ARTICLE

Treatment of age-related macular degeneration

Roland Bunting
Medical Retina fellow[1]

Robyn Guymer
Head
Macular Research Unit
Centre for Eye Research Australia

Professor[1]
University of Melbourne

[1] Royal Victorian Eye and Ear Hospital
Melbourne

Key words
anti-vascular endothelial growth factor, bevacizumab, choroidal neovascularisation, ranibizumab

Aust Prescr 2012;35:90–3

SUMMARY

Age-related macular degeneration is a common cause of visual loss. There may be choroidal neovascularisation or geographic atrophy.

Evidence is accumulating for the importance of avoidable risk factors in age-related macular degeneration, such as smoking and obesity.

Research confirms that there is an important hereditary component to the disease.

Anti-vascular endothelial growth factors have improved the outlook for patients suffering from neovascular age-related macular degeneration. Recent work has concentrated on refining the frequency and pattern of delivery of these drugs to the vitreous cavity.

There are few treatment options for geographic atrophy.

Introduction

Age-related macular degeneration is the leading cause of irreversible visual loss in Australia, and as the population ages its prevalence is increasing. Although the macula is only a small part of the retina the disease results in the loss of the central field of vision.

Pathology

In the early stage of the disease, drusen as well as pigmentary disturbances develop in the deep layers of the retina at the level of the retinal pigment epithelium/Bruch's membrane complex. Drusen are small deposits of extracellular material which appear as pale yellow deposits on fundoscopy, and accumulate preferentially in the macula (Fig. 1). Although not usually associated with any visual symptoms, they represent a risk of progression to the vision-threatening complications of late age-related macular degeneration.

Two types of late age-related macular degeneration are responsible for visual loss. These are choroidal neovascularisation, or 'wet' age-related macular degeneration, and geographic atrophy, or 'dry' age-related macular degeneration. The wet form accounts for approximately 10% of all cases of late age-related macular degeneration, but it is responsible for up to 90% of cases of severe visual loss.

In choroidal neovascularisation a network or 'membrane' of abnormal blood vessels breaks through into the retinal layers from the underlying choroid. This leads to haemorrhage, oedema and exudate beneath and within the retina (Fig. 2), often resulting in a rapid and profound loss of central vision. The subsequent formation of a fibrotic disciform scar (Fig. 3) leads to permanent visual loss.

Geographic atrophy is a much more gradual process. The loss of visual function is the result of progressive loss of photoreceptors and retinal pigment epithelium at the macula (Fig. 4).

Risk factors

The main ocular risk factor for late age-related macular degeneration is the presence of drusen and pigmentary abnormalities in the central macula. The greater the area of drusen at the macula the greater the risk of progression to loss of vision. These early changes can be detected with the direct ophthalmoscope or a slit lamp.

The major risk factors associated with late age-related macular degeneration are advancing age, smoking and a family history of age-related macular degeneration.[1] Current smoking increases the relative risk by 1.8 compared to those who have never smoked.

The increased risk to siblings is estimated at between two- and six-fold. Less consistently associated risk factors are high body mass index, cardiovascular disease, hypertension and a variety of dietary patterns.[2]

Genetics

Over the last 10 years genetic research has led to a better appreciation of age-related macular degeneration as an inherited disease. Variations in the complement factor H gene on chromosome 1 have been linked to a significantly increased risk of the disease. The complement factor H protein is involved in the regulation of the complement cascade. Its link with age-related macular degeneration implicates inflammation in the disease pathway. Several other genetic associations have been identified, including other complement-related genes. Genetic associations have been found for both early and late age-related macular degeneration. Research into the interaction

of genes and environmental risk factors is currently an area of active investigation.[3]

Treatment

Treatment options for the atrophic form of late age-related macular degeneration are still only in the clinical trial phase. However, the efficacy of treatment for neovascular age-related macular degeneration has improved dramatically over the last 10 years. This is particularly because of the anti-vascular endothelial growth factor (anti-VEGF) therapies. The improvement in the visual prognosis that has followed their introduction has made it all the more important that patients with this form of the disease are referred promptly. The main symptoms that should prompt early referral to an ophthalmologist are the new onset of central visual distortion or painless blurred central vision.

