

Update on photodynamic therapy with verteporfin for macular diseases

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Abstract

Choroidal neovascularization in the macula is a major cause of visual disability in developed countries. Age-related macular degeneration is one of the commonest underlying etiologies for choroidal neovascularization, while other conditions include pathologic myopia, idiopathic, post-choroiditis, iatrogenic, and other causes. There have been no good and safe treatments for choroidal neovascularization at subfoveal areas. Photodynamic therapy with verteporfin has been shown to be effective in reducing the likelihood of visual loss due to choroidal neovascularization in age-related macular degeneration, especially when the lesion has predominantly classic composition. Further evidence indicates the beneficial effects in age-related macular degeneration with progressive occult choroidal neovascularization of small size and also in subfoveal choroidal neovascularization of pathologic myopia. The indications and applications of photodynamic therapy have been expanding swiftly and this treatment modality may provide a new hope for diseases such as polypoidal choroidal vasculopathy and central serous chorioretinopathy, which are more prevalent in Asian populations.

Key words: Choroidal neovascularization, Macula, Photodynamic therapy

Introduction

Photodynamic therapy is a 2-step procedure involving the infusion of a light-activated drug (a photosensitizer) and the application of low-energy laser for treating a wide range of diseases characterized by unchecked or aberrant neovascularization.¹ Verteporfin (visudyne) is the first ophthalmic drug proven to be effective in the treatment of choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) and pathologic myopia (PM).^{2,3}

The current status of photodynamic therapy

After the establishment of safety and efficacy in several multicenter randomized studies, photodynamic therapy (PDT) using verteporfin has been approved for the treatment of predominantly classic subfoveal CNV due to AMD in more than 70 countries, including the USA in April 2000, Europe in July 2000, and the Hong Kong Special Administrative Region in June 2001. Approval has also been granted in 40 countries for the treatment of occult subfoveal CNV due to AMD and in 55 countries for the treatment of subfoveal CNV due to PM.⁴ At the present time, more than 300,000 patients with CNV have been treated worldwide using PDT with verteporfin. In several countries, the ophthalmic indications of PDT with verteporfin has continued to expand towards CNV or vasculopathy of some other etiologies such as

angioid streaks and central serous chorioretinopathy and is being used as off-label treatments or in clinical trials.

The pharmacodynamic properties of verteporfin

The first step of the treatment involves the intravenous administration of the photosensitizer. Upon entering the bloodstream, the photosensitizer binds itself to circulating low-density lipoprotein (LDL) and shows preferential affinity for abnormal vessels or tumors whose vascular endothelial cell membranes are usually rich in LDL-receptors. This is due to the fact that rapidly growing vascular tissues greatly depend on the supply of LDL.⁵ Also, the uptake of the liposomal formulation of verteporfin is faster than its aqueous formulation.⁶

The second step of PDT involves the activation of the photosensitizer using a specific dose of light at a particular wavelength. Slit-lamp delivery of a low-energy (non-thermal) wavelength of 689 nm (diode laser) light is most commonly adopted in ophthalmology.⁷ This triggers a chain of photochemical reactions resulting in the formation of singlet oxygen and reactive oxygen species, which are responsible for direct cytotoxic effects at the cellular level or in vascular endothelium.⁸

Occlusion of CNV by erythrocytes or thrombotic plaques, extravasation of erythrocytes, and damage to the neovascular endothelium and retinal pigment endothelium (RPE) were observed at 1 to 12 weeks after PDT with verteporfin for patients with predominantly classic CNV secondary to AMD or malignant melanoma of the uvea.⁹⁻¹¹ Increased vascular leakage from the CNV and adjacent normal choroid were observed immediately after verteporfin therapy followed by non-perfusion of the CNV 1 day later and partial closure of adjacent choroidal vessels at 1 week.¹²

The vascular thrombosis resulting from PDT with verteporfin instigates a partial or complete regression of the lesion. The lesion specificity of the treatment is reflected by the fact that neither the laser beam nor the drug infused alone is likely to affect the target tissue. The combination of accumulated drug dose and the specific laser beam trigger a local reaction at the target site without affecting the surrounding normal tissues.

Evaluations of the safety and therapeutic efficacy of PDT using verteporfin has been addressed in phase I and II studies, 3 subsequent large, randomized, double masked, and placebo-controlled studies, and numerous case series and reports.

The pharmacokinetic properties of verteporfin

Age, race, and gender have no clinically important bearings on the pharmacokinetic parameters of intravenous verteporfin. An *in vitro* study showed that 91% of the administered dose of liposomal verteporfin was found to

evenly bind to a range of lipoproteins varying from high-density lipoprotein (HDL) to LDL and very low density lipoprotein (VLDL).¹³ Verteporfin is metabolized minimally by liver and plasma esterases, with the majority of an intravenous dose excreted unchanged through the bile and then into the faeces.¹⁴ Less than 0.01% is excreted via the kidney.¹⁴ Verteporfin has a plasma half-life of 5 to 6 hours. Cytochrome P450 isoenzymes do not appear to have a role in verteporfin metabolism.¹⁴ Based on pharmacokinetic data, dose adjustments are generally not required for age, gender, race, and even for patients with mild hepatic or renal dysfunction.¹⁴ In addition, the rapid elimination of verteporfin from the body makes skin photosensitivity unlikely after 24 to 48 hours.

Phase I and II studies

According to a preclinical animal study and dose-ranging studies of the treatment of CNV, at least 4 factors affect the efficacy of verteporfin. These are the dosage of verteporfin, whether verteporfin is administered as a bolus injection or as an infusion, the dose of activating light, and the interval between drug administration and light activation.¹⁵⁻¹⁷

The safety, short-term visual, and fundus fluorescein angiography (FFA) effects of a single photodynamic therapy with verteporfin for CNV due to AMD in 5 different dosage regimens was evaluated in an open-label clinical trial in 4 centers.¹⁶ A single dose of verteporfin 6 or 12 mg/m², activated by light doses of 25 to 150 J/cm², achieved temporary cessation of fluorescein leakage at 1 week in 52% to 100% of 128 patients.

