Treating age-related macular degeneration

Age related macular degeneration affects approximately one in three of the population by age 75 years and is the commonest cause of blindness in the Western world, accounting for 54 per cent of all cases of registered blindness in people over 65 years. In this article, **James Self, Poorna Abeysiri and Professor Andrew Lotery** review the causal factors, the symptoms, how the disease progresses and discuss how best to treat the condition.

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Age-Related Macular Degeneration (ARMD) is the commonest cause of blindness in the Western world[1]. Multiple studies have shown that it affects approximately one in three of the population by age 75 years and this figure rises to one in two by age 85 years[1]. It is characterised by a loss of central vision attributable to degenerative and neovascular changes that occur at the interface between the neural retina and the underlying choroidal layer.

It affects the macular region of the eye. This is the oval, yellowish area containing xanthophylls pigment at the posterior pole, measuring approximately 5mm in diameter and is situated between the superior and inferior temporal arteries[2]. The fovea is a depression in the centre of the macula, measuring approximately 1.5mm in diameter, and is created by the peripheral displacement of nerve cells and fibres containing only photoreceptors[2]. The fovea is responsible for the most distinct vision, as incoming light has the greatest accessibility to the photoreceptors[2].

Classically, the early stages of ARMD involve the appearance of drusen in the macula. These are localised deposits lying between the basement membrane of the Retinal Pigment Epithelium (RPE) and Bruch's membrane. These can be described as hard (small, discrete yellowish-white spots) or soft (larger with less distinct edges). The 'soft' type is more commonly associated with the progression to severe visual loss from ARMD.

If hard drusen and areas of increased or irregular pigmentation at the level of the RPE are the only lesions present, the condition is best referred to as early Age-Related Maculopathy (ARM). The term ARMD is used to describe more advanced changes that are likely to be associated with visual impairment.

In the latter stages ARMD can take two forms:

- Dry ARMD (also referred to as geographic atrophy or non-exudative ARMD), which is seen in approximately 90 per cent of cases
- Wet ARMD (also known as neovascular, exudative or disciform ARMD), which is seen in approximately 10 per cent of cases.

This latter process results from the growth of abnormal blood vessels from the choroidal circulation through the Bruch's membrane. Choroidal neovascularisation has a number of important sequelae that are responsible for the majority of severe visual loss seen in ARMD. These sequelae are varied but to some extent include the inevitable consequences of leaky friable blood vessels (bleeding and exudation) growing beneath a delicate layer of retinal cells, which relies

on structural integrity and translucency for its function.

The main causal factors of ARMD

ARMD is a complex disease resulting from an interplay between genetic and other risk factors. By far the most important risk factors for ARMD are genetic predisposition and age. The incidence, prevalence, and progression of all forms of ARMD increase with advancing age[3] and it is rare before 55 years.

In recent years the discovery of a number of gene mutations and single nucleotide polymorphisms associated with ARMD have confirmed a significant hereditary component. Inflammation also seems to be important in the pathogenesis and progression of ARMD[4-7]. There is also growing evidence from studies of the complement factor H (CFH) gene and of Human Leukocyte Antigen (HLA) gene variants that ARMD is an immune mediated disease[8].

A variety of other risk factors have been suggested for ARMD. These include: hypertension, dyslipidaemia, cataract surgery, obesity, diabetes, atherosclerotic vascular disease and hyperopia[9-12]. However of these the strongest association is with cigarette smoking, which increases the risk of ARMD two fold[9,10].

Symptoms and disease progression

In the earliest stages of ARMD, no symptoms are present. Signs visible with an ophthalmoscope include drusen and/or irregular pigmentation at the RPE level. These signs are often hard to identify, and difficulty in diagnosis is made worse by the fact that approximately 90 per cent of the white population aged 40 years or older have one or two small, hard drusen at the macula of either eye[9]. As ARMD progresses, symptoms include blurring and/or distortion of central vision and (rarely) complete unilateral visual loss.

Symptoms and signs may stay unchanged for many years, may steadily progress or may worsen acutely. Some studies have shown that for patients with bilateral soft drusen, the risk of progressing to ARMD with loss of vision in one eye appears to be in the order of eight per cent per year over a three year period[13,14]. Similarly for patients with ARMD-related visual loss affecting one eye, the risk of losing vision in the fellow eye increases to between seven and 10 per cent annually[15,16].

Epidemiology and prevalence

ARMD is thought to affect approximately 50 million individuals worldwide[9,17] and the incidence is expected to double in the next 25 years due to an increase in the ageing population. Significant differences in prevalence rate and natural history exist between racial/ethnic groups and between different parts of the world[18,19].

