Polypoidal Choroidal Vasculopathy

Definition, Pathogenesis, Diagnosis, and Management

Chui Ming Gemmy Cheung, FRCOphth,1,2 Timothy Y. Y. Lai, MD,3 Paisan Ruamviboonsuk, MD,4 Shih-Jen Chen, MD,5 Youxin Chen, MD,6 K. Bailey Freund, MD,7,8 Fomi Gomi, MD,9 Adrian H. Koh, MD,10 Won-Ki Lee, MD,11 Tien Yin Wong, FRCS, PhD1,2

Polypoidal choroidal vasculopathy (PCV) is an age-related macular degeneration (AMD) subtype and is seen particularly in Asians. Previous studies have suggested disparity in response to intravitreal injections of anti–vascular endothelial growth factor (VEGF) agents between PCV and typical AMD, and thus, the preferred treatment for PCV has remained unclear. Recent research has provided novel insights into the pathogenesis of PCV, and imaging studies based on OCT suggest that PCV belongs to a spectrum of conditions characterized by pachychoroid, in which disturbance in the choroidal circulation seems to be central to its pathogenesis. Advances in imaging, including enhanced depth imaging, swept-source OCT, en face OCT, and OCT angiography, have facilitated the diagnosis of PCV. Importantly, 2 large, multicenter randomized clinical trials evaluating the safety and efficacy of anti-VEGF monotherapy and combination with photodynamic therapy (PDT) recently reported initial first-year outcomes, providing level I evidence to guide clinicians in choosing the most appropriate therapy for PCV. In this review, we summarize the latest updates in the epidemiologic features, pathogenesis, and advances in imaging and treatment trials, with a focus on the most recent key clinical trials. Finally, we propose current management guidelines and recommendations to help clinicians manage patients with PCV. Remaining gaps in current understanding of PCV, such as significance of polyp closure, high recurrence rate, and heterogeneity within PCV, are highlighted where further research is needed. Ophthalmology 2018;125:708-724 © 2018 by the American Academy of Ophthalmology

Age-related macular degeneration (AMD) is a major cause of blindness worldwide and is projected to affect 170 million persons by 2040, with 110 million in Asia alone.1 Polypoidal choroidal vasculopathy (PCV) is believed to be a subtype of neovascular AMD in which type I neovascularization is associated with an abnormal branching network of vessels (branching vascular network [BVN]), with aneurysmal dilations referred to as polyps.2 Significant variations in the epidemiologic, clinical, and imaging features and the natural history between PCV and typical neovascular AMD have been reported.2,3 Importantly, whereas intravitreal injections of anti–vascular endothelial growth factor (anti-VEGF) agents have been the standard of care for typical neovascular AMD for more than a decade, the preferred treatment for PCV has remained unclear. Recently, the first-year results of 2 major randomized trials have been released and have provided new evidence on optimal treatment for PCV: EVEREST-II compared intravitreal ranibizumab (IVT-R) monotherapy with combination therapy comprising IVT-R plus photodynamic therapy (PDT), whereas the PLANET study compared intravitreal afibercept (IVT-AFL) monotherapy with or without rescue PDT.4,5 The aim of this review was to summarize the latest evidence on the diagnosis and management of PCV, covering epidemiologic and risk factors, pathogenesis, definition and classification, and management options and to propose up-to-date management guidelines for clinicians managing patients with this condition.

Definition

Polypoidal choroidal vasculopathy is a vascular disease of the choroid first described in the 1990s. Clinically it is characterized by recurrent serosanguineous maculopathy and presence of orange nodules.6,7 Currently, there is no universally accepted definition of PCV. Most investigators base the diagnosis of PCV on indocyanine green angiography (ICGA) findings that demonstrate presence of polypoidal dilatations. In the absence of ICGA, accurately differentiating PCV from typical AMD remains challenging. As such, variability in incidence reported in different ethnic groups will at least in part be influenced by the frequency of ICGA. Other controversies remain as to whether PCV belongs to the AMD spectrum, because several hallmarks of AMD, including drusen, pigmented changes, and atrophy, are relatively uncommon in PCV. Recently, the importance of thick choroid (pachychoroid) in PCV led some investigators to suggest PCV falls within the pachychoroid spectrum of conditions that may have a different cause from AMD.
Epidemiologic Features and Risk Factors

Prevalence and Incidence

Although there are increasing data on the epidemiologic features of AMD in Asians, with reported prevalence of early AMD and late AMD ranging from 1.4% to 37.9% and 0.1% to 7.3%, respectively, there are few population-level studies on PCV, and accurate estimates of PCV prevalence is limited because of difficulties in diagnosing PCV from clinical examination and fundus photographs. Only 1 study, the Beijing Eye Study, has reported the prevalence of PCV in the general population at 0.3%, estimated based on photographic and OCT data.8 In clinic-based case series of Asian patients with neovascular AMD, the proportion of PCV based on ICGA findings has been estimated to be between 20% and 60%.8–17 In contrast, in white European patients, the proportion of PCV is only 8% to 13% in cases in which ICGA were performed.18

Risk Factors

Whereas risk factors for AMD, including genetic risk factors, have been investigated extensively, few studies have evaluated specific risk factors for PCV (Table 1). In general, these studies suggest that systemic factors for PCV and typical AMD are similar. For example, a consistent risk factor for both PCV and typical AMD is cigarette smoking.19–22 A case-control study in Singapore that directly compared risk factors for PCV and typical AMD showed that cigarette smoking was associated with both PCV and typical AMD (odds ratios, 4.4 and 4.9, respectively) to a similar extent.19 Other studies showed that higher body mass index is associated with PCV, as in typical AMD.26 Serum levels of inflammatory markers (e.g., C-reactive protein) also have been associated with PCV (Table 1).21,23 Some risk factors, such as chronic kidney disease, which has been associated with typical AMD, may be less important for PCV.24,25

Unlike typical AMD, the genetics of PCV are relatively unknown. Existing data suggest some genetic markers are shared between AMD and PCV, whereas others are more unique to PCV.20–29 However, many of these associations were not found consistently across studies. In a recent meta-analysis, 31 SNPs in 10 genes and loci exhibited significant associations with PCV with major pathways implicated in inflammation, lipid, and complement cascade.27 Although differences in genetic locus could imply differential implication on the pathogenesis or treatment outcomes of PCV and typical AMD, this remains to be determined.

