ARTICLE

Photodynamic therapy in the treatment of subfoveal choroidal neovascularisation

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Abstract

Subfoveal choroidal neovascularisation (CNV) is a major cause of visual disability, with age-related macular degeneration (AMD) the commonest cause. Confluent laser to CNV significantly reduces severe visual loss but the profound visual loss after treatment of subfoveal lesions and the high recurrence rate has meant its restriction to extrafoveal lesions. Developed initially as a treatment for cancers, photodynamic therapy (PDT) has been shown to successfully close CNV in the eye. Large international randomised placebo-controlled studies of the safety and efficacy of PDT with verteporfin are under way. The Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) study has demonstrated a reduction of visual loss in treated patients with any classic CNV. Subgroup analysis showed a greater benefit in predominantly classic lesions ($p < 0.001$, NNT: 3.6), increasing further for lesions with no occult component, roughly equivalent to pure classic ($p < 0.01$, NNT: 2.2) A significant benefit at 12 months has been shown in patients with CNV secondary to myopia in the Verteporfin in AMD (VIP) trial, but no benefit in pure occult lesions. Further research is required to establish cost-effectiveness and appropriate referral patterns in the UK and optimise treatment strategies. Further data are awaited from TAP/VIP. At present verteporfin PDT is indicated in eyes with subfoveal predominantly classic CNV secondary to AMD with visual acuity of 6/60 or better and lesions < 5400 μm in diameter. Juxtafoveal lesions meeting the above criteria and CNV secondary to pathological myopia should also be considered for treatment. The efficacy of treatment of larger lesions, juxtapapillary CNV, occult/no classic with high-risk characteristics (HRC) and CNV from other causes remains unclear. The treatment of minimally classic lesions and those with occult/no classic without HRC is not indicated.

The consequences of subfoveal choroidal neovascularisation (CNV) in the eye are a major cause of visual disability in the developed world today.[1–3] The combination of haemorrhage, subretinal fluid and eventual fibrosis extending into the retina causes profound visual loss over weeks or months. The vast majority of cases are caused by age-related macular degeneration (AMD), which sharply increases in prevalence with age, but other causes including pathological myopia, angioid streaks and punctate inner choroidopathy contribute a significant number of cases, especially in younger patients.

Attempts at treating CNV have proved disappointing to date. The Macular Photocoagulation Study (MPS) reported the results of confluent argon laser photocoagulation for subfoveal CNV in AMD between 1991 and 1994.[4–8] Although there was a statistically significant benefit for treated patients compared with the natural history of the disease, treatment was associated with a profound and immediate loss of vision, especially in eyes with a pre-treatment vision of better than 6/60.[7,8] Recurrence after confluent laser was frequently seen in the MPS and also in a study from the UK.[9] Although initially embraced by ophthalmologists worldwide, confluent laser has in recent years tended to be considered only in eyes with CNV lesions extending no closer than 200 μm from the centre of the fovea (extrafoveal).[6] As a result research effort has been directed towards new therapeutic options for subfoveal CNV which can offer the prospect of preservation or improvement of vision without initial loss of function.

Several therapies which show considerable promise are currently under investigation including photodynamic therapy, surgical foveal relocation and photon and proton radiotherapy. Transpupillary thermotherapy, indocyanine green (ICG)-guided laser to feeder vessels and laser to drusen are all at various stages of clinical study. Other potential therapeutic options are in the pre-clinical phase

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of development including sub- and epi-retinal implants, various forms of retinal pigment epithelial cell transplantation and neuroprotective agents.

In this article I will review the current position of one of these – photodynamic therapy – discuss the current evidence of its effectiveness and review the implications for future service delivery.

Development of photodynamic therapy

Photodynamic therapy (PDT) is a two-stage process involving the administration of a photosensitiser with subsequent activation within the target tissue or lesion by illumination with light of a wavelength specific to the photosensitiser but not strong enough to cause direct thermal damage. Subsequent action after excitation is based on the photosensitiser generating singlet oxygen and reactive intermediates which damage cellular proteins and nucleotides.[10,11] Porphyrin derivatives have shown greatest promise, including agents such as haematoporphyrin derivative and rose bengal. These agents have proved unsuitable for clinical application, however: the former produces prolonged skin photosensitivity while the latter, although effectively closing CNV, requires 27 times the clinically safe dose.[12]

Recent studies have investigated benzoporphyrin derivative monoacid A (BPD-MA, verteporfin), which is selectively taken up by rapidly proliferating cells such as tumour cells and tumour vascular endothelial cells.[13] When combined with liposomes or low density lipoproteins (LDL) uptake is enhanced in rapidly proliferating endothelial cells which express increased LDL receptors and transport.[14] After early work in the fields of cancer treatment and dermatology, *in vitro* and *in vivo* pre-clinical studies in the eye utilised experimental models of CNV,[15–18] corneal neovascularisation[19] and melanoma.[20,21]

