PHOTODYNAMIC THERAPY: A NOVEL APPROACH IN THE TREATMENT OF AGE RELATED MACULAR DEGENERATION

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Abstract

Choroidal neovascularization secondary to age-related macular degeneration or pathologic myopia can cause severe loss of central vision and lead to legal blindness. For many years thermal photocoagulation has been the preferred treatment for this disease, but it is only suitable for a small number of patients and may cause additional immediate visual loss after treatment. Photodynamic therapy (PDT) using verteporfin is a new therapeutic approach, which has shown to be beneficial in the treatment of such lesions in recently completed clinical trials. The treatment uses an intravenously administered photosensitive compound (verteporfin), which is activated by a non-thermal laser light. The induced photochemical reaction within the neovascular vessels leads to secondary occlusion. This mechanism allows selective occlusion of the neovascular complex while causing only minimal damage to surrounding retinal tissue. Therefore PDT can safely reduce the risk of vision loss in patients with CNV secondary to AMD and may even improve vision in patients with pathologic myopia as clinical studies demonstrated. The basic principle of photodynamic therapy, the results of the two major clinical trials as well as current treatment guidelines are describe in this review.

Introduction

Age related macular degeneration (AMD) is a degenerative eye disease that can cause severe and irreversible loss of central vision. While most patients with AMD experience only a slow, moderate loss of visual acuity due to atrophic changes of the retina, 10% of patients suffer from a severe and rapidly developing visual loss. According to literature and clinical experience up to 90% of this significantly effected group present with the neovascular form of AMD [1]. This form is characterized by the development of abnormal blood vessels under the retina, which leak fluid, lipids and blood. Over time the leakage leads to fibrosis of the central retina with loss of photoreceptors and concomitant vision decline. In North America and Europe this is the leading cause of legal blindness in people over 65 years of age [2].

While age related macular degeneration presents with numerous phenotypes, the etiology has been only poorly understood. Therefore any potential treatment will be limited to the prevention of visual loss, as long as the mechanisms leading to the development of choroidal neovascularization and the underlying role of changes in the RPE, Bruch's membrane and photoreceptors remain unclear. However, the pathological correlate for a poor prognosis can be clearly identified: it is the choroidal neovascularization[3]. Targeting this structure and thereby treating the severest form of AMD should have highest priority in our therapeutic considerations.

For many years conventional laser photocoagulation was the only approved treatment based on the criteria established by the Macular Photocoagulation Study (MPS) [4]. The thermal laser photocoagulation leads to a non-selective necrosis of the CNV and all adjacent outer retinal and inner choroidal structures. Many patients with subfoveal lesions experience immediate additional visual loss due to the destructive treatment [5]. Recurrence after therapy is not uncommon and seen in up to 50% of patients within two years. In addition the majority of patients with neovascular AMD do not meet the criteria for laser treatment because the lesion is too large or not well defined in angiography [6].

Other treatments like radiation and interferon therapy have been investigated and not shown to be beneficial. Transpupillary Thermal Therapy (TTT) still needs to prove it's role in the AMD treatment with supporting study data from clinical controlled trials [7,8].

Surgical approaches such as submacular surgery, macular rotation and translocation are highly invasive and therefore may not be suitable for large patient collectives of this age group. Also these techniques have to be investigated in larger clinical trials, to evaluate their true potential [9, 10, 11].

Photodynamic therapy (PDT) is a novel therapeutic approach, which has been recently approved by health authorities in various countries for the treatment of predominantly classic CNV secondary to AMD. The therapy combines the potential of non-thermal laser light to induce localized chemo-toxic reactions by activating a photosensitizer (light-activable compound) in neovascular tissue [12]. It allows a more selective treatment of the CNV due to a preferential concentration of the photosensitizer in the target tissue and the possibility in ophthalmology

to direct the light irradiation to the specific target area by using a laser light sources [13]. The induced photochemical reaction differs substantially from other treatments, as it does not involve any thermal or mechanical damage. Two major clinical trials demonstrated that PDT could safely reduce the risk for vision loss in patients with subfoveal CNV [14,15,16]. The therapy is currently recommended for patients with predominantly classic CNV in AMD or CNV secondary to pathologic myopia.

The principle of photodynamic vascular occlusion

Over the last decades photodynamic therapy has been used to treat various types of solid tumors for clinical or investigational purpose. Only recently the development of specific photosensitive agents such as verteporfin (benzoporphyrin derivate monoacid A, BPD-MA) [17,18] and the availability of more sophisticated light delivery systems have expended the possible therapeutic use to nononcologic applications [13,19,20,21,22,23,24].

One of the new applications is age related macular degeneration, where the subretinal neovascular complex is the target structure of photodynamic therapy (PDT). The aim of the treatment is the inactivation of the choroidal neovascular membrane with reduction of size and exudation of fluid under the surrounding neurosensory retina. This is achieved by the initiation of a photochemical reaction. In a two-step procedure first a photosensitizer (light-activable compound) is administered intravenously and accumulates in the CNV. In a second step the sensitizer is activated by light irradiation of a specific wavelength that is appropriate for the absorption by the dye [25].

When the molecules of the photosensitizer are activated by light, active forms of oxygen and free radicals are generated, which results in photochemical damage of endothelial cells. The destruction of the vascular endothelial cells leads partially to an instant thrombosis of neovascular structures [26]. Secondary vascular repair mechanisms will cause additional stabilization of the initiated barrier structure and also cause cessation of exudation from the CNV.

