

PHOTODYNAMIC THERAPY FOR AGE-RELATED MACULAR DEGENERATION: A NEW TREATMENT OPTION

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What is age-related macula degeneration (AMD)?

It is a degenerative eye disease that can cause severe irreversible loss of central vision in patients aged 50 and above. As the name implies, it occurs in the elderly.

Why is age related macula degeneration a public health issue?

Worldwide, age related macula¹ degeneration is the most common cause of legal blindness in individuals older than age 60. Its incidence is proportional to increasing age¹. It occurs in 10% of patients aged 66 – 74 years compared to 30% of patients aged 75 – 85 years of age². It assumes great importance in developed countries where people live longer because of better health care and the proportion of elderly increases over time.

What is the impact of AMD on patient's lifestyle?

Patients will experience increasing difficulty in performing normal daily tasks such as reading, telling the time and distinguishing colours or facial expressions³. This is due to a loss of central vision. As a further consequence of this loss of central vision, patients are less mobile and more prone to falls. Evidence shows that patients with wet AMD have a 70% increased risk of falling at least twice in 12 months⁴. Visual impairment can lead to anxiety depression, anger, reduced drive, tiredness and confusion⁵. Quality of life is also reported to be lower⁶.

What are the types of AMD?

AMD can be classified into either dry (non-neovascular) or wet (neovascular) types. The importance of this classification lies in the fact that less than 10 – 20% of patients have the wet type of AMD but the wet type of AMD (being neovascular) results in 90% of the severe loss of vision⁷. To put it in another perspective, 80% to 90% of severe visual loss in AMD is due to wet AMD^{8,9}. Dry AMD occurs in the form of drusen or pigmentary changes in the macular. Wet AMD presents with blood, hard exudates and fluid. These signs are picked up on slit lamp biomicroscopy.

Disease Progression of wet AMD

For patients with neovascular AMD, the visual prognosis is poor in the absence of treatment. Progression of neovascular AMD causes a rapid deterioration in visual acuity and contrast sensitivity. This in turn affects functional ability.

What investigations are required in the treatment of AMD?

Fluorescein angiography of the fundus is essential to confirm the diagnosis of wet AMD as well as to locate the position and type of choroidal neovascularisation (CNV). Fluorescein angiography detects the leakage of fluorescein dye from CNV. Other imaging techniques that can augment the diagnosis include indocyanine-green angiography (ICG-A). ICG-A is especially helpful when blood masks the fluorescence in fluorescein angiography.

TERMINOLOGY OF TYPES OF CNV

CNV can be divided into either classic or occult based on angiographic findings. Occult can be further subdivided into Type I or Type II.

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What were the treatments options available before the advent of photodynamic therapy (PDT)?

Before the advent of PDT, the mainstay of treatment of CNV was laser photocoagulation. The benefits of laser photocoagulation are proven in the Macula Photocoagulation Study Group^{6,10,11}. This showed that laser photocoagulation could reduce the risk of severe visual loss in patients with well defined extrafoveal, juxtafoveal and subfoveal CNV.

However, there were three drawbacks. The first was, when subfoveal CNVs were treated with laser, eyes would lose approximately three lines of vision immediately after treatment¹². This was due to the concomitant destruction of central vision. Secondly, there was a high incidence of persistent CNV and recurrent CNV after laser photocoagulation which caused further loss of vision after laser^{6,13,14}. Thirdly, only 13 – 26% of patients were eligible for laser photocoagulation under the MPS criteria¹⁵ and one of these criteria was that the CNV had to be well defined. This meant that many eyes were not treatable.

What are the other treatment options that have been used besides laser photocoagulation?

Submacular surgery, antiangiogenic therapy, radiation therapy and transpupillary thermotherapy have all been tried with varying success rates.

What is photodynamic therapy?

It is the first proven drug therapy available to treat wet AMD¹⁶. PDT is a 2-step process. It involves the intravenous administration of a light activated photosensitive drug (verteporfin) and its subsequent activation by a specific wavelength of

light (689nm) delivered via a non-thermal laser (as opposed to laser photocoagulation, which is thermal in nature). Following intravenous injection, there is enhanced uptake of verteporfin by neovascular endothelial cells in the CNV. Following activation by the laser, there is production of singlet and reactive oxygen radicals that selectively damage neovascular endothelial cells by causing thrombus formation and CNV occlusion. This allows specific destruction of CNV while sparing surrounding normal tissue¹⁶. This is especially useful in the treatment of subfoveal CNV. It destroys CNV vessels with minimal effect on the sensory retina and the RPE unlike laser photocoagulation.

What is the evidence in support of PDT?

The treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP)^{17,18} Study^{Report No 1 & 2} Group results demonstrated that the visual acuity benefits of verteporfin therapy for AMD patients with predominantly classic CNV subfoveal lesions are safely sustained for up to 2 years. The benefits of treatment were greatest in the subgroup with predominantly classic CNV. More treated eyes lost fewer than 15 letters. The average visual acuity in treated eyes was better. The average loss of vision from baseline was also less. More treated patients had improvement of vision. Fewer treated patient had losses of 6 lines or more. The conclusion was that PDT can preserve vision in a significant number of patients. Figure 1 shows the effective treatment of CNV by photodynamic therapy.

