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Photodynamic Therapy

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Introduction

Photodynamic therapy was approved in 2000 as an alternative treatment for patients with AMD of the exudative form, having been the first effective pharmacological treatment for this form of the disease.

Until then, laser photocoagulation was only successful in treating a small percentage of neovascular lesions (juxtafoveal and extrafoveal), excluding subfoveal lesions, which are more frequent.

With the emergence of antiangiogenic therapies, photodynamic therapy has been used less frequently.

However, it remains useful in three situations: in patients with systemic or ocular contraindications regarding intravitreal administration of antiangiogenic drugs, as an adjuvant, in combination with other drugs, and in the treatment of polypoidal choroidal vasculopathy and central serous chorioretinopathy.

Mechanism of action

Experimental studies[1,2] suggest that photodynamic therapy (PTD) causes endothelial cell lesions, with formation of clots and selective vascular occlusion. Endothelial cell membrane lesions appear to be caused by free radicals released when verteporfin is activated by non-thermal laser light. These free radicals react with endothelial cell membranes and circulating blood cells, inducing platelet activation and local clot formation.

The mechanisms by which PTD induces tissue destruction are not exactly known. Three related mechanisms of action have been proposed: cellular, vascular and immune[3]

The cellular mechanism, which is the most relevant, corresponds to the cytotoxic effects of free radicals on mitochondria, the endoplasmic reticulum and lysosomes.

When exposed to these radicals, endothelial cell membranes rupture, exposing the basal membrane, which causes platelet adhesion and aggregation.

Activated platelets release mediators such as histamine, thromboxane and TNF-α.

These mediators trigger a sequence of events, namely vasoconstriction, thrombosis, increased vascular permeability, blood stasis and hypoxia.

The proposed immune mechanism is based on the high concentrations of cytokines observed in patients subject to PDT, such as interleukin 2 and TNF–α.

It is equally admitted that PDT may decrease immune response by reducing antigen-presenting cell activity.

Standard treatment consists of endovenous infusion of verteporfin at a dose of 6 mg/m2 body surface, for 10 minutes.

Fifteen minutes after starting the infusion, the patient is treated with a diode laser with wavelength of 689 nm and light intensity of 600 mw/cm2, at a radiation dose of 50 J/cm2, with an exposure time of 83 seconds and a spot diameter corresponding to the diameter of the largest lesion plus 1mm.

These parameters have been studied and appear to be ideal, allowing maximum vascular effect with minimum photoreceptor and pigment epithelial cell damage.

Verteporfin activation by the diode laser induces temporary closure of the choroidal neovascular complex, through the mechanisms already described, causing little damage to adjacent retinal structures.

This characteristic doubtlessly represented a therapeutic advantage, since it allowed treatment of lesions whose location or size prevented use of other available therapies, namely conventional laser photocoagulation.

However, photodynamic therapy does entail some damage, although induced retinal lesions are smaller than that occurring following thermal laser photocoagulation. Laser fluence reduction protocols have been proposed in the attempt to reduce the extent of this damage.

Therapy schemes with more intense treatment regimes, including treatment every 2 months in the first 6 months, were also tested.

The efficacy and safety of the latter regime were compared with those of the standard regime[(4)].

No statistically significant differences were found between the two regimes in terms of visual improvement, number of retreatments and safety.

The intensive treatment regime in the first 6 months appears to be more effective in preventing severe loss of visual acuity; however, the difference observed after 24 months is not statistically significant, with loss of visual acuity greater than 6 lines being observed in 25% of patients treated with the intensive regime and 38% of patients treated with the standard regime.

