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Polypoidal choroidal vasculopathy and photodynamic therapy with verteporfin

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Abstract *Background:* We evaluated, in a nonrandomised, institutional, prospective study, the efficacy of photodynamic therapy (PDT) with verteporfin in age-related macular degeneration (AMD) eyes with polypoidal choroidal vasculopathy (PCV) and subfoveal exudation. *Methods:* A prospective clinical and angiographic study was done in 40 consecutive eyes with PCV treated with PDT using masked best-corrected visual acuity (VA) and fluorescein and indocyanine green angiographic features at baseline and over 2 years. *Results:* Twenty-one eyes completed 1-year follow-up and showed, after a mean 2.9 PDT sessions, VA improvement in 12 eyes, no change in five eyes, and VA decrease in four eyes. Leakage was absent at the retinal and choroidal level in 14 eyes at 1 year. Recurrence occurred in one eye during the first year. Six eyes completed 2 years of follow-up and showed, after a mean 4 PDT sessions, VA improvement in five eyes and VA decrease in one eye. Leakage was absent at the retinal and choroidal level in five eyes. Recurrence occurred in four of these six eyes during the second year of follow-up. No serious adverse events were observed during the 2 years of follow-up. *Conclusions:* PDT with verteporfin was shown to be safe and effective for treating AMD eyes with PCV with subfoveal involvement. VA improvement and absence of leakage were achieved, respectively, in 57.1% and 66.6% of the eyes at 1 year. Recurrences were more frequent during the second year of follow-up.

Keywords Polypoidal choroidal vasculopathy · PDT · Photodynamic therapy · Laser treatment · AMD

Introduction

Polypoidal choroidal vasculopathy (PCV) has been described for the last two decades [8, 13]. In 1985, Stern and colleagues [8] referred to it as "multiple recurrent serosanguinous retinal pigment epithelial detachments in black women." In 1990, Yannuzzi et al. [13] further described orange subretinal lesions as polypoidal dilations arising from the choroidal vascular network and proposed the name "idiopathic polypoidal choroidal vasculopathy." Indocyanine green angiography (ICG) was pointed out as superior to fluorescein angiography (FA) for detecting and characterizing these lesions [3, 7, 12]. Actually, atypical cases of age-related macular degeneration (AMD), when reexamined with ICG angiography, have been found to be present in about 8–13% of white patients with clinical appearance of exudative AMD [2, 12]. The natural course of the disease is associated with chronic, multiple, recurrent serosanguinous detachments of the retinal pigment epithelium (RPE) and neurosensory retina, and long-term preservation of good vision is possible [10]. Photodynamic therapy (PDT) using verteporfin has been shown to be

effective and safe in patients with subfoveal PCV [1, 6]. However, definitive clinical trials to establish the efficacy and safety of PDT in PCV are needed to confirm these observations.

The purpose of this study was to evaluate, in a non-randomised, institutional, prospective study, the efficacy and safety of PDT with Visudyne (verteporfin) in neovascular AMD eyes with PCV and subfoveal involvement.

Materials and methods

A prospective institutional study was performed in 40 consecutive eyes from 35 patients, 14 men and 21 women, with AMD and PCV who were treated with PDT with verteporfin between May 2000 and June 2004.

Inclusion criteria included the following: (1) symptomatic macular PCV with subfoveal exudation on FA, (2) juxtafoveal, subfoveal, or extrafoveal active macular polypoidal lesions on ICG, (3) best-corrected initial visual acuity (VA)≤20/40, (4) greatest linear dimension of active lesion ≤5,400 μm, (5) signs of AMD in the study eye.

Exclusion criteria included the following: (1) previous treatment for PCV (such as laser photocoagulation), (2) other fundus diseases such as diabetic retinopathy, vasculitis, high myopia (≥6 diopters), vein or artery occlusion, epiretinal membrane, angioid streaks, juxtafoveal telangiectasias type 2, trauma, or intraocular infection or inflammation, (3) any systemic contraindication to verteporfin or angiographic dyes, (4) choroidal neovascularisation (CNV) secondary to other causes such as high myopia, pseudohistoplasmosis, or idiopathic, (5) RPE tear or ripping, (6) absence of signs of AMD in the study eye and fellow eye.

