Advances in the management of age-related macular degeneration

TU HUYNH MB BS, MPH, PGDipOphthBS
ERWIN GROENEVELD MB BS, FRANZCO, FRCOphth

New treatments are becoming available for the leading cause of legal blindness in the elderly in the western world that not only halt the progression of visual loss but may improve visual outcomes.

Age-related macular degeneration (ARMD) is a slowly progressive, binocular loss of central vision due to deterioration of the retinal pigment epithelium in the macula. It is the leading cause of legal blindness in adults over 65 years of age in the western world. An ongoing study has found ARMD to be the principal cause of bilateral and unilateral noncorrectable blindness (visual acuity less than 6/60) in the aged population of the Blue Mountains, NSW, an area chosen for study as its demography is similar to the overall Australian population of this age.[1]

The management of ARMD is currently generating a large amount of literature because new treatment options are becoming available, the latest of these being pharmacological treatments aimed at blocking the action of vascular endothelial growth factor. In the past, most treatments were only able to halt the progression of visual loss. Hence the importance of early recognition and prompt treatment so that vision can be maintained at the best possible level. Recently, some new treatments have been developed that seem to not only halt the progression of visual loss but even improve visual acuity.

Dr Huynh is a Senior House Officer and Dr Groeneveld is a Visiting Ophthalmologist and Eye Surgeon at the Princess Alexandra Hospital, Brisbane, Qld.

Eye anatomy and physiology

The macula, located in the central part of the retina, is the area responsible for central vision (Figure 1). It is up to 5.5 mm in diameter, with the fovea at its centre, temporal and slightly inferior to the centre of the optic disc. The macula has a high concentration of cones, which allows for detailed central vision. The fovea, which is about 1.5 mm in diameter, has the highest density of cone cells and is the area of highest visual acuity. The central area of the fovea is free of blood vessels (the capillary-free zone).

Histologically, the retina consists of 10 layers, but functionally can be thought of as consisting of the neuroretina (the inner portion responsible for seeing), with its photoreceptors and neural connections, and the retinal pigment epithelium with Bruch's membrane. These two 'layers' together maintain the blood–retinal barrier and provide metabolic support to the photoreceptors. The choroid is a vascular layer between the retina and the sclera and forms the major source of blood supply to the outer half of the retina. Bruch's membrane lies between the choroid and the pigmented layer of the retina and is made up of five layers, including the basement membranes of each structure it lies between.

Causes of ARMD

ARMD is a multifactorial disease, although its exact aetiology is unknown. Several risk factors are recognised, primarily age but also smoking and a positive family history.

The dry form of the condition, affecting about 90% of people with ARMD, is slowly progressive. With age, the retinal pigment epithelium, for multiple reasons,

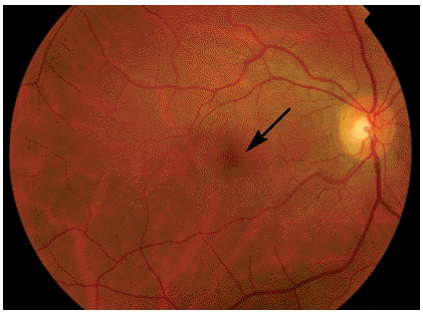

Figure 1. Normal retina, showing macular and foveal areas (arrow).

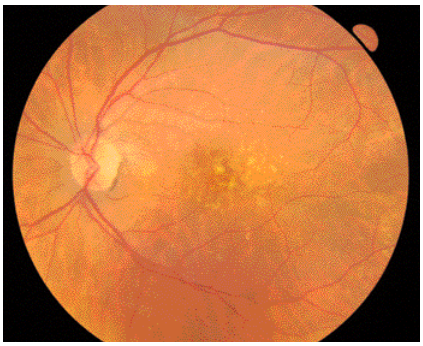

Figure 2. Dry age-related macular degeneration showing pale yellow deposits of drusen concentrated in the macular area.