Pathogenesis

Since the first description of PCV,4,7 there has been ongoing debate regarding the clinical nature and pathogenesis of this peculiar entity. When PCV was first reported, the authors’ clinical observations and angiographic interpretations led them to conclude that the vascular lesions were located in the inner choroid below Bruch’s membrane.30 Subsequently, several histopathologic studies described conflicting locations for PCV’s aberrant vessels (intra-Bruch’s membrane vs. choroid) and also showed evidence for newly proliferating fibrovascular tissue.31–35 The role of VEGF in the pathogenesis of PCV also is uncertain. Evidence of strong VEGF expression was found in vascular endothelial and retinal pigment epithelium (RPE) cells in some studies analyzing surgical specimens,36,37 but a lack of VEGF expression also has been reported.33 The concentration of VEGF in aqueous humor was found to be higher in eyes with PCV compared with normal controls, but seems much lower compared with eyes with typical neovascular AMD.38,39 Other studies reported elevated proinflammatory cytokine levels, including interleukin-1β and interleukin-23, in aqueous and vitreous samples, which support a role for inflammation in PCV.40,41 Animal studies also demonstrated that increased expression of serine protease HTRA1 may play a role in the pathogenesis of PCV because transgenic mice expressing human HTRA1 were found to develop retinal features of PCV.42

Clinical and imaging studies also have provided insights into pathogenesis.55 A paucity of drusen, pigmentedary changes, geographic atrophy, and disciform scar formation are features that often distinguish PCV from typical AMD.5 On spectral-domain (SD) OCT, the abnormal vascularization causing exudation in eyes with PCV (polyps and BVN) are identified consistently between an elevated RPE and the thin hyperreflective line representing the outer portion of Bruch’s membrane (Figs 1–3).44–46 These findings indicate that the neovascular lesions of PCV develop within Bruch’s membrane (below the basal lamina of the RPE) as a variant of type 1 neovascularization.47 However, several studies using enhanced depth imaging OCT have demonstrated choroidal thickening and other structural changes of the choroid in eyes with PCV (Figs 3 and 4). These findings are in contrast to choroidal thinning that often is observed in eyes with type 1 neovascularization occurring in typical AMD (occult CNV), suggesting different pathogenic mechanisms.48–50

There is evolving understanding of the interrelationship between pachychoroid, type 1 neovascularization, and PCV. The term pachychoroid originally was conceived to reflect choroidal congestion and choroidal hyperpermeability manifested by choroidal thickening, dilated choroidal vessels, and characteristic findings on ICGA. New information has broadened the original description of pachychoroid to emphasize additional qualitative features. These features include focal choroidal thickening that is localized to the disease focus and attributable to pathologically dilated Haller layer veins (pachyvessels). Pachyvessels are associated with focal attenuation of overlying choriocapillaris and Sattler layers, which brings them closer to the Bruch’s membrane–RPE complex.5 In patients with PCV, although the mean choroidal thickness, including the subfoveal area, is increased, there is pronounced interindividual variability. In one cohort that included more than 300 eyes with PCV, the mean subfoveal choroidal thickness was approximately 270 μm, but 40% of eyes showed subfoveal choroidal thickness of less than 200 μm.52 In these eyes, pachyvessels and related choroidal changes were associated topographically with sites of BVN ingrowth, which suggests that pachychoroid features underlie the
The pathogenesis of the type 1 neovascularization and PCV lesions, even in eyes with normal or subnormal choroidal thickness.\(^52\)

Furthermore, although AMD is the most common cause of type 1 neovascularization, a form of type 1 neovascularization associated with choroidal thickening (pachychoroid), but lacking soft drusen and other typical AMD findings, was reported recently.\(^53\) This condition was termed \textit{pachychoroid neovascularopathy} and was described as falling within a spectrum of pachychoroid-related disorders including pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and PCV.\(^53\text{—}57\) These studies provide further evidence that PCV is a pachychoroid-driven disorder with findings of similar choroidal features and the

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Ethnicity</th>
<th>Risk Factors</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cackett et al, 2011*</td>
<td>PCV, n = 123; controls, n = 1489</td>
<td>Chinese</td>
<td>Smoking</td>
<td>4.4</td>
<td>2.5—7.7</td>
</tr>
<tr>
<td>Nakata et al, 2013*</td>
<td>PCV, n = 581; controls, n = 793</td>
<td>Japanese</td>
<td>CETP rs3764261</td>
<td>1.50</td>
<td>1.17—1.92</td>
</tr>
<tr>
<td>Zhang et al, 2013*</td>
<td>PCV, n = 250; controls, n = 204</td>
<td>Chinese</td>
<td>CETP rs5882</td>
<td>1.63</td>
<td>1.25—2.12</td>
</tr>
<tr>
<td>Meng et al, 2015*</td>
<td>PCV, n = 291; controls, n = 221</td>
<td>Chinese</td>
<td>CAD, CETP rs3764261, LIPC rs1532085</td>
<td>3.381, 1.444, 1.393</td>
<td>1.377—8.302, 1.047—1.991, 1.084—1.789</td>
</tr>
<tr>
<td>Liu et al, 2014*</td>
<td>PCV, n = 233; controls, n = 275</td>
<td>Chinese</td>
<td>CETP rs3764261</td>
<td>1.80</td>
<td>1.30—2.49</td>
</tr>
<tr>
<td>Kikuchi et al, 2007*</td>
<td>PCV, n = 97; controls, n = 262</td>
<td>Japanese</td>
<td>CRP (&gt;0.95 mg/l)</td>
<td>3.53</td>
<td>1.49—8.40</td>
</tr>
<tr>
<td>Sakurada et al, 2015*</td>
<td>PCV, n = 22; controls, n = 20</td>
<td>Japanese</td>
<td>CRP, IP-10</td>
<td>1.014, 1.13</td>
<td>1.003—1.024, 1.04—1.22</td>
</tr>
<tr>
<td>Cheung et al, 2017*</td>
<td>PCV, n = 241; controls, n = 1824</td>
<td>Singaporeans; predominantly Chinese</td>
<td>Age, BMI, HDL cholesterol, axial length Genetics: CFH rs800292, ARMS2 rs10490924</td>
<td>0.62, 2.53</td>
<td>0.37—1.02, 1.56—4.11</td>
</tr>
</tbody>
</table>

\(\text{ARMs2} = \text{age-related maculopathy susceptibility protein 2}; \text{BMI} = \text{body mass index}; \text{CAD} = \text{coronary artery disease}; \text{CETP} = \text{cholesteryl ester transfer protein}; \text{CFH} = \text{complement factor}; \text{CRP} = \text{C-reactive protein}; \text{HDL} = \text{high-density lipoprotein}; \text{IP-10} = \text{interferon-\(\gamma\) inducible protein}; \text{nAMD} = \text{neovascular age-related macular degeneration}; \text{PCV} = \text{polypoidal choroidal vasculopathy.}\)

\(*\text{As compared with controls.}\)

Figure 1. Spectral-domain OCT scan (right) obtained through the polyp imaged in indocyanine green angiography (left) revealing multiple pigment epithelial detachments (PEDs), PED notch (arrow), and a sharp PED peak (arrowhead) corresponding to the polyp, which can be called a thumb-like protrusion. Meanwhile, this thumb-like protrusion contains a hyporeflective lumen within hyperreflective lesions adherent to the retinal pigment epithelium (asterisk).
occurrence of polypoidal lesions in eyes lacking typical AMD features.\textsuperscript{48–50,53,54,56,58–61}

\section*{Diagnostic Criteria}

Based on both new understanding of its pathogenesis and increasing data from imaging studies, the current thinking is that PCV is a variant of a type 1 neovascularization, presenting with clinical and imaging findings that differ from those of typical neovascular AMD. There are several traditional classifications of PCV and diagnostic criteria based on clinical and ICGA findings (Table 2). According to the Japanese Study Group guidelines,\textsuperscript{62} PCV may be diagnosed as definite or probable based on fundus examination, ICGA, or both. The EVEREST criteria first were used by the central reading center of the multicenter randomized clinical trial comparing IVT-R monotherapy, PDT monotherapy, and combination therapy of IVT-R and PDT.\textsuperscript{63,64} One study suggested that the Japanese PCV and EVEREST classification systems of flash fundus camera-based ICGA and confocal scanning laser ophthalmoscope based ICGA largely are similar, with the EVEREST study criteria having slightly higher specificity than the use of subretinal focal hyperfluorescence alone.\textsuperscript{65} Although ICGA traditionally is believed to be essential to diagnose PCV, OCT findings are more accessible and are actually highly reliable (Figs 1 and 2). Spectral-domain OCT B-scans commonly show highly protruded RPE with underlying moderate reflectivity, double-layer hyperreflective lines, and notched pigment epithelial detachment (PED). Future diagnostic criteria should aim to include multimodal imaging criteria.

