European Journal of Ophthalmology / Vol. 13 no. 8, 2003 / pp. 681-686

Sequential combined therapy for treatment of choroidal neovascularization in age-related macular degeneration: Photodynamic therapy and thermal laser photocoagulation

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PURPOSE. *To analyze the results achieved after treating extrafoveal choroidal neovascularization (CNV) recurrences with thermal laser photocoagulation (TLP) in patients who had previously undergone photodynamic therapy (PDT).*
PATIENTS AND METHODS. *Seven eyes (seven patients: four women and three men) that had been initially treated by PDT for CNV associated with age-related macular degeneration (ARMD) and then developed extrafoveal recurrences were treated with green argon TLP. All patients underwent a complete ophthalmologic evaluation and fluorescein angiography. Mean age was 74.4±4.4 years (range, 69 to 81 years). Five right eyes and two left eyes were treated. Mean follow-up after the beginning of the treatment with PDT was 18.0±3.5 months (range, 11 to 22 months). Follow-up after TLP was 6.8±1.0 months (range, 6 to 8 months).*
RESULTS. *Mean best-corrected visual acuity (BCVA) before treatment was 20/150 (range 20/400 to 20/40). After PDT it was 20/281 (range, 20/400 to 20/80), with a mean of 3.1±0.8 treatments (range, 2 to 4). After TLP, BCVA was 20/233 (range, 20/400 to 20/80), with no statistically significant difference from BCVA after PDT (p=0.06, Student's t-test paired data). In all cases total closure of CNV was achieved after only one session of TLP.*
CONCLUSIONS. *TLP could be helpful in association with multiple sessions of PDT in order to achieve a complete closure of subfoveal CNV secondary to ARMD. Further studies are required to confirm our findings. (Eur J Ophthalmol 2003; 13: 681-6)*

KEY WORDS. *Choroidal neovascularization, Photodynamic therapy, Thermal laser photocoagulation*

Accepted: July 21, 2003

INTRODUCTION

Age-related macular degeneration (ARMD) is an important cause of vision loss in aged people in Europe (1) and the United States (2). Choroidal neovascularization (CNV) is a form of ARMD in which abnormal blood vessels develop in the subretinal space, either between the neurosensory retina and retinal pigment epithelium and/or between the retinal pigment epithelium and the choriocapillaris, thus causing serious vision loss (3).

Treatment of CNV includes thermal laser photocoagulation (TLP) if CNV is extrafoveal and well demarcated

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(4, 5). Recently, photodynamic therapy (PDT) has proved useful in some forms of subfoveal CNV (6-8). However, reactivation of CNV is not uncommon, making retreatment necessary, sometimes in several sessions (6-8), the location and type of CNV determining the therapeutic approach (9). Recently, the combination of TLP and PDT has been proposed as more beneficial than either alone for juxtafoveal or extrafoveal CNV (10).

The purpose of this study was to analyze the results obtained after treating extrafoveal CNV recurrences with TLP in patients previously treated with PDT.

PATIENTS AND METHODS

Patient selection

Among those patients who had undergone one or more sessions of PDT for subfoveal classic CNV related to ARMD at our hospital between October 1999 and October 2001, those who later developed extrafoveal CNV were selected for TLP.

Inclusion criteria for PDT were as follows: pretreatment best-corrected visual acuity (BCVA) less than or equal to 20/40 (Early Treatment Diabetic Retinopathy Study [ETDRS] chart), no other ocular findings associated with ARMD, no previous foveal laser treatment, clinical evidence of subfoveal CNV occupying more than 50% of the lesion confirmed with fluorescein angiography (FA), CNV with a classic component of more than 50% confirmed by FA, area to be treated by PDT not within 200 µm of the border of the optic disk, and total diameter of the membrane less than 5400 µm.

Inclusion criteria for TLP treatment were as follows: presence of an area of well-demarcated FA leakage after PDT treatment in extrafoveal location (200 mm of the center of the avascular zone) and no leakage in the center of foveal avascular zone (200 mm). Areas with only late stain in FA and without fluorescein leakage were not considered as recurrences.

