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Photodynamic therapy for choroidal neovascularization in patients with multifocal choroiditis and panuveitis

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PURPOSE. *To evaluate the visual benefit of photodynamic therapy (PDT) with verteporfin in patients with choroidal neovascularization (CNV) secondary to multifocal choroiditis and panuveitis over a longer follow-up period.*

METHODS. *A total of 14 eyes of 12 patients (mean age 34 years) with a classic subfoveal CNV (13/14) or juxtafoveal CNV (1/14) were treated with PDT. Visual outcome was assessed by best-corrected visual acuity (VA). Morphologic characteristics of CNVs such as localization, size, and activity were monitored by fluorescein angiography.*

RESULTS. *Patients were followed for 3 to 45 months (mean 23 months). During this period, one to six PDTs (mean 2.4) were performed. At the time of the first PDT no acute inflammation was seen in the affected eyes. Improved or stabilized visual function (VA loss≤ 2 lines in the Early Treatment Diabetic Retinopathy Study chart) was observed in 71.4% of the eyes. A total of 78% of the eyes showed an inactive scar in the area of CNV after PDT. Treatment failure after PDT occurred due to uninfluenced CNV growth. No further complications were observed.*

CONCLUSIONS. *PDT in subfoveal or juxtafoveal classic CNV secondary to multifocal choroiditis and panuveitis stabilized or improved VA in the majority of patients over a longer follow-up period. No risk factor for failed VA rehabilitation could be defined. (Eur J Ophthalmol 2006; 16: 111-8)*

KEY WORDS. *CNV, Multifocal choroiditis, PDT, Uveitis*

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INTRODUCTION

Photodynamic therapy (PDT) is a fairly new therapeutic approach for choroidal neovascularization (CNV) in patients with age-related macular degeneration (ARMD) (1). Large prospective studies have demonstrated PDT to be efficient in improving the course of the disease especially in predominantly subfoveal classic CNV in ARMD with respect to visual stabilization as compared to the untreated control group (2-4).

Visual improvement was also reported after PDT in myopic patients with a subfoveal classic CNV (5, 6). Those observations suggest that PDT might be effective in most of the patients with subfoveal classic CNVs, and the effect might not be related to the underlying etiology.

CNV occurs in various inflammatory conditions (7-14). CNV development is one of the major vision-threatening complications in patients with multifocal choroiditis and panuveitis with a frequency of up to 46% of patients (13). The pathogenesis of CNV associated with multifocal choroiditis with panuveitis is not completely known. CNV appeared in patients with active uveitis but also in patients with clinically inactive uveitis. The active inflammation or the tissue injury resulting from previous inflammation is supposed to be an important CNV stimulus.

Extra- or juxtafoveal located CNVs can be treated by laser photocoagulation with significant stabilization of visual acuity as demonstrated in prospective randomized clinical trials (15, 16). In contrast, in patients with subfoveal classic CNV, laser photocoagulation did not achieve any

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improvement compared to the natural CNV course (17). Therefore, surgical removal of the CNV was suggested in this situation in patients with presumed ocular histoplasmosis but the overall final outcome was disappointing (18, 19).

Since the classic type of CNV is amenable to PDT, it was suggested that PDT should be beneficial for uveitic CNV. Among the different uveitis types, patients with multifocal choroiditis with panuveitis develop CNV most often. There are a few reports about the effect of PDT in CNV secondary to multifocal choroiditis with panuveitis (20-23) or to other inflammatory choroidopathies (24), but these reports included small numbers of treated patients or a shorter follow-up period. To evaluate the visual outcome and the morphologic changes after PDT in patients with CNV secondary to multifocal choroiditis with panuveitis, we performed a retrospective study. We were able to include more patients over a longer follow-up period than the published data up to date. Possible prognostic factors for good final outcome or visual acuity loss other than PDT were investigated.

MATERIALS AND METHODS

Patients

The diagnosis of multifocal choroiditis with panuveitis was made based on the following clinical criteria: bilateral multiple choroidal lesions of varying sizes (50–350 µm) at the posterior pole and midperiphery, or presence or history of anterior uveitis or vitritis (25). Systemic disease as a cause of uveitis was ruled out by extensive reviewing of systems and consultation with a rheumatologist.