\section*{Clinical and Imaging Features}

\subsection*{Clinical Features}

Polypoidal choroidal vasculopathy presents with a serosanguineous exudative maculopathy characterized by a paucity of drusen, pigmentary changes, geographic atrophy, and disciform scar formation,\textsuperscript{2} with common features of PCV summarized in Table 3.\textsuperscript{9,66} Polypoidal choroidal vasculopathy should be classified based on the location of the polyps: subfoveal, juxtafoveal, extrafoveal, peripapillary, or peripheral. Based on the presentation, PCV also can be classified into quiescent, exudative, or hemorrhagic subtypes. Quiescent PCV is not associated with subretinal or intraretinal fluid or hemorrhage. Exudative PCV is associated with subretinal fluid, neurosensory retinal thickening, PED, lipid exudation, or a combination thereof, but without

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image1}
\caption{Spectral-domain OCT scan (right) with corresponding fluorescein angiography (left) showing a double-layer sign (black arrowhead), pigment epithelial detachment notch (black arrow), and a thumb-like polyp containing hyperreflective rings with internal hyporeflective lumen (white arrow).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image2}
\caption{Spectral-domain OCT image (right) with corresponding fluorescein angiography (left) showing the pachychoroid feature of polypoidal choroidal vasculopathy.}
\end{figure}
hemorrhage. Polypoidal choroidal vasculopathy has been reported to have higher incidence of serous retinal detachment, greater serous retinal detachment height, and lower incidence of intraretinal edema than eyes with typical neovascular AMD. Hemorrhagic PCV is associated with subretinal or sub-RPE hemorrhage, with or without exudative changes. Eyes with PCV are more likely than typical neovascular AMD to demonstrate recurrent serous or hemorrhage PED, massive macular hemorrhage, breakthrough vitreous hemorrhage, or a combination thereof. This classification has not been validated, and correlation with visual outcome or treatment response has not been evaluated in detail.

**OCT Features**

The most commonly seen SD OCT features in PCV include PED, double-layer sign, thickened choroid, and sometimes focal choroidal excavation (Table 3; Figs 1–5). These features should alert a clinician of the possibility of PCV even in populations in which PCV prevalence is low or in which ICGA is not performed routinely. In addition to assisting the diagnosis of PCV, SD OCT also is useful in monitoring the changes in subretinal fluid, PED, or both after therapy.

Presence of subretinal fluid and intraretinal fluid are markers of active exudative activity and often correlate to areas of leakage on fluorescein angiography (FA). In PCV, different parts of the lesion complex may have different levels of activity. The predominant active component often can be determined by colocalization of the area of fluid with polyps, BVN, or both on ICGA or by colocalization of PED, BVN, or both on OCT. This detail may have impact on the choice of treatment method.

OCT angiography (OCTA) is a new imaging method to visualize the vasculature noninvasively and has been suggested to be a possible replacement for FA for diagnosis of typical neovascular AMD. OCT angiography depicts the abnormal vessels of PCV in 2 dimensions, like ICGA. However, the consistency of findings between OCTA and ICGA needs further investigation. Although the BVN generally could be visualized using OCTA, the detection rates of polyps using OCTA have been found to be considerably lower compared with ICGA. Possible reasons for an incomplete detection rate of polypoidal lesions with OCTA are signal attenuation from overlying structures and low blood flow speed within the polyps. Therefore, with the present technology, OCTA is unable to replace ICGA in the assessment of PCV.

### Indocyanine Green Angiography Features

Indocyanine green angiography traditionally has been the gold standard investigation tool used to diagnose PCV. Single or multiple polyps can be seen in the early phase of ICGA. As noted, both flash digital fundus photography ICGA or the confocal scanning laser ophthalmoscopy systems can detect at least 80% of the typical nodular lesions of the PCV, although the BVN and other features may be visualized better with confocal scanning laser ophthalmoscopy. Some groups have proposed to classify PCV further into different subtypes according to the appearances on ICGA (Table 3). However, there is no universal agreement on the visual prognosis related to these subclassifications. It has been suggested further that pulsatile polyps tend to rupture and

---

**Table 2. Polypoidal Choroidal Vasculopathy Diagnostic Criteria**

<table>
<thead>
<tr>
<th>Japanese Study Group Guidelines</th>
<th>EVEREST criteria (based on confocal scanning laser ophthalmoscopy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite PCV:</td>
<td>Focal hyperfluorescent lesions appearing before 6 minutes on ICGA, plus at least 1 of the following:</td>
</tr>
<tr>
<td>Elevated orange-red lesions on fundus examination, and/or</td>
<td>BVN on ICGA</td>
</tr>
<tr>
<td>Polypoidal lesions on ICGA</td>
<td>Pulsatility on dynamic ICGA</td>
</tr>
<tr>
<td>Probable PCV:</td>
<td>Nodular appearance when ICGA viewed stereoscopically</td>
</tr>
<tr>
<td>Only abnormal BVN seen on ICGA</td>
<td>Hypofluorescent halo on ICGA</td>
</tr>
<tr>
<td>or recurrent hemorrhagic or serous</td>
<td>Orange subretinal nodule on color photograph</td>
</tr>
<tr>
<td>RPE detachments, or both, without features of definite PCV</td>
<td>Associated massive submacular hemorrhage</td>
</tr>
</tbody>
</table>

BVN = branching vascular network; ICGA = indocyanine green angiography; PCV = polypoidal choroidal vasculopathy; RPE = retinal pigment epithelium.
Although FA is useful for diagnosis and classification of the choroidal vasculature, whereas type 2 was believed to be associated with choroidal neovascularization. A study using a similar classification reported that type A (corresponding to type 1) had the best visual outcome over 5 years. Recently, a study based on choroidal vascular features on SD OCT also supported there may be 2 subtypes of PCV: typical PCV with increased choroidal vascularity, as opposed to polypoidal choroidal neovascularization with low choroidal vascularity.83 More studies are needed to validate further the impact of this and other classification on visual prognosis and treatment strategies.84

Fluorescein Angiography Features

Although FA is useful for diagnosis and classification of typical neovascular AMD, the use of FA in PCV is relatively limited because of the inability of FA to visualize sub-RPE structures, including polyps. Furthermore, greater leakage with fluorescein dye, compared with ICGA, makes the lesions of PCV visualized on FA appear larger than those visualized on ICGA. Therefore, if FA is used as guidance for the use of PDT in PCV, an unnecessarily larger spot size may be applied.85 However, FA may be superior to ICGA for detecting and monitoring leakage of BVN.