Main clinical trials

The efficacy of PDT was evaluated in several multicentric, randomized clinical trials in patients with AMD with choroidal neovascularization, of which the following should be highlighted:

- Treatment of AMD with PDT (TAP studies)[(5,6,7,8,9)]
- Verteporfin in PDT (VIP studies)[(10,11)]
- Verteporfin in Minimally Classic Choroidal Neovascularization (VIM studies)[(12)]
- Visudyne in Occult Classic Choroidal Neovascularization (VIO study)[(13)]
- Meta-analysis of the TAP and VIP Studies[(14)]
- TAP Extension[(15)]

Many studies were subsequently performed in order to study and compare several therapeutic modalities, of which the following should be highlighted:

- Anti-Vascular endothelial growth factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in AMD (Anchor Study [(16,17,18)])
- Ranibizumab Combined with Verteporfin Photodynamic Therapy in Neovascular AMD (Focus[(19)])
- Summit Clinical Trial Program, which includes 3 studies: the Mont Blanc, Denali and Everest Studies[(20)]

TAP Study

This study provided the main evidence of PDT efficacy. It included two multicentric, double-blind, randomized, placebo-controlled studies, in Europe and the United States of America (Table 1).

Four hundred and two patients with classic subfoveal choroidal neovascularization were treated with PDT, while 207 patients were treated with placebo. The primary endpoint was the percentage of eyes for which losses of less than 15 ETDRS letters from baseline were observed at 12 and 24 months. PDT was significantly more effective than the placebo, both at 12 months (61% versus 46%) and 24 months (53% versus 38%).

These results were more significant in predominantly classic membranes.

Study Number of patients	Pred. classic Verteporfin	Pred. classic Placebo	p	All membranes Verteporfin	All membranes Placebo	p
TAP: 12 months N=609	67.3%	39.8%	<0.001	61.2%	46.4%	<
TAP: 24 months N=609	59.1%	31.3%	<0.001	53%	37.7%	<
TAP: 36 months N=476	58.1%	-				
TAP: 48 months	57%	-				

Table 1 - TAP study: percentage of eyes with loss <3 lines in the ETDRS chart

VIP Study

In this study, the efficacy and safety of Photodynamic Therapy were evaluated in patients with occult lesions (Table 2).

Results after 12 months were somewhat disappointing; however, efficacy was demonstrated in the treated group at 24 months (46.2% versus 33.3%). Subgroup analysis led to the conclusion that greater benefits were achieved in patients with small lesions (less than 4 disc areas) and/or visual acuity worse than 20/50. In these patient subgroups, the differences between the PDT group and the placebo group had greater statistical significance (51% versus 25%).

Study	MTRI verteporfin	MTRI Placebo	p
VIP 12 months	49%	45%	Ns
VIP 24 months	45%	32%	0.032
VIM 12 months 300 mw/cm^2	86%	53%	0.002
VIM 12 Months 600 mw/cm^2	72%	53%	0.08
VIM 24 months 300 mwcm^2	74%	38%	0.003
VIM 24 months 600 mwcm^2	47%	38%	0.45

Table 2 - VIP and VIM studies: percentage of eyes with loss <3 lines in the ETDRS chart.

VIM Study

The objective of this study was to determine the efficacy of photodynamic therapy in minimally classic membranes (where the classic component represents less than 50% of the neovascular lesion) sized below six disc areas (Table 2).

Additionally, the efficacy of reducing fluence to 50% (25J/cm2) relatively to standard parameters (50J/cm2) was also analysed.

In the standard laser light activation protocol, a wavelength of 689 nm and an intensity of 600 mw/cm2 are used for 83 seconds to achieve a fluence value of 50J/cm2.

In this study, no statistically significant efficacy was found at 12 and 24 months in the group of patients treated with the standard protocol. On the contrary, better results were observed for patients treated with the reduced fluence protocol, in terms of the primary endpoint (loss of visual acuity of less than 15 letters).

Based on these results, the study authors advise treatment of small minimally classic lesions with PDT, concluding that the reduced fluence protocol may be beneficial. The percentage of conversion of minimally classic lesions into predominantly classic lesions was also studied and treatment efficacy was demonstrated, irrespective of the fluence used.

The reduced fluence issue will also be referred in the Denali study.