VIP report No. 1 showed that PDT with verteporfin can safely increase the chances of stabilising or improving vision in patients with subfoveal CNV from pathologic myopia compared with placebo treatment¹⁹.

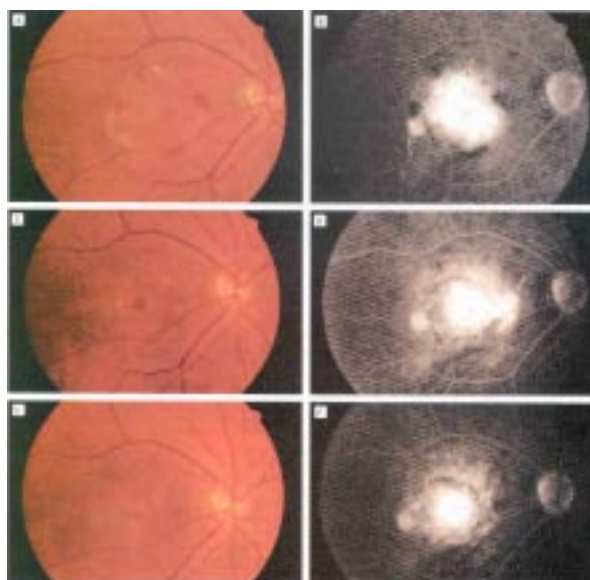


Figure 1: Example of verteporfin treatment of subfoveal choroidal neovascularization (CNV) in which no progression of classic CNV was noted by the month 12 examination beyond the area of the lesion identified at baseline. **A:** Color fundus photograph at baseline shows subretinal fluid under the center of the foveal avascular zone, with subretinal hemorrhage and lipid. **B:** Late-phase fluorescein angiogram at baseline shows leakage from classic (straight arrow) and occult (curved arrow) CNV. **C:** Color fundus photograph 3 months after initial treatment shows marked decrease in subretinal fluid, hemorrhage, and lipid. **D:** Late-phase fluorescein angiogram shows a decrease in the area of leakage within the area of the lesion identified at baseline, with some progression of leakage noted along the nasal aspect of the lesion (arrow). **E:** Color fundus photograph 12 months after initial treatment with retreatments applied at 3-, 6-, and 9-month follow-up examinations shows complete resolution of the subretinal fluid, hemorrhage, and lipid, with small area of fibrosis within the area of the lesion identified at baseline. **F:** Late-phase fluorescein angiogram shows some staining and questionable leakage within the central area of the lesion identified at baseline and no progression of leakage from the CNV boundaries identified at baseline.

(Figure 1 Photos courtesy of Archives of Ophthalmology)

VIP report No. 2 showed that PDT with verteporfin significantly reduced the risk of moderate and severe visual loss in subfoveal CNV composed of occult with no classic CNV²⁰.

What are the complications associated with PDT treatment?

Adverse effects of PDT treatment include transient visual disturbances, injection site pain, edema, inflammation or haemorrhage, transient photosensitivity reactions, severe visual loss within 7 days of treatment and back pain²¹.

What precautions do patient have to take after PDT?

Patients should take precautions to avoid exposing their skin to direct sunlight or bright halogen indoor light for 2 days. If drug extravasation occurs, infusion should be stopped, cold compression applied and the affected skin area should be protected from direct light to prevent a burn-like effect²¹.

If the patient has a severe decrease in vision of 4 lines or more within one week following treatment, no additional treatment is performed until recovery of vision has occurred²¹.

Verteporfin is contraindicated in patients with porphyria or a known allergy to the drug²¹. Verteporfin therapy should be carefully considered for use in patients with liver impairment²¹.

What can the family physician do?

Currently, the American Academy of Ophthalmology recommends an eye examination every one to few years for people over 65 years of age even in the absence of ocular symptoms²². Since age-related macular

degeneration occurs in people 50 years and above, it is actually logical for family physicians to encourage regular eye examinations when people reach this age.

An amsler grid is actually a useful examination technique to detect early AMD. The family physician or even the patient^{23,24} can easily do this. The rapid progression of neovascular AMD makes detection at an early stage likely to reduce the high risk of severe visual loss. The results of patients treated with laser photocoagulation showed that more patients with neovascular AMD are potentially treatable when symptoms have been present for less than two weeks²⁵. Since patients often present to primary care physicians, it is the onus of these physicians to refer them to the ophthalmologist in a timely manner.

CONCLUSION

PDT represents a major advance in the treatment of CNV and is especially useful in subfoveal CNV with a predominately classic component or occult CNV without classic component. It represents a major advancement in the treatment of subfoveal CNV and will impact greatly on a patient's quality of life.

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ABSTRACT

Age-related macular degeneration of the wet type causes severe visual loss. However, until the advent of photodynamic therapy, only a small proportion of patients were eligible for treatment by laser photocoagulation.

Photodynamic therapy presents a new treatment option for the wet type of age-related macular degeneration previously not treatable by laser. It represents a major advancement in the therapy of age-related macular degeneration.