Here lays the principle difference between PDT and conventional photocoagulation. The applied laser energy alone is not intensive enough to cause heating or thermal destruction of tissue. The light energy is used only to activate chemical processes within the dye molecules and the immediate surrounding tissue, e.g. surfaces of vascular endothelial cells [27]. The primarily induced pharmacological effect is not visible, even with ophthalmoscopy. In opposite to the conventional, thermal laser coagulation no necrosis or even loss of transparency appears on the retina in the treated area [12]. Clinical examination does not allow evaluation of the achieved therapeutic effect at this point. The successful occlusion of the CNV is clinically invisible during the first 1-2 weeks after treatment because outer retinal structures are not damaged. Functional examinations showed that recovery of photoreceptor function is possible and scotoma may disappear a few weeks after photodynamic therapy [28].

Without a doubt, photodynamic intervention does not eliminate the cause of AMD in general but rather treats the symptoms, especially those pathological mechanisms like invasive growth of new vessels and persistent exudation, which cause severe functional loss of the central retina.

Current status of photodynamic therapy

The vision stabilizing effects of photodynamic therapy have been investigated in large, randomized clinical trials (TAP/VIP) [14,15,16]. International, placebo controlled studies showed that in the majority of patients treated with photodynamic therapy and a sensitizer of the porphyrin group the progression of the disease could be stopped. The results of these studies lead to official approval of the method and the associated medication. Starting in December 1999 PDT was approved in the USA, European Community and Canada as well as in a number of Asian and Middle Eastern Countries. Meanwhile several thousands of patients have been treated worldwide.

Many ophthalmologists now have the opportunity to gain experience with this treatment method themselves. In the evaluation of photodynamic therapy one must consider not only the different parameters and the specific technical procedures. A number of other factors such as diagnostic features, careful selection, care and control of patients are critical to successful application of this form of therapy.

Indications for different forms of laser therapy

Photodynamic therapy is a laser procedure but ophthalmoscopic and angiographic features differ significantly from the typical features of conventional laser therapy. Especially the criteria for indicating PDT treatment vary from those established for photocoagulation.

Thermal laser therapy is mainly used for subfoveal CNV no larger than 2 disc diameters and a visual acuity of 0.1 (20/200). Photodynamic therapy allows the treatment of patients with better visual acuity and larger lesion size [29]. In principle the maximum treatment size for CNV lesions is only limited by the

laser equipment. Though, to achieve best treatment results patient should be at an early stage of the disease with a maximum of photoreceptor function.

Clinical and angiographic characteristics

The first example represents a typical patient suitable for photodynamic therapy. The picture of a 57 years old woman shows the central edema of the macular with intraretinal hemorrhages. The image reveals already atrophic changes underlying and surrounding the neovascular pathology (Fig. 1a). Fluorescein angiography clearly shows a well demarcated so called "classic" choroidal neovascularization in the early phase (Fig. 1b) with excessive leakage overlaying the boundaries in the late phase (Fig. 1c). The patient reported loss of reading ability about 4 months ago and complained of severe metamorphopsia. Visual acuity was 0.3 (20/60).
Usually no destructive funduscopic changes are visible in the first couple of weeks after photodynamic therapy. Some patients report a transient decrease in vision shortly after treatment. These visual disturbances usually can't be documented or objectified by visual acuity tests. They develop due to a transient increase in exudation during the first days after treatment and resolve within a few days. A follow up visit during this time is not necessary. A control visit is currently recommended after 3 months, based on study results. In case of a beneficial therapeutic effect and reduction of edema, exudation and hemorrhages can be observed clinically and angiographically (Fig. 1d,e).

Only a few cases show a lasting therapeutic effect after one treatment only [30]. A slight increase of CNV activity at the beginning does not prevent or exclude a later treatment success. Even 3 months after therapy a final decision about the long-term treatment effect cannot be made. A better evaluation can be made based on the 6 and 9 months results. The majority of patients don't present with active exudation, lipid deposits or hemorrhages at this point any more. These patients report a significant reduction or resolution of their metamorphopsia. Central visual acuity usually remains stable within + 2 lines. The patient of figure 1 had a visual acuity of 20/50 after 4 treatments (Fig. 1f-g).

The interpretation of the angiogram after treatment requires some experience, because it deviates from the results after conventional photocoagulation. The main difference is the persistent staining of the involuted membrane after therapy, which remains even years after successful treatment (Fig.1f,g). Signs of involution are stagnation of growth and resolution of active leakage. Angiography three months after treatment should show an unchanged, decreased or only minimal increased size of the membrane (Fig.1c,d). Important is the evaluation of the late phase of the angiogram, where a reduction of size and intensity of leakage should be present. Short-term follow-ups with fluorescein and ICG angiography demonstrated that this post-therapy CNV is not a recurrence as seen after photocoagulation. Instead this structure represents the residual central membrane, many times including the original feeder vessel.

The reduction of leakage from the neovascular complex in fluorescein angiography is a reliable parameter for the evaluation of treatment success. Cases, which show a good response after therapy, usually present with only minimal persistent leakage after 2 to 3 treatments. Another positive criteria is the appearance of a dark pigmented rim due to a reactive RPE hyperplasia. This can be observed both clinically and in the early phase angiogram. Unresponsive cases show continuation of leakage and no cessation of membrane growth.

