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# Efficacy and Safety of Intravitreal Aflibercept Treat and Extend for Polypoidal Choroidal Vasculopathy in the ATLANTIC Study: A Randomized Clinical Trial

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**Keywords**
Aflibercept · Efficacy · Monotherapy · Photodynamic therapy · Polypoidal choroidal vasculopathy

**Abstract**
***Importance:*** Polypoidal choroidal vasculopathy (PCV) is far less common and studied in a Caucasian population than in an Asian population, and the optimal treatment approach remains to be confirmed. ***Methods:*** A 52-week, double-masked, sham-controlled, phase 4, investigator-initiated randomized clinical trial (RCT) in naive symptomatic Caucasian patients with PCV treated with aflibercept in a treat-and-extend regimen (T&E) (intravitreal aflibercept injection [IVAI] T&E). Patients were randomized at week 16 to receive IVAI T&E plus either sham photodynamic therapy (PDT) or standard fluence PDT with verteporfin. The main outcome measures were changes in best-corrected visual acuity (BCVA)

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from baseline to 52 weeks and polyp occlusion at week 52. Data are presented as median (interquartile range [IQR]) for BCVA, number of IVAI, and change in central retinal thickness (CRT). ***Results:*** Of the 50 patients included in the study, 48 patients completed the 52 weeks of follow-up. During this period, a significant median (IQR) BCVA gain of 6 [2–12] Early Treatment Diabetic Retinopathy Study letters was observed for all patients ($p < 0.001$), after 8 (7–9) injections, with a significant reduction of −93.0 [−154.0, −44.0] µm in central macular thickness ($p < 0.001$). Using indocyanine green angiography, a complete occlusion of polypoidal lesions was documented in 72% of the cases. Still, no significant difference was detected between the sham PDT and the aflibercept PDT arms, at week 52, for BCVA change (6.5 [2–11] vs. 5 [2–13] letters ($p = 0.98$)), number of IVAIs (8.5 [7–9] vs. 8 [7–9] ($p = 0.21$)), change in CRT (−143 [−184; −47] vs. −89 [−123; −41.5] µm [$p = 0.23$]), and rates of complete polyp occlusion: 77 versus 68% ($p = 0.53$) or presence of fluid: 68 versus 57% ($p = 0.56$). No serious ocular adverse events were registered in the 2 arms. ***Conclusions and Relevance:*** To our knowledge, this is the first RCT to compare aflibercept T&E monotherapy with aflibercept T&E plus verteporfin PDT in a Caucasian population with PCV. Aflibercept monotherapy in a T&E showed to be effective and safe with a significant median BCVA improvement of 6 letters and a complete occlusion of polypoidal lesions in near 3 quarters of the eyes, at 1 year. As only 22% of the eyes underwent PDT treatment, the benefit of combined treatment for PCV in Caucasian patients could not be definitively elucidated from this study. ***Trial Registration:*** The clinical trial was registered in ClinicalTrials.gov Identifier NCT02495181 and the European Union Drug Regulating Authorities Clinical Trials Database EudraCT No. 2015-001368-20.



## Introduction

Polypoidal choroidal vasculopathy (PCV) is a disease of the choroidal vasculature characterized by the presence of polyp-like dilations and an abnormal branching vascular network [1–4]. Although this clinical entity is far more common in Asian individuals (25–65%) with neovascular age-related macular degeneration [5, 6], it has been increasingly recognized among Caucasian populations, in which it has been described as representing between 8 and 31.9% of neovascular age-related macular degeneration cases [7–10]. Despite sharing some clinical features and risk factors, these populations can have different genetic backgrounds, epidemiologic characteristics, natural history, and treatment outcomes, suggesting distinct pathophysiologic processes [5, 11–14]. However, the best treatment is neither well defined nor unanimous and studies in Caucasians are scarce [10, 15–19].

The Everest II study [3, 20, 21], performed in an Asian population, showed that combination with verteporfin photodynamic therapy (PDT) was superior to ranibizumab monotherapy in best-corrected visual acuity (BCVA) gains and complete polyp regression while requiring fewer injections. Nevertheless, the adverse events and long-term outcomes associated with PDT remain a concern [6, 22–24]. Moreover, the PLANET study [25, 26], a 2-year randomized clinical trial (RCT) designed to evaluate the efficacy and safety of treatment with intravitreal aflibercept injection (IVAI) in PCV and compare monotherapy with IVAI plus rescue PDT showed that functional and anatomical outcomes of IVAI monotherapy were noninferior to IVAI plus rescue PDT.

To our knowledge, no multicenter RCT has been conducted in Caucasian populations to evaluate the efficacy and safety of IVAI in a treat-and-extend (T&E) regimen for PCV as monotherapy or in combination with standard fluence verteporfin PDT (vPDT). Considering that several genetic variants associated with PCV do not appear to translate across ethnic lines [11, 14, 27–29], it is an important proof of concept to evaluate whether this combination regimen is superior to aflibercept monotherapy in Caucasian individuals. Hence, the present RCT evaluates the safety and efficacy of aflibercept monotherapy in a T&E regimen and the potential benefit of adding standard fluence PDT with verteporfin in a Caucasian population with treatment-naive PCV.

## Materials and Methods

*Participants*

The ATLANTIC study was an investigator-initiated randomized, double-masked, sham-controlled, phase 4, multicenter clinical trial conducted at 14 clinical sites that aimed to compare the 1-year efficacy and safety of IVAI T&E plus sham PDT (sPDT) with IVAI T&E plus vPDT (verteporfin, 6 mg/m$^2$; vPDT laser fluence, 50 J/cm$^2$) in patients with PCV. It was an investigator-initiated study performed by the European Vision Institute Clinical Research Network (EVICR.net) [30]. This study followed the Consolidated Standards of Reporting Trials (CONSORT), the reporting guidelines for RCTs, and the tenets of the Declaration of Helsinki. Approval for this study was obtained from each center's Ethics Committee and the relevant national authorities. All patients provided written informed consent to participate in this study, which was obtained from all

