REVIEW ARTICLE

Drug Safety 2006; 29 (3): 189-199
0114-5916/06/0003-0189/$39.95/0

A Preliminary Benefit-Risk Assessment of Verteporfin in Age-Related Macular Degeneration

Jason Wickens and *Kevin J. Blinder*

Barnes Retina Institute, Department of Ophthalmology, Washington University School of Medicine, St Louis, Missouri, USA

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Abstract

The prevalence of neovascular age-related macular degeneration (AMD) is expected to increase significantly during the next 20 years. New treatment alternatives to laser photocoagulation are on the horizon – the first of these, photodynamic therapy (PDT) with verteporfin, was approved by the US FDA in 2000. In this article we present a preliminary risk-benefit assessment of verteporfin in AMD, focusing on the landmark randomised, double-blind, placebo-controlled studies. The TAP (Treatment of Age-related macular degeneration with Photodynamic therapy) trial established the efficacy of PDT for classic subfoveal neovascularisation in AMD at 2 years follow-up. The VIP (Verteporfin in Photodynamic therapy) study concentrated on subfoveal occult-only lesions not included in the TAP study. After 2 years, treated eyes were less likely to experience visual loss. Exploratory analyses of TAP and VIP suggest that lesion size is a more significant predictor of the treatment benefit than either lesion composition or visual activity. The VIM (Visudyne® in Minimally classic) trial altered the standard PDT light fluence rate in the treatment of subfoveal minimally classic lesions. This trial again demonstrated a beneficial effect for those receiving treatment with PDT. The VIO (Visudyne® in Occult) trial, evaluating PDT in occult-only lesions as a confirmatory study of the VIP trial, did not achieve its primary end-point at 2 years. Further analyses are pending.

PDT with verteporfin has an excellent safety profile that has been established with >1 million treatment applications. Cost-effectiveness data are limited but suggest that PDT may be a cost-effective treatment modality. Other FDA-ap-

proved treatments (pegaptanib, ranibizumab and bevacizumab) for neovascular AMD are discussed, as well as investigational substances such as anecortave acetate.

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in individuals >50 years old.[1] It is generally categorised as non-neovascular ('dry') or neovascular ('wet'). Clinical features of non-neovascular AMD include hard and soft drusen, pigmentary changes and atrophy of the retinal pigment epithelium. Neovascular AMD is caused by choroidal neovascularisation (CNV), which develops when abnormal vessels from the choriocapillaris spread through breaks in Bruch's membrane into the space between the retinal pigment epithelium and the retina. These abnormal vessels can produce oedema, exudate and haemorrhage, and eventually fibrovascular scar formation. The damage to the retina can result in loss of central vision that may have a significant impact on the patient's ability to perform daily tasks. The vast majority of significant visual loss related to AMD is caused by the neovascular form.[2] The prevalence of neovascular AMD increases with age in Caucasians and is expected to increase significantly during the next 20 years, and it is estimated that 1 million people will develop neovascular AMD in the next 5 years in the US alone.[3]

The Macular Photocoagulation Study (MPS) Group described choroidal neovascular membranes as 'classic' or 'occult' based on features of fluorescein angiography.[4] Classic CNV is characterised by well defined early hyperfluorescence that leaks in later frames. Occult CNV can present as a fibrovascular pigment epithelial detachment or as late-phase hyperfluorescence of undetermined origin. The fibrovascular pigment epithelial detachment is characterised by stippled hyperfluorescence developing within 1–2 minutes of injection with either late staining or leakage. The other form of occult CNV is characterised by leakage seen between 2 and 5 minutes of injection without an identified source.[4]

The natural history of subfoveal CNV membranes, as reported in the TAP (Treatment of Age-related macular degeneration with Photodynamic therapy) study, is associated with severe vision loss (loss of ≥6 lines of visual acuity from baseline levels) at 2 years in 36% of untreated patients with predominantly classic lesions at baseline.[5] The MPS Group describe similar results with 37% having severe vision loss at 2 years, with the 4-year rate increasing to 47%.[6] Neovascular lesions with occult features are similarly associated with a poor natural history. The VIP (Verteporfin in Photodynamic therapy) study reported that 48% of untreated eyes with occult lesions were associated with severe vision loss at 2 years.[7]

