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Polypoidal choroidal vasculopathy: An update on current management and review of literature

Amit Harishchandra Palkar, Vikas Khetan

Abstract:

Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (nAMD), commonly seen in the Asian population. It is dissimilar in epidemiology, genetic heterogeneity, pathogenesis, natural history, and response to treatment in comparison to nAMD. Confocal scanning laser ophthalmoscopy-based simultaneous fluorescein angiography and indocyanine green angiography, spectral-domain optical coherence tomography (OCT) with enhanced depth imaging, swept-source OCT, and OCT angiography have improved the ability to detect PCV, understand its pathology, and monitor treatment response. A plethora of literature has discussed the efficacy of photodynamic therapy, anti-vascular endothelial growth factor (VEGF) monotherapy, and combination of both, but only a few studies with higher level of evidence and limited follow-up duration are available. This review discusses the understanding of PCV with respect to epidemiology, pathogenesis, clinical features, natural history, imaging techniques, and various treatment options. Recent clinical trials (EVEREST-II and PLANET study) have emphasized that either anti-VEGF monotherapy or combination treatment is equally capable to strike a balance between polyp regression and stabilization of visual acuity. The recurrent nature of the disease, the development of macular atrophy, and the long-term poor visual prognosis despite treatment are concerns that open avenues for further research.

Keywords:

Epidemiology, imaging, natural history, pathogenesis, polypoidal choroidal vasculopathy, treatment

Introduction

Polypoidal choroidal vasculopathy (PCV) is a distinct abnormality of the choroidal vasculature with characteristic branching vascular network (BVN) of choroidal vessels and surrounding polypoidal dilatation of the vessels on indocyanine green angiography (ICGA). It was thought to be a peculiar phenotype of neovascular age-related macular degeneration (nAMD) for some time.[1,2] It is now known that PCV shows distinct characteristics that can be distinguished from typical nAMD.[3,4]

The clinical value and relevance of ICGA were underestimated for nearly a decade since its clinical use in ophthalmology. The use of ICGA was recommended to identify PCV and demonstrated an ability to differentiate the disease from other chorioretinal diseases.[5] The development of swept-source optical coherence tomography (SS-OCT) has enabled definition of chorioretinal anatomy with enhanced resolution. Multimodal imaging allows an integrated evaluation of the choroidal abnormalities in PCV. So far that, it is now considered within a group of thickened choroidal entities termed pachychoroid spectrum.[6]

Photodynamic therapy (PDT) has been the mainstay in the treatment of PCV, following better visualization of the lesion on ICGA. With the experience of anti-vascular

Department of Vitreoretinal Services, Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, Chennai, Tamil Nadu, India

Address for correspondence:
Dr. Vikas Khetan, Department of Vitreoretina, Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18, College Road, Chennai - 600 006, Tamil Nadu, India.
E-mail: drvk@snmail.org

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endothelial growth factor (anti-VEGF) agents in new vessel diseases, they have been promising in PCV as well. They have widened the armamentarium in the treatment of PCV.[7] The efficacy of these agents as monotherapy or combination therapy with PDT has been demonstrated in the recent clinical studies.

The review summarizes the recent literature regarding the natural course of disease, imaging features, and treatment options with treatment trials, to study the transition in the understanding of PCV.

Historical Perspective

PCV was first described as polypoidal subretinal lesions causing serous retinal detachment (SRD) and hemorrhagic retinal detachment by Yannuzzi.[8] He proposed the term "idiopathic polypoidal choroidal vasculopathy" at the Annual Meeting of the American Academy of Ophthalmology in 1982. Kleiner and Johnson in 1984 described a peculiar hemorrhagic disorder of the macula with recurrent subretinal and sub-retinal pigment epithelium (RPE) bleeding and termed it as posterior uveal bleeding syndrome.[9] Later, Yannuzzi *et al*. expanded the description of the entity as a distinct choroidal abnormality, peripapillary in location, characterized by dilated and branching inner choroidal vessels with terminal reddish-orange, spheroid "polyp-like" lesions. They considered it as a subtype of choroidal neovascular (CNV) membrane causing recurrent serosanguinous detachments of the RPE and neurosensory retina. The lesions were not identified unless large enough to be clinically visible or imaged with fluorescein angiography (FA). Later, the nomenclature was revised to omit "idiopathic" to polypoidal choroidal vasculopathy or PCV.[10] The utility of ICGA and OCT imaging was realized, and early descriptions of PCV lesions were made.[2,11] The disease can clinically resemble AMD with hemorrhagic or serous pigment epithelial detachment, and it can be difficult to distinguish PCV from nAMD.

Epidemiology

Obtaining accurate estimate of the prevalence of PCV is limited often because its presentation is disguised as presumed exudative AMD. PCV is more prevalent in Black population and predominantly Japanese, including other Asians (22%–62%), than in White population (8%–13%) with a tentative diagnosis of nAMD.[12-22] Asian patients with PCV are younger when compared to patients with exudative AMD without PCV. PCV is more prevalent in Asian men and Caucasian women.[7,23-26] A comparative epidemiological study is needed to investigate these demographic differences between Asian and White populations.

PCV lesions are often located in the central macula in Asians, whereas the location seems more extrafoveal and peripapillary in White patients.[27] Moreover, PCV lesions may be located beyond the posterior pole causing peripheral exudative hemorrhagic chorioretinopathy or found together with macular lesion.[28-31] Bilaterality is present in 6%–24% of the Asian patients with PCV.[12] Large soft drusen frequently seen with nAMD without PCV is less prevalent in patients with PCV.[3]

Risk factors

Smoking is found to increase four-fold risk of PCV and nAMD.[32] Diabetes mellitus and end-stage renal disease show a higher prevalence in nAMD than PCV.[33] Central serous chorioretinopathy (CSCR) has been reported as a risk factor for PCV. Both entities though phenotypically different were found to have increased choroidal thickness (CT) and choroidal hyperpermeability in the affected as well as the fellow eye. Both conditions may be complicated by the development of CNV. The similarities found between CSCR and PCV suggest that they may be disease of the same spectrum.[34-37] Polypoidal lesions are also associated with tilted disc syndrome in myopic Asians eyes, angioid streak secondary to pseudoxanthoma elasticum, and radiation retinopathy.[38-41]

Cytokine analysis of the serum found C-reactive protein to be inconsistently associated with PCV. On the contrary, an increase of plasma homocysteine by 1 μmol/L conferred a 1.5-fold increased risk of PCV. Homocysteine is responsible for the endothelial injury, increased oxidative stress, promotion of thrombosis, and arteriosclerotic changes.[42,43] These arteriosclerotic changes predispose to the development of aneurysmal-like dilations seen in the polypoidal lesions. Arteriosclerotic and aneurysmal changes seen in PCV strongly suggest derangements in remodeling of extracellular matrix (ECM). Increased serum levels of matrix metalloproteinases (MMP-2 and MMP-9) in PCV eyes cause breakdown of the ECM.[44] Interleukin-1 β, a pro-inflammatory cytokine, was found in higher concentration in the vitreous aspirates of eyes with vitreous hemorrhage in PCV.[45] Aqueous levels of VEGF were found higher in PCV compared to controls though significantly lower than aqueous levels in nAMD. On the contrary, pigment epithelium-derived growth factor (PEDF), which is a potent natural angiogenesis inhibitor, was also found to be higher in these eyes.[46,47]

Genetics

The differences in age, gender, ethnicity, and cytokines expression indicate variable gene susceptibilities of PCV in different cohorts of population. PCV was considered a variant of nAMD because they have similar phenotypes.