Each patient was informed about the risks and benefits of the verteporfin therapy. Written informed consent was obtained following the Tenets of Helsinki.

Verteporfin therapy

Before each treatment, the area of fluorescein leakage in late fluorescein angiography (FA) was assessed using the Heidelberg Retina Angiograph (HRA) measurement tool. Areas of hypofluorescence due to blood next to the hyperfluorescent area were included in the maximal dimension of the lesions. Treatment was performed following the TAP recommendations (26). Each patient was intravenously administered 6 mg verteporfin/m^2 body surface over a period of 10 minutes. A diode laser (689 nm, intensity 600 mW/cm^2, 50 J/cm^2) was applied over the neovascular lesion 15 minutes after the infusion started.

Follow-up visits were scheduled in 6-week periods after each treatment. Patients who did not require a verteporfin retreatment after 3 months were then seen at 3-month intervals. Patients who received a PDT re-treatment after 3 months were then seen again in a 6-week period. At each visit best-corrected visual acuity (VA) at the ETDRS chart, slit-lamp examination, Goldmann tonometry, direct and indirect ophthalmoscopy, and FA using the HRA were performed.

TABLE I - DEMOGRAPHIC DATA OF THE INCLUDED PATIENTS

Patient no.	Sex	Age at onset, yr	Duration of symptoms, mo
1	M	25	24
2	F	40	0.3
3	F	13/14*	2/0.25*
4	F	56	8
5	M	39	4
6	F	29	0.25
7	F	35	1
8	F	28/28*	1/1*
9	F	35	1
10	M	71	1
11	F	38	2
12	F	30	0.5

*Right/lefteye

RESULTS

Demographic data and clinical signs

A total of 12 patients (9 female, 3 male) were included in the study (Tab. I). Two of the 12 patients developed CNVs in both eyes (Patient 8: at the same time). The age at the time of the first PDT varied from 13 to 71 years (mean 34 years).

All patients showed typical signs of multifocal choroiditis with panuveitis with multiple size-variable lesions in the posterior pole and the midperiphery. Besides a few inflammatory cells in the anterior chamber and/or vitreous no inflammatory uveitic activity such as chorioretinal infiltration was evident at the time of CNV. The 71-year-old patient did not show any typical signs of age-related macular degeneration. Myopia was found in 9/14 eyes (6/9 eyes: mean -4 diopters). Decreased VA was the patients' main complaint. The duration of symptoms (visual loss) lasted from 1 week to 24 months (Tab. II).

In all but one eye CNVs were located subfoveal. Patient 3 showed a juxtafoveal CNV in her left eye. We included this eye in our analysis despite the juxtafoveal location at the time of the first PDT for two reasons. The patient was also affected in the other eye, assuming the same underlying pathogenesis. The leakage extended to the subfoveal area at follow-up as a sign of uninfluenced CNV with increasing CNV size. The CNVs were associated with subretinal blood in 12 of 14 eyes. The CNV diameter ranged from 1.13 to 2.98 mm (mean 1.93 mm) prior to PDT. In all patients, the second eye was affected by multifocal choroiditis with panuveitis, whereas four patients showed a disciform scar, and two patients developed a CNV during the follow-up period (Patient 3: treated with PDT, Patient 11: extrafoveal CNV treated with laser photocoagulation).

Ten of 12 patients received oral corticosteroid therapy one time before or after the PDT. In 5/10 patients, this therapy was already started prior to the first PDT and was terminated before PDT (3/5) or after PDT (2/5). The corticosteroid therapy was a standard care prior to PDT consideration in those five patients. Recurrent uveitis in the non-treated eye including CNV development was the indication to start oral corticosteroid therapy in 4/10 patients. In another patient, CNV did not respond to recurrent PDT and therefore, oral corticosteroid therapy was initiated. In 3/14 eyes, extrafoveal CNVs were treated with laser photocoagulation 28, 6, and 3 months prior to the first PDT.