Prior to 2000, patients with neovascular AMD had limited treatment options for subfoveal CNV. Earlier, the MPS Group had proposed the use of thermal laser in the treatment of subfoveal CNV.[8] Although thermal laser was shown to reduce the risk of severe vision loss, the damage to central vision was immediate, permanent and difficult for patients to comprehend. The search for additional treatment modalities resulted in alternative therapies such as photodynamic therapy (PDT), submacular surgery, antiangiogenic therapy and transpupillary thermal therapy. PDT with verteporfin (Visudyne® [1]) was the first of these newer therapies to be shown to be effective in randomised controlled clinical trials and was approved by the US FDA in 2000.

This report provides a brief review of verteporfin and a preliminary benefit-risk assessment of verteporfin in AMD and focuses on the major clinical trials. A literature search was performed in PubMed from 1985 to the present day for articles with the keywords 'verteporfin', 'photodynamic therapy' and 'age-related macular degeneration'.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

1. Brief Description of Verteporfin

Verteporfin is a benzoporphyrin derivative monoacid ring A that is administered by intravenous infusion over 10 minutes at a recommended dose of 6 mg/m^2 of body surface area. Verteporfin is rapidly distributed throughout the body, with peak plasma levels occurring at the end of the infusion. The drug is transported in the plasma bound to low-density lipoproteins (LDLs). Neovascular tissue with rapidly proliferating endothelial cells and increased LDL receptors are thought to selectively bind the verteporfin-LDL complex.[9,10]

Verteporfin is activated 15 minutes after the infusion by the application of nonthermal laser light with wavelength 689nm and an intensity of 600 mW/cm^2 for 83 seconds, resulting in a light dose of 50 J/cm^2. The mechanism of action is thought to involve the formation of cytotoxic free radicals leading to damage of vascular endothelial cells and selective destruction of neovascular tissue via vasoconstriction, platelet aggregation and fibrin clot formation.[9,10]

Verteporfin is cleared by the liver without the involvement of cytochrome P450 enzymes. It is rapidly excreted in the bile and has a half-life of approximately 6 hours. Mild liver dysfunction, age, race and sex are not associated with clinically significant effects. Renal elimination is minimal.[11]

2. Evidence of Benefit with Verteporfin

The clinical effect of PDT with verteporfin in AMD has been evaluated in four large, randomised, double-blind, placebo-controlled studies. The TAP trial[5,12] included two identically designed trials conducted concurrently. The VIP study[7] evaluated AMD lesions not originally eligible for the TAP study, as well as pathological myopia. Retrospective exploratory analyses of the TAP and VIP studies led to the VIM (Visudyne® In Minimally Classic)[13] and VIO (Visudyne® in Occult) trials.[14]

Additional studies have evaluated specific population groups or provided clinical experience using a non-controlled open-label design. The JAT (Japanese Age-related Macular Degeneration Trial) was a small, open-label, prospective, non-controlled study.[15] The VAM (Verteporfin Therapy in Age-Related Macular Degeneration) was a large open-label, non-controlled study.[16]

The TAP[5,12] study included 609 people (402 PDT; 207 placebo) from centres in North America and Europe with classic or classic plus occult subfoveal CNV. Additional inclusion criteria were initial visual acuity in the affected eye of 73 to 34 letters (20/40–20/200) and lesion size <5400μm. The primary outcome measure was the proportion of eyes that had vision loss from baseline of <15 letters (≈3 lines). Patients were treated according to the standard PDT protocol described earlier. Retreatment was allowed every 3 months if fluorescein angiograms showed leakage. Control patients received intravenous dextrose 5% in water followed by identical laser light treatment to that received by the verteporfin group.

