AMERICAN ACADEMY OF OPHTHALMOLOGY®

Evolution of Polypoidal Lesions after Treatment of Polypoidal Choroidal Vasculopathy

Colin S. Tan, MMed (Ophth), FRCOphth,[1,2] *Louis W. Lim, MBBS, MMed (Ophth),*[1,2] *Philippe Margaron, PhD*[3]

Purpose: To evaluate the status and evolution of polypoidal lesions during the course of treatment of patients with symptomatic macular polypoidal choroidal vasculopathy (PCV).

Design: Comparative cohort study of randomly selected patients from a multicenter, randomized controlled clinical trial.

Participants: Thirty randomly selected patients from the EVEREST II study who were treated with combination ranibizumab and verteporfin photodynamic therapy (n = 15) or ranibizumab monotherapy (n = 15).

Methods: All patients were randomized at baseline and treated with a standardized treatment protocol. Indocyanine green angiography (ICGA) images were graded at the central reading center at baseline and months 3, 6, 12, and 24. Polypoidal lesions present at baseline were overlaid on ICGA images at subsequent visits to determine if these remained perfused or had regressed completely. New polypoidal lesions occurring at subsequent visits were similarly tracked to detail the evolution of each polypoidal lesion.

Main Outcome Measures: Complete polypoidal lesion regression over time.

Results: Complete polypoidal lesion regression was higher in the combination therapy group compared with the monotherapy group at all visits (month 12, 12 of 15 patients [80%] vs. 5 of 14 patients [35.7%]; $P = 0.016$). Persistence of baseline polypoidal lesions was lower in the combination therapy group: 1 of 15 patients (6.7%) versus 7 of 14 patients (50%) in the monotherapy group at month 12. Recurrences of polypoidal lesions that had regressed completely at an earlier time point were uncommon: 0% in the combination therapy group and 1 patient each at months 6 and 12 in the monotherapy group. Fewer new polypoidal lesions (arising after the baseline visit) were found in the combination therapy group at all visits (combination therapy: 2 of 15 [13.3%] vs. monotherapy: 4 of 14 eyes [28.6%] at month 12). Total polypoidal lesion area was significantly smaller in the combination therapy group compared with the monotherapy group throughout the study (0.013 mm^2 vs. 0.110 mm^2; $P < 0.01$ at month 12).

Conclusions: Combination therapy was associated with higher rates of complete polypoidal lesion regression and fewer persistent polypoidal lesions compared with monotherapy. Closed polypoidal lesions rarely reopened, regardless of the treatment. *Ophthalmology Science 2022;2:100082* © *2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Polypoidal choroidal vasculopathy (PCV) is an important disease that shares features with neovascular age-related macular degeneration. Polypoidal choroidal vasculopathy is differentiated from typical age-related macular degeneration by the presence of polypoidal lesions, which are believed to be aneurysmal dilatations of the abnormal neovascularization.[1] These lesions are best seen on indocyanine green angiography (ICGA),[2] where they have a nodular appearance on stereoscopic imaging.[3] The prevalence of PCV varies among different populations and is reported to be higher in Asians,[4,5] although recent studies have suggested that the prevalence of PCV among Western populations may be higher than previously believed.[6,7]

The management options for PCV include combination therapy with verteporfin photodynamic therapy (PDT) and intravitreal anti−vascular endothelial growth factor (VEGF) agents, or monotherapy with anti-VEGF agents.[8−11] The EVEREST II study[8,11] reported that patients treated with combination PDT and intravitreal ranibizumab experienced superior gains in best-corrected visual acuity and complete polypoidal lesion regression, as well as a larger decrease in central subfield retinal thickness assessed using spectral-domain OCT, compared with the group treated with intravitreal ranibizumab alone.

Although most clinical trials for retinal diseases often report outcomes in terms of best-corrected visual acuity, central subfield retinal thickness, and disease activity assessed using OCT, another important clinical outcome measure for PCV is the rate of complete polypoidal lesion regression.[12−14] It is believed that polypoidal lesion regression is important because polypoidal lesions that remain perfused are a potential source of disease activity and subsequently may demonstrate large subretinal hemorrhages, with resultant severe loss of vision.[15−19] The