In the UK, ARMD is the commonest cause of blindness in the elderly, accounting for over 54 per cent of all cases of registered blindness in people over 65 years[20] with a prevalence of 20–30 per cent[21]. ARMD is more prevalent in Caucasians than more darkly pigmented races[22], leading to the belief that melanin may be protective against development of choroidal neovascularisation. The uptake of zinc, a cofactor of antioxidant enzymes known to enhance antioxidant capacity, is significantly higher in brown irides (with higher melanocyte density) than blue irides and a similar effect in the fundii of dark individuals may be protective[23]. However, data pooled from large studies conducted in three continents reported no association between iris colour and ARMD[24].

Some debate exists as to whether being female is a risk factor for ARMD. Pooled data from a number of large studies revealed no sex differences in ARMD risk[24]. However, analyses from the Blue Mountains Eye Study suggest that the five year incidence of neovascular ARMD among women is double that of men (1.2 per cent *versus* 0.6 per cent)[3]. However, this may simply relate to the fact that there are more women than men in the elderly population.

ARMD: medical and social priority

Since the population older than age 65 years is the fastest growing segment of society, the burden of ARMD will grow significantly during the 21st century. It is estimated that by the year 2020, as many as eight million individuals worldwide aged 65 years and older could suffer from ARMD. Treatments for wet ARMD are most effective when applied quickly. Therefore increased awareness of the disease, rapid diagnosis and provision of appropriate services are imperative.

Prevention

Smoking is the only consistently identified modifiable risk factor for ARMD and as such, is probably the most important. Large studies have associated smoking with both the prevalence and incidence of ARMD and of progression to advanced ARMD[9,10,25].

There have also been a number of large randomised controlled trials into the use of dietary supplements for ARMD. The Age-Related Eye Disease Study (AREDS) compared high-dose dietary supplements of anti-oxidant vitamins C, E and beta carotene in combination with zinc and copper against placebo over more than six years[25,26]. This study demonstrated a protective effect of taking these vitamins with a reduction in visual loss for patients with moderate ARMD. Interestingly, during the trial, two large Scandinavian studies reported a four-fold increase in lung cancer in smokers supplemented with beta carotene[27,28]. Following this, smokers in the AREDS study were either withdrawn or given supplements without beta carotene. Other health concerns with prescribing high dose vitamin supplements for many years have included reduction in the protective effect of statins for cardiovascular disease from vitamin E, and the role of zinc in Alzheimer's disease and a possible increase in anaemia[29-31] – although no significant side effects were observed in the AREDS study.

The carotenoids – lutein and zeaxanthin – also have suspected benefits in ARMD[32], although definitive evidence of their long-term safety and efficacy is not yet available.

ARMD prevention is a complicated matter. Current practice varies but certainly encouraging patients to stop smoking and eat diet rich in vegetables, fish and low in fat seems good practice. AREDS high dose vitamin supplementation is available in several commercial preparations, but it is important to note that many over-the-counter preparations often contain significantly lower doses than those used in the trials and are probably ineffective.

Treatment – is there a cure?

Until relatively recently, thermal laser photocoagulation was the only treatment option for wet ARMD. In this treatment, a laser is applied via a slit lamp microscope to the retina. This allows photocoagulation of the area of the choroidal neovascularisation identified via angiography. Unfortunately, it also destroys the overlying neural retina. As such, this treatment is currently largely reserved for the minority of patients with extra-foveal choroidal neovascularisation.

In these patients, a small area of retinal damage can be sacrificed to obliterate choroidal neovascularisation growth. Unfortunately, the majority of patients have choroidal neovascularisation under the centre of the macula. Thermal laser here would obliterate central vision and therefore is not an attractive treatment. However, Photodynamic Therapy (PDT) was developed to minimise the collateral damage to the retina and underlying RPE. In this treatment, a photosensitising dye is administered via a peripheral vein and accumulates in the abnormal choroidal vessels, allowing targeted laser treatment to the abnormal vessels.

The first agent tested in phase III clinical trials and the only one approved for use is verteporfin. PDT with verteporfin has also been shown to be efficacious for some forms of wet ARMD[33,34]. Currently in the UK, PDT treatment is only available on the NHS for specific sub-types of wet ARMD. These are 'classic' and 'predominantly classic' lesions. This represents less than 50 per cent of wet ARMD lesions and so there is still a large number of patients for whom no treatment is currently available on the NHS.