As the therapy continuous the interpretation of persistent leakage in late angiography becomes increasingly difficult. Highly active exudation is easily observed with angiography. Minimal residual leakage is more difficult to observe. It is important to take into account that minimal, subretinal fibrosis through involution of the fibrovascular membrane causes a late pooling of fluorescein called "staining" and does not need additional treatment. Of absolute importance is the comparison of angiographic findings to the clinical presentation. This allows recognition and location of subretinal fibrosis and makes interpreting the angiogram easier.

Clinical experience shows that minimal residual leakage does not lead to reduction of visual acuity. And also that retreatment has little or no effect on the persistence of leakage.
Therefore at this point one would consider discontinuing retreatment while continuing to monitor functional and clinical progress closely.

Study Results

TAP-Study

Several clinical studies evaluated the effected of photodynamic therapy in the treatment of neovascularization secondary to age related macular degeneration. The majority of these clinical studies used verteporfin as a photosensitizer. Based on a phase III clinical trial called "TAP-Study" (**T**reatment of **a**ge-related macular degeneration with **p**hotodynamic therapy) [14,15] verteporfin became the first approved photosensitizer in ophthalmology within

the US, Canada and Europe.
In the TAP-Study 609 patients with subfoveal choroidal neovascularization secondary to AMD were randomly treated with verteporfin or placebo.

Table 1: Glossary of Terms relevant to PDT (modified from: *Schmidt-Erfurth U, Hasan T (2000) Mechanism of Action of Photodynamic Therapy with Verteporfin for the Treatment of Age-Related Macular Degeneration. Surv Ophthalmol 45: 195-214*)

Terms relevant to PDT	
Photocoagulation	Thermal modality to induce structural damage by absorption of high levels of light energy within biological chromophores such as melanin or hemoglobin
Photodynamic Therapy (PDT)	A non-thermal modality using light, an activable chromophore and oxygen to induce a localized cytotoxic reaction involving chemical radicals and oxidative processes
Photosensitivity	Phototoxic reactivity of tissue following light exposure due to prolonged retention of sensitizer, e.g. within skin or inner organs
Photosensitizer	A light-activable compound which produces highly toxic singlet oxygen radicals upon irradiation with light at its specific absorption peak
Photosensitizing potency	Determines the light dose required for optimum specificity
Type I reaction	Photodynamic process with formation of cytotoxic free radicals
Type II reaction	Interaction of excited sensitizer molecules with oxygen leading to the generation of singlet oxygen radicals, major mechanism of photochemical tissue damage

Primary inclusion criteria were a visual acuity of 20/200 to 20/40 on the ETDRS chart (early treatment diabetic retinopathy study chart) and clinical evidence of AMD. Angiographic criteria were subfoveal leakage from CNV, which included an obligate part of "classic' CNV and a facultative part of "occult" CNV. The CNV had to be more than 50% of the entire lesion. The maximum diameter of the lesion to be included was 5400µm (equivalent to 9 disc diameter). Starting December 1996 twenty-two study centers in North America and Europe participated in the TAP-Study.
Because of the lack of experience with the use of PDT in ophthalmology, this first clinical trial focused on patients with advanced stages of the disease, who had no therapeutic alternatives. Therefore it is not surprising that the mean visual acuity of recruited patients was 20/160 and the mean maximum diameter was as large as 4.5 disc diameters at baseline.

TAP-Study: Study procedure

The protocol for the TAP-Study included a standard protocol, refraction, best corrected visual acuity, contrast sensitivity (Pelli-Robson), fundus photography and fluorescein angiography. Follow up visits were performed every three months. Retreatment was performed, if the angiogram showed persistent leakage from CNV. Angiographic inclusion criteria were verified by an independent photograph reading center (The Wilmer Eye Institute, John Hopkins University, Baltimore). Patients were treated according to a 2/3 randomization: 3 patients were treated with visudyne; two patients received sham treatment (dextrose solution). Verteporfin therapy was applied using 6mg Verteporfin / m^2 body surface area. The infusion of the sensitizer was administered over a time of 10 minutes. Light irradiation (600mW/ m^2 at a light dose of 50J/ m^2) was applied 15 minutes after start of infusion using a diode laser with an emission wavelength of 692nm. All study personal, investigators, reading center and patients were masked for the duration of the study.

TAP-Study: Results

The two-year results of the TAP-Study were announced in March 2000. The results showed a significant difference regarding the risk of moderate to severe visual loss between the verteporfin treated groups compared to the placebo group. Verteporfin treated patients were also more than