https://doi.org/10.1016/j.xops.2021.100082
ISSN 2666-9145/21

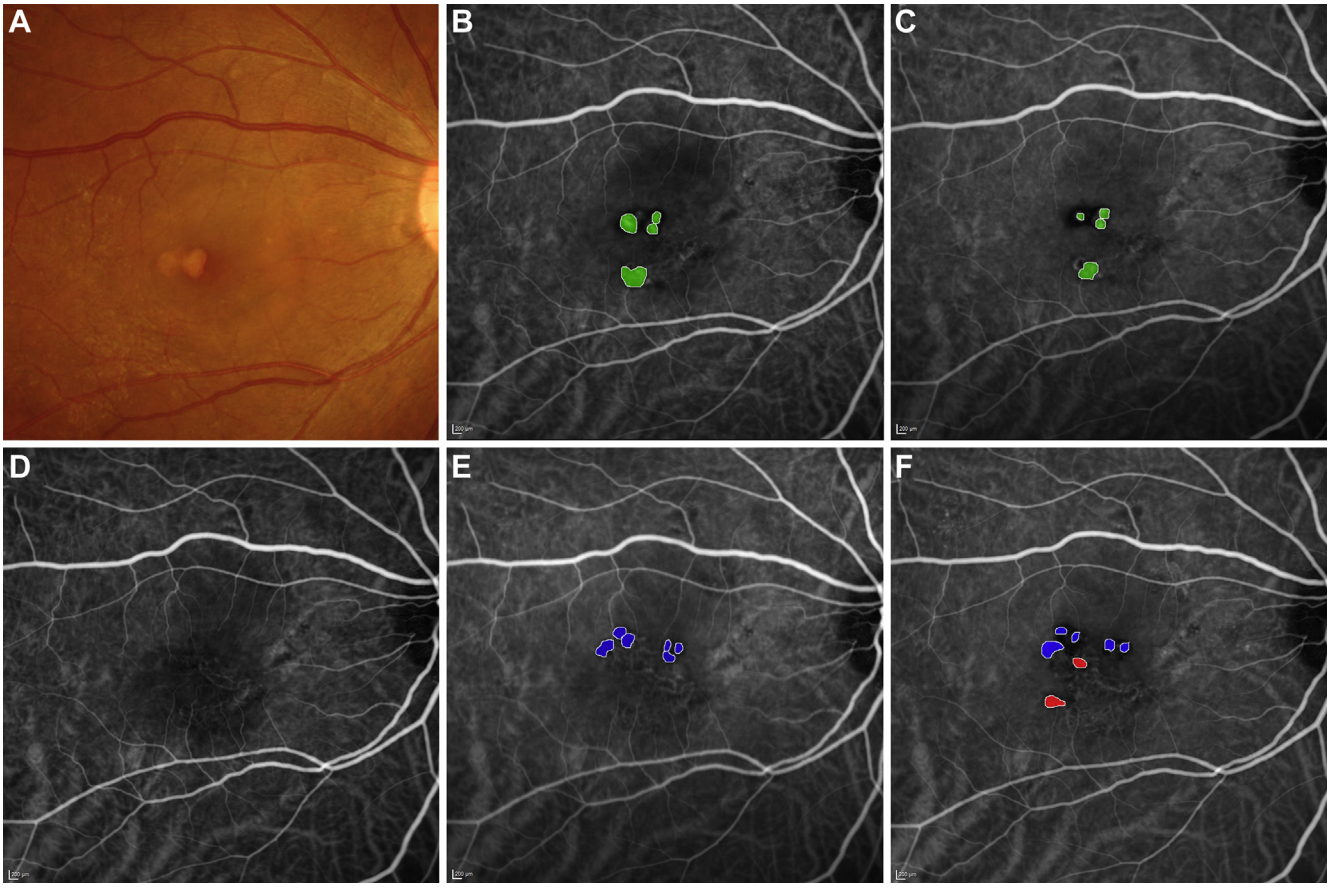

Figure 1. **A**, Color fundus photograph illustrating orange subretinal nodules and subretinal fluid. **B**, Indocyanine green angiogram (ICGA) obtained at baseline illustrating 3 polypoidal lesions (green). **C**, ICGA obtained at month 3 illustrating persistence of the 3 polypoidal lesions, although these have reduced in size. **D**, ICGA obtained at month 6 illustrating complete regression of all polypoidal lesions. **E**, ICGA obtained at month 12 highlighting the occurrence of 6 new polypoidal lesions (blue) that occur at a distinct location compared with the baseline polypoidal lesions. **F**, ICGA obtained at month 24 illustrating that 5 of the 6 new polypoidal lesions from month 12 are persistent, with 1 completely regressed. In addition, 2 new polypoidal lesions (red) have developed at this time.

EVEREST II study reported that rate of complete polypoidal lesion regression in the combination therapy group was almost double that of the monotherapy group at month 12 (69.3% vs. 37.4%; $P < 0.001$).[8]

Among articles that describe polypoidal lesion regression and changes in polypoidal lesion area, the results are typically reported in a dichotomous fashion (for example, polypoidal lesion completely regressed, closed vs. present) or as a mean polypoidal lesion area in each treatment group.[8] A key knowledge gap is how the individual polypoidal lesions evolve and whether the polypoidal lesions change in size, number, or both over the course of treatment. It is also unknown what proportion of polypoidal lesions detected during the course of follow-up are the result of persistence of the original polypoidal lesions present at baseline, the reopening of closed polypoidal lesions, and whether new polypoidal lesions have arisen over time. This knowledge may provide important insights into disease progression and response to various forms of treatment. The objective of this study was to evaluate the status and progression of individual polypoidal lesions at different time points among a cohort of patients with symptomatic macular PCV from the EVEREST II study.

Methods

This was a post hoc analysis of 30 randomly selected patients, 15 from each of the 2 treatment arms, from the EVEREST II study (ClinicalTrials.gov identifier, NCT01846273), which was a prospective, multicenter, randomized clinical trial of patients with symptomatic macular PCV. The detailed design and results of the study were previously reported.[8] In brief, 322 patients with active macular PCV were equally randomized to receive combination therapy of verteporfin PDT and intravitreal ranibizumab (the combination therapy group) or intravitreal ranibizumab with sham PDT (the monotherapy group).

All patients underwent multimodal imaging using standardized imaging protocols at 5 mandatory time points: baseline and months 3, 6, 12, and 24. Fluorescein angiography (FA) and ICGA were performed using the Heidelberg Spectralis device (Heidelberg Engineering). Dynamic FA and ICGA were performed for the first 30 seconds, followed by stereo pair images of the study eye at 1, 3, and 5 minutes (FA and ICGA) as well as at 10 and 20 minutes for FA.