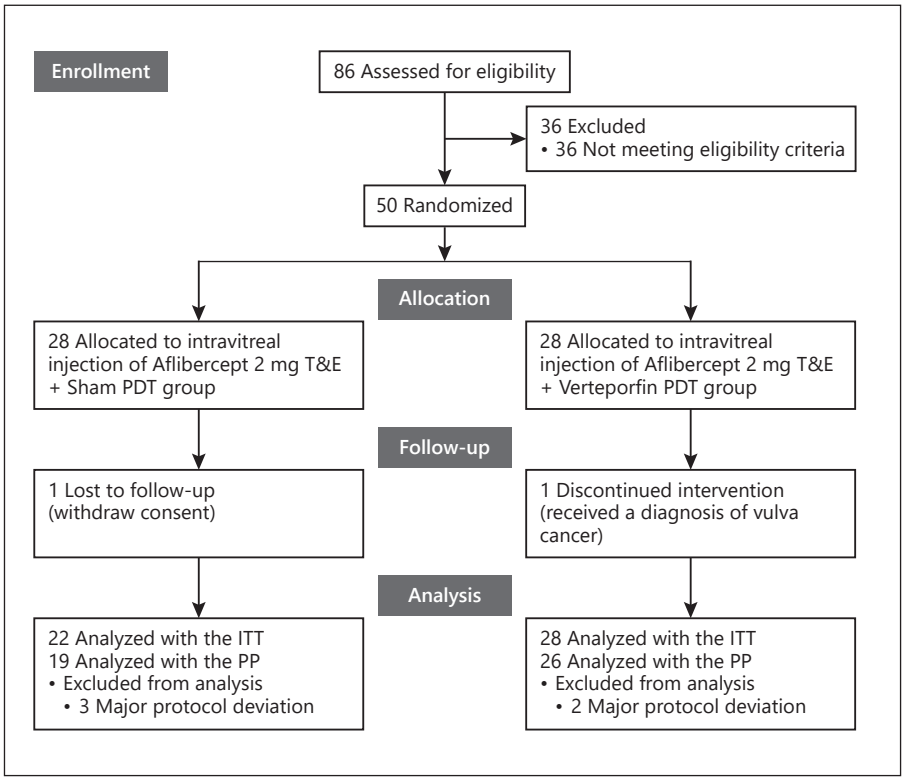


**Fig. 1.** CONSORT participant flow diagram. ITT, intention-to-treat; PDT, photodynamic therapy; PP, per-protocol; T&E, treat and extend.

participants in a manner consistent with the Declaration of Helsinki. No one received compensation or was offered any incentive for participating in this study.

Male and female patients with naive PCV were included in the study between February 2016 and September 2018. The patients were recruited from 14 clinical sites (9 in Portugal and 5 in Spain) and were followed up for 52 weeks. The inclusion and exclusion criteria along with the complete study protocol have been previously published [31]. In brief, the inclusion criteria were as follows: only treatment-naive patients, 50 years of age or older, were recruited. The diagnosis of PCV in the study followed the EVEREST criteria [3, 20, 21, 32], and the eye was assessed by a central reading center (CRC). Only eyes with a BCVA Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at study entry of 25–80 letters and greatest linear dimension of the lesion of 5,400 μm or less as assessed by fluorescein angiography and ICGA were included. After the screening phase, when eligibility was confirmed by the CRC, patients received initial dosing of 3 consecutive monthly IVAIs, 2 mg, at weeks 0, 4, and 8 (Fig. 1).

*Randomization*

Randomization was performed at week 16 by the coordinating center. It was done in blocks of 2 to achieve balance across treatment groups (IVAI T&E plus sPDT and IVA T&E plus vPDT) in each site, stratified by active or inactive polyps. A minimization scheme was employed to minimize, first, the imbalance in each stratum and then by the treatment group alone in case of ties. All patients received an IVAI at week 16, and sPDT or vPDT was mandatory whenever active polyps were documented by the CRC. Polyps were considered active when visible on ICGA and associated with subretinal and/or intraretinal, fluid in spectral domain-domain optical coherence tomography (SD-OCT) (Fig. 1).

*Additional Treatment with PDT*

The need for additional treatment with PDT was evaluated at weeks 28 and 40. An ICGA was performed whenever a decrease in BCVA of 5 or more ETDRS letters was found in association with macular fluid on SD-OCT. In the presence of active polyps confirmed with ICGA, sPDT or vPDT was mandatory, according to the protocol and randomization.

*Frequency of IVAI*

After week 16, the interval between IVAIs was guided by the presence of macular fluid observed on SD-OCT: IVAI was shortened by 2 weeks in the presence of fluid, whereas it was increased by 2 weeks in the absence of fluid. The maximum interval between injections was 12 weeks and the minimum was 6 weeks.

*Objectives*

The primary objective of the study was to evaluate the efficacy of intravitreal aflibercept in a T&E regimen as monotherapy or as a combined treatment with standard fluence PDT in naive patients diagnosed with PCV by comparing: (1) BCVA change at week 52 and (2) polyp occlusions at week 52. The secondary objectives included evaluating the safety of intravitreal aflibercept and vPDT treatments in patients with PCV and morphologically characterize the 2 treatment regimens.

**Table 1.** Demographic and clinical baseline characteristics of the participants

| Characteristics | *n* = 50 eyes |
|---|---|
| Women, *n* (%) | 25 (50) |
| Age, median (IQR), years | 73.5 (64–79) |
| BCVA, median (IQR), ETDRS letters | 66 (56–70) |
| Presence of macular drusen, *n* (%) | 34 (68) |
| Presence of preretinal, intraretinal, subretinal, and sub-RPE hemorrhages, *n* (%) | 9 (18) |
| Presence of BVN, *n* (%) | 48 (96) |
| Presence of polypoidal lesions, *n* (%) | 50 (100) |
| Macular | 48 (96) |
| Peripapillary | 5 (10) |
| Polyp area, median (IQR), $mm^2$ | 0.071 (0.041–0.105) |
| Total lesion area, median (IQR), $mm^2$ | 3.209 (2.045–5.295) |
| Presence of CNV–occult component, *n* (%) | 48 (96) |
| Presence of CNV–classic component, *n* (%) | 5 (10) |
| CRT, median (IQR), µm | 317.5 (275–397) |
| Macular choroidal thickness, median (IQR), µm[a] | 214.6 (157.2–272.1) |
| Presence of diffuse pachychoroid, *N* of *n* (%) | 9 of 45 (20) |
| Presence of focal pachychoroid, *N* of *n* (%) | 27 of 44 (61) |

BCVA, best-corrected visual acuity; BVN, branch vascular network; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; CRT, central retinal thickness; IQR, interquartile range. [a] Measured in the fovea, at 500 µm, and at 1,500 µm from the fovea.