Other than occluding the choroidal vasculature, PDT with verteporfin did not affect the retinal vasculature, retinal structures, retinal transparency, or global choroidal blood flow. Retinal ischemia or non-perfusion with associated vision loss appeared only at a light dose of 150 J/cm². Leakage recurred, however, in most of the lesions 4 weeks after treatment. The best regimen (regimen 4) was the one with verteporfin 6 mg/m², light dose of 50-100 J/cm², and activation 15 minutes after commencing infusion. This regimen resulted in the highest percentage of patients with occlusion of CNV at 1 week (100%, 21 of 21 eyes), 4 weeks (29%, 6 of 21 eyes) and 12 weeks (30%, 3 of 10 eyes). A light dose of 50 J/cm² achieved the best results with 57% (4 of 7 eyes) showing no angiographic leakage at 4 weeks. Patients with classic-containing subfoveal CNV were more likely to have complete occlusion of the lesion 1 week after treatment than those with occult but no classic components.¹⁶

Two of the above regimens (regimens 2 and 4) were further evaluated in a retreatment study.¹⁷ Both regimens involved verteporfin infusion of 6 mg/m² with one using a light dose of 100 J/cm² applied 20 minutes after the start of the verteporfin infusion (21 patients), while the other regimen used a light dose of 50, 75, or 100 J/cm² delivered 15 minutes after commencement of infusion (10 patients). One to 4 treatments with verteporfin therapy resulted in complete

occlusion of the classic subfoveal CNV in 25 patients 1 week after each treatment but fluorescein leakage reappeared 4 to 12 weeks after retreatment in almost all patients. Compared with baseline, there was reduction of fluorescein leakage and no specific ocular or systemic adverse events were reported even after multiple applications.

Photodynamic therapy for subfoveal choroidal neovascularization due to age-related macular degeneration

AMD in its exudative or wet form is the most frequent cause of blindness in people older than 50 years.¹⁸ Laser photocoagulation was comprehensively evaluated in the Macular Photocoagulation Study (MPS) but was shown to be beneficial only for pure classic membranes not involving the fovea.¹⁹ The value of submacular surgery and macular translocation surgery in treating subfoveal CNV of AMD are still not clear but appear less encouraging than originally supposed. These procedures are technically demanding and the results are unpredictable with a high rate of surgical and postoperative complications.²⁰⁻²² It is in this context that verteporfin, a new photosensitive drug, was first investigated in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study for its effectiveness at reducing the risk of vision loss in patients with CNV due to AMD.^{2,23}

Classic-containing subfoveal choroidal neovascularization secondary to age-related macular degeneration

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study report numbers 1 and 2

Patients with some classic-containing subfoveal CNV secondary to AMD and decreased visual acuity (20/40 to 20/200) were

recruited.^{2,23} Among the 609 eyes (verteporfin, n = 402; controls, n = 207), 242 or 40% (verteporfin, n = 159; placebo, n = 83) had predominantly classic CNV, 306 or 50% (verteporfin, n = 202; placebo, n = 104) were minimally classic, 54 (9%) had pure occult CNV, and the others were unclassified (**Table 1**). The standard treatment protocol consisted of an intravenous infusion of verteporfin 6 mg/m² over a 10-minute period, and 5 minutes later, the target lesion was exposed to a 689 nm light at a dose of 50 J/cm² for 83 seconds.

The primary outcome measure was achieved since verteporfin-treated eyes showed a significantly reduced risk of 3 lines of vision loss compared with placebo in the study population. The difference was first seen at 3 months and maintained at subsequent 12 and 24 months observations.^{2,23} However, at subgroup analysis, the statistical treatment benefit was found to be limited principally to eyes with a predominantly classic pattern of leakage on FFA (67% vs 40% at 12 months; 59% vs 31% at 24 months) but not to the group with minimally classic CNV (56% vs 55% at 12 months, 48% vs 44% at 24 months).

It is interesting to note that while verteporfin treatment reduced the chance of significant visual loss, it rarely resulted in significant visual improvement. Only 16% of verteporfin-treated patients and 10% of the control group had improvement in vision; only 6% of verteporfin-treated patients showed a 3-line improvement at 12 months. Moreover, 70% of verteporfin-treated patients and 77% of patients randomly assigned to placebo continued to lose vision during the follow-up period. Both groups started with a similar baseline median visual acuity of 20/80 while the median visual acuity at 24 months was 20/160 for verteporfin-treated patients and 20/200 for controls.^{2,23}

Table 1. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study (TAP) and Japanese Age-Related Macular Degeneration Trial (JAT) for age-related macular degeneration.

	TAP 1-year follow-up Randomized		JAT 1-year follow-up Non-randomized
Treatment	Verteporfin	Placebo	Verteporfin
Ethnic group	Caucasian	Caucasian	Japanese
Number of patients	402	207	64
Composition			
Predominantly classic	40%	41%	25%
Minimally classic	50%	50%	53%
Occult with no classic	10%	9%	14%
Baseline median visual acuity	20/80	20/80	20/100
Final median visual acuity	20/160 ⁺¹	20/200	20/80 ⁺²
Visual improvement (≥1 line)	26% (6% had 3 lines improvement)		53% (20% had ≥3 lines of improvement)
Loss of vision (≥1 line)	62%	77%	27%
Final visual acuity <20/200	51%	65%	16%
Mean visual acuity	-2.2 lines	-3.5 lines	+0.6 line (20/100 ⁺¹ → 20/80 ⁺¹)
No leakage by 1 year	19%	9%	44% (whole lesion) (classic component: 50%; occult component: 77%)
Progression of choroidal neovascularization	Classic: 43% Occult: 66%		Classic: 19% Occult: 14%
Mean accumulative number of treatments	3.4	3.7	2.8

Angiographically, the verteporfin-treated group had less progression of the lesion size beyond the baseline area at 12 and 24 months of follow-up. Angiographic leakage was also less readily observed with verteporfin therapy than placebo at 24 months but not at 12 months.^{2,23}

Occult with no classic choroidal neovascularization *Verteporfin in Photodynamic Therapy report number 2*

The Verteporfin in Photodynamic Therapy (VIP) Study was a complementary study to TAP. 339 eyes from 339 patients with AMD with subfoveal occult and no classic CNV or early classic-containing CNV with good vision (visual acuity better than 20/40) were recruited.²⁴

In the group of patients with occult with no classic CNV and presumed recent disease progression secondary to AMD, verteporfin-treated patients (n = 166) had less moderate or severe loss of vision (at least 15 letters loss) at 24 months (54% vs 67%; p = 0.02) but no statistically significant difference was seen at 12 months (51% vs 54%; p = 0.52) in comparison with the placebo-treated patients (n = 92).²⁴ Similarly, more favorable outcomes were seen in the verteporfin-treated patients at 24 months with regard to parameters such as overall changes in visual acuity, contrast sensitivity, and final visual acuity of 20/200 or worse. The median visual acuity dropped from 20/100 to 20/160 in the verteporfin-treated group and from 20/126 to 20/160 in the placebo-treated group.

