

## ARMD and CNV

### Age Related Macular Degeneration (ARMD), Choroidal New Vessels (CNV) and Other CNV Disorders

ARMD is the most prevalent of the causes of choroidal new vessels (CNV). Because the abnormality affects the macula, it can cause severe vision loss. CNV from ARMD is affecting an increasing number of people as the average age of the world population increases, and is the most frequent cause of severe vision loss in people over 50 years of age.



In a normal retina, the retinal pigment epithelium (RPE), shown in arrow, separates the choroidal layer from the retinal neurons or photoreceptors. The choroidal layer provides the blood supply to the retina. When the RPE is intact, it blocks the inward migration of small molecules from the choroidal vessels into the subretinal space. (All graphics/pictures courtesy of Novartis Ophthalmics, Inc).



In patients with early ARMD, accumulation of debris with thickening of the basement membrane of the RPE (Bruch's membrane) are the first clinically detectable signs (arrowed). These lesions are called Drusen. Vision may be good at this stage. (Reproduced with courtesy of Novartis Ophthalmics, Inc).



In the wet form of ARMD (neovascular ARMD), the development of drusen is associated with breaks in Bruch's membrane. These breaks may provide sites through which new abnormal blood vessels, or CNV, grow and proliferate from the underlying choroidal vessels. (Reproduced with courtesy of Novartis Ophthalmics, Inc).



These new abnormal blood vessels are fragile and leak blood and fluid, which can lead to detachment of the RPE or neurosensory retina, formation of a fibrovascular scar, and a loss of outer retinal tissue. These changes lead to distorted vision and may result in profound, irreversible central vision loss.

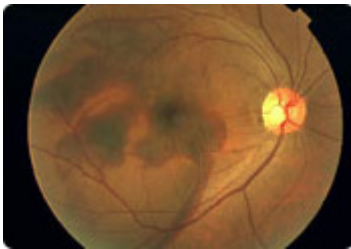
(Reproduced with courtesy of Novartis Ophthalmics, Inc).

### Polypoidal Choroidal Vasculopathy: Our Local Variant of ARMD?

Although typical form of ARMD (drusen, CNV and its sequelae) is seen among the elderly in our population, choroidal bleeding and CNV occurs more frequently in another distinct clinical manifestation that has a differing characteristics when compared to ARMD. This variant of maculopathy is referred to as polypoidal choroidal vasculopathy (PCV).

Typically, PCV is associated with more leakages and subretinal bleeding, and other features of ARMD such as drusen or mottling of the RPE are absent. Another distinguishing characteristic is that, unlike features of ARMD which are usually present in both eyes in an individual with ARMD, the fellow eye in a patient with PCV often appears completely normal. There is typically absence of drusen in the eye with PCV.

ARMD is seen in individual above the age of 50. PCV often occurs in the population of the same age-group. However, in PCV, frequently patients in their 40s were also affected.



Picture of the right eye of an Asian patient with typical massive subretinal bleeding from polypoidal choroidal vasculopathy, presumably a variant of ARMD, seen much more frequently in our local Asian population. Note absence of drusen.

The natural history and treatment of PCV in our population is not well defined at this stage. Until further knowledge is available regarding this entity, we generally employ the same treatment as ARMD in such situation. Sometimes,

vitrectomy surgery to drain the massive bleeding under the retina is used to limit the retina damage.

### The symptoms of ARMD

In mild cases, there may be little visual symptoms. However, with increasing disease severity the patient may notice distortion in vision or failing central vision. Reading or watching TV will be soon a difficulty, although the patient with ARMD can still navigate independent.

### Diagnosis of CNV

A dilated fundus examination by an Ophthalmologist is essential to make the diagnosis. Frequently, your eye doctor will order a test call fluorescein angiography to confirm the presence of a CNV complex, and to determine whether the lesion can be treated with laser treatment.

### Current Treatment for CNV

The mainstay of treatment is antiVEGF therapy laser and photodynamic treatment. Certain cases that is not suitable for either of these treatments may require surgical treatment. Most surgical treatments options are considered 'investigational' at this stage, although good results had been reported in many patients.

### Anti-Vascular Endothelial Growth Factor (AntiVEGF) Therapy for Choroidal Neovascularisation (CNV) Diseases

Since March 2006, we have been able to offer AntiVEGF treatment to patients with CNV due to AMD and other diseases. The two forms of AntiVEGF that are currently available are **Ranibizumab (Lucentis®)** and **Bevacizumab (Avastin®)** intravitreal injections.

AntiVEGF had been shown to be efficacious both in improving vision, and prevention of disease progression when given in a monthly intravitreal injection regime. In two large multicentre studies, (one comparing to Lucentis® sham injection, and another, a head to head comparison to PDT (Visudyne®) treatment), **about 35% of patients gained 2 to 3 lines of vision** (vs 11% in controls) and **95% of patients had stability in vision** (vs 63% in control) when they received Lucentis® intravitreal injections (the Phase III MARINA and ANCHOR trials, in publication).

