EVEREST Report 5: Clinical Outcomes and Treatment Response of Polypoidal Choroidal Vasculopathy Subtypes in a Multicenter, Randomized Controlled Trial

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See the appendix for the members of the EVEREST Study Group.

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P olypoidal choroidal vasculopathy (PCV) is an ocular disease characterized by abnormal vascular channels with terminal dilatations, which form the polyps (or polypoidal lesions).1,2 Although this condition occurs more commonly among some populations, such as Asians,3-5 recent evidence suggests that its prevalence among Caucasians may be higher than previously believed,6 thus emphasizing the global importance of this disease.

PCV is believed to be a variant of AMD, in particular, those with type I choroidal neovascularization.7,8 However, the visual prognosis and clinical outcomes of PCV are different from typical AMD.3,9 In addition, the clinical course of patients with PCV differs, with some patients experiencing a relatively mild course and retaining good visual acuity (VA), whereas others suffer frequent recurrences requiring multiple treatments, resulting in poor visual outcome.10,11 This is reflected in the literature on PCV, where the visual outcomes reported in different studies are highly variable,3,10,12 and has led some investigators to postulate that PCV may not be a single disease entity, but may instead consist of different subtypes, with variations in the clinical prognosis.1,5

A recent study13 described a novel classification for PCV subtypes and reported significant differences in visual outcomes among these subtypes over the 5-year study period. However, this earlier study was conducted at a single center and included PCV patients treated with photodynamic therapy (PDT), which was the standard of care at the time these patients were managed. The PCV classification system has not been applied to patients from other populations, and hence its utility and generalizability currently remain uncertain. If validated, this classification system may serve as a valuable imaging biomarker for prognosticating PCV.

Another key gap in our current knowledge is whether the differences in visual outcomes among PCV subtypes are also observed when PCV is treated with newer treatment modalities such as anti-VEGF agents or combination therapy of PDT and anti-VEGF injections.

The EVEREST study14 was the first multicenter randomized controlled trial on PCV. Because the treatment and follow-up protocols were standardized for all patients, this cohort forms an ideal platform to validate the classification system. The objectives of this study were to explore PCV subtype as a

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MATERIALS AND METHODS

The EVEREST study was a prospective, multicenter, randomized controlled trial of patients with macular PCV (registration no. NCT00674323 at clinicaltrials.gov). The study was approved by the respective institutional review boards of the study sites and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to enrollment in the study.

The study design, treatment protocols, and overall clinical outcomes have previously been described in detail. In brief, 61 patients diagnosed with symptomatic macular PCV were randomized equally into one of three treatment arms: (1) PDT with verteporfin (Visudyne; Novartis International AG, Basel, Switzerland) combined with intravitreal ranibizumab (Novartis), (2) intravitreal ranibizumab injections, (3) verteporfin PDT monotherapy, or (4) verteporfin PDT monotherapy.

Imaging Protocols

The imaging protocols and grading methods of the EVEREST study have been described in detail in an earlier report. All patients underwent indocyanine green angiography (ICGA) and fluorescein angiography (FA) using a confocal scanning laser ophthalmoscope (Heidelberg Retinal Angiograph [HRA]; HRA-C/HRA2/HRA Spectrals; Heidelberg Engineering, Heidelberg, Germany). Thirty-degree stereo-pair ICGA and FA images of the study eye were taken at 1, 3, 5, 10, and 20 minutes and graded by trained retinal specialists from the Central Reading Center (CRC; Fundus Image Reading Center, National Health Care Group Eye Institute, Singapore). The diagnosis of PCV was confirmed by the CRC using standardized diagnostic criteria, which consisted of the presence of early, focal hyperfluorescence on ICGA occurring within the first 5 minutes, together with at least one of the following six criteria: (1) nodular hyperfluorescence on stereoscopic examination, (2) hypofluorescent halo around the nodule, (3) branching vascular network, (4) pulsation of the polyp, (5) orange-red subretinal nodules corresponding to the hyperfluorescence on ICGA, or (6) massive submacular hemorrhage.

Optical coherence tomography (OCT) was performed using the Stratus OCT (Carl Zeiss Meditec, Dublin, CA, USA) using a fast macular scan protocol (6 × 6-mm radial scans).