However, PCV differs in the natural course of the disease and treatment response than nAMD. Genetic studies have identified susceptibility single-nucleotide polymorphisms (SNPs) in multiple genes in both PCV and nAMD. An updated meta-analysis identified 31 SNPs in 10 genes/loci that are associated with PCV susceptibility, including ARMS2, HTRA1, CFH, C2, CFB, RDBP, SKIV2L, CETP, 4q12, and 8p21.[48] These genes are related to ECM, basement membrane, complement cascade, lipid metabolism, cellular apoptosis, and inflammation. In contrast, variants in ELN, LIPC, LPL, ABCA1, VEGF-A, TLR3, LOXL1, SERPING1, and PEDF have no significant association with PCV. Furthermore, 12 polymorphisms at the ARMS2-HTRA1 locus were found to have different effects in PCV and nAMD. The different molecular mechanisms leading to the pathophysiologic differences of PCV and nAMD remain unknown. The meta-analysis represented cohorts of Asian population, especially Japanese and Chinese, and the polymorphisms yet remain unknown in non-Asians.

Pathogenesis

PCV lesions have been described earlier based on studying human specimens obtained during vitreoretinal surgery or enucleation. MacCumber *et al*. were the first to report a thick fibrovascular membrane (FVM) within the Bruch's membrane with many vascular ingrowths from the choroid into the Bruch's membrane.[49] Lafaut *et al*. also described an intra-Bruch's FVM seen with saccular, thin-walled aneurysmal vessels that appeared to be of venular rather than arteriolar origin.[50] In the PCV tissues collected during macular translocation surgery, Terasaki *et al*. found a polypoidal vascular complex within the Bruch's space below the RPE. It contained dilated, thin-walled vessels without pericytes, which corresponded with the orange-colored polyp. These vessels were surrounded by macrophages and fibrin material. A similar fibrovascular complex with dilated vessels, which were not choroidal vessels, was found in the subretinal space. A positive immunohistochemical stain to anti-VEGF in the RPE and vascular endothelial cells confirmed it to be subretinal neovascularization.[51] Conversely, Shiraga *et al*. only found an FVM under the sensory retina and above the RPE without a polypoidal vascular complex in a surgically excised membrane in submacular hemorrhage (SMH).[52]

Okubo *et al*. characterized the thin-walled dilated aneurysmal vessels to have hyaline-like appearance in the vessel walls, similar to vessels in the branch retinal vein occlusion.[53] They were identified as large choroidal arterioles with an inner elastic layer by Kuroiwa *et al*.[54] The walls of these arterioles were thick and showed sclerotic change associated with an increase in basement membrane-like materials together with collagen fibers. This is referred to as "hyalinization" which involves extensive replacement of the smooth muscle component by amorphous pseudocollagenous tissue of a poorly defined nature. Hyalinized vessels are characterized by extravasation of plasma protein and deposition of basement membrane-like material. This arteriosclerotic change seen in the choroid is similar to the change seen in other organs such as brain, kidneys, and pancreas.[44] Ross *et al*. found PCV with retinal artery macroaneurym with similar arteriosclerotic changes and epidemiological profile of Black, hypertensive elderly women.[55] The dilated hyalinized choroidal vessels allow massive exudation of fibrin and blood plasma to raise choroidal tissue pressure sufficient to produce protrusion of choroidal tissues through the weakened or disrupted RPE and Bruch's membrane. The hyalinized choroidal vessels are negative for α-smooth muscle actin (SMA) expression compared to immunoreactive for α-SMA in pericytes of CNV vessels. This indicates disappearance of smooth muscles cells of choroidal vessels due to the increased intraluminal pressure resulting from systemic hypertension.[44] However, no association was found between diastolic blood pressure and PCV.[32] VEGF positivity was recognized in macrophages, fibroblast-like cells, and RPE cells, but not in vascular endothelial cells, unlike CNV.[44] With significant lower aqueous levels of VEGF in PCV eyes, VEGF may hardly contribute to the occurrence of PCV.[46] These findings point out the inconsistency in the pathogenic processes of CNV in nAMD and PCV. Nevertheless, the possibility that PCV and CNV can occasionally exist in the same eye simultaneously cannot be ruled out. They may either coexist incidentally, or CNV can grow secondarily as a result of a wound repair reaction to a collapse of the RPE or Bruch's membrane in advanced PCV.

CNV is a granulation tissue proliferation that later undergoes fibrosis, typically representing a wound repair response.[56] The polypoidal complex of PCV predominantly lacks this granulation or fibrosis. Yet, fibrotic scars develop in PCV secondary to RPE tears or sequelae of subretinal hemorrhage (SRH).[57-60] Following SMH, an irreversible injury sets into the sensory retinal tissue. This is attributed to the limitation of the passage of nutrients to the retina, shrinkage of the outer retinal layers due to clot formation, and release of toxic substances, such as fibrin, iron, and hemosiderin. Toxic effects of subretinal blood can be demonstrated 24 h after hemorrhage.[61] As the SMH resolves, there is often a subsequent subretinal scar formation.

Clinical Features

The characteristic lesions of PCV are protruding orange-red nodular lesions.[1,57] They are usually located at the posterior pole, in the macular or peripapillary region, but peripheral PCV lesions are reported [Figure 1].[28,29,31]

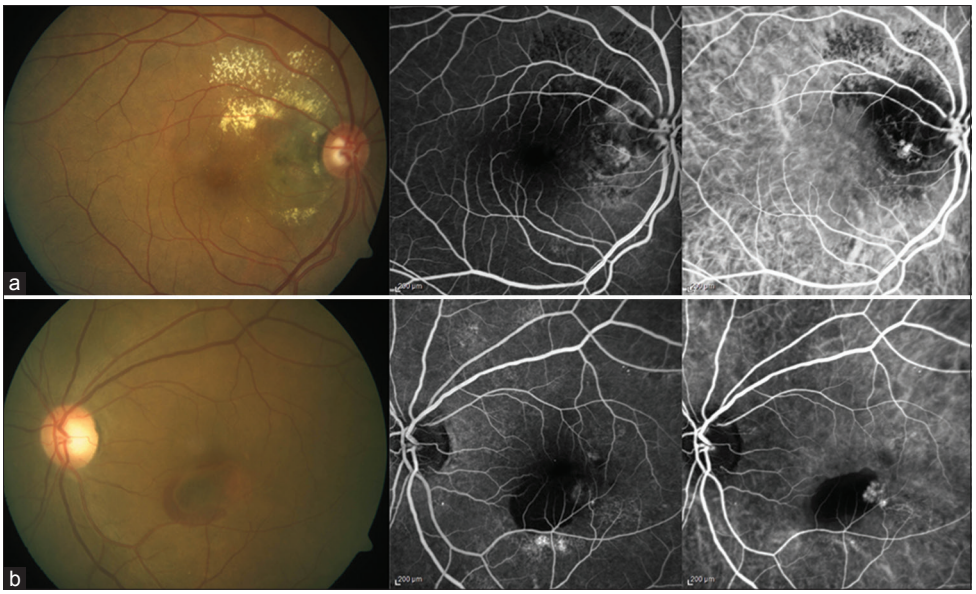

Figure 1: (a) Peripapillary polypoidal choroidal vasculopathy with subretinal pigment epithelium hemorrhage (gray-green) and hard exudates (top left); fluorescein angiography featuring classic choroidal neovascular membrane (top middle) and indocyanine green angiography detecting the polypoidal lesion within the blocked cyanescence due to hemorrhage below the retinal pigment epithelium (top right). (b) A well-circumscribed hemorrhagic pigment epithelial detachment with orange-red nodular lesions at the temporal edge of the pigment epithelial detachment and subretinal hemorrhage (bottom left); stippled hyperfluorescence on fluorescein angiography (bottom middle) and a small branching vascular network with single polypoidal lesion identified on indocyanine green angiography (bottom right)

The nodular lesions are usually accompanied with serous exudation and hemorrhage that may lead to pigment epithelial detachments (PEDs), SRD, SRH, subretinal fibrin, intraretinal lipids, hard exudates, and drusens.[62,63] Polyp lesions are mostly present at the margin and inside the serosanguinous PED, which may appear as a "notch sign." A notch in the margin of a large PED frequently indicates the site of polypoidal lesions. Microrips of the RPE and RPE tears could be found at the margins of the PEDs.[64,65] When associated with hemorrhage, the SRH may block the view of the nodular lesions. In such cases, they are observed on ICGA and easily visible with OCT. Furthermore, the view of the fundus is sometimes obscured by vitreous hemorrhage.