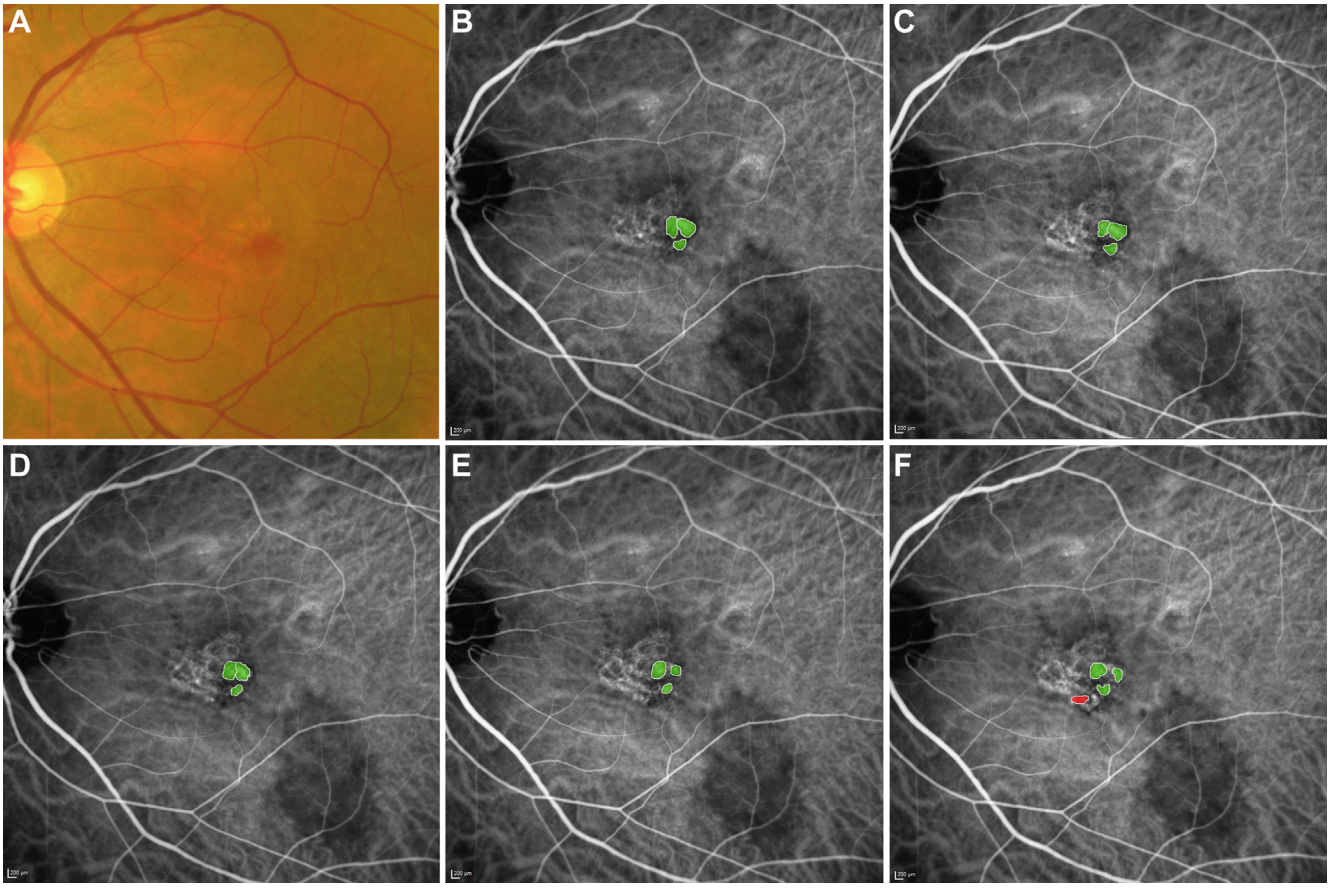

Figure 2. A, Color fundus photograph. **B**, Indocyanine green angiogram (ICGA) obtained at baseline, illustrating 3 polypoidal lesions (green). **C**–**F**, ICGAs obtained months 3, 6, 12, and 24, respectively, showing these remaining patent. At month 24 (**F**), a new polypoidal lesion (red) has arisen at a distinct location.

Image Grading

All images obtained at the 5 mandatory time points were graded by certified graders (C.T.S. and L.W.L.) from the central reading center (CRC; Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore, Republic of Singapore). The diagnosis of PCV was confirmed using a standardized protocol,[3,8,20,21] which required the presence of early focal hyperfluorescence on ICGA occurring within the first 5 minutes, together with at least 1 of the following criteria: (1) nodular appearance of the hyperfluorescent lesion on stereoscopic examination, (2) hypofluorescent halo around the nodule, (3) presence of a branching vascular network, (4) pulsation of the nodule on dynamic ICGA, (5) orange-red subretinal nodules on color fundus photography, or (6) presence of submacular hemorrhage of 4 disc areas or more.

Indocyanine green angiography images at baseline and follow-up visits were graded for the presence of polypoidal lesions. Each polypoidal lesion that was identified using the above criteria was mapped out using the Heidelberg Eye Explorer version 1.7.1.0 (Heidelberg Engineering). The area of each polypoidal lesion was measured using the measurement tools of the Heidelberg Eye Explorer, as previously described.[3]

Post Hoc Review of Indocyanine Green Angiography

In a post hoc review by graders from the CRC, ICGA images from the 5 time points were evaluated in sequence, with reference made to the lesions detected at baseline. The CRC graders remained masked to the treatment arm and to the clinical outcomes of all the patients evaluated. All ICGA images were overlaid with Photoshop version 19.1.6 (Adobe, Inc), using the major retinal blood vessels and the visible portion of the optic disc as landmarks to ensure alignment. Before evaluating the ICGA images, graders confirmed that the major vessels from successive images were aligned correctly. The transparency of the layers then was adjusted to allow comparisons between visits. This process allowed graders to precisely determine whether a polypoidal lesion detected at subsequent visits coincided in location with a lesion originally present at baseline or whether it was occurring at a different location (Fig 1).