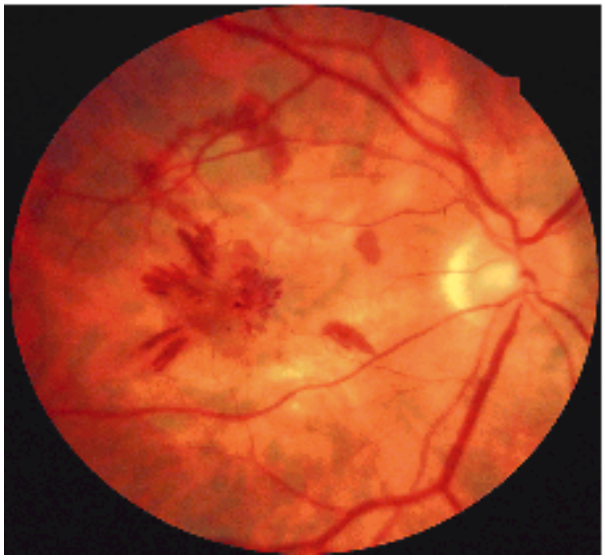
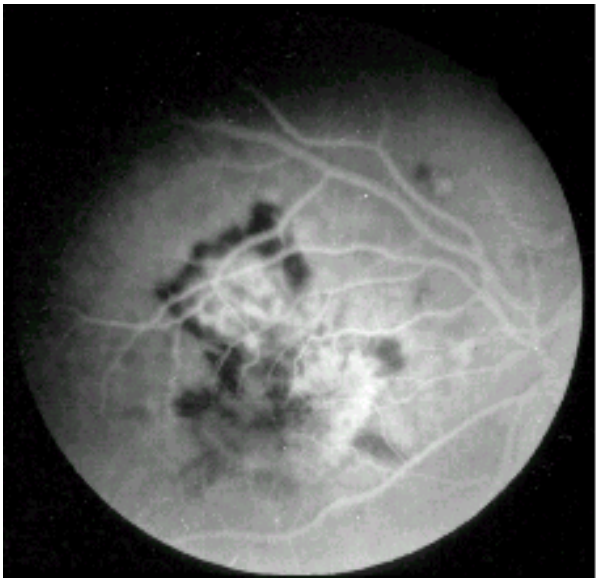


Fig. 1a Ophthalmoscopy before treatment shows neovascular AMD with typical characteristics, such as macular edema with retinal thickening and subretinal hemorrhages.

Fig. 1b,c Fluorescein angiography pre-treatment shows a subfoveal, well demarcated, so called “classic” CNV, with heavy leakage in the late phase (1c).



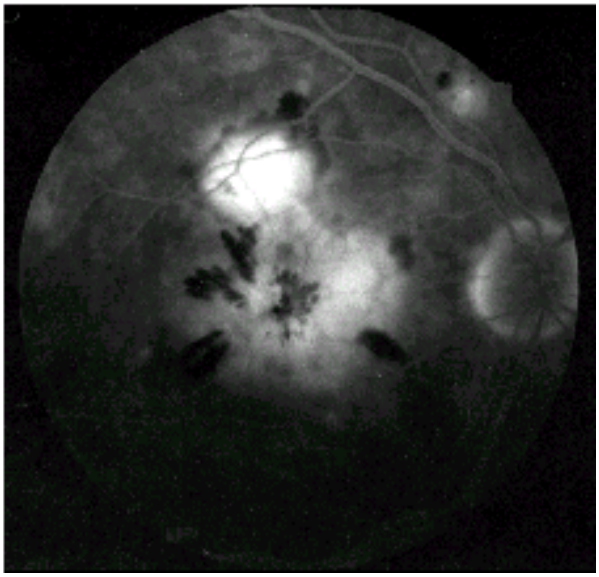
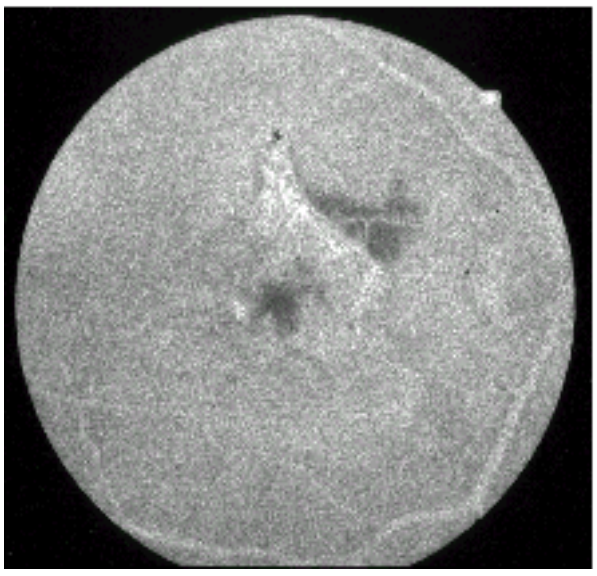
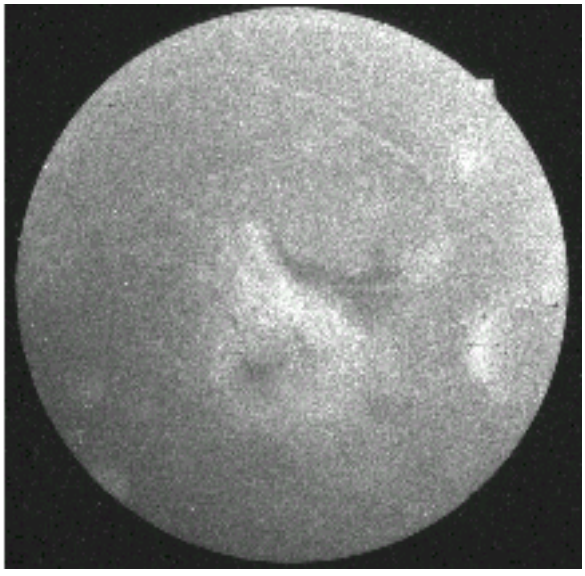


Fig. 1d,e Three months after the first PDT treatment a reduction of edema, exudation and hemorrhages can be observed angiographically.





