Preserving vision with verteporfin photodynamic therapy

Yit Chiun Yang

Wet age-related macular degeneration (AMD) is the leading cause of blindness in the elderly population. Verteporfin photodynamic therapy (PDT) is significantly effective in preventing visual loss in patients with subfoveal choroidal neovascularization caused by exudative AMD. This article reviews verteporfin PDT and discusses treatment and evolving appraisal guidance.

Age-related macular degeneration (AMD) affects the elderly population and is the leading cause of blindness in the western world (Bressler and Gills, 2000). It is generally classified into two forms: non-neovascular (also called dry) AMD or neovascular (also called exudative or wet) AMD. Although only 20% of all cases are affected by the neovascular form, it accounts for more than half of all cases of blind and partial sight registrations as the risk of severe and rapid visual loss with this form is much higher than in the dry form (Bressler et al, 1988; Evans and Wormald, 1996; Owen et al, 2003).

Neovascular AMD is characterized by the growth of abnormal, fragile, new blood vessels, known as choroidal neovascularization (CNV), which develop most commonly in the central part of the macular area and the fovea. The fovea and macular area are responsible for central visual function essential for fine and detailed visual tasks such as reading, close work, watching television and recognizing faces. These abnormal blood vessels leak fluid, lipid and blood, which cause progressive fibrosis of the central macula resulting in progressive central visual loss (Bressler et al, 1982). Most cases of CNV are caused by AMD, but less commonly, especially in younger patients, CNV can occur in pathological myopia, angioid streaks, presumed ocular histoplasmosis syndrome and punctate inner choroidopathy.

Histologically, CNV growth can be limited to the choroidal layer beneath the retinal pigment epithelium or it can penetrate the retinal pigment epithelium into the subretinal space just beneath the neurosensory retina. These two main subtypes of CNV growth, distinguishable by their contrasting appearances on fluorescein angiography, are termed as 'classic' or 'occult' CNV. Classic CNV corresponds to the subtype of CNV that has penetrated the retinal pigment epithelium layer into the subretinal space and which is associated with a more aggressive course and more rapid visual decline. Therefore, it is important in clinical practice to assess patients with fluorescein angiography to determine whether their neovascular AMD lesion consists of the classic, occult or mixed type of CNV (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) Study Groups, 2003a).

Although it is sometimes difficult to determine the dimensions of a poorly-defined lesion to calculate the treatment spot size, experienced retinal specialists can interpret fluorescein angiograms of patients with neovascular AMD reproducibly to determine suitability for initiation of verteporfin therapy.

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is defined as the use of a photosensitizing agent in combination with light energy to achieve a therapeutic effect (Dougherty et al, 1998). This modality has been used in the treatment of certain solid tumours, for example basal cell carcinoma, skin melanoma and bladder neoplasia, with photosensitizers which have an affinity for tumour cells or tumour neovascular tissue enabling the photodynamic effect to be selectively maximized in the abnormal tissues. The same basic principle applies in the treatment of CNV in neovascular AMD.

The photosensitizer verteporfin (Visudyne, Novartis Ophthalmics AG, Basel, Switzerland),

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or benzoporphyrin derivative monoacid A, administered in a liposomal formulation, is a lipophilic agent taken up by neovascular endothelium rich in low-density lipoprotein (LDL) receptors via a process of receptor-mediated endocytosis (Gaffney et al, 1985; Allison et al, 1994; Schmidt-Erfurth et al, 1995). Subsequent application of the non-thermal laser light of 689 nm to the target tissue results in transformation of the photosensitive verteporfin molecules, generating cytotoxic free radicals and reactive singlet oxygen (Schmidt-Erfurth and Hasan, 2000).

Cell death occurs in the endothelium from damage to cell membranes and intracellular components, resulting in platelet aggregation and thrombus formation within the choroidal neovascular tissue, with minimal damage to the non-neovascular channels and neurosensory retina (Schmidt-Erfurth et al, 1994a,b).

