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Transpupillary thermotherapy of juxtafoveal recurrent choroidal neovascularization

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PURPOSE. *To evaluate the effectiveness of low power transpupillary thermotherapy (TTT) in treating juxtafoveal recurrent choroidal neovascularization (CNV) after laser photocoagulation in patients with age-related macular degeneration (ARMD).*
METHODS. *Eight eyes of eight patients with ARMD and juxtafoveal recurrent CNV were treated with low power TTT, delivered using an 810-nm diode laser with 350 mW, 2.0 mm spot, and 1-minute duration. Visual acuity (VA) ranged from 20/100 to 20/50. Treatment effect was evaluated by fluorescein angiography, indocyanine green angiography, and VA measurements (Early Treatment Diabetic Retinopathy Study) at 1-week, 2-week, and monthly follow-up visits.*
RESULTS. *No retinal damage was visible ophthalmoscopically during treatment. At the first follow-up visit, seven eyes had obliteration of CNV and one eye required a second TTT application. VA was unchanged in six eyes, improved in one eye, and worsened in one eye. Recurrences occurred in all eyes between 1 and 7 months after TTT and were treated with photodynamic therapy (PDT). More than two PDT treatments were performed in each eye in the year after recurrence.*
CONCLUSIONS. *Low power TTT is as able to close juxtafoveal recurrent CNV as is high power conventional laser photocoagulation but does not prevent recurrences. Further intervention with TTT in order to treat recurrences is under investigation. (Eur J Ophthalmol 2003; 13: 453-60)*

KEY WORDS. *Age-related macular degeneration, Choroidal neovascularization, Diode laser, Transpupillary thermotherapy*

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INTRODUCTION

The Macular Photocoagulation Study (MPS) has shown that the indications and benefits of laser photocoagulation in patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (ARMD) are very limited (1-3). Particularly questionable are the benefits of laser photocoagulation of subfoveal CNV, owing to the immediate loss of vision frequently resulting from thermal damage (4,5); therefore, the recent experimentation in search of alternative therapies is justified.

Photodynamic therapy (PDT) with verteporfin has been shown to reduce the risk of visual loss in patients with ARMD with predominantly classic subfoveal CNV (6, 7). Transpupillary thermotherapy (TTT) with 810-nm diode laser has been proposed recently for the treatment of occult CNV secondary to ARMD. The benefit of TTT for occult CNV has been reported in a nonrandomized pilot study by Reichel et al (8). Furthermore, Newsom et al reported that TTT could be effective in the treatment of both classic and occult CNV secondary to ARMD (9).

If alternative, less destructive treatments become

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available, then their potential advantages with respect to conventional laser photocoagulation deserve to be evaluated also for the management of CNV lesions outside of the macular center.

Juxtafoveal recurrent lesions, recurring after conventional laser photocoagulation, represent a reasonable indication for considering a less destructive TTT subthreshold photocoagulation protocol as an alternative to retreatment with conventional MPS protocol, which often produces ablation of foveal tissue.

TTT is a large spot size, low irradiance, long exposure duration, IR diode laser subthreshold photocoagulation protocol (10, 11). In the treatment of CNV, TTT is aimed to produce a localized hyperthermia or low thermal elevation, substantially lower than the temperature elevations produced with short-pulse, high-irradiance conventional photocoagulation protocols. Therapeutic results of TTT in the treatment of occult subfoveal CNV have been reported using large laser spot settings of 1.2, 2.0, and 3.0 mm in diameter, with a power/diameter ratio of 247 mW/mm, for a 60-second laser exposure (8). This laser dose was empirically found effective in causing obliteration of the CNV with no or negligible retinal damage at the time of treatment in lightly pigmented eyes. Acceptable therapeutic results were also obtained in occult CNV using 186 mW/mL by Algvere et al (12).

Juxtafoveal recurrent CNV, however, normally present with special characteristics that suggest the use of a reduced power/irradiance TTT in order to avoid excessive heat and possible damage to the neural retina. Stasis has been observed at lower levels of hyperthermia in immature tumor vessels with respect to mature normal microcirculation (13). We can presume that a neovascular membrane of recent onset may be more sensitive to heat than an old fibrovascular lesion. Recurrent CNV are generally detected early, when they are still immature and probably more thermally labile. In addition to a possible higher thermal susceptibility, other factors, such as the presence of scar from previous laser photocoagulation (higher laser absorption, higher thermal elevation) and corresponding choroidal atrophy (less efficient heat removal by choroidal blood flow), suggest the use of a lower power with respect to the 247 mW/mm typically used for occult subfoveal CNV.