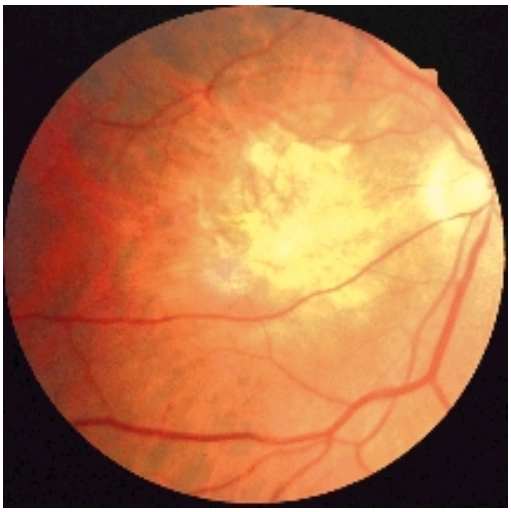
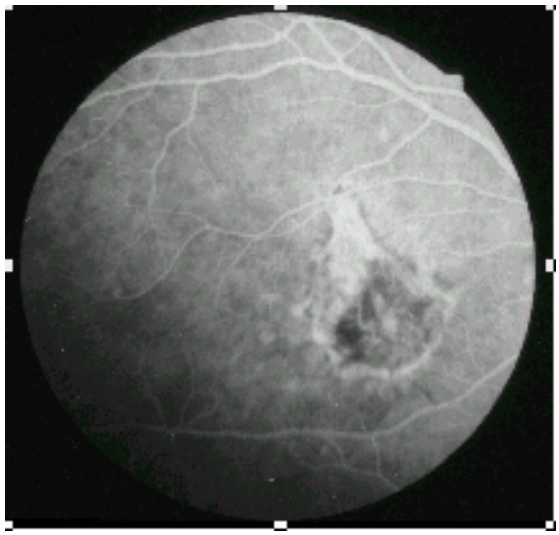
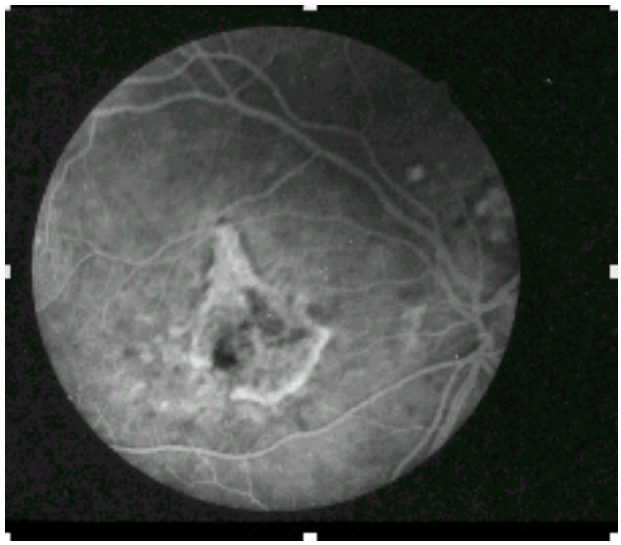


Fig. 1f-h Two years after initial therapy and 3 PDT retreatments ophthalmoscopy reveals no evidence of fluid or hemorrhages in the macula. Some mild atrophic changes, which in part were present before therapy, can be observed (Fig. 1f). Angiography shows no active leakage from CNV. The involuted membrane is still present and shows some staining in the late phase of angiography (Fig. 1h). At this point no further retreatments are indicated and the patient should be observed.





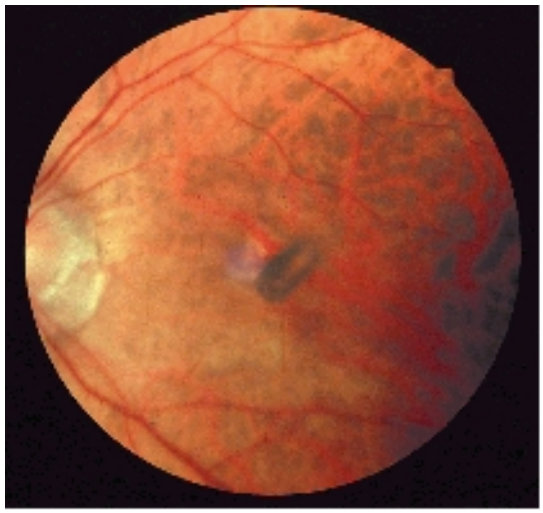


Fig. 2a Ophthalmoscopy before treatment shows a typical CNV with increased hyperpigmentation due to pathologic myopia in a 54 years old woman.

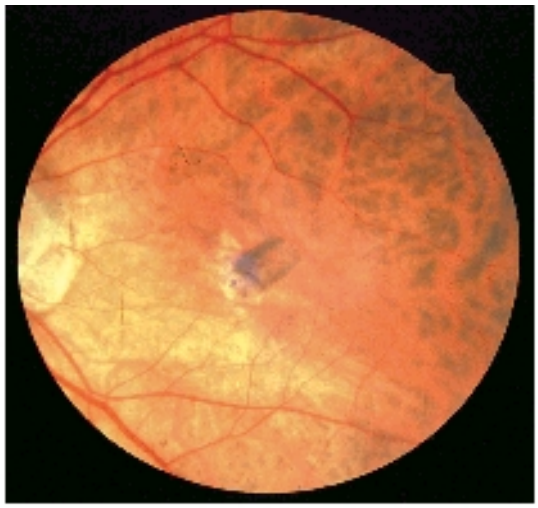
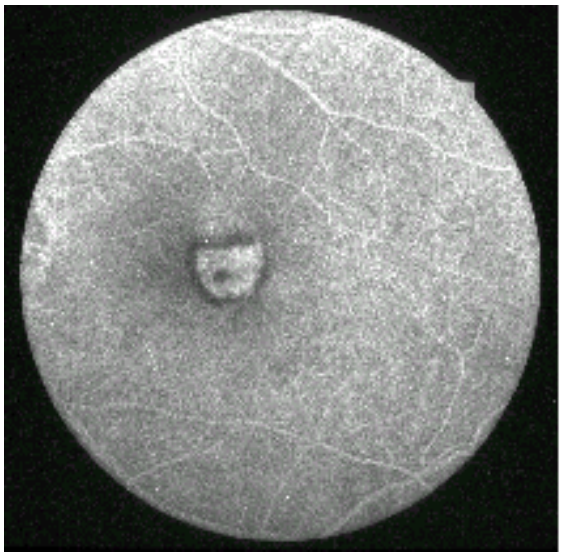


