

# Photodynamic therapy with verteporfin following transpupillary thermotherapy for CNV evolving from an initially occult to a predominantly classic form, in patients with AMD

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## Abstract

The purpose of this paper is to evaluate photodynamic therapy (PDT) in the management of choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) that converted from occult CNV to classic CNV after treatment with transpupillary thermotherapy (TTT).

One hundred and fifty-four eyes of 130 patients with symptomatic occult CNV were treated between June 2000 and August 2001. We have analyzed data from patients treated with PDT because of a conversion from occult to classic CNV after TTT.

The results were that twenty-four of 154 eyes developed a predominantly classic CNV; 20 eyes of 19 consecutive patients were treated with PDT with verteporfin. The mean follow-up period was 10 months. The mean delay for retreatment with TTT was 3 months; 3 eyes initially presented a pure occult CNV, 15 a minimally classic CNV, 1 an occult CNV with pigment epithelial detachment, and 1 a large macular subretinal hemorrhage with a subfoveal focal hot spot. The average classic component within a lesion before TTT was 20%. Recurrence of classic CNV was noted in the first 3 months for 14 eyes. Visual acuity improved in 5 eyes by  $\geq 2$  lines, and in 2 eyes by 1 line; 4 of 20 eyes had stabilized visual acuity; 7 eyes had a visual acuity decline of  $\geq 2$  lines; 2 eyes lost 1 line. All patients had reduction of metamorphopsia and reduction of exudation; 14 eyes had a little subretinal fibrosis and some partially atrophic areas; 6 eyes had slightly increased leakage in the late phase of the angiogram.

In conclusion, association of TTT and PDT appears to be safe and may help practitioners to manage some difficult

cases. This study seems to confirm the great efficacy of PDT in CNV with recent activity.

**Keywords:** age-related macular degeneration; choroidal neovascularization; photodynamic therapy; transpupillary thermotherapy

## Introduction

In many economically advanced nations, age-related macular degeneration (AMD) is one of the most frequent causes of severe vision loss among patients aged 60 years or over, and the most frequent cause of legal blindness.<sup>1,2</sup> In France, for example, there are currently over 1 million patients with AMD, indicating a very high prevalence. Moreover, demographic trends in France suggest that the prevalence of AMD will probably increase dramatically in the years ahead. By definition, AMD is an age-related condition, and one of the most important demographic trends facing the economically advanced world at present is the increasing average age of the population. By the year 2020, the number of people in France aged 60 years or over will reach approximately 17 million (Institut national de la statistique et des études économiques). It is projected that, compared with current levels, by the year 2025 the number of patients with AMD in France will increase threefold approximately (Institut national de la statistique et des études économiques).

In AMD, vision is damaged mainly through the development of choroidal neovascularization (CNV). Fortunately, the majority (almost 92%) of patients with AMD do not develop

## Materials and methods

Twenty-four eyes of 22 patients were treated between June 2000 and August 2001. All patients were older than 60 years and presented occult subfoveal CNV secondary to AMD. Patients were included in this retrospective study only if they had been followed up for at least 6 months. One patient had a past history of extrafoveal photocoagulation 3 years previously, and was excluded from the study. Patients with any significant ocular disease (other than AMD) and eyes with evidence of a tear of the RPE were also excluded. In addition, one patient who was included in the study (patient 1) had one eye which had previously been treated by PDT for a predominantly classic lesion; this eye was excluded from the study.

All eligible patients had best-corrected Snellen visual acuity of 20/400 or better. With regard to their disease all patients were informed that it was possible to choose conservative observation with no treatment, and that TTT was an investigational treatment. When PDT was discussed with patients they were given complete information about modalities, benefits, and risks. All patients were informed that the combination of the two treatments might be associated with some effects on central vision, effects that could not be defined in advance. All patients gave written informed consent before each treatment.

Twenty eyes of 19 patients were included in this study. Clinical preoperative data were collected, and included the patient's age, sex, and affected eye, and the results of complete bilateral ocular examinations. These included best-corrected visual acuity, slit-lamp ophthalmoscopy, applanation tonometry, and fundus examination with evaluation of the macula (using a 3-mirror Goldman lens, a Volk Area Centralis® lens, a Volk Super 66 Stereo Fundus Lens®, or a Volk SuperMacula 2.2). In all patients, measurement of Snellen best-corrected visual acuity was determined, and also compared and evaluated on a retroilluminated Lighthouse for the Blind (Low Vision Products, New York, NY) distance visual acuity test chart (using a modified Early Treatment Diabetic Retinopathy Study chart) at a test distance of 4 m. At the baseline examination, contrast threshold for large letters was measured using a Pelli-Robson chart (with a Snellen visual acuity equivalent and at a distance of 1 m from the contrast chart). At all follow-up visits, patients had a complete general ophthalmologic examination. Special care was taken to record whether patients had noted a significant visual acuity loss or metamorphopsia.