The results of the TAP study showed a significant reduction in the risk of vision loss with PDT with verteporfin compared with placebo plus laser light treatment after 12 and 24 months (table I). After 12 months, 61% of PDT recipients achieved the primary endpoint versus 46% of those receiving placebo ($p < 0.001$),[12] with similar results at 24 months (53% vs 38%; $p < 0.001$).[5] Verteporfin-treated eyes were more likely to experience visual improvement of ≥1 lines (16% vs 7%; p-value not reported) and more likely to avoid severe vision loss of ≥6 lines (85% vs 76%) in the first year.[12] Subgroup analyses suggested predominantly classic lesions (≥50% of the area of the lesion) benefitted most with PDT with verteporfin. After 12 months, 67% of PDT recipients lost <15 letters of visual acuity from baseline versus 39% of those receiving placebo ($p < 0.001$);[5] after 2 years the results were similar (59% vs 31%; $p < 0.001$).[12] Minimally classic lesions (<50%) were not shown to statistically differ between treatment groups in primary visual outcome at either 12 or 24 months (table I).[5,12] The mean number of PDT treatments was 3.4 in the first year and 2.2 in the second year. The TAP Extension study[17] indicated that patients with predominantly classic lesions received a mean of 1.3 PDT treat-

Table I. Patients (pts) achieving primary outcome of <3-line (<15 letters) vision loss from baseline after photodynamic therapy (PDT) with verteporfin compared with placebo (PL) in the TAP[5,12] (Treatment of Age-related macular degeneration with Photodynamic therapy) and VIP[7] (Verteporfin in Photodynamic therapy) studies after 12 and 24 months

Lesion type	Month	PDT [no. pts (%)]	PL [no. pts (%)]	p-Value
TAP study[a]				
All lesions	12	246 (61)	96 (46)	<0.001
	24	213 (53)	78 (38)	<0.001
Predominantly classic CNV	12	107 (67)	33 (39)	<0.001
	24	94 (59)	26 (31)	<0.001
Predominantly classic with no occult CNV	12	61 (77)	12 (27)	<0.001
	24	63 (70)	11 (25)	
Predominantly classic with occult CNV	12	38 (55)	21 (54)	
	24	31 (45)	15 (47)	
Minimally classic	12	113 (56)	57 (55)	0.85
	24	96 (48)	46 (44)	0.58
VIP study[b]				
Occult with no classic CNV	12	81 (49)	46	0.515
	24	75 (46)	33	0.023
Occult with no classic CNV and either lesion size ≤4 disc areas or visual acuity <20/50	24	63 (51)	25	0.001
Occult with no classic CNV and >4 disc areas and visual acuity ≥20/50	24	12 (28)	48	0.09

a Eligibility criteria: age ≥50y; AMD; subfoveal CNV; classic component; GLD ≤5400μm; BCVA 20/40–20/200.

b Eligibility criteria: age ≥50y; AMD; subfoveal CNV; area of CNV at least 50% of lesion area; GLD ≤5400μm; BCVA ≥20/100. If classic component, then visual acuity letter score >70; if no classic component, then recent disease progression within last 3mo or evidence of haemorrhage from CNV.

AMD = age-related macular degeneration; **BCVA** = best corrected visual acuity; **CNV** = choroidal neovascularisation; **GLD** = greatest linear dimension.

ments from year 2 to year 3, suggesting a continued decrease in the treatment rate.

The VIP[7,18] study included 339 people (225 PDT; 114 placebo) mainly with subfoveal occult-only lesions. Inclusion criteria included initial visual acuity ≥50 letters (20/100), lesion size ≤5400μm and evidence of disease progression within the last 3 months (if no classic component). The study included patients with mixed classic and occult if visual acuity was ≥70 letters (20/40); however, this group was small (59 of 225 patients receiving PDT and 22 of 114 placebo recipients). As in the TAP study, the primary endpoint was vision loss from baseline of <15 letters.