The present study was aimed to assess whether TTT, performed at reduced power and irradiance, is effective to close juxtafoveal recurrent CNV in patients with ARMD.

PATIENTS AND METHODS

Eight consecutive patients with ARMD and juxtafoveal recurrent CNV that recurred after laser photocoagulation were treated with low power TTT. Informed consent was obtained before the treatment. Patients were informed that TTT is an investigational treatment for CNV and detailed explanations were given on the potential risks and benefits with respect to a retreatment with conventional laser photocoagulation. Patients were aware that TTT can eventually result in a photocoagulative effect on the retinal tissue not dissimilar from that produced by conventional laser treatment. They were also assured that the extension of TTT on the foveal side had not been superior to that indicated by the MPS protocol for laser photocoagulation. In case of CNV persistence or recurrence, the decision for a second TTT application or conventional laser photocoagulation or PDT was taken in accordance with the patient.

The patients, five men and three women, were all phakic, over 55 years of age (average 69 years), and had signs of ARMD and juxtafoveal CNV that had recurred after a previous laser photocoagulation in accordance with the MPS protocol. Persistence or recurrence of CNV, diagnosed with fundus biomicroscopy and angiographic examinations, had been observed in the first 2 months after photocoagulation in seven eyes and after 1 year in one eye. Patients complained of new symptoms of metamorphopsia from 1 to 3 weeks. Preoperative best-corrected visual acuity (VA) ranged from 20/50 to 20/100. The recurrent membranes were classic in six eyes and occult in two eyes. They were within the laser scar or extended no more than 200 μm beyond the border of the scar. One day before TTT and at all follow-up visits, the patients underwent a general ophthalmologic examination, fundus photography, fluorescein angiography (FA), and indocyanine green angiography (ICGA). Clinical evaluation included Early Treatment Diabetic Retinopathy Study VA and fundus biomicroscopy with a three-mirror Goldmann lens. FA and ICGA were performed with the standard technique using the Topcon digital system (Ijssel, The Netherlands) or the Heidelberg Retinal Angiographer (Heidelberg, Germany).

TTT was delivered with an 810-nm diode laser (IRIS Medical OcuLight SLx, IRIDEX Corp., Mountain View, CA) through a slit lamp and a three-mirror Goldmann lens. An aerial laser beam of 2 mm diameter (2.15 mm on the retina) was used for all cases, as it was adequate to completely cover the CNV. The angiographically evident lesion at the foveal side was covered without reaching the macular center. A second treatment in one eye was performed including subfoveal leakage. The laser scar was partially included in the treatment. The laser settings were 350 mW power (power/diameter ratio 163 mW/mm, irradiance 9.64 W/cm^2) and 60 seconds duration. Special care was taken during the treatment to monitor possible whitening of the retina and to stop the laser promptly if this occurred. Patients were seen in post-treatment follow-up visits at week 1 and 2 and then monthly at months 1, 2, and 3. Follow-up continued every 3 months until the appearance of recurrence.

RESULTS

Patient characteristics and results are summarized in Table I. Retinal whitening was not observed during any TTT treatment in any patient. In seven of eight eyes, recurrent CNV appeared obliterated at the first follow-up examination (Figs. 1 and 2). Fluorescein leakage within the area of treatment persisted, although reduced in size, in one eye. The patient accepted a second TTT application 3 weeks after the first TTT treatment, when CNV had a late ill-defined leakage reaching the foveal center. Retinal damage was not seen ophthalmoscopically during the treatment, but the patient complained of decreased vision in the following days. One week after the second treatment, CNV was closed and VA was reduced five lines (from 20/50 to 20/160) (Fig. 3). In the following month, VA improved two lines to 20/100. A subfoveal recurrence occurred 4 months after the second TTT and was treated with PDT. A further extrafoveal recurrence 2 months later was closed with a new low power TTT application. Figure 4 shows the early and late effects of TTT on this CNV. Persistent residual neovascularization was treated after 2 and 4 weeks and recurrences were not seen in the following 6 months. The seven eyes in which a single TTT application resulted in obliteration of CNV had recurrences 1 to 7 months after the treatment. Recurrences involved the macular center in six patients who underwent immediate PDT treatment. In one patient, the recurrence was juxtafoveal and without visual symptoms. This patient refused a further TTT treatment as well as laser photocoagulation. He came back 1 month later with a large subfoveal neovascular membrane, which was treated with PDT.