Fluorescein and indocyanine green (ICG) angiographies (Topcon TRC 501A, Imagenet system, Kodak MegaPlus Camera with high resolution CCD) were performed at the baseline visit for all patients, and every 3 months (3, 6, 9, and 12 months) at the follow-up visits. Fluorescein angiograms alone were taken 1 and 2 months after each TTT treatment, even if visual acuity had improved or stabilized. If visual acuity had decreased, additional ICG angiography was performed.

TTT was performed through a Haag-Streit 900 BQ slit lamp (with an adaptor TTT) using a modified infrared diode laser at 810 nm (Viridis Twin with software designed for TTT, Quantel Medical, Clermont-Ferrand, France). Five beam-widths are available: 500, 1000, 2000, 3000, and 4000  $\mu\text{m}$ . One drop of topical anesthetic was put in the eye before placement of a 3-mirror Goldmann lens. The slit lamp was used for careful observation throughout the 60-second duration of the treatment, ensuring that the spot was centered and that the lesion did not visibly change during treatment. The green filter of the 900 BQ slit lamp was used so that the laser spot could be easily seen and centered just before the procedure.

All 20 eyes had a 3000  $\mu\text{m}$  spot size. This was sufficient to cover the entire CNV, with a small, secure border. The initial power was between 450 and 800 mW, depending on the level of fundus pigmentation, the degree of serous detachment of RPE, and whether the patient was phakic or had previously undergone cataract surgery. If patients were pseudophakic, power was decreased and varied between 450 and 550 mW. Because no retinal whitening was observed, reinitiation of treatment was not required. No patients required a retreatment after 1 month. A second TTT was performed if there was an increase in subretinal exudation, or development of subfoveal minimally classic CNV.

When any change was noticed in the occult component of a predominantly classic CNV, PDT with verteporfin was considered. During a separate consultation, patients were informed about the characteristics of classic CNV, and following a comprehensive discussion, all patients consented to the second procedure with PDT. PDT with verteporfin was performed as described elsewhere.<sup>12</sup>

Retreatment with PDT was considered if there was progression of fluorescein leakage from CNV or a moderate persistent leakage at the follow-up examination. Every 3 months, fluorescein angiography permitted assessment of fluorescein leakage (if any), progression or stabilization of CNV, and indications for retreatment or observation only. In addition, a complete general ophthalmic examination was performed at each follow-up visit. ICG angiography was performed if extension or reactivation of occult CNV was suspected, and every 6 months for all patients.

## Results

Results and patient characteristics are summarized in Tables 1–4. Twenty eyes of 19 consecutive patients were treated. All patients had symptoms, such as metamorphopsia or significant visual acuity loss, arising from occult subfoveal CNV. Symptom duration was approximately 2 months (range 1–4 months). There were 5 men and 14 women in this study, with a median age of 78 years (range 70–91 years). Seven patients (35%) had advanced AMD in the fellow eye, and associated severe vision loss. The mean follow-up time was 10 months (range 6–14 months).

Table 4. TTT and PDT parameters - CNV classification.

Patient	Parameters TTT			Parameters PDT			Classification of CNV	CNV post TTT	Low-vision rehabilitation
	power (mw)	duration (sec)	spot size (µm)	power (mw)	duration (sec)	spot size (µm)			
1	500	60	3000	600	83	3800	minimally classic (30%)	predominantly classic	unnecessary
2	550	60	3000	600	83	3000	minimally classic (30%)	predominantly classic	unnecessary
3	550	60	3000	600	83	5000	minimally classic (30%)	predominantly classic	yes
4	800	60	3000	600	83	4800	minimally classic (20%)	predominantly classic	yes
5	800	60	3000	600	83	4800	minimally classic (30%)	predominantly classic	yes
6	500	60	3000	600	83	4800	minimally classic (10%)	predominantly classic	yes
7	500	60	3000	600	83	4800	occult/plaque	predominantly classic	yes
8	600	60	3000	600	83	5000	minimally classic (10%)	predominantly classic	unnecessary
9	450	60	3000	600	83	4200	minimally classic (10%)	predominantly classic	yes
10	800	60	3000	600	83	4600	minimally classic (10%)	predominantly classic	yes
11	800	60	3000	600	83	5200	minimally classic (20%)	predominantly classic	yes
12	800	60	3000	600	83	4600	minimally classic + PED	predominantly classic	yes
13	800	60	3000	600	83	4200	minimally classic (30%)	predominantly classic	unnecessary
14	550	60	3000	600	83	4400	occult/plaque	predominantly classic	yes
15	800	60	3000	600	83	3800	minimally classic (30%)	predominantly classic	yes
16	550	60	3000	600	83	4400	minimally classic (10%)	predominantly classic	yes
17	500	60	3000	600	83	4200	minimally classic (30%)	predominantly classic	yes
18	800	60	3000	600	83	4800	minimally classic (20%)	predominantly classic	yes
19	800	60	3000	600	83	4200	minimally classic (30%)	predominantly classic	yes
20	800	60	3000	600	83	5200	occult/plaque	predominantly classic	yes