The funduscopic findings and visual acuity (VA) vary depending on the time of initial presentation of the patient. VA depends on the degree of exudation and is usually good in the absence or minimal subretinal fluid or hemorrhage at the fovea. SRH or SMH may occur because of the rupture of the abnormal areas of vascular dilation or aneurysmal venules. SMH in the subfoveal region, particularly when massive (>4 disc diameter area or thick hemorrhage beyond the temporal arcades), induces an abrupt decrease in the VA and can lead to RPE and outer retinal degeneration.

Imaging

Fluorescein angiography

PCV appears as occult CNV or minimally classic AMD on fluorescein angiography (FA) because BVN in PCV is located in Bruch's membrane. They may sometimes appear as "classic" CNV because of an increased hyperfluorescence due to the atrophy of overlying RPE or subretinal fibrin deposition or presence of type 2 CNV.[66,67] The RPE in FA hampers visualization of the BVN beneath it unless in case of overlying RPE atrophy or less pigmented fundus. Serosanguinous complications of PCV further block the underlying polypoidal abnormalities. These drawbacks of FA are superseded by ICGA.

Indocyanine green angiography

Indocyanine green absorbs and emits near-infrared light, which readily penetrates the RPE. In addition, the dye has a higher binding affinity to plasma proteins and does not leak rapidly from the choriocapillaris as against fluorescein. PCV primarily involves the inner choroidal vasculature, and so, ICGA remains the gold standard to diagnose PCV.[2] The indications of performing an ICGA are clinical findings of serosanguinous maculopathy with one of the following: clinically visible orange-red subretinal nodules; spontaneous massive SRH; notched or hemorrhagic PED; a lack of response to anti-VEGF therapy. ICGA characteristics of PCV include the presence of single or multiple focal areas of hyperfluorescence arising from the choroidal circulation within the first 6 min after injection of the dye, with or without an associated BVN. The orange-red subretinal nodules correspond to the ICGA hyperfluorescence that are polypoidal aneurysms or dilations at the edge of the BVN. Pulsations in polyps can be observed only in video ICGA. Active polyps are those having a hypofluorescent

halo around it, indicating fluid surrounding the polyp. ICGA enables viewing the total lesion area (all polyps and the BVN), making it amenable to plan treatment with laser or PDT.[68] Kawamura *et al*. classified PCV based on ICGA into two types: Type 1, both feeder and draining vessels are visible on ICGA and numerous network vessels; Type 2, neither feeder nor draining vessels are detectable and the number of network vessels is small.[69] ICGA is now considered gold standard in differentiating PCV from classic or occult CNV associated with typical nAMD. However, ICGA is invasive, time-consuming, and not widely available in many clinics.

Optical coherence tomography

Spectral-domain OCT (SD-OCT) allows high-resolution cross-sectional images to study the retinochoroidal morphologic changes. It can localize the lesions and define their extent more precisely. Several reports have described characteristic features as follows [Figure 2]:

1. A sharp peak-like or thumb-like PED with underlying moderate reflectivity within the peak, most likely representing the polyp itself[70,71]
2. Tomographic notch: "V"-shaped depression between two PEDs or at the margin of a large PED[65,72,73]
3. A moderate hyperreflective ring surrounding an area of hyporeflectivity located underneath the PEDs probably represents the lumen of the polypoidal lesions. They are attached to the posterior surface of the RPE and correspond in location with polypoidal lesions seen by ICGA[65,73]
4. The double-layer sign, consisting of two hyperreflective lines, is believed to represent the separation of the RPE from Bruch's membrane by the BVN and corresponds to the extent of late geographic hyperfluorescence on ICGA.[72]

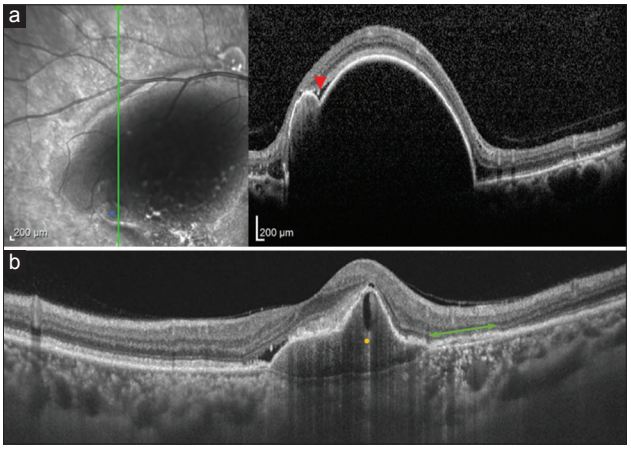

Figure 2: (a) A "V" depression between two pigment epithelial detachments – "notch" sign (red arrowhead) with moderate hyperreflectivity below the smaller pigment epithelial detachment representing polypoidal lesion beneath. (b) Thumb-shaped pigment epithelial detachment with an abutting moderate hyperreflective ring with surrounding hyporeflective area (yellow dot) demonstrating the lumen of the polypoid lesion. Two hyperreflective membranes (green line with arrows), a double membrane sign, correlating with the branching vascular network

Lui *et al*. reported a high sensitivity and specificity of OCT over ICGA with these features.[74] Its ability as a screening modality can be harnessed when ICGA is not available and may be able to differentiate PCV from CNV in nAMD.

Enhanced depth imaging mode of the SD-OCT and SS-OCT provides clearer images of sub-RPE structures and shows agreeable efficacy to study the PCV lesions and choroidal features.[75] Subfoveal CT is an important and objective parameter in the clinical diagnosis of PCV and nAMD.[35,76-80] However, CT measurement may not entirely reflect the detailed structural and functional alterations within the choroid in different exudative maculopathy. Choroidal vascular characteristics were used to subclassify PCV into two subtypes – typical PCV with thick choroid and PCV without thick choroid (polypoidal CNV). The former has significantly higher vascular area, which is consistent with the pachychoroid spectrum in which choroidal vessel dilatation plays a key role in the pathogenesis. The later subtype of polypoidal CNV has similar choroidal vascular characteristics to eyes with AMD and may be similar treatment response.[69,81,82] ICGA and OCT correlate well at baseline findings of polypoidal lesions in PCV. However, discrepancy may be seen during treatment to monitor efficacy. Polypoidal lesions persisted more often on OCT after treatment despite improvement evident on ICGA and OCT.[83]

Optical coherence tomography angiography

OCT angiography (OCTA) uses a split-spectrum amplitude-decorrelation algorithm, to noninvasively detect the blood flow in the retina and structural changes simultaneously. The flow patterns of PCV has confirmed the location of the polyps and BVNs in the compartment space between the RPE and Bruch's membrane rather than in the choroid.[84-87] BVNs are better delineated on OCTA than on ICGA but do not show the polyps as clearly as ICGA.[88] This may be attributed to the slower flow velocity resulting either from an abrupt dilatation or from an partial obstruction of the lumen of the polyp or turbulent flow in it.[85,88] However, a recent study using layer-by-layer OCTA analysis revealed that the BVN may be located in a range from inner side to outer side of Bruch's membrane.[88] Besides, the PCV seems to have a three-dimensional structure, with the polyps located at the inner-most part, the BVN outer to the polyps, and a feeding vessel stalk even outer and at the choroidal layer.[88] However, the presence of hemorrhage, fluid, fibrosis, or exudates may mask the images below the RPE. In addition, artifacts and auto-segmentation are the limitations of OCTA that cautions interpretation of the images.

