Age-related macular degeneration

Age-related macular degeneration is the leading cause of irreversible loss of vision in the west, accounting for up to 50% of all blind registrations. With an ageing population age-related macular degeneration will have a discernible impact on society and the NHS. This article outlines our current level of understanding of age-related macular degeneration and treatment strategies.

The incidence of age-related macular degeneration (ARMD) increases with each decade over the age of 50 years to affect 20–30% of over-75-year-olds (Evans and Wormald, 1996). Irreversible impairment of the macula occurs resulting in progressive loss of central vision. There are 214 000 people in the UK with visual impairment, suitable for blind registration, caused by ARMD and this is expected to rise to 239 000 by 2011 (Owen et al, 2003). Much progress in our understanding has been made over the past decade but exact causes and mechanisms of this condition remain a challenge.

Type of disease

Until a few months ago ARMD was considered a degenerative disease that typically affected the macula (Young, 1987). The macula is a small area of central retina that is important for reading, colour and fine vision. The standard description given was of accumulation of lipofuscin and other waste products from retinal metabolism in the retinal pigment epithelial (RPE) cells and Bruch's membrane. Thickening of Bruch's membrane ensues, which in turn leads to a decrease in metabolic exchange between choroid and RPE. The retina is metabolically dependent on this exchange and, as a result, degeneration of the outer neuroretina, RPE, Bruch's membrane and the choroid occur.

This has been revolutionized by the discovery that approximately 50% of the risk of ARMD is attributed to a single gene which encodes for complement factor H (CFH) (Hageman et al, 2005). This is unexpected in that ARMD has now become a strongly inherited disease and the pathophysiology may well be one of chronic inflammation. As these findings are very recent a widely accepted description of the nature of ARMD has not been formed.

Risk factors

Of all modifiable risk factors, smoking is the most consistent in the literature. There is a dose-dependent relationship with ARMD, particularly with the neovascular form of ARMD, and this risk remains in ex-smokers. The relative risk in women smoking 25 cigarettes a day is 2.4 (95% confidence interval (CI) = 1.4–4.0 compared with women who never smoked) (Seddon et al, 1996). The other major risk factors are not modifiable. These include age, family history, and the presence of a mutation in the CFH gene.

Sunlight exposure is complex to investigate and as a result conflicting data appear in the literature; however, an effect cannot be excluded. A possible protective effect of aspirin and statins has been suggested.

Cardiovascular disease is associated with increased risk of advanced ARMD and hypertension may also be related. Physical activity and lower body mass index have been associated with a reduced risk. Diets rich in antioxidants reduce the risk of the neovascular form of ARMD. This is discussed further in the treatment section.

The Beaver Dam study in 1992 (Klein et al, 1992) showed that women have twice the incidence of ARMD. Studies in post-menopausal women and women on hormone replacement therapy suggest oestrogen may be protective but the association is not strong. Furthermore, Caucasians are affected more than other races. Early ARMD does occur in Afro-Caribbeans but the advanced form of the disease is less common in this group. Socioeconomic status is not associated with ARMD.

Diagnosis and classification of ARMD

ARMD is a clinical diagnosis in people over the age of 50 years. Diagnosis and classification depends on clinical features and fluorescein angiogram. Early disease is age-related maculopathy (ARM) and late disease is age-related macular degeneration (AMD) (Bird et al, 1995).

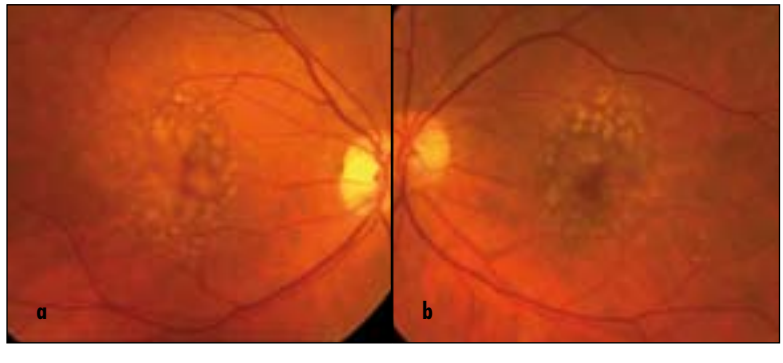
Early disease: ARM

The first sign of ARM is the appearance of yellow, subretinal deposits clustered in the macula (*Figure 1*) called

