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Short-term reaction of choroidal neovascularization and choriocapillaris to photodynamic therapy in age-related macular degeneration

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PURPOSE. *To identify the number of primary angiographic nonresponders to photodynamic therapy (PDT) with verteporfin, to determine the rate and speed of reperfusion of choroidal neovascularization (CNV) within a short observation period of only 5 weeks, and to examine the reaction of the underlying choroidal vessels.*
METHODS. *PDT according to the TAP regimen was carried out in 36 eyes with subfoveal classic CNV secondary to age-related macular degeneration. The response to PDT was examined 1 (T_1) and 5 (T_2) weeks following treatment. At all visits distant visual acuity was measured and both fluorescein and indocyanine green angiography was carried out.*
RESULTS. *One week after treatment (T_1), complete closure of classic CNV had not been achieved in 17% of eyes (primary angiographic nonresponders). At T_2, 91% of eyes showed reperfusion of the CNV. In 83% of the primary angiographic nonresponders the CNV size was larger than before treatment. Choroidal shadowing was present in 82% at T_1 and in 48% at T_2.*
CONCLUSIONS. *Primary angiographic PDT nonresponders are relatively rare; however, in contrast to former reports, they exist and can be identified by follow-up examination 1 week after PDT. Recurrence of leakage occurred earlier than expected and may require closer follow-up and earlier retreatment than recommended by the TAP trial. (Eur J Ophthalmol 2003; 13: 687-92)*

KEY WORDS. *Age-related macular degeneration, Choroidal neovascularization, Control intervals, Photodynamic therapy*

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INTRODUCTION

Based on the results of the TAP study (1), photodynamic therapy (PDT) with verteporfin is advocated for treatment of predominantly classic choroidal neovascularization (CNV) secondary to age-related macular degeneration (ARMD). The effect of treatment is verified angiographically 3 months after PDT, and treatment is repeated if fluorescein leakage is present in the treated area. It is unknown, however, how many cases do not respond to the first PDT and how long it takes for the lesion to reperfuse in cases that had shown a primary response, as well as the reaction of the underlying choroid in the irradiated area.

The aim of this study was to identify the number of primary angiographic nonresponders 1 week after the

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first PDT, to determine the rate and speed of reperfusion of the CNV within a short observation period of only 5 weeks, to examine the immediate effect on the choriocapillaris in the irradiated area, and to follow the degree of choriocapillary recovery.

MATERIALS AND METHODS

Thirty-six eyes of 36 patients with subfoveal classic CNV secondary to ARMD were treated by PDT with verteporfin (Visudyne). The response to PDT was assessed 1 week (T_1) and 5 weeks (T_2) after therapy.

Before treatment (T_0) and at each follow-up examination, the best-corrected distant visual acuity was determined using a logarithmic chart, and fluorescein and indocyanine green (ICG) angiography was performed (Rodenstock scanning laser ophthalmoscope). Scanning laser ophthalmoscopic systems have a confocal ability, so light from nonconjugate planes is rejected. This allows for recording of a specific plane with less interference of the background than in fundus camera systems. Lesion size (greatest linear diameter and total area occupied) was measured digitally (HIKO, Pirmasens, Germany) on fluorescein angiograms. Leakage or staining was evaluated by fluorescein angiography (Figs. 1, 2). Perfusion of the choriocapillaris was evaluated by comparing the intensity of ICG fluorescence before and after treatment with ICG angiography employing a computer-assisted overlay and subtraction procedure. Within the treatment area, a difference of more then 20% was regarded as a post-treatment shadowing of the choriocapillaris.

The treatment regimen used was equivalent to that described in the TAP investigation. Thirty milliliters verteporfin (Visudyne) in a dose of 6 mg/m^2 body surface area (dissolved in a 5% dextrose solution) was infused over a 10-min period. Fifteen minutes after the start of the infusion laser treatment was performed using a 689-nm diode laser and delivering 50 J/cm^2 at an intensity of 600 mW/cm^2 over 83 s. The spot size corresponded to the lesion size determined as the greatest linear diameter on fluorescein angiography plus 1000 µm.