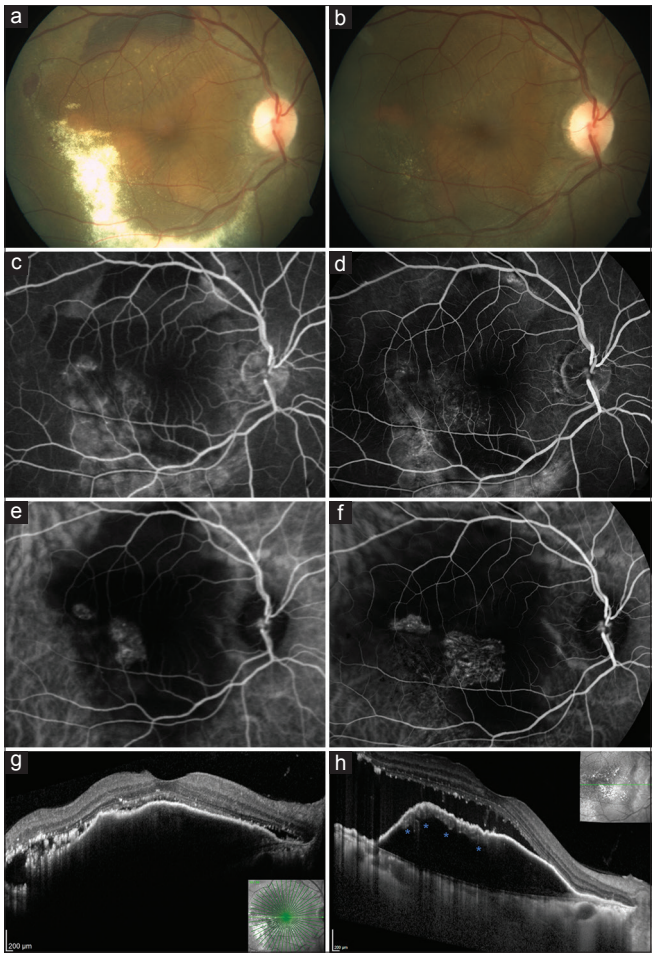

Figure 3: A 51-year-old woman with diminution of vision (OD-20/30) had (a) hemorrhages both in the subretinal pigment epithelium and subretinal space extending to the arcades with massive exudation. (c) Fluorescein angiography shows blocked fluorescence due to subretinal and sub-retinal pigment epithelium hemorrhage with stippled hyperfluorescence inferotemporal to fovea, which is identified as branching vascular network with polypoidal lesions at the temporal edge of the lesion in indocyanine green angiography (e). (g) The spectral-domain optical coherence tomography B-scan shows a subfoveal hemorrhagic pigment epithelial detachment, with minimal subretinal fluid and hyperreflective hard exudates. She received intravitreal aflibercept monotherapy and status post five injections, (b) exudation, subretinal and sub-retinal pigment epithelium hemorrhage reduced clinically, with persistent stippled fluorescence in fluorescein angiography (d), better delineation of branching vascular network with indocyanine green angiography (f). (h) Spectral-domain optical coherence tomography B-scan demonstrates subretinal fluid, pigment epithelial detachment with serous conversion and reduction in size and branching vascular network abutting the retinal pigment epithelium (blue asterisk)

Natural History (Why to Treat?)

The natural history of PCV has been studied after long-term observation of cases since its description.[1,9,10,89,90] It indicates that PCV is a chronic persistent disease of the choroid that undergoes recurrences and spontaneous resolution of leakage and hemorrhage at macula. In the process, it culminates into degeneration of the RPE and sensory retina at the macula and severe visual loss.

Uyama *et al*. described the natural history of PCV. Two distinct patterns were observed: (1) exudative characterized by serous PED and SRD and (2) hemorrhagic characterized by hemorrhagic PED and SRH at the macula.[60] Polypoidal CNV in the form of small aneurysmal dilations of vessels resembling cluster of grapes has a high risk of bleeding and leakage. These recurring aneurysmal dilations arise from postcapillary venules or capillaries. They disappear on occlusion by a thrombus only to grow into dilations at other areas. These dilations can either leak to give rise to exudative pattern or rupture to develop hemorrhages. When small dilations rupture, small hemorrhages develop; however, venules rupture to develop massive hemorrhage.

The underlying process as to why spontaneous hemorrhage occurs is still unknown. The accelerated infiltration from the polyp lesions into the sub-RPE space increases the tension on the PED flap. It is followed by PED microrips that lead to an acute decompression of the PED, increased blood flow in the polyp, and eventually rupture of the polyp.[64]

The main cause of severe visual loss is due to macular manifestation in PCV. Persistent serous detachment of the macula leads to atrophy of the RPE and sensory retina. Subretinal fibrovascular proliferation markedly damages the macula function. Moreover, finally, persistent massive SMH damages the RPE and photoreceptors, leading to degeneration.[62]

A good VA at initial examination has a favorable outcome. Cluster of grapes on ICGA indicates a high risk for poor visual outcome. The progression of PCV is slow and visual outcome is favorable than in nAMD. An important difference between eyes with CNV in nAMD and PCV is the relative paucity of subretinal fibrosis and disciform scarring in the later.[60,91] However, the overall visual outcome of PCV is relatively poor over the natural course of the disease if untreated.

Management

Categorization and activity of polypoidal choroidal vasculopathy (when to treat?)

PCV is clinically classified as follows:[68]

1. Quiescent: Polyps in the absence of subretinal or intraretinal fluid or hemorrhage
2. Exudative: Exudation without hemorrhage, which includes sensory retinal thickening, neurosensory retinal detachment, PED, and subretinal lipid exudation
3. Hemorrhagic: Any SRH or sub-RPE hemorrhage with or without other exudative characteristics.

The PCV lesion, whether active or inactive, decides the impact of any treatment intervention. There are currently no universally recognized criteria for defining

the disease activity. PCV is considered as active if there is clinical, OCT, or FA/ICGA evidence of any one of the following: vision loss of 5 or more letters (ETDRS chart) or equivalent; subretinal fluid or intraretinal fluid; PED; SRH or sub-RPE hemorrhage; or fluorescein leakage. An active, symptomatic PCV lesion is one which causes the loss of central VA and needs treatment initiation. The circumstance of active, asymptomatic can be considered for treatment at the physician's discretion.

What to treat?

In treatment-naïve patients, the entire PCV lesions (polyps plus BVN) as identified on ICGA require to be treated. The initial goal of treatment is angiographic regression of polyps on ICGA. The efficacy of the treatment is usually measured in terms of change in best-corrected VA (BCVA) and central retinal thickness (CRT) along with complete regression of polyps.

How to treat?

There is currently a wide spectrum of treatment options available for PCV, including thermal laser photocoagulation (TLP), verteporfin PDT (vPDT), anti-VEGF therapy, and various combinations of these therapies.

Thermal laser photocoagulation

ICGA-guided direct TLP of the polyps can be considered at extrafoveal location of the lesion. However, photocoagulation of the whole lesion compared to the polyps appears to be more efficacious.[92] Stabilization or improvement in the vision was observed in 78% cases, after TLP of extrafoveal lesion along with clinical and angiographic resolution of maculopathy. However, 10.7% of cases reported recurrence of polyps and subsequent CNV.[93] TLP for subfoveal leads to decrease in VA in 54%, ascribed to recurrent exudation or hemorrhage and atrophy at the fovea.[92] Certainly, in effect to this risk, direct TLP is not recommended for the initial therapy of active juxtafoveal or subfoveal PCV.[93] Feeder vessel TLP achieved resolution of neurosensory detachment in 60% and improvement in VA in half of the cases.[94]

Verteporfin photodynamic therapy

Mechanism

PDT uses a photosensitizing agent verteporfin that preferentially accumulates in the abnormal neovascular endothelial cells through their increased expression of low-density lipoprotein receptors. Verteporfin produces a photochemical reaction when activated by nonthermal laser in the far-red spectrum and produces selective vascular occlusion by thrombosis. The far-red wavelength allows good penetration through melanin, blood, fibrotic tissue, enabling effective treatment of pigmented or hemorrhagic lesions located within the choroid. Laser spot size is determined by the greatest linear dimension (GLD) of the lesion based on ICGA. Verteporfin is infused intravenously at a dose of 6 mg/m^2 of body surface area over 10 min, followed by application of 689 nm laser 15 min after initiation of infusion with a light dose of 50 J/cm^2 over 83 s.[95-97]

Outcomes

In a systematic review and meta-analysis on the longer-term visual outcome of PCV eyes treated with PDT monotherapy, visual outcome was stable until 2 years but worsened at 3 years and 5 years [Table 1].

