# Photodynamic Therapy with Verteporfin in Age-related Macular Degeneration

*a report by*
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Age-related macular degeneration (AMD) is the leading cause of severe vision loss in individuals aged greater than fifty years.[1] AMD is generally categorized as non-neovascular (dry) or neovascular (wet). Clinical findings of non-neovascular AMD include drusen, pigmentary changes, and atrophy of the retinal pigment epithelium with resultant gradual visual decline. Neovascular AMD occurs when choroidal neovascularization (CNV) penetrates through compromised areas of Bruch's membrane and into the potential space between the retina and retinal pigment epithelium. Neovascularization can present with subretinal and intra-retinal edema, exudation, hemorrhage, and eventually a fibrovascular scar resulting in profound loss of central visual acuity. The vast majority of AMD related visual loss is caused by the neovascular form.[2] With the aging US population, clinicians can expect to see an exponential increase in neovascular AMD over the next twenty years; in fact, it is estimated that one million individuals will develop neovascular AMD in the next five years in the US alone.[3]

Prior to 2000, patients with neovascular AMD had limited treatment options for subfoveal CNV. The Macular Photocoagulation Study (MPS) Group had proposed thermal laser for the treatment of subfoveal lesions.4 Although thermal laser was shown to reduce the risk of severe vision loss (≥6 lines from baseline), damage to central vision from the treatment itself was immediate, permanent, and difficult for patients to comprehend. This led to a search for alternative treatments such as photodynamic therapy (PDT), submacular surgery, and anti-angiogenesis drugs. PDT with verteporfin was the first of these new modalities to be shown to be effective in randomized controlled clinical trials and was approved by the US Food and Drug Administration (FDA) in 2000.

Verteporfin is a benzoporphyrin derivative that is administered via intravenous infusion over a ten-minute period at a concentration of 6mg/m$^2$ of body surface area. Verteporfin is rapidly distributed throughout the body, bound to low-density lipoproteins (LDLs). Since neovascular tissue is rich in LDL receptors, verteporfin-LDL complexes preferentially accumulate in choroidal neovascular membranes.[5,6] Fifteen minutes after administration, verteporfin is then activated in vivo with the application of 689nm non-thermal laser at an intensity of 600mW/cm$^2$ for 83 seconds directly over the choroidal neovascular complex. Activation results in the formation of cytotoxic, free radicals that cause selective vasoconstriction, platelet aggregation, and fibrin clot formation in choroidal neovascular tissue resulting in vessel closure.[5,6]

The clinical efficacy of PDT with verteporfin for AMD has been evaluated in four large, randomized, double-blind, placebo-controlled studies. The treatment of AMD with photodynamic therapy (TAP) study showed a significant reduction in the risk of vision loss with PDT with verteporfin in patients with classic or classic plus occult subfoveal CNV. After 24 months, 53% of PDT recipients achieved the primary endpoint (<15 letters vision loss) versus 38% of those receiving placebo ($p<0.001$).

Subgroup analysis suggested predominantly classic lesions (≥50% of lesion area) benefited the most; after two years, 59% of PDT treated patients lost less than 15 letters versus 31% of those receiving placebo in this subgroup. The mean number of PDT treatments in the first year overall was 3.4 and 2.2 in the second year.[7,8]

The verteporfin in photodynamic therapy (VIP) study evaluated the effects of treatment with PDT with verteporfin in mainly occult lesions. At 24 months, 46% of PDT treated eyes versus 33% of placebo were less likely to lose 15 letters of visual acuity ($p=0.023$). Patients were also less likely to suffer severe vision loss (≥6 lines) in the verteporfin treated group (29% vs. 47%, $p=0.001$). Further subgroup analysis revealed that the greatest benefit was seen in patients with lesion size ≤4 disc areas (regardless of visual acuity) or visual acuity worse than 20/50 (regardless of lesion size).[9,10]

Analysis of the TAP and VIP studies has suggested that lesion size is a more significant predictor of the treatment benefit than lesion composition or visual acuity.[11] Minimally classic and occult lesions that were four disc areas or smaller were found to have similar visual acuity outcomes to those reported for

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**Important Safety Information**

Visudyne is indicated for treatment of predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia, or presumed ocular histoplasmosis. Visudyne is contraindicated for patients with porphyria or known hypersensitivity to any component of Visudyne.