RESULTS

Before treatment, 100% of eyes showed leakage from classic CNV. One week after PDT (T_1), CNV was closed in 83% of cases. Only 17% still showed CNV perfusion on fluorescein angiography. However, mean lesion size in those eyes was reduced by 78% as compared to baseline. Five weeks following PDT (T_2), one eye had developed a large macular hemorrhage and

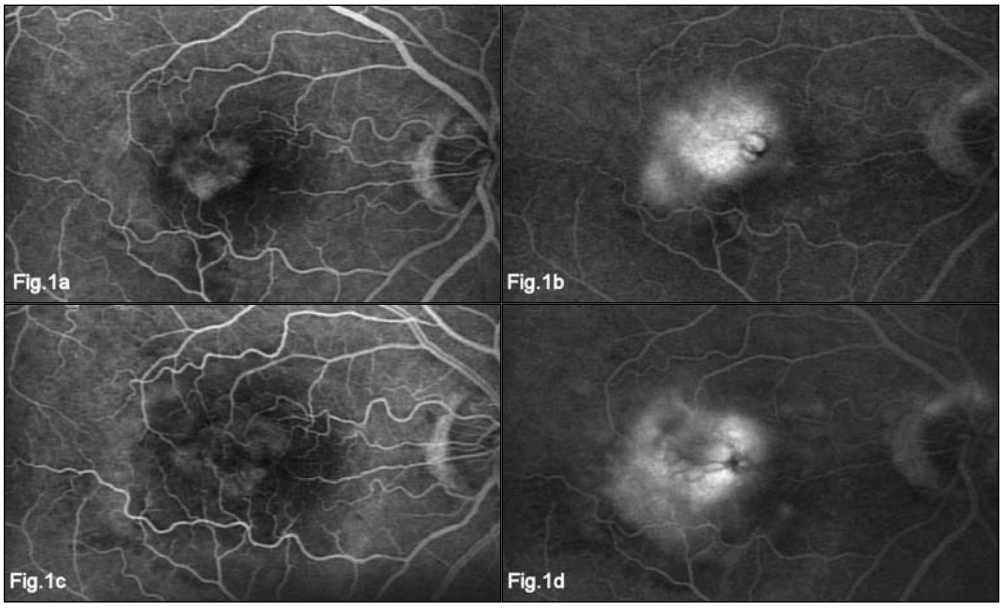

Fig. 1 - *Pretreatment angiogram of a patient displaying leakage* **a)** *early phase;* **b)** *late phase angiogram. Five weeks after photodynamic therapy, both lesion size and leakage have increased* **c)** *early phase;* **d)** *late phase angiogram.*

was excluded from further evaluation. In the remaining 35 eyes, the CNV was still closed in only 9% and new leakage within the previous CNV area was present in the remaining 91% (Fig. 3); the lesion size was reduced only 39% as compared to baseline. The area of new leakage was smaller than 50% of the original lesion size in 40%, larger than 50% in 17%, and larger than 100% in 34% of the eyes (Fig. 4, left column). However, in 8% of the eyes, the reperfused area was outside the fovea and could be treated successfully by argon laser.

In 83% of eyes that had shown the CNV to be perfused on fluorescein angiography at T_1, the area of new leakage was larger than 100% of the original lesion size at T_2.

ICG angiography before PDT showed a regular filling of choriocapillaris and choroidal vessels besides a small rim of slight hypofluorescence surrounding the CNV. One week after PDT (T_1), a dark choriocapillaris shadowing in the treated area was apparent in 82% of eyes. The hypofluorescent area was round, displayed sharp edges, and corresponded to the individual treatment spot size used. Five weeks after PDT (T_2), partial return of choriocapillary fluorescence was noticed, but shadowing was still apparent in 48% of cases (Fig. 5).

Mean distant visual acuity was 0.18 at baseline and 0.19 at T_2 (Fig. 6).