PCV Subtyping

Additional detailed post hoc grading of the ICGA and FA images was independently performed by two Reading Center–certified retinal specialists (CST and THL) to determine the PCV subtype, using a classification system previously described (Fig. 1). The PCV subtype grading from both graders were compared using κ coefficients. Both graders were masked to the treatment arm and clinical outcomes of the patients. In addition, the classification of PCV was performed after the conclusion of the treatment phase and was not known to the study investigators. Therefore, the clinical judgment and treatment decisions of the study investigators were not influenced by the PCV subtype.

The abnormal vascular channels of the PCV lesion seen on dynamic ICGA were reviewed to classify them into interconnecting channels or branching vascular networks. Interconnecting channels (Fig. 2) consisted of a network of fine, criss-crossing vessels that had no specific point of origin and no specific direction of flow when observed on dynamic ICGA. The vessels of the interconnecting channels usually filled simultaneously. In contrast, the flow within branching vascular networks (Fig. 3) occurred in distinct directions, usually radiating toward the periphery to supply the polyps. On dynamic ICGA, filling of the branching vascular networks often originated from a specific point (commonly a feeder vessel). FA images were assessed for the presence of significant late leakage from the PCV lesion.

Type A PCV had polyps with interconnecting channels. Type B PCV had polyps with branching vascular networks but no significant leakage on FA, and type C PCV had polyps with branching vascular networks and significant leakage on FA. The logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA), central subfield retinal thicknesses, and polyp closure rates were compared between the three PCV subtypes at baseline and at each of the subsequent study visits until 6 months (the primary study endpoint).

Statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). χ² tests were used to compare the proportions of various groups, and unpaired t-tests were used to compare means, with P < 0.05 considered statistically significant. To account for the potential impact of treatment on the outcomes, ANCOVA was performed, using PCV subtype, baseline visual acuity, PCV lesion size, and treatment as variables.

RESULTS

Of the 61 patients, 1 patient subsequently dropped out of the study. Among the 60 patients who completed the study, 41 were males (68.3%) and 19 were females (31.7%), with a mean age of 65.3 years (range, 46 to 84 years; SD, ±9.2 years). Among these, 54 patients (90%) had angiograms that were gradable for the PCV subtype, whereas the remaining 6 had ungradable vascular channels and hence could not be reliably subtyped at baseline. Of the 54 patients, 8 (14.8%) had type A PCV, 27 (50%) had type B, and 19 (35.2%) had type C. There were no significant differences in mean age, sex, or laterality among the three subtypes (Table 1).

There was good intergrader agreement for the PCV subtypes, with a κ coefficient of 0.934.

Visual Outcomes

The variation of mean BCVA among the PCV subtypes is shown in Figure 4A. Baseline BCVA differed significantly among the three PCV subtypes (67.1 letters versus 58.7 versus 43.5 among types A, B, and C, respectively; ANOVA, P < 0.001). Performing post hoc analysis with Bonferroni correction, BCVA among patients with Type C PCV was worse compared with type A (P = 0.001) and type B (P = 0.002), but there was no significant difference in baseline VA between types A and B.

At 6 months, BCVA was highest among patients with type A compared with types B and C (80.1 letters versus 67.2 versus 50.4, respectively; P < 0.001), with the differences among the three subtypes all statistically significant (type A versus B, P = 0.038; type A versus C, P < 0.001; type B versus C, P < 0.001).

The proportion of patients with good BCVA (defined as BCVA equivalent to 20/40 or better) is shown in Figure 4B. At baseline, 50% of patients with type A PCV had good VA compared with 29.6% for type B and 0% for type C (P = 0.007). At 6 months, this increased to 100% vs. 51.9% vs. 10.5% (P < 0.001).