Younger, smaller GLD (<3600 um), better baseline VA, less hemorrhaging, and presence of a serous macular detachment at baseline were independent predictive factors associated with visual improvement.[120,145]

Recurrences

Akaza *et al*.[128,136] reported recurrence rate in PCV eyes treated with PDT as 64% at 2 years and 77% at 3 years. Kang *et al*.[142] reported recurrence rate of 78.6% and Saito *et al*.[145] with 44% at 5 years. Recurrences are responsible for deterioration in VA in the long term. Although cumulative number of PDT session in the 1st year was ≤2, damage to the normal choroidal

Table 1: Photodynamic therapy monotherapy: Summary of studies from systematic review and meta-analysis

Minimum follow-up (months)	Change in visual acuity[a]	Summary of studies[b] (*n*=49)
12	−0.115, 95% CI: −0.144-−0.087	20 studies;[98-117] showed improved visual acuity; <20% eyes lost 3 lines
24	−0.066, 95% CI: −0.116-−0.016	19 studies;[101,118-135] 13/19, vision returned to near baseline (two studies[131,133] showed improved vision in eyes treated with PDT combination). 6/19, dropped below baseline; 2/4[118,120] reported experience with reduced fluence PDT.
36	−0.027, 95% CI: −0.134-0.079	10 studies;[136-144] 6/10, visual outcome worsened after the 1st year and 5 of them gradually returning to near baseline, but the cohort[136] worsened at 3 years of follow-up.
		4/10[137-140] studies reported improved visual acuity at 60 months

[a]Pooled data from 29 studies for visual outcome that included 1669, 701, and 316 eyes with 1, 2, and at least 3 years of follow-up, respectively, [b]Studies with at least 1 year of follow-up with minimum 30 eyes that reported visual acuity were included. Studies in which PDT was not the primary treatment for PCV with submacular hemorrhage, tilted disc were excluded. CI = Confidence interval

vasculature and the RPE remains a concern for repeated PDT.[141]

Complications

Post-PDT SRH, massive suprachoroidal hemorrhage, RPE tears, and microrips at the margin of the PED are the reported complications of PDT for PCV.[146-149] Hirami *et al*. found SRH in 28 (30.8%) of 91 eyes post-PDT, developing within 1 month of treatment and vitreous hemorrhage in 6 (6.6%) eyes. However, 82% of them maintained or improved VA. Large laser spot size may or may not be associated with increased risk of vitreous hemorrhage.[146,147] However, standard fluence PDT was reported with increased risk of hemorrhagic complications by Rishi *et al*.[147] However, there has been no direct comparison between reduced fluence and full fluence PDT in PCV. Regardless of the factors, visual outcome after PDT in eyes with PCV does not appear to be affected by the presence or absence of hemorrhagic complications.

Limitations

PDT has demonstrated its ability to cause the regression of polyp-like dilations in spite of the relative lack of visual improvement within 2 years.[4] In the EVEREST study, polypoidal lesion closure rate was significantly higher in the PDT monotherapy arm (71.4%) and PDT combined with ranibizumab arm (77.8%) compared to ranibizumab monotherapy arm (28.6%). However, the PDT arm achieved less visual gain (+7.5 letters) compared to ranibizumab arm (+9.2 letters).[150] In addition, PDT alone is ineffective in causing regression of the BVN or in resolving exudative activity arising from the BVN.[68]

Anti-vascular endothelial growth factor therapy

The rationale of intravitreal anti-VEGF therapy in PCV was based on the reports of Tong *et al*. and Matsuoka *et al*. that showed a strong expression in PCV specimens and upregulation of VEGF in the aqueous.[46,47] Several case series and reports demonstrated the ability of bevacizumab (a full-length anti-VEGF antibody) to decrease the exudation and improve or stabilize VA but minimal to no change in polyp regression.[30,151-155] Whether the size of the drug hampers penetration into the sub-RPE space remains elusive. A weak RPE after previous treatment such as PDT may allow penetration through the RPE.[156]

Ranibizumab, an antibody fragment with smaller size, was speculated to overcome this barrier. Early studies with intravitreal ranibizumab (IVR) reported temporary stabilization of vision and reduction in exudation in PCV.[157-161] Subsequent studies with more patients and longer follow-up reported 17%–40% of patients achieved ≥0.3 logMAR (15 letters or more) improvement in BCVA. The studies followed a regimen of monthly injections for 3 months, followed by as needed retreatments or continuous monthly injections and the mean number of injections 4.5 (4.2–5.2) over 12 months [Table 2].

The EVEREST study compared the use of IVR and PDT for the treatment of PCV and concluded that PDT is more effective than IVR in achieving regression of polyps; however, the visual outcome was better in the ranibizumab monotherapy arm than in the PDT arm despite the lack of statistical power.[150] The LAPTOP study is a prospective multicenter randomized trial that compared the vision-improving effect of IVR and PDT in PCV. At month 12, more patients in the ranibizumab arm had a VA gain of at least 0.2 logMAR compared with the PDT arm (31% vs. 17%; $P = 0.039$).[167] At month 24, it was confirmed that IVR achieved better visual outcomes than PDT ($P = 0.004$). In addition, although several patients in the PDT arm showed improvement in vision, approximately 15% of patients showed more than six lines of vision loss. Polyp closure rate was not assessed.[134] A high-dose ranibizumab monotherapy (2 mg/0.05 ml) was tolerated well with good efficacy and safety profile but lacked long-term follow-up.[171,172]

Few studies with 24–36 months follow-up demonstrated significant improvement in VA at 12-month interval but stabilized subsequently.[168-170,173] With longest follow-up of 6 years as yet, Hikichi[174] reported a mean improvement of −0.10 logMAR unit ($P = 0.008$) after 3 months of IVR, from baseline BCVA (0.34 ± 0.37) logMAR unit and sustained until 2.5 years ($P = 0.034$). However, it returned to a baseline level at 3 years (0.32 ± 0.39) and maintained at the end of 6 years (0.36 ± 0.37). The study found an improvement in the mean foveal thickness of −115 um ($P = 0.014$) at 3 years and −123 um ($P = 0.005$) at 6 years, but exudative changes persisted despite mean of 21.5 ± 10.1 injections over 6 years. This was attributed to the limited effect of anti-VEGF monotherapy to cause regression of the polypoidal lesion and BVN. Moreover, progressing RPE atrophy and significant macular atrophy contributed to the poor visual gain in these patients.[175]

PCV is a chronic disorder and warrants a continuous long-term follow-up, with or without retreatments, and yet, the visual outcome would fail to improve at a point. It adds to poor patient compliance, economic burden, and safety concerns. This emphasized individualized treatment strategies based on the response to IVR in the first 12–24 months, to ensure uninterrupted follow-up and maintain improved VA. The treat-and-extend (TAE) regimen effectively improved VA in PCV eyes responding to IVR while reducing the number of injections.[176,177]

Pigment epithelial tears, post-injection SRH and vitreous hemorrhage, and RPE atrophy are few complications reported.[175,178,179] A favorable response to anti-VEGF therapy was found in young patients, with better baseline