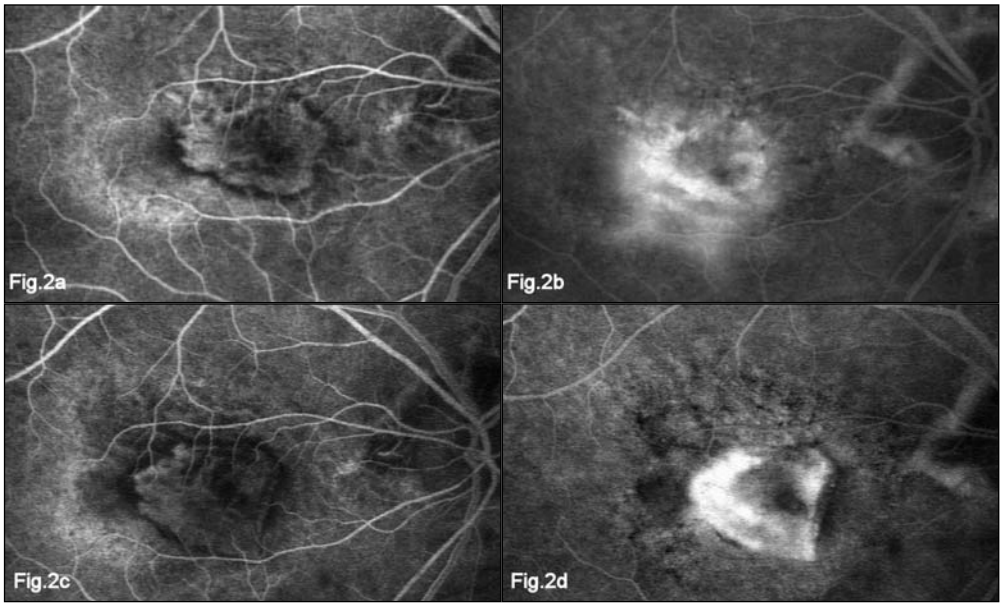

Fig. 2 - *Pretreatment angiogram of a patient displaying leakage* **a)** *early phase;* **b)** *late phase angiogram. Five weeks after photodynamic therapy, leakage has disappeared and only staining can be seen* **c)** *early phase;* **d)** *late phase angiogram.*

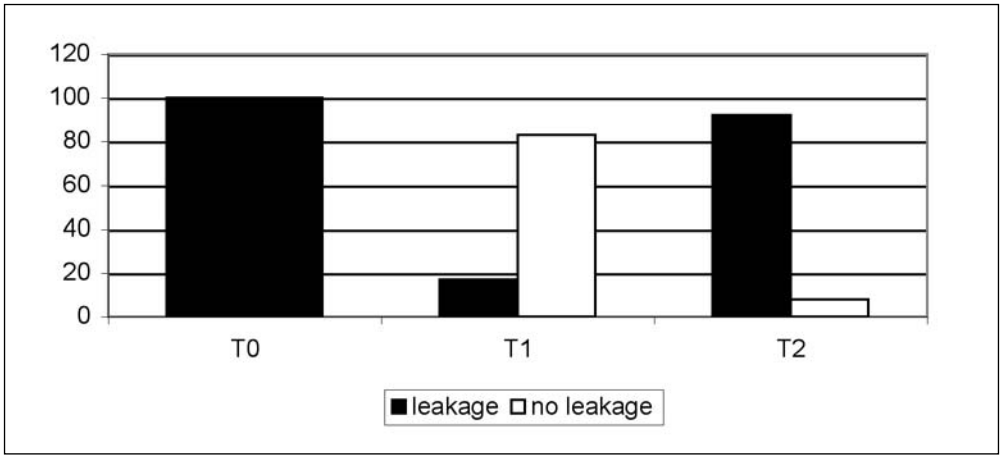

Fig. 3 - *Percentage of patients with perfused or closed choroidal neovascularization at different visits.*