Photodynamic therapy: Frequency, re-treatments, visual and morphologic outcome

One to six (mean 2.4) PDT applications were necessary in these patients. Recurrent or non-responding CNVs required a re-treatment in 9/14 eyes (Tab. II). The re-treatments were performed after at least 3 months after the first or consecutive application. The time interval of the re-treatments was within the first year after the first PDT in 6/9 eyes (one to three re-treatments).

TABLE II - CNV CHARACTERISTICS PRIOR TO PDT AND VA OUTCOME AFTER PDT

Patient	CNV size, mm	Follow-up, mo	Number of PDTs	VA prior to PDT	VA at follow-up	Morphology at follow-up
1	2.72	45.6	1	20/100	20/800	Scar
2	1.13	39.7	4	20/400	20/63	Scar
3 OD	1.48	33.8	6	20/100	20/200	Scar
OS	1.4	17.1	3	20/100	20/63	Scar
4	2.03	25.5	1	20/250	20/400	Scar
5	1.6	39.0	2	20/80	20/40	Scar
6	1.8	24.6	3	20/40	20/200	Scar
7	2.83	7.1	2	20/80	20/400	Scar
8 OD	1.64	16.6	2	20/160	20/25	Scar
OS	1.5	16.7	2	20/125	20/200	Active CNV
9	2.89	9.3	1	20/200	20/20	Scar
10	2.98	3.9	1	20/100	20/80	Active CNV
11	1.65	4.2	1	20/40	20/32	Scar
12	1.34	39.1	5	20/100	20/200	Scar

CNV = Choroidal neovascularization; PDT = Photodynamic therapy; VA= Visual acuity; OD = Right eye; OS = Left eye

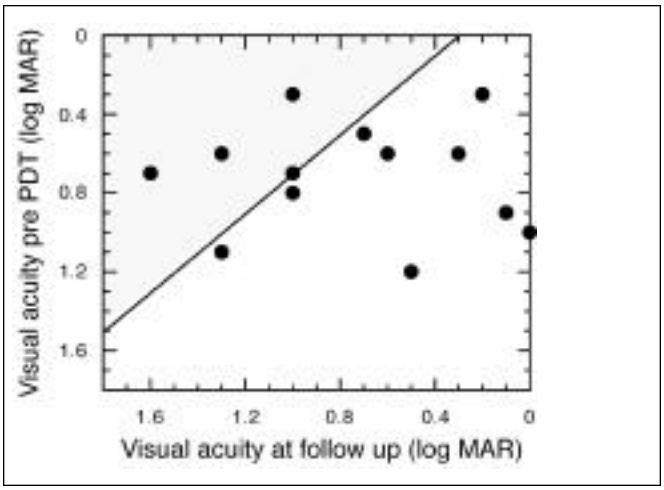

Fig. 1 - *Visual acuity (logMAR, Early Treatment Diabetic Retinopathy Study [ETDRS]) outcome in patients with multifocal choroiditis with panuveitis after photodynamic therapy (PDT). Data points on the slope and left of the slope (grey background) represent a loss of three or more lines in the ETDRS chart. Data points right of the slope represent stabilized (loss of fewer than three lines in the ETDRS chart) or improved visual acuity after PDT.*