Results at 12 months showed no statistical difference between treatment groups in primary visual outcome, with 49% of PDT recipients versus 46% of those receiving placebo losing <15 letters of visual acuity.[7] At 24 months, however, verteporfin-treated eyes were less likely to deteriorate with 46% of PDT recipients versus 33% of those receiving placebo losing <15 letters of visual acuity (p = 0.023). The percentage of patients with severe vision loss (≥6 lines lost) was less in the verteporfin group (29% vs 47%; p = 0.001). Subgroup analyses in patients with occult CNV with no classic component revealed increased benefit with PDT with verteporfin if either the lesion size was four disc areas or less (regardless of visual acuity) or visual acuity worse than 20/50 (regardless of lesion size) [table I]; the greatest benefit coming when both these features were present. However, the subgroup characterised by lesions larger than four disc areas and visual acuity of 20/50 or better was found to have no treatment benefit with verteporfin (table I). Indeed, this latter subgroup was associated with an increased rate of vision loss; however, the VIP authors state that these subgroup analyses data should be interpreted with caution because of the small number of patients. Ten (4.4%) patients treated with verte-

porfin experienced acute (within 7 days) severe vision loss of ≥20 letters. The mean number of treatments was five over the 2-year period.

Exploratory analyses of the TAP and VIP studies further evaluated the effects of lesion size, visual acuity and lesion composition on visual acuity change with PDT and suggested that lesion size is a more significant predictor of the treatment benefit than either lesion composition or visual acuity.[19] Minimally classic and occult lesions that were four disc areas or smaller were found to have similar visual acuity outcomes to those reported for predominantly classic lesions with baseline mean sizes of less than four disc areas. However, predominantly classic lesions were the only lesion composition that retained a treatment benefit for PDT in larger lesions.

The VIM trial involved 117 patients in a phase II trial comparing standard and reduced light fluence rates with placebo in subfoveal minimally classic lesions. Standard fluence, as defined in previous studies, was 50 J/cm^2, while reduced fluence was 25 J/cm^2. Inclusion criteria were visual acuity of 20/250 or better for lesions four MPS disc areas or less and 20/50–20/250 for lesions between four and six MPS disc areas.[13]

The 2-year visual outcome data for the VIM trial demonstrated a benefit for treatment with PDT. Seventy-four percent of those receiving PDT with reduced fluence lost <15 letters compared with 47% of those receiving PDT with standard fluence ($p = 0.03$). Of the two treatments, only reduced fluence PDT was more effective than placebo (38%; $p = 0.003$). Angiographic outcomes showed a decreased rate of conversion to predominantly classic CNV with both reduced (5%; $p = 0.007$) and standard (3%; $p = 0.002$) fluence PDT compared with placebo (28%).[13]

The VIO trial, a phase III trials, was designed to evaluate PDT in the treatment of occult with no classic lesions. A preliminary analysis of the 2-year data revealed that PDT did not achieve the primary end point; further analyses are pending.

The JAT[15] study included 64 Japanese patients with subfoveal CNV classified as minimally classic (39), predominantly classic (16) and occult with no classic (9). Inclusion criteria included lesion size <5400μm and baseline vision of 20/40–20/200. The 12-month data suggested that verteporfin had a stabilising effect on vision. Progression of disease was described in 19% of classic and 14% of occult lesions. The median number of treatments was three.

The VAM[16] study was designed to provide additional clinical experience and gather more information on the safety of verteporfin therapy. It included 4435 patients at 222 centres in the US and Canada with subfoveal predominantly classic CNV who received verteporfin in an expanded access programme. Similarly to previous studies, additional inclusion criteria included baseline vision of 20/40–20/200 and lesion size not >5400μm. Follow-up was collected for only 9 months, until PDT with verteporfin became commercially available. A total of 6701 treatments were administered during the study, and analysis revealed no additional safety concerns.

Additional clinically relevant measures of visual function have been evaluated. PDT is reported to have a beneficial effect on contrast sensitivity. Data from the TAP study suggested that after 24 months, patients treated with PDT were less likely to lose at least 6 or 15 letters of contrast sensitivity than placebo recipients (21% vs 45% and 7% vs 12%, respectively; both $p < 0.05$).[20] Subgroup analyses reveal that predominantly classic lesions as well as minimally classic lesions were associated with a reduced rate of contrast sensitivity loss. Sixteen percent of predominantly classic lesions treated with verteporfin lost six or more letters of contrast sensitivity versus 54% of those treated with placebo. In the minimally classic group, the difference was not as large, with 26% of verteporfin-treated eyes versus 41% of placebo-treated eyes losing six or more letters of contrast sensitivity.