Lucentis had received FDA approval on 30th June 2006. The cost of a single injection is about

RM4500 currently.

A related AntiVEGF, **Bevacizumab (Avastin®)** is also used extensively in similar manner although the drug was developed and indicated for colorectal cancer chemotherapy. The *off-label use* of Bevacizumab in the eye had been shown to be safe and efficacious in case series published previously. The effects are *similar* to Lucentis® although currently there are no randomized control trials to compare Avastin® to sham control, or PDT, nor there any control trials comparing Lucentis® and Avastin® to see if Avastin is similarly efficacious.

The push for Avastin® injection was primarily driven by the fact that Lucentis® at that time was not available for clinical use (but results from phase II and III trials was so encouraging that retinal specialists are compelled to try something similar while awaiting FDA approval for Lucentis®) and that Avastin® is much cheaper (RM1000 per injection) as compared to Lucentis®. Lucentis®, the Fab fragment of an antiVEGF antibody, was developed from the monoclonal antibody Bevacizumab®.

More importantly, at time of writing, we have given about 100 Lucentis® and 450 Avastin® injections, and our results mirrored the experience reported elsewhere. AntiVEGF injection is currently the treatment of choice for vast majority of patients with CNV and this is sometimes used in combination with PDT treatment.

In summary, patients with AMD/CNV and other disorders with CNV can now expect a greater likelihood in their chance of having an improvement in vision (which was marginal even with PDT (Visudyne®) treatment previously) and also virtually complete stabilization of vision when treated with AntiVEGF such as Lucentis®. More research is currently ongoing to determine the effect of combination treatments (i.e. AntiVEGF with PDT) on the durability and efficacy of such treatment.

#### **Role of Vitamins (antioxidants) in ARMD**

In patients with extensive intermediate drusen, large drusen, non-central geographic atrophy, or advanced ARMD or vision loss due to ARMD in one eye, supplementary antioxidants plus zinc should be considered. The Age-related Eye Disease Study Group in 2001 had reported a one-third risk reduction with respect to development of severe ARMD in patients who took the supplements over a 6 year period. The formulation used in the study was: Vitamin C 500mg; Vitamin E 400 IU; beta carotene 15mg; Zinc (80mg of zinc oxide) and copper (2mg as cupric oxide).

Patients who are current smokers or previous smokers should not take this supplement as beta carotene may increase the risk of lung cancer or cardiovascular diseases in this group of patients.

#### **Treatment Options in PCV**

What is known is that the natural history and treatment for PCV is not well established. This is an area of intense research. However, if there is demonstrable CNV on angiogram, the treatment options as used in CNV due to ARMD may be effective.

#### **Thermal Laser Therapy**

Thermal laser treatment is effective to treat CNV that is not too large, well defined, and located outside the macular region of the retina. This is a very effective treatment and has the advantage of being very economical. However, some patients may need recurrent treatment.

#### **Photodynamic Therapy for Age-Related Macular Degeneration**

Age-related macular degeneration (AMD) is a deterioration or breakdown of the macula. The macula is a small area at the center of the retina in the back of the eye that allows us to see fine details clearly and perform activities such as reading and driving. In the wet form of AMD, abnormal blood vessels may grow in a layer beneath the retina, leaking fluid and blood and creating distortion or a large blind spot in the center of your vision.

Photodynamic therapy (PDT)--an outpatient procedure involving the use of a special light-activated drug--may be used to treat some patients with the wet form of AMD with fewer visual side effects than other treatments. The benefit of PDT is that it inhibits abnormal blood vessel leakage associated with

wet macular degeneration, limiting damage to the overlying retina.

In PDT, the inactive form of the drug is usually injected into a vein in the arm, where it travels to and accumulates in abnormal blood vessels under the center of the macula. A special low-intensity laser light targeted at the retina activates the drug only in the affected area, damaging the abnormal blood vessels under the retina and leaving normal blood vessels intact.

Patients who are treated with PDT will become temporarily sensitive to bright light (photosensitive). Care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for several days.

PDT therapy is not effective for treatment of the **dry form** of AMD, caused by aging and thinning of the tissues of the macula. While photodynamic therapy may preserve vision for many people, PDT may not stop vision loss in all patients. The abnormal blood vessels may regrow or begin to leak again. Every three months, a repeat examination including a fluorescein angiogram (a dye test) is required. Multiple PDT treatments may be necessary.

Massive subretinal blood may be drained surgically if warranted. In limited fresh subretinal bleeding, there are anecdotal reports that injection of a special medical grade gas into the eyeball followed by face-down posturing (as much as possible, day and night) for a week can displace the blood from the macular, thus limiting scarring response and vision loss.

## Screening