The patients were observed at 3-month intervals. Clinical observation, fundoscopy, fundus photography, FA, ICG, and masked VA evaluation with Early Treatment Diabetic Retinopathy Study (ETDRS) charts were performed at each visit.

PDT treatments or retreatments were applied in the presence of subfoveal juxta or extrafoveal active polypoidal lesions on ICG and subfoveal exudation on FA (Figs. 1, 2). Lesions were considered active in the presence of early and late hyperfluorescence on ICG and subfoveal leakage on FA. PDT treatments were performed within 3-month intervals using the standard protocols of the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) [9] and Verteporfin in Photodynamic Therapy (VIP) [11] trials, with a few modifications. The same light dose of 50 J/cm^2 and the same 3-month intervals between treatments were used. However, we chose to treat the lesion with the size visualised on ICG (largest diameter plus 1 mm). When more than one polypoidal vascular lesion was present and separated by more than 1 mm, two treatments with different spot sizes were used. Not all the haemorrhage area

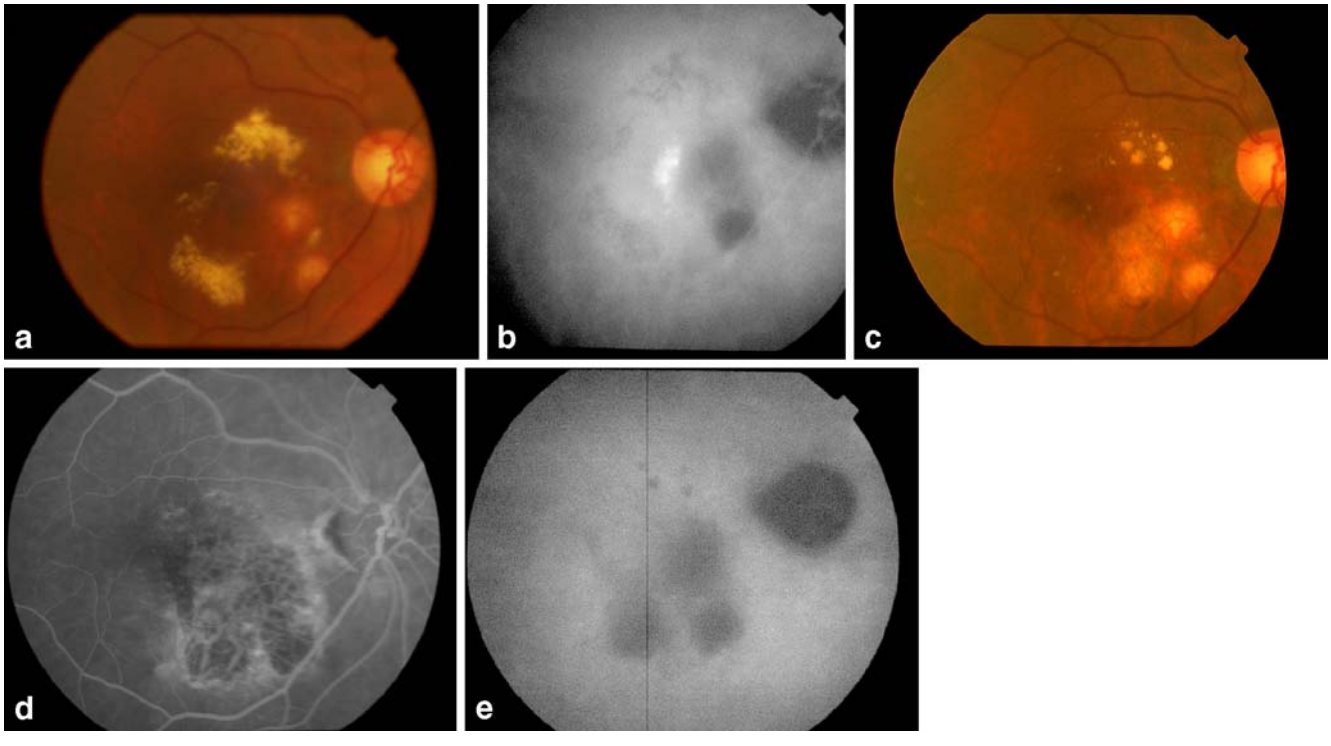

Fig. 1 Case 15. Color picture (**a**) and ICG (**b**) at baseline. Subfoveal polypoidal lesion on ICG and ring of lipid exudation on color picture. At 1 year and after one PDT treatment, almost complete reabsorption of lipid exudation is observed on color picture (**c**). FA shows late staining, and on ICG there is a complete regression of polyps (**d** and **e**). VA improved from 20/320 to 20/200.

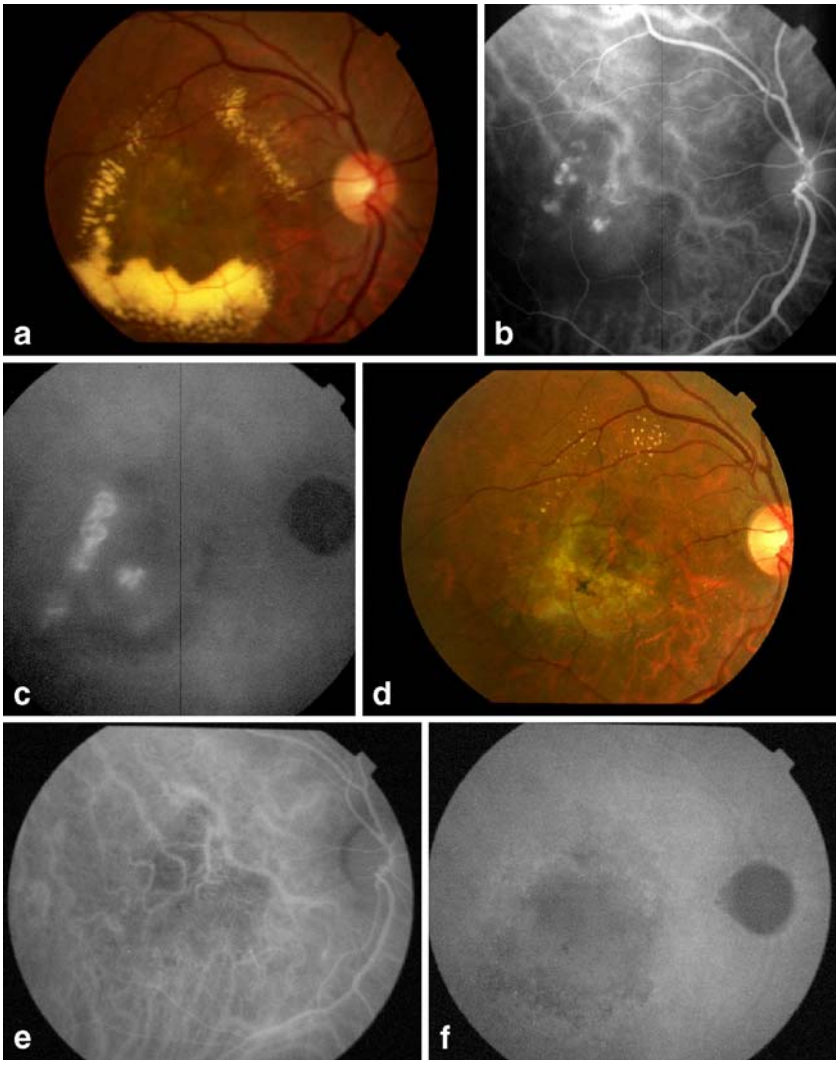

Fig. 2 Case 4. Subfoveal polypoidal lesion with lipid exudation at baseline: **a** color picture, **b** early ICG, and **c** late ICG. One year later and after two PDT sessions, there was reabsorption of lipid exudation and complete regression of polypoidal subfoveal lesions (**d** color picture, **e** early ICG, **f** late ICG). VA improved from 20/400 to 20/250.

