Abnormal vasculature in patients with polypoidal choroidal vasculopathy (PCV) consists of a branching vascular network (BVN) with polypoidal lesions at the lesion borders, and it is best visualized by indocyanine green angiography (ICGA). PCV is reported to be prevalent in 20% to 50% of Asian patients with presumed neovascular age-related macular degeneration (AMD);1-6 this discrepancy may arise from the different criteria for polyp (uncertain polyp) and the different types of ICGA devices used in each study. Prevalence of PCV in Caucasian patients is 4% to 12%, which may be underestimated, as ICGA is not performed routinely.

PCV is associated with multiple recurrent serosanguineous detachments of the retinal pigment epithelium (RPE) and neurosensory retina with leakage and bleeding specifically coming from the polyps initially. It is generally accepted that PCV has a better visual prognosis than typical neovascular AMD, as progression is slow and subretinal fibrous proliferation is unusual. However, the visual prognosis is variable over its natural course and is not as good as previously thought.1-6

Therapeutic approaches to PCV include thermal laser photocoagulation, verteporfin photodynamic therapy (PDT), anti-VEGF therapy, and combination therapy. However, there is no consensus on optimal disease management. Furthermore, the course of PCV may vary, and its nature may change, so individualized plans for long-term treatment are likely required.

INITIAL THERAPY FOR TREATMENT-NAÏVE PCV

Many reports have demonstrated excellent short-term efficacy of PDT for treating PCV. Complete polyp regression was achieved in 80% to 95% of cases, and this was well translated into resolution of the exudative changes and stabilization or improvement of vision at the 1-year follow-up.7-10 However, persistence of BVN and polyp recurrence remain key limitations of PDT.11-14 Akaza et al15 reported recurrent polyps in 33 of 43 eyes (77%) at 3 years’ follow-up, of which more than 40% had
more than one recurrence. Repeated PDTs are usually required, and the visual outcomes at 3 or even 2 years are not as good as those at 1 year.15,16 The reasons for vision decrease include chorioretinal atrophy, persistent exudation despite polyp regression, and fibrous scarring. Repeated PDT exposure may result in extensive choroidal nonperfusion and VEGF upregulation, especially if spot size is large, predisposing to recurrent neovascularization and atrophic changes of RPE (Figure 1). Small vascular lesions, better initial vision, less hemorrhage, and the absence of subfoveal polyps have been suggested as pretreatment factors favoring better visual outcomes.17-19

Use of anti-VEGF agents is another treatment option investigated in PCV as initial therapy based on the findings of increased VEGF levels in aqueous and tissue samples. Previous studies indicated that anti-VEGF therapy may reduce leakage in PCV but was ineffective for inducing regression of polyps (Figure 2).20-22 In the prospective, randomized EVEREST study, which compared the 6-month results among patients who received PDT combined with ranibizumab, PDT monotherapy, or ranibizumab monotherapy for PCV, complete regression of polyps was achieved by only 30% of patients in the ranibizumab monotherapy arm.

Figure 2. A PCV case treated by intravitreal injection of bevacizumab. FA, ICGA, and OCT show an active PCV associated with pigment epithelial detachment and sensory retinal detachment (A and B). One month after 2 injections, decreases of leakage, fluid collection, and the height of PED are observed (C and D). Visual acuity improved from 0.3 to 0.5; however, vascular lesions of PCV are persistent.
Nonetheless, visual acuity improved at 6 months despite persistence of polyps, possibly due to ranibizumab’s strong antileakage effect. Although continuous injections seem to be required (more than 60% of patients received the maximum number of 6 injections), such findings suggest that anti-VEGF agents may successfully control the exudative changes associated with polyps. In about 30% of eyes, polyps completely regressed as well, either spontaneously or due to treatment.\(^{23}\)

Despite disappointing long-term efficacy of PDT, most investigators believe that PDT should play a major role in the treatment of PCV. Given currently available data, complete polyp regression is a desirable endpoint to reduce the risk of polyp rupture and chronic leakage as well as the burden of retreatment, at least in the initial intervention. In patients who achieve initial favorable responses (polyp regression) following PDT, additional treatment would not be required for at least 1 year for most of them and 2 years for half of them.