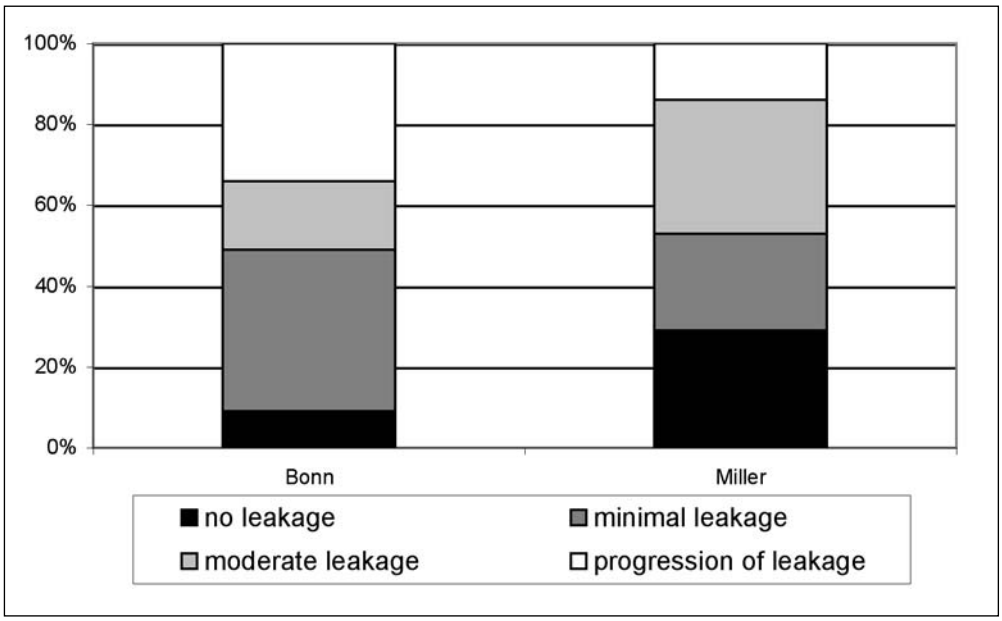

Fig. 4 - *Percentage of patients with absence of leakage, minimal leakage (area occupied smaller than 50% compared to baseline), moderate leakage (area occupied larger than 50% compared to baseline), and progression of leakage (area occupied larger than 100% compared to baseline). Comparison of angiographic findings between our study 5 weeks post photodynamic therapy (PDT) (n = 35) and Miller et al (3), 1999, 4 weeks post PDT (regimen 4, n = 22).*

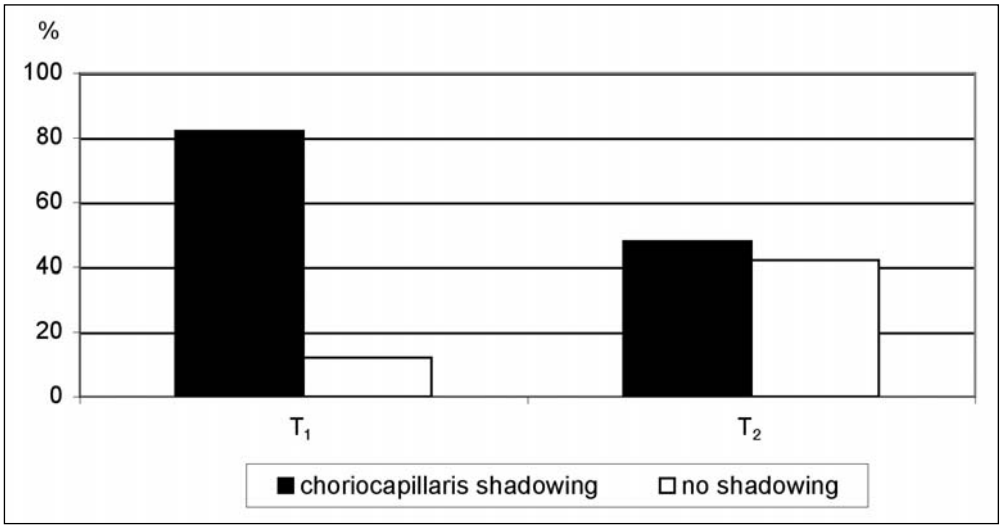

Fig. 5 - *Percentage of patients with choriocapillary shadowing/no shadowing at different visits.*

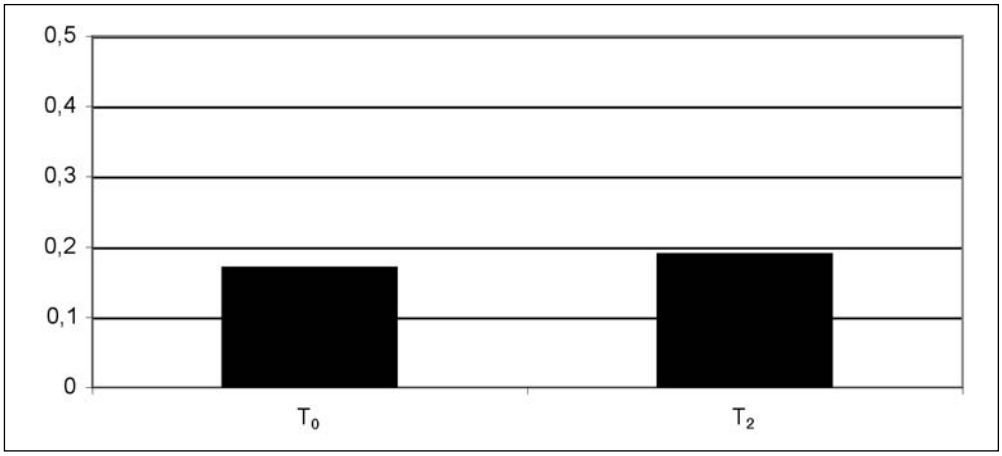

Fig. 6 - *Mean distant visual acuity before (T_0) and 5 weeks after photodynamic therapy (T_2).*

DISCUSSION

The present study reports new observations after routine application of the treatment recommendations for ARMD with PDT derived from the TAP study reports (1, 2).