Each polypoidal lesion identified at baseline was tracked at subsequent visits to determine its evolution (Fig 2). Several predefined terms were used to describe each polypoidal lesion. For every polypoidal lesion detected at baseline, its status at each subsequent visit was classified as persistent when evidence was found on ICGA of a lesion at the same location that met the diagnostic criteria for polypoidal lesions stated above. It was defined as completely regressed when no evidence of a

Table 1. Evaluation of Complete Polypoidal Lesion Regression

Time Point	Month 3	Month 6	Month 12	Month 24
Evaluation by eye				
Combination therapy				
Polypoidal lesion closure				
From baseline	14/15 (93.3%)	14/15 (93.3%)	14/15 (93.3%)	14/15 (93.3%)
From month 3	—	0	0	0
From month 6	—	—	1/1 (100%)	0
From month 12	—	—		1/2 (50%)
Monotherapy				
Polypoidal lesion closure				
From baseline	2/15 (13.3%)	5/15 (33.3%)	7/14 (50%)	7/13 (53.9%)
From month 3	—	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)
From month 6	—	—	3/4 (75%)	4/4 (100%)
From month 12	—	—	—	2/4 (50%)
Evaluation of individual polyp regression				
Combination therapy				
Polypoidal lesion closure				
From baseline	48/49 (97.96%)	48/49 (97.96%)	48/49 (97.96%)	48/49 (97.96%)
From month 3	—	0	0	0
From month 6	—	—	3/3 (100%)	3/3 (100%)
From month 12	—	—	—	1/1 (100%)
Monotherapy				
Polypoidal lesion closure				
From baseline	17/39 (43.6%)	23/39 (59.0%)	23/33 (69.7%)*	28/37 (75.6%)†
From month 3	—	2/4 (50%)	0/2 (0%)*	2/4 (50%)†
From month 6	—	—	2/3 (66.7%)*	4/4 (100%)†
From month 12	—	—	—	2/8 (25%)†

— = not applicable.
*One patient lost to follow-up at month 12.
†Two patients lost to follow-up at month 24.

polypoidal lesion was detected at the location of the original polypoidal lesion on ICGA. A recurrent polypoidal lesion was defined as a polypoidal lesion occurring at the same precise location as an earlier polypoidal lesion, where complete regression had been noted on ICGA on at least 1 prior visit. New polypoidal lesions were defined as polypoidal lesions arising at a location where no polypoidal lesion had been detected at earlier visits.

Statistical analysis was descriptive in nature and was performed using IBM SPSS software version 23 (SPSS, Inc). Chi-square tests were used to compare categorical variables, whereas *t* tests were used to compare continuous variables. Patient consent and institutional review board approval were obtained at the respective study sites. The described research adhered to the tenets of the Declaration of Helsinki.

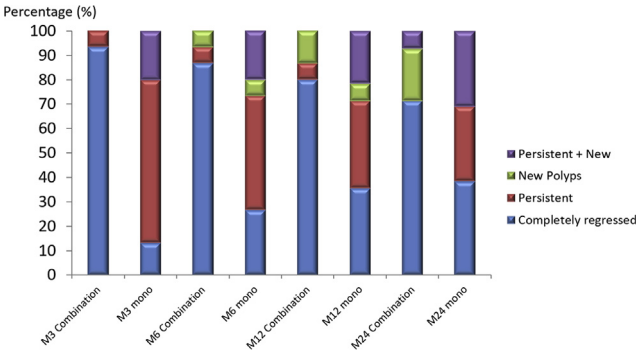

Figure 3. Bar graph showing the proportions of eyes with persistent, new, or recurrent polypoidal lesions at each time point. M = month.

Results

Of the 30 randomly selected patients, 15 received combination therapy and 15 received ranibizumab monotherapy. At baseline, both groups were comparable in terms of polypoidal lesion characteristics. The median number of polypoidal lesions in the combination group was 3 (mean, 3.3 lesions; range, 1−8 lesions), compared with 3 lesions (mean, 2.6 lesions; range, 1−6 lesions) in the monotherapy group ($P = 0.512$). The median total polypoidal lesion area per eye was 0.27 mm^2 (mean, 0.42 mm^2; range, 0.04−2.12 mm^2) in the combination group compared with 0.29 mm^2 (mean, 0.46 mm^2; range, 0.05−1.39 mm^2) in the monotherapy group ($P = 0.595$). The evolution of polypoidal lesions was evaluated at the level of each eye and also by assessing each polypoidal lesion individually.

Evaluation of Polypoidal Lesion Evolution for Each Eye

Complete Polypoidal Lesion Regression. The rate of complete polypoidal lesion regression was higher in the combination therapy group compared with the monotherapy group at all time points (Table 1). In the combination therapy group, 14 of 15 eyes (93.3%) showed complete