Theoretically, combining PDT, with its angioocclusive effects, and anti-VEGF therapy, with its antiangiogenic and antipermeability effects, may lead to synergistic treatment effects in PCV. Recent studies have suggested that combination therapy has some advantages over PDT monotherapy, including a reduction in required PDT number, more rapid absorption of fluid, and fewer hemorrhagic events.\(^{24,25}\) Furthermore, adding an anti-VEGF agent can modulate VEGF upregulation resulting from PDT-induced tissue hypoxia. Most experts in Asia agree that a differential diagnosis is difficult in 20% to 30% of cases because ICGA features are ambiguous (uncertain poly) between PCV and choroidal neovascularization (CNV). In these patients, combination therapy would ensure that the standard of care is met for both conditions. Optimal sequence, interval, and injection number in combination therapy are as yet unclear.

The ideal way to treat PCV lesion without recurrence is to close all vascular components. Hence, thermal laser should be considered when all lesion components (polyps and BVN) are located sufficiently away from the fovea. Peripapillary PCV is a good candidate for thermal laser.

**SECONDARY CNV**

Persistent or recurrent exudation may occur in the absence of polyps due to leakage from persistent BVN after PDT. Based on the features of fluorescein angiography (FA) and optical coherence tomography (OCT) as well as different treatment responses, several studies have suggested that persistent BVN may evolve into secondary CNV, mostly sub-RPE CNV (Figure 3). This occurs in 20% to 40% of cases treated with PDT within 2 years.\(^{26-28}\) Spectral-domain OCT showed that BVNs and polypoidal lesions lie between a displaced RPE and the outer part of Bruch membrane, indicating that PCV represents an intra-Bruch CNV. BVN may exist as a latent form of CNV in most treatment-naïve PCV lesions, and PDT may play some role in activating this lesion. In these patients, recent data shows that additional PDT is less effective and fails to improve or maintain visual acuity, while results with anti-VEGF agents appear promising.\(^{26-28}\) This underscores the need to modify treatment as PCV progresses.
TREATMENT FOR RECURRENT LESIONS AFTER PDT

Considering disappointing results in patients treated by repeated PDT, clinicians should strive for reducing the frequency and extent of PDT to decrease the risk of choroidal ischemia and RPE atrophy when performing retreatment. Recurrent exudation may be associated with recurrent polyp or secondary CNV or both, which can be differentiated only by ICGA. With polyps absent, anti-VEGF monotherapy is recommended first, while vaso-occlusive treatment is elected (combined with anti-VEGF) when demonstrable symptomatic polyps appear on ICGA. Anti-VEGF therapy may be used first-line on lesions where polyps were questionable, expecting spontaneous or therapeutic regression of would-be polyps and resolution of exudative changes. Additional PDT is reserved for nonresponsive eyes. Likewise, even though definitive polyps are observed, anti-VEGF monotherapy may be chosen first in patients with previous history of multiple PDTs or atrophic RPE changes or lesions refractory to 2 or 3 consecutive PDTs. Also, low-fluence PDT or selective PDT targeting the leaking polyps may reduce PDT-related complications while maintaining efficacy.

SUMMARY

In newly diagnosed or treatment-naïve patients, the exudative changes of PCV usually derive from active polyps. However, BVN or secondary CNV, alone or in conjunction with polyps, may contribute to exudative manifestations in PCV that is chronic or previously treated. Individualized plans for long-term treatment, using PDT, anti-VEGF, and laser, are likely required. PDT (usually combined with anti-VEGF agent use) is recommended in the initial therapy for subfoveal or juxtafoveal PCV. For persistent or recurrent lesions, retreatment should be adjusted according to individual angiographic and clinical features in an effort to reduce the frequency and extent of PDT. In particular, anti-VEGF agents may be the only useful current treatment option for lesions without definitive polyp (probably associated with secondary CNV), and repeated use of PDT should be avoided. ICGA should be included in follow-up examinations as well as the initial diagnostic workup.

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