The greatest therapeutic benefit occurred in the group with a smaller baseline lesion size (≤ 4 MPS disc area)

regardless of the visual acuity, or in the group with an initial visual acuity of 20/50⁻¹ or worse irrespective of baseline lesion size (**Figure 1**). It should be noted that in the VIP study for purely occult CNV, most of the patients treated with verteporfin continued to lose vision after 24 months. In the VIP study, only 13% of verteporfin-treated patients and 5% of control patients with purely occult CNV had any visual improvement after 24 months. The number of treatments required was 3.1 in the first year and 1.8 in the second year in the verteporfin-treated group compared with 3.5 and 2.4 treatments, respectively, for the placebo-treated group.

In the group of patients with classic-containing CNV with good visual acuity, there was a moderate loss of vision in 10 of 16 patients in the verteporfin-treated subgroup and 3 of 3 patients in the control subgroup. As for the minimally classic CNV at 2 years follow-up, the rates were 19 of 38 and 10 of 18, respectively. However, the sample size is too small to draw any statistically significant conclusions.²⁴

Asian patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration

Japanese Age-Related Macular Degeneration Trial Study Group

The Japanese Age-Related Macular Degeneration Trial (JAT) was a prospective, open-label, and non-controlled study performed in 5 centers to determine the safety and efficacy of PDT with verteporfin in subfoveal CNV secondary to AMD in non-Caucasian patients.²⁵ Sixty four Japanese

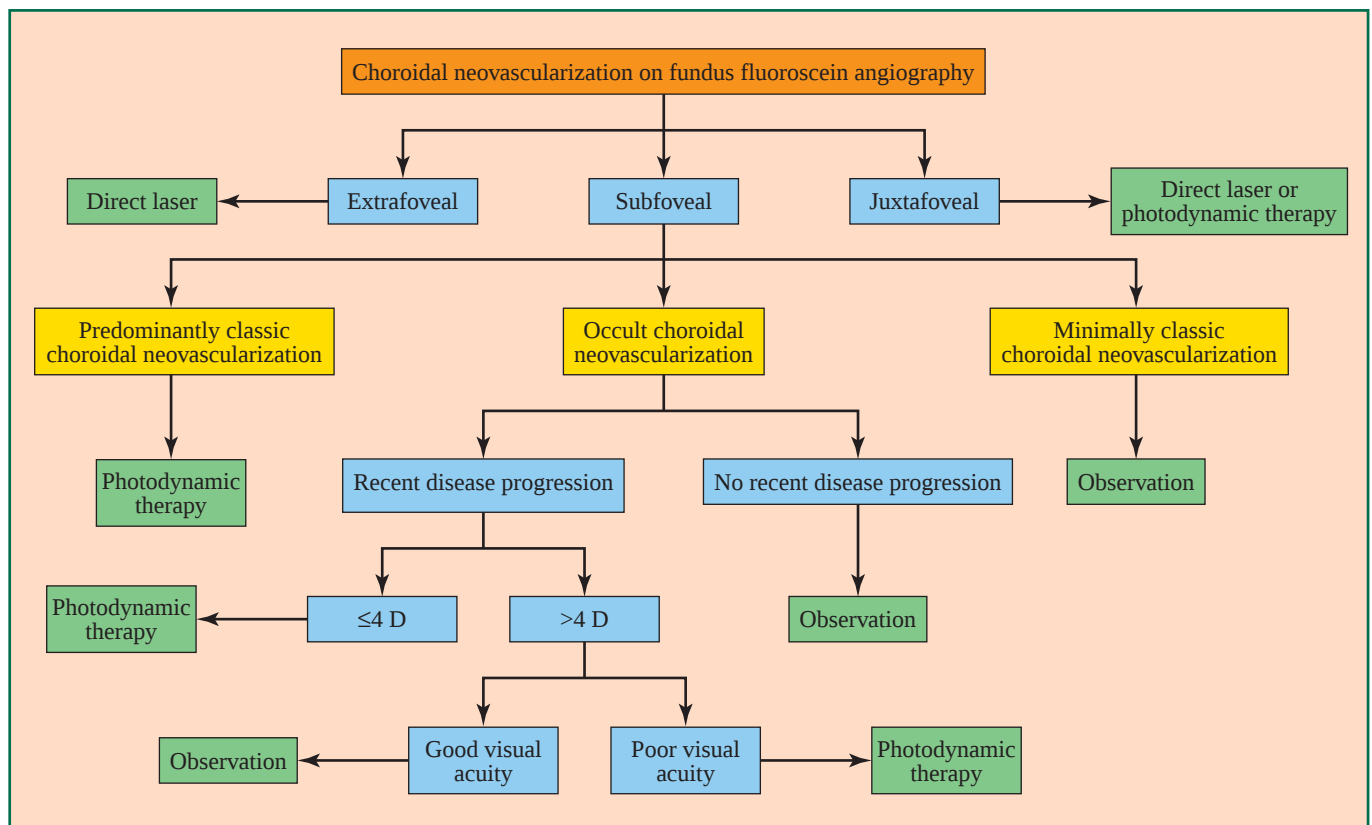


Figure 1. Flow chart for the management of choroidal neovascularization in age-related macular degeneration.

patients with at least some classic CNV at the baseline examination were enrolled and followed-up for 12 months (Table 1). The post-PDT treatment results were more encouraging than those observed in the Caucasian patients from the TAP study since more patients in JAT experienced vision gain and reduced loss of vision after 1 year. The median visual acuity improved from Snellen equivalent of 20/100⁺¹ at baseline to 20/80⁻¹ at 12 months. Angiographically, CNV progression was observed in 19% and 14% of patients with classic CNV and occult CNV, respectively, while 50% and 77%, respectively, had no leakage at the 12-month final visit. The mean number of treatments was only 2.8 compared with 3.4 treatments in the TAP study.²⁵

Follow-up, subgroup or combined analysis

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study report number 3

In the retrospective subgroup analysis on pure classic CNV, baseline lesion composition influenced the visual outcomes in patients with AMD receiving PDT with verteporfin.²⁶ Patients with pure classic CNV (predominantly classic lesions without occult CNV) tended to have better visual outcomes than patients with predominantly classic lesions (with some occult component). The better treatment results may be attributed to smaller lesions and lower levels of VA at baseline among patients with pure classic CNV.

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study report number 4

Verteporfin therapy reduced the risk of contrast sensitivity loss in a randomized study of subfoveal CNV in AMD (verteporfin therapy [n = 402]; placebo [n = 207]) at months 12 and 24.²⁷ The beneficial effect has been demonstrated in both predominantly classic or minimal classic CNV but is greater in the subgroup of patients with predominantly classic subfoveal CNV.