*Outcomes*

The primary outcomes were a change in BCVA from baseline to week 52 and polyp occlusion at week 52. Secondary outcomes included: (1) a change in BCVA at week 16 and over the follow-up period; (2) BCVA stabilization (BCVA change from baseline between −4 and 4 ETDRS letters), gain or loss of 5 or more, 10 or more, or 15 or more ETDRS BCVA letters at week 52; (3) complete or partial polyp occlusion and presence of active polyps at weeks 16 and 52; (4) presence of leakage on fluorescein angiography at week 52; (5) change in central retinal thickness and presence of fluid over time as assessed with SD-OCT; (6) total number of injections and vPDT; and (7) frequency and severity of ocular and non-ocular adverse events.

*Statistical Analysis*

Based on the previous studies, a very small difference in BCVA changes is expected between treatment arms [20, 21], meaning that a large sample size may be needed to test for differences between arms. Therefore, and since there is a low prevalence in the general population of these patients, a feasibility assessment was performed within the EVICR.net in Portugal and Spain to estimate the population size. Due to this, 50 patients were planned for this study (25 from each country) to be recruited in a 1-year period.

Categorical variables are summarized with frequencies and percentages, and numerical variables are presented as median and interquartile range (IQR), due to the small sample size and the non-normal distribution of the data, tested using the Shapiro-Wilk test. To test for statistically significant differences between treatment groups (intravitreal aflibercept associated with vPDT and intravitreal aflibercept associated with sPDT), the Fisher's exact test was used for categorical variables, and the non-parametric Mann-Whitney test was used for continuous variables. The Wilcoxon test was used to compare numerical variables between visits.

The intention-to-treat (ITT) and per-protocol populations were used for analyses. The analysis with the ITT population, considered the main analysis, included all randomized patients receiving at least 1 study treatment and having a baseline and at least 1 pos baseline measurement for the primary outcome. Patients with protocol violations likely to affect the study outcome were excluded by masked review. Carrying forward of the last observation was used to compensate for data missing from the primary outcome. The per-protocol population was defined as the subset of patients in the ITT population with availability of measurements of the primary variable with no imputation conducted for missing data. The primary efficacy analysis with the ITT population and with the per-protocol population yielded similar results.

Two additional analysis were performed in order to assure the integrity of our results. An exploratory analysis was conducted with only the eyes that effectively received PDT in each group: 11 eyes from the sPDT group and 11 eyes from the vPDT group. To handle missing data in the primary outcome, a more efficient and robust statistical methodology than LOCF was perfomed. Multivariable missing data were imputed using multiple imputation by chained equations, with continuous variables imputed using a linear regression model and the binary variables using a logistic regression model. A total of 10 datasets were imputed and then combined using Rubin´s rule to obtain the final estimates for the model (see online suppl. Data Analysis; see www.karger.com/doi/10.1159/000518235 for all online suppl. material).

**Table 2.** Primary and secondary outcomes

| Outcomes | Treatment group | | | *p* value |
|---|---|---|---|---|
| | total (*n* = 50 eyes) | IVAI plus sPDT (*n* = 22 eyes) | IVAI plus vPDT (*n* = 28 eyes) | |
| Median (IQR) | | | | |
| BCVA change from baseline to 52 wk, ETDRS letters | 6 (2–12) | 6.5 (2–11) | 5 (2–13) | 0.98 |
| CRT change from baseline to 52 wk, µm | −93.0 (−154.0;−44.0) | −143 (−184;−47) | −89 (−123.0;−41.5) | 0.23 |
| Injections from baseline to 52 wk, *n* | 8 (7–9) | 8.5 (7–9) | 8 (7–9) | 0.21 |
| Mean interval between injections from baseline to 52 wk, days | 46 (41.8–57.7) | 43.3 (41.9–49.1) | 46.5 (41.3–58) | 0.26 |
| BCVA change from baseline to 16 wk, letters | 4 (−1; 7) | 4 (−2; 10) | 4 (−1; 7) | 0.97 |
| CRT at 16 wk, µm | 247 (219–300) | 255 (226–303) | 237 (210–270) | 0.19 |
| Macular choroidal thickness at 16 wk, µm[1] | 209.2 (173.6–263.3) | 214.2 (161.9–255.0) | 204 (173.6–263.4) | 0.68 |
| Total PCV lesion area at 52 wk, mm$^2$ | 0 (0–0.005) | 0 (0–0) | 0 (0–0.013) | 0.69 |
| *N* (%) | | | | |
| Interval between injections of 8–12 wk | 14 (28) | 5 (23) | 9 (32) | 0.72 |
| Presence of fluid at 52 wk | 21 (42) | 9 (41) | 12 (43) | <0.99 |
| Presence of polyps at 52 wk | 13 of 47 (28) | 5 of 22 (23) | 8 of 25 (32) | 0.53 |
| Presence of active polyps at 52 wk | 4 of 47 (9) | 1 of 22 (5) | 3 of 25 (12) | 0.61 |
| Presence of complete polyps occlusion at 52 wk | 34 of 47 (72) | 17 of 22 (77) | 17 of 25 (68) | 0.53 |
| Presence of partial polyps occlusion at 52 wk from baseline | 7 of 47 (15) | 2 of 22 (9) | 5 of 25 (20) | 0.42 |
| Presence of polyps without occlusion at 52 wk | 6 of 47 (13) | 3 of 22 (14) | 3 of 25 (12) | >0.99 |
| No FA leakage at 52 wk | 30 of 46 (65) | 15 of 21 (71) | 15 of 25 (60) | 0.54 |
| Presence of polyps at 16 wk | 31 (62) | 15 (68) | 16 (57) | 0.56 |
| Presence of active polyps at 16 wk | 22 (44) | 11 (50) | 11 (39) | 0.57 |
| Presence of complete polyps occlusion at 16 wk | 19 (38) | 7 (32) | 12 (43) | 0.56 |
| Presence of partial polyps occlusion from baseline at 16 wk | 20 (40) | 12 (55) | 8 (29) | 0.09 |
| Presence of polyps without occlusion at 16 wk | 11 (22) | 3 (14) | 8 (29) | 0.31 |
| Presence of fluid at 16 wk | 31 (62) | 15 (68) | 16 (57) | 0.56 |