Although ICGA is considered by many as the most reliable means for diagnosing PCV, it is not performed routinely in many parts of the world, particularly in areas where PCV is uncommon. De Salvo et al86 reported that based on a combination of 3 of the following 4 OCT-based signs—multiple PEDs, sharp PED peak, PED notch, and rounded sub-RPE hyporeflective area—they were able to diagnose PCV based on OCT with a sensitivity of 94.6% and specificity of 92.9% from a cohort of 51 patients from the United Kingdom. In another study comparing 113 eyes where PCV is uncommon. De Salvo et al86 reported that based on a combination of 3 of the following 4 OCT-based signs—multiple PEDs, sharp PED peak, PED notch, and rounded sub-RPE hyporeflective area—they were able to diagnose PCV based on OCT with a sensitivity of 94.6% and specificity of 92.9% from a cohort of 51 patients from the United Kingdom. In another study comparing 113 eyes with PCV and 75 eyes with neovascular AMD, a combination of 2 of the following 3 signs—PED, double-layer sign, and thumb-like protrusion—was reported to detect PCV with sensitivity of 89.4% and specificity of 85.3%.

Table 3. Summary of Common Clinical and Imaging Features of Polypoidal Choroidal Vasculopathy

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Imaging features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reddish-orange nodular structures beneath the retina</td>
<td>PED</td>
</tr>
<tr>
<td>Serous neurosensory detachment</td>
<td>May be sharp PED peak, PED notch, septae, M-shaped PED.</td>
</tr>
<tr>
<td>Subretinal fibrosis</td>
<td>When corresponding to the polyps on ICGA images, polyps frequently appear as sharp inverted V-shaped anterior protrusions or dome-shaped elevations of RPE on SD OCT, and they have been called thumb-like polyps or PED peaks (Fig 1).</td>
</tr>
<tr>
<td>Serous or hemorrhagic pigment epithelial detachment, or both</td>
<td>May contain hyperreflective rings with internal hyporeflective lumens.</td>
</tr>
<tr>
<td>RPE atrophy</td>
<td>Double-layer sign</td>
</tr>
<tr>
<td>FD OCT features</td>
<td>Presence of 2 highly reflective layers (the RPE and a sub-RPE layer) within the area of the network of vessels</td>
</tr>
<tr>
<td>PED</td>
<td>Although it can be detected in several fundus diseases, approximately 85% to 95% of the eyes within PCV showed double-layer sign (Fig 2).</td>
</tr>
<tr>
<td>Fuchchoroid (enhanced depth imaging OCT or swept-source OCT)</td>
<td>Fuchchoroid (enhanced depth imaging OCT or swept-source OCT)</td>
</tr>
<tr>
<td>Thickened choroid (often &gt;300 μm).</td>
<td>Type 1 (type A): ICGA fill abnormal choroidal vasculature simultaneously with other choroidal vessels to form BVN and polyps.</td>
</tr>
<tr>
<td>May be associated with choroidal vascular hyperpermeability on ICGA.</td>
<td>Type 2 (types B and C): feeding vessels are common and on fill with ICGA after the filling of choroidal arterioles and are emptied rapidly. Type 2 PCV generally have larger lesion size on ICGA and significantly thinner choroid compared with type 1.</td>
</tr>
<tr>
<td>Choriocapillaris and Sattler layers usually are attenuated at sites of polypoidal disease, but Haller vessels are markedly dilated.</td>
<td>May be used to classify into subtypes:</td>
</tr>
<tr>
<td>May exhibit focal choroidal excavation (Fig 4), which can be associated with choroidal diseases, including PCV, as well as CSC, AMD, and CNV, but it is most prevalent in PCV (6.0%).</td>
<td>Polyps: single, cluster, string configuration, pulsatile vs. nonpulsatile</td>
</tr>
<tr>
<td>In en face OCT</td>
<td>Type 1 (type A): ICGA fill abnormal choroidal vasculature simultaneously with other choroidal vessels to form BVN and polyps.</td>
</tr>
<tr>
<td>PCV lesions and the lesions are seen as RPE rings with inner reflectivity with or without a BVN (Fig 5).</td>
<td>Type 2 (types B and C): feeding vessels are common and on fill with ICGA after the filling of choroidal arterioles and are emptied rapidly. Type 2 PCV generally have larger lesion size on ICGA and significantly thinner choroid compared with type 1.</td>
</tr>
<tr>
<td>The polyoidal lesions detected on en face OCT generally correlate well with the lesions seen in ICGA.</td>
<td>FA</td>
</tr>
<tr>
<td>See Table 2.</td>
<td>Usually appear as occult NV</td>
</tr>
<tr>
<td>May be used to classify into subtypes:</td>
<td>Classic NV pattern can be seen in a small proportion of cases. PCV appearing as classic CNV on FA may be associated with poorer visual prognosis.</td>
</tr>
<tr>
<td>Polyps: single, cluster, string configuration, pulsatile vs. nonpulsatile</td>
<td>AMD = age-related macular degeneration; BVN = branching vascular network; CNV = choroidal neovascularization; CSC = central serous choriorretinopathy; FA = fluorescence angiography; ICGA = indocyanine green angiography; NV = neovascularization; PCV = polypoidal choroidal vasculopathy; PED = pigment epithelial detachment; RPE = retinal pigment epithelium; SD = spectral-domain.</td>
</tr>
</tbody>
</table>
These studies suggest that SD OCT signs can be very helpful as a screening tool in areas where ICGA is not performed routinely. However, for planning of PDT treatment, information from ICGA remains essential.87

**Treatment Options**

Unlike typical neovascular AMD, where intravitreal anti-VEGF therapy has been the mainstay of care for over a decade, currently a wide spectrum of treatment options for PCV exists. These include focal laser photocoagulation, verteporfin PDT, anti-VEGF therapy ( aflibercept, ranibizumab, and bevacizumab), and various combinations of these therapies. Advantages and disadvantages of individual methods have been summarized in Table 4.

**Focal Laser Therapy**

Focal laser long has been used to ablate extrafoveal and extramacular polyps identified on ICGA.7,82,88-92 Stabilization or even improvement of vision has been described in these reports. However, limitations include scarring and recurrence. Focal laser therapy largely has been superseded by newer therapeutic options, but nevertheless remains a useful therapeutic option for extrafoveal polyps. Combination with anti-VEGF therapy has been described to be effective in eyes with extramacular PCV in which exudation or hemorrhage extends to the fovea.93 A combination with anti-VEGF, selective PDT, or both has been described to be effective in recurrent PCV.94

**Verteporfin Photodynamic Therapy**

Before the advent of anti-VEGF therapy, PDT was used widely for PCV, and favorable results have been published in many clinical studies.2,22,63,95-99 However, as further experience with PDT accumulated, reports with longer follow-up showed less favorable results.100 A meta-analysis of 29 studies with 3-year visual outcomes reported mean best-corrected visual acuity (BCVA) improvement at years 1 and 2, but returned to baseline after 3 years or more. Other concerns include persistence of the BVN and rare incidences of complications, including subretinal hemorrhage, choroidal infarction, and RPE tear.101-103 This experience has somewhat dampened the initial enthusiasm for PDT as monotherapy for PCV, particularly in eyes with good presenting vision. Modifications to the settings of PDT, such as limitation of spot size to include only active polyps, but not the BVN,94 and reduced-fluence PDT,106,107 have been proposed to reduce the frequency of these rare adverse events.

