Polypoidal Choroidal Vasculopathy: Review of the Managements

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Abstract

Purpose of Review: This study aims to review the articles relevant to diagnosis and updates in the management of Polypoidal Choroidal Vasculopathy (PCV).

Recent Findings: PCV manifests as recurrent hemorrhagic and exudative serosanguinous detachment at the posterior pole and reddish-orange subretinal nodule. PCV is usually diagnosed by Indocyanine Green Angiography (ICGA) characterized by polypoidal lesions and Brach Vascular Network (BVN). Using multimodal imaging, they found that polyps may be aneurysmal lesions, however, recently suggested that they are tangled glomerular like structures. Currently, the underlying mechanism of the PCV remains to be elucidated. As our knowledge about the pathophysiology of PCV increase, new treatment strategies are evolving. Several treatments have been implemented like, monotherapy with Anti-Vascular Endothelial Growth Factor (VEGF), anti-VEGF therapy in combination with Photodynamic Therapy (PDT), monotherapy with PDT as well as retinal photocoagulation alone or in combination with other treatments. Current studies pointed out that Combination therapy of PDT and Anti-VEGF and Monotherapy with Anti-VEGF are associated with better visual outcome. However, recent studies show that Combination therapy is not superior to monotherapy with Anti-VEGF, especially Aflibercept, in the visual outcome, Although the rate of polyp regression is higher in Combination therapy.

Summary: There is no optimal treatment strategy for PCV, and our knowledge about pathophysiology and management of PCV continue to evolve. Recent studies showed that the Anti-VEGF monotherapy could be effective as the combination therapy in term of visual outcome. We need further studies issue the optimal treatment strategy with a strong level of evidence.

Keywords: Branching Vascular Network; Combination Therapy; Intravitreal Anti-VEGF; Photodynamic Therapy; Polypoidal Choroidal Vasculopathy; Serosanguinous Retinal Pigment Epithelium Detachment

Abbreviations: BVN: Branched Vascular Network; Anti-VEGF: Anti-Vascular Endothelial Growth Factor; ICGA: Indocyanine Green Angiography; OCTA: Optical Coherence Tomography-Angiography; OCT: Optical Coherence Tomography; PDT: Photodynamic Therapy; PED: Pigment Epithelial Detachment; PCV: Polypoidal Choroidal Vasculopathy

Introduction

Currently, the underlying mechanism of the PCV remains to be elucidated, and correspondingly the management is controversial. In 1990, Kleiner, et al. described a group of patients with recurrent hemorrhagic episodes and exudative serosanguinous detachment at the posterior pole as a posterior uveal bleeding syndrome [1]. Yannuzzi, et al. at the same year described the disease as a new entity, different from those previously considered as a subtype of AMD, characterized by polypoidal vascular lesions, which was named as idiopathic polypoidal choroidal vasculopathy [2]. They both described various aspects of one disease and the common key clinical feature of this disease was reddish-orange nodule on funduscopy. Earlier studies postulated that Polypoidal lesions directly arise from the choroidal inner layer. Since then, the pathophysiology of PCV has not been well understood, till in the era of multimodal imaging, new aspects of the BVN (branched vascular network) as a new finding, was described as neovascularization tissue between RPE and Bruch membrane that today, is easily detectable on SD-OCT, OCTA, and ICG. By using multimodal imaging, investigators suggested that PCV is a variant of type 1 neovascularization, and the polyps originate from the vascular network, instead directly from choroidal vessels [3-6].
using OCT-A, the polyps were found to be aneurysmal dilation of vessels wall of the vascular network rather than a fleshy mass, so-called them “Aneurysmal vasculopathy” [5,7], nonetheless it is challenging to detect the polyoidal lesions on OCTA probably due to low internal flow, in contrast to the BNVs [8]. Recently, by using swept-source OCTA, the polyps have been described as tangled of vessels at the border of branch vascular network instead of a true aneurysm and interestingly they depicted the treatment response of the polyps to the anti-VEGF with imaging [9].