was included in the area to be treated, unlike the standard protocols in TAP [9] and VIP [11]. In the presence of extensive haemorrhages, only 500 μm of the haemorrhage adjacent to the PCV visualised on ICG was included in the treatment spot. Retreatments were applied if ICG showed any juxtafoveal, extrafoveal, or subfoveal vascular polypoidal active lesion associated with subfoveal leakage on FA.

We considered the recurrence of PCV to be present when an active ICG lesion and subfoveal FA leakage reappeared following at least two consecutive visits (3-month intervals) with no treatment (equaling a 9-month interval).

All patients were older than 60 years of age at the time of diagnosis and presented with signs of AMD, including at least one intermediate drusen (between 63 and 125 μm) and focal areas of hyper- and/or hypopigmentation, and/or large drusens (≥125 μm). Only patients with 12 or more months of follow-up were considered for the evaluation of results.

The criteria for diagnosis of PCV are summarised in Table 1. The diagnosis was positive only in the presence of ICG features, and treatment was performed if an active lesion was evident and subfoveal leakage was observed on FA.

In all cases, stereo color and red-free fundus photographs and stereo fluorescein and digital ICG angiograms were obtained with the Topcon ImageNet system. Images were reviewed by two independent reviewers (R.S., J.R.F.A.) at each 3-month interval and before any decision for treatment/no treatment/retreatment. Any disagreement was resolved by a third reviewer (J.G.C.V.).

VA was tested by a masked observer using the ETDRS chart, and the best-corrected VA was obtained in all patients. The evolution of VA was classified into three groups: VA improvement (one or more lines), unchanged,

Table 1 Diagnosis criteria for PCV (*RPE* retinal pigment epithelium, *CNV* choroidal neovascularisation)

Biomicroscopy and stereo red-free photography	FA	ICG
Reddish-orange lesions	Serosanguinous detachment of the RPE and neurosensory retina	Early and intermediate phases: dilated network of inner choroidal vessels with terminal hyperfluorescent aneurysm-like dilatations or "polyps"
Hypopigmentation of RPE	CNV	
Subretinal and sub-RPE haemorrhages		
Hard exudates		Late phases: two patterns — (1) washout (nonleaking lesions), (2) hyperfluorescence (active lesions)

and VA loss (less than three lines, with severe meaning loss of three or more lines).

The study was approved by an internal review committee and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Each included patient signed an informed consent form after being instructed on the experimental character of the PDT treatment for PCV.

Results

Forty consecutive eyes of 35 patients, 21 women and 14 men, with an average age of 76.3±5 years (range 60–87) were enrolled in the study. These eyes represented 10% of all consecutive AMD eyes submitted to PDT between May 2000 and June 2004.

Eighteen patients aged 75.6±7.6 years, nine men and nine women representing 21 eyes, completed 1 year of follow-up. PCV lesions were subfoveal in 20 eyes and juxtafoveal in one eye (case 8, Table 2). The mean number of PDT sessions was 2.9±0.9. VA improved in 12 eyes

Table 2 Evolution of VA, number of PDT sessions, presence or absence of ICG active lesions and FA leakage (exudation), and recurrences at 12 and 24 months (*SD* standard deviation)