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study report number 5

This was an open-label and extended observation of predominantly classic CNV (n = 105) up to 3 years of treatment.²⁸ The absence of a comparative arm in the TAP extension study, however, necessitates extra caution during interpretation of the results of this study. Vision outcomes for verteporfin-treated patients were stable from 2 to 3 years and the corresponding Snellen equivalents were 20/160⁺¹ and 20/160, respectively. An additional 1.3 treatments were required between 24 and 36 months. No new safety concerns that would preclude multiple PDT treatments were noticed although severe visual loss was occasionally seen.

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study and Verteporfin in Photodynamic Therapy report number 1

In these exploratory analyses, it was found that lesion size (p = 0.01) was more important than lesion components (p = 0.18) and visual acuity (p = 0.53) as the predictive factors in determining treatment outcomes, especially in

minimally classic CNV (p = 0.03) and occult CNV with no classic lesions (p = 0.03), but not in patients with predominantly classic CNV.²⁹

Most importantly, in minimally classic and purely occult lesions with a small lesion size (4.0 disc areas or less) the post-PDT outcomes were favorable and similar to those of predominantly classic lesions. In other words, lesion composition is less important for smaller lesions.

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study and Verteporfin in Photodynamic Therapy report number 2

Standard angiographic interpretations such as lesion composition, size, morphologic response to treatment during follow-up (e.g., absence of leakage) are still the standards in determining the treatment and retreatment with PDT.³⁰ There is a high level of agreement between observers if the standards and terms are followed.

Recommendations for treatment

A recommended treatment algorithm, with a summary of the results from TAP, VIP-AMD, and MPS studies, is shown in the flow chart (Figure 1).

Photodynamic therapy for subfoveal choroidal neovascularization secondary to pathologic myopia Verteporfin in Photodynamic Therapy report numbers 1 and 3

PM has been reported as a major cause of blindness in many developed countries, particularly in young working populations.^{31,32} The condition is associated with a number of retinal and macular abnormalities, including chorioretinal atrophy, posterior staphyloma, lacquer crack, macular hemorrhage, retinal detachment, and CNV, all of which are the result of excessive axial lengthening. CNV accounts for much of the irreversible visual loss in both older and younger age groups. The estimated risk of developing CNV from PM varies from 4% to 10%.³³⁻³⁵ The outcomes of untreated CNV in PM is not clear but, in general, they are considered to be poor.³⁶ In a series of Asian patients with myopic subfoveal CNV, the best corrected visual acuity (BCVA) reduced by 2.0 lines at the 3-year follow-up. The loss of vision continued with a reduction of 5.0 lines after 5 years and 5.7 lines after 10 years.³⁷ Avila et al observed 70 eyes with untreated CNV in a predominantly Caucasian population — a 49% reduction in VA was observed after an average follow-up of 41 months.³⁷

In the VIP-PM study, 120 eyes from 120 patients were randomly assigned to verteporfin therapy (81 eyes) or placebo treatment (39 eyes) at 26 study centers with follow-ups 1 year and 2 years after treatment.^{3,38} Unlike those patients with AMD, the CNV in PM contained more classic components and was smaller in size. In the verteporfin-treated group, 85% were predominantly classic and 63% of patients had a lesion size of less than or equal to 1 MPS disc area.³

The 1-year results of the VIP trial demonstrated that, in patients with subfoveal CNV due to PM, verteporfin-treated patients had a higher chance of vision stabilization than the placebo group (72% vs 44%). The primary outcome measures, visual loss of less than 8 letters or 1.5 lines, was reached at the 1-year follow-up visit.³ The study also demonstrated that verteporfin therapy could increase the likelihood of having visual improvements, although small, for verteporfin-treated patients (26 of 81; 32%) compared with patients given placebo (6 of 39; 15%). The treatment group had less moderate visual loss (6% vs 26%) or severe visual loss (7% vs 8%) compared with placebo. The final BCVA of 20/40 or better was 26% in the treatment group and 15% in the placebo group.³

In the second year of follow-up, some beneficial outcomes of using verteporfin therapy continued (**Table 2**). However, the primary outcome of a loss of less than 8 letters from the baseline could not be maintained (64% vs 49%). This might be due to a true loss of efficacy of the treatment with time, an adverse effect on the retina secondary to additional treatments, or to an improvement of vision in the control group as part of a healing process. Having said that, PDT treatment is still currently advisable for subfoveal CNV in PM, considering the fact that more eyes in the verteporfin-treated group had improvement of at least 5 letters (1 line) or 15 letters (3 lines) of visual acuity. Furthermore, the median change in visual acuity from baseline favored the verteporfin-treated group with a gain of 0.2 lines in the verteporfin-treated group compared with a loss of 1.8 lines in placebo group.

In FFA, progression of CNV and leakage from CNV were observed in similar proportions in patients with or without verteporfin treatment — 35% and 44%, respectively, in the verteporfin-treated group at the 2-year follow-up.³⁸ However, verteporfin-treated patients were more likely to have smaller

lesions (no more than 1 disc area in size) compared with placebo-treated patients (55% vs 36%) at the end of the second year.³⁸

The average number of applications of verteporfin treatment was 3.4 in the first year with an additional 1.7 treatments in the second year. Angiographic outcomes indicated that the verteporfin-treated patients had more classic CNV than the placebo group. This may explain the relatively higher number of treatments in the verteporfin-treated group; 5.1 treatments in the 2 years of follow-up compared with 4.6 treatments in the placebo group. There was very little further reduction in visual acuity after the first 6 months of follow-up.³⁸

Asian patients with subfoveal choroidal neovascularization secondary to pathologic myopia

In the VIP study, 91% of the patients were Caucasian and only 4% were Asian.³ In a prospective study of myopic CNV, with a majority of Chinese patients, the VIP verteporfin infusion protocol and standard laser energy level achieved similar visual outcomes of stable vision at the 1- and 2-year follow-up visits (**Table 2**).³⁹ The number of retreatments were 1.7 and 2.3 in the first and second years, respectively; significantly less than those required for the Caucasians in the VIP study.³⁸ Possible explanations for this difference include selection bias or the presence of a different healing process of the retinal pigment epithelium in different races, and warrant further investigation. Studies have also shown that patients younger than 55 years respond better to PDT than the older age group.^{39,40} An example of treatment and retreatment of CNV in PM is illustrated in **Figure 2**.

Photodynamic therapy for expanded indications

PDT with verteporfin is well tolerated by most patients. The procedure is relatively non-invasive and the treatment

Table 2. Photodynamic therapy and myopic choroidal neovascularization — 2-year follow-up.