CLINICAL TRIALS IN PHOTODYNAMIC THERAPY

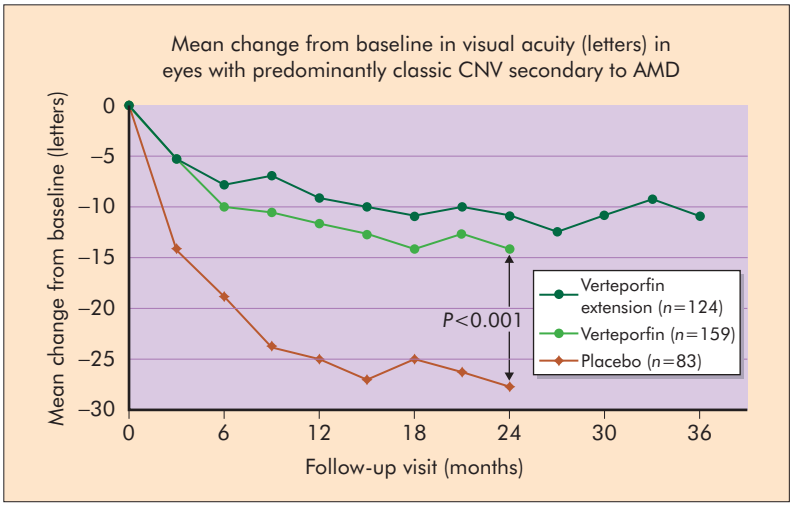
Several large-scale, multicentre clinical trials have been performed to investigate the efficacy of PDT in AMD and other causes of CNV (TAP Study Group, 1999, 2001; VIP Study Group, 2001; Saperstein et al, 2002; TAP and VIP Study Groups, 2003b). In particular two major trials, namely the TAP investigation and the VIP study, have led to the regulatory approval of verteporfin PDT for use in patients with predominantly classic lesions and in patients with occult lesions.

TABLE 1.
Effectiveness of verteporfin PDT in the TAP study

Lesion characteristics		Verteporfin % maintaining vision*	Placebo % maintaining vision*	*P* value
Any classic 12 months		61%	46%	<0.001
Predominantly classic	12 months	67%	39%	<0.001
	24 months	59%	31%	<0.001
Classic no occult 12 months		77%	31%	<0.001

*<15 letters lost is the TAP endpoint, equivalent to maintenance of vision; PDT = photodynamic therapy; TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy

Figure 1. Verteporfin vs placebo: preservation of visual acuity over 2 and 3 years. From separate study. No placebo comparison was made in the extension study. AMD = age-related macular degeneration; CNV = choroidal neovascularization. Adapted from Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group (2001, 2002).



The TAP study

The TAP investigation, comprising two randomized, double-masked, placebo-controlled clinical trials, was designed to determine whether PDT with verteporfin could reduce the risk of vision loss in patients who have subfoveal CNV in AMD (TAP Study Group, 1999, 2001). In total, 609 patients with classic-containing subfoveal CNV lesions caused by wet AMD were enrolled, with 402 patients given verteporfin PDT and 207 given placebo.

Visual acuity, obtained with a standard logMar visual acuity chart, was used as the primary outcome measure. The primary end point selected for efficacy analysis was a loss of three lines or more of visual acuity (non-responder) at 12 and 24 months. Primary efficacy was expressed in terms of proportions of patients responding (avoiding loss of three lines) in the verteporfin PDT group *vs* placebo. Contrast sensitivity, lesion size and effect on leakage were measured as secondary outcomes.

At the 24-month follow-up examination in AMD patients with predominantly classic CNV, 59% of verteporfin-treated patients had lost less than 3 lines of visual acuity compared with 31% of placebo patients ($P<0.001$) (TAP Study Group, 2001) (*Table 1*). Also, fewer verteporfin-treated patients had severe vision loss, defined as visual acuity losses of six lines or more (15% *vs* 36%). Improvements of three lines or more were observed in 9% of verteporfin-treated patients and 4% of patients given placebo. Treatment benefits were evident as early as 3 months after initial treatment and were sustained through the 1- and 2-year follow-up periods (*Figure 1*).