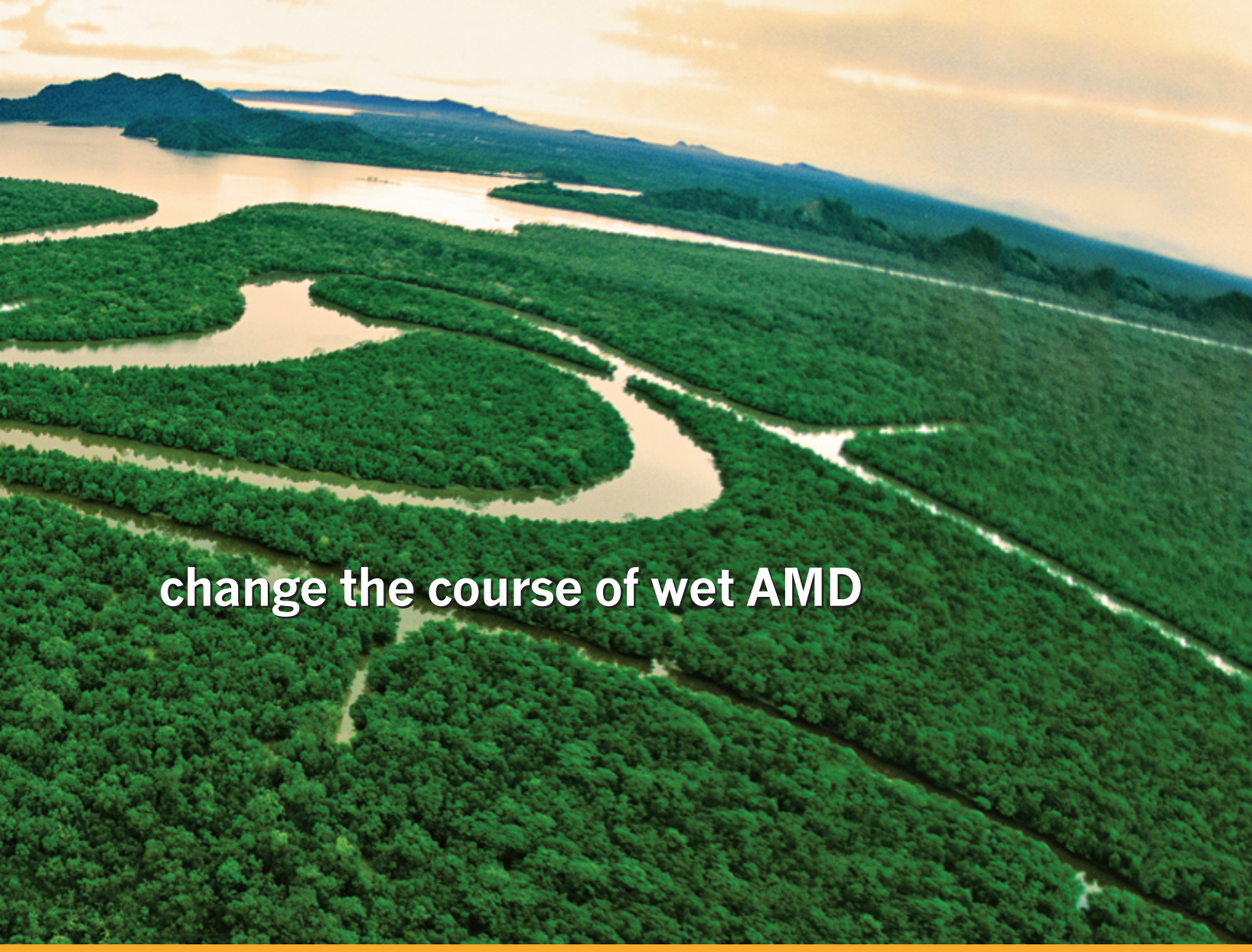
Infusion-related transient back pain occurred with Visudyne only. Verteporfin infusion induces temporary photosensitivity; patients should avoid exposure of skin and eyes to direct sunlight or bright indoor light for 5 days. To prevent extravasation, avoid fragile hand veins in favor of larger antecubital veins.