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IVAI, sPDT, sham photodynamic therapy; vPDT, standard fluence photodynamic therapy with verteporfin; CRT, central retinal thickness; IQR, interquartile range; PCV, polypoidal choroidal vasculopathy. [1] Macular choroidal thickness was measured in the fovea and at 500 µm and 1,500 µm from the fovea.

Results for the primary objectives (i.e., change in BCVA from baseline to week 52 and polyp occlusion at week 52) were considered statistically significant if a test reached an α level of 0.025. A 2-sided value of $p < 0.05$ was considered statistically significant in the secondary analyses. All analyses were performed with Stata, version 16.1 (StataCorp).

## Results

*Baseline Characteristics*

Fifty Caucasian individuals with naive PCV, from Portugal and Spain, were included in the study. Completion rates were 95% in the IVAI T&E plus sPDT group and 96% in the IVAI T&E plus vPDT group (Fig. 1). The median (IQR) age of the patients was 73.5 (64–79) years. Twenty-five patients (50%) were women, and the overall median (IQR) baseline BCVA ETDRS letter score was 66 (56–70) (Table 1). At baseline, the median (IQR) macular choroid thickness was 214.6 (157.2–272.1) µm and polyps were present in all 50 eyes (100%), being predominately located in the macula macular in 48 eyes (96%) and with a median (IQR) polyp area of 0.071 (0.041–0.105) mm$^2$ (Table 1). A branching vascular network was observed in 48 eyes (96%), while soft or intermediate macular drusen were identified in 34 cases (68%). The presence of pachyvessels was observed in 27 of 44 eyes (61%), and intraretinal and subretinal hemorrhages were identified in 9 eyes (18%) (Table 1).

*Randomization*

At week 16, 22 patients were randomized to IVAI T&E plus sPDT and 28 patients to IVAI T&E plus vPDT. From baseline to week 16, a significant median (IQR) BCVA gain of 4 (−1, 7) ETDRS letters was observed for all patients ($p < 0.001$). Complete polyp occlusion was documented in 19 eyes (38%) at week 16 and presence of fluid

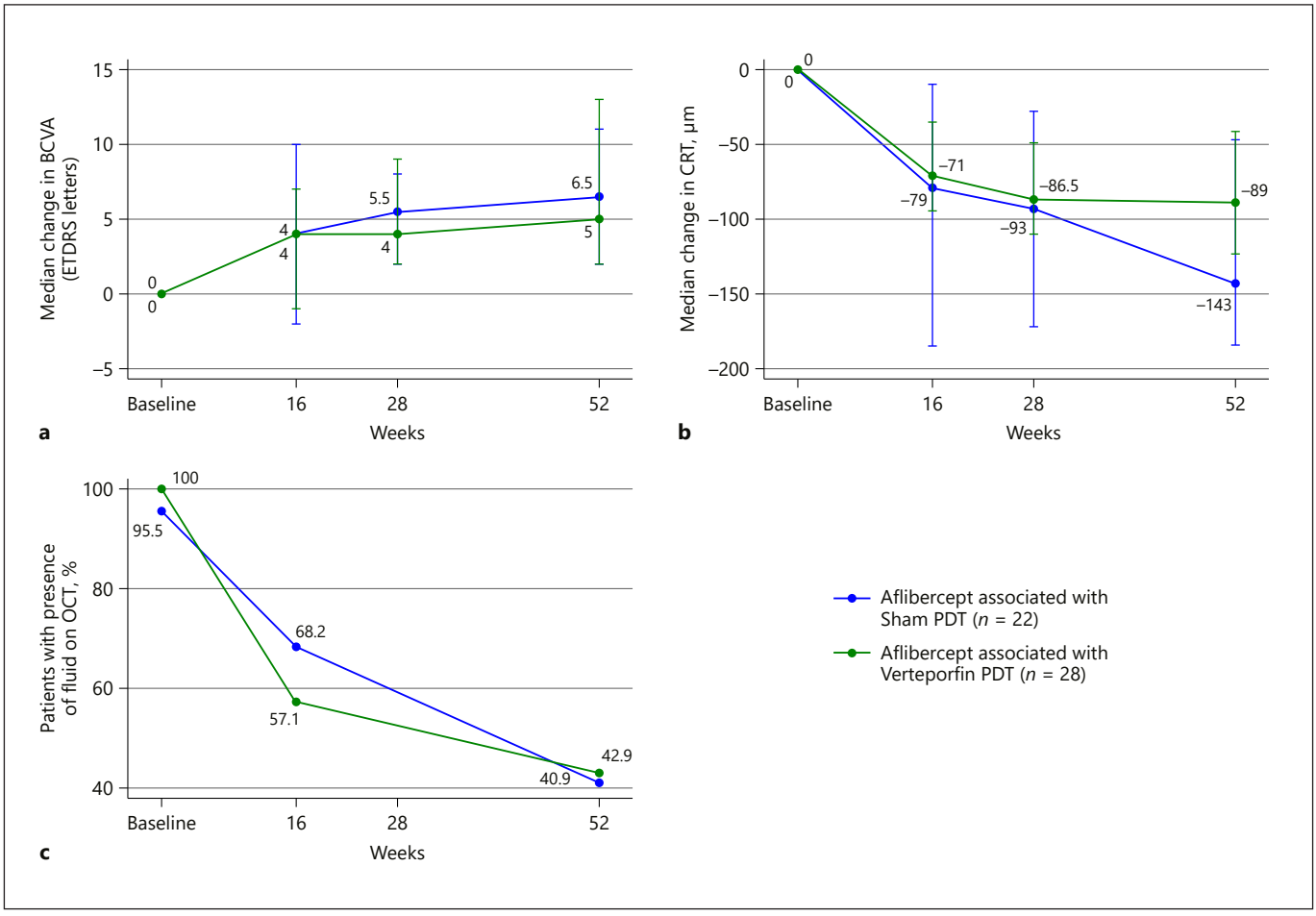


**Fig. 2.** Functional and anatomic outcomes. **a** Change in BCVA from baseline to week 52. **b** Change in CRT) from baseline to week 52. **c** Proportion of patients with the of fluid detected on OCT over 52 weeks. CRT, central retinal thickness; OCT, optical coherence tomography; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