Treatment parameters

PDT was performed as previously described in the literature (6). In short, a solution containing 6 mg/m^2 of body surface of verteporfin (Visudyne, Novartis Co., Bülach, Switzerland) was injected in the dorsal vein of the hand with a continuous infusion pump (30 ml over 10 min). Fifteen minutes after the beginning of the infusion (5 minutes after its end), the drug was activated through the application of a diode laser at 689 nm (Visulas 690s, Carl Zeiss, Jena, Germany) at an intensity of 600 mW/cm^2. The laser was applied over the retinal lesion with one single spot, with a diameter 1000 µm wider than the lesion, for 83 seconds. The laser was precalibrated to release 50 J/cm^2 and was applied with a contact lens (Widefield, Ocular Instruments, Bellevue, USA).

Patients were instructed to avoid direct sunlight for 48 hours and wear low (4%) transmittance sunglasses.

TLP was performed using confluent direct green argon (514 nm wavelength, Nidek AC-230, Nidek Co., Tokyo, Japan) using a Goldmann contact lens (Ocular Instruments Co.) with 200 µm spot diameter, time 0.5 seconds, and sufficient intensity to obtain uniform whitening of the overlying retina, covering the lesion.

The procedure was explained to the patients, and written informed consent was obtained before treatment.

Ophthalmologic evaluation

All patients were evaluated 1 and 3 months after PDT by means of a complete ophthalmologic examination that consisted of BCVA determination with ETDRS charts, slit-lamp examination, anterior and posterior segment biomicroscopy, intraocular pressure determination, and FA, which included early and late frames (up to 10 minutes) in order to determine the presence and degree of CNV activity.

Treatment decision-making

Treatment or retreatment decision-making was based in all cases on FA. All patients were treated by PDT and returned for follow-up at 1 month and at 3 months. If FA proved leakage showing CNV activity that extended from the center of the foveal avascular zone, the patient was retreated by PDT. If an area of well-demarcated FA leakage in extrafoveal location was noted, the patient was treated by TLP.

When no fluorescein leakage from CNV was noted or when only late stain from a previously treated site appeared in FA the patients were instructed to return for follow-up at 3 months.

RESULTS

Seven (four women, three men) of 267 patients (2.6%) (7 of 282 eyes, 2.5%) who had received one or more sessions of PDT for subfoveal CNV were selected and treated by TLP for extrafoveal CNV.

Total follow-up of the patients after first PDT treatment was 18.0±3.5 months (range, 11 to 22 months). After TLP, follow-up was 6.8±1.0 months (range, 6 to 8 months).

Mean age was 74.4±4.4 years (range, 69 to 71 years). Five patients received treatment in the right eye and two in the left eye. Follow-up after PDT treatment was18.0±3.5 months (range, 11 to 22 months). After TLP, follow-up was 6.8±1.0 months (range, 6 to 8 months).

BCVA in our patients at baseline was 20/150 (range, 20/400 to 20/40). In all patients, CNV were subfoveal and predominantly classic. The patients are described in Table I.

Mean greatest linear diameter of the extrafoveal CNV was 4682±1130 μm (range, 3361 to 6958 μm).

The average number of PDT treatments was 3.1±0.8 (range, 2 to 4). No recurrences appeared after TLP in the follow-up period in these patients, with only one laser session required in all cases.

After PDT, mean BCVA was 20/281 (range, 20/400 to 20/80). After TLP, BCVA was 20/233 (range, 20/400 to 20/80). No statistically significant differences between BCVA after PDT and after laser treatment were observed (p=0.06, Student's t-test paired data). In all patients, extrafoveal CNV was totally closed after one session of photocoagulation. FA controls were performed at 15 days and at 1 month.