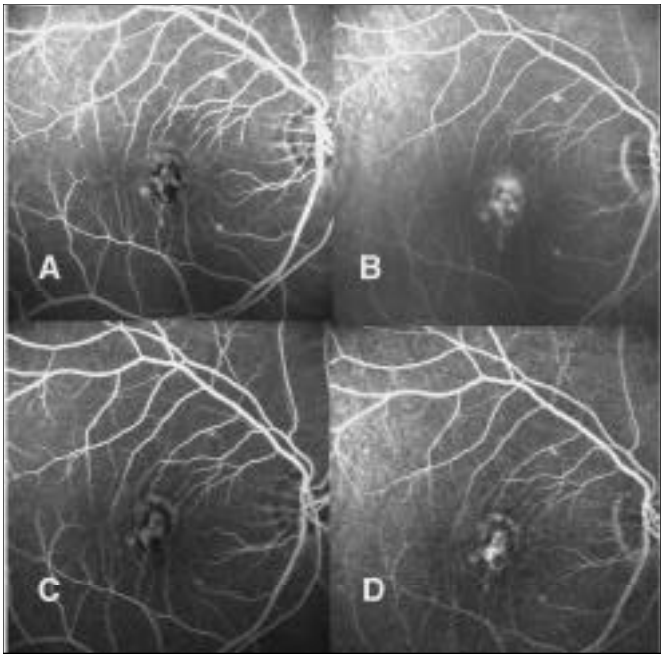

Fig. 2 - *Patient 8, right eye: Fluorescein angiography (FA) early and late phase prior to the photodynamic therapy (PDT) (**A–B**) showed a classic subfoveal choroidal neovascularization (CNV) with leakage in late FA (visual acuity 20/160). A total of two PDTs were applied. At the last examination, 16 months after the first and 11 months after the second PDT, there was no active CNV detectable (**C–D**). Late FA (**D**) demonstrates staining but no more leakage in the area of CNV (visual acuity 20/25).*

The other 3 patients required one, five and six re-treatments after 16, 28, and 24 months, respectively. None of the patients reported side effects after receiving verteporfin.

Fifty percent of the patients were seen for a follow-up period of more than 2 years after PDT (follow-up: 3–45 months, mean 23 months) (Tab. II).

A loss or improvement of three or more lines on the ETDRS chart was considered to be a decrease or increase in VA, respectively. A loss of fewer than three lines in the ETDRS chart was considered to be stabilized VA. Figure 1 illustrates the VA outcome in all patients. Stabilized or improved VA was observed in 10/14 (71.4%) eyes (data points right of the slope in Fig. 1). A loss of more than three lines was seen in 4/14 (28.6%) eyes (data points on the slope or left of the slope in Fig. 1). In the majority of patients, there was no active CNV visible by ophthalmoscopy or FA. In the area of the formerly active CNV, a disciform scar was found in 12/14 eyes. Two patients received PDT re-treatment at the last visit. All patients with loss of more than three lines after PDT showed scarring after uninfluenced CNV growth[(1)]. No recurrent CNV was observed (Tab. II).

To evaluate possible risk factors for severe visual loss other than PDT, age, sex, previous laser photocoagulation treat-

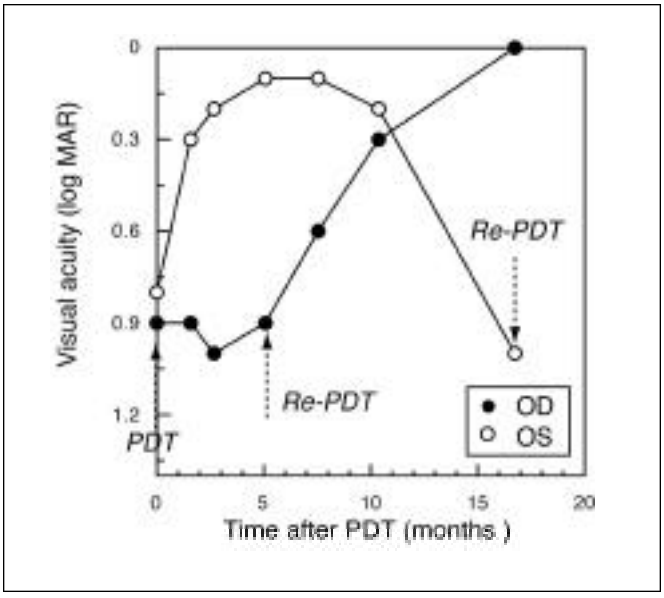

Fig. 3 - *Patient 8: Visual acuity (logMAR) outcome over a period of 15 months after the initial photodynamic therapy in both eyes. Filled symbols represent the right, unfilled symbols the left eye.*

(1) CNV localized at the same retinal area with increasing size and/or uninfluenced or increased activity at the time of the follow-up visit.

ment, and CNV size and location were compared between the groups with visual stabilization and with visual loss using analysis of covariance. For none of these factors could a significant difference between the two groups be found.

