Photodynamic Therapy for Age-related Macular Degeneration in a Clinical Setting: Visual Results and Angiographic Patterns

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• PURPOSE: To evaluate the visual outcome of patients with subfoveal choroidal neovascularization due to age-related macular degeneration, who received photodynamic therapy (PTD) in a clinical setting and to identify potential predictive visual and angiographic factors.

• DESIGN: Interventional case series.

• METHODS: The study included 74 patients with subfoveal choroidal neovascularization who underwent PDT from January 2000 to March 2001 and completed at least 1 year follow-up. All patients received verteporfin PDT and were followed clinically, with fluorescein angiography (74 eyes), and with indocyanine green angiography (65 eyes). A review of the medical records and angiograms was performed.

• RESULTS: Mean follow-up was 15.6 months. Patients received a mean of 3.4 treatments per year. Sixty-six percent lost less than 3 Snellen lines of visual acuity. Three patients (4%) experienced profound visual acuity loss to finger counting. Final visual acuity was positively correlated with lesion size and visual acuity at presentation. Visual outcome was worse in the presence of cystoid macular edema. On indocyanine green angiography, a round hypofluorescent spot was seen at the site of the PDT, with maintenance of medium and large choroidal vessels.

• CONCLUSION: Smaller lesion size and better visual acuity at presentation were good predictive signs, whereas cystoid macular edema was found to be a poor prognostic sign for visual outcome following PDT. (Am J Ophthalmol 2004;137:258–264. © 2004 by Elsevier Inc. All rights reserved.)

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AGE-RELATED MACULAR DEGENERATION IS THE LEADing cause of legal blindness in white persons aged 50 years and older in the United States, with choroidal neovascularization accounting for the majority of cases.[1–3] Photodynamic therapy (PDT) has been reported to result in vaso-occlusion of choroidal neovascularization, with minimal effect on the sensory retina and the retinal pigment epithelium.[4] The Treatment of Age-Related Macular Degeneration With PDT (TAP) Study Group[5,6] concluded that PDT is a safe and effective mode of treatment for patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration.

The purpose of this retrospective study was to evaluate the visual acuity of patients with subfoveal choroidal neovascularization caused by age-related macular degeneration after administration of PDT in a clinical setting. We also sought to identify possible predictive visual and angiographic factors for the outcome of this treatment.

METHODS

THE STUDY WAS CONDUCTED AT OUTPATIENT OPHTHALmology clinics in a university-affiliated medical institution. We reviewed the clinical charts and fluorescein and indocyanine green angiographies of 74 consecutive patients with subfoveal choroidal neovascularization due to age-related macular degeneration who were treated with verteporfin PDT from January 2000 to March 2001 and who completed at least 1 year of follow-up. All the patients (74 eyes) had fluorescein angiography, and 65 patients (65 eyes) had indocyanine green angiography.

The PDT was administered according to the TAP study[5] protocol, with follow-up every 3 months for at least 1 year (to May 2002). The need for repeated treatment was

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determined by the clinician, usually after 3 months if fluorescein leakage was noted. Fluorescein angiography was performed in all cases on initial and all follow-up visits with or without indocyanine green angiography. When both modes were used, they were performed sequentially, using the confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph; Heidelberg Engineering GmbH, Dossenheim, Germany).

Patient characteristics retrieved from medical charts included age, sex, Snellen visual acuity, treatment spot size, greatest linear dimension (including the choroidal neovascularization, the area of leakage, and areas of blocked fluorescence in the lesion, according to the TAP study),[5,6] number of treatments, and side effects. The angiographies were reviewed by two examiners (R.A.-S. and R.E.). The fluorescein angiography features recorded were percentage of classic choroidal neovascularization (a predominantly classic lesion was defined as a lesion in which classic choroidal neovascularization accounted for ≥50% of the area of the entire lesion at baseline[5]), presence of cystoid macular edema before PDT or during follow-up, and presence of retinal pigment epithelium detachment at presentation or after treatment. The indocyanine green angiography frames were screened for retinochoroidal anastomoses, a hypofluorescent area corresponding to the treatment spot, pigment epithelium detachment (which is well-demarcated on confocal indocyanine green angiography as an area of blocked fluorescence[7]), and retinal pigment epithelium tear.