Table 2: Ranibizumab monotherapy for polypoidal choroidal vasculopathy

Study, design, year	Number of eyes; regime	Follow-up (months)	Mean number of injections	Mean difference (logMAR units)	Decrease in the CRT (um)	Polypoidal regression rate	BVN
Koh *et al*.[150] (EVEREST) RCT, 2012	21 eyes IVR only group, 3 monthly IVR (0.5 mg), then PRN	6	5.2±1.2	9.2 letters	−65.7	6 (28.6)	-
Hikichi *et al*.[162] Prospective, 2012	85 eyes, 3 monthly IVR (0.5 mg), then PRN	12	4.2±1.3	−0.22 (*P*=0.001)	−113 (*P*=0.001)	32 (40) eyes	Abnormal choroidal vessels remained
Matsumiya *et al*.[163] Retrospective, 2013	30 PCV eyes, 3 monthly IVR (0.5 mg), then PRN	12	4.2±1.3	−0.04 (*P*=0.33)	−0.94 (*P*<0.001)	-	-
Ogino *et al*.[164] Prospective, 2013	23 Subfoveal PCV eyes, 3 monthly IVR (0.5 mg), then PRN	12	6.1±2.8	−0.01 (*P*=0.63)	−82 (*P*=0.008)	-	-
Mori *et al*.[165] Prospective, 2013	50 eyes, 3 monthly IVR (0.5 mg), then PRN	12	4.72±1.68	−0.05 (*P*<0.01)	−87.5 (*P*<0.01)	17/47 (36)	BVN unchanged 26 (58); enlarged 18 (40)
Kokame *et al*.[166] (PEARL-1) Prospective, 2014	13 eyes, monthly IVR (0.5 mg) for 12 months	12	12	−0.18 (*P*=0.012)	−113 (*P*=0.011)	5 (38) eyes	BVN persisted in all 13 eyes
Oishi *et al*.[167] (LAPTOP) Randomized clinical trial, 2013	46 eyes, 3 monthly IVR (0.5 mg), then PRN	12	4.5	−0.11 (*P*=0.019)	−107.7 (*P*=0.115)	-	-
Hata *et al*.[168] Retrospective, 2015	70 eyes, 3 monthly IVR (0.5 mg), then PRN	12 24	6.66±4.23	−0.10 (*P*=0.025) −0.06	−146.9 (*P*<0.001)	-	-
Matsumiya *et al*.[169] Retrospective, 2015	32 eyes, 3 monthly IVR (0.5 mg), then PRN	24	5.7	−0.03 (*P*=0.0004)	−97 (*P*=0.63)	-	-
Kang and Koh[170] Retrospective, 2013	36 eyes, 3 monthly IVR (0.5 mg), then PRN	36	11.45±7.81	+0.10 (*P*=0.307)	−74.14 (*P*=0.45)	No complete regression	-

CRT = Central retinal thickness, BVN = Branching vascular network, RCT = Randomized controlled trials, IVR = Intravitreal ranibizumab, PRN = Pro-re-nata, PCV = Polypoidal choroidal vasculopathy, logMAR = Logarithm minimum angle of resolution

VA, smaller lesion size, smaller size of the largest polyp, single polyp, absence of cluster of grapes on ICGA.[180-183] The subfoveal CT decreases with ranibizumab and may be associated with PCV activity.[184,185] On the contrary, PCV eyes with thick choroids were associated with poor anatomical outcomes in comparison to thin choroids that showed the greatest extent of anatomical improvement but lacked significance in terms of visual outcomes.[186] PCV with choroidal hyperpermeability on ICGA may also show poor response to anti-VEGF monotherapy.[187] Furthermore, VEGF levels were lower in eyes affected by PCV with thick choroid, and anti-VEGF treatment response was correlated with baseline VEGF level.[188]

Nonresponders to ranibizumab are refractory to repeated treatments with poor visual gains.[176] A retrospective study reported that eyes refractory to ranibizumab had significant improvement after switching to aflibercept.[189] A prospective study comparing bevacizumab and ranibizumab found no difference in the number of injections, improvement in vision, or decrease in mean central foveal thickness.[190] Similar results were reported on comparing ranibizumab and aflibercept. However, in addition, aflibercept-treated eyes had more frequent polyp regression (34%–75%) than ranibizumab-treated eyes (22%). Ranibizumab "nonresponders" who were switched to aflibercept treatment demonstrated reduced exudation, resolution

of PEDs and polyp closure, reduced CT, and stable or improved vision.[189,191-194]

Vascular endothelial growth factor-Trap monotherapy

Aflibercept (Eylea, Regeneron, Tarrytown, NY, USA) is a soluble decoy receptor fusion protein consisting of the binding domains of VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G-1, allowing for binding to all isoforms of VEGF-A, VEGF-B, and placental growth factor. Intravitreal aflibercept (IVA) injections dosed every 2 months after 3 initial monthly doses, either in pro-re-nata (PRN) regimen, fixed-dose (FD) regimen, or TAE regimen, demonstrated improvement in both visual and anatomical outcome achieving statistical significance. In addition, regression of polypoidal lesion was observed as well with variable response to the BVN. It remains the safest option in peripapillary PCV, in which PDT is precluded [Table 3].

Inoue *et al*. in a comparison of FD to PRN regimens showed a trend toward better visual outcomes in FD group at the end of 1 year although the difference did not reach statistical significance. Although the number of injections administered was less in the PRN group, the polypoidal lesion closure rates were similar and BVN persisted in all cases [Figure 3].[199] A retrospective analysis of 3-year follow-up with aflibercept monotherapy consistently showed VA to be significantly better in the FD group than in the PRN group (P = 0.031), for at least 1 year. Young age and better baseline VA were associated with better VA at long-term follow-up.[200] Furthermore, aflibercept in TAE regimen effectively maintains the macula in a dry state

Table 3: Aflibercept monotherapy for polypoidal choroidal vasculopathy

Study, design, year	Number of eyes; regime	Follow-up (months)	Mean number of injections	Mean difference (logMAR units)	Decrease in the CRT (um)	Polypoidal regression rate	BVN
Yamamoto *et al*.[192] Retrospective, 2015	90 eyes, 3 monthly IVA (2 mg), then 2q8	12	7.1±0.3	−0.14 (P<0.001)	−111 (P<0.001)	46/83 (55.4%) Complete regression 27/83 (32.5%) Partial regression	11/82 (13.4%) Decrease in BVN size
Hara *et al*.[195] Retrospective, 2016	29 eyes, 3 monthly IVA (2 mg), then PRN	12	3.9±1.9	−0.14 (P<0.0001)	−136 (P<0.005)	14 eyes (74%)	-
Lee *et al*.[196] Prospective, multicentric, 2017	35 eyes, 3 monthly IVA (2 mg), then 2q8 FDR	12	8	9.0±18.1 letter improvement (P<0.001)	−111.6 (P<0.01)	26 (66.7%) Complete regression	14 (35.9%) - BVN size increased 2 eyes - RPE tear 12 (32.5%) Recurrence with fluid
Hosokawa *et al*.[197] Retrospective, 2017	37 eyes, 3 monthly IVA (2 mg), then TAE	12	8.2	−0.16 (P<0.001)	−145.7 (P<0.001)	19 (51.4%)	15 (40.5%) poor response or recurrence
Oshima *et al*.[198] Prospective, multicentric, 2017	50 eyes, 3 monthly IVA (2 mg), then 2q8 FDR	12	8	−0.21 (P<0.0001)	−117.2 (P<0.0001)	29 (72.5%) (P<0.0001)	Leaking BVN reduced to 6 (15%) (P<0.0001)
Inoue *et al*.[199] Prospective, 2015	42 eyes, 25 FDR, 17 PRN	12	7.0 5.9±2.9	−0.16 (P<0.001) −0.09 (P=0.03)	−194 (P<0.01) −180 (P<0.001)	12 (48%) 9 (52.9%)	CT: −34 (P<0.01) −21 (P=0.004) BVN persisted in all eyes
Maruyama-Inoue *et al*.[200] Retrospective, 2017	33 eyes; 23 FDR, 10 PRN	36	15.3±4.6 9.0±8.9	−0.16 (P=0.019) −0.20 (P=0.006) −0.05 (P>0.05)	−96 (P<0.001), −100 (P=0.024) −84 (P=0.376)		CT: −31(P<0.001) −36 (P=0.002) −17 (P=0.451)
Morimoto *et al*.[201] Retrospective, 2017	58 eyes; TAE	12 24	7.71±0.16 5.45±0.30	−0.15 (P<0.01) −0.12 (P<0.01)	−112 (P<0.01) −130 (P<0.01)	32 (55.2%)	−32 (P<0.01) −36 (P<0.01)