Early non-controlled clinical studies demonstrated that PDT with verteporfin caused temporary abolition of leakage from subfoveal CNV for up to 4 weeks without closure of overlying retinal vessels.[22] Dose ranging studies of several regimens suggested that the optimum parameters were 6 mg/m^2 (approximately 0.15 mg/kg), infusion of verteporfin over 10 min with irradiation of 689 nm light 15 min after commencement of infusion at 600 mW/cm^2 irradiance and 50 J/cm^2 light dose (fluence).[22,23] Closure of retinal vessels occurred at fluence levels of 150 J/cm^2 or above. The effectiveness of multiple retreatments was studied in an open investigation of 31 patients.[23] Treatment was repeated in the presence of persistent leakage of fluorescein 2–4 weeks after previous treatment up to a maximum of four times. At follow-up 3 months after the final treatment visual acuity was maintained (± 2 logMAR lines) and the area of leaking classic CNV was reduced.

Other photosensitisers are currently undergoing early clinical or pre-clinical trials including SnET2, Miravent MV6401, NPe6 and ATX-S10(Na).[24–27]

Randomised controlled clinical trials of PDT with verteporfin

Two randomised clinical trials of PDT with verteporfin (Visudyne; Novartis Ophthalmics, Duluth, USA) are currently in progress: the Treatment of AMD with Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) trials. In 1999 the 1 year interim results from the TAP study were published.[28] In addition unpublished details are in the public domain giving headline results from the 2 year TAP and 1 year VIP results with further publications imminent.

TAP study

At enrolment into the TAP study, patients had subfoveal CNV lesions with a greatest linear dimension up to 5400 μm on stereoscopic fluorescein angiography with definite evidence of a classic component and a best corrected visual acuity (VA) of approximately 6/12–6/60 using a logMAR chart. Lesions could be new or recurrent after extrafoveal confluent laser and have other contiguous components such as blood, serous pigment epithelial detachment or pigment, but were required to comprise greater than 50% CNV. Patients were age 50 years or over.

Six hundred and nine patients were recruited at 22 centres in Europe and North America and randomised in a ratio of 2:1 between treatment and control. Treated patients received a 10 min intravenous infusion of verteporfin followed 5 min after the end of the infusion by an 83 s continuous application of low dose 689 nm diode laser at a fluence of 50 J/cm^2. The treated zone of retina comprised a circular spot with a diameter equal to the greatest linear dimension in micrometres of the entire CNV lesion including all components contiguous to the CNV measured from 35 mm transparencies with the addition of 1000 μm margin of error.

Control patients received an intravenous infusion of dextrose 5% followed by the standard laser application. VA was measured using a standardised refraction protocol and a logMAR chart at 2 m. Study personnel and patients were fully masked for the 2 year duration of the study. Photographs were graded at a central reading centre. Patients were followed at 3 month intervals and zones of persistent or new leakage on angiography were retreated using the same protocol. Follow-up was completed in 94% of patients at 12 months and 87% at 24 months.

The primary endpoint of stable or improved vision was defined as less than 15 letters lost on a logMAR chart, roughly equivalent to 2 Snellen lines. The frequency of stable or improved vision in each group was: 12 months – 61% treated, 46% placebo ($p < 0.001$); 24 months – 53% treated, 37% placebo ($p < 0.001$). At 12 months a visual improvement (≥ 15 logMAR letters) occurred in 16% of treated and 7% of placebo patients. Subgroup analysis relating visual outcome to baseline lesion component showed greater benefits for individuals with predominantly classic CNV (≥ 50%)

Table 1. *Effectiveness of verteporfin PDT therapy in the TAP study*

Lesion characteristics	Verteporfin < 15 letters lost[a]	Placebo < 15 letters lost[a]	p	NNT (95% CI)
Any classic				
12 months	246/402 (61%)	96/207 (46%)	<0.001	6.8 (4.3–15.3)
Predominantly classic				
12 months	107/159 (67%)	33/84 (39%)	<0.001	3.6 (2.5–6.6)
24 months	94/159 (59%)	26/83 (31%)	<0.001	3.6 (2.5–6.6)
No occult (pure classic)				
12 months	72/94 (77%)	15/49 (31%)	<0.001	2.2 (1.6–3.3)

[a]< 15 letters lost is the TAP endpoint, equivalent to maintenance of vision.
NNT, number needed to treat.

and those with no occult component. For predominantly classic lesions the frequency of maintenance or improvement of vision was: 12 months – 67% treated, 39% placebo ($p < 0.001$); 24 months – 59% treated, 31% placebo ($p < 0.001$). For lesions with no occult component frequencies at 12 months were: 73% treated, 23% placebo ($p < 0.01$). Results are summarised in Table 1 together with numbers needed to treat (NNT) and 95% confidence limits. Secondary endpoints of contrast sensitivity, percentage persistently leaking classic and greatest lesion diameter were significantly improved in the treatment group. Average number of treatments in the treated group was 3.4 in the first 12 months, 2.2 in the second and 5.6 overall.