3. Safety Profile

A meta-analysis of the safety data from the TAP and VIP studies at 24 months reported a similar tolerability profile for verteporfin and placebo.[21] The most common systemic adverse event was in-

jection site reactions occurring in 13.1% and 5.6% of the verteporfin and placebo groups, respectively ($p < 0.001$). Other statistically significant adverse systemic events included back pain (infusion-related), photosensitivity reactions and constipation (table II). The most common eye adverse event was visual disturbance (table III). The TAP study reported visual disturbance in 22.1% of verteporfin-treated patients and 15.5% of placebo recipients ($p = 0.054$), with the VIP trial reporting 41.8% versus 22.8% ($p < 0.001$), respectively. A visual disturbance included abnormal vision, visual field defect and vision decrease that were reported by patients but not objectively measured, except acute severe visual acuity decrease. Abnormal vision descriptions included haziness, blurriness, photopsias, distortion or a decrease in depth perception. Visual field changes were described as dark-colored spots. Adverse eye events were reported usually within 7 days of treatment and were transient, not affecting the net vision outcome benefit.

Acute severe visual acuity decrease, defined as a 4-line loss within 7 days after PDT with verteporfin, occurred in three (0.7%) verteporfin-treated patients in TAP and ten (4.4%) verteporfin-treated patients in VIP.[22] An additional case from the VIP study was later identified. The visual decrease was associated with subretinal fluid (three patients), subretinal and subretinal pigment epithelium haemorrhage (four), a greenish subfoveal lesion (three) or no morphological abnormality (three). All but two patients experienced the loss after the first treatment and most patients did not receive subsequent PDT. The visual results at the 24-month examination following the event were similar to placebo in their respective trials.[22]

The VAM study reported an overall incidence of any adverse event of 16.4%.[16] Investigators considered adverse events to be associated with verteporfin therapy in 6.8% of patients. One death, secondary to pancreatitis, was considered possibly related to therapy. The most common adverse event was decreased vision (2.9%). Additional ocular adverse events included abnormal vision (2.1%) and eye pain (0.6%). The most frequently noted nonocular events were headache (1.3%), injection site reaction (1.0%) and back pain (0.7%). Photosensitivity reactions were described in two (<0.1%) patients. Acute severe visual acuity decrease was reported in 35 (0.8%) patients, 25 (0.6%) of which were thought to be associated with verteporfin therapy. The visual decrease was associated with subretinal haemorrhage (11 patients), increased subretinal fluid (8), retinal capillary non-perfusion (2), retinal detachment (1) and retinal depigmentation (1). Eleven eyes had no evidence of retinal abnormality.

PDT is recommended for predominantly classic CNV with or without occult CNV regardless of size. Small minimally classic lesions may also benefit from PDT. Future analyses of the VIM trial will provide additional data regarding this group of patients. Occult CNV without classic CNV should be considered, pending the official publishing of the VIO study, for PDT in small lesions (four disc areas or less) or vision acuity <20/50 if there is evidence of recent disease progression. The definition of recent disease progression includes either haemorrhage from CNV, increased lesion size equivalent to 10% increase in the greatest linear dimension or decreased visual acuity of at ≥1 line within the previous 3 months.[23] To date, approximately

Table II. Tolerability profile of photodynamic therapy with verteporfin (PDT; n = 627) compared with placebo (PL; n = 321). Combined adverse systemic event data from the TAP (Treatment of Age-related macular degeneration with Photodynamic therapy) and VIP (Verteporfin in Photodynamic therapy) studies[21]

Event	PDT [no. of patients (%)]	PL [no. of patients (%)]	p-Value
Injection site reactions	82 (13.1)	18 (5.6)	<0.001
Back pain (infusion related)	15 (2.4)	0 (0)	0.004
Photosensitivity reactions	15 (2.4)	1 (0.3)	0.016
Constipation	15 (2.4)	1 (0.3)	0.016
Sleep disorder	10 (1.6)	0 (0)	0.019