Mr Ahmed N El-Amir *is Specialist Registrar in Ophthalmology,* **Mr Mandeep S Sagoo** *is Specialist Registrar in Ophthalmology and* **Mr Lyndon da Cruz** *is Consultant Ophthalmic Surgeon in the Medical Retina and Vitreo-retinal Services, Moorfields Eye Hospital, London EC1V 2PD*

Correspondence to: Mr AN El-Amir

Figure 1. a. Right and (b) left eye showing soft drusen underneath the macula. Drusen appear as yellow accumulations usually discreet but sometimes with indistinct borders that are the first clear sign of early macular degeneration. This type of drusen carries high-risk of progression to wet macular degeneration.



drusen. Pigmentary changes in the RPE also occur, representing RPE atrophy and hypertrophy.

Drusen can have different appearances in size, consistency and number. These differences denote risk of progression to late disease and are therefore important. Drusen contain a heterogeneous combination of substances including proteins associated with chronic and acute inflammatory responses, and lipids. They are deposited between RPE and Bruch's membrane.

Patients with ARM often have good vision.

Late disease: AMD

AMD is usually divided into two main groups: wet (exudative, neovascular) and dry (atrophic). Wet AMD accounts for up to two thirds of late disease and 15% of all patients. Wet AMD is suspected clinically when blood, lipid exudates and subretinal fluid are seen (*Figure 2*). For the diagnosis to be confirmed, however, a fluorescein angiogram needs to be carried out.

Angiography further allows the classification of wet disease. The most important and commonest form is the presence of subretinal choroidal neovascular membranes (CNV). There are other features such as retinal angiomatous proliferation and RPE detachment (*Figure 3*) but these are uncommon and untreatable at present. Therefore, the discussion will be limited to the nature and treatment of CNV.

CNV extend from the choroid, through defects in Bruch's membrane to lie underneath the RPE. The new vessels can break through RPE to lie between RPE and neuroretina. These new vessels are fragile and abnormal and can cause sub-RPE or subretinal haemorrhage, and/or exudation of fluid and lipid. Each of these can lead to acute central visual decline. Eventually the overlying macula loses its function and forms a hypertrophic scar (disciform scar), the end stage of the wet form of AMD (*Figure 4*).

Dry AMD accounts for 85% of all cases and it involves RPE cell death with overlying photoreceptor atrophy. This results in central or para-central scotomas. Classically it is slowly progressive and better tolerated because of the gradual nature of visual loss.

Figure 2. An example of a patient with a severe wet degeneration in the right eye. a. There are areas of haemorrhage, fluid leakage and there is a retinal pigment epithelial (RPE) tear. b. Fluorescein angiography clearly demonstrates the RPE tear as well as leakage from the new and abnormal blood vessels.

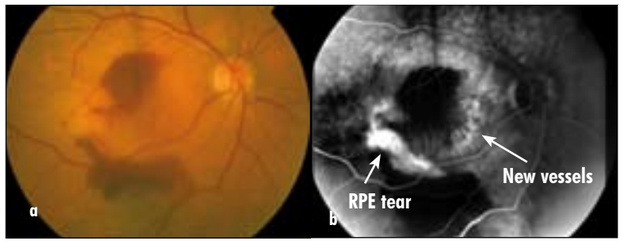
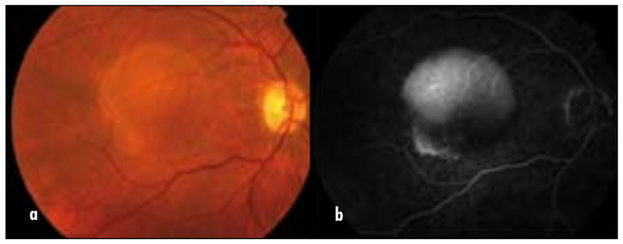


Figure 3. A pigment epithelial detachment. This is one form of wet degeneration that is characterized by (a) a dome-shaped collection of fluid under the macula. b. This shows up clearly on fluorescein angiography with pooling of the dye in the same area.