Despite the advances in imaging modalities, ICGA still, remains as the gold standard of diagnosis of PCV. Choroidal hyperpermeability is a prominent feature of PCV that is evident particularly in the middle and late phases of angiogram which appears as multifocal hypercyanescence area around choroidal vessels [10]. ICGA also illustrates the polyps as early hypercyanescent spots as well BVN as hypercyanescent networks above thickened choroid.

Recently, several studies have focused on the valuable role of the OCT in the diagnosis of PCV disease. By which, shallow and irregular PED (double-layer sign) seems to be representative of BNVs that are well appreciated by OCTA and ICGA. Further polyoidal lesions may show characteristic features of PED including; thumb like, peaked, notched or double-layer PED consist of a hyperreflective ring around a low internal reflective area; that was described well by the numerous studies [11]. Researchers have launched several trials addressing optimum management for controlling PCV. In this review, we summarized different treatments for PCV treatments.

**Polypoidal Choroidal Vasculopathy Management**

As our knowledge about the underlying pathophysiology of PCV increase, new treatment strategies are evolving.

Based on etiology of PCV several treatments have been used like, monotherapy with anti-VEGF, anti-VEGF therapy in combination with photodynamic therapy (PDT), monotherapy with PDT as well as retinal photocoagulation alone or in combination with other treatments.

**Monotherapy with Anti-Vascular Endothelial Growth Factor Agents**

Previous investigations showed that the VEGF level in aqueous of PCV patients is higher than normal but less than exudative-AMD patients. Although less favorable responses to anti-VEGF have been expected in PCV patients [12]. But some studies have shown benefits of monotherapy with anti-VEGF. Several anti-VEGF drugs were introduced to manage neovascularization manifestations of ocular diseases. Here, we provide the articles based on Anti-VEGF treatment only; and the other studies that have compared Anti-VEGF drugs with Combination therapy (Anti-VEGF with PDT), will be discussed later in the Combination therapy section.

**Bevacizumab:** There are few studies of using bevacizumab for the management of PCV. Cheng and associates observed an increase in Visual Acuity (VA) and decrease in Central Retinal Thickness (CRT) after Pro Re Nata (PRN) intravitreal injection of 2.5Mg bevacizumab (Avastin, double dose) which maintained through the 12 months of follow up and Polyp regression occurred moderately. At month 6, polyps resolved in 3 eyes (9.4%), reduced in 11 eyes (34.4%) and increased in 4 eyes (12.5%). After 12 months ICGA revealed features of resolved polyps in 5 eyes (16.1%), reduced polyps in 10 eyes (32.3%) and increased polyps in 5 eyes (16.2%) [13]. While Tsujikawa et al. showed BCVA improvement initially at month 3, they failed to demonstrate significant improvement in VA after PRN treatment with 1.25mg injection of bevacizumab, no matter if the initial treatment were a single injection of IVB or 3 monthly injections. Nonetheless, CRT decreased significantly during 12 months of follow up [14].

Notably, Bevacizumab failed to make remarkable polype regression in both studies.