in 31 eyes (62%). Only 22 eyes (44%) presented with persistent active polyps at week 16 and were randomized to receive vPDT or sPDT along with IVAI T&E (Table 2), corresponding to 11 eyes in each group (50% of the IVAI T&E plus sPDT and 39% of the IVAI T&E plus vPDT eyes; $p = 0.57$).

*Treatments*

A median (IQR) of 8 (7–9) IVAI was administered from baseline to week 52. No meaningful differences were detected for the number of IVAIs between the sPDT group and the vPDT group median (IQR): 8.5 (7–9) versus 8 (7–9) ($p = 0.2$) or for the interval between injections: 43.3 (41.9–49.1) versus 46.5 (41.3–58) days ($p = 0.26$). Moreover, following the T&E regimen, 14 eyes (28%) were being treated with an interval between 8 and 12 weeks at week 52, with no significant difference between the 2 arms (IVAI plus sPDT, 5 of 22 eyes [23%] vs. IVAI plus vPDT, 9 of 28 eyes [32%]; $p = 0.72$). The number of PDT treatments was similar in both groups of patients qualified for sham or active PDT: 11 of 22 versus 11 of 28. Only 1 patient, from the sPDT group, required additional treatment at week 28, according to the protocol.

*Primary Efficacy Outcomes*

A rapid and significant improvement in BCVA was observed after the initial dosing for both groups and continued until week 52, with a median (IQR) change in BCVA of 6 (2–12) ETDRS letters, with no significant difference between the 2 arms at week 16 (IVAI plus sPDT, 4 [−2, 10] vs. IVAI plus sPDT, 4 [−1, 7] letters; $p = 0.97$)

**Table 3.** Safety results at week 52

| AEs | Participants with AEs, *n* (%) | | |
|---|---|---|---|
| | treatment group | | |
| | total (*n* = 50) | IVAI plus sPDT (*n* = 22) | IVAI plus vPDT (*n* = 28) |
| Any AE | 25 (50) | 9 (41) | 16 (57) |
| Any ocular AE | 11 (22) | 7 (32) | 4 (14) |
| Study eye | 11 (22) | 7 (32) | 4 (14) |
| Fellow eye | 6 (12) | 3 (14) | 3 (11) |
| Any nonocular AE | 20 (40) | 6 (27) | 14 (50) |
| Any SAE | 3 (6) | 1 (5) | 2 (7) |
| Any ocular SAE | 0 | 0 | 0 |
| Any nonocular SAE | 3 (6) | 1 (5) | 2 (7) |
| Vulvar skin cancer | 1 (2) | 1 (5) | 0 |
| Abdominal hernia | 1 (2) | 0 | 1 (4) |
| Auricular fibrillation with pacemaker implantation | 1 (2) | 0 | 1 (4) |
| Any AE related to study drug | 2 (4) | 0 | 2 (7) |
| Any ocular AE | 2 (4) | 0 | 2 (7) |
| Study eye | 2 (4) | 0 | 2 (7) |
| IVAI related | 2 (4) | 0 | 2 (7) |
| PDT related | 1 (2) | 0 | 1 (4) |
| Any nonocular AE | 0 | 0 | 0 |
| Any AE leading to discontinuation of the study group | 1 (2) | 0 | 1 (4) |
| Any AE leading to interruption of the study drug | 1 (2) | 0 | 1 (4) |
| Any APTC-classified event | 0 | 0 | 0 |
| Any death | 0 | 0 | 0 |

APTC, Antiplatelet Trialists' Collaboration; IVAI, intravitreal aflibercept injection; SAE, serious adverse event; PDT, photodynamic therapy; sPDT, sham photodynamic therapy; vPDT, standard fluence photodynamic therapy with verteporfin; AE, adverse event.

or at week 52 (IVAI plus sPDT, 6.5 [2–11] vs. IVAI plus sPDT, 5 [2–13] letters; $p = 0.98$) (Table 2; Fig. 2). Complete polyps occlusion occurred in 72% of the eyes, and it was similar in the 2 arms (Table 2).

*Secondary Efficacy Outcomes*

The proportion of patients with a BCVA gain of 5, 10, or 15 ETDRS letters, BCVA loss of 5, 10, or 15 ETDRS letters, or with stable BCVA at week 52 was similar in both groups, IVAI plus sPDT versus IVAI plus vPDT ($p = 0.32$). The median (IQR) central retinal thickness decreased significantly with treatment from baseline to week 16, and from week 16 to week 52 ($p < 0.001$), with no difference between the 2 arms: −143 (−184; −47) versus −89 (−123; −41.5) μm ($p = 0.23$) at week 52 (Fig. 2). The number of eyes with fluid at week 16 was 31 (62%), and at week 52 was 21 (42%), with no difference between the 2 arms ($p > 0.99$) (Table 2).

*Additional Analysis*

An exploratory analysis comparing eyes with active polyps at week 16 that were randomized to receive sPDT or vPDT showed no significant anatomical or functional difference at week 52. Regarding the missing data in the primary outcomes, we compared the results between case complete analysis (without imputed data), LOCF, and multiple imputation approaches (online suppl. data). The multiple imputation approach showed no significant differences from the previous analysis using LOCF. For that reason, the results shown are the ones from the LOCF analysis.