In Patient 5, besides the treatment of the active neovascular recurrence, low power TTT also was performed on a quiescent CNV adjacent to the laser scar and preceding laser photocoagulation. Treatment resulted in obliteration of the only active lesion.

Before recurrences, VA was unchanged in six eyes, improved one line in one eye, and worsened three lines in one eye (Patient 7, who received a second

TABLE I - PATIENT DATA

Patient	Age, years	Sex	Type of CNV	Preoperative Visual acuity	Postoperative Visual acuity	Neovascular Response	Recurrence time, months
1	66	M	Classic	20/100	20/100	Obliteration	2
2	65	M	Classic	20/100	20/80	Obliteration	1
3	75	F	Classic	20/64	20/64	Obliteration	7
4	65	F	Occult	20/64	20/64	Obliteration	2
5	70	M	Occult	20/100	20/100	Obliteration	6
6	68	M	Classic	20/80	20/80	Obliteration	5
7	72	M	Classic	20/50	20/100	Obliteration*	4
8	74	F	Classic	20/100	20/100	Obliteration	3

*After a second transpupillary thermotherapy treatment for persistent choroidal neovascularization (CNV)

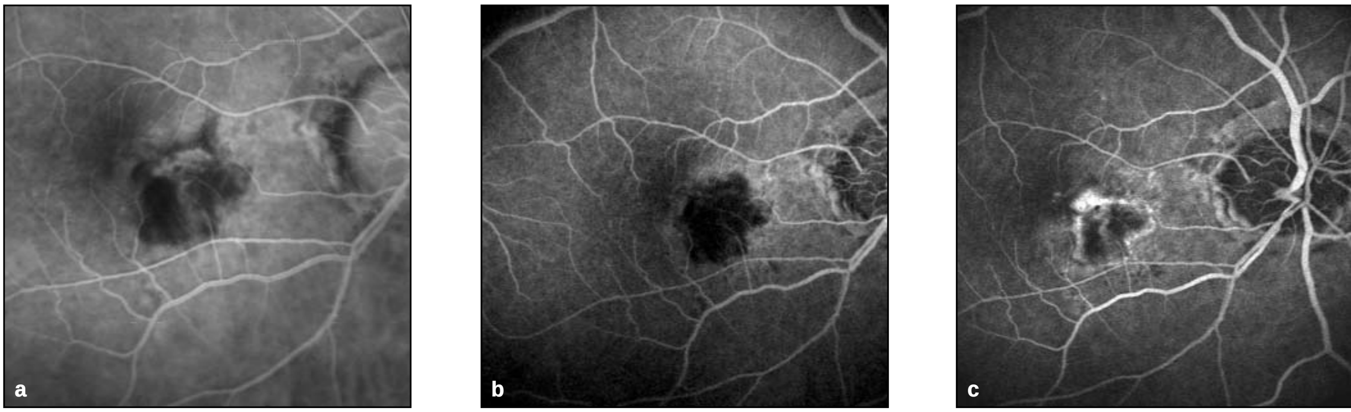

Fig. 1 - a) *Preoperative fluorescein angiography of Patient 1 shows a juxtafoveal choroidal neovascular recurrence within and along the superotemporal border of a laser scar.* **b)** *Fluorescein angiography 1 week after transpupillary thermotherapy (TTT) shows obliteration of choroidal neovascularization.* **c)** *Two months after treatment, fluorescein angiography shows a subfoveal neovascular recurrence.*