**Ranibizumab:** There are more studies of using Ranibizumab in PCV treatment in the literature. Matsumya failed to show improvement in VA of the PCV patients treated with ranibizumab PRN during 12 months in comparison to the AMD patients that demonstrated significant visual improvement [15]. Hikichi, et al. observed significant improvement in BCVA and CRT, one month after 3 monthly injections of ranibizumab in 81 eyes with PCV, which maintained for 12 months follow up. Although polyoidal lesions disappeared 12 months after the first injection in 39% of cases, the abnormal vessels were visible in ICGA, remained until the end of the survey [16]. Results of other studies were similar [17,18]. However, in DRAGON Study, a randomized control trial of 0.5 mg Ranibizumab in PCV and non-PCV (nAMD) patients with two different regimens: monthly in the first year followed by PRN at the second year, and PRN regimen during 2 years; They showed improvement of VA and CRT in both PCV and non-PCV groups. There was no significant difference between the two regimens [19]. Interestingly PEARL1 study, prospective trial of Ranibizumab monthly injections in 13 patients, revealed the same results. They showed significant improvement in VA and decreased central foveal thickness [20]. Joo Cho and colleagues [21], in a retrospective study, comprised efficacy of 3 monthly injections of ranibizumab vs. bevacizumab followed by PRN reinjection protocol. Almost no significant differences were found in short term efficacy between these two drugs for PCV treatment. The average foveal thickness decreased from 322 µm to 274 µm and from 338 µm to 286 µm respectively in the bevacizumab and ranibizumab group. No significant difference in term of VA gain, foveal thickness decrement, and the rate of polyp regression was observed between two groups [22]. Results of another study revealed that anti-VEGF therapy is less effective in the treatment of PCV than AMD. It has been reported that choroidal hyperpermeability and thickness are correlated with reduced response to the intravitreal ranibizumab [23]. Interestingly, Joo Cho et al. also reported a negative association between choroidal hyperpermeability and response to anti-VEGF therapy. Their survey indicated that BCVA and...
Photodynamic therapy was the first effective treatment for exudative AMD and after that became the standard of care in the treatment of symptomatic PCV [32,33]. It uses a photosensitizer agent to absorb a specific wavelength of the light spectrum and consequently causes interaction between tissue and oxygen [34]. Several studies have evaluated PDT in the treatment of PCV [35]. Although short term findings denote steady visual function after PDT, a decline in visual acuity and unfavorable outcomes are frequent [36-38]. Yamashita and associates reported a decrease in nonperfusion choriocapillaris and subretinal hemorrhage after treatment with reducing flounce PDT with the similar visual outcome to other reports with full flounce PDT treatment after a short follow up, in a prospective study [39]. While Mitamura, et al. observed a mild superiority for short term (3 months) therapeutic effects of PDT in comparison with single and triple bevacizumab injection [40]. Although, the 2 years follow up of 44 patients with PCV treated with 3 monthly injections of ranibizumab showed better long term visual outcomes, but a higher recurrence rate in comparison with PDT was observed [41]. The former group retreated if needed in follow up with intravitreal ranibizumab. The latter group retreated with PDT as required in the follow-up period.

Oishi and associates ran a prospective, multicenter, and randomized trial named LAPTOP study to compare the effect of PDT and ranibizumab in patients with PCV. After 12 months, 17.0%, 55.3%, and 27.7% of the eyes in the PDT subgroup demonstrated 0.2 logMAR units gain, no change, or 0.2 logMAR units loss in VA, respectively. The results for ranibizumab subgroup were 30.4%, 60.9%, and 8.7% respectively. Functional outcomes were significantly better in the ranibizumab subgroup. However, improvement of CRT was similar in both groups. Therefore, intravitreal injection of ranibizumab seems to lead in better visual outcomes for treatment of PCV in this study [42]. 60% of LAPTOP study participants were followed for five years, and the analyses were repeated. Nonetheless, more than 70% of the eyes were converted to aflibercept. The significant difference in VA between two groups maintained after five years. The proportion of eyes which gained 0.3 logMAR unit retained in the ranibizumab group and decreased in the PDT group. Of note, approximately leakage in FA and the polypoidal lesion were detected in 70% of eyes in both groups (same poly regression). CRT was decreased in both groups, although dry macula achievement was higher in the PDT group [43].

Combination Therapy

Combination therapy of PDT and steroids

There are few studies compare combination therapy of steroids and PDT or triple therapy, adding anti-VEGF to them, in managing PCV. A retrospective study of comparing PDT monotherapy in 12 eyes and Combination therapy of Intravitreal Triamcinolone Acetonide (IVTA) with PDT in 15 eyes of PCV patients. At two year results, they found no additional benefit of adding IVTA to PDT [44]. Two studies on triple therapy (PDT+IVTA+anti VEGF) in PCV was done. A retrospective study was comparing triple therapy with Bevacizumab, IVTA, and PDT in 24 patients to PDT monotherapy in 16 patients. At two year results, they found that triple therapy reduces complication such as postoperative hemorrhage and increase the interval between treatment periods and also the visual outcome [45]. A Prospective study on triple therapy with intravitreal Aflibercept, intravitreal Dexamethasone and PDT on 17 eyes was done recently. After 1 year, they showed a significant and stable response in the majority of studied eyes [46]. Further control studies on adding steroids should be done.
Combination therapy of PDT and anti-VEGF