The change in BCVA from baseline for each subtype is illustrated in Figure 5. At 6 months, patients with type A PCV had the largest gain in BCVA (13.0 letters) compared with type
FIGURE 1. Color fundus photographs and angiographic images of PCV subtypes. (A) Color fundus photograph, illustrating orange nodules and pigment epithelium detachments (PEDs). (B) ICGA showing the polyps and interconnecting channels (type A PCV). (C) Early FA. (D) Late FA illustrating pooling but not leakage. (E) Color fundus photograph illustrating large orange nodules and subretinal hemorrhage. (F) ICGA illustrating the polyps and branching vascular network. (G) Early FA illustrating pooling within the polyp and PED. (H) Late FA, illustrating pooling but no leakage. (I) Color fundus photograph illustrating polyps with surrounding exudates. (J) ICGA illustrating the polyps and branching vascular network. (K) Early FA illustrating leakage supero-temporal to the fovea. (L) Late FA illustrating increased leakage from the region of the PCV lesion.
FIGURE 2. Interconnecting channels. (A) ICGA showing early filling of the interconnecting channels. Several fine vessels are seen supplying the polyp superiorly. (B) ICGA showing complete filling of the interconnecting channels. A network of fine vessels is seen in the region between the polyps.

FIGURE 3. Branching vascular network. (A) Early filling of the ICGA showing flow originating from a feeder vessel and radiating in opposite directions. Early filling of the polyps is observed at the distal edges of these vessels. (B) Additional filling of the branching vascular network and cluster of polyps. (C) Complete filling of the branching vascular network and polyps.

TABLE 1. Baseline Characteristics of PCV Subtypes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type A (n = 8)</th>
<th>Type B (n = 27)</th>
<th>Type C (n = 19)</th>
<th>All Cases (n = 54)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (mean ± SD)</td>
<td>65.3 (9.5)</td>
<td>65.5 (10.8)</td>
<td>66.4 (7.5)</td>
<td>65.8 (9.4)</td>
<td>0.941</td>
</tr>
<tr>
<td>Sex (number/%)</td>
<td>0.646</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (75.0)</td>
<td>18 (66.7)</td>
<td>15 (78.9)</td>
<td>39 (72.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (25.0)</td>
<td>9 (33.3)</td>
<td>4 (21.1)</td>
<td>15 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Study eye</td>
<td>0.772</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>5 (62.5)</td>
<td>13 (48.1)</td>
<td>10 (52.6)</td>
<td>28 (51.9)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3 (37.5)</td>
<td>14 (51.9)</td>
<td>9 (47.4)</td>
<td>26 (48.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline visual acuity (letters) (mean ± SD)</td>
<td>67.1 (9.6)</td>
<td>58.7 (13.9)</td>
<td>43.5 (15.9)</td>
<td>54.6 (16.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRT (μm) (mean ± SD)</td>
<td>341.6 (137.4)</td>
<td>258.6 (77.7)</td>
<td>333.2 (101.2)</td>
<td>297.2 (102.3)</td>
<td>0.018</td>
</tr>
<tr>
<td>Baseline total lesion area (mm²) (mean ± SD)</td>
<td>1.96 (1.7)</td>
<td>3.81 (3.1)</td>
<td>4.70 (5.1)</td>
<td>3.85 (3.8)</td>
<td>0.239</td>
</tr>
<tr>
<td>Baseline polyp area (mm²) (mean ± SD)</td>
<td>0.23 (0.1)</td>
<td>0.28 (0.4)</td>
<td>0.22 (0.1)</td>
<td>0.25 (0.3)</td>
<td>0.739</td>
</tr>
<tr>
<td>Treatment group</td>
<td>0.107</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDT and ranibizumab</td>
<td>5 (62.5)</td>
<td>8 (29.6)</td>
<td>3 (15.8)</td>
<td>16 (29.6)</td>
<td></td>
</tr>
<tr>
<td>Ranibizumab and sham</td>
<td>2 (25.0)</td>
<td>8 (29.6)</td>
<td>10 (52.6)</td>
<td>20 (37.0)</td>
<td></td>
</tr>
<tr>
<td>PDT and sham</td>
<td>1 (12.5)</td>
<td>11 (40.7)</td>
<td>6 (31.6)</td>
<td>18 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>
B (8.5 letters) and type C (6.9 letters), although this difference was not statistically significant ($P = 0.449$).

The proportion of patients who maintained or gained vision relative to baseline was reviewed (Table 2). At 6 months, 87.5% of patients with type A PCV gained at least five letters of vision, compared with 55.6% for type B and 47.4% for type C ($P = 0.33$). The frequency of gain of $\geq 15$ letters was 25.0% for type A, 25.9% for type B, and 21.1% for type C.