These results demonstrate that PDT with verteporfin reduces the risk of moderate and severe vision loss in selected patients with subfoveal CNV resulting from AMD.

In addition, treatment with verteporfin PDT reduced the risk of patients losing contrast sensitivity, with the greatest effect in patients with predominantly classic subfoveal CNV secondary to AMD (*Figure 2*) (Rubin and Bressler, 2002). As many everyday tasks involve the

recognition of lower contrast objects such as recognizing faces and watching television, contrast sensitivity is a very important aspect of overall visual function (Owsley and Sloane, 1987; Rubin et al, 1994). Treated patients are therefore more likely to have better contrast sensitivity and be able to perform a wider range of visual tasks. Verteporfin therapy also reduced leakage from classic CNV and restricted lesion growth.

Long-term stabilization

The long-term stability of verteporfin therapy has been supported by results from an open label extension of the TAP study into the third and fourth year (TAP Study Group, 2002). Patients originally assigned to verteporfin treatment continued to maintain stable visual acuity levels into the fourth year of follow up. The mean number of retreatments needed was 1.3 in the third year and 0.4 in the fourth. Despite this evidence that treatment benefits are sustained long-term, caution appears warranted in the absence of comparison with an untreated group during the extension and since not all patients in the TAP investigation participated in the extension study.

Since the launch of verteporfin therapy in clinical practice, early results obtained from treatment of patients outside clinical trial conditions have been very encouraging. Audit data from a national surveillance programme of NHS practice – covering those patients reaching 12 months' follow-up – show that responder rates to verteporfin therapy were similar to, or better than, those seen in the TAP investigation (Talks et al, 2003).

Effectiveness analysis for PDT with verteporfin compares favourably with trials of other interventions (Sharma, 2001) (*Table 2*). Sharma noted in the 2001 paper that in terms of numbers needed to treat, a metric that compares treatment success to the natural history, PDT for the treatment of subfoveal CNV is one of the most effective treatments in medicine.

The results of an effectiveness analysis applied to the TAP data, calculating the number of patients needed to treat for a single patient to benefit, show that for patients with predominantly classic CNV, it is necessary to treat 3.6 patients for one to benefit (Harding, 2001). For patients diagnosed with predominantly classic CNV with no occult, the number needed to treat approaches two.

SAFETY

Verteporfin PDT is well tolerated. In the TAP investigation, where withdrawals as a result of adverse events were very low, the most commonly encountered adverse events (from baseline to month 24) included visual disturbance (22.1% *vs* 15.5% for placebo), injection site reactions (15.9% *vs* 5.8%), photosensitivity reactions (3.5%) and infusion-related back pain (2.5%).

In all studies, most adverse events were mild to moderate and transient in nature. There was no evidence of increased or cumulative toxicity with each subsequent treatment course of verteporfin therapy. Serious adverse events associated with treatment occurred in 3.8% of verteporfin-treated patients and 1.4% of placebo patients.

DISCUSSION

Verteporfin PDT has been evaluated by well-designed clinical trials and has been proven to

Figure 2. Contrast sensitivity changes in predominantly classic choroidal neovascularization from TAP Investigation. TAP = Treatment of Age-Related Macular Degeneration with Photodynamic Therapy. From Rubin and Bressler (2002).