Treatment	Verteporfin in Photodynamic Therapy Study (26 centers) ²⁸		Lam et al (Hong Kong) ³⁹
	Verteporfin	Placebo	Verteporfin
Ethnic group	Majority Caucasian	Majority Caucasian	Chinese
Number of eyes	81	39	22
Follow-up	Prospective, 2 years	Prospective, 2 years	Prospective, 2 years
Median age (years)	51	46	47
Median baseline visual acuity (log MAR)	20/64+1 (0.52)	20/64-2	20/100 (0.70)
Median visual acuity at 2 years (log MAR)	20/64+2 (0.50) Gain 0.2 line	20/100+1 Drop 1.6 lines	20/60 (0.47) Gain 2.3 lines
Mean log MAR best corrected visual acuity	-	-	0.59 to 0.56 Gain 0.3 lines
Improved by ≥3 lines	12%	0%	27.3%
Improved by ≥1 lines	39%	13%	36.4%
Stable or improved vision	15%	31%	27.3%
Decreased by ≥1 lines	46%	57%	36.4%
Decreased by ≥3 lines	21%	29%	0%
Best corrected visual acuity 20/40 or better	30%	18%	36%
Number of treatments	5.1	4.6	2.3

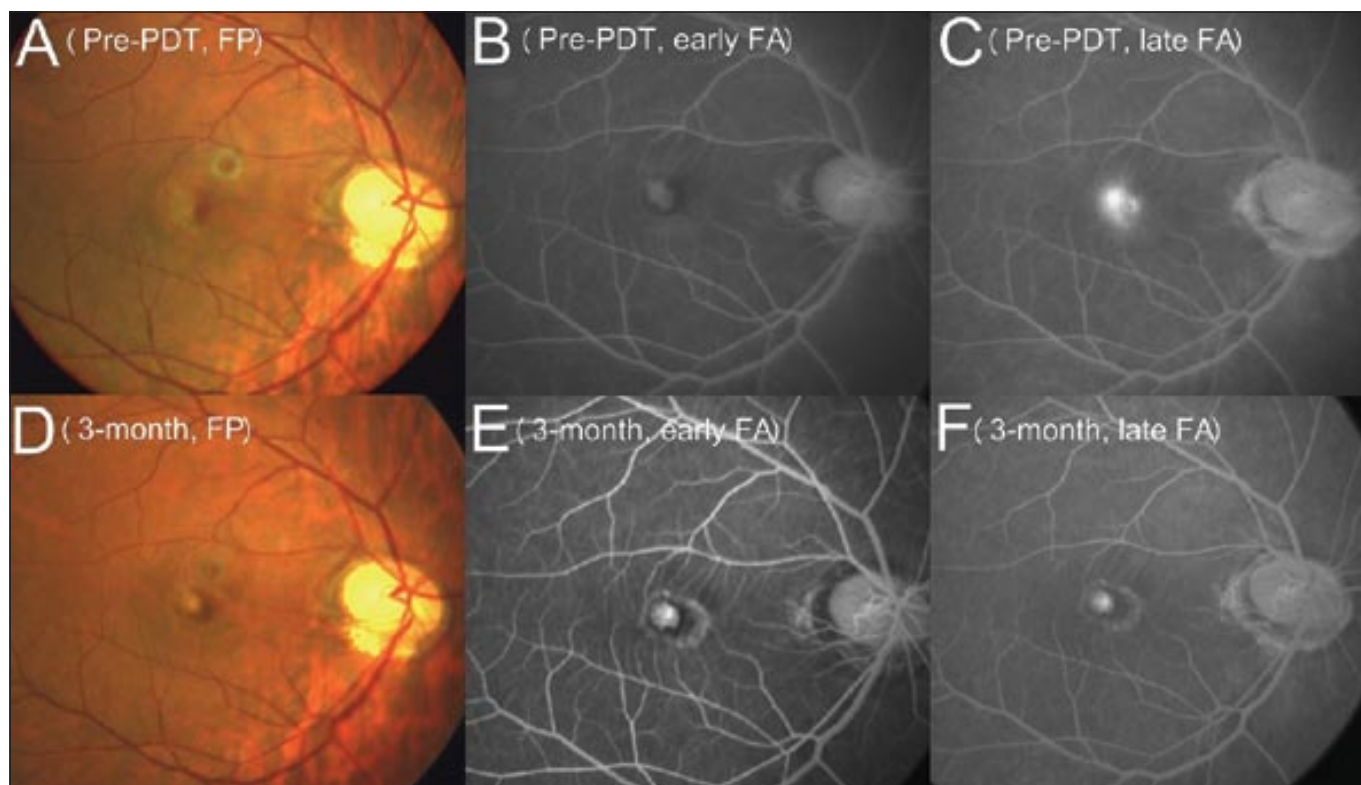


Figure 2. Right eye of a 44-year-old Chinese man with myopia of -11.00 D. (a) Fundus photograph revealed a small subfoveal lesion with subretinal hemorrhage; (b) early-phase fundus fluorescein angiography showing a tiny well-defined choroidal neovascularization; (c) late-phase fundus fluorescein angiography demonstrating profuse angiographic leakages from the choroidal neovascularization; (d) fundus fluorescein angiography photograph 3 months after photodynamic therapy revealing a small contracting lesion with a rim of hyperplastic retinal pigment epithelium; (e) early-phase fundus fluorescein angiography showing a circumscribed lesion with hyperfluorescence; and (f) late-phase fundus fluorescein angiography showing the same level and dimension of hyperfluorescence compatible with scar staining. The angiographic morphology remained the same in subsequent follow-ups with a stable best corrected visual acuity of 20/70 at 2-year follow-up. (Reprinted from Lam et al with permission from *Br J Ophthalmol*.³⁹)

Table 3. Indications for photodynamic therapy other than age-related macular degeneration or pathologic myopia.