Two other studies – VALIO (Verteporfin Therapy with Altered Light in Occult choroidal neovascularization) and VER (Verteporfin Early Retreatments) were also performed.

In the VALIO study, the efficacy of laser treatment at 15 and 30 minutes was evaluated and compared.

Since no statistically significant differences were observed between these two therapeutic modalities, it was decided to maintain the 15 minutes used in standard treatment.

The objective of the VER study was to determine whether it would be beneficial to reduce treatment intervals to 6 weeks in the first 6 months.

Since no increase in efficacy was found relatively to the standard regime (treatment every 3 months), it was advised that the usual treatment regime be maintained.

Study	MTRI verteporfin	MTRI Placebo	p
VIP 12 months	49%	45%	Ns
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VIO Study

The VIO study was designed to determine PDT indications in occult lesions with no classic component. Although the complete results report has not been published, the primary endpoint had not been reached at 12 and 24 months; therefore, no significant benefits were demonstrated for the treatment of occult membranes with PDT.

These results led the EMEA to remove occult membranes from the list of photodynamic therapy indications (April 2007).

Meta-analysis of the TAP and VIP studies

The meta-analysis of the TAP and VIP studies was a retrospective analysis in which lesion size, composition and visual acuity at baseline were considered, as well as possible relations between these parameters and study results.

The objective of this meta-analysis was to explain the apparent discrepancies found between the TAP and VIP study results, considering the following:

- in the TAP study, treatment was found to be beneficial in predominantly classic and occult lesions, whereas it was found not to be beneficial in minimally classic lesions;
- in the VIP study, treatment of occult lesions was found to be more beneficial in small lesions (≤4 disc areas) and/or visual acuity <20/50.

This meta-analysis revealed that the most important factor in predicting final visual acuity in patients treated with PDT appears to be lesion size.

Therefore, treatment of small lesions (≤4 disc areas) will be beneficial for all types of lesions, including occult lesions with no classic component, provided lesions are recent.

Regarding classic membranes, treatment benefits extend to lesions > 4 DA and non-recent lesions.

TAP Extension

Some patients that completed the 2-year TAP were enrolled in a 3-year extension study, for a total duration of 5 years (60 months), under an open-label regime.

The main objective of this study was to obtain long-term visual acuity and 5-year safety data in patients with subfoveal choroidal neovascularization treated with photodynamic therapy.

Patients having completed month 24 of the TAP study were eligible to participate in the study extension, irrespectively of having been included in the treatment or the placebo group and of lesion characteristics at baseline. In the TAP study extension, visual outcomes remained stable between month 24 and month 60, even in patients with low retreatment rates.

No safety problems were found leading to contraindications being associated to retreatment with photodynamic therapy in the 5 years of study duration. No safety problems were found in bilateral treatment.

PDT Safety

The most complete and extensive PDT safety data were published in the meta-analysis of the TAP and VIP studies, where a comparison with placebo was performed. PDT is considered a safe treatment, with rare side effects, of little significance (Table 3).

Choroidal hypoperfusion associated to PDT has been documented in fluorescein and ICG angiography in the first days after treatment and, more rarely, in the following months. Controversy exists regarding the cumulative effect of treatment in permanent occlusion of the normal choriocapillaris and the association between this hypoperfusion and eventual functional consequences[(21)].

Ocular effects	Non-specific visual disorders Transient loss of visual acuity (18% vs. 0%) Severe loss of visual acuity (≥ 20 letters up to 7 days after PDT) (0.7% vs. 0%) Scotomatous alterations (6% vs. 3.4%)
Systemic effects	Injection site reactions (13% vs. 5.6%) Lower back pain (2.4% vs. 0%) Hypersensitivity reactions (3% vs. 0%) Sleep pattern alterations (1.6% vs. 0%)

Table 3 - PDT adverse effects

Combined treatments

Combined approaches for treating exudative AMD have been investigated as a mean of improving treatment efficacy and reducing treatment frequency.