We calculated the correlation among the initial visual acuity, the change in visual acuity, and the final visual acuity, and the relationship of each of these factors to the greatest linear dimension at presentation. The final visual acuity was also correlated with number of treatments, percentage of classic choroidal neovascularization, and presence of cystoid macular edema and pigment epithelium detachment.

Snellen visual acuity scoring was transformed to logarithm of the minimal angle of resolution (logMAR) units for the statistical analysis. We performed the Pearson χ^2 test, *t* test, and the Fisher exact test, using SPSS software (version 10, Professional Statistics Release, Chicago, Illinois, USA). The main outcome measures were visual acuity at 1 year; correlation between lesion size at presentation, initial visual acuity, and the final visual acuity; and correlation between angiographic features and final visual acuity.

RESULTS

WE TREATED 74 PATIENTS (74 EYES) WITH SUBFOVEAL CHOroidal neovascularization due to age-related macular degeneration during the study period. Patient demographics are presented in Table 1. The choroidal neovascularization data are presented in Table 2, and the visual acuity data in Table 3. The mean number of treatments per eye during the first year was 3.4 (Table 2). The mean greatest linear dimension increased from 2,841 μm (standard deviation [SD] = 1,212 μm; median, 3,000 μm) to 3,670 μm (SD = 1,286 μm; median, 4,125 μm). The mean Snellen visual acuity decreased from 6/12 (20/40) to 6/38 (20/125), and in logMAR units from 0.3 (SD = 0.28; median, 0.5) to 0.8 (SD = 0.5; median, 0.6; Table 3).

TABLE 1. Patient Demographics

n	74 Patients/74 Eyes
Sex	
Male	40
Female	34
Treated eye	
Right	40
Left	34
Age (yr)	55–92
Mean	76.3 (SD = 8.3)
Median	77
Follow-up (mos)	12–22
Mean	15.6 (SD = 3.6)
Median	14.1

TABLE 2. Choroidal Neovascularization Data

Predominantly classic CNV	65
Minimally classic CNV	6
Fully occult CNV	3
Initial GLD (μm)	300–5,800
Mean	2,841 (SD = 1,212)
Median	3,000
Final GLD (μm)	1,200–6,000
Mean	3,670 (SD = 1,286)
Median	4,125
No. of treatments (per eye)	1–8
Mean treatments per year	3.4

CNV = choroidal neovascularization; GLD = greatest linear dimension (of lesion).

TABLE 3. Visual Acuity Data

Initial (mean)	6/7.5–6/90 (6/24)
Mean (logMAR)	0.6 (SD = 0.28)
Median (logMAR)	0.5
Final (mean)	6/6–LP(6/38)
Mean (logMAR)	0.8 (SD = 0.5)
Median	0.6

LP = light perception; logMAR = logarithm of the minimal angle of resolution; SD = standard deviation.

TABLE 4. Visual Acuity Distribution After Photodynamic Therapy

	3 Months n (%)	6 Months n (%)	9 Months n (%)	> 12 Months n (%)
≥ 3 line increase	5 (6.7)	8 (10.8)	5 (6.8)	8 (10.8)
1–3 line increase	25 (33.8)	20 (27.0)	21 (28.4)	12 (16.2)
No change	22 (29.7)	16 (21.6)	16 (21.6)	10 (13.5)
1–3 line decrease	13 (17.6)	19 (25.7)	14 (18.9)	19 (25.7)
> 3 line decrease	9 (12.2)	11 (14.9)	18 (24.3)	25 (33.8)

n = 74 at all time points.

TABLE 5. Visual Acuity Distribution at ≥12 Months: Comparison With the TAP Report—1[5]

	All Patients* (N = 74) n (%)	Pr. Class* (n = 65) n (%)	TAP** (n = 402) n (%)
≥ 3 line increase	8 (10.8)	8 (12.3)	24 (6.0)
1–3 line increase	12 (16.2)	12 (18.5)	42 (10.4)
No change	10 (13.5)	12 (18.5)	87 (21.6)
1–3 line decrease	19 (25.7)	12 (18.5)	93 (23.1)
> 3 line decrease	25 (33.8)	21 (32.3)	166 (38.8)

Pr. class. = patients with predominantly classic choroidal neovascularization; TAP = Treatment of Age-Related Macular Degeneration With PDT Study Group.
*Snellen VA.
**ETDRS chart.