Choroidal neovascularization other than age-related macular degeneration or pathologic myopia	Idiopathic choroidal neovascularization (Figure 3) ⁴¹⁻⁴⁴ Choroidal neovascularization arising from central serous chorioretinopathy ^{45,46} Choroidal neovascularization secondary to ocular histoplasmosis syndrome ^{47,48} Choroidal neovascularization and choroiditis ^{41,49-52} Choroidal neovascularization from angioid streaks ^{53,54} Retinal dystrophy and choroidal neovascularization ⁵⁵⁻⁵⁸ Iatrogenic choroidal neovascularization or post-laser choroidal neovascularization ⁵⁹⁻⁶¹ Recurrence and persistent choroidal neovascularization after macular translocation ^{62,63} Choroidal neovascularization secondary to osteoma, or other tumor ⁶³⁻⁶⁵
Choroidal neovascularization of different age groups	Choroidal neovascularization in pediatric groups ^{49,66}
Choroidal neovascularization other than subfoveal locations	Juxtafoveal choroidal neovascularization of pathologic myopia ⁶⁷ Juxtafoveal, extrafoveal, or peripapillary choroidal neovascularization ⁶⁸
Other choroidal or retinal vascular diseases	Polypoidal choroidal vasculopathy (Figure 4) ⁶⁹⁻⁷¹ Central serous chorioretinopathy (Figure 5) ⁷²⁻⁷⁵ Choroidal hemangioma ⁷⁶⁻⁷⁹ Retinal capillary angioma ^{80,81} Choroidal melanoma ^{82,83} Vasoproliferative tumor ⁸⁴

results are more reproducible even in different settings in comparison with surgical interventions. Selectivity, safety, and the encouraging findings from the TAP and VIP studies regarding PDT with verteporfin support the rationale to extend the treatment indication to subfoveal CNV secondary to other diseases.⁴¹ PDT has recently been applied for the treatment of diseases other than CNV secondary to AMD

and PM. These applications are summarized in **Table 3** and examples are shown in **Figures 3, 4, and 5**.⁴¹⁻⁸⁴

Safety and tolerability

PDT with verteporfin has been shown to be safe for patients of different races and with CNV secondary to different

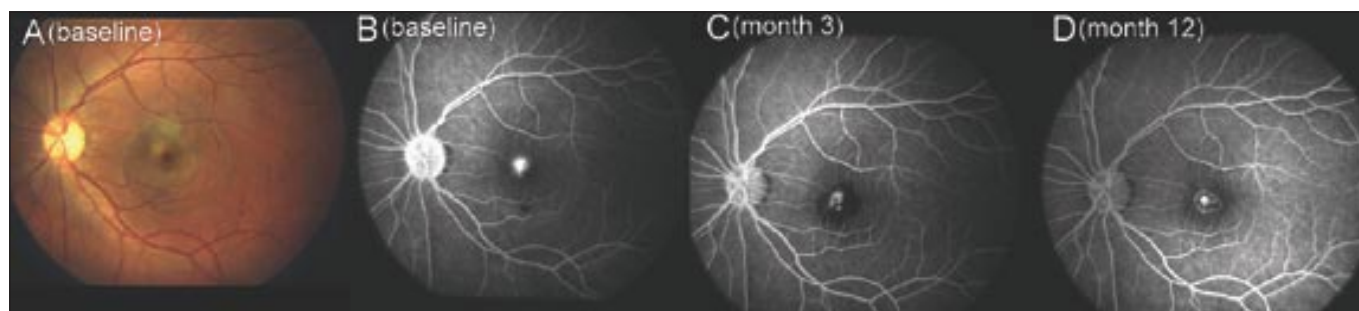


Figure 3. A 33-year-old Chinese woman with idiopathic choroidal neovascularization in the left eye and a visual acuity of 20/50. (a) Fundus photograph showing a subfoveal idiopathic choroidal neovascularization with subretinal fluid and hemorrhage; (b) early-phase fundus fluorescein on presentation showing an active vascular choroidal neovascularization with early profuse fluorescein leakage; (c) 3 months after initial photodynamic therapy showing persistent activity with slow oozing from the choroidal neovascularization together with bleeding and the patient required second photodynamic therapy; (d) late-phase fundus fluorescein at 12 months, showing a smaller eccentric fibrotic scar after contraction of the original subfoveal choroidal neovascularization. A ring of hyperfluorescence caused by the retinal pigment epithelium window defect due to the original extension of the choroidal neovascularization could be seen. The vision at 1 year was 20/20. (Reprinted from Chan et al with permission from *Ophthalmology*.⁴²)