TAE = Treat-and-extend: The injection interval is extended by 2 weeks up to a maximum of 12 weeks, if there are no exudative changes, or shortened by 2 weeks to a minimum interval of 4 weeks, if any exudative changes are seen at the visit, FDR = Fixed dose regime, CT = Choroidal thickness, logMAR = Logarithm minimum angle of resolution, CRT = Central retinal thickness, BVN = Branching vascular network, RCT = Randomized controlled trials, IVA = Intravitreal aflibercept, PRN = Pro-re-nata

and achieves good visual outcomes in 2 years, along with regression of polypoidal lesions in 55.2% cases.[201]

Aflibercept monotherapy consistently reduced the CT in PCV eyes. This suggests that aflibercept penetrates into the choroid and makes it thinner, which is consistent with previous *in vivo* and human study.[202,203] It is known that IVA inhibits choroidal vascular hyperpermeability and has a possible vasoconstrictor effect on the choroidal vasculature.[204,205] This may affect the choroidal circulation, influence of which explains outer retinal atrophy. CT tended to decrease more in the FD group than in the PRN group. However, it does not result in deleterious visual changes in the short-term though it might cause visual decline in the long term.[206] Better visual outcomes and decreased monitoring burden favor the FD regimen although treatment costs are likely to be much higher compared to a PRN dosing regimen. To reduce the treatment burden, studies comparing IVA combined with PDT and FD IVA monotherapy are warranted. Although a lack of long-term outcomes yet, TAE regimen can be a potential option.

The PLANET study,[207] a randomized, double-masked, sham-controlled prospective study, evaluated aflibercept monotherapy compared to combination aflibercept and deferred rescue PDT in PCV patients. After 3 initial monthly aflibercept injections, all patients were treated with FD regimen to month 12. In addition, patients were evaluated for rescue criteria, which included (1) BCVA less than or equal to 73 ETDRS letters; (2) presence of new or persistent fluid on OCT; (3) evidence of active polyps on ICGA; and either (4) BCVA loss, no change, or insufficient gain (<5 letters gain); or (5) BCVA gain more than 5 letters but less than 10 letters and PDT was determined to be of rescue. A large proportion (87.9% and 85.7% in the aflibercept monotherapy arm and combination arm, respectively; $P = 0.84$) did not meet the rescue criteria. Both treatment arms achieved similar BCVA gain (10.7 vs. 10.9 letters) and polyp regression rates (38.9% vs. 44.8%, respectively; $P = 0.32$). Over 80% of patients had no signs of polyp activity at week 52. Rescue PDT could not achieve visual significant visual gain. Polyp closure rate was similar, irrespective of receiving active rescue PDT or not. The PLANET study thus concluded that no significant additional benefit was demonstrated by adding rescue PDT in patients receiving FD aflibercept at week 52. However, no evidence exists of the benefit of PDT if combined with aflibercept at baseline.

Combination therapy

Rationale

vPDT causes thrombosis of the polypoidal lesions, and anti-VEGF therapy reduces the exudation arising from the BVN. In addition, anti-VEGF may also counteract the upregulation of VEGF following PDT, responsible for the development of secondary CNV membrane and recurrence of PCV. Theoretically, a combination of the two therapies is an attractive option as it potentially targets both components of the PCV complex, i.e., the polypoidal lesions and the BVN.[208-213]

Intravitreal anti-vascular endothelial growth factor monotherapy versus photodynamic monotherapy

Table 4 summarizes the efficacy in mean change in BCVA and CRT with polypoidal regression rate compiled from two meta-analyses comparing the monotherapies. Anti-VEGF agents compared to PDT induce more CRT reduction although at a variable follow-up point. Moreover, both monotherapies are equivalent in terms of BCVA change. This confirms the notion that reduction of CRT does not necessarily indicate a good visual outcome. Further, PDT is more effective than anti-VEGF therapy in regressing polypoidal lesions.[213,217,218] The interpretation of these findings is limited by the substantial heterogeneity in the studies included in the meta-analysis. Nevertheless, these findings suggest that neither PDT monotherapy nor anti-VEGF monotherapy is the best option for the treatment of PCV although each possesses distinct advantages over the other. Considering the shortcomings of the two monotherapies, combination therapy may allow for more comprehensive treatment.

Combination treatment versus photodynamic monotherapy

Two systematic reviews and meta-analysis[214,215] suggested that combination of PDT and anti-VEGF therapy had more potential in achieving early and maintaining better long-term visual outcomes than PDT monotherapy. Additional PDT sessions induce SRH and ischemic damage to choroidal tissue, explaining the loss of improvement in VA in the PDT monotherapy. Combining anti-VEGF agent reduces leakage, resolves fluid, and decreases the risk of development of SRH, post-PDT application. However, the reduction in CRT is maintained over a short period.

Combination treatment versus intravitreal anti-vascular endothelial growth factor monotherapy

The meta-analysis[215,217] indicates that combination treatment is more effective in improving BCVA and polypoidal regression with no significant difference in CRT reduction. Hence, polypoidal regression is as important as reduction in CRT to achieve a good visual outcome, which in turn is brought into effect by PDT in the combination therapy.

Combination treatment versus photodynamic monotherapy versus intravitreal anti-vascular endothelial growth factor monotherapy

The EVEREST study was a landmark phase 3, double-blind, multicenter, randomized control clinical