Table III. Adverse eye events after photodynamic therapy with verteporfin (PDT; n = 402 and 225) or placebo (PL; n = 207 and 114) in the TAP (Treatment of Age-related macular degeneration with Photodynamic therapy) and VIP (Verteporfin in Photodynamic therapy) studies[21]

Event	TAP			VIP		
	PDT [no. of pts (%)]	PL [no. of pts (%)]	p-Value	PDT [no. of pts (%)]	PL [no. of pts (%)]	p-Value
Visual disturbance	89 (22.1)	32 (15.5)	0.054	94 (41.8)	26 (22.8)	<0.001
Vision decreased	41 (10.2)	13 (6.3)	0.132	67 (29.8)	15 (13.2)	<0.001
Acute severe vision decrease	3 (0.7)	0 (0)	0.555	10 (4.4)	0 (0)	0.018
Visual field defect	24 (6)	7 (3.4)	0.242	34 (15.1)	8 (7.0)	0.036
Cataract	60 (14.9)	31 (15)	1.00	30 (13.3)	10 (8.8)	0.285

pts = patients.

350 000 patients have been treated with PDT, with >1 million treatments administered.

4. Combination Therapy

In addition to its effect on neovascularisation, it has been reported that PDT may induce vascular endothelial growth factor (VEGF) production, as well as damage to the choriocapillaris and retinal pigment epithelium.[24] Corticosteroids are known to have anti-inflammatory properties and have also been suggested to have antiangiogenic effects.[25-28] Few studies have evaluated intravitreal corticosteroids in the treatment of neovascular AMD. Intravitreal triamcinolone as monotherapy for CNV has been reported to have a beneficial effect on vision at 6 months.[29] A larger randomised controlled study, however, found no significant effect on vision at 12 months, but showed slowed lesion growth at 3 months.[30]

It has been suggested that the combination of intravitreal triamcinolone with PDT may reduce the inflammatory effects potentially induced by PDT as well as limit the recurrence of neovascularisation.[30] Spaide et al.[31] reported a small non-comparative case series that showed a reduction in loss of visual acuity with combination therapy and a reduction in the number of PDT treatments over 12 months. The 26 eyes in the study included 13 newly diagnosed with neovascular AMD and 13 that had previous PDT. The 12-month data showed a 2.5 line mean improvement in visual acuity in the newly diagnosed group, whereas the previously treated group showed an improvement of 0.44 lines. Retreatment rates were 1.2 for both groups. Safety data showed that 38.5% of patients experienced increased (>24 mmHg) intraocular pressure. Cataract progression was not evaluated and no patients developed endophthalmitis.

In a retrospective analysis, Rechtman et al.[32] reported on 14 eyes treated with PDT and intravitreal triamcinolone. The 18 month follow-up data showed 57% lost <15 letters of visual acuity. The mean number of PDT treatments was 2.57 in the first year. In this series, 28.5% of patients experienced increased intraocular pressure (>22 mmHg) and 50% of phakic eyes had progression of cataracts.

5. Cost Effectiveness

In an effort to estimate the cost effectiveness of PDT with verteporfin, studies have assessed quality-adjusted life-year gains. A UK study suggested that PDT was cost effective in treating predominantly classic lesions with better initial vision.[33] The cost effectiveness diminished, however, with decreased baseline vision.

The cost effectiveness of PDT is reported to improve with longer follow-up data. Sharma et al.[34] reported that after 2 years PDT for classic CNV was marginally cost effective. A subsequent analysis using 5 years of follow-up data suggested that PDT was a very cost-effective treatment by conventional standards.[35] The authors conclude that the reasons for the improved cost effectiveness were an increasing treatment benefit with time and substantially less treatments after 2 years of therapy.

6. Alternative Therapies

Alternative therapies to PDT continue to be evaluated for neovascular AMD. In this section, several of these therapies are briefly reviewed including pegaptanib, ranibizumab, bevacizumab, anecortave acetate, submacular surgery and transpupillary thermal therapy.