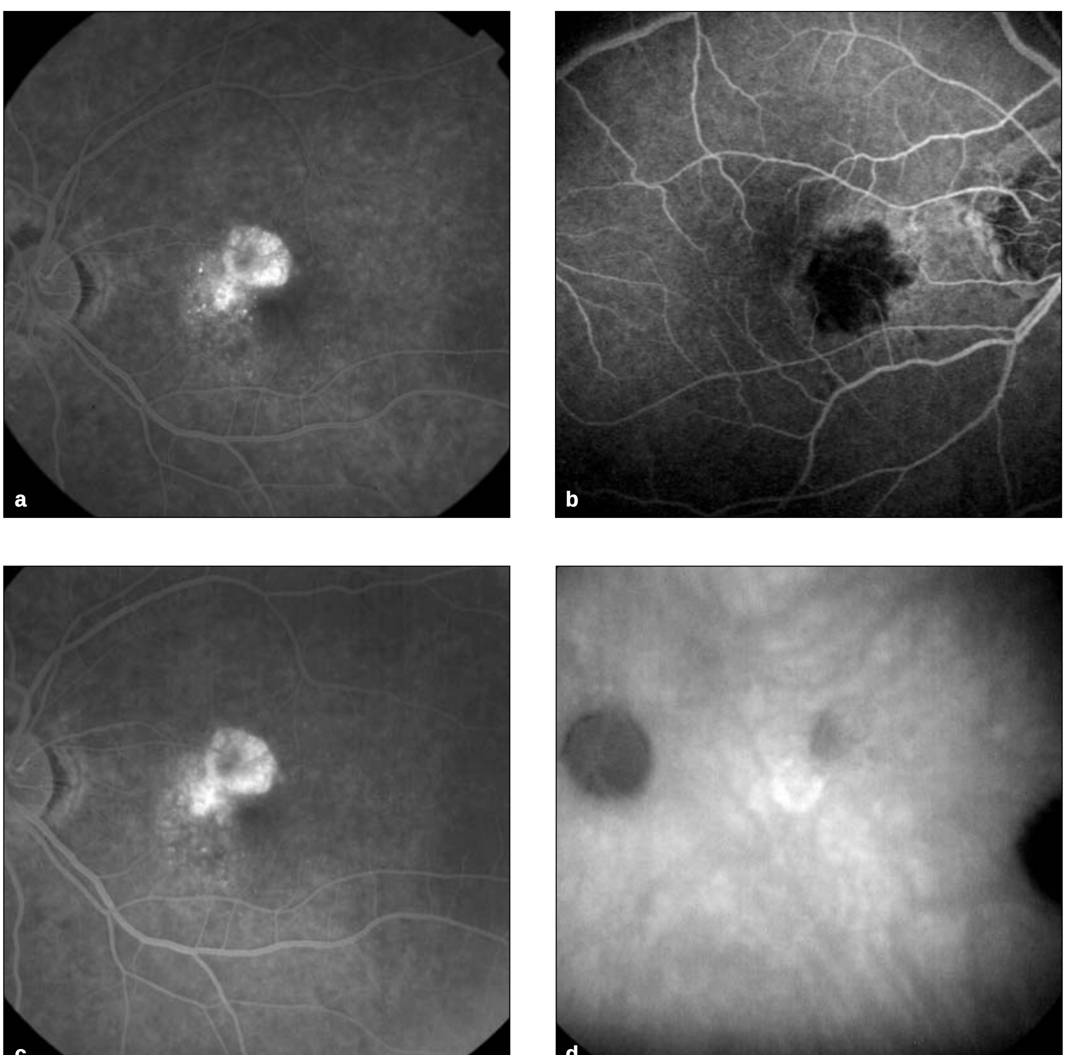

Fig. 2 - a, b) *Preoperative fluorescein and indocyanine green (ICG) angiography of Patient 5 show occult choroidal neovascularization (CNV) adjacent to a laser scar. The occult CNV includes a quiescent neovascular membrane already present before laser photocoagulation and an active hot spot of recent appearance.* **c, d)** *Two weeks after transpupillary thermotherapy (TTT) covering both the neovascular components fluorescein and ICG angiography show disappearance of the only active neovascularization.*