Fig 2b Ophthalmoscopy one year after initial therapy.



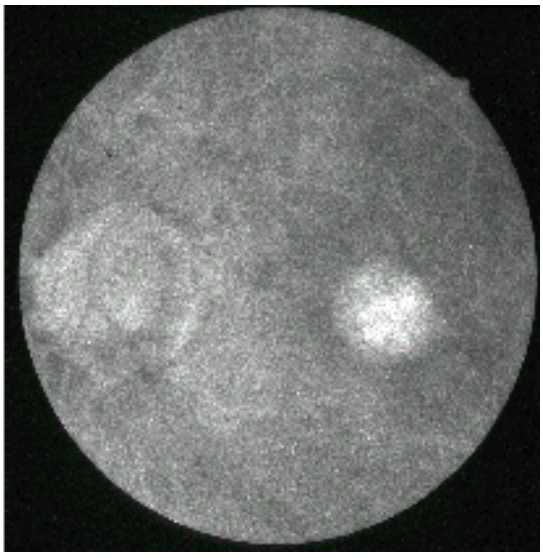
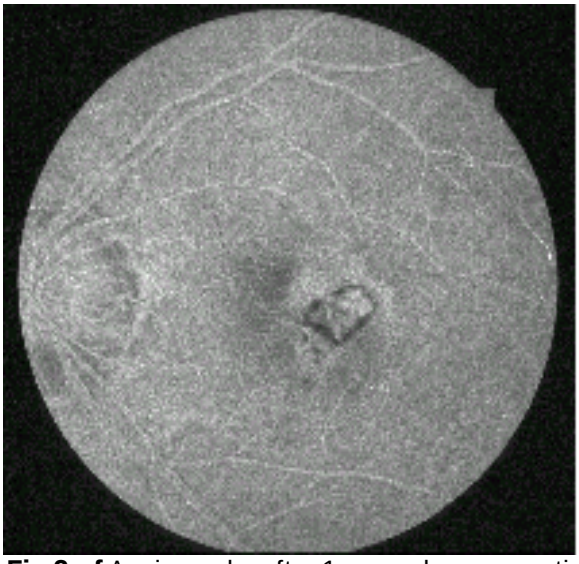


Fig 2c,d Angiography shows typical small classic CNV due to pathologic myopia before treatment.



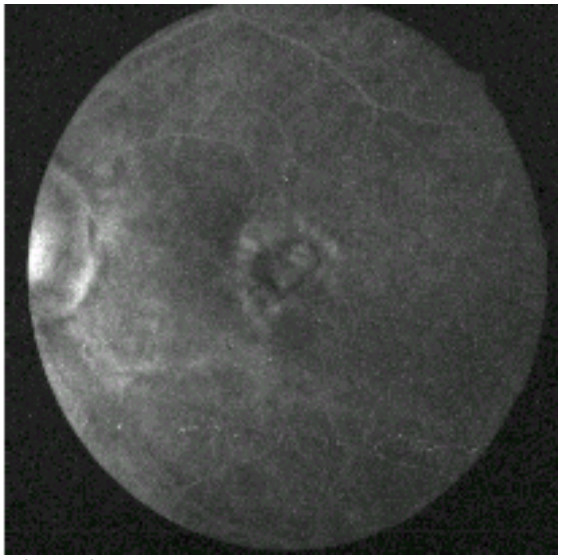


Fig 2e,f Angiography after 1 years shows cessation of leakage from CNV.

twice as likely to stabilize their baseline visual acuity. In addition 13% of verteporfin patients compared to 7% of placebo patients had an increase in visual acuity > 1 line. Results of contrast sensitivity testing and angiographic outcomes such as lesion growth and evidence of leakage were in favor of the verteporfin treated group.

TAP-Study: Subgroup analysis

Critical for the understanding of the mechanism of PDT were the angiographic subgroup analysis of the TAP trial. The results showed that the treatment benefit was dependent on the area of classic CNV with regard to the entire lesion. Lesions with predominately classic CNV responded best to the therapy and had the greatest chance for long-term vision stabilization. Fifty-nine percent of verteporfin treated patients with predominately classic CNV lost fewer than 15 letters at the month 24 examinations compared to 31% in the control group [15]. However one third of the placebo patients presented with a stabilization of visual acuity as well, which should be carefully considered before advising invasive treatments for these patients.