Many non-randomized studies reported successful treatment using combinations of PDT, corticosteroids and antiangiogenic agents[(22,23,24)].

The Focus trial[(19)] showed that combination therapy using PDT and Ranibizumab was superior to PDT alone in efficacy and also reduced the need for repeat PDT sessions.

A merely illustrative comparison of the Anchor[16] and Focus[19] trials showed more favourable results in terms of visual acuity gain in the Anchor patients, which included only treatment naïve patients, suggesting that adding PDT to Ranibizumab may not increase the visual acuity gain.

The SUMMIT program, which includes three randomized clinical trials - DENALI, EVEREST and MONT BLANC, was designed to compare a combination therapy with PDT and ranibizumab with ranibizumab monotherapy.

The DENALI study[26] is a two-year, randomized, double-blind multicentric study conducted at 45 centres in the United States and five centres in Canada.

Enrolled patients with subfoveal CNV of all angiographic subtypes were randomized to receive either ranibizumab monotherapy, a combination of ranibizumab and standard fluence (ST) PDT or a combination of ranibizumab and reduced-fluence (RF) PDT.

This study investigated the efficacy and safety of combined therapy involving PDT and antiangiogenic drugs, namely ranibizumab 0.5 mg, administered intravitreally.

Combining verteporfin PDT with ranibizumab 0,5 mg (with 3 ranibizumab loading doses followed by additional injections on a monthly as-needed basis) can improve visual acuity from baseline at month 12 by 5,3 letters for verteporfin ST PDT and 4,4 letters for verteporfin RF PDT combination therapy versus 8,1 letters for ranibizumab alone.

Althought the primary objective (to demonstrate non-inferiority of at least one of the verteporfin combination arms to ranibizumab monotherapy) was not met, combination therapy reduced the number of injections required: 5,1 verteporfin SF PDT and 5,7 verteporfin RF PDT combination therapy versus 10,5 for ranibizumab alone.

Reduced fluence did not provide a clinical benefit over standart fluence in verteporfin PDT combination arms.

MONT BLANC, a similar study conducted at 50 centres throughout Europe, enrolled subjects with subfoveal CNV of all angiographic subtypes, who were randomized to receive either ranibizumab monotherapy or ranibizumab in combination with standard fluence PDT.Preliminary visual acuity results at 12 months revealed the non-inferiority of the combined treatment (PDT+Ranibizumab), when compared with Ranibizumab alone; the number of treatments and safety evaluation were similar in both groups.

These results and those from Focus trial suggest that PDT with standard fluence may be useful in combination with Ranibizumab for treating predominantly classic, minimally classic or occult AMD lesions.

Certain angiographic lesion subtypes, such as retinal angiomatous proliferation (RAP) and polypoidal choroidal vasculopathy appear to respond differently to PDT treatment [24,25] when compared to predominantly classic, minimally classic or occult lesions.

It is unclear whether they are more likely to benefit from a combination therapy. Polypoidal choroidal vasculopathy (PCV) may be considered as a well-defined subtype of AMD with a distinct natural history characterized by multiple recurrences and specific response to treatment. PCV often follows a remission-relapsing course and usually has a good visual prognosis. However, up to half of patients may have persistent bleeding and leakage, leading to vision loss.

The EVEREST study (part of the SUMMIT programme) is being performed in Asia and is designed to compare and evaluate the efficacy and safety of verteporfin PDT alone or in combination with ranibizumab, with that of ranibizumab monotheraphy for symptomatic macular PCV.

EVEREST trial[(27)] demonstrated that verteporfin PDT combined with ranibizumab or alone was statistically superior to ranibizumab monotherapy in achieving complete polyp regression in PCV patients (primary end point). The proportion of patients with at least a complete regression of polyps at any time-point during the study was significantly larger with verteporfin PDT combined with ranibizumab (83,32%) or alone (85,7%) versus ranibizumab monotherapy (42,9%). At month 6, a decrease in mean polyp area from baseline was seen in all three treatment groups. The largest decrease was seen with verteporfin PDT combined with ranibizumab followed by verteporfin PDT monotherapy, and ranibizumab monotherapy.