Severe vision decrease (≥4 lines) was reported within 7 days in 1% to 5% of patients. Partial recovery occurs in some patients. Do not re-treat these patients until vision completely recovers to pretreatment levels and potential benefits and risks of subsequent treatment are carefully weighed.

The most frequently reported adverse events (10% to 30% incidence) were injection site reactions (including extravasation and rashes), blurred vision, decreased visual acuity, and visual field defects.

Please see brief summary of Prescribing Information on adjacent page.

**References: 1.** Schmidt-Erfurth U, Hasan T. Mechanisms of action of photodynamic therapy with verteporfin for the treatment of age-related macular degeneration. *Surv Ophthalmol.* 2000;45:195-214. **2.** Kaiser PK. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: 5-year results of two randomized clinical trials with an open-label extension. TAP report no. 8. *Graefes Arch Clin Exp Ophthalmol.* 2006;244:1132-1142. **3.** Data on file, Novartis Pharmaceuticals Corporation.

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**INDICATIONS AND USAGE**
Visudyne® (verteporfin for injection) therapy is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis.

There is insufficient evidence to indicate Visudyne for the treatment of predominantly occult subfoveal choroidal neovascularization.

**CONTRAINDICATIONS**
Visudyne® (verteporfin for injection) is contraindicated for patients with porphyria or a known hypersensitivity to any component of this preparation.

**WARNINGS**
Following injection with Visudyne® (verteporfin for injection), care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. In the event of extravasation during infusion, the extravasation area must be thoroughly protected from direct light until the swelling and discoloration have faded in order to prevent the occurrence of a local burn which could be severe. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.

Patients who experience severe decrease of vision of ≥4 lines within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician.

Use of incompatible lasers that do not provide the required characteristics of light for the photoactivation of Visudyne could result in incomplete treatment due to partial photoactivation of Visudyne, overtreatment due to overactivation of Visudyne, or damage to surrounding normal tissue.

**PRECAUTIONS**
**General**
Standard precautions should be taken during infusion of Visudyne® (verteporfin for injection) to avoid extravasation. Examples of standard precautions include, but are not limited to:

- A free-flowing intravenous (IV) line should be established before starting Visudyne infusion and the line should be carefully monitored.
- Due to the possible fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably antecubital, be used for injection.
- Small veins in the back of the hand should be avoided.

Extravasation of Visudyne, especially if the affected area is exposed to light, can cause severe pain, inflammation, swelling or discoloration at the injection site.

If extravasation does occur, the infusion should be stopped immediately. The extravasation area must be thoroughly protected from direct light until swelling and discoloration have faded in order to prevent the occurrence of a local burn, which could be severe. Cold compresses should be applied to the injection site *(see WARNINGS)*. Oral medications for pain relief may be administered.

Visudyne therapy should be considered carefully in patients with moderate to severe hepatic impairment or biliary obstruction since there is no clinical experience with verteporfin in such patients.

There is no clinical data related to the use of Visudyne in anesthetized patients. At a >10-fold higher dose given by bolus injection to sedated or anesthetized pigs, verteporfin caused severe hemodynamic effects, including death, probably as a result of complement activation. These effects were diminished or abolished by pretreatment with antihistamine and they were not seen in conscious, nonsedated pigs. Visudyne resulted in a concentration-dependent increase in complement activation in human blood *in vitro*. At 10 µg/mL (approximately 5 times the expected plasma concentration in human patients), there was mild to moderate complement activation. At ≥100 µg/mL, there was significant complement activation. Signs (chest pain, syncope, dyspnea, and flushing) consistent with complement activation have been observed in <1% of patients administered Visudyne. Patients should be supervised during Visudyne infusion.

**Information for Patients**
Patients who receive Visudyne will become temporarily photosensitive after the infusion. Patients should wear a wristband to remind them to avoid direct sunlight for 5 days. During that period, patients should avoid exposure of unprotected skin, eyes or other body organs to direct sunlight or bright indoor light. Sources of bright light include, but are not limited to, tanning salons, bright halogen lighting and high power lighting used in surgical operating rooms or dental offices. Prolonged exposure to light from light-emitting medical devices such as pulse oximeters should also be avoided for 5 days following Visudyne administration.