There were a similar number of deaths and serious adverse events in each group. Less than 2% of patients were withdrawn due to adverse events, with the following being commoner in treated patients at 12 months: transient visual disturbance – 18% treated, 12% placebo; injection site events – 13% treated, 0 placebo; transient photosensitivity reactions – 3% treated, 0 placebo; low back pain – 2% treated, 0 placebo.

VIP study

At the time of writing only limited headline results are available from the VIP study with no peer review and so results need to be interpreted with caution. The VIP trial enrolled three classes of patient with subfoveal CNV: (1) small classic lesions with VA better than 6/12; (2) lesions with an occult component but no classic CNV with documented evidence of progression of lesion size or loss of acuity or the presence of haemorrhage at baseline indicating a high risk of progression; (3) lesions secondary to pathological myopia. Study design is identical to the TAP study with a 24 month follow-up and 2:1 randomisation between treatment and placebo groups. Two hundred and fifty-eight patients with occult CNV secondary to AMD with no classic CNV but with high-risk characteristics as outlined above. The frequency of stable or improved vision at 24 months was: 45% treated, 32% placebo ($p = 0.03$). There was also a significant effect on lesion size, and smaller lesions with poorer vision benefited most.

One hundred and twenty patients have been enrolled into the study of CNV in pathological myopia. Lesions required a classic component and either evidence of myopia on fundal examination or an axial length of $\geqslant 26.5$ mm. The frequency of maintenance of improvement of vision at 12 months was 86% in treated patients compared with 67% in placebo patients ($p = 0.01$).

Implications of the TAP and VIP results

Clinical evidence

The evidence from the TAP study indicates that PDT with verteporfin safely reduces the risk of visual loss from subfoveal CNV with a classic component in patients with AMD. The subgroup analysis of influence of lesion component at baseline showed a larger benefit in eyes with predominantly classic lesions and the greatest in those with no occult component, roughly equivalent to pure classic. Interpretation of the statistical significance of these results is made easier when the NNT analysis is considered, allowing some assessment of the clinical significance for affected patients. A balanced position has been taken by the TAP study group, who have recommended treatment for patients with 50% or more classic (predominantly classic) subfoveal CNV secondary to AMD. In this group the NNT was 3.6 at 12 months and 24 months and this compares well with an NNT calculation for the prevention of severe visual loss after panretinal scatter photocoagulation for proliferative retinopathy with high-risk characteristics of 14.3 (95% confidence interval, 9.9–25.8).[29] The Cochrane Eyes and Vision Group have interpreted the results as indicating that the benefit is restricted to patients with no occult component;[30] the NNT improved to 2.2 in the 143 patients in this subgroup.

To date the TAP and VIP studies have not demonstrated a clinically significant benefit for lesions with minimally (< 50%) classic CNV while for high-risk occult lesions with no classic component the treatment benefit is modest. Before treatment can be recommended for these lesions further details need to be published in the peer-reviewed literature.

The 12 month data on pathological myopes has shown a statistically significant benefit and probably justifies inclusion of this cause of CNV, at least at this stage. Whether the results in myopes can be generalised to other causes of CNV such as punctate inner

Table 2. *Indications for photodynamic therapy with verteporfin*

Indicated
- Subfoveal CNV secondary to AMD, predominantly classic, VA 6/60 or better, lesions ≤ 5400 μm (TAP criteria)
- Juxtafoveal lesions meeting the above criteria
- CNV secondary to pathological myopia

Probably indicated
- Lesions greater than 5400 μm subject to limitations of laser spot size

Possibly indicated
- Juxtapapillary lesions with subfoveal extension
- Occult with no classic component (pure occult) with high-risk characteristics
- CNV from other causes

Not indicated
- <50% classic
- Pure occult without high-risk characteristics
- RPE tears

choroidopathy and angioid streaks is questionable. Indications for verteporfin PDT based on the currently available data are summarised in Table 2.

Several limitations exist in the currently available data from the TAP study which make interpretation of the results difficult. The duration of the benefit has been shown for only 12 months for the pure classic group and 24 months for predominantly classic lesions. Further data from 2 years of follow-up will be available from the TAP study but not for periods beyond this time point. Because of positive results it is highly unlikely that placebo-controlled studies will receive ethics approval in future years, as has been acknowledged by the Cochrane Eyes and Vision Group.[30] This means that clinicians will need to base their clinical decisions on a single 2 year study without knowing the longer-term chances of maintenance of vision in a disease in which the vision can be expected in the normal course of events to deteriorate.