Pegaptanib (Macugen®) was recently approved in the US for the treatment of neovascular AMD. Pegaptanib is a pegylated aptamer that acts as a VEGF inhibitor, designed specifically to inhibit the 165-amino acid isoform. The administration route is by intravitreal injection. Two concurrent randomised controlled trials evaluated the safety and efficacy of pegatanib when injected every 6 weeks for 48 weeks compared with a sham injection (VEGF Inhibition Study in Ocular Neovascularization [VISION] trial).[36] Inclusion criteria included baseline vision of 20/40–20/320 with subfoveal CNV <12 total disc areas in size and with ≥50% activity. Occult lesions and minimally classic lesions were included if there was evidence of disease progression in the past 3 months. PDT with verteporfin was permitted for patients with predominantly classic lesions determined by the investigator. The primary efficacy endpoint was vision loss (<15 letters) from baseline to 54 weeks.

The 12-month data revealed that the number of patients losing <15 letters from baseline was 206 (70%) with pegaptanib versus 164 (55%) with the sham injection ($p < 0.001$). Severe vision loss (≥6 lines) was twice as likely to occur in the sham group (10% vs 22%; $p < 0.001$). Pegaptanib-treated patients were more likely to have stable or improved vision than the control group (33% vs 23%; $p = 0.003$). Ocular adverse events that occurred more commonly in the pegaptanib-treated eyes than in the sham-treated eyes included eye pain, floaters, punctuate keratitis, cataracts, inflammation, visual disturbance, discharge and corneal oedema. The most serious adverse events that occurred in pegaptanib recipients were endophthalmitis (1.3%), traumatic cataract (0.6%) and retinal detachment (0.7%). Of the total endophthalmitis cases, 8 of 12 cases were associated with protocol violations, the most common being lack of eyelid speculum use.

While the safety profile of pegaptanib may not be as desirable as that of PDT, because of the invasive nature of its intravitreous route of administration, it does seem to have slightly expanded indications for AMD. One must consider this, along with the higher frequency of treatments and follow-up visits when compared to verteporfin therapy.

Ranibizumab (Lucentis®) is a recombinant humanised antibody to VEGF and is administered by intravitreal injection. The MARINA (Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumabin the treatment of Neovascular AMD) trial is an ongoing phase III randomised controlled study including 716 patients (two-thirds with occult disease) randomised to sham injection or ranibizumab 0.3 or 0.5mg once a month for 2 years. Preliminary 12-month data showed that 95% of ranibizumab-treated patients lost <15 letters from baseline (the primary endpoint) compared with 62% in the sham-treated group ($p = 0.0001$).[37] Additionally, patients in the ranibizumab treatment groups were more likely to have an improvement in the vision. Safety data reported <1% incidence of uveitis and endophthalmitis.

The ANCHOR (Anti-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularization in AMD) study is a phase III randomised, multicentre, double-blind trial comparing ranibizumab with PDT with verteporfin in 423 patients with predominantly classic CNV secondary to AMD. After 12 months, 94% and 96% of patients treated with ranibizumab 0.3 and 0.5mg, respectively, achieved the primary efficacy endpoint of maintaining or improving visual acuity, compared with 64% of those treated with PDT ($p < 0.0001$). On average, patients treated with ranibizumab improved, while those treated with PDT declined.[38]

The FOCUS (RhuFab V2 Ocular treatment Combining the Use of Visudyne® to evaluate Safety) trial is an ongoing randomised phase I/II trial investigating PDT versus PDT plus ranibizumab. Preliminary 12-month data reported that the PDT with ranibizumab group were less likely to lose ≥15

letters (90% vs 68%; p = 0.0003) than those receiving PDT alone.[37] Safety analysis revealed an increased risk of uveitis in the ranibizumab-treated patients compared with earlier studies. There was no significant difference in nonocular events between the groups.

Bevacizumab (Avastin®) is a full-length recombinant humanised anti-VEGF antibody that is approved by the FDA for the treatment of metastatic colorectal cancer. Michels et al.[39] recently reported on the systemic administration of bevacizumab for the treatment of CNV secondary to AMD in the SANA (Systemic Avastin® for Neovasuclar AMD) study. Their series consisted of nine patients with subfoveal CNV who were treated with systemic bevacizumab at 2-week intervals for a total of 2–3 treatments and followed-up after 12 weeks. Patients tolerated the therapy well, and improvements were reported in visual acuity, optical coherence tomography (OCT) imaging and angiographic outcomes. To reduce the potential for systemic complications, the intravitreal route of administration would seem to be preferable. Rosenfeld et al.[40] reported OCT findings after intravitreal injection of bevacizumab as treatment for CNV secondary to AMD. They found resolution of subretinal fluid 1 week post-injection in a patient who was responding poorly to therapy with pegatanib.