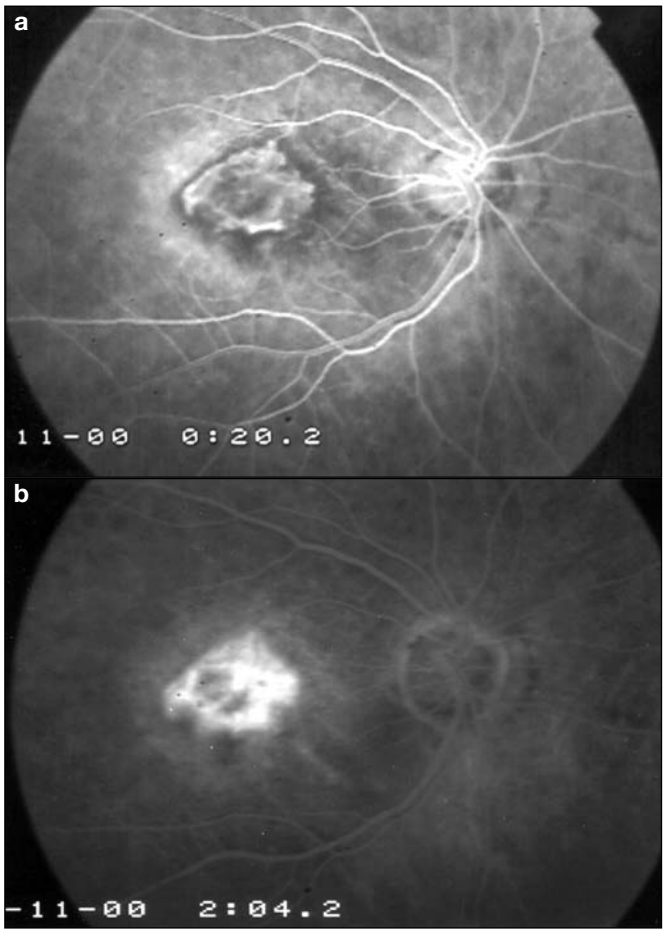

Fig. 1 - *Middle and late phases of fluorescein angiography show subfoveolar classic choroidal neovascularization associated with age-related macular degeneration.*

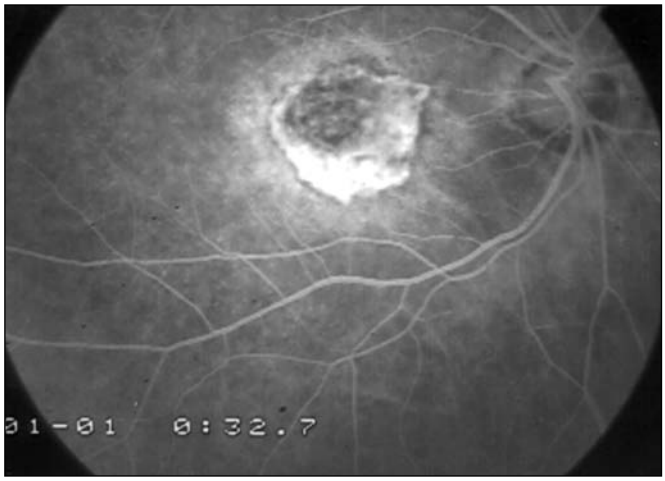

Fig. 2 - *Middle phase of fluorescein angiography of the same eye in Figure 1 three months after photodynamic therapy treatment with leakage from choroidal neovascularization.*

Case report

A 69-year-old woman attended our hospital with loss of vision in her right eye (RE) and metamorphopsia in October 2000. BCVA in RE was 20/126 and a classic subfoveal CNV (Fig. 1, a and b) was diagnosed by FA.

PDT was performed, and 3 months later (January 2001) BCVA was 20/166 and leakage from CNV (Fig. 2) was found in FA. A new PDT treatment was performed. In April 2001 BCVA was 20/132. FA showed staining but no leakage (Fig. 3). Three months later (June 2001), BCVA was 20/252 and an area of well-demarcated FA leakage in extrafoveal temporal loca-