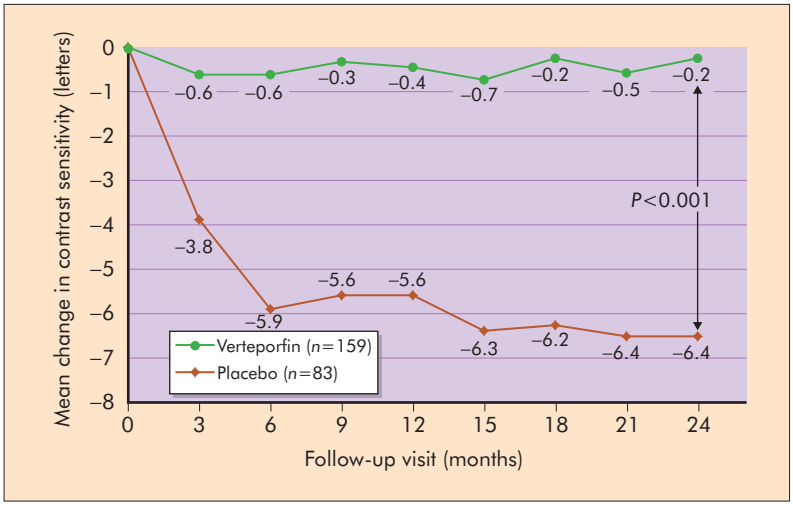


TABLE 2.
Comparison of effectiveness analysis in ophthalmic and non-ophthalmic trials*

PDT Effectiveness Analysis (24 months)	
Lesion composition	NNT
Any classic	6.7
Predominantly classic	4
Classic with no occult	2
NNT analysis in other ophthalmic and non-ophthalmic clinical trials	
Patient group	NNT
Early Treatment Diabetic Retinopathy Study (1987)	5
Diabetes Control and Complications Trial (1995)	15
Treatment of diastolic blood pressure of 90–109 mmHg (Medical Research Council Working Party, 1985)	128

*Sharma (2001). NNT = number needed to treat; PDT = photodynamic therapy

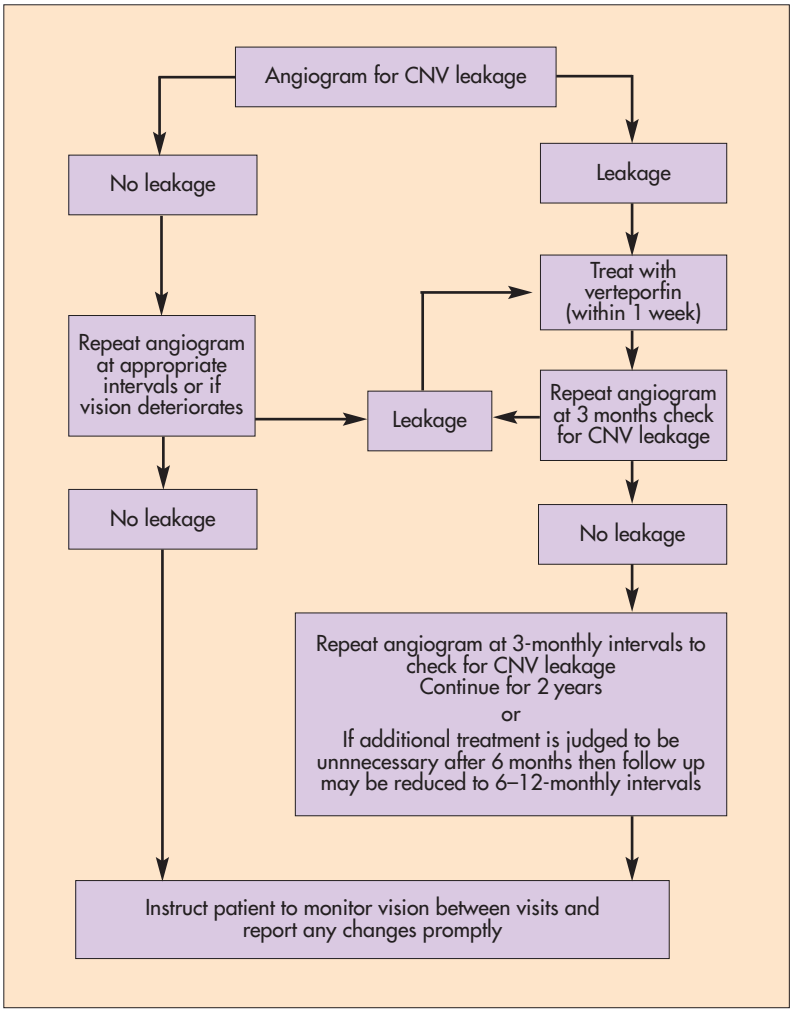
be efficacious for a sizeable proportion of patients with subfoveal CNV secondary to wet AMD who are at risk of developing severe visual loss from their disease. The magnitude of the treatment benefit means that patients with treatable forms of the disease can now hope for as much as a 70% chance of avoiding significant visual loss.