Laser photocoagulation

The membrane of new vessels can be ablated by direct application of a thermal laser. As this treatment also destroys the retina overlying the new vessels, it is suitable only for lesions away from the central macula or fovea. While it can in some cases give a permanent regression of vessels, a large proportion of the membranes unfortunately recur after treatment. The main drawback is that more than 80% of lesions are under the fovea at the time of presentation, making them unsuitable for laser photocoagulation. It still remains a viable treatment today for lesions that are away from the fovea (extrafoveal).

Photodynamic therapy

In the early 2000s photodynamic therapy began to be used for subfoveal neovascular age-related macular degeneration. It involves the intravenous infusion of the photosensitve drug verteporfin, which preferentially accumulates in the neovascular tissue. Application of a low energy, non-thermal laser over the affected part of the retina results in free radical formation and secondary selective thrombotic closure of the abnormal vessels.

The effect is temporary and regular three-monthly treatments are often required. A further drawback

Fig. 1 **Drusen in the central macula in age-related macular degeneration**

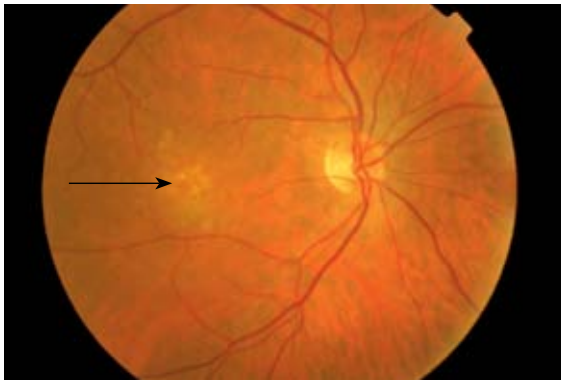


Fig. 2 **Subretinal haemorrhage in choroidal neovascularisation**

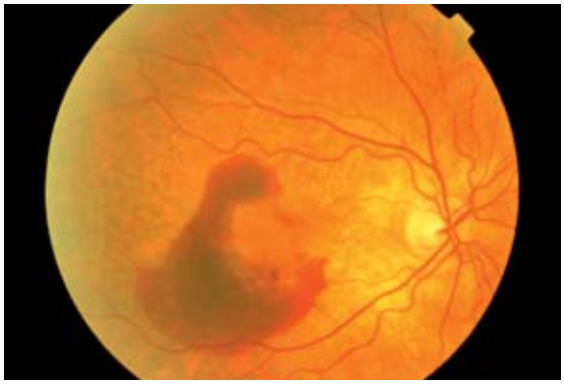


Fig. 3 **Fibrotic scar as the end result of late age-related macular degeneration**

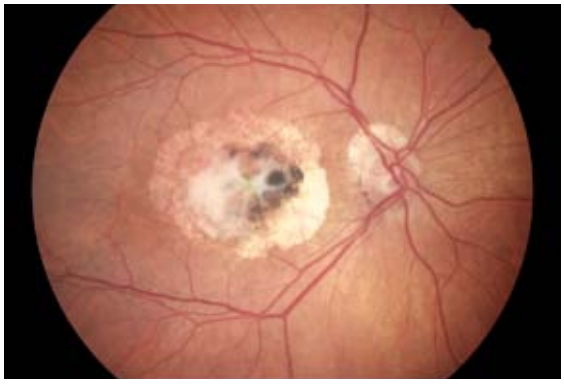
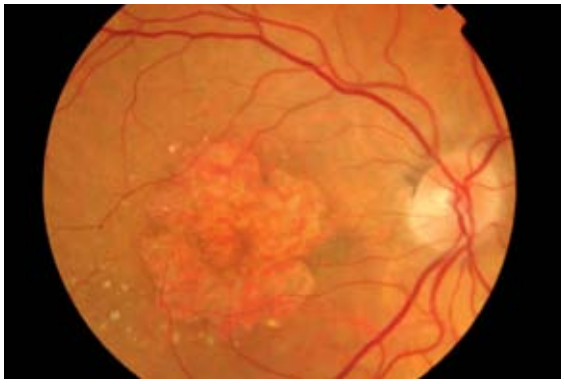