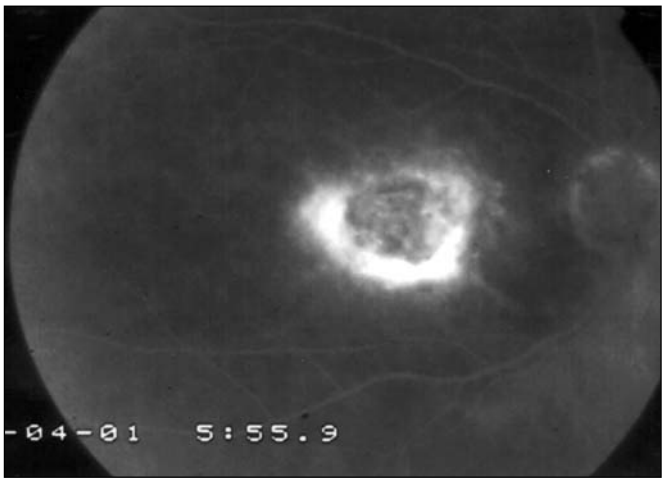

Fig. 3 - *Three months after second photodynamic therapy treatment fluorescein angiography (late phase) showed staining but no leakage.*

tion was found (Fig. 4) with no leakage in the center of foveal avascular zone.

TLP as described previously (4) was performed in July 2001. Fifteen days later, BCVA was 20/400 with extrafoveal CNV totally closed. Two months later (August 2001), BCVA was 20/200 with closure of the CNV (Fig. 5). In the last follow-up visit of the patient in July 2002, BCVA was 20/200 and visual field (Humphrey 745i, Carl Zeiss Ophthalmic Systems, Inc., Dublin, CA) showed an absolute scotoma in the area treated by TLP and a partial scotoma (sensibility 7 dB, age-corrected sensibility loss 14 dB) in the central fixation area that had been treated by PDT.

DISCUSSION

One of the most important advances in the treatment of subfoveal CNV is PDT with Visudyne. The results after 2 years of a randomized clinical trial suggest that it may reduce the risk of vision loss in patients with predominantly classic subfoveal CNV caused by ARMD with or without occult CNV (7). Similarly, PDT may reduce the risk of vision loss in patients with subfoveal lesions composed of occult with no classic CNV, with either smaller lesions or lower levels of visual acuity (8).

However, although PDT may mean a potential benefit for these patients, the socioeconomic impact of verteporfin therapy is considerable (11), and it must

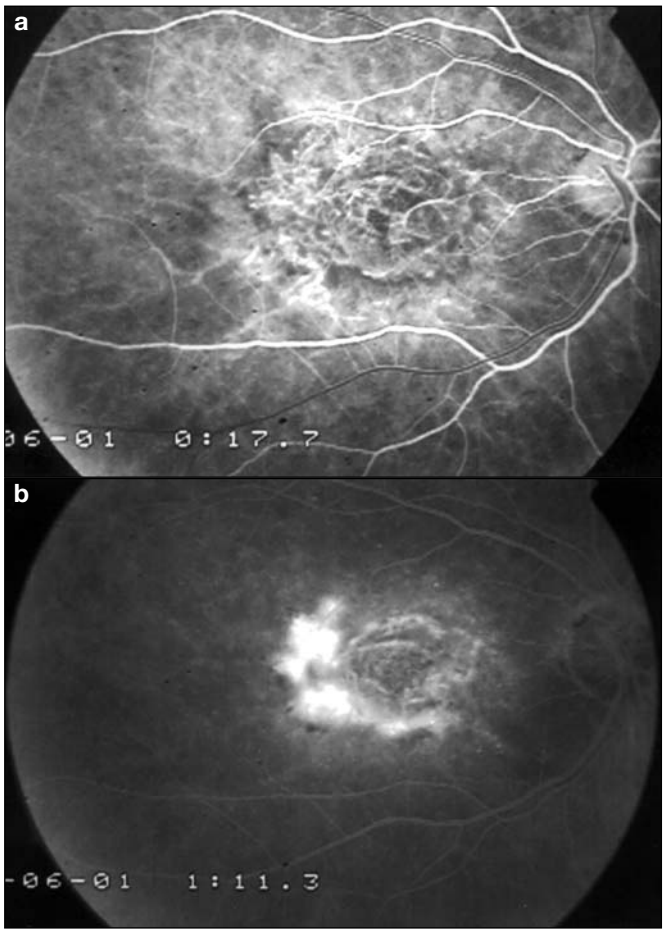

Fig. 4 - *Six months after second photodynamic therapy treatment an area of well-demarcated fluorescein leakage appears in extrafoveal temporal location (a: early phase; b: late phase), with no leakage in the center of foveal avascular zone.*