	Initial VA 20/	VA 12 months 20/	No treat 12 months	Lines 12 months	VA 24 months	Lines 24 months	No treat 24 months	Clinical/ angiographic status 12 months	Clinical/ angiographic status at 24 months	Recurrences
1. AC	200	160	4	1				No exudation		
2. AC	400	400	3	0				Exudation		
3. AFS	100	100	4	0				Exudation		
4. ADS	400	250	2	2				No exudation		
5. CHC	50	40	4	1	40	1	6	Exudation	No exudation	Recurrence
6. CHC	40	25	4	2	50	−1	6	Exudation	No exudation	Recurrence
7. EJ	63	200	3	−5				No exudation		
8. ES	50	50	2	0	40	1	2	No exudation	No exudation	Recurrence at 1 year
9. FPSD	400	200	4	3				Exudation		
10. FPSD	80	640	3	−9				No exudation		
11. JSM	160	160	2	0				No exudation		
12. JNM	400	200	2	3				No exudation		
13. JP	160	400	3	−4				No exudation		
14. JPF	50	25	2	3				No exudation		
15. MFN	320	200	1	2	200	2	1	No exudation	No exudation	
16. MGB	400	200	2	3				No exudation		
17. MFB	100	160	4	−2				No exudation		
18. MR	160	100	4	2				Exudation		
19. MIVC	80	40	2	3	50	2	3	No exudation	Exudation	Recurrence
20. MJSF	100	50	4	3	63	2	6	Exudation	No exudation	Recurrence
21. MRF	160	160	2	0				No exudation		
Mean	184	179	2.9		73		4			
SD	138	150	0.9		62		2.2			
Range	40–400	25–640	1–4		40–200		1–6			

(57.1%) and was unchanged in five eyes (23.8%). VA decreased in four eyes (19%) by less than three lines in one eye and by three lines in three eyes (Table 2). Mean initial VA acuity of these 21 eyes was $20/200^{+2}$ (range 20/40 to 20/400), and mean final VA at 12 months was $20/200^{+3}$ (range 20/25 to 20/640).

Leakage was absent at the retinal and choroidal level in 14 eyes (66.6%) at 1 year. Recurrence occurred in one eye during the first year (case 8, Table 2). The number of eyes with VA less than 20/200 decreased from six at time of enrollment to four at 1 year. The number of eyes with VA ≥20/50 increased from four to six during the same period.

Six eyes completed 2 years of follow-up and showed, after 4±2.2 PDT sessions, VA improvement in five eyes (less than three lines) and VA decrease in one eye (one line). Mean initial VA acuity of these six eyes was $20/100^{+1}$ (range 20/40 to 20/320), and mean VA at 24 months was $20/63^{-2}$ (range 20/40 to 20/200). Recurrence occurred in four of these eyes during the second year of follow-up (Table 2). Leakage was absent at the retinal and choroidal level in five of these six eyes at 2 years.

Severe subretinal and sub-RPE haemorrhage occurred in one eye (case 13) more than 1 month after the PDT session, causing significant VA loss and fibrosis. VA decrease occurred in three other eyes at 1 year (cases 7, 10, 17) and in another eye between the 18- and 24-month visits (case 6). Subfoveal fibrosis was responsible for VA decrease in cases 6 and 7, and subfoveal atrophy was related to VA decrease in cases 10 and 17.

Baseline classification of the neovascular lesion of the study eye, using only FA, showed occult choroidal neovascularisation (OCNV) in all 21 eyes. ICG showed a dilated network of inner choroidal vessels with terminal hyperfluorescent aneurysm-like dilatations and/or "polyps" in all the cases.

No significant side effects were observed during the study, including RPE ripping or tears, severe acute VA loss, development of secondary CNV, photosensitivity, low back pain, or catheter-induced complications.

Discussion

Our study evaluated the safety and efficacy of PDT with Visudyne in AMD eyes with juxtafoveal or subfoveal PCV on ICG and subfoveal exudation on FA. As far as we know, only a prospective study was published until now regarding PDT in PCV [1].