The VIP-Study

A second trial using Verteporfin as a photosensitizer was designed to investigate the efficacy of PDT treatment for occult membranes as well as small classic membranes in AMD, which were not included in the TAP-Study [16]. Overall the entire population included mainly patients with occult CNV without classic components, plus some patients with a component of classic CNV and with vision better than 20/40. A second part of the VIP trial investigated the effect on CNV in pathologic myopia.
The one-year results for occult membranes only were somehow disappointing: no significant difference was found between the e verteporfin treated group compared to the placebo group. Based on these results and in combination with the findings of the TAP-Study, PDT was recommended and approved for patients with predominately classic CNV only. However the recently (March 2001) announced two-year results may change those recommendations[31]:
At the 24-month examination, 46% of those patients treated with Verteporfin therapy lost less than 3 lines of vision, or 15 letters, on a standard eye chart (moderate vision loss) compared to 33% of patients on placebo (p=0.023). The difference of 13% between the treated and placebo group was statistically significant and higher than the 4% difference (p=0.51) seen at 12 months. With respect to severe vision loss, 70% of Verteporfin treated patients lost less than 6 lines of vision, or 30 letters, on a standard eye chart versus 53% of patients on placebo, a difference of 17% (p=0.001). Again, this result was higher than the 8% difference (p=0.14) seen at 12 months. At the 24-month time point, Verteporfin also showed statistically significant outcomes for other visual acuity endpoints (e.g. improvement of visual acuity and contrast sensitivity.).

VIP-Study: Subgroup analysis (occult CNV)

In those patients with occult CNV without classic components, who comprised approximately 75% of patients enrolled in the VIP-Study, results were found to be similar to those achieved in the overall population. At 24 months, a difference of 14% was found between the treatment and placebo groups with respect to the avoidance of moderate vision loss (Visudyne 45% vs. placebo 31%; p=0.03). Additionally, an 18% difference between treatment groups was found with respect to the avoidance of severe vision loss (Visudyne 71% vs. placebo 53%; p=0.004). This compares to differences between treatment groups of 4% (p=0.51) and 10% (p=0.07) seen at 12 months for moderate and severe vision losses, respectively [31].

These subgroup results and currently ongoing studies, which were designed to optimize treatment parameters for occult and classic CNV, may change the recommendations of Verteporfin therapy in AMD in the near future.

While additional subgroup analyses are ongoing, preliminary results suggest that the benefit of Visudyne therapy is greatest in patients presenting with relatively small lesions or lower levels of visual acuity (an approximate Snellen equivalent of less than 20/50). This subgroup comprised about 70% of study patients with occult CNV without classic components. Visudyne therapy may not be beneficial for individual patients presenting with both large lesions (>4 disc areas) and good visual acuity (approximately 20/50 or better) according to the press release by QLT Phototherapeutics Inc. in February 2001. During the two-year period, Visudyne treated patients received an average of five treatments. No new safety concerns were found.

Photodynamic therapy for pathologic myopia

Also reported were two-year results from a separate Phase IIIb multi-center randomized placebo-controlled study involving 120 patients with a similar but distinct condition referred to as CNV due to pathologic myopia. Inclusion criteria were fundus manifestations consistent with diagnosis (e.g. lacquer crackers) and ei-

ther a spherical equivalent greater than 6 diopters or an axial length at least equal to 26.5 mm. Study procedure and follow ups were performed according to the TAP Study protocol.
In the primary analysis performed at 12 months, it was found that patients showed a definite benefit from Visudyne therapy with respect to the primary endpoint. Specifically, 86% of Visudyne treated patients lost less than three lines of vision, or 15 letters, on a standard eye chart, compared to 67% of patients administered a placebo (p=0.01). The percentage difference dropped over the second year from 19% to 7% in favor of Visudyne (p=0.38). However, the percent of patients who showed an improvement in vision after treatment with Visudyne was much higher than placebo. Forty percent of Visudyne treated patients gained one or more lines of vision versus 13% of those treated with placebo (p=0.003). Furthermore, 12% of
Patients treated with Visudyne experienced an increase of three or more lines of vision compared to 0% of those on placebo (p=0.03) [16,31].

Figure 2a illustrates the typical features of CNV in pathologic myopia including a central edema without intraretinal hemorrhages and the absence of degenerative changes, which are typical for AMD. PDT shows excellent results in these patients. Visual acuity improvements of up to 6 lines have been described especially in younger patients. Several cases present with regression of the subretinal membrane after a few treatments. Only (Fig. 2b, e,f). Good prognostic criteria are a hyperplastic, pigmented rim and a small surrounding area of retinal atrophy, which is presenting as a window defect in angiography (Fig. 2c,d). Ophthalmoscopy reveals local scarring with partial fibrosis, which depends on the preexisting area of fibrosis [32].
Myopic patients need less retreatment in general. In our experience PDT retreatment should be discontinued, when RPE hyperplasia occurs, because this can be interpreted as a factor for continuing good remission [33]. Nevertheless patients should be monitored for any changes as discussed for AMD patients.