If treated patients must go outdoors in daylight during the first 5 days after treatment, they should protect all parts of their skin and their eyes by wearing protective clothing and dark sunglasses. UV sunscreens are not effective in protecting against photosensitivity reactions because photoactivation of the residual drug in the skin can be caused by visible light.

Patients should not stay in the dark and should be encouraged to expose their skin to ambient indoor light, as it will help inactivate the drug in the skin through a process called photobleaching.

Following Visudyne treatment, patients may develop visual disturbances such as abnormal vision, vision decrease, or visual field defects that may interfere with their ability to drive or use machines. Patients should not drive or use machines as long as these symptoms persist.

**Drug Interactions**
Drug interaction studies in humans have not been conducted with Visudyne.

Verteporfin is rapidly eliminated by the liver, mainly as unchanged drug. Metabolism is limited and occurs by liver and plasma esterases. Microsomal cytochrome P450 does not appear to play a role in verteporfin metabolism.

Based on the mechanism of action of verteporfin, many drugs used concomitantly could influence the effect of Visudyne therapy. Possible examples include the following:

Calcium channel blockers, polymyxin B or radiation therapy could enhance the rate of Visudyne uptake by the vascular endothelium. Other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics and griseofulvin) could increase the potential for skin photosensitivity reactions. Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, ß-carotene, ethanol, formate and mannitol, would be expected to decrease Visudyne activity. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane $A_2$ inhibitors, could also decrease the efficacy of Visudyne therapy.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
No studies have been conducted to evaluate the carcinogenic potential of verteporfin.

Photodynamic therapy (PDT) as a class has been reported to result in DNA damage including DNA strand breaks, alkali-labile sites, DNA degradation, and DNA-protein cross links which may result in chromosomal aberrations, sister chromatid exchanges (SCE), and mutations. In addition, other photodynamic therapeutic agents have been shown to increase the incidence of SCE in Chinese hamster ovary (CHO) cells irradiated with visible light and in Chinese hamster lung fibroblasts irradiated with near UV light, increase mutations and DNA-protein cross-linking in mouse L5178 cells, and increase DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. Verteporfin was not evaluated in these latter systems. It is not known how the potential for DNA damage with PDT agents translates into human risk.

No effect on male or female fertility has been observed in rats following intravenous administration of verteporfin for injection up to 10 mg/kg/day (approximately 60- and 40-fold the human exposure at 6 mg/m$^2$ based on $AUC_{inf}$ in male and female rats, respectively).

**Pregnancy**
***Teratogenic Effects: Pregnancy Category C.***
Rat fetuses of dams administered verteporfin for injection intravenously at ≥10 mg/kg/day during organogenesis (approximately 40-fold the human exposure at 6 mg/m$^2$ based on $AUC_{inf}$ in female rats) exhibited an increase in the incidence of anophthalmia/microphthalmia. Rat fetuses of dams administered 25 mg/kg/day (approximately 125-fold the human exposure at 6 mg/m$^2$ based on $AUC_{inf}$ in female rats) had an increased incidence of wavy ribs and anophthalmia/microphthalmia.

In pregnant rabbits, a decrease in body weight gain and food consumption was observed in animals that received verteporfin for injection intravenously at ≥10 mg/kg/day during organogenesis. The no observed adverse effect level (NOAEL) for maternal toxicity was 3 mg/kg/day (approximately 7-fold the human exposure at 6 mg/m$^2$ based on body surface area). There were no teratogenic effects observed in rabbits at doses up to 10 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Visudyne should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

**Nursing Mothers**
Verteporfin and its diacid metabolite have been found in the breast milk of one woman after a 6 mg/m$^2$ infusion. The verteporfin breast milk levels were up to 66% of the corresponding plasma levels. Verteporfin was undetectable after 12 hours. The diacid metabolite had lower peak concentrations but persisted up to at least 48 hours.

Because of the potential for serious adverse reactions in nursing infants from Visudyne, a decision should be made whether to discontinue nursing or postpone treatment, taking into account the importance of the drug to the mother.