Table 2. Evolution of Polypoidal Lesion by Eyes

	Month 3	Month 6	Month 12	Month 24
Combination therapy				
Persistent polypoidal lesions				
From baseline	1/15 (6.7%)	1/15 (6.7%)	1/15 (6.7%)	1/14 (6.7%)
From month 3	—	0	0	0
From month 6	—	—	0/1 (0%)	0
From month 12	—	—	—	0/1 (0%)
Total	1/15 (6.7%)	1/15 (6.7%)	1/15 (6.7%)	1/14 (7.14%)
New polypoidal lesions	0	1/15 (6.7%)	2/15 (12.4%)	5/14 (35.7%)*
Recurrent polypoidal lesions				
From baseline	—	0	0	0
From month 3	—	0	0	0
From month 6	—	—	0	0
From month 12	—	—	—	0
Total	—	0	0	0
Total eyes with polypoidal lesions	1/15 (6.7%)	2/15 (13.4%)	3/15 (20%)	4/14 (28.6%)*
Monotherapy				
Persistent polypoidal lesions				
From baseline	13/15 (86.7%)	10/15 (66.7%)	7/14 (50%)	6/13 (46.1%)
From month 3	—	2/3 (66.7%)	2/3 (66.7%)	2/3 (66.7%)
From month 6	—	—	1/4 (25%)	0/4 (0%)
From month 12	—	—	—	2/4 (50%)
Total	13/15 (86.7%)	10/15 (66.7%)	9/14 (64.3%)	8/14 (57.1%)
New polypoidal lesions	3/15 (20%)	4/15 (26.7%)	4/14 (28.6%)†	4/13 (30.7%)‡
Recurrent polypoidal lesions				
From baseline	—	1/15 (6.7%)	0	0
From month 3	—	0	0	0
From month 6	—	—	0	1/13 (7.7%)
From month 12	—	—	—	0
Total	—	1/15 (6.7%)	0	1/13 (7.7%)
Eyes with polypoidal lesions	13/15 (86.7%)	11/15 (73.4%)	9/14(64.3%)	8/13 (61.5%)

— = not applicable.
*One patient lost to follow-up at month 24.
†One patient lost to follow-up at month 12.
‡Two patients lost to follow-up at month 24.

polypoidal lesion regression at month 3. The proportion with complete polypoidal lesion regression remained high at month 6 (13 of 15 eyes [86.7%]) and month 12 (12 of 15 eyes [80.0%]), before decreasing slightly at month 24 (9 of 14 eyes [64.3%]; Fig 3). In contrast, the proportion of eyes with complete polypoidal lesion regression was significantly lower among the monotherapy group at month 3 (2 of 15 eyes [13.3%]; $P < 0.0001$), month 6 (4 of 15 eyes [26.7%]; $P = 0.001$), and month 12 (5 of 14 eyes [35.7%]; $P = 0.016$). At month 24, the proportion of eyes in the monotherapy group with complete polypoidal lesion regression was 38.5% (5 of 13 eyes; $P = 0.180$).

Persistence of Polypoidal Lesions Present at Baseline. When evaluating persistence of baseline polypoidal lesions, only 1 eye (6.7%) in the combination therapy group showed a single persistent polypoidal lesion throughout the study. In contrast, in the monotherapy group, the proportion of eyes with persistent baseline polypoidal lesions was 86.7% at month 3, 66.7% at month 6, 50% at month 12, and 46.2% at month 24 (Table 2).

Occurrence of New Polypoidal Lesions. New polypoidal lesions occurred in the combination group at month 6 (1 eye [6.7%]), month 12 (2 eyes [13.3%]), and month 24 (5 eyes [33.3%]; Table 2). All the new polypoidal lesions that developed at months 6 and 12 were treated successfully and had regressed completely by the subsequent standardized ICGA evaluation, and none of them persisted. In contrast, the rate of new polypoidal lesion occurrence was higher in the monotherapy group. New polypoidal lesions occurred in 3 of 15 eyes (20%) at month 3, 4 of 15 eyes (26.7%) at month 6, 4 of 14 eyes (28.6%) at month 12, and 4 of 13 eyes (30.8%) at month 24. Of the new polypoidal lesions that occurred, some polypoidal lesions persisted until at least the subsequent time point.

Recurrence of Polypoidal Lesions. Recurrence of polypoidal lesions that had been demonstrated to have fully regressed was relatively uncommon in both groups (Table 2). In the combination group, none of the polypoidal lesions that had completely regressed subsequently recurred through month 24. This was true of both baseline polypoidal lesions and new polypoidal lesions that subsequently occurred, all of which were treated. In the monotherapy group, 1 eye each (6.7%) experienced a recurrence of baseline polypoidal lesions at months 6 and 24. In the eye with recurrence at month 6, 1 of 6 baseline polypoidal lesions (16.7%) recurred after closure at month 3, whereas

Table 3. Evolution of Polypoidal Lesion by Total Number of Polypoidal Lesions

	Month 3	Month 6	Month 12	Month 24
Combination therapy (no., proportion of polypoidal lesions)				
New polypoidal lesions	0	3	2	12
Persistent polypoidal lesions				
From baseline	1/49 (2.04%)	1/49 (2.04%)	1/49 (2.04%)	1/49 (2.04%)
From month 3	—	0	0	0
From month 6	—	—	0/3 (0%)	0/3 (0%)
From month 12	—	—	—	0/1 (0%)
Total	1	1	1	1
Recurrent polypoidal lesions				
From baseline	—	0	0	0
From month 3	—	0	0	0
From month 6	—	—	0	0
From month 12	—	—	—	0
Total	—	0	0	0
Total no. of polypoidal lesions detected	1	4	3	13
Monotherapy (proportion of polypoidal lesions)				
New polypoidal lesions	4	6	9	9
Persistent polypoidal lesions				
From baseline	22/39 (56.4%)	15/39 (38.4%)	10/33 (30.3%)	9/37 (24.3%)
From month 3	—	2/4 (50%)	2/4 (50%)	2/4 (50%)
From month 6	—	—	1/3 (33%)	0/4 (0%)
From month 12	—	—	—	6/8 (75%)
Total	22	17	13	17
Recurrent polypoidal lesions				
From baseline	—	1	0	0
From month 3	—	0	0	0
From month 6	—	—	0	1
From month 12	—	—	—	0
Total	—	1	0	1
Total no. of polypoidal lesions detected	26	24	22	27

— = not applicable.

for the eye with recurrence at month 24, the recurrence was from a single new polypoidal lesion that developed at month 6 and was closed at month 12.