Subsequent Roundtable meetings[(28)] with international experts in retinal diseases had been held annually since 2007 and had formulate practical guidelines on diagnosis and management of PVC.

When considering PCV, ICGA is strictly necessary to confirm or to exclude the diagnosis. Then treatment should be considered for active symptomatic PCV and can be considered for active asympomatic PCV. The ICGA –guided thermal laser photocoagulation may be considered for extrafoveal polyps.

For the inicial treatment of active juxtafoveal and subfoveal PCV, the recommendation is either combination of standard fluence verteporfin PDT and 3x antiVEGF intravitreal injections at monthy intervals or ICGA-guided standart fluence verteporfin PDT. The combination treatment should be considered when there is leakage from polyps and from associated branching vascular network, or when there is large amount of subretinal fluid or exudation associated with PED. Other conditions that suggest the choice of combination treatment are ICGA images ambiguous or combining features of PCV and CNV. On the other hand antiVEGF monotherapy may be considered for initial treatment if verteporfin PDT is contraindicated or is not possible.

Monthy monitoring includes visual acuity, slit-lamp biomicroscopy and OCT. Three months after inicial treatment FA, ICGA and OCT shoud be performed.

If there is incomplete regression of polyps at this time, retreatment with verteporfin PDT alone or with antiVEGF in association shoud be considered. If there is complete regression of polyps at 3 months detected by ICGA but there is leakage on FA, subsequent antiangiogenic treatment is recommended.

Some manuscripts, studies and retrospective reports demonstrated that total polyp regression or complete disappearance of PCV lesions occurred in 56–95% of ≥200 eyes treated with verteporfin PDT[(29)].These studies indicated that many verteporfin-treated patients had stable or improved vision
(Table 4), with outcomes that compared favourably with the natural history of PCV.s

Authors	Spaide 2002	Chan 2004	Silva 2005	Hussain 2005	Mauget-Faÿsse 2006
Type	R	P	R	P	P
N	16	22	21	9	30
Age (average)	70.5	66.6	75.6	67.2	67
VA increase 12M	56.3%	45.5%	28.6%	0.0%	-
VA stabilization 12M	31.3%	50.0%	57.1%	100.0%	-
VA decrease 12M	12.5%	4.5%	14.3%	0.0%	-

VA increase 24M		0.0%	
VA stabilization 24M		100.0%	
VA decrease 24M		0.0%	
Comments	**Average follow-up 12M**	**6 eyes at 24M**	**Mean VA improved from 0.50 to 0.38 logMAR**

R – Retrospective; P – Prospective.

Table 4 - PDT and PCV. Results from different studies.

More recently aflibercept has shown good results in treating PCV. These results appear to be superior to those obtained with ranibizumab with a complete regression of polypoidal lesions ranging from 55.4%. to 69.2% at one year, and with a mean number of 7 injections[(30, 31).]

Three randomised clinical trials on naïve PCV patients are beeing runned – Everest II, Planet and Atlantic. The Everest II is a phase 4, 2-year RCT comparing Ranibizumab alone with a combined teraphy of Ranibizumab plus Verteporfin PDT in 321 Asian patients. Estimated primary completion date is April 2017[(32)]. The Planet RCT enrolled 331 patients in ASIA and 2 European countries. It is a phase 3-4, 1-year study comparing Aflibercept alone with Aflibercept plus Verteporfin PDT in patients with PCV. Estimated Primary completion date is August 2016[(33)] Atlantic Study, is a phase 4, 1-year RCT, being runned in Portugal and Spain, comparing intravitreal treat and extend aflibercept monotherapy with aflibercept treat and extend regimen with adjunctive PDT in patients with PCV. Estimated primary completion date is November 2017[(34)]

>> References

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