Results of a preliminary single-treatment dose-escalation study by Miller et al (3) showed that 100% of classic CNV were closed 1 week after PDT with a treatment regimen similar to the one later used in the TAP trial (6 mg/m^2 verteporfin, 50 J/cm^2 light dose, 15-min interval from infusion start to irradiation). Our results employing the same parameters 1 week following first PDT, however, demonstrate persistent leakage from classic CNV in 17% of cases. Although mean lesion size was reduced markedly in those eyes compared to baseline, PDT seems to be less successful than expected in terms of angiographic outcome, at least in some patients.

In the TAP investigation, first follow-up examination was performed 3 months after therapy. At that time, 92.8% of eyes with classic CNV present at baseline displayed leakage from classic CNV again and were scheduled for retreatment (90.8%) (1). Our results show, however, that as early as 5 weeks following the first PDT, CNV recurred in a comparable number of cases (91%). These findings are consistent with those found in a phase 1 and 2 trial where drug application regimens similar or identical to ours were used (50, 75, and 100 mg/cm^2, interval from infusion start to irradiation 15 min) and where follow-up examination 4 weeks after first PDT showed recurrence of leakage from classic CNV in 71% of cases (3) (Fig. 4).

PDT with verteporfin is said to close CNV selectively without damaging retinal or choroidal vessels in the treatment area (4, 5). However, hypofluorescent areas corresponding to the spot size used can be identified on ICG angiography. Although there is the theoretical possibility that they may be the result of a change of transparency of the retinal pigment epithelium in the irradiated area (6), they are mostly thought to represent choroidal hypoperfusion (7, 8). This effect has been shown to be transient and intensity of ICG fluorescence was reestablished to 90% compared to baseline (7) 3 months after PDT. Our results demonstrate hypofluorescence of the choriocapillaris in 82% of cases 1 week after the first PDT. Choriocapillary hypofluorescence decreased to 48% of the cases 5 weeks after the first PDT. This finding confirms the observations by Hager et al (9), who also reported choroidal fluorescence after PDT to improve partially (9), with the maximum of recovery in the first 4 weeks. They also showed that this trend toward improvement remains the same after multiple PDT.

The results of our study raise the following issues that need to be addressed in a larger, possibly multicenter study:

In our patients, the few eyes with CNV that were not fully occluded/quiescent one week after first PDT showed a more aggressive course with less chance of a successful outcome in the follow-up. However, our observation is only based on a small series of six eyes and therefore is anecdotal. If in a larger number of eyes this trend proves to be statistically significant, it would be necessary to perform angiography one week after PDT routinely to identify such eyes.

The same number of CNV that are reperfused after 3 months are already patent 5 weeks post-PDT (7, 9). Consequently, it might be advisable to cut the presently observed TAP treatment interval of 3 months in half. A multicenter randomized double-blind study that addresses this question, the Verteporfin in Early Retreatment (VER) study, is presently being conducted (10).

Reperfusion frequently does not seem to occur simultaneously over the entire lesion, but first in a confined area containing the main feeder. A similar observation has been made by Schmidt-Erfurth and coworkers using ICG angiography (8). Therefore, it may be advantageous to identify these areas as early as possible and to retreat them immediately without waiting for them to grow again.

When reviewing publications dealing with PDT, it is apparent that several terms are being used for different phenomena. Thus, for the sake of better comparability of future studies, we suggest the following nomenclature: reperfusion, opening up of preexisting vascular channels within a CNV; progression, growth of a known CNV beyond its former limits; recurrence, new evidence of CNV after complete absence; staining, area of fluorescence that does not change its diameter from early to late phase of angiography; leakage, area of fluorescence that grows in diameter from early to late phase of angiography.

Finally, we encourage identification of techniques that help to quantify the amount of both leakage and

exudative detachment. We are currently investigating the value of vitreous fluorophotometry and optical coherence tomography for this purpose.

In conclusion, primary PDT nonresponders (in terms of early angiographic outcomes) are relatively rare; however, in contrast to former reports, they exist and can be identified by follow-up examination one week after PDT. Recurrence of leakage was shown to occur in 91% of cases 5 weeks after PDT and may therefore require closer follow-up and earlier retreatment than recommended in the TAP study.

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