Case report 1: Patient 8 (Figs. 2-4)

This 28-year-old woman reported decreased vision in both eyes lasting 1 month. Multifocal choroiditis with panuveitis was first diagnosed 1 year prior to these acute visual complaints and was inactive since then. There was no history or signs typical of other ocular or systemic diseases. VA was 20/160 in her right eye and 20/125 in her left eye. Slit-lamp biomicroscopy revealed a normal anterior segment except for vitreous cells in the right eye. Both eyes showed a classic subfoveal CNV with bleeding and more than 20 medium-sized (100–300 µm) choroidal lesions at the posterior pole and in the midperiphery. FA confirmed the presence of a classic subfoveal CNV measuring 1.64 mm and 1.5 mm in the right and left eye, respectively (Fig. 2, A–B: right eye, Fig. 4, A–B: left eye). PDT was performed in both eyes without any complications.

VA did not improve initially after PDT in her right eye. FA revealed a reduced and inactive CNV at her 3-month visit after PDT. Another 2 months later (5 months after the initial PDT), a reactivated subfoveal CNV was evident and, therefore, a second PDT was applied. Eleven weeks after this second PDT, decreased CNV activity (Fig. 2, C–D) and significant improvement in VA were found, as illustrated in Figure 3.

In her left eye, VA increased to 20/32 and remained stable until 16 months after the first PDT (Fig. 3). In Figure 4, the initial active subfoveal CNV (A–B) with leakage in the late FA is shown. One year after PDT, the CNV showed staining but no leakage in FA and, therefore, no PDT retreatment was necessary. At the same time, additional surrounding choroidal lesions but no inflammatory cells in the anterior or posterior chamber were present (Fig. 4, C–D). Four months later (16 months after the first PDT), the patient reported reduced vision in her left eye and VA had dropped to 20/200. Figure 4, E–F, shows the reactivated subfoveal CNV involving the choroidal lesions detected at the preceding visit and therefore a second PDT was performed. The patient is now living abroad and was not available for a follow-up examination.

Case report 2: Patient 6 (Fig. 5)

A 29-year-old otherwise healthy woman had decreased VA in her left eye lasting 1 week. Multifocal choroiditis with panuveitis was first diagnosed 11 years ago and had been inactive for the last 11 months. She was treated with oral corticosteroids over 4 weeks, 11 months prior to this visit. On her first visit, VA was 20/200 in her right eye and 20/40 in her left eye. Ophthalmoscopy revealed vitreous cells, an active subfoveal classic CNV, and approximately 10 100–300 µm choroidal lesions at the posterior pole in the left eye (FA in Fig. 5, A–B), and a disciform scar in the right eye. Three months after PDT, VA was stable in her left eye though the patient complained of decreased vision compared to the initial visit. FA revealed an increased area of leakage at this time (Fig. 5, C–D). Therefore, PDT