TABLE 6. Side Effects and Complications

Complications	n (%)
Severe visual loss to hand motion or counting fingers	3 (4.0)
Backache	3 (4.0)
Ocular discomfort	2 (2.7)

Table 4 shows the Snellen visual acuity at 3, 6, 9, and 12 months or more. After 1 year, the visual acuity improved in 27%, remained stable in 13.5%, decreased by less than three lines in 25.7%, and decreased by three lines or more in 33.8%. When the nine patients with minimally classic and fully occult choroidal neovascularization were excluded (Table 5), the estimated visual loss of less than three lines after 12 months was 67.7% (compared with 66.2% for the whole group of 74 eyes).

The side effects and complications are listed in Table 6. Low back pain occurred in three patients (4%). Ocular discomfort and itching occurred in two patients, 1 to 3 days following treatment. Three patients (4%) experienced profound visual loss to finger counting due to submacular hemorrhage, occurring 2 and 3 months after the third PDT in two patients, respectively, and 2 months after the fifth PDT in one patient. Two of the patients recovered vision to 6/60. The third patient developed vitreous hemorrhage and underwent pars plana vitrectomy, with final visual acuity of counting fingers. Skin light toxicity was not reported.

There was a positive correlation between the initial greatest linear dimension, visual acuity at presentation, and final visual acuity for all patients ($r = .265$ and $r = .351$, respectively; $P = .028$ and $P = .003$, respectively; Pearson correlation). That is, eyes presenting with smaller lesion and better visual acuity had better visual outcome. The subgroup of patients with predominantly classic choroidal neovascularization had better visual outcome as well ($r = .27$ and $r = .378$, $P = .046$ and $P = .004$, Pearson correlation). The latter subgroup also showed a positive correlation between greatest linear dimension and initial visual acuity alone ($r = .251$, $P = .005$; Pearson correlation). That is, patients with predominantly classic choroidal neovascularization presenting with smaller lesion had better initial visual acuity as well. No correlation was found in the whole group between final visual acuity and number of treatments per eye or percent of classic choroidal neovascularization at presentation ($P = .114$ and $P = .082$, respectively; Pearson correlation) or in the subgroup of patients with predominantly classic choroidal neovascularization, between number of treatments and percent of classic choroidal neovascularization ($P = .131$ and $P = .765$, respectively; Pearson correlation).

The fluorescein angiography and indocyanine green angiography features of the 74 patients (74 eyes) were reviewed. Fluorescein angiography was done in 74 eyes and indocyanine green angiography in 65. Fluorescein angiography revealed cystoid macular edema in 24 eyes, of which 12 (50%) lost less than 3 lines of visual acuity. There was a statistically significant correlation between the presence of cystoid macular edema and worse visual outcome ($P = .041$; χ^2 test). However, there was no statistically significant difference between the presence of cystoid macular edema and worse initial visual acuity; patients without cystoid macular edema had a mean logMar visual acuity of 0.69 (SD = 9.29), whereas patients without cystoid macular edema had a mean logMar visual acuity of 0.63 (SD = 0.3; $P = .315$, student t test). Of the 12 eyes with cystoid macular edema that lost more than 3 lines of visual acuity, 6 had retinochoroidal anastomoses on indocyanine green angiography. There was no statistically significant difference in the size of the choroidal neovascularization between eyes with and without cystoid macular edema ($P = .72$, t test).