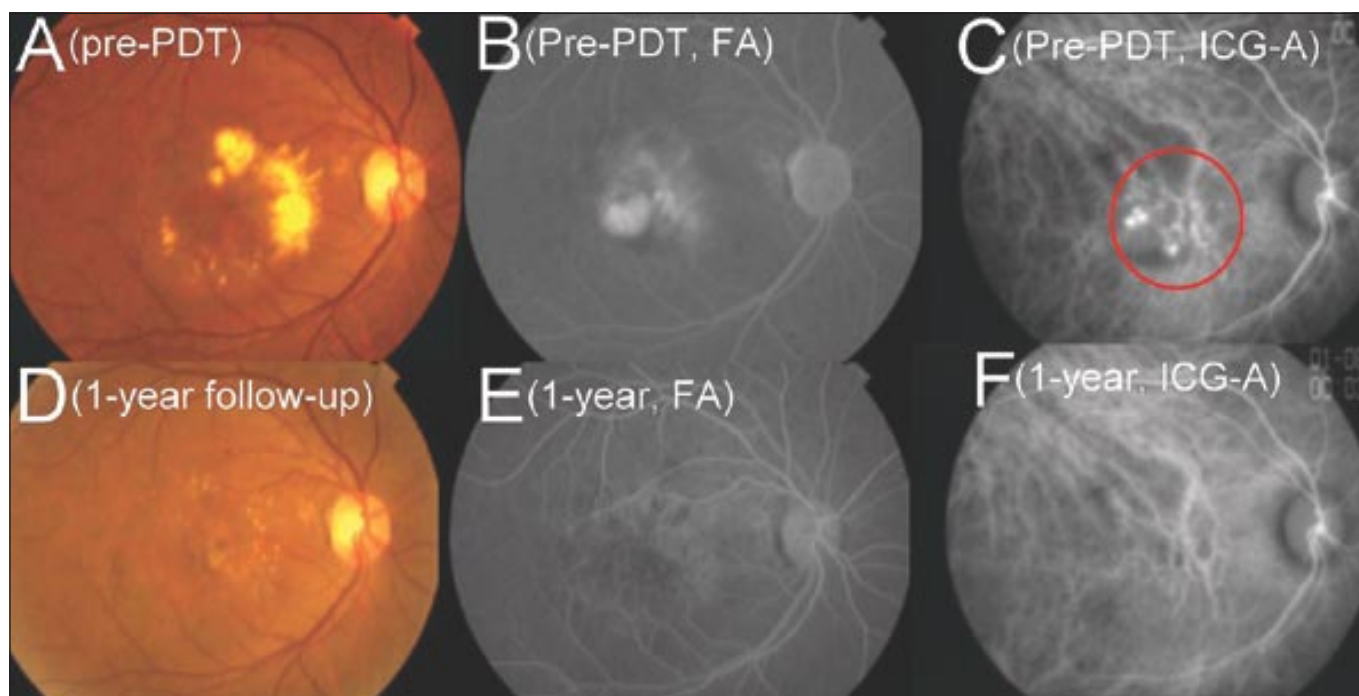


Figure 4. A patient with exudative maculopathy in the right eye secondary to polypoidal choroidal vasculopathy. (a) Fundus photograph showing dense circinate subretinal exudates around the macula; (b) mid-phase fundus fluorescein angiography demonstrating a pocket of pigment epithelium detachment with uniform hyperfluorescence and retinal pigment epithelium window defect with mild leakage; (c) mid-phase indocyanine green angiography showing multiple polypoidal vascular lesions and interconnecting vessels arising from the dilated anterior choroidal vessels — the red circle represents the size and location of the laser delivery at choroidal vascular abnormalities; (d) fundus photograph at 12 months revealing an almost complete absorption of the hard exudates; (e) mid-phase fundus fluorescein angiography at 1 year follow up showing only a retinal pigment epithelium window defect without angiographic leakage; (f) mid-phase indocyanine green angiography at 1 year follow up showing complete regression of the polyps, interconnecting vessels, and narrowing of the originally dilated choroidal vessels as shown by the arrows. (Reprinted from Chan et al with permission from *Ophthalmology*.⁶⁹)

diseases. No life-threatening side effects or treatment-related deaths have been reported in the various large randomized studies.^{2,3,23,24,38} Most of the adverse events were generally mild and usually occurred early in the first year of follow-up (Table 4).^{2,23}

Approximately 1.7% of patients with AMD in the first year of TAP study,² 1.3% of patients with PM in VIP study³ and 4.8% of patients with AMD in the 2-year VIP study²⁴ were withdrawn from the studies due to

PDT-related adverse events. The treatment-related complications or side effects of PDT can be categorized into systemic-, ocular-, and infusion site-related; these are summarized in Table 5.

One of the most serious and unpredictable adverse events is severe visual loss shortly after treatment. This occurs more commonly in occult CNV secondary to AMD. In the VIP-AMD 2-year study, 4.4 % (10 of 225 patients) experienced an acute loss of vision by ≥ 20 letters (4 lines) of visual

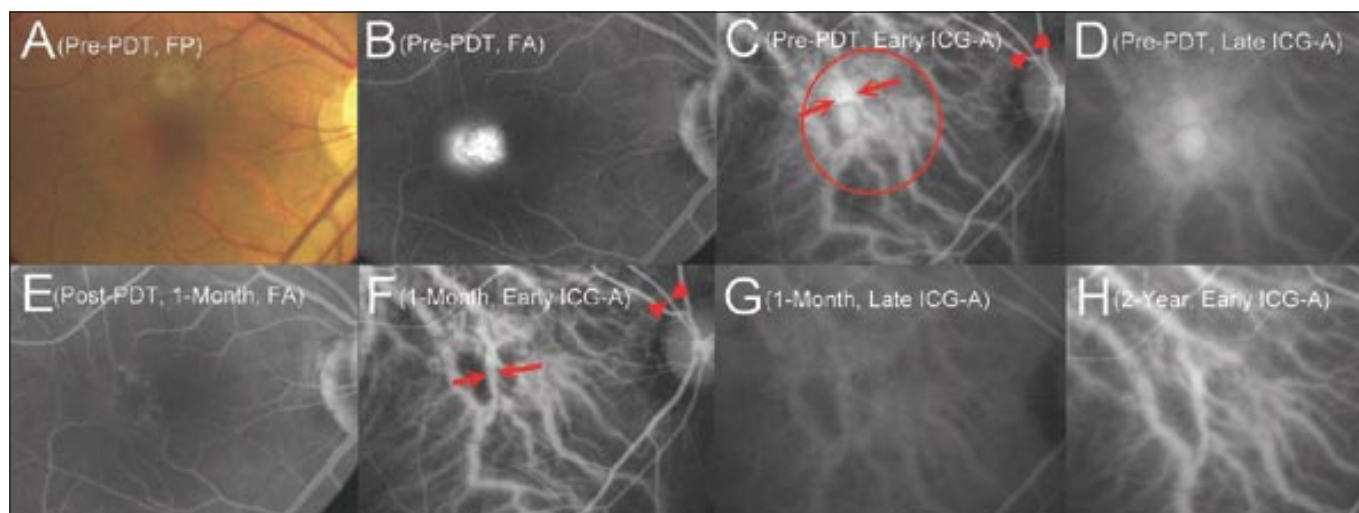


Figure 5. Right eye of a 48-year-old Chinese woman, with central serous chorioretinopathy manifesting as persistent combined focal retinal pigment epithelium leakage and serous pigment epithelium detachment. (a) Fundus fluorescein angiography showing serous pigment epithelium detachment of 800 μm in diameter and a pocket of subretinal fluid with precipitates; (b) late-phase fundus fluorescein angiography demonstrating a uniformly filled pocket of hyperfluorescence within the serous pigment epithelium and a focal retinal pigment epithelium leakage adjacent to it; (c) early phase of the indocyanine green angiography showing dilated choriocapillaries in the macular area — the closed arrow marks the diameter of the reference retinal arteriole and the open arrow marks the 2 sides of the most dilated choroidal vessels at the fovea, the red circle represents the size and location of the laser spot delivery during photodynamic therapy; (d) late phase of the indocyanine green angiography revealing a loculated hyperfluorescence caused by the pigment epithelium detachment and a diffuse hyperfluorescence in the macula secondary to extravascular leakage from the congested choroidal vessels; (e) late-phase fundus fluorescein angiography 1 month after photodynamic therapy showing complete resolution of the subretinal fluid and the serous pigment epithelium detachment; (f) the calibers of the originally dilated choroidal vessels appeared narrower in size as shown by the open arrows in the early phase of the indocyanine green angiography at 1 month follow-up; (g) no extravascular leakage in the late phase of the indocyanine green angiography; (h) the choroidal vasculature remodeling persisted as shown in the early phase of the indocyanine green angiography at the 2-year follow-up. (Reprinted from Chan et al with permission from *Br J Ophthalmol*.⁷²)

Table 4. Adverse events after photodynamic therapy with verteporfin (data extracted from the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study and other reports).