Table 4: Summary of comparison of monotherapies and combination treatment

Groups	Mean change in BCVA from baseline	Mean change in CRT from baseline	Polypoidal regression rate	Adverse effect
		PDT monotherapy versus anti-VEGF mono		
Yong *et al*., 2015[213]	PDT is comparable to anti-VEGF therapy at all follow-up time points111	PDT was more effective in CRT reduction than anti-VEGF at 6 months posttreatment (*P*=0.002) (WMD, 44.94; 95% CI, 16.44-73.44) with heterogeneity (I2=30.3%)	PDT was more effective than anti-VEGF in achieving regression of polyps. (OR: 6.85; 95% CI: 2.15-21.79; *P*=0.001) with heterogeneity (I^2=64.4%)	
Qian *et al*., 2018[214]		Anti-VEGF therapy significantly reduced CRT compared with PDT at 3 months (*P*=0.04) with no heterogeneity (I2=0%)	PDT was more effective than anti-VEGF in achieving regression of polyps at 3 months and 6 or more months (*P*<0.00001, I^2=36%; and *P*=0.0001, *I*2=0% respectively)	
		Combination treatment versus PDT monotherapy		
Wang *et al*., 2014[215]	Combination therapy was significantly better at 12 months (WMD: 0.11, 95% CI: 0.012-0.21; *P*=0.028) with I^2=0% and 24 months (WMD: 0.21; 95% CI: 0.054-0.36; *P*=0.008) with I^2=0% Improvement in mean VA seemed to decrease with time in the PDT monotherapy group	No statistically significance in the change in CRT though was greater in the combination group than the PDT monotherapy group	No statistically significant difference between groups	Significantly lower rate of retinal hemorrhage in the combination treatment group. (OR: 0.32; 95% CI: 0.14-0.74; *P*=0.008) with I^2=5.10%
Qian *et al*., 2018[214]	Combination treatment resulted in significantly greater improvements in BCVA than PDT monotherapy at 3, 6, 12, and 24 months after treatment in patients with PCV (*P*=0.03 with I^2=0%; *P*=0.005 with I^2=0%; *P*=0.02 with I^2=21%; and *P*<0.0001 with I^2=50%, respectively)	Combination treatment resulted in significantly greater reductions in CRT at 3 months than PDT alone (*P*=0.02)	No significant differences in polyp regression were observed between the two groups	Combination therapy had significantly lower incidence of subretinal hemorrhage during the follow-up period, (*P*=0.02) with no heterogeneity (I^2=38%)
		Combination treatment versus anti-VEGF monotherapy		
Liu *et al*., 2017[216]	Combination treatment was significantly better than IVR monotherapy group at 12 (WMD: 0.132; 95% CI, 0.029-0.234, *P*=0.012) with heterogeneity I^2=0% and 24 months (WMD: 0.234; 95% CI, 0.071-0.398, *P*=0.005) with heterogeneity I^2=6.3%	N/A	N/A	N/A
Qian *et al*., 2018[214]	Combination treatment resulted in significantly greater improvements compared with anti-VEGF treatment at 6 and 24 months (*P*=0.001; *P*<0.00001, respectively), with no heterogeneity (I^2=0%; I^2=0%, respectively)	No significant differences in CRT reduction at follow-up point of 6 and 12 months	Significant proportion of polyp regression at 3 and ≥6 months in the combination therapy (*P*<0.00001; *P*<0.0001, respectively) with no heterogeneity I^2=35%	No significant difference in the incidence of subretinal haemorrhage (*P*=085) (I^2=0%)

WMD = Weighted mean differences, CI = Confidence interval, OR = Odds ratio, CRT=Central retinal thickness, BCVA = Best-corrected visual acuity, PDT = Photodynamic therapy, VEGF = Vascular endothelial growth factor

trial that compared the efficacy of PDT with or without ranibizumab 0.5 mg and ranibizumab monotherapy. At month 6, the polyp closure rate was significantly lower in the ranibizumab monotherapy group (28.6%) compared

with the PDT monotherapy group (71.4%; $P < 0.01$) and the PDT with ranibizumab group (77.8%; $P < 0.01$). The study was not powered to detect the differences in VA, but there were more letters gained in the combination arm (10.9 ± 10.9 letters) and the ranibizumab monotherapy arm (9.2 ± 12.4 letters) than the PDT monotherapy arm (7.5 ± 10.7 letters).[150]

Recently, the EVEREST II study[218] revealed that the combination arm achieved superior BCVA gain (8.3 vs. 5.1 letters; $P = 0.013$), along with superior anatomical outcome, including higher polyp closure rate (69.3% vs. 34.7%; $P < 0.01$) and higher proportion with absence of disease activity (79.5% vs. 50.0%) at month 12 compared with ranibizumab monotherapy. The combination arm also required fewer injections (mean 5.2 vs. 7.3 injections over 12 months), with 50.6% of patients in the combination arm requiring only 3–4 injections over 12 months, which was significantly lower than that in the monotherapy arm (26.2%).

The meta-analysis demonstrates the efficacy of combination therapy over monotherapies in improving anatomical and functional outcome in PCV eyes.[213,215,217,218] A systematic review of retrospective studies analyzing the cohorts of combination treatment showed overall improvement in the VA at every year until 3 years of follow-up. At 1 year, the significant polyp regression rate was observed at 64.6% (anti-VEGF before PDT) and 76% (anti-VEGF after PDT) of eyes.[219] However, it is unclear whether PDT should have been administered at the beginning of treatment or during follow-up of anti-VEGF therapy. The Fujisan study compared the outcome of initial or deferred PDT combined with IVR. Both initial PDT (within 1 week following first IVR injection) and deferred PDT (PRN PDT after 3 monthly IVR injections) combined with IVR to treat PCV show the similar visual and anatomical improvements at 12 months. Initial PDT combination leads to significantly fewer additional treatments and suggests early introduction of PDT.[220]

Ranibizumab monotherapy versus aflibercept monotherapy

Subgroup comparison of anti-VEGF monotherapy, in two recent large randomized controlled trials (EVEREST II and PLANET), has been reported.[207,218] At 1 year, signi fi cant VA improvement was seen in eyes treated with ranibizumab monotherapy (+5.1 letters in EVEREST) and afl ibercept monotherapy (+10.8 letters in PLANET). This was accompanied by polyp closure rates of 34.7% and 38.9% (ranibizumab monotherapy arm in EVEREST II and a fl ibercept monotherapy arm in P LANET, respectively). The mean number of injections in the monotherapy arms was 7.3 (EVEREST II, PRN after 3 initial monthly doses) and 8.1 (PLANET, fi xed bimonthly dosing after 3 initial monthly doses). A head-to-head randomized controlled comparison is warranted to study the effectiveness of the two anti-VEGF agents.

Treatment of Submacular Hemorrhage

The incidence of massive SMH with PCV is 2.5% in the 1st year, and this proportion increased to approximately 30% within 10 years.[221] PCV has been found to be the cause of SMH in 20%–63.3% of cases.[222-225] The visual outcome depends on presenting BCVA, the duration, thickness, extent of hemorrhage, thinner neurosensory retinal thickness at presentation, and disruption of ellipsoid zone.[226-231] The aim of treatment is to displace the hemorrhage before irreversible damage to photoreceptors occurs. SMH secondary to PCV is treated with pneumatic displacement or vitrectomy with pneumatic displacement. For pneumatic displacement, an expansile gas (undiluted volume of 0.3 mL of perfluoropropane or 0.5 mL sulfur hexafluoride) is injected through the pars plana. This is followed by an anterior chamber paracentesis to reduce the intraocular pressure and prone positioning for 24 h to 2 weeks.[232]

However, pneumatic displacement of SMH alone does not address the underlying disease; the procedure should be combined with either PDT or intravitreal anti-VEGF.[233-237] PDT penetration is limited by the presence of blood and is facilitated with pneumatic displacement to treat the lesion. In cases of thin SMH, anti-VEGF monotherapy alone may be effective and save from rhegmatogenous retinal detachment or choroidal hemorrhage with pneumatic displacement.[238-242] In thicker SMH (>450 um), combination of pneumatic displacement with anti-VEGF therapy helps achieve rapid improvement in VA and reduction in foveal thickness although the effect equalizes with monotherapy.[225]

To hasten displacement of subretinal blood away from the center of fovea, enzyme-induced lysis of the clot by tissue plasminogen activator (rt-PA) was demonstrated. It can be either injected into the vitreous cavity with pneumatic displacement or injected into the subretinal space together with air following vitrectomy or into the subretinal space after vitrectomy followed by direct evacuation of the liquefied clot. rt-PA has a short half-life and a favorable safety profile at a dose ranging from 25 to 100 ug in 0.1 ml.[232,243] The choice of anti-VEGF agent for coapplication with rt-PA should be considered before any intervention. Klettner *et al*. found, *in vitro* studies, that aflibercept was cleaved by rt-PA-induced plasmin while ranibizumab was functionally unaltered and concluded that coapplication of aflibercept with rt-PA may reduce its antiangiogenic activity.[244] The management of SMH is dependent on several factors, including timing, visual prognosis, general health of the patient, and compliance to face down positioning.

nAMD-associated SMH exhibited poor visual outcome in the long term. PCV-associated SMH exhibits a superior short-term visual outcome compared to nAMD-associated SMH, due to less fibrovascular proliferation and less rapid subretinal scaring. However, the long-term visual prognosis becomes gradually similar to nAMD associated SMH, given the underlying chronic nature of recurrent hemorrhage leading to RPE atrophy in PCV.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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