Evaluation of Total Number of Polypoidal Lesions in Each Group

Tables 1 and 3 summarize the results based on total number of polypoidal lesions in all eyes at various time points.

Complete Polypoidal Lesion Regression. In the combination therapy group, 48 of 49 polypoidal lesions (97.6%) present at baseline had completely regressed by month 3, and none of these recurred throughout the 24-month follow-up. In contrast, among eyes in the monotherapy group, only 17 of 39 baseline polypoidal lesions (43.6%) completely regressed at month 3, and the proportion progressively increased to 59.0% (23 of 39) at month 6, 69.7% (23 of 33) at month 12, and 75.6% (28 of 37) at month 24 (Table 1).

Persistence of Polypoidal Lesions Present at Baseline. Only 1 polypoidal lesion (2.0%) in the combination group persisted through month 24 (Table 3). For the monotherapy group, the proportion of baseline polypoidal lesions that persisted at subsequent visits was 22 of 39 at month 3, 15 of 39 at month 6, 10 of 33 at month 12, and 9 of 37 at month 24. The proportion of persistent polypoidal lesions (whether from baseline or arising at a previous time point) as a percentage of the total number of detected polypoidal lesions was lower in the combination group compared with the monotherapy group: 25% versus 70.8% at month 6, 33.3% versus 59.1% at month 12, and 7.6% versus 63% at month 24.

Occurrence of New Polypoidal Lesions. Over 2 years, a total of 17 new polypoidal lesions were observed in the combination group, compared with 28 lesions in the monotherapy group. The total number of new polypoidal lesions arising was relatively lower from months 3 to 12 in the combination group compared with the monotherapy group in the first year (0 vs. 4 at month 3, 3 vs. 6 at month 6, and 2 vs. 9 at month 12). At month 24, the total number of new polyps arising since the month 12 visit was 12 in the combination group compared with 9 in the monotherapy group.

Recurrence of Polypoidal Lesions. As previously described, no recurrences took place in the combination group and only 2 polypoidal lesions recurred in the monotherapy group over the 24-month period.

Total Polypoidal Lesion Area

The total polypoidal lesion area per eye was significantly smaller among the combination group (range, 0.005−0.013 mm^2) compared with the monotherapy group (range, 0.110−0.376 mm^2) from months 3 through 12. This

difference was especially evident when evaluating the area of persistent baseline polypoidal lesions at subsequent visits. At month 24, the area of baseline polypoidal lesions remained small in the combination therapy group (0.05 mm^2), and most of the mean polypoidal lesion area was accounted for by new polypoidal lesions (0.097 mm^2; 96.9% of total mean polypoidal lesion area). In contrast, in the monotherapy group, the mean area of baseline polypoidal lesions was 0.091 mm^2 (58.7%), compared with 0.064 mm^2 (41.3%) for new polypoidal lesions.

Discussion

In this study, we evaluated the evolution of polypoidal lesions in PCV over 24 months and proposed standardized terminology to describe the precise nature of polypoidal lesions. An important and novel finding is that polypoidal lesions seen at a particular time point may consist of either persistent polypoidal lesions or new polypoidal lesions arising at different locations. In contrast, recurrence of polypoidal lesions at the same location is relatively uncommon after these polypoidal lesions have completely regressed, regardless of the treatment.

Important differences were observed in the composition of polypoidal lesions, depending on the treatment administered. Among patients receiving combination therapy of PDT and intravitreal ranibizumab, 48 of 49 polypoidal lesions present at baseline regressed by month 3 after the initial treatment with PDT and 3 intravitreal ranibizumab injections. None of these polypoidal lesions subsequently recurred within a 24-month period, illustrating that combination therapy achieves long-term regression of polypoidal lesions until at least month 24. With the exception of 1 persistent polypoidal lesion, all polypoidal lesions seen at subsequent visits were new polypoidal lesions, arising at distinct locations where polypoidal lesions were not previously seen. Photodynamic therapy is believed to produce selective vascular occlusion. Verteporfin preferentially accumulates in abnormal vascular endothelial cells[22] and, when irradiated with the PDT laser, results in the creation of cytotoxic free radicals and photothrombosis, which may account for the definitive polypoidal lesion occlusion.

The composition of polypoidal lesions in the monotherapy group was quite different. Some polypoidal lesions present at baseline persisted throughout the 24-month period despite monthly follow-up and active treatment with intravitreal ranibizumab when disease activity was present. Similarly, some of the new polypoidal lesions developing at subsequent time points also persisted, illustrating that treatment with ranibizumab monotherapy was less efficacious in terms of polypoidal lesion regression. As a result, eyes treated with monotherapy showed a combination of both baseline and new polypoidal lesions over the course of follow-up. Ranibizumab results in antiproliferative and antipermeability effects on patients with neovascular age-related macular degeneration,[23,24] and it is likely that the drug acts in the same manner for polypoidal lesions. It is interesting to note that the proportion of baseline polypoidal lesions that completely regressed increased progressively from months 3 to 24. After these lesions had completely regressed, recurrences were rare, at least until month 24. It is possible that ranibizumab monotherapy may require more time to achieve complete polypoidal lesion regression. It would be interesting to observe if newer anti-VEGF agents, which may potentially be more efficacious in achieving a fluid-free retina, may increase the rate of complete polypoidal lesion regression.