**Anti–Vascular Endothelial Growth Factor Monotherapy**

After reports from the pivotal clinical trials in typical neovascular AMD, anti-VEGF therapy has superseded PDT as the first line of therapy.108-110 Early studies suggested that despite a limited polyp regression rate with anti-VEGF monotherapy (25%-40%),111 anti-VEGF monotherapy has favorable visual outcomes. The PEARL studies115 consisted of 2 open-label studies of PCV using monthly IVT-R 0.5 mg (PEARL 1 study) or 2.0 mg (PEARL 2 study). In both studies, significant improvement in mean BCVA was accompanied by reduction in subretinal hemorrhage, subretinal fluid, or both.113 The LAPTOP study116 is a phase 4 prospective, multicenter, randomized trial comparing the effect of PDT and IVT-R in PCV using a pro re nata retreatment regimen (Table 5). At both month 12 and month 24, patients in the IVT-R arm achieved better visual outcomes than patients in the PDT arm.116 However, angiographic results were not evaluated in these studies.

Another anti-VEGF agent, aflibercept, also has been approved for the treatment of typical neovascular AMD.
The efficacy of IVT-AFL administered every 8 weeks after 3 monthly loading doses in neovascular AMD has been demonstrated in the VIEW studies, which compared the efficacy and safety of IVT-AFL and IVT-R in patients with neovascular AMD. Within the VIEW study population, baseline ICGA was available in 88 of 101 Japanese patients, among whom PCV was confirmed in 29 eyes (33%). A post hoc analysis reported that the visual acuity and retinal thickness outcomes in the PCV and non-PCV eyes receiving IVT-AFL were comparable. However, angiographic changes were not available in this post hoc analysis. Several other case series have reported favorable visual outcome and polyp regression rate ranging from 48% to 75% in patients with PCV treated with IVT-AFL.

There have been fewer studies reporting the results of bevacizumab for PCV. Favorable outcomes in improving vision and macular exudation, but limited polyp regression, have been reported.

### Key Clinical Trials

The EVEREST-I study was the first randomized controlled trial in PCV that compared the efficacy and safety of IVT-R monotherapy, PDT monotherapy, and combination therapy with IVT-R and PDT in 61 patients. The primary end point was polyp regression based on ICGA results at month 6. The results demonstrated PDT alone or combined with IVT-R achieved a significantly higher polyp regression rate (71.4% and 77.8%, respectively) compared with IVT-R monotherapy (28.6%). Despite the lower polyp closure rate, IVT-R monotherapy achieved higher visual gain than PDT monotherapy (+9.2 letters vs. +7.5 letters), although the difference was not statistically significant. The results of EVEREST suggested the need for larger studies with longer follow-up with visual acuity as the primary end point.

This gap was addressed in 2 pivotal randomized controlled trials (EVEREST-II and PLANET) evaluating anti-VEGF and combination therapy (Tables 5 and 6) providing level 1 evidence to help guide clinicians in the optimal management of PCV. EVEREST-II compared IVT-R monotherapy with combination therapy of IVT-R plus PDT at baseline, whereas PLANET compared IVT-AFL monotherapy with or without rescue PDT, which was available after 3 months. Both studies reported significant visual acuity gain in the anti-VEGF monotherapy arms at 1 year (+5.1 letters in EVEREST-II; +10.8 letters in PLANET). Polyp closure rates were 34.7% (EVEREST-II) and 38.9% (PLANET). Fifty-one percent of eyes in EVEREST-II had no disease activity (defined as absence of persistent or new polyps based on OCT, FA, ICGA, and color fundus examinations) at 12 months, whereas 81.7% of eyes in PLANET had no active polyps (active polyps defined as polyps with leakage on FA, subretinal or intra-retinal fluid on OCT, or presence of new hemorrhage). The mean number of injections was 7.3 (EVEREST-II) and 8.1 (PLANET). These results were corroborated further by the DRAGON study, a phase 4 randomized, double-masked, multicenter trial based in China comparing the efficacy of IVT-R monotherapy using a monthly fixed dosing regimen versus a pro re nata regimen. At baseline, 41.7% of the 334 enrolled patients were diagnosed with PCV based on ICGA results. Significant improvement in BCVA was
Table 5. Updated Randomized Trials in Polypoidal Choroidal Vasculopathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti–Vascular Endothelial Growth Factor Agent</th>
<th>Treatment Arms</th>
<th>Duration (mos)</th>
<th>Best-Corrected Visual Acuity (Early Treatment Diabetic Retinopathy Study Letters)</th>
<th>Polyp Closure Rate (%)</th>
<th>No. of Anti–Vascular Endothelial Growth Factor Treatments</th>
<th>No. of Active Photodynamic Therapy Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVEREST 1†‡</td>
<td>Ranibizumab PRN</td>
<td>Ranibizumab 3 + PRN</td>
<td>6</td>
<td>49.0 9.2</td>
<td>28.6*</td>
<td>5.2</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ranibizumab 3 + PRN + Verteopin PDT</td>
<td></td>
<td>57.2 7.5</td>
<td>71.4*</td>
<td>4.2</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ranibizumab PRN + PDT</td>
<td></td>
<td>56.6 10.9</td>
<td>77.8*</td>
<td>4.2</td>
<td>1.7</td>
</tr>
<tr>
<td>EVEREST-II§</td>
<td>Ranibizumab PRN</td>
<td>Ranibizumab 3 + PRN</td>
<td>12†</td>
<td>61.2 5.1</td>
<td>34.7†</td>
<td>7.3</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ranibizumab PRN + PDT</td>
<td></td>
<td>61.1 8.3†</td>
<td>69†</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verteopin PDT</td>
<td></td>
<td>68 4</td>
<td>Not reported</td>
<td>5.8</td>
<td>5.8</td>
</tr>
<tr>
<td>LAPTOP [10,11]</td>
<td>Ranibizumab PRN</td>
<td>Ranibizumab 3 + PRN</td>
<td>12†</td>
<td>84</td>
<td>4</td>
<td>Not reported</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verteopin PDT</td>
<td></td>
<td>88 −2 (loss)</td>
<td>NA</td>
<td>2.2</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab monthly/PRN</td>
<td>Ranibizumab monthly vs.</td>
<td>24</td>
<td>68 12.7**</td>
<td>Not reported</td>
<td>8.4</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab PRN</td>
<td>Ranibizumab PRN</td>
<td></td>
<td>69 9.4</td>
<td></td>
<td>8.4</td>
<td>NA</td>
</tr>
<tr>
<td>DRAGON subgroup analysis [10,11] (41.7% of enrolled patients with PCV)</td>
<td>Ranibizumab monthly/PRN</td>
<td>Ranibizumab monthly vs. Ranibizumab PRN</td>
<td>24</td>
<td>68 12.7**</td>
<td>Not reported</td>
<td>11.2</td>
<td>NA</td>
</tr>
<tr>
<td>FUJISAN [12]</td>
<td>Ranibizumab PRN</td>
<td>Ranibizumab 3 + PRN + initial PDT</td>
<td>12</td>
<td>54.3 8.1*</td>
<td>62.1</td>
<td>4.5</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ranibizumab 3 + PRN + deferred PDT</td>
<td></td>
<td>54.9 8.8*</td>
<td>54.8</td>
<td>6.8</td>
<td>1.45*</td>
</tr>
<tr>
<td>PLANET [13]</td>
<td>Afiblercept 8-wk fixed dosing</td>
<td>Afiblercept 3 + Q8</td>
<td>12†</td>
<td>57.7 10.7**</td>
<td>38.9</td>
<td>8.1</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afiblercept + rescue PDT†</td>
<td></td>
<td>59 10.9**</td>
<td>44.8</td>
<td>8.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