**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**
Approximately 90% of the patients treated with Visudyne in the clinical efficacy trials were over the age of 65. A reduced treatment effect was seen with increasing age.

**ADVERSE REACTIONS**
Severe chest pain, vasovagal and hypersensitivity reactions have been reported. Vasovagal and hypersensitivity reactions on rare occasions can be severe. These reactions may include syncope, sweating, dizziness, rash, dyspnea, flushing and changes in blood pressure and heart rate. General symptoms can include headache, malaise, urticaria, and pruritus.

The most frequently reported adverse events to Visudyne® (verteporfin for injection) are injection site reactions (including pain, edema, inflammation, extravasation, rashes, hemorrhage, and discoloration) and visual disturbances (including blurred vision, flashes of light, decreased visual acuity and visual field defects, including scotoma). These events occurred in approximately 10%-30% of patients. The following events, listed by Body System, were reported more frequently with Visudyne therapy than with placebo therapy and occurred in 1%-10% of patients:

| | |
|---|---|
| **Ocular Treatment Site:** | Blepharitis, cataracts, conjunctivitis/conjunctival injection, dry eyes, ocular itching, severe vision decrease with or without subretinal/retinal or vitreous hemorrhage |
| **Body as a Whole:** | Asthenia, fever, flu syndrome, infusion-related pain primarily presenting as back pain, photosensitivity reactions |
| **Cardiovascular:** | Atrial fibrillation, hypertension, peripheral vascular disorder, varicose veins |
| **Dermatologic:** | Eczema |
| **Digestive:** | Constipation, gastrointestinal cancers, nausea |
| **Hemic and Lymphatic:** | Anemia, white blood cell count decreased, white blood cell count increased |
| **Hepatic:** | Elevated liver function tests |
| **Metabolic/Nutritional:** | Albuminuria, creatinine increased |
| **Musculoskeletal:** | Arthralgia, arthrosis, myasthenia |
| **Nervous System:** | Hypesthesia, sleep disorder, vertigo |
| **Respiratory:** | Cough, pharyngitis, pneumonia |
| **Special Senses:** | Cataracts, decreased hearing, diplopia, lacrimation disorder |
| **Urogenital:** | Prostatic disorder |

Severe vision decrease, equivalent of ≥4 lines, within 7 days after treatment has been reported in 1%-5% of patients. Partial recovery of vision was observed in some patients. Photosensitivity reactions usually occurred in the form of skin sunburn following exposure to sunlight. The higher incidence of back pain in the Visudyne group occurred primarily during infusion.

The following adverse events have occurred either at low incidence (<1%) during clinical trials or have been reported during the use of Visudyne in clinical practice where these events were reported voluntarily from a population of unknown size and frequency of occurrence cannot be determined precisely. They have been chosen for inclusion based on factors such as seriousness, frequency of reporting, possible causal connection to Visudyne, or a combination of these factors:

| | |
|---|---|
| **Ocular Treatment Site:** | Retinal detachment (nonrhegmatogenous), retinal or choroidal vessel nonperfusion |
| **Nonocular Events:** | Chest pain and other musculoskeletal pain during infusion |

Store Visudyne between 20-25°C (68-77°F).

Visudyne hotline number **(1-877-736-2778)**

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predominantly classic lesions that were less than four disc areas. However, for larger lesions, only classic lesions demonstrated a treatment benefit from PDT.

The Visudyne® in minimally classic (VIM) trial compared standard versus reduced light fluence in PDT for patients with minimally classic subfoveal CNV. Standard fluence was 50J/cm$^2$ in previous studies while reduced fluence in the VIM study was 25J/cm$^2$. The 24-month data from the VIM study showed that 74% of patients receiving reduced fluence lost less than 15 letters versus 47% of those receiving standard fluence ($p=0.03$).[12] The Visudyne® in occult (VIO) study was designed to evaluate PDT in the treatment of occult lesions with no classic component. Early analysis of the two-year data from this study revealed that PDT treatment did not meet the primary end-point in this subgroup.