Anecortave acetate is an angiostatic synthetic cortisol derivative that is reported to inhibit angiogenesis by blocking the matrix metelloproteinases necessary for vascular endothelial cell migration. Modification of its original cortisol backbone has resulted in a novel angiostatic cortisene that exhibits none of the normal corticosteroid bioactivity.[41] It is administered by juxtascleral injection and is presently pending US FDA approval for the treatment of neovascular AMD.

The clinical efficacy of anecortave acetate and safety outcomes were evaluated in a randomised controlled study in patients with subfoveal CNV secondary to AMD.[42] Inclusion criteria included lesion size <12 disc areas, angiographic evidence of CNV activity in ≥50% of lesions (active CNV with ≥50% classic component, or area of classic CNV at least 1.6mm^2) and baseline vision of 20/40–20/320. Retreatment by juxtascleral injection was performed at 6 months if needed. Results at 12 months showed that, compared with placebo, patients treated with anecortave acetate were more likely to experience a loss of <15 letters (79% vs 53%). Treatment effect was increased when the subgroup of predominantly classic was analysed. Severe vision loss was less frequent in the anecortave acetate group (3% vs 23%). One must use caution when interpreting the data of this study, however, as 41% of study participants exited the study prior to month 12 (last observation carried forward for data analysis). Safety data for anecortave acetate showed it to be similar to placebo. The adverse events most commonly associated with the injection included ptosis, ocular pain, subconjunctival haemorrhage, ocular pruritis, hyperaemia and foreign body sensation. These were typically mild and transient in nature.

Anecortave acetate appears to have many potential advantages over other treatment modalities, including a low frequency of administration, a desirable safety profile and efficacy of treatment effect. Further studies are presently ongoing, including a prophylactic treatment protocol for fellow eyes at risk for progression to CNV.

The SST (Submacular Surgery Trials) studies were designed to evaluate the treatment effect of submacular surgery versus observation for subfoveal lesions.[43] Inclusion criteria included neovascular lesions that contained at least some classic component and <9 disc areas in size. Vision range was 20/100–20/800. A successful outcome was defined to be either improvement or ≤1 line of vision loss at 24 months. Results demonstrated no statistical difference between the groups, which led the authors to conclude that submacular surgery is not recommended in such lesions.

Transpupillary thermal therapy involves the use of a laser with wavelength 810nm. Laser energy is applied at 800mW using a 3mm spot size with a duration of 60 seconds. The treatment effect of transpupillary thermal therapy in occult CNV was evaluated in a randomised controlled trial versus sham treatment (TTT4CNV).[44] Preliminary 2-year

data suggest no statistically significant difference in treatment effect between the treatment groups; additional subgroup analyses are pending.

7. Conclusion

The treatment of subfoveal CNV related to AMD remains a therapeutic challenge. The development of PDT with verteporfin offers an alternative option to thermal laser, which is associated with decreased progression of vision loss, as shown in the results of large randomised controlled trials. The safety profile of verteporfin in these studies indicates that, overall, PDT is well tolerated. The adverse effects are largely transient and do not appear to increase with subsequent treatments. Acute severe vision loss, although rare, remains a serious adverse event especially in occult lesions. Combination therapy with antiangiogenic agents may play an increasing role in the future treatment of neovascular AMD.

Acknowledgements

No sources of funding were used to assist in the preparation of this review.

Kevin Blinder is a member of the Speakers Bureau for Novartis and Eyetech.

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Correspondence and offprints: Dr *Kevin J. Blinder*, Barnes Retina Institute, 1600 South Brentwood Blvd, 8th floor, St Louis, MO 63144, USA.
E-mail: kjblinder@pol.net