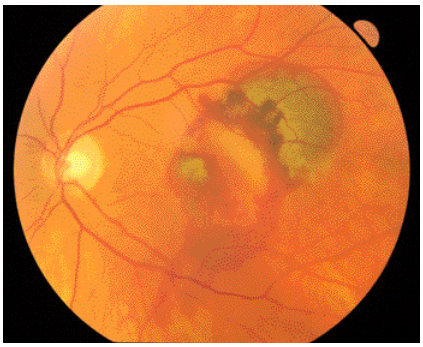

Figure 3. Wet age-related macular degeneration showing neovascular bleeding around the macula, with some macular oedema and perhaps retinal pigment epithelium detachment.

fails to provide proper metabolic support to the photoreceptors and this leads to the accumulation of small yellow–white amorphous deposits (drusen) underneath the retina that do not affect vision (Figure 2). With advanced dry ARMD (geographic atrophy), the retinal pigment epithelium cells degenerate and atrophy and central vision is lost. Geographic atrophy progresses slowly over many years.

Alternatively, if Bruch's membrane is compromised, neovascular complexes from the choroid may grow into the subpigment epithelial and subretinal spaces. This process is called choroidal neovascularisation. These new blood vessels tend to be abnormal and leak, leading to oedema and/or bleeding and disruption of visual function. If not treated this leads to dense fibrovascular scarring that can involve the whole macular area. This form of the disease is the 'wet', exudative or neovascular form of ARMD (Figure 3).

Wet ARMD is responsible for 90% of cases of severe visual loss in elderly patients. The dry form may evolve into the wet form in about 10% of cases.

Clinical features

The most common symptoms of ARMD are blurring of central vision, metamorphopsia and reduced vision. The blurring and distortion occur first and can often be missed by patients, who then present later with central loss of vision. Metamorphopsia is a subjective distortion of central vision that is best detected using an Amsler grid. All patients who have ARMD or are at risk of ARMD should have such a grid to self-monitor their central vision. Patients need to test one eye at a time in good light, wearing corrective spectacles or contact lenses. Any distortion of central vision would cause straight gridlines to appear wavy when vision is fixed on a central spot in the grid.

The early stages of ARMD are characterised by minimal visual loss with drusen and pigmentary changes in the retinal pigment epithelium. In patients with more advanced disease, the fundus may also show patchy chorioretinal atrophy (in geographic atrophy) or macular oedema and/or bleeding in the exudative form. These patients with more advanced ARMD, whether dry or wet, will have central visual scotomas (areas of loss of vision).

Diagnosis and classification

In addition to an assessment of visual acuity and a full ophthalmological assessment, patients with exudative ARMD need fluorescein angiography to examine the retinal and choroidal vasculature.

Angiographic fundus photography requires a fundus camera and experience in interpreting the results. Choroidal neovascularisation is recognised as areas of fluorescein leakage. It is described by location in relation to the fovea and as occult or classic depending on the pattern of leakage. A well-demarcated area of early hyperfluorescence with continuing leakage obscuring lesion boundaries is defined as classic choroidal neovascularisation. Occult choroidal neovascularisation is either a late leakage from an undetermined source or a fibrovascular detachment of the retinal pigment epithelium. Lesions are categorised according to the proportions of classic and occult leakage present; subcategorisation is important for prognosis and treatment.

Treatment of ARMD

Treating ARMD is difficult due to the degenerative nature of the disease and the nature of the tissue involved. The latest advances in therapeutic approaches to ARMD revolve around the understanding of vascular endothelial growth factor and the development of molecules that block its effects. These new drugs have shown such efficacy in preliminary studies that the previously most recent medical treatment, photodynamic therapy, is fast becoming obsolete.

Antioxidants

In the Age-Related Eye Disease Study (AREDS), treatment with vitamin C, vitamin E, zinc and beta-carotene supplements slowed the progression of dry ARMD compared with placebo.[2] This reduction in the risk of developing advanced ARMD was in the order of 20 to 30% and was found only in patients with moderate to advanced age-related maculopathy. The mechanism of how these supplements works is unknown.

Several antioxidant supplements based on the formula used in the AREDS are readily available over the counter – for example, Macuvision and Ocuvite Preservision. These supplements and meticulous surveillance of patients are the mainstay of treatment for dry ARMD.

Thermal laser photocoagulation

The use of hot lasers (argon or krypton lasers) to treat wet ARMD has limited application nowadays as, apart from photocoagulating the choroidal neovascular tissue, the treatment also causes permanent damage to surrounding tissues and an immediate reduction in central vision when used near or on the fovea.