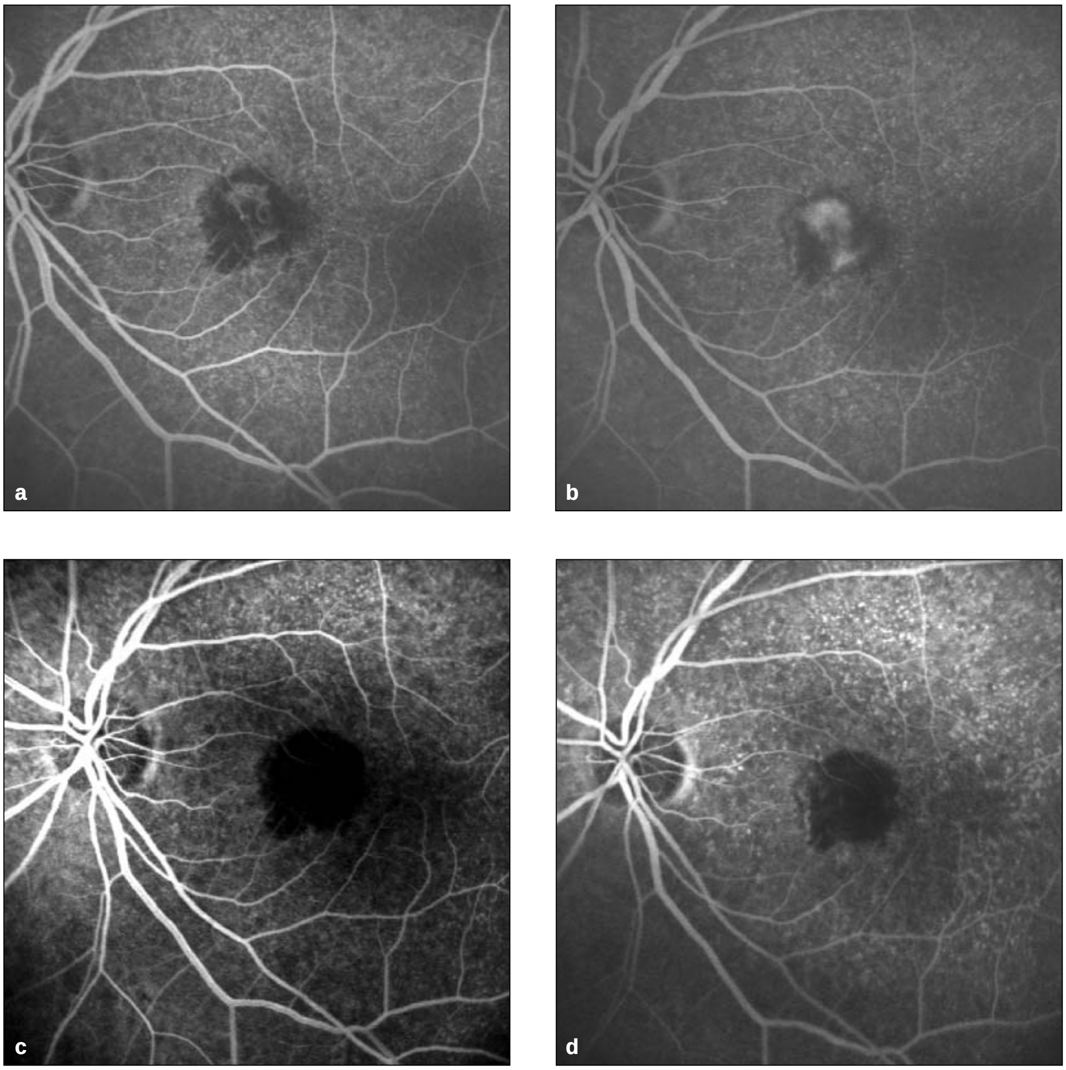

Fig. 3 - a, b) *Early and late fluorescein angiography of Patient 7 before the second transpupillary thermotherapy (TTT) application show choroidal neovascular recurrence with subfoveal leakage.* **c, d)** *Early and late fluorescein angiography 3 months after a second TTT application show obliteration of choroidal neovascularization.*

TTT application including the macular center). In the year after recurrences, all eyes received at least two PDT applications and showed stability or further worsening of VA.

DISCUSSION

In the present study we tested low power TTT for juxtafoveal choroidal membranes recurring after laser photocoagulation in ARMD, assuming that this subgroup of neovascular membranes could be particularly suitable and indicated to benefit from this kind of treatment.

A reduced power, roughly 2/3 of that generally used for the TTT treatment of occult subfoveal CNV (8, 9), was chosen in this study. Consequently, the irradiance, ultimately responsible for the thermal elevation in a given pigmentation, was also reduced in the same proportion.