Newer biological treatments are emerging that inhibit the function of Vascular Endothelial Growth Factor (VEGF). This growth factor appears to be the major stimulus for the development of choroidal neovascularisation. The first drug in this class to have phase III evidence of benefit is pegaptanib[22.] This is an oligonucleotide aptamer that binds the major ocular VEGF isoform VEGF165. Randomised controlled trials of pegaptanib, given as six weekly intravitreous injections for at least 48 weeks, have demonstrated it is an effective treatment in all types of wet AMD[35]. It is expected that pegaptanib will receive its drug licence shortly in the UK (it is already available in the USA).

Also in development is ranibizumab. This is an active fragment of a humanised murine anti-VEGF antibody active against all four isomers of VEGF. A Phase III trial of ranibizumab is currently underway following promising phase I and II results[36]. These anti-VEGF treatments represent a new generation of biological treatments that

provide an exciting addition to our treatment options for wet ARMD.

UK service provision

Currently, in the UK, referrals to an ophthalmologist for ARMD come from many sources including general practitioners, optometrists, casualty doctors and other hospital practitioners involved with patients who are over 65 years. Current advice from the Royal College of Ophthalmologists suggests that optometrists can reassure patients with minimal symptoms or signs of ARM and should not refer further.

Referral from the primary sector should occur when there is evidence of moderate ARMD, where visual impairment begins to interfere with normal lifestyle or there is significant visual loss requiring diagnosis or blind registration[30]. Referring practitioners also need to be aware of the urgent nature of referrals for patients with recent onset of distortion or visual loss and who still have good vision (6/60 or better). These patients may have treatable wet ARMD and should be referred urgently to either the ophthalmic casualty department or to the outpatient clinic following discussion with the local ophthalmologist[21].

Access to ARMD services in the UK

PDT laser treatment is available via 50 regional centres, each serving a population of approximately one million patients. It is not clear yet when pegaptanib or other novel anti-VEGF agents will be introduced into the NHS and what centres will be allowed to provide this treatment. The *National Institute for Health and Clinical Excellence* (NICE) is not planning to publish guidance on their use until 2007, and it is unclear whether commissioners (or local budget holders) will introduce these agents prior to this.

The ability to treat all patients with wet ARMD and not just sub-types combined with the need for six weekly reviews for repeated intra-vitreal injections means that a significant increase in infrastructure and ophthalmic personnel will be needed in order to meet demand. These novel anti-VEGF agents could revolutionise provision of care for ARMD but only if resources are in place to meet this demand.

Conclusion

ARMD is a major health problem that will only get worse as the population ages. Significant progress has been made in understanding the molecular steps leading to wet ARMD and this has translated into novel treatments, specifically the development of inhibitors of VEGF such

as pegaptanib.

Molecular insights into the complex nature of the disease have also come from genetic studies and this, in turn, should lead to more gene directed therapies in the future. These rapid recent advances in knowledge and treatment options mean that it is a very exciting time to be involved in the research and management of ARMD ■ GM

Conflict of interest: Professor Lotery has received travel grants and attended advisory board meetings for Novartis and Pfizer. The other authors have no declared conflict of interest

Key points

- ARMD is a very common disease.
- It is the commonest cause of registered blindness in the western world.
- It is characterised by a loss of central vision attributable to degenerative and neovascular changes.
- Smoking is the only consistently identified modifiable risk factor.
- Progress in genetics research is successfully unravelling the molecular events that lead to this disease.
- Anti-VEGF treatments represent an exciting new tool for treatment.