*Adverse Events*

The overall incidence of adverse events (AEs) was similar in both groups: IVAI plus sPDT, 31 (43%) versus IVAI plus sPDT, 41 (57%). The AEs were documented as unrelated to the study drug (aflibercept and/or verteporfin) in 65 cases (90%), as unlikely to be related in 2 cases

(3%), as possibly related in 2 cases (3%), and only as related in 3 cases (4%). Of all AEs, 57 (79%) were considered mild, 12 (17%) moderate, and 3 (4%) severe. The ocular AEs represented 19 (26%) of all 72 AEs, with no ocular severe AE being described. The most frequent ocular AE was eye pain, and it was described in 2 cases in the sPDT group and 3 cases in the vPDT group. The study drug was temporarily interrupted in 1 patient (2%) and permanently discontinued in 1 patient (2%) (Table 3).

## Discussion

The ATLANTIC study is the first multicenter RCT to compare IVAI in a T&E regimen as monotherapy with a combined treatment, adding standard fluence PDT, in a Caucasian population with PCV. Other multicenter RCTs examining PCV were previously performed exclusively in Asian populations, such as the EVEREST II [20, 21] or with a minor proportion of Caucasian patients, as observed in PLANET [25, 26], and the T&E regimen was not used or was only allowed in the second year. The study here presented confirmed the good functional and anatomic results of IVAI monotherapy already described in the PLANET study but extends these findings to a Caucasian population and for the use of a T&E regimen. A median significant BCVA gain of 6 ETDRS letters was observed with 28% of the eyes being treated with an interval between 8 and 12 weeks at week 52. Similar to EVEREST II [20, 21], the ATLANTIC study compared the use of standard fluence PDT with sham PDT in patients with PCV. However, there are important differences between the present study and EVEREST II, mainly the smaller sample size, and the use of aflibercept in T&E regiment instead of ranibizumab "as needed" and, unlike in EVEREST II [20, 21], patients in the ATLANTIC study were eligible to PDT only at week 16. Because only 1 patient met the criteria for PDT retreatment after week 16, the benefits of additional PDT at weeks 28 or 40 in our study could not be elucidated. This too differs from the PLANET study [25, 26], in which rescue criteria were used and <20% of patients met the criteria for PDT.

Rates of complete or partial occlusion of polypoidal lesions are highly variable across studies with different protocol designs, drugs, or treatment regimens, and the functional and anatomical benefits are controversial [20–22, 25, 26, 33–38]. In the EVEREST II study [20, 21], the combined treatment was associated with significantly higher rates of polyp occlusion and better BCVA outcomes. In PLANET [25, 26], complete closure rates of polypoidal lesions were similar in the 2 arms. The Fujisan study [38] showed that both early and deferred PDT had similar functional and anatomical results at 12 months. In our study, the closure of polypoidal lesions was determined by a CRC using ICGA. We followed a T&E regimen only after week 16 and up to week 52. Deferring PDT did not result in a significant reduction of the injection burden, and the T&E regimen meant that patients would receive treatment with IVAI even when their polyps were considered inactive. Following this protocol, only 44% of the eyes had active polyps 8 weeks after the loading dose, and only 22% were eligible for PDT with verteporfin. A complete polyp occlusion at week 52 occurred in 72% of the eyes, which are higher rates when compared to the monotherapy results at the EVEREST II or PLANET studies and could be related with the smaller area of polyps in our Caucasian population when compared with the polyp's area described in Asian studies [20, 21, 25, 26]. Moreover, a sub-analysis comparing patients receiving IVAI T&E plus sPDT treatment (11 eyes) with those receiving IVAI T&E plus vPDT (11 eyes) showed no significant anatomical or functional differences, thus favoring the ineffectiveness of adding vPDT. Although our study did not demonstrate any anatomical or functional benefit with the combined regimen, validating the results of monotherapy obtained in the PLANET study [24, 25], our comparative results should be analyzed very carefully due to the limitations of the study that include the small sample size (50 patients), the rate of patients randomized to PDT (44%), the short follow-up period (1 year), the short interval to detect differences between treatment groups (36 weeks), and differences in the number of injections, all together preventing more definitive conclusions.

The good functional and anatomical results of the monotherapy with aflibercept in a T&E regimen in the ATLANTIC study (Table 2) can be explained by the presence of shared findings with Asian populations, but, more important, they can translate the more specific characteristics of Caucasian PCV eyes [7, 8, 10, 18, 22, 24]. Interestingly, we found a high prevalence of macular polypoidal lesions (96%) in contrary to some other literature descriptions of PCV in Caucasian populations [7, 8], and the presence of focal (20%) or diffuse pachychoroid (61%) observed in the present study was similar to that reported in Asian populations [6, 11, 20, 21, 25, 26]. However, the median older age (73.5 years), the high prevalence of soft and intermediate drusen (68%), the small polyp area, the low prevalence of intraretinal and subretinal haemorrhages (18%), and the high rate of complete polyp occlusion (72%) are quite different from Asian populations and bring the PCV cases in our Caucasian population closer to age-related macular degeneration characteristics. Additionally, potential genetic differences in

a Caucasian population [11–14, 29] when comparing to an Asian population, cannot be excluded. Of note, part of the population of our study was evaluated in a recent work, which revealed significant phenotypic and genetic differences among Asian and Caucasian patients with PCV, particularly in the expression of specific polymorphisms which can be associated with increased risk for PCV [14].

*Limitations and Strengths*

Our study has some limitations that should be clearly identified. First, although there was no statistically significant difference between the 2 treatment arms, the low statistical power of the sample size limits the clinical value of the comparative results. Second, vPDT was performed only once in 11 patients. Third, limiting the study to 1-year follow-up may prevent the potential detection of a significant difference in the number of injections, which is one of the clinical reasons to do add-on PDT.

Nevertheless, the ATLANTIC study had also important strengths. First, to our knowledge, this is the first multicenter RCT performed in a Caucasian population of patients with PCV that evaluated a T&E regimen with IVAI with or without PDT. Second, according to the study design, only patients with a diagnosis of PCV confirmed by a CRC were included. Third, all patients started with initial dosing of intravitreal aflibercept, and PDT was performed only in patients with active polyps diagnosed with ICGA, which is reflective of clinical practice.