The Macular Photocoagulation Study (MPS) showed significant long-term benefits of thermal laser treatment of choroidal

neovascular tissue outside the fovea, but lesions outside the fovea account for only 13 to 26% of cases.[3] The use of the argon laser was useful for about 5% of cases of wet ARMD, and in 50% of these cases it represented a cure.

Photodynamic therapy

Photodynamic therapy involves selective destruction of abnormal endothelial cells by low-energy red laser (a cool laser) activation of a photosensitive dye that accumulates in endothelial cells of the abnormal neovascularisation after intravenous injection. The dye used is verteporfin (Visudyne), a porphyrin derivative. Studies of verteporfin have shown a statistically significant treatment benefit for certain neovascular lesions by slowing down or halting the loss of further vision.[4] Over the last few years, photodynamic therapy has replaced laser photocoagulation for the treatment of most cases of choroidal neovascularisation where it occurs under the foveal centre.

Photodynamic therapy is expensive – about $2670 per treatment, of which $2000 is the cost of the drug itself. Patients need repeated treatments to maintain choroidal neovascularisation destruction. Currently, some patients qualify for subsidised verteporfin treatment.

Vascular endothelial growth factor blockers

The discovery in the 1980s of vascular endothelial growth factor (VEGF) and its role in abnormal blood vessel growth has led to the development of new treatments for wet AMRD.

VEGF is a platelet-derived growth factor and its many effects include promoting the growth of vascular endothelial cells and inducing increased vascular permeability, underlying its important roles in inflammation and angiogenesis (Table 1). Levels of VEGF are increased by hypoxia and can be upregulated by a number of other growth factors. There are four principal isoforms of VEGF with varying amino acid sequence lengths; the predominant VEGF165 seems to be the most physiologically active form. VEGF can be cleaved by several proteinases into bioactive products, which may also be pro-angiogenic. There are two VEGF receptors, both with crucial roles in vascular development. VEGFR2 seems to be the major mediator of the angiogenic, permeability and mitogenic activities of VEGF; VEGFR1 may play a more important role in haematopoiesis.

Elevated VEGF levels in the aqueous and vitreous humour of people with neovascular conditions of the eye have been described in the literature.[5] It is still unclear whether hypoxia is the main driving force in the development of choroidal neovascularisation in wet ARMD. However, it is hypothesised that VEGF plays a pivotal role in the development of choroidal neovascularisation and that its inhibition could be a viable method of treating neovascular ARMD.

Recombinant antibodies that inhibit VEGF at various sites in its pathway have been developed and are used to treat various diseases, particularly cancers. Several have been used for ocular disease, namely bevacizumab (Avastin), ranibizumab (Lucentis) and pegaptanib (Macugen). These anti-VEGF agents, of which only ranibizumab is TGA-approved for ARMD, are discussed below and compared in Table 2. The authors are not aware of any other VEGF inhibitors in clinical use for ARMD; however, there are other treatments on trial.

Bevacizumab

Bevacizumab, or rhuMab VEGF, is a mouse–human chimeric immunoglobulin that has a high affinity for the VEGF molecule. It has been developed primarily for the antiangiogenesis of tumours, and has been approved by the TGA for use in adjuvant therapy for advanced colorectal carcinoma. Its use in the eye is strictly off-label and as yet is not supported by any randomised controlled clinical trials.

Table 1. Properties of vascular endothelial growth factor

- Potent stimulator of angiogenesis by promoting the growth of vascular endothelial cells derived from arteries, veins and lymphatics
- Potent inducer of vascular permeability and fenestration
- Proinflammatory agent, induces the expression of several adhesion molecules in the endothelium that regulate leukocyte adhesion during inflammation
- Neuroprotective agent
- Vessel survival factor

However, the volume of reports indicates that intravitreal bevacizumab has been widely and safely adopted in the treatment of wet ARMD, and there is good anecdotal and observational data currently supporting its use in this way.

Bevacizumab for the treatment of advanced colorectal cancer is costly, but the lower dosages used in the eye mean that one injection of bevacizumab for the treatment of ARMD costs in the vicinity of $100.