The relative proportion of persistent and new polypoidal lesions varies with treatment regimen, as well as the period of treatment. Earlier in the course of treatment, at the month 3 review, most polypoidal lesions present in both treatment groups consisted of persistent polypoidal lesions. Over time, however, the proportion of new polypoidal lesions increased as more baseline polypoidal lesions regressed. In the combination therapy group, new polypoidal lesions accounted for most polypoidal lesions present from month 6 and beyond. In contrast, in the monotherapy group, at months 12 and 24, the number of persistent and new polypoidal lesions were almost equal. The total area of polypoidal lesions also showed interesting differences that reflected the different distribution of polypoidal lesion types (persistent, new, or recurrent) between the 2 treatment arms. The mean area of polypoidal lesions was smaller among eyes in the combination therapy group at all time points. More importantly, more than 90% of the total polypoidal lesion area in the combination group was accounted for by new polypoidal lesions. In contrast, the percentage of total polypoidal lesion areas accounted for by persistent polypoidal lesions in the monotherapy group was larger.

An important observation is that in eyes receiving combination therapy, new polypoidal lesions arising at locations where polypoidal lesions were not previously detected on ICGA account for most polypoidal lesions detected at subsequent visits. This emphasizes the importance of definitive imaging investigations[3] to detect the precise locations of these new polypoidal lesions should treatment with PDT be considered. New polypoidal lesions occurred as early as month 3 in the monotherapy group, whereas they started to appear only from month 6 in the combination group. It is possible that this could be the result of the suppressive effect of the combination of PDT and ranibizumab on the PCV lesion, which may modify the vascular structures, delaying the onset of new polypoidal lesions. An evaluation of the growth of the PCV lesion showed that the branching vascular network reduced slightly in size at months 3 and 6 in the combination group, whereas it continued to grow despite active treatment in the monotherapy group.

Interestingly, recurrences of polypoidal lesions, defined as the presence of a polypoidal lesion at the same precise location as a polypoidal lesion that had previously completely regressed, were relatively rare. Only 2 of 30 eyes demonstrated recurrences over a 24-month period, and both were in the group receiving anti-VEGF monotherapy. It seems that as soon as a polypoidal lesion has regressed, either with combination therapy or anti-VEGF monotherapy, it is uncommon for it to recur.

Although earlier reports on PCV treatment often discuss changes in best-corrected visual acuity or central subfield

retinal thickness, not all describe the rates of polypoidal lesion complete regression. Importantly, even among studies reporting the presence of polypoidal lesions, they do not distinguish among persistent, new, or recurrent polypoidal lesions. It remains to be seen whether this distinction is clinically important. However, it is essential to first recognize that polypoidal lesions detected at subsequent visits may be of different types and to use accurate and consistent terminology to describe them before this evaluation can be performed.

We observed that the composition of polypoidal lesions varies with treatment regimen. This may yield interesting insights on the mechanisms of action of the various treatments on polypoidal lesions and may provide confirmation of their efficacy. It is also useful to counsel patients on the possible outcomes depending on treatment administered. The 12-month results of the EVEREST II study showed that eyes in the combination therapy arm demonstrated significantly higher rates of complete polypoidal lesion regression compared with the monotherapy arm (69.3% vs. 34.7%; $P < 0.001$).[8]

The strengths of the study are that all patients were selected randomly from a multicenter, randomized controlled clinical trial and underwent prospective, monthly follow-up. In this randomized cohort, we saw similar results in terms of complete polypoidal lesion regression in both treatment arms compared with the results of the main study cohort, which validates the selection of this sample. All patients were imaged using standardized imaging protocols and were managed according to a treatment protocol, depending on the randomization group. The diagnosis of PCV was confirmed by a CRC that is experienced in PCV clinical trials, and the review of the ICGA images in this study was performed by experienced graders. The status of each polypoidal lesion was carefully assessed by overlaying ICGA images with the baseline and earlier angiograms to precisely track each polypoidal lesion longitudinally.

A potential limitation is that standardized ocular imaging was performed and graded only at specific intervals, and it is possible that polypoidal lesions may have arisen, and possibly regressed, during the interval between imaging tests, especially in the 11 months between months 12 and 24. However, this reflects the clinical setting where ICGA is not frequently performed. Another potential limitation is the small number of patients studied. Despite this, polypoidal lesions that received different treatment methods still fared differently. Future studies studying the full EVEREST II set of patients will definitely be helpful.

In conclusion, this study proposed specific terminology to describe individual polypoidal lesions when evaluating PCV treatment. The composition of different types of polypoidal lesions in an eye varies depending on the treatment administered and during the course of the disease. This enhances our understanding of the evolution of PCV lesions and may be of clinical relevance.

Footnotes and Disclosures

Originally received: August 4, 2021.
Final revision: October 29, 2021.
Accepted: November 11, 2021.
Available online: November 17, 2021. Manuscript no. D-21-00141.

[1] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore, Republic of Singapore.

[2] Fundus Image Reading Centre, National Healthcare Group Eye Institute, Singapore, Republic of Singapore.

[3] Novartis, Basel, Switzerland.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): C.S.T.: Financial support — Novartis; Lecturer — Roche, Bayer

P.M.: Employee and Equity owner — Novartis Pharma AG, F. Hoffmann-La Roche AG

Presented as a poster at: American Academy of Ophthalmology Annual Meeting, October 2019, San Francisco, California.

HUMAN SUBJECTS: Human subjects were included in this study. Institutional Review Board/Ethics Committee approval was obtained at the respective study sites, and the described research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Tan, Lim, Margaron

Analysis and interpretation: Tan, Lim, Margaron

Data collection: Tan, Lim

Obtained funding: Study was performed as part of regular employment duties at National Healthcare Group Eye Institute (Tan CS, Lim LW) and Novartis (Margaron). No additional funding was provided.