The relative effect of individual treatments during a course of therapy remains unknown. It is possible that only the first few treatments during the TAP study were beneficial. Much of the loss of vision in the TAP study occurred during the first 6 months, with this loss being greater in placebo patients than those receiving active treatment. Changes of vision in both groups were small thereafter, raising the possibility of fewer or more frequent treatments restricted to the first 6 months being at least as effective and possibly more cost-effective.

Safety issues have not been large in verteporfin PDT but a transient visual loss developing by 48 hours and persisting for up to 4 weeks is seen in some patients and merits further investigation. Indocyanine green imaging has shown that choriocapillaris closure occurs over a similar time period and could be associated or causative.[31]

Longer-term effects need to be established such as the potential for retinal pigment epithelium (RPE) atrophy suggested by primate work in which histological RPE cell disruption was demonstrated[18] and the phase I/II retreatment study in which some RPE atrophy was seen after multiple treatments administered at 2–4 week intervals over the 3 months of follow-up.[23]

To monitor safety issues in the UK a surveillance programme has been registered with the Safety and Efficacy Register of New Interventions and Treatments (SERNIP) by a newly established PDT Users Group. The frequency of retreatments in the TAP and VIP studies was selected at 3 months partly to allow RPE recovery and regrowth, and should probably not be shortened to less than 2 months.

Further work on case selection is required to identify those patients who will benefit most. An interim analysis of patients treated in the TAP study who had improved vision suggested that those with better outcomes were younger, had better VA in the fellow eye, smaller lesion size and tended to have eccentric lesions.[32]

Retreatments during the TAP study were performed at the discretion of the clinical centre depending on the persistence or recurrence of angiographic leakage. However, other factors such as clearance of subretinal fluid, stabilisation of vision or the development of low levels of vision might indicate that retreatment is not required. Patterns of leakage may also prove an important variable: it may be appropriate to leave persistent leakage from CNV eccentric to the fovea untreated at follow-up.

Service development in the UK

Epidemiological data on the frequency of AMD and its various subtypes are limited. Estimating the frequency of eyes developing new AMD that might meet criteria for verteporfin PDT can only be from indirect data. Studies that have reported frequencies of AMD predate the current angiographic classification of exudative AMD and so cannot predict accurately the frequency of patients with lesions that might meet treatment criteria based on the extent of classic CNV. AMD accounts for 48% of registrations in the UK as blind or partially sighted. Between April 1990 and March 1991 in England and Wales there were 802 new registrations per 100 000 population over age 65 years due to AMD, with a total for all age groups of approximately 16 000 cases in the year.[33] In one study 26% of eyes with exudative AMD met the criteria used in the MPS in which the lesion size

was up to 3.5 disc areas and so, because all MPS patients would reasonably be expected to meet PDT criteria, this probably represents an underestimate.[34] If in 5% of eyes with new exudative AMD the lesions remain extrafoveal and treatable with confluent laser, then it seems reasonable that a further 30% might be eligible for PDT, giving an estimated 5000 patients per annum requiring treatment in England and Wales. However, this is likely to be higher with the known underreporting of visual disability through BD8 registration and a proportion of patients requiring treatment to both eyes.

Data on quality of life have been collected on a subset of patients within the TAP and VIP studies and will help to inform the debate around clinical effectiveness, but of greatest importance to purchasers of health care in the UK will be information on cost-effectiveness. Following the TAP protocol will require a minimum of eight fluorescein angiograms and a probable average of four treatments over 2 years, at significant expense to the NHS in staff and drug costs. However, as clinical data accumulate from treating centres the number of treatments needed is likely to fall.

If verteporfin PDT is to be established in the UK under the NHS the capacity of the hospital eye service will need to be expanded considerably. Stereoscopic angiography is essential to accurate lesion classification and so departments of medical illustration will need training and additional personnel. Ophthalmologists will require training in the interpretation of images to ensure accurate detection and measurement of occult and classic lesions and an increase in numbers of medical, nursing and other ancillary staff will be required.

Summary

Current evidence supports the use of PDT with verteporfin for a limited number of patients with subfoveal CNV. There is insufficient evidence at present to support its widespread use in all patients with CNV from AMD or other causes. To minimise the danger of indiscriminate use at this early stage in the introduction of PDT, treatment should be restricted to those patients in whom a treatment benefit has been definitely demonstrated. Much research is still needed to establish the optimum treatment regime, its cost-effectiveness and its impact on health services.

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