## Conclusions

The ATLANTIC study is the first multicenter RCT to compare monotherapy with aflibercept in a T&E regimen with a combined treatment with standard fluence PDT conducted in a Caucasian population with PCV. The monotherapy in a T&E regimen was effective and safe with a significant improvement in BCVA and a complete occlusion of polypoidal lesions in about 3 quarters of the eyes. As only 22% of the eyes underwent PDT treatment, the benefit of combined treatment for PCV in Caucasians could not be definitively elucidated from this study.

## Statement of Ethics

This study followed the CONSORT, the reporting guidelines for RCTs, and the tenets of the Declaration of Helsinki. Approval for this study was obtained from each center's Ethics Committee and the relevant national authorities. All patients provided written informed consent to participate in this study, which was obtained from all participants in a manner consistent with the Declaration of Helsinki. No one received compensation or was offered any incentive for participating in this study.

## Conflict of Interest Statement

Dr. Silva reported receiving personal fees as a consultant for Allergan, Alimera Sciences, Bayer, Novartis, Roche, Novus Nordisk, and Thea Pharmaceuticals; Luis Arias reported being a member of the Advisory Boards for Allergan, Bayer, Novartis, and Roche. João P. Marques reported receiving personal fees as a consultant for Bayer. Maria L. Cachulo reported being a member of the advisory boards for Allergan and Novartis. João Figueira reported being a member of advisory boards for Alimera, Allergan, Bayer, Bhoeringer, and Novartis. Sara Vaz-Pereira reported receiving personal fees as a consultant for Bayer, Novartis, and Alimera Sciences. Francisco Cabrera reported receiving personal fees as a consultant for Bayer, Allergan, Novartis, Brill-Alimera, Roche, Alcon, and Dorc. Anniken Bures reported receiving from Bayer consultation fees (advisory board), speaker fees, and travel fees (for meetings) and reported receiving from Allergan consultation fees (advisory board), speaker fees, and travel fees (for meetings). J.G. Cunha-Vaz reported receiving personal fees as a consultant for Carl Zeiss, Meditec, Alimera Sciences, Allergan, Bayer, Novartis, Oxular, and Roche; and Sanofi. Joaquim Murta is a member of the scientific advisory board of Alcon. No other conflicts were reported.

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## Author Contributions

Conceptualization was performed by C.F.; J.P.M., and R.S.; formal analysis was performed by R.A.C. and S.N.; funding acquisition was performed by J.C.-V. and R.S.; investigation was performed by R.S., L.A., C.F., S.N., J.P.M., M.L.C., J.F., P.B., M.H.M., I.P., J.C.S., L.D., P.R., A.C., S.V.-P., A.M., F.C., A.B., L.M., A.F.-V-S., S.B., A.K., C.M.G.C., J.C.-V., and J.M. Methodology was performed by R.S., J.P.M., C.F., and S.N. Project administration was conducted by R.S. Resources were provided by J.C.-V. and R.S.; Supervision was performed by R.S. Writing–original draft was performed by C.F., and R.S. Writing–review, and editing was performed by C.F., R.A.C., S.N., M.H.M., and R.S. All the authors have read and agreed to the published version of the manuscript. Antonio Campos, MD, Centro Hospitalar de Leiria; Marta Vilafranca, MD, Instituto de Oftalmologia; Dr. Gama Pinto, Joaquim Prates Canelas, MD, Centro Hospitalar Universitário de Lisboa Norte, EPE–Hospital de Santa Maria; André Magalhães Oliveira, MD, Hospital Insular de Gran Canaria (Las Palmas) provided support to ensure the subinvestigator responsibilities. Vitor Agoas, MD, Instituto de Oftalmologia; Dr. Gama Pinto was the principal investigator until his retirement. Sónia Simões, BSc, and Daniel Silva, MSc, assisted in project co-

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## Data Availability Statement

Data is available upon request to the corresponding author.