Combination therapy with PDT and anti-VEGF injection thought to improve outcomes and may decrease adverse effects of each treatment [47,48]. In a noteworthy study, Gomi and colleagues assessed the efficacy of combination therapy of PDT and IVB in comparison to monotherapy with PDT. BCVA was better in the combination therapy group, especially, in the short term follow up (p-value = 0.0016 after one month and 0.048 after 12 months for the difference in BCVA between two groups). Furthermore, subretinal hemorrhage was significantly lower in the combination therapy group [49]. Also, Murako, et al. found superiority for combination therapy rather than monotherapy in improving subfoveal retinal thickness and choroidal thickness as well as BCVA [50]. EVEREST study, a multicenter, double-masked randomized clinical trial studied 59 eligible patients of PCV to determine if there is any superiority for combination therapy of PDT and ranibizumab vs. monotherapy with ranibizumab. They randomized the participants 1:1:1 for receiving verteporfin PDT (6 mg/m2) + ranibizumab 0.5 mg, verteporfin PDT (6 mg/m2) + sham injection, or ranibizumab 0.5 mg + sham PDT. Although the follow up period was not enough (6 months), they succeeded to demonstrate more potency for combination therapy and monotherapy with PDT to regress polyps completely in comparison with monotherapy with ranibizumab but failed to show a significant difference in BCVA [51]. Therefore, the authors ran Everest II with larger sample size and longer follow up period (24 months). Visual acuity gain in combination therapy was 8.3 letter at month 12 compared with 5.1 of the monotherapy group (p=0.01). Furthermore, polyp regression was significantly higher in combination therapy arm compared with monotherapy (69.3% vs. 34.7%, respectively P<.001). Nonetheless, the number of Anti-VEGF injections was smaller in the combination therapy group (4 vs.7) [52]. Therefore, in addition to better visual outcomes, combination therapy may lead to lower recurrence rate, due to more polyp regression. Other studies attempted to elucidate the difference between treatments [53]. A multicenter randomized control trial named FUJISAN study evaluated the efficacy of deferred or initial PDT in combination with intravitreal ranibizumab. Patients received 3 consecutive Injection of ranibizumab in both groups with or without PDT at baseline. At month 3 PDT administered if polypoidal lesion existed with subretinal fluid on ICGA and BCVA was below 0.7. At month 12, they found no significant difference in BCVA improvement and CRT reduction between the two groups. The polyp regression also was not significantly different between the groups (62.1% and 54.8% in the initial PDT and later PDT arm respectively (P = 0.53)), but the number of ranibizumab injection was fewer in the initial PDR group [54].

Despite previous studies, which noted that combination therapy is more effective than monotherapy with anti-VEGF drugs, PLANET study did not determine the additive potential of adding PDT. This double-masked, randomized, controlled clinical trial included two arms. In the first arm, patients with PCV received monotherapy with 3 monthly injections of aflibercept followed by IAI injection every 4 weeks if rescue therapy was needed at week 12 (aflibercept monotherapy). Patients in the second arm treated with 3 monthly injections of aflibercept, which was followed by IAI plus PDT every 4 weeks if rescue therapy was needed at week 12 (aflibercept +PDT group). When the rescue criteria were no longer met during the study, injection intervals were gradually extended to 8 weeks. If rescue therapy was not needed at week 12, IAI injection extended to every 8 weeks. After 52 weeks, no inferiority of IAI monotherapy to IAI/PDT was observed for change in BCVA, moderate vision loss avoidance, reduction in polypoidal lesions area, rate of complete regression of polypoidal lesions and central retinal thickness reduction. At week 52, 38.9% and 44.8% of the patients with monotherapy with IVA and combination therapy had no polypoidal lesions, respectively [55]. In the 2-year results of PLANET study, they reported the same results, over 96 weeks, IAI monotherapy was noninferior to IAI with rescue PDT [56].