References

1. Klaver CC, Wolfs RC. Age specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. *Archives of Ophthalmology* 1998; **116**: 653–59
2. Snell RA. Clinical Anatomy of the eye. Lemp MA. Second edition. 1998. USA, Blackwell-Science
3. Mitchell P, Wang JJ, Foran S, *et al*. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology* 2002; **109**: 1092–7
4. Hageman GS, Luthert PJ, Victor Chong NH, *et al*. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retin Eye Res* 2001; **20**: 705–32
5. Anderson DH, Talaga KC, Rivest AJ, *et al*. Characterization of beta amyloid assemblies in drusen: the deposits associated with aging and age-related macular degeneration. *Exp Eye Res* 2004; **78**: 243–56
6. Penfold PL, Madigan MC, Gillies MC, *et al*. Immunological and aetiological aspects of macular degeneration. *Prog Retin Eye Res*. 2001; **20**: 385–414
7. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. *Arch Ophthalmol* 2004; **122**: 598–614
8. Goverdhan SV, Howell MW, Mullins RF, *et al*. Association of HLA Class I and Class II Polymorphisms with Age-Related Macular Degeneration. *Invest Ophthalmol Vis Sci* 2005; **46**: 1726–34
9. Klein R, Peto T, Bird A, *et al*. The epidemiology of age-related macular degeneration. *Am J Ophthalmol*. 2004; **137**: 486-95
10. Tomany SC, Wang JJ, van LR, *et al*. Risk factors for incident age-related macular degeneration: pooled findings from 3 continents. *Ophthalmology* 2004; **111**: 1280-7
11. Seddon JM, Cote J, Davis N, Rosner B. Progression of age related macular degeneration: association with body mass index, waist circumference and waist-hip ratio. *Archives of Ophthalmology* 2003; **121**: 785–92
12. Chaine G, Hullo A, Sahel J, *et al*. Case control study of the risk factors for age related macular degeneration. *British Journal of Ophthalmology* 1998; **82**: 996–1002
13. Smiddy WE, Fine SL. Prognosis of patients with bilateral macular drusen. *Ophthalmology* 1984; **91**: 271–7
14. Holz FG, Wolfensberger TJ, Piguet B, *et al*. Bilateral macular drusen in age-related macular degeneration. Prognosis and risk factors. *Ophthalmology* 1994; **101**: 1522-8
15. Gregor Z, Bird AC, Chisholm IH. Senile disciform macular degeneration in the second eye. *BrJ Ophthalmol* 1977; **61**: 141-7
16. Strahlman ER, Fine SL, Hillis A. The second eye of patients with senile macular degeneration. *Arch Ophthalmol* 1983; **101**: 1191–3
17. van LR, Klaver CC, Vingerling JR, *et al*. Epidemiology of age-related maculopathy: a review. *Eur J Epidemiol* 2003; **18**: 845–54
18. Klein R, Clegg L, Cooper LS, *et al*. Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study. *Arch Ophthalmol* 1999; **117**: 1203–10
19. Klein R, Klein BE, Marino EK, *et al*. Early age-related maculopathy in the cardiovascular health study. *Ophthalmology* 2003; **110**: 25–33
20. Evans J. Causes of blindness and partial sight in England and Wales 1990-1991. Studies on medical and population subjects. London, Her Majesty's Stationary Office 1995; **57**
21. Royal College of Ophthalmologists. A national research strategy for ophthalmology 2002
22. Friedman DS, Katz J, Bressler NM, *et al*. Racial differences in the prevalence of age-related macular degeneration: the Baltimore Eye Survey. *Ophthalmology* 1999; **106**: 1049–55
23. Kokkinou, D. The pigmentation of the human iris influences the uptake and storage of zinc. *Pigment Cell Research* 2004; **17**: 515-18
24. Smith W, Assink J, Klein R, *et al*. Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology* 2001;**108**: 697-704
25. Clemons TE, Milton RC, Klein R, *et al*. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. *Ophthalmology* 2005; **112**: 533–9
26. A randomized, placebo-controlled, 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* 2001;**119**: 1417-36
27. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med* 1994; **330**: 1029–35
28. Omenn GS, Goodman GE, Thornquist MD, *et al*. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N *Engl J Med* 1996; **334**: 1150–5
29. Suh SW, Jensen KB, Jensen MS, *et al*. Histochemically-reactive zinc in amyloid plaques, angiopathy, and degenerating neurons of Alzheimer's diseased brains. *Brain Res* 2000; **852**: 274–8
30. Cheung MC, Zhao XQ, Chait A, *et al*. Antioxidant supplements block the response of HDL to simvastatin-niacin therapy in patients with coronary artery disease and low HDL. *Arterioscler. Thromb Vasc Biol* 2001; **21**: 1320–6
31. Rulon LL, Robertson JD, Lovell MA, *et al*. Serum zinc levels and Alzheimer's disease. *Biol Trace Elem Res* 2000; **75**: 79–85
32. Bylsma GW, Guymer RH. Treatment of age-related macular degeneration. *Clin Exp Optom* 2005; **88**: 322–34
33. Bressler NM, Bressler SB, Haynes LA, *et al*. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: four-year results of an open-label extension of 2 randomized clinical trials: TAP Report No. 7. *Arch Ophthalmol* 2005; **123**: 1283–5
34. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration. *Am. J. Ophthalmol* 2001; **131**: 541–60
35. Gragoudas ES, Adamis AP, Cunningham ET, *et al*. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004; **351**: 2805–16
36. Michels S, Rosenfeld PJ. Treatment of neovascular age-related macular degeneration with Ranibizumab/Lucentis. *Klin. Monatsbl. Augenheilkd* 2005; **222**: 480-4