In addition to neovascular vessel closure, the free radicals and inflammatory response following PDT may induce localized vascular endothelial derived growth factor (VEGF) production, and damage the choriocapillaris and retinal pigment epithelium.[13]

sterile and infectious endophthalmitis, increased susceptibility to infection, elevated intra-ocular pressure, and retinal detachment.[20-23]

Alternative treatments to PDT have now focused primarily on intra-vitreal injections of anti-angiogenic therapy focusing on the VEGF molecule. Of these, ranibizumab, a recombinant humanized antibody to VEGF, has shown the most promise in randomized controlled trials. When compared directly with PDT with verteporfin (ANCHOR phase III trial at 12 months), 94% and 96% of patients, treated with ranibizumab 0.3mg and 0.5mg respectively, achieved the primary efficacy endpoint of maintaining or improving visual acuity versus 64% of those treated with PDT ($p<0.0001$).[24]

Patients receiving intra-vitreal anti-VEGF treatment are often on regular dosing schedules of every 4–6 weeks. It is unclear what particular dosing schedule is optimal or if repeated injections are necessary for complete and persistent resolution of CNV. Frequent injections place patients at a small but repeated risk of endophthalmitis and also place a significant burden

*Age-related macular degeneration is the leading cause of severe vision loss in individuals aged greater than fifty years.*

The anti-inflammatory properties of corticosteroids are well known and intra-ocular triamcinolone acetonide has recently been found to be an encouraging adjunct to PDT in patients with CNV secondary AMD.[14] It is possible that the favorable effects of triamcinolone are due to the steroid's intrinsic anti-angiogenic properties and the downregulation of inflammatory pathways which are inherent to neovascular complexes.[15-18]

Triamcinolone may also be beneficial by limiting cytokine-induced edema and VEGF production that ensues in retinal tissue adjacent to PDT treated areas.[13,19] Spaide et al. 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 treatment-naïve CNV patients and 13 patients with previous PDT treatment. A 2.5 line mean improvement in visual acuity was observed in the newly treated group; while the previously treated group improved a mean of 0.44 lines.[14] Potential complications of intra-vitreal triamcinolone include

on the healthcare system due to repeated follow up visits. PDT may thus still play an important role in the form of combination therapy, by reducing the need for multiple retreatments.

The on-going FOCUS phase I/II trial compares PDT versus PDT plus ranibizumab. Preliminary one-year data showed that patients treated with PDT plus ranibizumab were less likely to lose ≥15 letters (90% v 68%; $p=0.0003$) than those receiving PDT alone.[25]

The treatment of neovascular AMD continues to be a therapeutic challenge. The development of PDT with verteporfin was a major step in treating subfoveal lesions without the use of thermal laser. Newer treatments such as intra-vitreal anti-VEGF treatment now have an integral role in treating neovascular AMD, but have drawbacks of frequent dosing schedules, infection risk, and high healthcare costs. Further studies are needed to determine if PDT in combination with these agents will play an increasing role in the future treatments of CNV. ■