With this procedure, we treated eight eyes, and obtained obliteration of the neovascular membrane in seven eyes with a single application and in one eye with two applications. Closure of CNV was documented by FA and ICGA 1 to 2 weeks after TTT. The same efficacy was seen for classic (six eyes) and occult (two eyes) membranes. VA did not decline as result of the treatment, with the exception of Patient 7, after a sec-

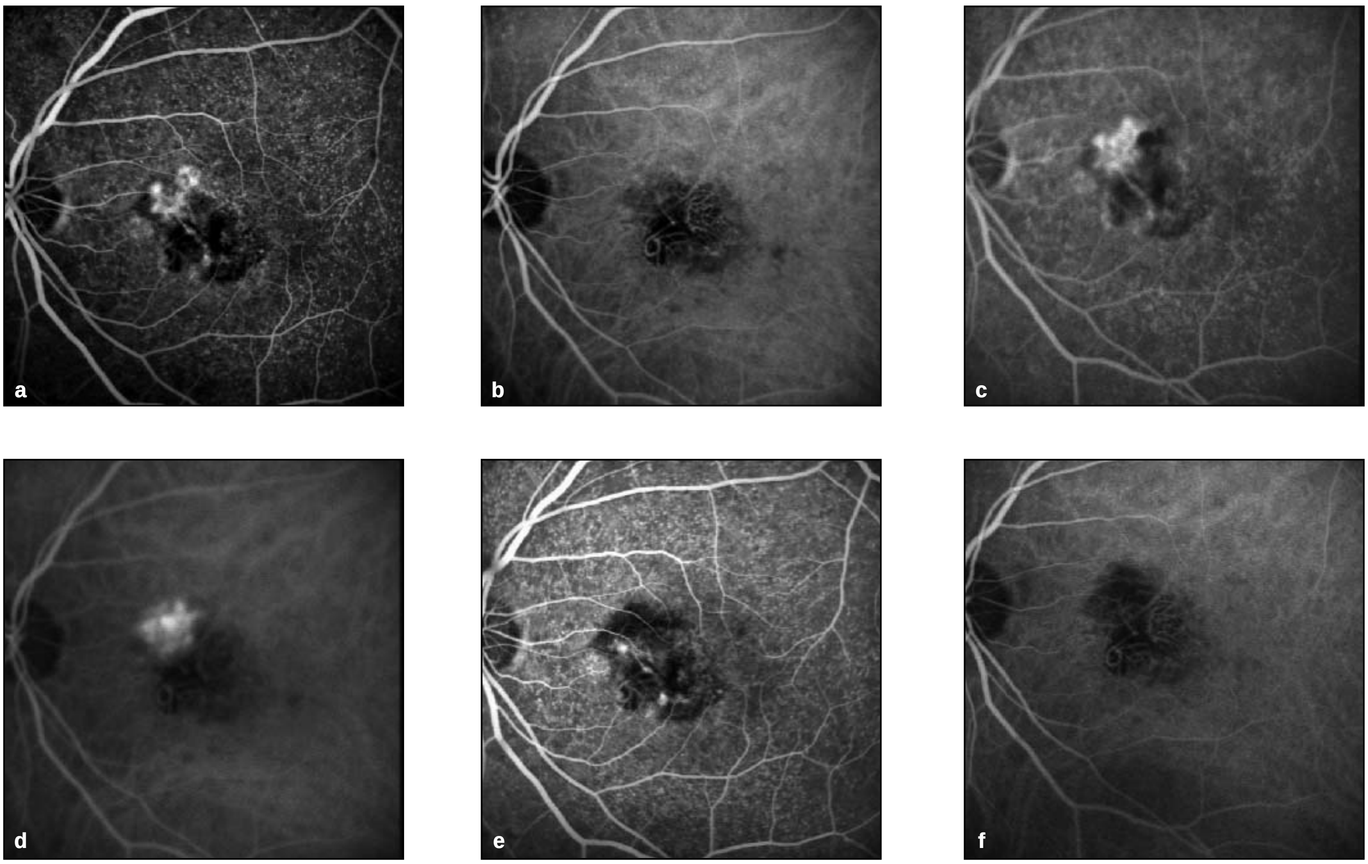

Fig. 4 - a) *Fluorescein angiography shows an extrafoveal recurrent classic choroidal neovascularization (CNV) occurring in Patient 7.* **b)** *CNV is minimally fluorescent on indocyanine green (ICG) angiography.* **c, d)** *Fluorescein and ICG angiography 1 hour after transpupillary thermotherapy (TTT) demonstrates increased permeability of the neovascular membrane.* **e, f)** *Obliteration of the CNV is shown by fluorescein and ICG angiography 1 week after TTT.*

ond TTT application performed for a persistent CNV, with ill-defined leakage reaching the macular center.