Safety issues

PDT is minimally invasive and well tolerated and therefore can be safely used in large patient collectives. This is especially important for elderly patients, who are many times suffering from additional age related diseases like hypertension or diabetes. The clinical trials confirmed the favorable safety profile of PDT with verteporfin as no serious safety concerns were identified during the time of treatment. The most frequently reported adverse events attributed to the treatment were injection site events (15.9 % / TAP Study) and visual disturbances (22,1% / TAP Study). Extravasation of the drug is the most serious complication in this group, because it can lead to severe skin necrosis if not treated properly. Photosensitive reactions were infrequent, occurring in only 3.5 % of study patients. In the TAP Study 2.5% of patients complained of infusion-related backpain. Allergic reactions were uncommon and less frequent in the verteporfin treated group compared to the placebo group (2.0% versus 3.9%). In addition, during the VIP trial for AMD patients, 4% of patients experienced a severe vision decrease within 7 days of treatment, which was transient in some of these cases [15].
In general patients should be advised to avoid direct sunlight for at least 48h (5 days according to FDA regulations). They should were special protective sunglasses, which shield their eyes from direct sun or halogen light. Because of the characteristic of verteporfin, patients with decreased liver function should be aware of possible prolonged photosensitivity. Patients with porphyrinuria or allergies to benzoporphyrine derivates (e.g. verteporfin) should be excluded from any treatments.

Guidelines for photodynamic therapy

New therapies require the development of clear treatment guidelines. Especially for a successful treatment it is necessary to identify the group of patients, who will benefit of this therapeutic approach. In the case of photodynamic therapy the criteria for treatment indication are based on objective diagnostic features. Most important are the nature of the disease itself (choroidal neovascularization secondary to AMD or pathologic myopia) and angiographic and functional aspects. Other factors such as size and location of the CNV as well as potential risk factors may also play a role.

Angiographic Criteria

Angiographic characteristics are the base for any treatment decision. Based on the study data it seems that the area covered by so-called **"classic" CNV** relates to the treatment effect. 100% classic lesions seem to respond best to the treatment. Based on the TAP Study results [14,15], treatment for lesions with at least 50% classic CNV is recommended currently. However, the latest results of the VIP Study may change those recommendations and further studies will show, in which way the therapy can be further improved.

The **Lesion size** is determined on mid and late phase angiographic images. The laser device limits the maximum treatment spot size. If the lesion

exceeds that diameter, one should only treat the active part of the lesion. In lesions larger then 5400µm, visual recovery seems unlikely and the reason to pursue with the treatment can only be preservation of the visual filed. Here a comparison with the also effected partner eye maybe of use to evaluate potential progression of the membrane and scaring process.

Photodynamic therapy is approved for the treatment of subfoveal lesion only. Extrafoveal membranes should be treated with thermal laser according to the guidelines developed by the MPS Study Group. More controversy is the treatment of **juxtafoveal CNV**, when the leakage already touches upon the foveal avascular zone. In these cases thermal laser is more likely to compromise central visual acuity. The TAP Study results showed that PDT for recurrent CNV after laser therapy is less efficient [15]. This is of special importance considering that up to 70% of juxtafoveal CNVs show recurrence after therapy according to the MPS-Study results [6]. Also patients with small, classic, juxtafoveal membranes had a most favourable outcome in the TAP Study. However, as long as a conventional treatment is possible without affecting the foveal avascular zone, no PDT should be indicated.

Visual acuity is a more subjective treatment criteria. Inclusion criteria for the TAP Study were a visual acuity of 20/40 to 20/200 Snellen equivalent. Again patients with visual acuity below 20/200 might be treated for preservation of visual field in selected cases.
In our experience, small membranes with poor visual acuity should be treated once and observed carefully with functional and angiographic follow up after 4 to 6 weeks. In case of no functional or anatomical improvement the treatment should be discontinued and thermal laser intervention should be discussed [4].

PDT: Whom not to treat

Currently PDT treatment should not be considered under the following circumstances:

1. Chorioretinal anastomosis (or retinal angiomatous proliferations), which can be seen in 5 - 10% of patients with predominantly classic CNV, don't respond to the treatment. A reason could be the increased blood flow through the retinal anastomosis, which may cause a "wash-out" effect of the dye secondary to increased perfusion of the neovascular complex.

2. Fibrovascular detachment of the pigment epithelium. All adverse events with significant visual loss after treatment (see: results of the phase III clinical trials) were seen in patients presenting with this subtype of occult neovascularization. Treating these lesions can cause a rupture of the retinal pigment epithelium (RIP-Syndrome) with severe vision loss.

PDT: Future Indications

PDT allows a selective occlusion of vascular tissue through secondary alterations of the vascular structure itself. As long as angiography reveals a classic choroidal neovascular complex a therapeutic effect can be achieved. Therefore limiting the application of PDT to the treatment of CNV in AMD or pathologic myopia seems not to be sensible. Other patients with choroidal neovascularization secondary to RPE scaring, trauma, multifocal choroiditis and angioid streaks could potentially benefit from the treatment as well. However, regardless of the indication angiography remains to be the basis for any treatment decision.

PDT: Current Benefit and Perspectives

Photodynamic therapy has been approved only recently. To date clinical experience is mainly based on only two major clinical trials (TAP, VIP) [14,15,16]. These studies were the first major trials evaluating efficacy and safety of PDT in ophthalmology. With the rapidly increasing number of treatments new indications and treatment strategies will develop. For example combined therapeutic approaches using PDT and feeder vessel coagulation or the additional application of antiangiogenetic substances seem to be promising and are currently evaluated in clinical trials.
Another important approach is to optimize the treatment parameters by shortening treatment intervals as it is investigated in an ongoing German multicenter trail [34]. The results of these studies may help us in future to treat patients more efficiently and with even better visual results.
Finally new photosensitizers continue to be developed, which may have improved characteristics for PDT of ocular structures.
At this point PDT is recommended for patients with predominantly classic CNV secondary to AMD or pathologic myopia. However, we are just beginning to explore the broad potential of this exciting new treatment modality.

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