Numerous open-label case series of intravitreal bevacizumab for the treatment of wet AMD have been published with up to one year of follow-up. Two retrospective consecutive series of intravitreal bevacizumab injections showed relatively consistent improvements in anatomical and visual acuity (up to 38% three-line improvements at three months) with no significant safety concerns within the first year of follow-up.[6,7] Both reports demonstrated clear effectiveness with intravitreal bevacizumab treatment.

Ranibizumab

Ranibizumab (rhuFab VEGF) is a 48-kDa Fab (fragment of antibody containing the antigen-binding site) portion of the

Table 2. Comparison of VEGF blockers

Feature	Bevacizumab (rhuMab VEGF; Avastin)	Ranibizumab (rhuFab VEGF; Lucentis)	Pegaptanib (Macugen)
Size of molecule	149 kDa	48 kDa	50 kDa
Type	IgG molecule (two identical light chains)	Fab fragment of IgG	28-nucleotide length RNA
Affinity	All isoforms of VEGF	All isoforms of VEGF (100 times affinity of bevacizumab)	VEGF165
Evidence	Observational and anecdotal	Randomised	Randomised
Treatment regimen	Intravitreal injection	Intravitreal injection	Intravitreal injection
Cost per injection	A$100	A$2000	US$995 (about A$1050)
Availability in Australia	TGA-registered but not PBS-listed for colorectal cancer; used off-label in ARMD	PBS-listed for wet ARMD	Not TGA-registered
Marketing	Roche	Novartis	Pfizer

ABBREVIATIONS: VEGF = vascular endothelial growth factor; PBS = Pharmaceutical Benefits Scheme; ARMD = age-related macular degeneration.

parent molecule bevacizumab. It has an affinity for all isoforms of VEGF of about 100 times that of its parent.[8] It is postulated that the Fab fragment would penetrate the retinal layers better than a larger molecule.[9]

Ranibizumab is PBS-listed for the treatment of wet ARMD. The recommended dose is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given monthly, and a qualified ophthalmologist experienced in intravitreal injections must administer it.

A cost-effectiveness model applied to ranibizumab versus bevacizumab has reported that ranibizumab needs to be 2.5 times as effective as bevacizumab to be comparably cost-effective.[10]

Both the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular ARMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in ARMD) studies showed prevention of moderate vision loss (more than 15 letters) in 95% of patients at 12 months.[11,12] The two-year data of the MARINA study showed an improvement in visual acuity of at least three lines was maintained in 30% of patients. At the 0.5 mg dose, 90% of patients lost fewer than 15 letters on visual acuity testing, 33% of patients had a greater than 15-letter gain, 70% had no loss of letters and 42% of patients ended 6/12 or better. The mean letter difference between the group treated with 0.5 mg ranibizumab and the control group was 21.4 letters.

There are also trials in progress comparing ranibizumab with photodynamic (Visudyne) therapy, comparing different injection regimens and exploring the combination of ranibizumab and photodynamic therapy.

Pegaptanib

Pegaptanib is a 28 base-length RNA oligonucleotide with a high affinity for the VEGF165 molecule. It acts as an aptamer (an oligonucleic acid or peptide molecule that binds a specific target molecule) by binding the VEGF165 molecule and preventing VEGF receptor activation.

Pegaptanib was approved for use in the treatment of wet ARMD in the USA in 2004. As yet it has not been approved for any use in Australia and recently the pharmaceutical company has withdrawn its application for approval in Australia. In the USA, pegaptanib costs about US$995 (about A$1050) per injection.

In two concurrent, multicentre, randomised, double-masked, sham-controlled studies (the VISION [VEGF Inhibition Study in Ocular Neovascularization] trials), patients with wet ARMD were randomised to receive intravitreal pegaptanib or sham subconjunctival placebo injection every six weeks for a total of 54 weeks.[13] Patients were eligible for enrolment if they were over 50 years of age and had visual acuity between 6/12 and 6/96 in the study eye and better than 6/240 in the other eye. All subtypes of choroidal neovascularisation (predominantly classic, minimally classic and occult) were included. Significant adverse effects noted were vitreous floaters, vitreous opacities and anterior chamber inflammation. Endophthalmitis developed in 12 of the 1053 patients, eight of these cases were deemed to be associated with a

deviation from sterile protocols. Six cases of retinal detachments associated with intravitreal injections and five cases of traumatic cataract were also reported.