## References


1. *Bressler NM, Bressler SB, Fine SL, "Age-related macular degeneration",* Surv Ophthalmol *(1988); 32 (6):pp. 375–413.*
2. *Ferris III FL, Fine SL, Hyman L, "Age-related macular degeneration and blindness due to neovascular maculopathy", Arch* Ophthalmol *(1984); 102:pp. 1,640–1,642.*
3. *Bressler NM, Bressler SB, Congdon NG, et al., "Potential public health impact on age-related eye disease study results: AREDS report no. 11",* Arch Ophthalmol *(2003); 121:pp. 1,621–1,624.*
4. *Macular Photocoagulation Study Group, "Subfoveal neovascular lesions in age-related macular degeneration: guidelines for evaluation and treatment in the macular photocoagulation study",* Arch Ophthalmol *(1991); 109:pp. 1,242–1,257.*
5. *Schmidt-Erfurth U, Hasan T, "Mechanisms of action of photodynamic therapy with verteporfin for the treatment of age-related macualar degeneration",* Surv Ophthalmol *(2000); 45 (3):pp. 195–214.*
6. *Scott LJ, Goa KL, "Verteporfin",* Drugs Aging *(2000); 16:pp. 139–146.*
7. *Bressler NM, "Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic Therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two year results of 2 randomized clinical trials-TAP report 2",* Arch Ophthalmol *(2001); 119:pp. 198–207.*
8. *Treatment of Age-related macular degeneration with Photodynamic therapy Study Group, "Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one year results of 2 randomized clinical trials-TAP report"* Arch Ophthalmol *(1999); 117:pp. 1,329–1,345.*
9. *Verteporfin in Photodynamic Therapy Study Group, "Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization: VIP report no. 2",* Am J Ophthalmol *(2001); 131:pp. 541–560.*
10. *Bressler NM, "Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization-verteporfin in photodynamic therapy report no. 2",* Am J Ophthalmol *(2002); 133:pp. 168–169.*
11. *Blinder KJ, Bradley S, Bressler NM, et al., "Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1",* Am J Ophthalmol *(2003); 136:pp. 407–418.*
12. *Azab M, Boyer DS, Bressler NM, "Visudyne in Minimally Classic Choroidal Neovascularization Study Group. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration: 2-year results of a randomized clinical trial",* Arch Ophthalmol *(2005); 123:pp. 448–457.*
13. *Schmidt-Erfurth U, Schlotzer-Schrehard U, Cursiefen C, et al., "Influence of photodynamic therapy on expression of vascular endothelial growth factor (VEGF), VEGF receptor 3, and pigment epithelium-derived factor",* Invest Ophthalmol Vis Sci *(2003); 44:pp. 4,473–4,480.*
14. *Spaide RF, Sorenson J, Maranan L, "Photodynamic therapy with verteporfin combined with intravitreal injection of triamcinolone acetonide for choroidal neovascularization",* Ophthalmology *(2005); Feb; 112(2):pp. 301–304.*
15. *Antoszyk AN, Gottlieb JL, Machemer R, Hatchell DL, "The effects of intravitreal triamcinolone acetonide on experimental pre-retinal neovascularization",* Graefes Arch Clin Exp Ophthalmol *(1993); 231:pp. 34–40.*
16. *Ciulla TA, Criswell MH, Danis RP, Hill TE, "Intravitreal triamcinolone acetonide inhibits choroidal neovascularization in a laser-treated rat model",* Arch Ophthalmol *(2001); 119:pp. 399–404.*
17. *Penfold PL, Wen L, Madigan MC, et al., "Triamcinolone acetonide modulates permeability and intercellular adhesion molecule-1 (ICAM-1) expression of the ECV304 cell line: implications for macular degeneration",* Clin Exp Immunol *(2000); 121:pp. 458–465.*
18. *Wang YS, Friedrichs U, Eichler W, et al., "Inhibitory effects of triamcinolone acetonide on bFGF-induced migration and tube formation in choroidal microvascular endothelial cells",* Graefes Arch Clin Exp Ophthalmol *(2002); 240:pp. 42–48.*
19. *Rogers AH, Martidis A, Greenberg PB, Puliafito CA, "Optical coherence tomography findings following photodynamic therapy of choroidal neovascularization",* Am J Ophthalmol *(2002); 134:pp. 566–576.*
20. *Danis RP, Ciulla TA, Pratt LM, Anliker W, "Intravitreal triamcinolone acetonide in exudative age-related macular degeneration",* Retina *(2000); 20:pp. 244–250.*
21. *Gillies MC, Simpson JM, Billson FA, et al., "Safety of an intravitreal injection of triamcinolone: results from a randomized clinical trial",* Arch Ophthalmol *(2004); 122:pp. 336–340.*
22. *Jonas JB, Kreissig I, Hugger P, et al., "Intravitreal triamcinolone acetonide for exudative age related macular degeneration",* Br J Ophthalmol *(2003); 87:pp. 462–468.*
23. *Bucher RS, Hall E, Reed DM, et al., "Effect of intravitreal triamcinolone acetonide on susceptibility to experimental bacterial endophthalmitis and subsequent response to treatment",* Arch Ophthalmol *(2005); May, 123(5):pp. 649–653.*
24. *Rosenfeld PJ, Rich RM, Lalwani GA, "Ranibizumab: Phase III Clinical Trial Results",* Ophthalmol Clin North Am *(2006); Sep; 19(3):pp. 361–372.*
25. *"New data from two leading clinical studies show Lucentis® is first therapy to improve vision in patients with wet age-related macular degeneration (AMD)", June 18, 2005, http://dominoext.novartis.com*