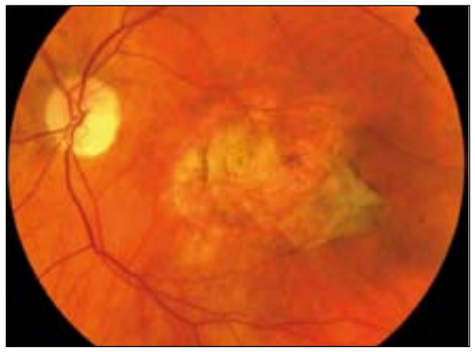
History, examination and investigations

Patients usually present complaining of painless loss of vision, metamorphopsia (distortion) and scotomas. The classic description is of straight lines becoming blurred and distorted. Visual acuity is assessed for near and distance and the presence of scotomas documented. The Amsler grid is used to highlight and document metamorphopsia.

All patients presenting with vision loss in this age group will have a dilated eye examination in order to identify or exclude the clinical features of ARMD. If there is a suspicion of wet AMD a fluorescein angiogram is arranged. This is the only way to diagnose CNV, define its subtype and locate its position. The latter two features define whether the CNV is treatable or not. Fluorescein may cause nausea, vomiting and rarely anaphylaxis and therefore appropriate consent and facilities need to be available.

If new vessels are found under the macula they are measured in terms of area relative to blood and subtyped based on their leakage behaviour on the angiogram. The two types of membranes are 'occult' and 'classic' and they can be found in the same lesion. The description of CNV, therefore, consists of a term to express its extent and type. This will define, as discussed later, which of the currently available approved treatments to offer.

Figure 4. Macular scar in the left eye of a patient who has had wet macular degeneration. The scar is the end point lesion that denotes total macular damage and loss of central vision.



Optical coherence tomography is a new non-invasive retinal imaging technique. It provides a cross-sectional picture of the retina allowing the visualization of anatomical layers. Despite its advantages, optical coherence tomography cannot replace dynamic angiography in the investigation and management of CNV, but remains a useful adjunct.

Treatments

Currently, treatment for ARMD falls in two areas: first, preventing progression from ARM to AMD, and second, the treatment of CNV (the presence of which is proven by fluorescein angiography).

Prevention of progression

The Age-Related Eye Disease Study (AREDS) was a large multicentre study with approximately 3600 participants (AREDS Research Group, 2001). The average follow up was 6.3 years. The aim was to investigate whether daily high dose antioxidants vitamin C (500 mg), vitamin E (400 IU) and beta-carotene (15 mg) as well as zinc (80 mg) could decrease the progression from early disease (ARM) to late neovascular AMD. Copper 2 mg was added to prevent anaemia.

In patients with at least moderate disease in one eye, e.g. large drusen, extrafoveal atrophy and those with advanced wet AMD in the other eye, the risk of developing advanced AMD in the study eye at 5 years was 28% for placebo, 23% for antioxidants alone, 22% for zinc alone and 20% for zinc and antioxidants. It was only in the last group who received antioxidants and zinc in which the odds ratio reduction was statistically significant (odds ratio = 0.72; 99% CI = 0.52–0.98). Therefore, in high-risk ARM there was a proven preventative effect of the antioxidants and zinc.

This treatment is the only one of proven benefit for patients with ARM. Although this regimen is safe, beta-carotene has been associated with a higher risk of lung cancer in current smokers and ex-smokers. Thus, beta-carotene is excluded from the combination in smokers and ex-smokers.

Treatment for late wet AMD

Argon laser

The first proven treatment for CNV in late wet AMD was destruction of the new vessels with thermal argon laser. The Macular Photocoagulation Study Group (1991) demonstrated that in cases with vessels that were away from the centre of the macula (extrafoveal), or worse near the centre (juxtafoveal), there was long-term benefit to sight if the vessels were obliterated by argon laser. Laser destroys the overlying retina but as long as the centre of the macula (fovea) is not lasered this is often tolerated by patients. The main problem is that recurrence of vessels can occur in up to 60% of treated cases and this almost always occurs under the fovea. This treatment is still used for extrafoveal CNV.