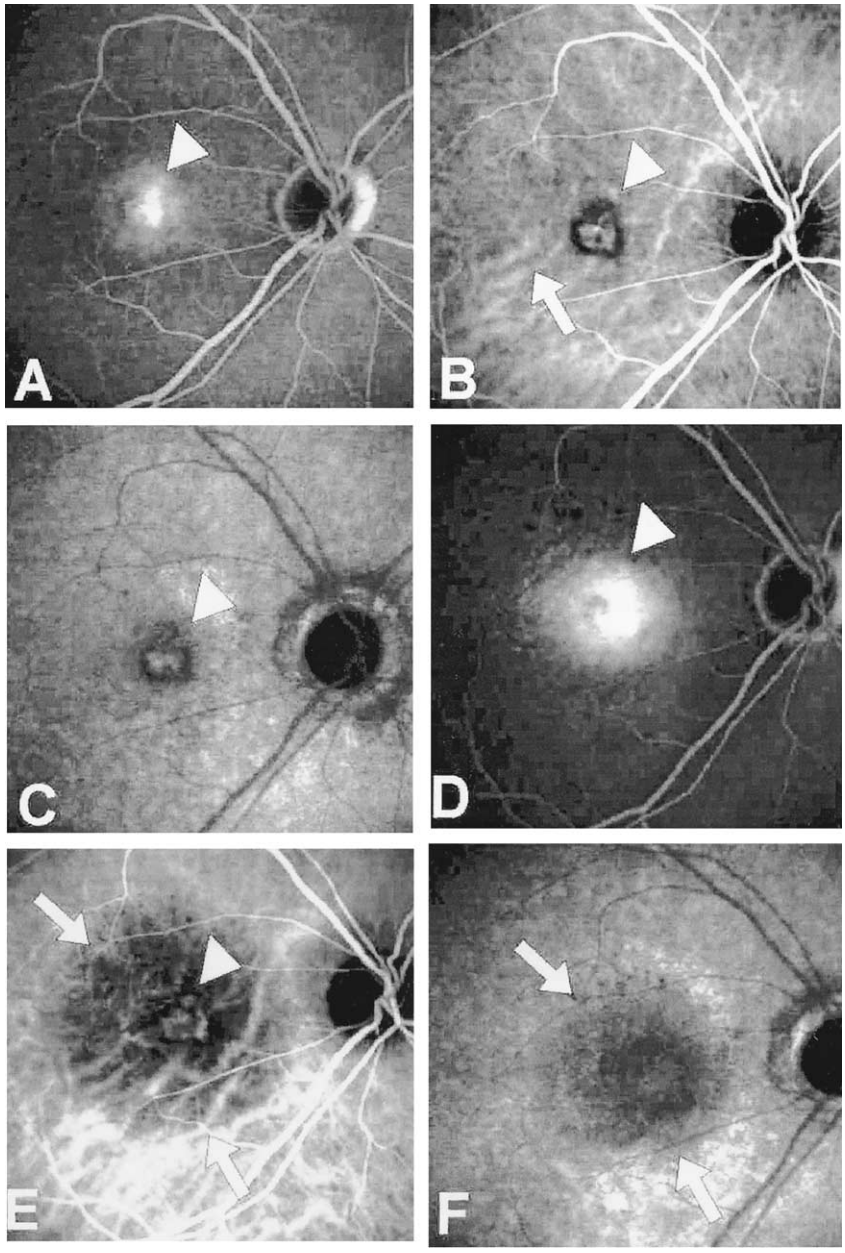

FIGURE 1. (A) Fluorescein angiography, pretreatment image: late leakage from classic subfoveal choroidal neovascularization (arrowhead). (B) Indocyanine green angiography, pretreatment image: midphase showing the classic subfoveal choroidal neovascularization (arrowhead) and the medium and large choroidal vessels (arrow). (C) Indocyanine green angiography, pretreatment image: late phase showing the subfoveal choroidal neovascularization (arrowhead). (D) Fluorescein angiography, posttreatment image: 3 months following third photodynamic therapy (PDT). Leaking subfoveal choroidal neovascularization (arrowhead). (E) Indocyanine green angiography, posttreatment image: 3 months following third PDT. Midphase angiogram showing the choroidal neovascularization (arrowhead) and a round hypofluorescent area corresponding to the treatment spot (arrows). The medium and large choroidal vessels are delineated against the hypofluorescent treatment spot. (F) Indocyanine green angiography, posttreatment image: 3 months following third PDT. Late-phase angiogram showing the hypofluorescent treatment area (arrows).

In all 65 eyes, indocyanine green angiography was performed before treatment, and 10 to 12 weeks after every PDT, together with the fluorescein angiography. In all the eyes examined with indocyanine green angiography, there was a round hypofluorescent area, corresponding to the treatment spot (Figure 1), with enhanced imaging of the

medium and large choroidal vessels in the treated area. Retino-choroidal anastomoses were found in nine eyes.

Seven patients with recurrent choroidal neovascularization after previous thermal laser treatment for extrafoveal choroidal neovascularization were included in the study. Visual acuity outcome was similar to that of the other patients, with 71.4% losing less than 3 Snellen lines ($P = 1.00$; Fisher exact test).