by only approximately 5–12°C, and empirical data suggest that retinal coagulation occurs at 51°C. This is far less than the temperatures (approximately 80°C) approached with conventional laser photocoagulation. Aside from a real photothermal laser effect, which depends on the extent and the duration of the rise in tissue temperature, TTT may favor some photochemical processes because of the low-irradiance level and the long exposure time. With TTT, reparative mechanisms may restore the abnormal neovascularized tissue, first to its abnormal stabilized state, and in time to a state of comprehensive repair.

In a study of temperature profiles in the retina and choroid, different photocoagulations were performed using various wavelengths.<sup>24</sup> This study showed that the total percentage of light absorbed within the RPE and choroid was three times lower at a near-infrared wavelength of 514–580 nm, but with a deeper penetration for the 810 nm wavelength used in TTT. This is why the TTT wavelength seems to be adapted to subfoveal CNV treatment, in order to minimize photoreceptor damage. However, it is very difficult to apply precisely sufficient irradiation in TTT because of the absence of an easily identifiable and controlled clinical endpoint. Moreover, if any retinal whitening is observed during TTT, the risk of macular burns increase. Additionally, if the patient had cataract surgery before or if the serous detachment of RPE associated with CNV is small (<250 µm on Optical Coherence Tomography [OCT]), the power of TTT irradiation should be decreased. Indeed, retinal absorption is minimal in the absence of hemorrhage or pigment. Depending on the wavelength, absorbing macular structures include especially chromophores (melanin, xanthophyll, hemoglobin, and pigments), but above approximately 530 nm, absorption of xanthophyll is minimal. One problem still remains: with AMD, the absorbing species in the eye are abnormal, and likely to change greatly, thereby contributing to complicated laser tissue effects. Novel chromophoric species develop and pathologic structures include a heterogeneous combination of absorbing, less-absorbing and non-absorbing tissues. These changes often increase with time, especially with occult CNV, because of its typically insidious course. Even if long-wavelength light is able to penetrate a cataractous lens with some efficiency (and most patients with AMD have some degree of cataract), pseudophakic eyes are more likely to present iatrogenic coagulation, justifying special precautions, including irradiation at reduced power.

No burning or acute destruction is directly induced unless retinal whitening or color change is observed. TTT can stress retinal cells, killing some of them – macular burns have been reported as complications of TTT for CNV secondary to AMD. Of course, one of the most important effects of TTT is that it gradually dries up the exudate associated with CNV. The precise nature of the reactions underlying the various changes mentioned above remains to be elucidated.

Because of the possibility of overtreatments and foveal destruction, particularly with pseudophakic eyes, TTT was always carefully applied, with appropriate parameters

reduced in such eyes, so that even minor harmful changes in the retina, such as the development of a light-gray appearance, were scrupulously avoided. Given this degree of clinical caution, it must be recognized that some patients may have been undertreated. Nevertheless, 10 (50%) of the 20 eyes were pseudophakic, and only 4 eyes required a second TTT. No macular burn was observed in any patient treated with TTT in our experiment. Precautions such as observing patients continuously and asking them to report any burning sensations immediately (apart from a barely perceptible heat sensation or smarting), may have contributed to the successful avoidance of retinal complications in this study. Besides, it seems important to note that an interesting effect of TTT was a high rate of decrease of metamorphopsia, contributing to a sensation of visual improvement, similar to some of the results of epimacular membrane surgery.