Overall responsibility: Tan, Lim, Margaron

Abbreviations and Acronyms:
CRC = central reading center; **FA** = fluorescein angiography; **ICGA** = indocyanine green angiography; **PCV** = polypoidal choroidal vasculopathy; **PDT** = photodynamic therapy; **VEGF** = vascular endothelial growth factor.

Keywords:
Anti-VEGF therapy, Indocyanine green angiography, Photodynamic therapy, Polypoidal choroidal vasculopathy.

Correspondence:
Colin S. Tan, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Republic of Singapore. E-mail: Colintan_eye@yahoo.com.sg.

References

1. Dansingani KK, Gal-Or O, Sadda SR, et al. Understanding aneurysmal type 1 neovascularization (polypoidal choroidal vasculopathy): a lesson in the taxonomy of 'expanded spectra'—a review. *Clin Exp Ophthalmol*. 2018;46(2):189–200.

2. Ciardella AP, Donsoff IM, Yannuzzi LA. Polypoidal choroidal vasculopathy. *Ophthalmol Clin North Am*. 2002;15(4):537–554.
3. Tan CS, Ngo WK, Chen JP; EVEREST Study Group. EVEREST study report 2: imaging and grading protocol, and baseline characteristics of a randomised controlled trial of polypoidal choroidal vasculopathy. *Br J Ophthalmol*. 2015;99(5):624–628.
4. Wen F, Chen C, Wu D, Li H. Polypoidal choroidal vasculopathy in elderly Chinese patients. *Graefes Arch Clin Exp Ophthalmol*. 2004;242(8):625–629.
5. Maruko I, Iida T, Saito M, et al. Clinical characteristics of exudative age-related macular degeneration in Japanese patients. *Am J Ophthalmol*. 2007;144(1):15–22.e2.
6. Lorentzen TD, Subhi Y, Sørensen TL. Prevalence of polypoidal choroidal vasculopathy in white patients with exudative age-related macular degeneration: systematic review and meta-analysis. *Retina*. 2018;38(12):2363–2371.
7. Kokame GT, deCarlo TE, Kaneko KN, et al. Anti-vascular endothelial growth factor resistance in exudative macular degeneration and polypoidal choroidal vasculopathy. *Ophthalmol Retina*. 2019;3(9):744–752.
8. Koh A, Lai TYY, Takahashi K, et al. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2017;135(11):1206–1213.
9. Tan CS, Hariprasad SM, Lim LW. New paradigms in polypoidal choroidal vasculopathy management: the impact of recent multicenter, randomized clinical trials. *Ophthalmic Surg Lasers Imaging Retin*. 2018;49(1):4–10.
10. Lee WK, Iida T, Ogura Y, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(7):786–793.
11. Lim TH, Lai TYY, Takahashi K, et al. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the EVEREST II randomized clinical trial. *JAMA Ophthalmol*. 2020;138(9):935–942.
12. Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. Polypoidal choroidal vasculopathy: definition, pathogenesis, diagnosis, and management. *Ophthalmology*. 2018;125(5):708–724.
13. Cho JH, Park YJ, Cho SC, et al. Posttreatment polyp progression and risk of massive submacular hemorrhage in eyes with polypoidal choroidal vasculopathy. *Retina*. 2020;40(3):468–476.
14. Zhao XY, Zhang WF, Meng LH, et al. The polyp regression rate and treatment prognosis of different interventions for polypoidal choroidal vasculopathy: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. 2021;259(4):855–872.
15. Tan CSH, Wong HT, Lim BA, et al. Polypoidal choroidal vasculopathy causing massive suprachoroidal haemorrhage. *Eye*. 2007;21(1):132–133.
16. Uyama M, Wada M, Nagai Y, et al. Polypoidal choroidal vasculopathy: natural history. *Am J Ophthalmol*. 2002;133(5):639–648.
17. Jung JH, Lee JK, Lee JE, Oum BS. Results of vitrectomy for breakthrough vitreous hemorrhage associated with age-related macular degeneration and polypoidal choroidal vasculopathy. *Retina*. 2010;30(6):865–873.
18. Matsuo Y, Haruta M, Ishibashi Y, et al. Visual outcomes and prognostic factors of large submacular hemorrhages secondary to polypoidal choroidal vasculopathy. *Clin Ophthalmol*. 2021;15:3557–3562.
19. Cho SC, Cho JH, Park KH, et al. Massive submacular haemorrhage in polypoidal choroidal vasculopathy versus typical neovascular age-related macular degeneration. *Acta Ophthalmol*. 2020;99(5):706–714.
20. Tan CS, Ngo WK, Lim LW, Lim TH. A novel classification of the vascular patterns of polypoidal choroidal vasculopathy and its relation to clinical outcomes. *Br J Ophthalmol*. 2014;98(11):1528–1533.
21. Tan CS, Lim LW, Ngo WK, et al. EVEREST report 5: clinical outcomes and treatment response of polypoidal choroidal vasculopathy subtypes in a multicenter, randomized controlled trial. *Invest Ophthalmol Vis Sci*. 2018;59(2):889–896.
22. Miller JW, Walsh AW, Kramer M, et al. Photodynamic therapy of experimental choroidal neovascularization using lipoprotein-delivered benzoporphyrin. *Arch Ophthalmol*. 1995;113(6):810–818.
23. Heier JS, Antoszyk AN, Pavan PR, et al. Ranibizumab for treatment of neovascular age-related macular degeneration. A phase I/II multicenter, controlled, multidose study. *Ophthalmology*. 2006;113(4):633–642.
24. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419–1431.