PCV is a relatively well-defined entity [2–4, 7, 8, 10, 12, 13]. In our study, all the eyes presented signs of AMD, and the diagnosis of PCV was based on clinical and angiographic features (Table 1). In the presence of recurrent serous-sanguineous subretinal and/or sub-RPE detachments, the diagnosis is evident. When only FA is performed, these exudative lesions are classified in most cases as occult without classic CNV. ICG shows a typical pattern of choroidal vessels with terminal hyperfluorescent aneurysm-like dilations or "polyps" in the early and/or intermediate phases. In late phases these lesions may become hypofluorescent due to a washout effect (inactive lesions), or they may remain hyperfluorescent-active lesions. All the cases we submitted to PDT with Visudyne presented juxtafoveal or subfoveal ICG-active lesions and exudation on FA, with VA loss due to these lesions.

We found that PDT was effective and safe for treating PCV in AMD eyes in a series of 21 eyes at 1 year of follow-up. A total of 12 eyes (57.1%) showed some VA improvement at 1 year, with six eyes (28.5%) gaining three lines. The small group of six eyes with 2 years of follow-up showed VA improvement in 83.3% of cases (less than three lines) and VA loss in 16.6% of the eyes (one line). The higher final VA at 2 years when compared with the final VA at 12 months is not a result of progressive VA improvement. In fact, these six eyes presented a higher initial VA, and three out of six had some VA decrease between 12 and 24 months.

Recurrence of active lesions occurred in 4.7% of the eyes during the first year of follow-up and in 66.6% during the second year. The higher recurrence rate in eyes with longer follow-up was not followed by significant VA loss.

In our series all patients were Caucasian. Females represented 50% of the patients with 1 year of follow-up and 60% of the 35 patients included in the study. This is in accordance with other series with predominantly white or black populations, in which 18–47% of the patients were male [5, 12].

Our study has one important limitation: It had no control group. If we consider FA classification, almost all of these eyes would have clinical indications for PDT (OCNV with small lesions and/or VA 20/50). A control group would not be ethically acceptable in these cases.

The natural course of the disease is becoming progressively better understood. The disease has a remitting–relapsing course and is associated clinically with chronic, multiple, recurrent serosanguinous detachments of the RPE and neurosensory retina. Long-term preservation of good vision can be obtained. Approximately half the patients with PCV lesions in the posterior pole may have a favourable course without treatment [10]. In the remaining half, the disorder may persist for a long time with occasional repeated bleeding and leakage, resulting in severe macular damage and VA loss. Eyes with a cluster of grape-like polypoidal dilations of the vessels may have a higher risk for severe visual loss [10]. Most of the series analysing the natural history of PCV describe lesions in the posterior pole, differentiating macular from extramacular and/or peripapillary polyps [1, 4, 5, 10, 12, 13]. Macular involvement ranged from 25% [12] to 94% [10]. The analysis of VA outcome must consider location of polyps. Kwok et al. [4] followed the natural history of nine eyes with macular involvement after a follow-up ranging from 5 to 60 months and found VA improvement of two lines in

only one eye (11.1%), VA change of one line in one eye, and VA decrease of two lines in seven eyes (77.7%). Uyama et al. [10] followed 14 eyes with PCV (13 with macular involvement) for a mean period of 39.9 months and described VA improvement of two lines in five eyes (35.7%) and VA decrease of two lines in four eyes (28.5%). In our series we only treated eyes with macular involvement and juxtafoveal or subfoveal lesions. Despite this, PDT treatment with Visudyne has shown better results at 1 year than natural history. VA stabilisation or improvement was achieved in 80.9% (gain of two lines in 47.6%), and VA loss of two lines was present in 19% of the eyes.

Laser photocoagulation has been proposed for treating PCV lesions [4, 5, 10]. VA decrease of two lines has been shown to occur in 24–44% of the treated eyes with peripapillary and/or macular extrafoveal lesions [4, 5, 10]. Laser treatment of juxtafoveal or subfoveal lesions is not feasible and will promote immediate VA loss. PDT with Visudyne is an alternative.