Figure 1 illustrates a typical result of treating a lesion with PDT after TTT. An unusual case was patient 1, an 89-year-old woman who was seen for severe loss of central visual acuity with metamorphopsia in her right eye. The patient's left eye was asymptomatic. Baseline examination showed visual acuity at 20/100 in her right eye and 20/63 in her left. Fundus examination revealed a large foveal serous retinal detachment, associated with hemorrhage and focal hyperpigmentation in the right eye. Fluorescein angiography showed a "borderline" predominantly classic lesion (the classic component occupied 50% of the total area of the lesion). This result was subsequently confirmed by ICG angiography. The patient's right eye met eligibility criteria for PDT with verteporfin, which was therefore administered. At that time, the left eye already had a minimally classic lesion (the classic component occupied 20% of the total area of the lesion), and the classic component was juxtafoveal. Because the patient had no symptoms related to this eye, no treatment was given.

One month after PDT with verteporfin, visual acuity in the right eye had improved to 20/50, and metamorphopsia decreased; no change was observed in the left. Two months after the treatment, the patient had symptoms of CNV in both eyes. Visual acuity in the treated eye had decreased with visual symptoms increased; angiographic examination showed activation of the occult CNV and little increase of leakage from classic CNV. Minimally classic CNV was still present in the fellow eye, although the proportion of classic CNV had increased. Because of the cost of PDT (at that time patients had to be pay for verteporfin, and this patient could not afford it), the patient was treated with TTT for both eyes. Three months later, the patient's right eye had to be retreated for progression of fluorescein leakage, and her left eye had developed a predominantly classic CNV. Since by this time patients were no longer required to pay for verteporfin, PDT was performed on both eyes. At 12 months of follow-up, visual acuity in the left eye was 20/25, with no symptoms, and no fluorescein leakage on angiography. At approximately 15 months of follow-up, visual acuity in the right eye was 20/80 with no metamorphopsia, no fluorescein leakage on

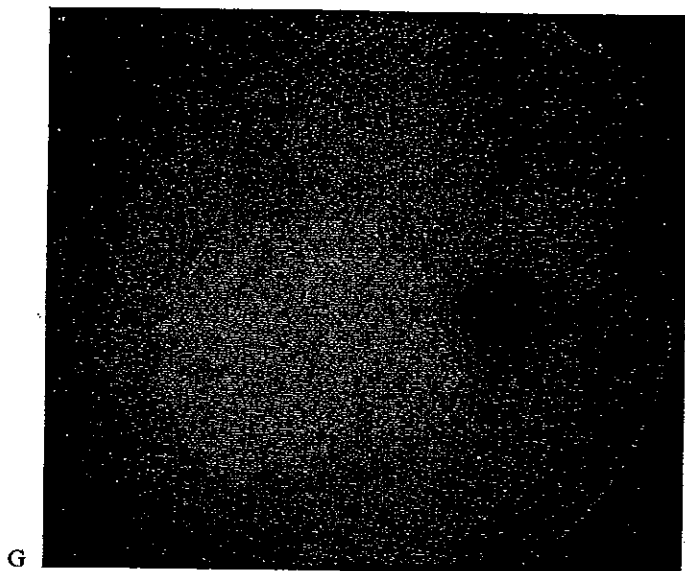


Figure 1. Continued

angiography, and partially atrophic macular areas. This case is interesting because it shows that, under the circumstances specified, the combination of TTT and PDT was effective in both eyes, despite the fact that the two eyes differed in their clinical presentation.

Another remarkable point is that sometimes the initial classic component of CNV does not correspond to the principal spot of the predominantly classic CNV observed after TTT. The more active area of the classic component is often just contiguous to the initial area, suggesting that TTT has stabilized the classic part a little, but not enough to prevent a highly aggressive recurrence. Another very important point is that this study seems to confirm the great efficiency of PDT in CNV with recent activity.

It should be noted that clinical examination and angiography detected only the decrease in exudation. OCT evaluation was not obtained, even though the information provided by this non-invasive technique seems to be regarded increasingly as essential in retinal pathology.

Moreover, the absence of a randomized clinical trial comparing this treatment with no treatment of occult CNV is problematic, but multicenter clinical trials, the Transpupillary Thermotherapy of Occult Subfoveal Choroidal Neovascular Membrane (CNV) secondary to AMD (known as "TTT4CNV"), are now beginning and should in time evaluate the effectiveness of TTT. We should also analyze the results of the Verteporfin In Minimally classic CNV (VIM) Trial.

To conclude, it is important to perform a careful follow-up of patients treated with TTT for CNV secondary to AMD, within the first 3 months, especially if their lesion is composed of minimally classic CNV. The combination of TTT and PDT appears to be safe and may help practitioners to manage certain difficult cases. Further

research is still needed to improve visual outcomes in such patients, and to explain clearly what is at present merely a hypothesis.

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