Photodynamic therapy

CNV under the fovea posed a problem in that destructive thermal laser to the fovea would cause further loss of sight. This has been resolved with the advent of photodynamic therapy (PDT). This is a laser technique that renders new vessels susceptible using a sensitizing dye and a low intensity laser to treat the vessels. The retina is spared, as the laser intensity is low. The treatment has to be carried out repeatedly at intervals of 3 months for optimal effect. The aim is to halt or slow the disease progression.

In 2003 the National Institute for Clinical Excellence (NICE) issued guidance on the use of PDT based on two major studies. The Treatment of AMD with Photodynamic Therapy study (1999) was the first multicentre randomized clinical trial. The results showed that for classic subfoveal CNV lesions at 12 months, 61% treated with PDT had lost fewer than 15 letters of visual acuity from baseline compared with 46% in the placebo group. The Verteporfin in Photodynamic Therapy Study Group (2001) was a multicentre randomized trial conducted to evaluate patients with subfoveal CNV that lacked a classic component. At 24 months, a statistically significant difference was seen with 54% in the PDT group compared to 67% in the placebo group losing more than 15 letters.

PDT involves a 10-minute infusion of a light-sensitive agent, verteporfin, followed by an 83-second illumination of the CNV with a low intensity laser. As the dye renders the patient photosensitive precautions to limit exposure to sunlight are recommended for 48 hours.

PDT is a new technique and expertise on its use is rapidly evolving. NHS funding for this treatment, steered by NICE guidance, is currently available for patients who have classic with no occult subfoveal CNV and visual acuity of 6/60 or better. It was not recommended for patients with predominantly classic subfoveal CNV and no guidance was published for occult CNV. It is estimated in the UK that 5000–7500 patients per year may fulfil these criteria for treatment. This amounts to a small proportion of AMD patients who can be treated in this way.

These three treatments, prevention with antioxidants and zinc, argon laser and PDT, are the only proven licensed treatments available in the UK. Others are likely to become available over the next few years.

New treatments

Macugen (pegaptanib)

Macugen (Eyetech Pharmaceuticals Inc., New York, and Pfizer Inc.) is an RNA oligonucleotide (aptamer) that has high selective binding capacity similar to an antibody. It is a selective vascular endothelial growth factor (VEGF) antagonist. The presence of VEGF activates vascular endothelial cells to induce angiogenesis and is thought to be the major signal for CNV in AMD.

Based on two phase 2/3 randomized trials, Macugen received US Food and Drug Administration (FDA) marketing approval in December 2004. It is currently being

appraised by NICE, with guidance expected around 2007. Results showed that in patients receiving Macugen 0.3 mg, 70% lost less than three lines of visual acuity, compared to 55% of patients receiving sham injection (Gragoudas et al, 2004). Macugen is administered by an intravitreal injection every 6 weeks. Adverse events included endophthalmitis (1.3%) and retinal detachment (0.6%), which were associated with severe visual loss in 0.1% of patients.

Lucentis (ranibizumab)

This is a humanized antibody fragment which binds and inhibits VEGF-A. It is delivered by an intravitreal injection on a monthly basis. In May 2005 Novartis reported unpublished phase 2 trial results as showing improved vision at 3 and 6 months. These phase 2 data are said to show significant stabilization or improvement in vision following treatment. The data are unpublished but this is the first claim of proven improved vision in AMD treatment. The drug is not licensed anywhere as yet.

Retaane (anecortave acetate)

This is a newer anti-angiogenic drug. It is a synthetic derivative of cortisol, which inhibits growth factors and endothelial cell division and migration. Retaane is delivered as a posterior juxtascleral depot every 6 months. This avoids sight-threatening complications associated with intraocular injections. The FDA has preliminarily reviewed and accepted data presented in May 2005. Studies have shown that after 1 year 79% of patients treated maintained their vision, compared to 53% of those who received sham treatment (D'Amico et al, 2003).