Fig. 4 **Geographic atrophy, one form of late age-related macular degeneration**



is that photodynamic therapy, while less destructive than thermal laser, usually results in atrophic areas within the central macula where the treatment was applied. The overall effect of photodynamic therapy is a slowing in the rate of progression of visual loss in neovascular age-related macular degeneration. It virtually never improves vision, but does continue to find a role in the treatment of some variants of age-related macular degeneration such as idiopathic polypoidal choroidal vasculopathy and other rare macular diseases.

Anti-vascular endothelial growth factor drugs

All previous treatments for age-related macular degeneration have now been almost completely superseded by anti-VEGF drugs. VEGF has long been suspected to be a mediator in choroidal neovascularisation.[4] Two anti-VEGF drugs, ranibizumab and bevacizumab, are currently in regular clinical use.

Ranibizumab

Ranibizumab is an antibody fragment directed against the A isoform of human VEGF. Two phase III clinical studies named ANCHOR and MARINA found vastly superior visual outcomes with four-weekly injections of ranibizumab compared to photodynamic therapy or sham injections, with all angiographic subtypes of sub-foveal membranes responsive to treatment.

In ANCHOR,[5] patients with the angiographically defined 'classic' form of choroidal neovascularisation were enrolled. The average change in vision at 12 months in the ranibizumab-treated group was an improvement of 11 letters on a standard acuity chart, compared with a loss of nine letters in the photodynamic therapy group.

The MARINA study[6] looked at the response in those defined angiographically as minimally-classic or occult choroidal neovascularisation, a subgroup which did not respond well to photodynamic therapy. After 12 months there was a 7-letter gain for ranibizumab-treated patients compared with a 10-letter loss in a sham treatment group. Stabilisation of vision was achieved in 94% of the treatment group, compared with 62% of the sham group.

Ranibizumab is expensive (around $2000 per dose). There is a large burden from ongoing monthly injections, in a large and growing population of patients, with treatment continuing for many years.

Bevacizumab

Bevacizumab is a significantly less expensive anti-VEGF drug. It is a full-length antibody used in the treatment of metastatic colorectal cancer. Although it is not approved for use in age-related macular degeneration, bevacizumab is frequently used 'off label' as an alternative to ranibizumab.

The Comparison of Age-related macular degeneration Treatment Trial (CATT)[7] was designed to compare the efficacy of bevacizumab to ranibizumab. It also investigated whether an 'as required' injecting regimen, based in part on high-resolution retinal imaging, could give visual outcomes as good as those with regular monthly injections. After 12 months there was equivalent efficacy both between the two drugs and between the two dosing regimens. Potentially, these data have important implications for the cost and streamlining of treatment services.

Procedure

Anti-VEGF drugs are injected into the vitreous cavity. The standard technique involves instillation of local anaesthetic and dilute povidone iodine drops, and a sterile eyelid speculum. A dose of 0.05 mL of the anti-VEGF drug is then given by trans-scleral injection through a 30-gauge needle. This is commonly performed in a treatment room setting.

Adverse effects

The ocular risks are low and relate mainly to the mechanical process of injecting into the vitreous cavity. They include endophthalmitis, at a rate of approximately 1 in 2000, traumatic cataract, and retinal detachment. Transient symptoms of ocular surface discomfort, bruising and floaters are common, but severe discomfort, worsening vision, or a persisting shadow in the vision should prompt early review by the specialist.