NA = not applicable; PCV = polypoidal choroidal vasculopathy; PDT = photodynamic therapy; PRN = pro re nata.

*Primary end point: verteporin PDT combined with ranibizumab or verteporin PDT alone was superior to ranibizumab monotherapy in achieving complete polyp regression; P < 0.01.
†Primary end point was reported at month 12 although these studies had follow-up after 12 months.
‡Primary end points at month 12: ranibizumab with PDT achieved superior best-corrected visual acuity gain (P = 0.013) and polyp regression (P < 0.001) compared with ranibizumab monotherapy.
§Primary end point: more patients in ranibizumab arm had a visual acuity gain of ≥0.2 logarithm of the minimum angle of resolution compared with verteporin PDT (31% vs. 17%; P = 0.039) at month 12.
¶Visual acuity conversion based on Early Treatment Diabetic Retinopathy Study letters = 100 − 50 × log10 (decimal).
††Primary end point: not reported in subgroup analysis.
‡‡Only 15% of patients met rescue PDT criteria.
**Table 6. Summary of Study Designs of EVEREST-II Study and PLANET Study**

<table>
<thead>
<tr>
<th>EVEREST-II</th>
<th>PLANET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study description</strong></td>
<td>A 24-month, phase 4, randomized, double-masked, multicenter study comparing ranibizumab monotherapy with ranibizumab plus PDT.</td>
</tr>
<tr>
<td><strong>Study objective</strong></td>
<td>To demonstrate that ranibizumab combined with vPDT is superior to ranibizumab monotherapy with respect to: (1) change in mean BCVA (Letters) from baseline at month 12 and (2) complete polyp regression assessed by ICGA at month 12.</td>
</tr>
<tr>
<td><strong>Anti-VEGF agent</strong></td>
<td>Ranibizumab</td>
</tr>
<tr>
<td><strong>Anti-VEGF dosing</strong></td>
<td>Three initial monthly followed by PRN if retreatment criteria are met*</td>
</tr>
<tr>
<td><strong>PDT in combination arm</strong></td>
<td>Performed at baseline in all cases randomized to combination arm and repeated according to retreatment criteria*</td>
</tr>
<tr>
<td><strong>No. of participants</strong></td>
<td>322 318</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescence angiography; ICGA = indocyanine green angiography; PCV = polypoidal choroidal vasculopathy; PDT = photodynamic therapy; VEGF = vascular endothelial growth factor; vPDT = verteporfin photodynamic therapy.

*EVEREST II** retreatment criteria:
1. Loss of BCVA because of condition under study or disease activity seen on OCT.
2. Only ranibizumab will be given if last PDT treatment is <3 mos earlier.
3. If ≥3 mos since last PDT treatment, ICGA or FA should be performed.
   a. If ICGA or FA shows active PCV (PCV and leakage) involving macula with greatest linear dimension of total lesion area <5400 µm, ranibizumab plus vPDT or sham PDT will be administered according to randomization.
   b. If ICGA or FA does not show active PCV (PCV and leakage) involving macula with greatest linear dimension of total lesion area <5400 µm, ranibizumab monotherapy will be administered.

**PLANET** study rescue criteria:
1. BCVA ≤73 ETDRS letters.
2. New or persistent fluid on OCT.
3. Evidence of active polyps on ICGA.
4. Deterioration, no change, or insufficient gain in BCVA (<5-letter gain).
5. BCVA improvement of more than 5 letters but less than 10 letters, and investigator determines PDT may be of additional benefit.

Rescue PDT could be performed if criteria 1, 2, 3, and 4 or criteria 1, 2, 3, and 5 were met.

Achieved in both PCV and non-PCV patients in the monthly arm (+12.7 letters vs. 11.2 letters) and the pro re nata arm (9.4 letters vs. 8.4 letters) at 24 months (Table 5).

Based on these clinical trial data, anti-VEGF monotherapy with either ranibizumab or aflibercept can achieve visual improvement and reduction in disease activity and can be considered as first-line treatment in patients with PCV. Direct comparison between studies based on the absolute number of letters gained may suggest some advantage using aflibercept (+10.8 letters in PLANET) compared with ranibizumab (5.1 letters in EVEREST-II) when used as monotherapy. However, differences in baseline BCVA should be considered, because eyes with lower baseline BCVA (as in PLANET) generally can be expected to achieve a larger magnitude of improvement (Table 5). Differences in dosing regimens (Tables 5 and 6) also should be considered a potential factor underlying any differences in absolute BCVA change reported.

**Combination Therapy**

Combination therapy of PDT and anti-VEGF therapy has been reported to achieve significantly better visual outcomes than PDT alone and to reduce the rate of PDT-related hemorrhages. In the EVEREST-I study, the combination therapy arm achieved slightly higher polyp closure rate compared with PDT monotherapy, but the difference was not statistically significant. Patients in the combination arm also achieved the highest BCVA gain numerically (10.9 letters) compared with patients in the ranibizumab monotherapy arm (9.2 letters) or the PDT monotherapy arm (7.5 letters) at month 6, but these differences were not statistically significant. In the EVEREST-II study, the combination arm achieved superior BCVA gain (8.3 vs. 5.1 letters; P = 0.013), a higher proportion of patients with BCVA of 69 letters or more (69.0% vs. 58.8%), a higher polyp closure rate (69.3% vs. 34.7%; P < 0.01), and a 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 to 4 injections over 12 months, which was significantly lower than that in the monotherapy arm (26.2%). However, currently there are no clear criteria to identify this subgroup at baseline. These results suggest that although ranibizumab monotherapy is safe and achieves moderate BCVA gains in PCV, combination therapy with PDT is superior in terms of BCVA gain and polyp closure and can reduce the number of ranibizumab injections required in the first year of treatment.
In addition to combination therapy performed at baseline, deferred combination has been evaluated in the FUJISAN study, which compared the outcomes of initial or deferred PDT combined with IVT-R. In this study, patients were evaluated after 3 monthly IVT-R injections. In patients who met the retreatment criteria, deferred combination treatment was performed. The study reported similar BCVA and polyp closure outcomes at 1 year between patients with initial PDT and those with deferred PDT. With this approach, more than half of the patients in the deferred arm (17 of 31 patients) did not require PDT, although patients in this arm had significantly more injections (3.8 vs. 1.5 injections in addition to 3 loading doses).