When the patients in this cohort were subdivided by treatment group, and the visual outcomes of each treatment group were analyzed according to PCV subtypes, similar patterns were observed, with type A PCV having the best visual outcomes, followed by type B and then type C.

To account for the possible interactions of PCV subtype with baseline BCVA, baseline lesion area, and treatment type, ANCOVA was performed with these factors included in the model. PCV subtype ($P = 0.008$) and baseline VA ($P < 0.001$) were significant factors affecting final BCVA, whereas treatment type was not significant.

**Figure 4.** (A) Mean BCVA of PCV subtypes. (B) Proportion of PCV patients with BCVA 20/40 or better.
FIGURE 5. (A) Gain in BCVA among the subtypes of PCV. (B) Change in mean CRT among the subtypes of PCV.

<table>
<thead>
<tr>
<th></th>
<th>Type A PCV ( n = 8 )</th>
<th>Type B PCV ( n = 27 )</th>
<th>Type C PCV ( n = 19 )</th>
<th>All Cases ( n = 54 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients who gained at least one line of vision</td>
<td>87.5% (7)</td>
<td>55.6% (15)</td>
<td>47.4% (9)</td>
<td>57.4% (31)</td>
<td>0.328</td>
</tr>
<tr>
<td>Proportion of patients who gained at least two lines of vision</td>
<td>50% (4)</td>
<td>33.3% (9)</td>
<td>47.4% (9)</td>
<td>40.7% (22)</td>
<td>0.494</td>
</tr>
<tr>
<td>Proportion of patients who gained at least three lines of vision</td>
<td>25% (2)</td>
<td>25.9% (7)</td>
<td>21.1% (4)</td>
<td>24.1% (13)</td>
<td>0.928</td>
</tr>
</tbody>
</table>
Outcomes of Polypoidal Choroidal Vasculopathy Subtypes

Central Retinal Thickness
At baseline, central subfield retinal thickness (CRT) showed an overall significant difference between PCV subtypes (Table 1). Following initiation of treatment, CRT improved in all PCV subtypes (Fig. 5). At 6 months, the CRT was thickest for type C PCV followed by type B and type A (201.7 vs. 188.7 vs. 183.8 μm, P = 0.66).

Polyp Closure Rate and Change in Lesion Area
The overall rate of polyp closure at 6 months did not differ among the three PCV subtypes (62.5% vs. 51.9% vs. 63.2% for types A, B, and C, respectively; P = 0.71). At baseline, the total lesion area was smaller for type A compared with types B and C, although the difference was not statistically significant. In contrast, the polyp area at baseline were similar for all three PCV subtypes (P = 0.74).

At 6 months, the polyp area had reduced to 0.019 mm² for type A PCV, compared with 0.050 mm² for type B and 0.045 mm² for type C, with no significant differences in polyp area among the three subtypes (P = 0.68).

DISCUSSION
In this study, we evaluated the use of PCV subtypes as a novel imaging biomarker among East Asian patients from a multicenter randomized, controlled trial and found that visual outcomes differed significantly among the three subtypes. This demonstrates the relevance and applicability of the classification system to patients from various Asian populations.

An earlier paper evaluated the visual outcomes of PCV subtypes among consecutive patients from a single tertiary center. In that study, patients with type A PCV had the best visual outcomes at 5 years, with 80% having VA of 20/40 or better at 5 years. In contrast, the proportion of patients with good VA among type B PCV was 66.7% and 7.7% with type C. In this current study, the absolute VA was best for patients with type A PCV, intermediate in type B, and worst for type C throughout the study period (Fig. 4). This demonstrates that the distinction in clinical outcomes between the PCV subtypes is observed in the initial months following the start of treatment. In addition, the proportions of patients with VA 20/40 or better at 6 months is comparable to the 1-year outcome described in our earlier paper.

Analyzing the change in VA from baseline, patients with type A PCV had the largest gain in VA (13.0 letters) compared with 8.5 letters for type B and 6.9 letters for type C.