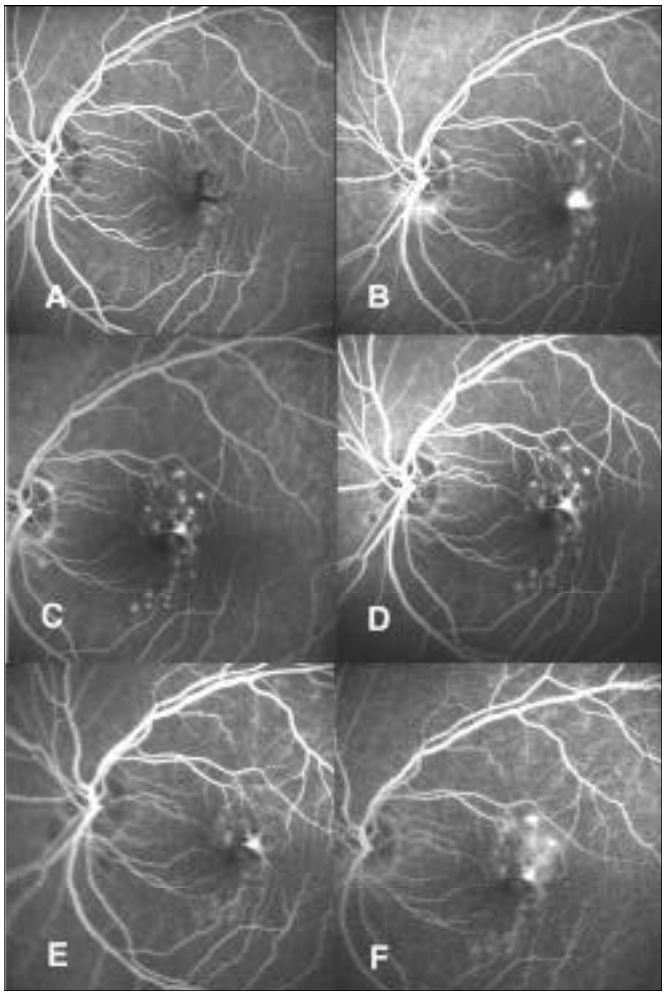

Fig. 4 - *Patient 8, left eye: Fluorescein angiography (FA) early and late phase prior to the photodynamic therapy (PDT) (**A–B**) showed a classic subfoveal choroidal neovascularization (CNV) with leakage in late FA (visual acuity [VA] 20/125). One year after PDT there was no active CNV detectable (**C–D**) (VA 20/32). Sixteen months after PDT a recurrent subfoveal CNV was evident with leakage in late FA (VA 20/200) (**E–F**).*