## References


1 Yannuzzi LA, Sorenson J, Spaide RF, Lipson B. Idiopathic polypoidal choroidal vasculopathy (IPCV). Retina. 1990;10(1):1–8.
2 Yannuzzi LA, Ciardella A, Spaide RF, Rabb M, Freund KB, Orlock DA. The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. Arch Ophthalmol. 1997;115(4):478–85.
3 Koh A, Lai TYY, Takahashi K, Wong TY, Chen LJ, Ruamviboonsuk P, 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):1206–13.
4 Dansingani KK, Gal-Or O, Sadda SR, Yannuzzi LA, Freund KB. 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.
5 Wong CW, Yanagi Y, Lee WK, Ogura Y, Yeo I, Wong TY, et al. Age-related macular degeneration and polypoidal choroidal vasculopathy in Asians. Prog Retin Eye Res. 2016;53:107–39.
6 Cheung CMG, Lai TYY, Ruamviboonsuk P, Chen SJ, Chen Y, Freund KB, et al. Polypoidal choroidal vasculopathy: definition, pathogenesis, diagnosis, and management. Ophthalmology. 2018 May;125(5):708–24.
7 Lafaut BA, Leys AM, Snyers B, Rasquin F, De Laey JJ. Polypoidal choroidal vasculopathy in Caucasians. Graefes Arch Clin Exp Ophthalmol. 2000;238(9):752–9.
8 Liew G, Hyun-JinDo HD, Hooper C, Chia EM, Mitchell P, Ong S, et al. Prevalence of polypoidal choroidal vasculopathy in Caucasian patients as estimated from optical coherence tomography signs. Eye. 2021 Mar;35(3):1011–2.
9 Kokame GT, deCarlo TE, Kaneko KN, Omizo JN, Lian R. Anti-vascular endothelial growth factor resistance in exudative macular degeneration and polypoidal choroidal vasculopathy. Ophthalmol Retina. 2019 Sep;3(9):744–52.
10 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 Dec;38(12):2363–71.
11 Honda S, Matsumiya W, Negi A. Polypoidal choroidal vasculopathy: clinical features and genetic predisposition. Ophthalmologica. 2014;231(2):59–74.
12 Ma L, Li Z, Liu K, Rong SS, Brelen ME, Young AL, et al. Association of genetic variants with polypoidal choroidal vasculopathy: a systematic review and updated meta-analysis. Ophthalmology. 2015;122(9):1854–65.
13 Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. Lancet. 2018;392(10153):1147–59.
14 Jordan-Yu JM, Teo K, Fan Q, Gana JC, Leopando AK, Nunes S, et al. Phenotypic and genetic variations between Asian and Caucasian polypoidal choroidal vasculopathy. Br J Ophthalmol. 2020:317537.
15 Gharehbagh SS, Subhi Y, Sørensen TL. Efficacy of aflibercept for polypoidal choroidal vasculopathy in Caucasians. Acta Ophthalmol. 2018 Feb;96(1):e94–5.
16 Hatz K, Prünte C. Polypoidal choroidal vasculopathy in Caucasian patients with presumed neovascular age-related macular degeneration and poor ranibizumab response. Br J Ophthalmol. 2014;98(2):188–94.
17 Agorogiannis EI, Pearce IA, Yadav S, Parry DG, Beare NAV. Clinical outcomes in Caucasian patients with polypoidal choroidal vasculopathy. Eye. 2018;32(11):1731–9.
18 van Dijk EHC, Mohabati D, Veselinovic S, Chung WH, Dijkman G, Boon CJF. The spectrum of polypoidal choroidal vasculopathy in Caucasians: clinical characteristics and proposal of a classification. Graefes Arch Clin Exp Ophthalmol. 2021 Feb;259(2):351–61.
19 Lorentzen TD, Subhi Y, Sørensen TL. Presenting characteristics and prevalence of polypoidal choroidal vasculopathy in Scandinavian patients with treatment-naïve exudative age-related macular degeneration. Acta Ophthalmol. 2018 Aug;96(5):475–80.
20 Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H, et al. Everest study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. Retina. 2012;32(8):1453–64.
21 Lim TH, Lai TYY, Takahashi K, Wong TY, Chen LJ, Ruamviboonsuk P, et al. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the EVEREST II randomized clinical trial. JAMA Ophthalmol. 2020 Sep;138(9):935–42.
22 Silva RM, Figueira J, Cachulo ML, Duarte L, Faria de Abreu JR, Cunha-Vaz JG. Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin. Graefes Arch Clin Exp Ophthalmol. 2005;243(10):973–9.
23 Koh AH, Chen LJ, Chen LJ, Chen SJ, Chen Y, Giridhar A, et al. Polypoidal choroidal vasculopathy: evidence-based guidelines for clinical diagnosis and treatment. Retina. 2013;33(4):686–716.
24 Leal S, Silva R, Figueira J, Cachulo ML, Pires I, De Abreu JRF, et al. Photodynamic therapy with verteporfin in polypoidal choroidal vasculopathy: results after 3 years of follow-up. Retina. 2010;30(8):1197–205.
25 Lee WK, Iida T, Ogura Y, Chen SJ, Wong TY, Mitchell P, 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):786–93.
26 Wong TY, Ogura Y, Lee WK, Iida T, Chen SJ, Mitchell P, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy: two-year results of the Aflibercept in Polypoidal Choroidal Vasculopathy Study. Am J Ophthalmol. 2019 Aug;204:80–9.
27 Zhang X, Wen F, Zuo C, Li M, Chen H, Wu K. Association of genetic variation on chromosome 9p21 with polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52(11):8063–7.
28 Chen H, Liu K, Chen LJ, Hou P, Chen W, Pang CP. Genetic associations in polypoidal choroidal vasculopathy: a systematic review and meta-analysis. Mol Vis. 2012;18:816–29.
29 Gotoh N, Yamada R, Nakanishi H, Saito M, Iida T, Matsuda F, et al. Correlation between CFH Y402H and HTRA1 rs11200638 genotype to typical exudative age-related macular degeneration and polypoidal choroidal vasculopathy phenotype in the Japanese population. Clin Exp Ophthalmol. 2008 Jul;36(5):437–42.
30 Cunha-Vaz J, Martinho C. Developing an international network for clinical research in ophthalmology: the European Vision Institute Clinical Research Network (EVICR.net). Clin Invest. 2011;1(3):375–80.

31 Marques JP, Farinha C, Costa MÂ, Ferrão Â, Nunes S, Silva R. Protocol for a randomised, double-masked, sham-controlled phase 4 study on the efficacy, safety and tolerability of intravitreal aflibercept monotherapy compared with aflibercept with adjunctive photodynamic therapy in polypoidal choroidal vasculopathy: the ATLANTIC study. BMJ Open. 2017;7(8):e015785.
32 Tan CS, Ngo WK, Chen JP, Tan NW, Lim TH, Koh A, et al. EVEREST study report 2: Imaging and grading protocol, and baseline characteristics of a randomised controlled trial of polypoidal choroidal vasculopathy. Br J Ophthalmol. 2015 May;99(5):624–8.
33 Morimoto M, Matsumoto H, Mimura K, Akiyama H. Two-year results of a treat-and-extend regimen with aflibercept for polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol. 2017;255(10):1891–7.
34 Inoue M, Arakawa A, Yamane S, Kadonosono K. Short-term efficacy of intravitreal aflibercept in treatment-naive patients with polypoidal choroidal vasculopathy. Retina. 2014; 34(11):2178–84.
35 Hosokawa M, Shiraga F, Yamashita A, Shiragami C, Ono A, Shirakata Y, et al. Six-month results of intravitreal aflibercept injections for patients with polypoidal choroidal vasculopathy. Br J Ophthalmol. 2015;99(8):1087–91.
36 Oishi A, Tsujikawa A, Yamashiro K, Ooto S, Tamura H, Nakanishi H, et al. One-year result of aflibercept treatment on age-related macular degeneration and predictive factors for visual outcome. Am J Ophthalmol. 2015;159(5): 853–60.
37 Saito M, Kano M, Itagaki K, Sekiryu T. Efficacy of intravitreal aflibercept in Japanese patients with exudative age-related macular degeneration. Jpn J Ophthalmol. 2017 Jan;61(1): 74–83.
38 Gomi F, Oshima Y, Mori R, Kano M, Saito M, Yamashita A, et al. Initial versus delayed photodynamic therapy in combination with ranibizumab for treatment of polypoidal choroidal vasculopathy: the Fujisan Study. Retina. 2015;35(8):1569–76.