Among patients with type A PCV, 87.5% gained at least five letters of VA, compared with 55.6% and 47.4% for types B and C, respectively. In contrast, when analyzing the proportion who gained ≥15 letters, the rate was higher for type B PCV compared with type A. This may be due to a “ceiling effect,” which has previously been described. Because patients with type A PCV started with better baseline VA compared with both other subtypes, there was less potential for a large gain in VA. However, as noted above, the absolute VA was better for type A PCV patients at all study visits.

Although it may be argued that the variations in visual outcomes among the three PCV subtypes are influenced by the difference in VA observed at baseline, we believe this is precisely the point of the classification. The results from this paper, together with those of our earlier study, illustrate that there are subtypes of PCV who have better VA even on initial presentation, and this good VA is seen in the early months of treatment and maintained even up to 5 years. In both studies, all patients were enrolled when they first presented with visual symptoms, suggesting that the differences in visual outcomes may be part of the natural history of these subtypes.

The reason why type A PCV had better outcomes compared with type B appears to be related to the type of vascular network supplying the PCV lesion. It is possible that the interconnecting channels seen in type A represent a milder form of the disease, compared with the branching vascular networks. An earlier study comparing different types of PCV reported variations in genetic markers among the two groups. Genetic variations may be a possible explanation for differences in visual outcomes, although this has not been explored in this study.

To account for the possible interactions between PCV subtype, baseline VA, treatment group, and baseline lesion area and their effect on the final VA, analysis using ANCOVA was performed. The results showed that both PCV subtype and baseline VA were significant factors affecting the final VA. However, treatment type did not affect the visual outcome.

Earlier studies have described various methods of classifying PCV, but did not compare the clinical outcomes among the various groups. An earlier classification by Yuzawa et al. identified two groups of PCV; “polypoidal CNV” was diagnosed based on the presence of both feeder and draining vessels, which were visible on ICGA. In contrast, in “typical PCV,” neither feeder nor draining vessels were detectable. Although there are similarities between the features described by Yuzawa et al. and the interconnecting channels and branching vascular network described in this paper, the differentiation between the two types of vascular channels in our series was based primarily on an assessment of the pattern and direction of flow within the channels on dynamic ICGA and not based on the presence or absence of feeding and draining vessels.

The relevance of our classification system may be seen in the differentiation of clinical outcomes by taking into account both the type of abnormal vascular channels supplying the polyps and the presence or absence of leakage on FA. Although types B and C may be similar to the “polypoidal CNV” previously described, we showed that it is important to further distinguish these two subtypes based on the presence of FA leakage in view of the distinct differences in visual outcomes. Differentiating between types A and B is also important because there were significant differences observed between the two subgroups in this study, as well as in an earlier study.

The strengths of this study are the inclusion of patients from a randomized, controlled trial, who had standardized monthly monitoring of VA and OCT. This allows the review of early changes in VA and retinal thickness among PCV subtypes, which has not previously been described. In addition, standardized imaging and grading protocols were used, and patients were managed using a standardized treatment regimen, reducing the chance that variability in the treatment given may have influenced the visual outcomes. Both the study investigators and patients were unaware of the PCV subtype, as this post hoc analysis was performed only after patients had completed the study. Hence, the investigators could not have been influenced by prior knowledge of the PCV subtypes or the likely prognosis. Even though a review of the outcomes of PCV subtypes within each treatment group generally showed a similar trend in VA outcomes among the PCV subtypes, subdividing the patients by both PCV subtype and treatment group resulted in small numbers. This was addressed by the use of ANCOVA, and our analysis showed that treatment group did not influence final visual outcome.

This study is not without limitations. A relatively small number of patients were included, and the duration of follow-up was short (6 months). However, we previously showed that the trends in VA were observed up to 5 years. In addition, the distribution of the patients with different PCV subtypes was...
not equal in all three treatment arms. In future, prospective studies of the response of each PCV subtype to different treatments over longer treatment durations will be required to further validate this classification.

In summary, our results support the existence of at least three distinct subtypes of PCV that may influence the treatment response and final visual outcome. The PCV subtypes also reflect the natural behavior of the disease before any therapy and the visual acuity that a patient with PCV may present with. PCV subtypes may be a useful imaging biomarker to prognosticate and classify patients with PCV.

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References


APPENDIX

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