However, there is a discrepancy among the reports, for example, in term of VA improvement and the rate of polyp regression. In the EVEREST-II study, the VA gain was 5.1 letter in the ranibizumab monotherapy group; which was lower than reported in DRAGON study (9.4 letters). In the PLANET study, VA gain was reported to be 10.7 in the aflibercept monotherapy group that was also higher than the other two studies. It is speculated that this discrepancy may be related to the different baseline VA in the monotherapy groups that were 61.2 in EVEREST II, 54.6 in DRAGON, and 57.7 in the planet study, as the poorer baseline VA may be associated with a higher number of the VA gain. Polyp regression was similar in anti-VEGF monotherapy arms of the studies. (34.7% in the EVEREST-II study and 38.9% in the planet study) In contrast, poly regression was different in the combination treatment arm of the studies (69.3% vs. 44.8% in EVEREST-II and PLANET, respectively). This inconsistency may be related to the different treatment protocol between two studies, in the PLANET study all the participant received 3 consecutive monthly injections after then they randomized into treatment arms; contrary to EVEREST-II that the participant randomized at baseline. Also, a small number of the participant in the PLANET study received rescue PDT (less than 15% of precipitant) due to study protocol, as such a larger number of the subjects are warranted to compare the results of the studies.

Up to now, no treatment can regress the BVN part of PCV. Long term outcomes of an investigation on the effect of the intravitreal bevacizumab for BVN, showed no improvement in CRT and BCVA after 24 months follow up [58].

Hemorrhagic outcomes for standard dose PDT was higher than reduced dose PDT based on some studies [38,59]. Other studies attempt to seek this effect in combination therapy with
intravitreal anti-VEGF injection. Sagong et al. observed significant improvement in BCVA 12 months after reduced flouence PDT (300 mW/cm²) combined with single-dose IVB [60]. However, Lee and associates reported a greater reduction in CRT and mean subfoveal choroidal thickness with higher polyp regression rate in full dose PDT combined with IVB rather than combination therapy with half-dose PDT. Although the BCVA was similar after 12 months, the mean number of IVB injections was 1.03 in the full-dose group and 2.80 in the half-dose group [61]. Improvement in BCVA was observed after treatment of PCV with reduced flouence PDT combined with IVR [62,63]. Sakurai reported significant visual improvement with reduced flouence PDT/IVR after 12 months, but no significant visual improvement occurred in the IVR group. Nonetheless, CRT was decreased in both groups with no significant difference between the two groups. The number of injections was mildly higher in the monotherapy group [64].

**Conclusion**

However, new imaging advances have provided new horizons to recognize the etiology and natural course of this disease. Still, there is no optimal treatment strategy for PCV. Although choosing treatment strategies depend on many items such as accessibility and financial implication of therapeutic approach, stage of PCV progression, and patient adherence to the treatment regimen. As recurrent hemorrhagic and serous detachment in the course of treatment can lead to degeneration and atrophy of the outer retina, retinal pigment epithelium, and choriocapillaris, the early diagnose of PCV patients, is a critical issue [6,9].

Results of some studies showed that the Anti-VEGF monotherapy could be effective as combination therapy. Although the rate of polyp regression differed between different Anti-VEGF agents, it seems that complete polyp regression may be occurred more in combination therapy than monotherapy (at least based on EVEREST 2 and FUJISAN study) [52,54].

Based on PLANET study in case of diagnosis in the early stages of PCV, Anti-VEGF monotherapy specially aflibercept can lead to acceptable outcomes without the need to further rescue PDT.

We should consider the cost issue, availability, and patient adherence to treatment. Anti-VEGF monotherapy has some advantages. For example, the need for ICGA before treatment and the complications associated with PDT, such as hemorrhage and macular atrophy may be eliminated. The disadvantage of these regimen is cost implication and an increased number of injection-related risks and patient adherence [6,9,51,52,55,56].

In contrast, combination therapy can lead to the advantage of fewer injections and can be useful in patients with lower compliance with treatment follow-ups. In another hand, the complete polyp regression may be more than monotherapy that may lead to fewer recurrences. However, we should consider the risk of complication associated with PDT such as macular atrophy, submacular hemorrhage, and choroidal ischemia, in particular in patients with good VA, as long as the accessibility of ICG and verteporfin for PDT [6,51,52,54-56].

We need further studies issue the optimal treatment strategy with a strong level of evidence.

**References**