Adverse events	Percent of patients
Systemic	
Photosensitivity and sunburn	3.0
Infusion-related back pain	2.2
Allergic reactions	1.2
Cardiac arrest	Extremely rare
Infusion site-related	
Injection site reaction (edema, extravasation, hematoma, fibrosis, hypersensitivity, inflammation, and pain)	13.4
Ocular	
Increasing macular hemorrhage	29.0
Transient blurring of vision	22.1
Vitreous hemorrhage	1.0
Retinal capillary non-perfusion	0.2
Acute severe visual loss	0.7*
Retinal pigment epithelium rip	Rare
Photodynamic therapy-induced secondary choroidal neovascularization	Rare
Lacquer crack	Rare

* 4.4% in the occult choroidal neovascularization of age-related macular degeneration in the Verteporfin in Photodynamic Therapy Study.

acuity within 7 days of treatment.²⁴ Most of these events happened after the first treatment, and only half of the patients regained part of the lost vision. In most of the patients no obvious causes or changes were noticed in FFA, although some patients later developed extensive subretinal fluid, choroidal hypofluorescence, and macular hemorrhage. The acute

severe visual loss accounted for the majority of patient withdrawals (9 of 10) in this group of patients.²⁴ In TAP-AMD study, the incidence of acute visual loss was only 0.7% (3 of 402 treated patients)³ and the same problem was not reported in the VIP-PM study.^{3,38} An increase in subretinal or intra-retinal hemorrhage at the month 3 examination was more

Table 5. Factors to be considered when offering photodynamic therapy.

1.	What is the primary disease or specific cause of the choroidal neovascularization? A: Accurate diagnosis is important in the treatment of photodynamic therapy. Choroidal neovascularization secondary to different underlying diseases may have different outcomes with and without treatments. Indocyanine green angiography may also be required in certain conditions, especially to distinguish occult age-related macular degeneration from central serous chorioretinopathy and polypoidal choroidal vasculopathy.
2.	Is it an active choroidal neovascularization that requires treatment? A: Early decision is required for treating aggressive lesions, whereas a conservative approach may be adopted for indolent or inactive lesions.
3.	Where is the location and is photodynamic therapy the best to be considered? A: Subfoveal, juxtafoveal, extrafoveal, peripapillary, or maculopapillary location of the choroidal neovascularization affect the decision in considering the best possible treatment.
4.	What is the size of the lesion and what is the size of the choroidal neovascularization? A: Smaller lesions generally have better outcomes and lesion size of larger than 5 600 μm may not be covered by the laser spot of photodynamic therapy. Any blood clot, especially a thick one, occupying >50% of the lesion may not be suitable for photodynamic therapy.
5.	What is the angiographic composition — classic or occult? A: Percentage of classic or occult generally applied specially to choroidal neovascularization of age-related macular degeneration and it affects the outcomes of photodynamic therapy.
6.	What is the baseline visual acuity? A: Any visual acuity of less than 20/200 at presentation may not be cost-effective with treatment by photodynamic therapy especially if the fellow eye has good vision.
7.	Any poor prognostic signs for the photodynamic therapy? A: Retinal pigment epithelium tear, chorioretinal anastomosis, chronic cystoid changes at neurosensory retina, retinal pigment epithelium depigmentation, and thick blood clot are the signs suggestive of guarded outcomes with photodynamic therapy.
8.	What is the condition of the fellow eye? A: The visual acuity and the healthiness of the fellow eye are important determinants in considering photodynamic therapy.
9.	Any absolute or relative contraindications for photodynamic therapy? A: Porphyria, severe hepatic disease, pregnancy, and previous side effects from photodynamic therapy.
10.	Any safer or better alternative? A: The different modalities of treatment for macular choroidal neovascularization change with time. Observation or other treatment options, both surgical or medical, should be explored and discussed with the patients.

likely in the eyes receiving placebo (45%) compared with the eyes treated with verteporfin (29%).

Photosensitivity reactions presented as mild to moderate sunburn caused by direct sunlight exposure within the first 24 hours of drug administration.¹⁴ Maximum skin photosensitivity occurred 1.5 hours after administration of intravenous (IV) verteporfin and the duration of photosensitivity was dose-dependent (2.0 to 6.7 days with verteporfin 6 to 20 mg/m^2). Mean duration of photosensitivity with IV verteporfin 6 mg/m^2 was 2 days.⁸⁵ A sun or strong light protection period of 24 to 48 hours was adequate to avoid adverse photosensitivity events, although some regulatory authorities have recommended a longer protection period of 5 days.³⁸ A strong light aversion period of 24 hours was recommended in the VIP-AMD study. The reported photosensitivity complication was only 1% compared with 3% in the TAP-AMD study with 48 hours protection.^{2,3}

Some of the reported complications are avoidable, particularly inadvertent infusion site extravasation. The incidence of this adverse event decreased dramatically with experience and awareness.

Infusion-related pain was transient and resolved after verteporfin infusion. The mechanism for the back pain is still not known but has been suggested to be an idiosyncratic syndrome caused by the liposomal formulation.⁸⁶ The speculation that infusion-related back pain may be renal in origin has not been substantiated by the growing clinical evidence.

In a case series, 24 of 250 patients (9.6%) developed verteporfin infusion-associated pain. The pain does not seem to be prevented by plentiful oral hydration. There are no predictive factors at baseline other than a history of back pain during a previous infusion. Back pain was the commonest (21 of 24 patients) infusion-related discomfort, while other painful complaints related to the leg, groin, chest, and shoulder are also occasionally possible.⁸⁶ In another study, patients with verteporfin-associated infusion pain had a large but transient reduction in their circulating neutrophils or neutrophil margination temporally related to the development of pain.⁸⁷ Slower infusion may be considered for such patients.

Serious complications reported after the marketing of PDT include cardiopulmonary arrest, non-cardiac chest pain, syncope, and tears of the retinal pigment epithelium 4 to 6 weeks after verteporfin therapy.⁸⁸⁻⁹¹

Conclusions

PDT with verteporfin has been shown to reduce the risk of moderate and severe vision loss in selected patients with subfoveal CNV due to AMD and increase the chance of stabilized or improved visual acuity in patients with subfoveal CNV due to PM. Over time, the efficacy and safety of verteporfin have also been demonstrated in other diseases with a continued expansion of the clinical indications where verteporfin is being used. Studies have shown that accurate angiographic assessment of lesion composition is essential before treatment. Other important factors for assessment

include baseline visual acuity, size of the lesion, location of the lesion, and angiographic interpretation for retreatment (Table 5). Precise diagnosis of the underlying diseases, correct stratification of subgroups, identification of disease activities, and avoidance of treatment in poor prognostic groups are useful tips for achieving better results with PDT. Other treatment modalities for CNV, including systemic,

periocular, or intraocular corticosteroids, submacular surgery, macular translocation surgery, transpupillary thermotherapy, and the use of various angiogenesis inhibitors, are always open options for patients. The ultimate choice of the modality used should be based on the nature of the disease to be treated and extensive discussions between the physician and the patient.

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