The PLANET study evaluated deferred, rescue PDT combination therapy. Qualification for rescue PDT was based on insufficient gain in BCVA and evidence of leakage from active polyps (Table 6). A large majority of patients did not meet these rescue criteria after 3 initial monthly IVT-AFL injections (94.9% and 93.2% in the IVT-AFL monotherapy arm and combination arm, respectively), and less than 15% of patients in either arm met rescue criteria over the course of 12 months ($P = 0.84$). Both treatment arms achieved similar BCVA gains (10.7 letters vs. 10.9 letters, respectively), and polyp regression rates (38.9% vs. 44.8%, respectively; $P = 0.32$). More than 80% of patients had no signs of polyp activity at week 52. The PLANET study thus concluded that if anti-VEGF monotherapy was selected for treatment of PCV, aflibercept monotherapy achieved significant BCVA gains in more than 85% of patients with PCV and no significant additional benefit could be demonstrated at week 52 by adding rescue PDT based on their criteria. There are ongoing studies to evaluate the safety and efficacy of aflibercept combined with prompt PDT.

Current Management Guidelines and Recommendations for Clinicians

The most important goal of treatment of treatment-naïve PCV, as in typical neovascular AMD, should be achieving the best possible visual outcome while minimizing the treatment burden. In this respect, results of both the EVEREST-II and PLANET studies showed that anti-VEGF monotherapy as well as combination therapy with PDT give excellent functional visual outcomes at 1 year, similar to results of typical neovascular AMD, and thus are acceptable initial treatment options in patients with symptomatic PCV.

Therefore, when deciding on the best treatment option for each patient, differences in individual patients and settings (such as prevalence of PCV and accessibility of ICGA and PDT), lesion characteristics, and presenting visual acuity should be considered (Table 7). Advantages of anti-VEGF monotherapy include eliminating the need for access to ICGA and PDT, thus potentially simplifying logistics and lowering financial burden. The risk of uncommon complications related to PDT also were eliminated. However, the number of anti-VEGF injections when given as monotherapy can be expected to be higher than when given in combination with PDT, as demonstrated in EVEREST-II. Thus, patients who are not committed to regular follow-up and multiple injections (average, 7–8 over 12 months) may not achieve the same visual benefit as described in clinical trials. Although the risk related to intravitreal injection is low, the cumulative risk does increase in patients undergoing repeated injections. In contrast, initial combination therapy may reduce the need for retreatment up to 1 year based on currently available evidence. In contrast, the need for special equipment and the high cost of verteporfin PDT in many countries remain major barriers to the use of combination therapy as first-line treatment. In patients with very good presenting vision, there is also concern of worsening of vision after combination therapy. There are suggestions that certain features of the PCV lesion, such as size and configuration of polyps or choroidal hyperpermeability, thickness, or both may help to predict eyes with a more favorable response to combination therapy. However, these factors have yet to be evaluated in clinical trials.

Future Research and Gaps

As this review has shown, significant advances in our understanding of various management approaches have been made, and recent results from the large randomized controlled trials described herein have better informed the risks and benefits of various treatment options for PCV.

A key gap in our understanding of optimal management for PCV is the importance of polyp closure. One of the major advantages of combination therapy seems to be achievement of higher polyp closure rates. However, there is no clear evidence for a direct association between higher polyp closure rate and better visual outcome. Neither is there clear evidence of a direct association between higher polyp closure rates and lower recurrences during extended follow-up. Recurrence rates are reported to be as high as 40% to 78.6% after 3 years. In recurrent cases, repeated sessions of PDT have been postulated to damage choriocapillaris and retinal pigment epithelium, leading to long-term visual loss. The 1-year data from trials reported above are unable to detect these changes. Thus, studies with longer follow-up will be required to evaluate recurrence rates and long-term visual outcomes.

Another important gap is the lack of patient, clinical, and imaging biomarkers that may predict response to therapy. As demonstrated in the EVEREST-II study, half of the patients responded very well to combination therapy and required only 3 to 4 ranibizumab injections over 12 months. Similarly, in the FUJISAN study, more than 50% of patients were treated with ranibizumab monotherapy and did not require additional deferred PDT. These results suggest significant heterogeneity within PCV, which may be reflected in differences in choroidal thickness, and choroidal vascular hyperpermeability. These differences in turn may be explained at least partially by differences in genetic background. Some clinical studies have suggested that eyes with thicker choroids may respond poorly to anti-VEGF monotherapy. Other results suggest that the presence of choroidal vascular hyperpermeability may predict more favorable response to combination therapy. However, these biomarkers have been evaluated in just small clinical case series. The current
1 Diagnosis of PCV: PCV should be diagnosed by ICGA at presentation in all cases.
   Rationale: There are many macular disorders that mimic PCV, such as central serous chorioretinopathy, vascularized PED, and type 3 neovascularization (retinal angiomatous proliferation). It is important to treat based on an accurate diagnosis.

2 Treatment goal: The most important goal of treatment of treatment-naïve PCV should be achieving the best possible visual outcome while minimizing the treatment burden.
   The secondary goals are achieving complete polyp closure and minimizing adverse events, RPE atrophy, and recurrence.

3 Initial treatment: both anti-VEGF monotherapy as well as combination anti-VEGF therapy and PDT* are acceptable initial treatment options in patients presenting with symptomatic PCV.
   Rationale: EVEREST-II and PLANET studies demonstrated level I evidence that anti-VEGF monotherapy as well as combination therapy give excellent functional visual outcomes at 1 year. Current evidence suggests that anti-VEGF monotherapy and combination therapy achieve comparably favorable outcomes up to 1 year; therefore, the choice between these 2 methods may depend on other factors, including Accessibility to ICGA diagnosis and confirmation of PCV;
   Accessibility to and expertise with verteporfin PDT laser equipment;
   Presenting visual acuity;
   Lesion characteristics: number, size, and location of polyps;
   Affordability and availability of reimbursement for treatments; and
   Ability of patients to return for regular and long-term follow up at frequent intervals.
   When discussing anti-VEGF monotherapy, please note there may be differences between anti-VEGF agents:
   There are no head-to-head studies to compare directly between different anti-VEGF agents. There is currently no evidence to support extrapolation of the above study results to off-label use of bevacizumab.
   If ranibizumab is used, the EVEREST-II study demonstrated clearly that combination therapy with PDT is preferred to ranibizumab monotherapy and is supported by superior visual and angiographic outcomes and reduced need for repeat injections during the first year of treatment.
   If aflibercept is used, the PLANET study suggests there is no additional benefit in combining with PDT as a rescue therapy. However, there are currently no data as to whether combination at baseline has any additional benefit to aflibercept. Patients who opt for aflibercept monotherapy should be prepared to adhere to fixed dosing as used in the PLANET study.