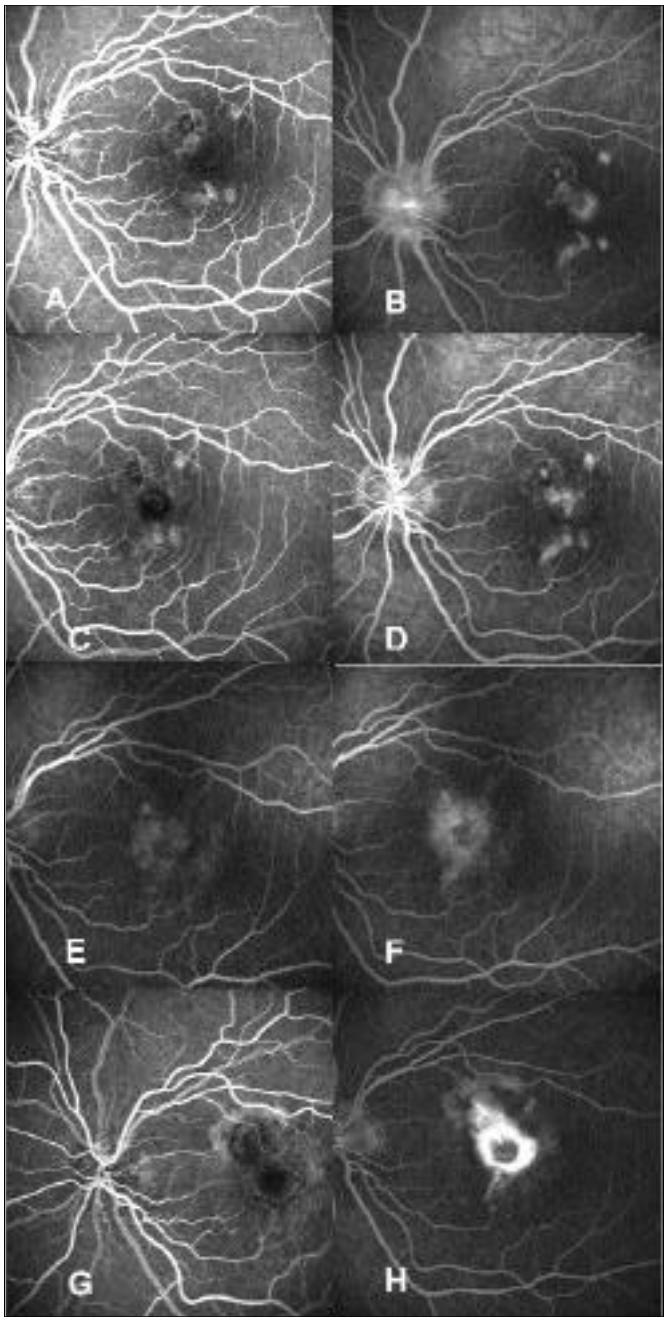

Fig. 5 - *Patient 6, left eye: Fluorescein angiography (FA) early and late phase prior to the photodynamic therapy (PDT) (***A–B***) showed a classic subfoveal choroidal neovascularization (CNV) with leakage in late FA (visual acuity [VA] 20/40) and multiple hyperfluorescent choroidal lesions in the posterior pole without leakage.*
FA showed an increasing area of leakage of the subfoveal CNV 3 months after the first PDT (VA 20/40; **C–D***) and 8 months after the first (5 months after the second PDT) (VA 20/125;* **E–F***).*
G *and* **H** *show an inactive disciform scar with staining 24 months after the first/5 months after the third PDT (VA 20/200).*

was repeated in this eye. Five months after the second PDT, VA had dropped to 20/125 and, again, a larger area of leakage was visible (Fig. 5, E–F). After the third PDT, VA dropped further to 20/200. At the last examination, 24 months after the initial and 5 months after the most recent PDT, an inactive subfoveal CNV without evidence of uveitic activity was found (Fig. 5, G–H).

DISCUSSION

In this study, we have demonstrated that patients with multifocal choroiditis with panuveitis without an associated disease, who developed subfoveal or juxtafoveal CNVs, may benefit from PDT using verteporfin. We have followed a fairly large number of patients with this uncommon disorder over a period of 2 or more years in 50% of the eyes treated. Visual acuity was stabilized or improved in 10/14 eyes (71.4%). Most of the eyes exhibited an inactive scar at their final consultation.

Those results are similar to the visual outcome after PDT in subfoveal predominantly classic CNV in ARMD. There, 59% of the treated patients lost fewer than three lines after 2 years (27). It can be assumed that the common final pathways in the CNV angiogenesis in ARMD and multifocal choroiditis with panuveitis are similar. Any process that destroys the integrity of the choriocapillaris–, RPE–, and Bruch's membrane–complex induces a high risk for CNV. Inflammatory mediators can further result in migration and proliferation of the capillary endothelial cells. Independently, the development of a chorioatrophic scar itself may result in a direct contact between the choroid and the subretinal space, resulting in an ingrowth of choroidal capillaries under the RPE and the retina.

Our results are in concordance with the reports on patients with multifocal choroiditis with panuveitis and CNV treated with PDT by Rogers et al (21) and Spaide et al (20). The former reported an improved or stabilized visual acuity in three patients with subfoveal CNV after one to two PDTs after a follow-up of 11 to 15 months. Similarly, Spaide et al (20) described a visual benefit after one to three PDTs in seven patients having a subfoveal CNV after a 3- to 18-month follow-up period. In both studies, PDT was performed one to three times, fewer compared to our patient group. The reason for the fewer PDT re-treatments in both reports is not known. The longer follow-up period in our group, which harbors a potentially higher risk of disease reactivation, might account for this observation. It

may also be speculated that the course of the inflammatory disease may differ between all those patients.

Among the four patients who showed a VA loss of more than three lines, other than PDT, no potential risk factors for visual loss could be defined. Sex, age at onset, duration of symptoms, CNV size, previous photocoagulation of an extrafoveal CNV, or number of PDTs did not differ significantly from the group that benefited from PDT. There is profound evidence that PDT is followed by a local inflammatory reaction and this might be increased in patients with underlying uveitis. Corticosteroids by their anti-inflammatory and antiangiogenic properties could therefore provide a synergistic effect on the CNV treatment. As shown by Spaide et al (28), intravitreal triamcinolone application in combination with PDT seems to be beneficial for reducing CNV activity in ARMD. Therefore, in patients with sustained CNV activity, CNV growth, and visual loss despite repeated PDT, an anti-inflammatory treatment such as intravitreal triamcinolone injections or high-dose systemic treatment may be indicated.

In summary, we have shown that PDT is an efficient and safe treatment in mainly subfoveal classic CNVs in multifocal choroiditis with panuveitis that occurs without associated disease. More than 71.4% of the patients experienced stabilized or improved vision over a longer follow-up period. Patients with severe visual loss despite PDT showed uninfluenced CNV growth but no CNV recurrence.

The authors have no commercial interest.

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