DISCUSSION

OUR FINDINGS SHOW THAT PDT IS WELL TOLERATED IN A clinical setting and minimizes visual loss in patients with choroidal neovascularization due to age-related macular degeneration. After 12 or more months of follow-up, 33.8% of our patients lost more than 3 Snellen lines of visual acuity. Of the 65 patients with predominantly classic choroidal neovascularization who completed at least 12 months of follow-up, 32.3% lost more than 3 lines of visual acuity. Twenty-seven percent of the patients had improved visual acuity (Table 5). Our series, without control subjects, compares favorably to the randomized, double-masked, multicenter TAP trial of verteporfin (Table 5).[5,6]

There was a positive correlation between initial and final visual acuity and between greatest linear dimension at presentation and final visual acuity: eyes presenting with better visual acuity and smaller lesions had a better visual outcome. Our results differ from the VIP trial (report 2),[8] which demonstrated that eyes with smaller lesions or lower levels of visual acuity responded better to PDT. The difference between our results and the VIP trial may be caused by the dissimilar natural history of occult and classic choroidal neovascularization. Our series includes eyes with predominantly classic choroidal neovascularization, whereas the VIP study reported on fully occult lesions. Previous studies have shown that visual acuity is worse in eyes that have predominantly classic subfoveal choroidal neovascularization than in eyes with occult choroidal neovascularization.[9–11] The natural history of occult choroidal neovascularization is variable, and visual acuity may be preserved for a long time period, whereas eyes with predominantly classic choroidal neovascularization tend to lose vision more rapidly. Thus, the better visual outcome in eyes with predominantly classic lesions presenting with smaller choroidal neovascularization and better visual acuity in our series may reflect the benefit of the early therapeutic intervention in a group of patients with poor natural history. In contrast, the results of the VIP study may point to the fact that eyes with occult choroidal neovascularization that have documented decline in vision benefit more from PDT compared with eyes that have higher levels of visual acuity because of the better natural history of these eyes. No correlation was found between final visual acuity and either percent of classic choroidal neovascularization at presentation or number of treatments per eye.

Patients with evidence of cystoid macular edema on fluorescein angiography at presentation or during follow-up had a worse visual outcome than those without cystoid macular edema: 12 of the 24 eyes with cystoid macular edema lost less than 3 lines of Snellen acuity ($P = .041$; χ^2 test). The presence of cystoid macular edema was detected by Soubrane and associates[12] in all forms of neovascular age-related macular degeneration, including classic and occult choroidal neovascularization, pigment epithelial detachments, and disciform scars. In their series, the occurrence of cystoid macular edema was not related to the duration of symptoms nor to the location, extent, or type of choroidal neovascularization and was compatible with useful vision, especially in patients with occult choroidal neovascularization. In the Foveal Photocoagulation Study, Bressler and associates[13] noted the presence of a well-demarcated area of hyperfluorescence that represented fluorescein pooling in compartmentalized space anterior to the choroidal neovascular leakage in one third of the eyes with well-defined subfoveal choroidal neovascularization associated with age-related macular degeneration. Although the observed "loculated fluid" conformed to the pattern of cystoid macular edema, the authors stated that it may have also pooled within an area deep to the sensory retina. No information was given on the visual acuity of the patients presenting with this fluorescein angiographic finding. In a recent study,[14] cystoid macular edema was demonstrated on optical coherence tomography imaging in 46% of 61 eyes with subfoveal choroidal neovascularization associated with age-related macular degeneration, more commonly in choroidal neovascularization containing classic component. The presence of cystoid macular edema and increased foveal thickness correlated with decreased visual acuity, as was noted in our study. The authors suggested that the retinal thickening (macular edema) may be a contributing factor to the decreased visual acuity in patients with age-related macular degeneration.[14]

Cystoid macular edema has been described as one of the angiographic features of retinochoroidal anastomoses in the setting of neovascular age-related macular degeneration. In our series, 6 of the 12 eyes with cystoid macular edema that lost more than 3 lines of Snellen acuity also had retinochoroidal anastomoses on indocyanine green angiography. Retinal choroidal anastomses have been reported in 21% to 28% of eyes with newly diagnosed occult choroidal neovascularization secondary to exudative age-related macular degeneration in two recent series.[15,16] The presence of a retinochoroidal anastomoses in patients with exudative age-related macular degeneration, as suggested by Kuhn and associates[17] and supported by Slakter and associates,[15] is a poor prognostic sign for laser treatment outcome. Thus, the presence of an retinochoroidal anastomoses in 6 of the 12 eyes, with cystoid macular

edema in our series, may have been related to the poor visual outcome for PDT treatment in this subgroup of patients.