Surgery

Surgery for late neovascular AMD was pioneered in the USA in the early 1990s. The technique involves lifting the entire retina, including the macula, and rotating it around the optic nerve. The rotation moves the macula away from the subretinal new vessels and places it on healthy subretinal tissues. Although the techniques are complex, they have been refined over the past 10 years and have become reproducible in large numbers. It appears from the large series available in the literature that surgery has the ability to restore vision in patients with severe visual loss. Up to half of the patients in studies had good visual recovery (Mruthyunjaya et al, 2004). Currently NICE's guidance regarding surgery is that there is sufficient evidence for it to be offered as an experimental treatment with appropriate consent.

Other treatments

Trans-pupillary thermotherapy (TTT) is a form of laser treatment that uses lower temperatures than conventional thermal laser, thus producing less damage. A large multicentre trial failed to show any statistically significant benefit for this treatment (Reichel et al, 2005). As with TTT a large randomized trial of radiotherapy failed to show that it would be effective in the treatment of AMD (Marcus et al, 2004).

Outcomes

The annual incidence of progression of ARMD and visual loss in a patient with bilateral drusen is 85. The prognosis for dry AMD is significantly better than for wet AMD. For wet AMD the risk of CNV in the contralateral eye is 10% per year. In all forms the loss of vision is permanent and usually leads to registration as a blind person. However, AMD does not cause total loss of vision. Peripheral vision is retained and patients can compensate by learning to use this field of vision. Patients tend to have a lower quality of life and a higher incidence of depression and anxiety.

Cost

The yearly economic burden of AMD was estimated to be between €51.3 and €101.1 million in the UK, France, Germany and Italy (Bonastre et al, 2002). However, this figure is likely to have been grossly underestimated as it did not take social service costs into account. In 2003 the Guide Dogs for the Blind Association reported their estimate of the lifetime cost of a woman in residential care with ARMD to be £196 876 (Langley-Hawthorne, 2003). This is compared to the lifetime costs for the elderly with cataracts which was estimated to be £19 120.

The costs for new treatments have also been estimated. The cost effectiveness of PDT was between $86 721 and $173 984 per additional quality-adjusted life years (QALY) at 2 years compared to laser cost of $5629 per QALY gained (Sharma et al, 2001). These figures are likely to be similar with the newer treatments as they become available.

Rehabilitation

Low visual aids

Optical and non-optical interventions can contribute to patients coping with the effects of ARMD. However, low motivation can be the most difficult hurdle for both the patient and practitioner to overcome when embarking on rehabilitation. There are a vast number of optical low visual aids (LVAs):

1. LVAs for reading include hand magnifiers and spectacle magnifiers. By increasing object size and decreasing viewing distance the object can be seen by the part of the retina outside the damaged area. In some patients with para-central scotoma magnification may place the image into the scotoma. Minification in this case is more helpful.
2. Those that aid distance vision (such as telescopes).
3. Electronic aids such as closed circuit television and electronic video magnifiers. These are expensive, but some health authorities and associations can loan these.

Non-optical measures involve learning new skills for daily living. Contrasting colours are used to help distinguish objects and rooms to make them low vision-friendly. White text on a black background on computer screens is easier for AMD patients to read than conventional screens. The provision of large books, clocks and telephones is helpful.

Eccentric fixation

This technique involves utilizing functioning retina adjacent to the scotoma. Patients often learn by moving their head or eyes to fixate off centre so the target object is seen by unaffected retina. With a motivated patient this technique can achieve good reading speeds and some prefer it to hand-held magnifiers.

Mobility

Patients can experience difficulties with mobilizing safely as a result of sight loss. Mobility training involves the use of well-defined, contrasting-coloured lines to mark the edge of paths or steps. Improved lighting and furniture layout help patients to mobilize more confidently and increase independence.

Conclusions

ARMD remains a major public health issue for the world being a major cause of blindness. For the first time treatments are becoming available that can stabilize and even improve vision for this disabling disease. As our understanding of the origin of the disease improves the potential for treatments will increase. Sadly, despite current treatments and our advancing knowledge the reality for many patients remains the use of LVAs and rehabilitation. The future will hopefully bring a change to this. BJHM

Conflict of interest: none.