There is a theoretical risk of systemic effects from the intravitreal administration of these drugs, based on those seen with systemic anti-VEGF treatments. These are mainly related to arterial thromboembolic complications such as stroke. A small increased risk of arterial thromboembolic complications in an elderly population is difficult to determine, with large numbers needing to be followed to confirm a small increase in risk. To date no statistically significant increased risk has been confirmed, although ongoing safety studies continue.

Prevention

The Age-Related Eye Disease Study (AREDS)[8] investigated the use of high dose antioxidants (vitamin C, vitamin E and beta carotene) combined with zinc over a five-year period to slow progression of disease. Results suggested a modest benefit in slowing progression in only certain subgroups of early age-related macular degeneration. Much debate has ensued regarding the risks and benefits

of long-term high-dose supplementation. The Age-Related Eye Disease Study 2 (AREDS2) is re-investigating the use of different combinations and doses of the antioxidant vitamins along with other supplements including lutein, zeaxanthin and omega-3 long-chain polyunsaturated fatty acids.[9]

Future therapies

Research is continuing to refine and tailor the delivery of the existing anti-VEGF therapies on an individual patient basis. This is according to the behaviour of an individual's neovascular membrane and the appearance of the retina on various imaging techniques during follow-up. Further efforts are looking into other anti-VEGF drugs, formulations with a longer half-life in the vitreous cavity, alternative means of delivery to the retina, and combination treatments. Predictors of the response to treatment are also being researched to further individualise the treatment protocols. Much effort is going into understanding the underlying pathophysiology of age-related macular degeneration to allow interventions that prevent or delay the onset and its progression.

Conclusion

Age-related macular degeneration is the leading cause of irreversible visual impairment in Australia, with the neovascular form of late age-related macular degeneration responsible for the large majority of cases of severe visual loss. The introduction of the anti-VEGF therapies has revolutionised the outlook for patients suffering this devastating form of the disease. When symptoms of visual distortion or central visual loss are reported, early review by an eye-care professional and referral as appropriate to specialised care remains key to improving an individual patient's prognosis. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

7. Photodynamic therapy improves vision in patients with neovascular age-related macular degeneration.

8. A persistent shadow in the vision after treatment with ranibizumab requires rapid referral to a specialist.

Answers on page 103

REFERENCES

1. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol 2010;10:31.
2. Chong EW, Wong TY, Kreis AJ, Simpson JA, Guymer RH. Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. BMJ 2007;335:755.
3. Robman L, Baird PN, Dimitrov PN, Richardson AJ, Guymer RH. C-reactive protein levels and complement factor H polymorphism interaction in age-related macular degeneration and its progression. Ophthalmology 2010;117:1982-8.
4. Wells JA, Murthy R, Chibber R, Nunn A, Molinatti PA, Kohner EM, et al. Levels of vascular endothelial growth factor are elevated in the vitreous of patients with subretinal neovascularisation. Br J Ophthalmol 1996;80:363-6.
5. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432-44.
6. Rosenfeld PJ, Brown DM, Heier DS, Boyer DS, Kaiser PK, Chung CY, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
7. Martin DF, Maguire MG, Ying GS, Runwald JE, Fine SL, Jaffe GJ; CATT Research Group. Ranbizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897-908.
8. Age-Related Eye Disease Study Group. A randomized, placebo-controlled, 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.
9. National Eye Institute. Age-related Eye Disease Study 2. ClinicalTrials.gov registration number: NCT 00345176.

Macular Degeneration Foundation

The Macular Degeneration Foundation is a national organisation based in Sydney, which aims to reduce the incidence and impact of macular degeneration in Australia.

The Macular Degeneration Foundation website contains fact sheets on macular degeneration, lifestyle advice, information for families and carers, quarterly newsletters with tips for those with low vision, and links to related websites.

Contact

Website	www.mdfoundation.com.au
Email	info@mdfoundation.com.au
Support line	1800 111 709
Head office	MD Foundation, Suite 902, Level 9, 447 Kent Street, Sydney NSW 2000