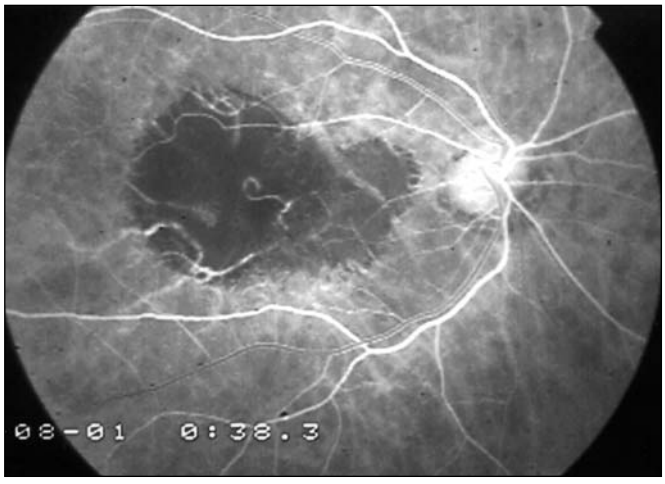

Fig. 5 - *Two months after thermal laser photocoagulation fluorescein angiography (middle phase) shows closure of the choroidal neovascularization.*

be borne in mind that treatment does not prevent the need for periodic re-evaluation of these patients every 3 months in order to evaluate the activity of the CNV with biomicroscopy and/or FA and/or optical coherence tomography.

We started performing PDT in predominantly classic CNV associated with ARMD in October 1999, finding in some cases a complete closure of the subfoveal and juxtafoveal component of the CNV (no leakage in 200 mm from the center of the foveal avascular zone), with more or less severe atrophic changes in the subfoveal area as well as areas of well-demarcated FA leakage in extrafoveal locations (>200 mm from the center of the foveal avascular zone). In these cases we started sequential combined therapy with PDT and TLP in November 2000.

TAP and VIP study group investigators have published the guidelines for using verteporfin in PDT (9). In this recent article, the authors consider the possibility of performing thermal laser treatment after PDT therapy if a small extrafoveolar area of well-demarcated FA leakage is confirmed.

Argon TLP in extrafoveal CNV fits the current indication of treating CNV in extrafoveal location (4, 9) with the advantages of achieving a total closure of CNV with thermal laser (12) at a lower cost for the patient and/or the health system. Yet the main advantage of this approach might be the maintenance of the central visual field by means of a less aggressive procedure such as PDT and limitation of CNV growth by photocoagulation, at the risk of the appearance of an absolute scotoma in the treated area.

The TAP trial showed that patients required an average of 3.4 treatments during the first year and 2.2 treatments the second year (7). We have needed an average 3.1 treatments in 282 eyes, and one further session of TLP in 7 of them, in an average follow-up of 18.0±3.5 months.

Reactivation rate after TLP has been reported to be 0 to 52% at 2 years (13-17) and 59 to 62% at 5 years (15, 16). In our series of eyes pretreated with PDT, we have found no CNV reactivation after TLP, although the number of eyes involved was very low and follow-up limited. We might expect that with longer follow-up recurrences would appear.

The risk of scar growth has also been frequently described for TLP (13). Although the appearance of subretinal fibrosis has been described for PDT, the scar does not seem to enlarge as frequently as after TLP (18, 19).

TLP produces an absolute paracentral scotoma opposed to the pre-existing relative scotoma caused by the CNV (20) and the relative scotoma, smaller or identical compared with pretreatment findings, which appears after treatment with PDT (21). Yet the limitation of the dimension of the lesion by TLP is probably worth taking the risk of developing a paracentral scotoma.

We believe that TLP could be helpful in association with multiple sessions of PDT in order to achieve a complete closure of subfoveal CNV secondary to ARMD. Further studies with longer follow-up and a greater number of patients are required in order to confirm our findings and to determine the real benefit of TLP in association with multiple sessions of PDT in the treatment of CNV associated with ARMD.

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