Age-Related Eye Disease Study Research Group (2001) A randomized, placebocontrolled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* **119**(10): 1417–36

Bird AC, Bressler NM, Bressler SB et al (1995) An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* **39**(5): 367–74

Bonastre J, Le Pen C, Anderson P et al (2002) The epidemiology, economics and quality of life burden of age-related macular degeneration in France, Germany, Italy and the United Kingdom. *Eur J Health Econ* **3:** 94–102

D'Amico DJ, Goldberg MF, Hudson H et al; Anecortave Acetate Clinical Study Group (2003) Anecortave acetate as monotherapy for treatment of subfoveal neovascularization in age-related macular degeneration: twelve-month clinical outcomes. *Ophthalmology* **110**(12): 2372–83

Evans J, Wormald R (1996) Is the incidence of registrable age-related macular degeneration increasing? *Br J Ophthalmol* **80**(1): 9–14

Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group (2004) Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* **351**(27): 2805–16

Hageman GS, Anderson DH, Johnson LV et al (2005) A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci USA* **102(20)**: 7227–32

Klein R, Klein BE, Linton KL (1992) Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* **99**(6): 933–43

Langley-Hawthorne C (2003) *The Costs of Blindness. An analysis of the costs of visual impairment and blindness in the United Kingdom.* Guide Dogs for the Blind Association. Ethical Strategies Ltd, Kingston upon Thames www.healthyeyes.org.uk/fileadmin/healthy-eyes/downloads/costs-of-blindness.doc

Macular Photocoagulation Study Group (1992) Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. *Arch Ophthalmol* **109**(8): 1109–14. Erratum in: *Arch Ophthalmol* **110**(6): 761

Marcus DM, Peskin E, Maguire M et al; AMDRT Research Group (2004) The agerelated macular degeneration radiotherapy trial (AMDRT): one year results from a pilot study. *Am J Ophthalmol* **138**(5): 818–28

Mruthyunjaya P, Stinnett SS, Toth CA (2004) Change in visual function after macular translocation with 360 degrees retinectomy for neovascular age-related macular degeneration. *Ophthalmology* **111**(9): 1715–24

National Institute for Clinical Excellence (2003) *Guidance on the use of photodynamic therapy for age-related macular degeneration.* National Institute for Clinical Excellence, London (www.nice.org.uk)

Owen CG, Fletcher AE, Donoghue M, Rudnicka AR (2003) How big is the burden of visual loss caused by age related macular degeneration in the UK. *Br J Ophthalmol* **87:** 312–17

Reichel E, Musch DC, Blodi BA, Mainster MA and TTT4CNV Study Group (2005) Results From the TTT4CNV Clinical Trial. *Invest Ophthalmol Vis Sci* **46:** E-Abstract 2311

Seddon JM, Willett WC, Speizer FE, Hankinson SE (1996) A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA* **276**(14): 1141–6

Sharma S, Brown GC, Brown MM, Hollands H, Shah GK (2001) The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* **108**(11): 2051–9

Treatment of Age-related macular degeneration with Photodynamic Therapy Study Group (1999) Photodynamic therapy of subfoveal choroidal neovascularisation in age-related macular degeneration with verteporfin. One-year results of 2 randomised clinical trials - TAP report 1. *Arch Ophthalmol* **117:** 1329–45

Verteporfin in Photodynamic Therapy Study Group (2001) 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 2. *Am J Ophthalmol* **131**(5): 541–60

Young RW (1987) Pathophysiology of age-related macular degeneration. *Surv Ophthalmol* **31**(5): 291–306

KEY POINTS

- Age-related macular degeneration (ARMD) is the leading cause of loss of vision in the west.
- ARMD is no longer considered a degenerative disorder as new advances have shown that it is strongly inherited and its pathophysiology is related to chronic inflammation.
- Smoking is a major modifiable risk factor.
- Early disease is known as age-related maculopathy (ARM) and late disease is known as AMD. There are two forms of AMD: wet and dry.
- Proven licensed treatments includes high dose antioxidants and zinc to help prevent progression of ARM. Laser and photodynamic therapy treatments are used for the treatment of neovascular AMD.
- New treatments include anti-vascular endothelial growth factor drugs and surgery.
- Most patients have poor prognosis for central vision and require visual aids and rehabilitation.
- Newer treatments are on the horizon and this field is likely to change rapidly in the near future.