4 Commencing treatment with anti-VEGF monotherapy** may be preferred under the following circumstances:
   Lack of access to ICGA, PDT or both (logistically, financially, or both).
   ICGA features are uncertain or equivocal for PCV, for example, when massive submacular hemorrhage masks definitive diagnosis of PCV.
   Ocular features that limit effective application of PDT, e.g., location of polyps in proximity to optic disc, poor view such as that resulting from presence of thick or vitreous hemorrhage or dense cataract, and multifocal location or lesions with greatest linear dimension of >5400 μm. Systemic contraindications to PDT, e.g., drug sensitivity, porphyria, or photosensitive dermatitis.
   Clinical features suggest low probability of PCV (e.g., patient from ethnic groups with lower PCV prevalence, lack of serosanguineous maculopathy clinically).

5 Commencing treatment with combination therapy may be preferred if:
   Commitment to adhere to monitoring and retreatment is a concern.
   Combination therapy results in significant reduction in total number of ranibizumab injections over 12 months without compromising visual outcome or safety. The main reason behind reduced need for treatment is thought to be related to higher rate of complete polyp closure when using combination therapy compared with monotherapy with either aflibercept or ranibizumab.

6 Treatment regimen: patients who start with anti-VEGF monotherapy should either be treated using fixed dosing following the PLANET study (3 initial monthly aflibercept injections followed by 8 weekly injections) or be monitored monthly if following a PRN regimen as in the EVEREST-II study (3 initial monthly ranibizumab injections followed by monthly monitoring and PRN re-treatment). Premature cessation of treatment, particularly if monitoring is irregular, may lead to less favorable results than those reported above. There is concern that sudden hemorrhage may occur in cases with residual polyps after discontinuation of anti-VEGF therapy.
   The second year of the PLANET study will assess the efficacy of aflibercept using a treat-and-extend regimen. There is currently no evidence to support extrapolation of the above study results to off-label use of bevacizumab.

7 Monitoring of treatment response:
   After initial therapy, patients should be monitored for adequate response based on BCVA and OCT results. Particularly in patients who are receiving anti-VEGF monotherapy, ICGA should be considered if there is suboptimal response based on BCVA and OCT monitoring. In these cases, addition of PDT to the anti-VEGF regimen should be considered if active polyps are identified on ICGA.
   Note: The rescue criteria used in the PLANET study are based on the hypothesis that aflibercept monotherapy is noninferior to aflibercept plus PDT. Thus, the PLANET study cannot address what would be the outcome of combination therapy if PDT were used in the same ways as in the EVEREST-II study.

Table 7. Current Management Guidelines and Recommendations for Clinicians

In conclusion, PCV is a common subtype of neovascular AMD, particularly in Asian populations. In this review, we proposed guidelines and recommendations to help clinicians manage patients with PCV, based on the latest available body of evidence is insufficient to allow us to provide recommendations and guidance in these aspects of management. Future clinical trials will be needed to address each of these knowledge gaps.

BCVA = best-corrected visual acuity; ICGA = indocyanine green angiography; OCTA = OCT angiography; PCV = polypoidal choroidal vasculopathy; PDT = photodynamic therapy; PED = pigment epithelial detachment; PRN = pro re nata; RPE = retinal pigment epithelium; SD = spectral-domain; VEGF = vascular endothelial growth factor.

*Current evidence on PDT is based predominantly on studies using full-fluence PDT.
evidence from clinical studies and randomized trials. There remain important gaps in our understanding of PCV, such as significance of polyp closure, which highlighted the need for further research.

References


56. Fung AT, Yannuzzi LA, Freund KB. Type 1 (sub-retinal pigment epithelial) neovascularization in central serous chorioretinopathy masquerading as neovascular age-related macular degeneration. Retina. 2012;32(9):1829–1837.


Footnotes and Financial Disclosures

Originally received: September 19, 2017. 
Final revision: November 9, 2017. 
Accepted: November 9, 2017. 
Available online: January 10, 2018. 
Manuscript no. 2017-2142.

1 Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Republic of Singapore.

2 Duke-NUS Medical School, National University of Singapore, Singapore, Republic of Singapore.

3 Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China.

4 Department of Ophthalmology, Rajavithi Hospital, Bangkok, Thailand.

5 Department of Ophthalmology, Taipei Veterans General Hospital, and School of Medicine, National Yang-Ming University, Taipei, Taiwan.

6 Department of Ophthalmology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China.

7 Vitreous Retina Macula Consultants of New York, and The LuEsther T. Mertz Retinal Research Center of New York, New York.

8 Department of Ophthalmology, New York University School of Medicine, New York, New York.

9 Department of Ophthalmology, Kyogo College of Medicine, Kyogo, Japan.

10 Eye & Retina Surgeons, Camden Medical Centre, Singapore, Republic of Singapore.

11 Department of Ophthalmology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Financial Disclosure(s): The author(s) made the following disclosure(s): C.M.C.: Consultant — Bayer, Novartis; Financial support — Bayer, Novartis, Roche, GlaxoSmithKline; Nonfinancial support — Bayer, Allergan, Topcon

T.Y.L.: Consultant — Bayer, Novartis, Allergan, AbbVie, Genentech; Financial support — Bayer, Novartis, Allergan, AbbVie, Genentech

P.R.: Consultant and Financial support — Bayer, Novartis, Allergan

S.-J.C.: Consultant and Financial support — Bayer, Novartis, Allergan

Medical Image Integration

Y.X.C.: Consultant and Financial support — Bayer, Novartis; Nonfinancial support — Topcon

K.B.F.: Consultant — Optovue, Optos, Heidelberg Engineering, Genentech, GrayBug Vision; Financial support — Genentech/Roche

F.G.: Consultant, Financial support, and Lecturer — Bayer, Novartis Pfizer, Santen; Nonfinancial support — Topcon

A.H.K.: Financial and Nonfinancial support — Bayer Healthcare, Allergan, Alcon, Boeringher Ingelheim, Bayer, Carl Zeiss Meditec, Heidelberg, Novartis, Topcon, Santen

W.-K.L.: Financial and Nonfinancial support — Bayer Healthcare, Novartis

T.Y.W.: Consultant and Financial support — Bayer, Novartis, Abbott, Allergan, Bayer, Genentech, Novartis, Roche, Pfizer

Supported by the National Medical Research Council Singapore, Republic of Singapore. The sponsor or funding organization had no role in the design or conduct of this research.

HUMAN SUBJECTS: No human subjects were included in this study.

Author Contributions:

Conception and design: Cheung, Wong

Analysis and interpretation: Cheung, Lai, Ruamviboonsuk, S.-J.Chen, Freund, Gomi, Koh, Lee

Data collection: Cheung, Lai, Ruamviboonsuk, S.-J.Chen, Freund, Gomi, Koh

Obtained funding: none

Overall responsibility: Cheung, Lee, Wong

Abbreviations and Acronyms:

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; BVN = branching vascular network; FA = fluorescein angiography; ICGA = indocyanine green angiography; IVT-AFL = intravitreal aflibercept; IVT-R = intravitreal ranibizumab; OCTA = OCT angiography; PCV = polypoidal choroidal vasculopathy; PDT = photodynamic therapy; PED = pigment epithelial detachment; RPE = retinal pigment epithelium; SD = spectral-domain; VEGF = vascular endothelial growth factor.

Correspondence:

Chui Ming Gemmy Cheung, FRCOphth, Singapore Eye Research Institute, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751, Republic of Singapore. E-mail: gemmy.cheung.c.m@singhealth.com.sg.