Managing patient expectations therefore demands time and care so that they are well informed about the disease, the treatment benefits and aims of verteporfin therapy and the visual prognosis. At the outset, physicians need to caution patients that treatment is not designed to restore vision. Most will likely continue to experience some difficulty in reading small print for example.

Final guidance issued by the National Institute for Clinical Excellence (NICE) (2003) recommends that all patients with classic or occult subfoveal CNV and best-corrected visual acuity of 6/60 or better should receive verteporfin therapy. Those patients with predominantly classic lesions containing some occult component will receive verteporfin therapy as part of a Department of Health-funded nationwide clinical study (the VPDT Cohort Study). Plans are therefore underway to enable eye units to provide verteporfin therapy in line with the clinical recommendations from NICE.

It should be noted that no recommendation has been made by NICE for patients with occult subfoveal CNV as verteporfin was not licensed for this indication when the NICE appraisal process began. Since the licence for the selected occult indication was obtained in the European Union countries, including the UK, encouraging results have been obtained with verteporfin therapy in this important subgroup of patients. Patients with occult subfoveal CNV should be treated on the basis of clinical need and judgment.

Figure 3. Treatment pathway: verteporfin treatment and follow-up procedure. CNV = choroidal neovascularization. Adapted from Verteporfin Roundtable 2000 and 2001 Participants et al (2002).



CONCLUSION

The wet form of advanced AMD is an acute and often progressive disease. There is good evidence from randomized controlled trials and clinical audit experience that verteporfin therapy improves the chance of avoiding appreciable loss of vision in neovascular AMD. Evidence of longer-term maintenance of vision through 3 and 4 years of treatment provides further encouragement for both patients and physicians that verteporfin PDT can preserve visual acuity and contrast sensitivity in the long term. Verteporfin therapy has been proven to have a very low risk of adverse effects and is well tolerated by patients.

Following recent NICE guidance recommending verteporfin therapy in selected patients with wet AMD, the challenge lies ahead for ophthalmologists and other eye care workers to ensure that suitable patients can be referred and treated promptly with verteporfin therapy so that maximum visual benefit can be obtained from this promising treatment modality (*Figure 3*). This is also an exciting opportunity for medical retina services to improve care for all patients with CNV, through development of robust pathways to provide improved referral, diagnostic and rehabilitation services which are vital for the success in management of patients with AMD. HM

Conflict of interest: The author was co-investigator in the TAP and VIP studies and is currently an investigator in several clinical studies evaluating current and investigational treatments in age-related macular degeneration and diabetic retinopathy.

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KEY POINTS

- Verteporfin therapy is significantly effective in preventing visual loss in patients with subfoveal choroidal neovascularization (CNV) caused by wet age-related macular degeneration (AMD), with treatment benefits sustained long-term.
- Treated patients are also more likely to have better contrast sensitivity and be able to perform a wider range of visual tasks.
- The National Institute for Clinical Excellence has recognized the clinical- and cost-effectiveness of verteporfin photodynamic therapy in patients having classic with no occult subfoveal CNV, and recommended treated for patients with predominantly classic with occult CNV as part of a nationwide clinical study.
- Wet AMD can progress rapidly: individuals with early wet AMD and without serious loss of vision will need to be fast-tracked through the referral and waiting list processes in order to receive treatment before further loss of vision occurs.