With TTT, Reichel et al reported (8) decreased exudation in 15 of 16 eyes with subfoveal occult CNV secondary to ARMD, none of which had received previous laser photocoagulation. In all cases FA showed late staining of subretinal fibrosis after TTT (8). For spot size of 2 mm, these authors used a mean power level of 492 mW, significantly higher than the 350 mW used in the present study. With this lower power/irradiance TTT, all lesions in our study appeared completely obliterated with no late FA leakage or ICGA staining.

From the case series reported by Reichel et al, all membranes included in that study were described as long-lasting fibrovascular plaques (8). On the contrary, in our patients the neovascular membranes were classic or occult hot spot of recent appearance. The apparently more sensitive response to TTT of our cases may be explained with the different tissular characteristics of the recurrent lesions as well as the enhanced photothermal effect resulting from higher absorption by adjacent scar and from less efficient heat removal owing to underlying choroidal atrophy.

Newsom et al reported a series of 44 eyes in which TTT produced obliteration of 75% of predominantly classic CNV and 78% of predominantly occult CNV (9). In this study, CNV lesions recurring after laser photocoagulation were not included. For a 2-mm aerial laser beam, these authors used power levels between 400 and 650 mW, intended to produce a faint retinal graying endpoint following the 60-second exposure (9). Moderate or severe visual loss after TTT was reported in 27% of eyes by Newsom et al (9) and in 25%

of eyes by Reichel et al (8). With the aim of minimizing the risk of foveal damage, we chose the use of a lower power, assuming that it could achieve equally effective results in our subgroup of CNV.

The mechanism of action of TTT in closing CNV is unclear. Thrombosis of tumor vessels has been histologically observed after TTT in choroidal melanomas (14). With the same mechanism, TTT could close CNV in ARMD. The early vascular changes induced by TTT on CNV recently described by Lanzetta et al seem to support this concept (15). In Patient 7, we documented angiographically early damage to the vessel wall and successive vascular obliteration after treatment of neovascular recurrence. The recurrent CNV in our patients were of recent appearance, presumably composed of immature neovascular membranes, which may be particularly responsive to a prolonged low intensity laser exposure, especially if photothermally enhanced by the presence of the scar. In Patient 5, we noted that low power TTT treatment that covered the recurrent CNV and a preexisting inactive occult CNV resulted in obliteration of the first with no apparent modification of the latter. This observation seems to support the hypothesis that active immature neovascularization is probably more thermally labile than long-term quiescent vasculature. TTT, however, could also produce a thermal vascular obliteration in an analogous fashion to conventional laser photocoagulation (11). We can also suppose in some our cases a selective obliterative effect of TTT on subtle feeder vessels inside the scar, with consequent ischemia of dependent neovascular extensions.

In the present study, recurrences after TTT occurred in all eyes within 7 months. In this regard, TTT performed with our modalities does not seem to be preferable to conventional laser photocoagulation according to the MPS findings (16,17). In the juxtafoveal CNV trial of the MPS, 32% of the treated eyes had persistence of CNV at the periphery of the laser treated area (2, 17). In our series, CNV persisted after TTT in only one case, in which it was then obliterated by a second TTT application. We should take note that a subthreshold long pulse diode laser exposure is able to close juxtafoveal recurrent CNV with an obliterative effectiveness not inferior to conventional high power laser photocoagulation. TTT has the advantage of a more selective effect for the neovascular membrane. However, the limited destruction of chorioretinal tissue around the CNV could leave the environmental production of angiogenic factors unmodified and explain the constant appearance of recurrences.

PDT is able to restrain the progression of CNV with a series of periodic treatments (6). In one of our cases persistent obliteration of a neovascular recurrence was obtained after multiple TTT applications. It is reasonable to assume that recurrences may occur for a long period of time, because with TTT, as well as with PDT, we only treat the neovascular complication of ARMD and not the disease itself. We have learned from PDT studies that repeated treatment can be very rewarding. The present study could be expanded to evaluate whether periodical low power TTT treatments in eyes with recurrent juxtafoveal CNV may result in lasting or definitive inhibition of the neovascular proliferation. Repeated low power TTT exposures could sterilize laser scar inducing miscarriage of re-growing neovascular structures.

The reduction of vision observed in a patient of our series with suspected subfoveal extension of CNV should suggest avoiding retreatments in this occurrence. Further investigation could also be aimed at finding the minimal dose of long pulse diode laser irradiation able to obliterate juxtafoveal CNV, minimizing the risk of foveal damage even after repeated treatments.

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