As far as we know, only a prospective study was published until now on PDT in PVC. Chan et al. [1] reported that from a group of 22 PCV eyes from 21 Asian patients (four extrafoveal, two juxtafoveal, and 16 subfoveal lesions) treated with a mean number of 1.6 PDT sessions, 21 (95%) had achieved a VA stabilisation or improvement at 1 year of follow-up. In 13 eyes (59%) there was a VA gain of two lines, and in 50% of the cases had a final VA of 20/50. Three of the four eyes with extrafoveal lesions showed an improvement of three lines, with a final VA of 20/50. Our results are not as impressive. However, there are some differences between the series regarding potential impact on VA prognosis. The presence of extrafoveal lesions is one of them and is responsible for 27% of the cases with a final VA of 20/50 and for 23% of the eyes with VA gain of two lines in the series of Chan et al. [1]. Other differences are related to race (all of our patients are Caucasian), AMD (all of them had signs of AMD in both eyes), and older age (mean of 75.6 years in our series vs. mean of 66.6 years in Chan et al.'s series [1]). How these factors contribute is yet to be established.

We have treated only AMD patients with juxtafoveal or subfoveal PCV active lesions. Only one eye presented a juxtafoveal lesion, and its behaviour was apparently similar to subfoveal lesions, with the exception of being the only one with a recurrence in the first year of follow-up.

Most patients with evidence of PCV in one eye eventually develop similar lesions in the fellow eye [2]. We found bilateral PCV in 14.3% of the patients. However, 31.4% of the 35 patients presented disciform scar in the contralateral eye. The nature of the neovascular lesion originating the disciform scar was impossible to establish at that point. A PCV origin could not be ruled out in these cases.

The selection of the spot size for PDT may be a controversial issue. The ICG hot spots would probably indicate the size of the lesions to be treated. As other authors have done [1], we chose to treat the lesion with the size visualised on ICG (largest diameter plus 1 mm).

Leakage was absent at the retinal and choroidal level in 66.6% and 83.3% of the treated eyes at 12 and 24 months, respectively (Table 3). The number of treatments necessary to close the PCV lesion was widely variable (range of one to six over 24 months). The mean number of treatments was 1.9 and four at 12 and 24 months, respectively. These numbers are lower than the number of PDT sessions necessary to treat predominantly classic, OCNV, or minimally classic lesions [9, 11]. However, they are higher than those shown by Chan et al. [1].

One of the characteristics of PCV is the existence of recurrent subretinal and sub-RPE serosanguinous detachment. During follow-up, recurrence of exudation occurred in one eye up to 12 months and in four of the six eyes during the second year of follow-up. The longer the follow-up, the higher the probability of recurrence. More cases with longer follow-up times are necessary to evaluate the recurrence rate in PCV eyes treated with PDT. How PDT affects recurrence rate is yet to be determined. VA decrease was not related to recurrence rate.

In conclusion, PDT with verteporfin is effective and safe for treating active PCV lesions with subfoveal exudation. VA improvement and absence of leakage at 1 year occurred, respectively, in 57.1% and 66.6% of the eyes. The longer the follow-up, the greater the probability of recurrence.

Table 3 VA change, absence of leakage, and number of treatments at 12 and 24 months

Follow-up (*N*=)	VA improvement	VA no change	VA decrease %	Absence of leakage	No treatments: SD (range)
12 months (*N*=21)	12 eyes (57.1%) <3 lines: 6 eyes (28.5%) =3 lines: 6 eyes (28.5%)	5 eyes 23.8%	4 eyes 1–2 lines: 1 eye (4.7%) =3 lines: 3 eyes (14.2%)	14 eyes (66.6%)	2.9±0.9 (1–4)
24 months (*N*=6)	5 eyes (83.3%) <3 lines: 83.3%	0	1 eye (16.6%) <3 lines: 16.6%	5 eyes (83.3%)	4±2.2 (1–6)

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