai *et al.* found no visual improvement but rather increased risk of cataract formation and ocular hypertension with additional intravitreal TA in PCV eyes treated with PDT.[7]

The benefits of treatment with combination therapy are short-lived. The initial visual improvement starts to diminish after 6–12 months and final visual improvement at 2 years is not significantly better than at baseline. It is believed by some authors that the synergistic effect of combination therapy gets reduced if PDT application is performed days after anti-VEGF injection. The optimal protocol is also not defined for combination treatment with variable drugs and/or regimen used in most of the studies. Also, the full fluence PDT carries inherent side effects, which can be decreased with reduced fluence PDT.

Anti-VEGF agents may also cause adverse reactions. Several recent publications have reported retinal pigment epithelium tears associated with the use of intravitreal anti-VEGFs in CNV.[8] In a recent study, the prevalence of macular atrophy within and around the CNV border increased to 74% at a mean period of 6 years from 45% at baseline. Mean area of lesion increased from about 2 to 3 mm^2. A majority of patients showed macular atrophy after long-term anti-VEGF treatment.[9]

The authors have studied the long-term efficacy of PDT with anti-VEGF, which has been never studied in Indian population.[10] They have also studied the role of TA in the same study. Adverse effects of anti-VEGF and PDT were minimal and not thoroughly described. This study is very important as there is minimal literature on PCV in Indian settings, despite it being such a rampant disease in our country.

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