To the best of our knowledge, the association between either cystoid macular edema or retinochoroidal anastomoses and the visual outcome for PDT has not been published to date, and it may point to subgroups of choroidal neovascularization that are less responsive to PDT, possibly requiring alternative or adjunctive treatment (such as intravitreal anti-vascular endothelial growth factor, intravitreal corticosteroids, or surgery). Further studies in this area are warranted to clarify the clinical implication of this observation.

The presence of a hypofluorescent area corresponding to the PDT spot on indocyanine green angiography was consistent. Hypofluorescence is demonstrated regularly on fluorescein angiography following PDT; it is most pronounced 1 week after treatment and resolves slowly during the following weeks, suggesting transient choroidal nonperfusion rather than masking.[18] A study of two human eyes enucleated 1 week following PDT reported a round hypofluorescence corresponding to the treatment spot on both fluorescein angiography and indocyanine green angiography.[19] On fluorescein angiography, the hypofluorescence was consistent throughout the angiogram. On indocyanine green angiography, in the early phases, there was a round hypofluorescent area with sharp demarcation, and in the late stages, the hypofluorescence was still present, with maintenance of the vascular pattern of the medium- and large-caliber vessels. Histopathologic studies of the same human eyes showed damage to the choriocapillary endothelium, followed soon after by recanalization of the occluded choriocapillaries, without significant alterations of the retinal pigment epithelium or the neural retina. The histologic results were consistent with the indocyanine green angiography findings. The authors suggested that indocyanine green angiography may serve as a clinical tool for documentation of photodynamic vascular effects.[19] Clinicopathologic study of a classic subfoveal choroidal neovascularization removed by submacular surgery 4 weeks after PDT, showed evidence of endothelial cell degeneration with platelet aggregation, thrombus formation, and vascular occlusion.[20] A clinicopathologic case series of eight eyes of eight patients who underwent submacular surgery for choroidal neovascularization after having previously received PDT[21] presents data from patients who refused repeat treatment with PDT or who developed submacular hemorrhage after initial PDT. The histologic specimens revealed partial vascular occlusion of the choroidal neovascularization 3 days after PDT, which was not present in later specimens. However, the later specimens demonstrated evidence of vascular damage as well.

The effect of PDT on perfusion and vascular integrity of choroidal neovascularization and surrounding choroid was studied by confocal indocyanine green angiography.[22] The study showed reduction in size with persistence of choroidal neovascularization, mainly of the choroidal feeding complex. Regrowth of the choroidal neovascularization, mainly from the feeding vessels, occurred regularly but did not reach baseline dimensions. Choriocapillary occlusion occurred at the surrounding choroid exposed to the photoactivation. Changes in the choroidal filling pattern and hypofluorescence persisted during long-term follow-up, especially after multiple PDT sessions. A reduction in perfusion within the PDT area, including the surrounding choroid was noted. The hypofluorescent area seen on indocyanine green angiography was 4.3 times greater than the original size of the choroidal neovascularization, and the mean diameter of the round hypofluorescent region was identical with the mean diameter of the treatment spot. The hypofluorescent area was larger in early than in the late phase indocyanine green angiography and persisted for as long as 16.5 months. The repair mechanisms in the choroidal neovascularization and the normal choroidal structures occurred slowly. We performed indocyanine green angiography 8 to 12 weeks after each PDT. Our findings were similar to those of Schmidt-Erfurth and associates.[22] The hypofluorescent spot was larger than the choroidal neovascularization, was larger in the early than in the late phase indocyanine green angiography, and persisted for months (Figure E and F). Medium- and large-caliber choroidal vessels were apparent in the early and middle phases of the study. Choroidal neovascularization was seen as well, probably due to recanalization. The hypofluorescent spot most probably represents the depletion of the choriocapillaries following PDT.[18,19,22] However, previous histopathologic studies in animals have shown PDT-induced damage to the retinal pigment epithelium as well.[23,24]

In conclusion, the results of our clinical consecutive case series should be compared with caution to those of the carefully designed TAP[5,6] and VIP[8] studies. Nevertheless, our preliminary study shows similar good visual outcome following PDT in a clinical setting as shown in the TAP study, which used a similar number of treatments per year. A better visual outcome was noted in the patients with smaller lesions and better visual acuity at presentation. Therefore, we recommend that PDT be performed as early as possible in the course of the disease. The visual outcome of patients with cystoid macular edema and retinochoroidal anastomoses was guarded, and we suggest that these subgroups be followed more critically and informed of a possible worse prognosis until further studies and treatment modalities become available.

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