Other agents

Several other agents are being tested for treatment against ARMD. One agent, VEGF-TRAPR1R2 (Regeneron Pharmaceuticals), is a recombinant fusion protein containing portions of both VEGFR-1 and VEGFR-2 fused to the Fc portion of human IgG.

Another type of agent is the small interfering RNAs (siRNAs), which inhibit intracellular gene expression. These could be used to manage wet ARMD by inhibiting the expression of VEGF. There are currently two siRNAs undergoing clinical trials, Cand-5 and siRNA-027. Cand-5 targets all isoforms of VEGF while siRNA-027 is an siRNA against the VEGFR-1. These molecules are undergoing phase I and II trials.

Finally, there has been some investigation into the use of drugs that cause collapse of blood vessels (e.g. combretastatin A-4) to cause endothelial collapse in ocular neovascularisation.

Conclusion

A significant proportion of the elderly population will, unfortunately, experience some form of visually impairing ARMD.

For dry ARMD, supplementation with antioxidants may help more advanced cases but careful surveillance is the mainstay of management.

Treatment options for wet ARMD include laser photocoagulation, photodynamic therapy and the new pharmacological treatments aimed at blocking the action of VEGF. Photodynamic therapy has largely replaced laser photocoagulation for the treatment of most cases of choroidal neovascularisation, including those in which it occurs under the fovea. The VEGF blockers offer a new approach to the treatment of wet ARMD, directed at antiangiogenesis. Ranibizumab (Lucentis) is currently the only VEGF inhibitor approved by the TGA for the treatment of wet ARMD, and is listed on the PBS.

Thus, there are now some treatments for wet ARMD that not only halt the progression of visual loss but may improve visual outcomes. However, some are not available in Australia, although they may be with time, and those that are available are expensive. It is still important, therefore, to recognise the symptoms and signs of ARMD and to refer these patients to specialist treatment early to halt the progression at a stage where vision allows a satisfactory quality of life. MT

References

1. Foran S, Wang JJ, Mitchell P. Causes of visual impairment in two older population cross-sections: the Blue Mountains Eye Study. Ophthalmic Epidemiol 2003; 10: 215-225.
2. Age-Related Eye Disease Study Research Group, SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: AREDS Report No. 22. Arch Ophthalmol 2007; 125: 1225-1232.
3. Moisseiev J, Alhalel A, Masuri R, Treister G. The impact of the macular photocoagulation study results on the treatment of exudative age-related macular degeneration. Arch Ophthalmol 1995; 113: 185-189.
4. Azab M, Benchaboune M, Blinder KJ, et al. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: meta-analysis of 2-year safety results in three randomized clinical trials: treatment of age-related macular degeneration with photodynamic therapy and verteporfin in photodynamic therapy study report no. 4. Retina 2004; 24: 1-12.
5. Ferrarra N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004; 25: 581-611.
6. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. Retina 2006; 26: 383-390.
7. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 2006; 113: 363-372.
8. Chen Y, Wiesmann C, Fuh G, et al. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. J Mol Biol 1999; 293: 865-881.
9. Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of ranibizumab (rhufabv2) after a single intravitreal administration. Invest Ophthalmol Vis Sci 2005; 46: 726-733.
10. Raftery J, Clegg A, Jones J, Tan SC, Lotery A. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol 2007; 91: 1244-1246.
11. Boyer DS, Antoszyk AN, Awh CC, Bhisitkul RB, Shapiro H, Acharya NR; MARINA Study Group. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007; 114: 246-252.
12. Kaiser PK, Brown DM, Zhang K, et al. Ranibizumab for predominantly classic neovascular age-related macular degeneration: subgroup analysis of first-year ANCHOR results. Am J Ophthalmol 2007; 144: 850-857.
13. VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group, D'Amico DJ, Masonson HN, Patel M, et al. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. Ophthalmology 2006; 113: 992-1001.

Further reading

1. Chopdar A, Chakravarthy U, Verma D. Age related macular degeneration. BMJ 2003; 326: 485-488.
2. Gottlieb JL. Age-related macular degeneration. JAMA 2002; 288: 2233-2236.
3. Fine SL, Berger JW, Maguire MG, Ho AC. Age-related macular degeneration. N Engl J Med 2000; 342: 483-492.

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