

Managing neovascular age-related macular degeneration: a step into the light

Robyn H Guymer

Treatment targeting vascular endothelial growth factor is revolutionising AMD management

Age-related macular degeneration (AMD) is the most common cause of blindness and visual disability in the Western world.^{1,2} In AMD, vision is lost either from a slow atrophic process (dry AMD) or from a much more rapid and destructive process of choroidal neovascularisation (wet AMD). Wet AMD accounts for the vast majority of severe vision loss. Around 15% of people over 50 years of age (approximately 750 000 Australians) have some signs of AMD, which include pigment disturbance and yellow deposits, called drusen, in the macula. These early changes, sometimes referred to as age-related maculopathy or early AMD, do not usually cause symptoms, but they do increase the risk of developing the sight-threatening complications of AMD (or “late” AMD), which result in 1%–2% of people in this age group losing significant vision. The prevalence of these early changes rises exponentially with age, so that nearly two out of three people who reach the age of 90 will have early AMD, with one in four having a significant loss of vision as a result of progressing to late AMD.¹ Including both direct and indirect costs of visual impairment, AMD cost Australia \$2.6 billion in 2005, and this figure is expected to grow to \$6.5 billion over the next 20 years.³ With its enormous impact on quality of life and economic burden to the community, an effective treatment has been keenly sought.

Until photodynamic therapy became available in 2000, clinicians treating wet AMD were confined to the use of destructive thermal laser photocoagulation, which destroys the abnormal blood vessels but also the overlying neural retina. While this treatment was better than the condition's natural history, it was only used in a small group of patients whose blood vessels were well delineated and not located under the centre of the macula (fovea). Photodynamic therapy, on the other hand, employs a low-powered laser that activates a photosensitive dye to achieve preferential destruction of the choroidal neovascularisation, allowing treatment of lesions under the fovea. Although an advance in treatment, few patients who have photodynamic therapy retain reading or driving vision and virtually none improve on their presenting vision.

Further advances in treatment have recently been made, following the discovery that vascular endothelial growth factor (VEGF) is a major driver for the abnormal blood vessel growth in wet AMD.⁴ There are now many drugs that are directed towards blocking VEGF at various sites in its pathway. These drugs have treatment implications in several diseases, particularly cancers, but their impact is now being felt in ophthalmology, due to unprecedented success in treating wet AMD. Recent publications in the *New England Journal of Medicine* presented results from two large prospective randomised controlled trials investigating the efficacy and safety of ranibizumab as a new treatment for AMD.^{5,6} Ranibizumab is a humanised antigen-binding fragment of a recombinant monoclonal antibody directed at the VEGF protein. In the two trials, collectively involving over a thousand subjects, ranibizumab was injected into the vitreous humor on a monthly basis for

2 years, and the results compared with sham injections in one study⁵ and with photodynamic therapy in the other study.⁶ In both studies, average visual acuity at 12 months had improved by one line on an eye chart in the ranibizumab-treated groups, compared with a reduction in vision in the control groups.^{5,6} In the study by Rosenfeld et al, 95% of the ranibizumab-treated group maintained relatively stable vision, compared with only 62% of the sham group. Visual acuity improvement of 15 letters (three lines) or more was seen in about a third of the ranibizumab-treated group, compared with 10% of the sham group.⁵ Similar results were seen in the study comparing ranibizumab treatment with photodynamic therapy.⁶

The most feared complication of intravitreal injections — bacterial infection inside the eye — occurred in about one in every 2000 injections, or about 1% of the patients in these studies. Potential systemic side effects from anti-VEGF treatments are arterial thromboembolic events, such as stroke and myocardial infarction. There was no statistically significant difference in the risk of arterial thromboembolic events between the anti-VEGF treatment and control groups in these two studies, but the numbers affected were higher in the treated groups.^{5,6} Further studies are ongoing to monitor for these adverse events.

Ranibizumab was approved by the United States Food and Drug Administration for treatment of wet AMD in June 2006, and, although still awaiting registration in Australia, it is available here through a special Therapeutic Goods Administration access scheme. The current cost of ranibizumab is \$2000 per injection (with a subsidy scheme in place after three injection payments).

Clinical trials are ongoing to evaluate whether less frequent injections of ranibizumab may be equally efficacious. In current clinical practice, many clinicians have adopted a flexible re-treatment regimen, using visual acuity, clinical appearance and optical coherence tomography scanning of the macula to guide the decision to re-treat. How long treatment needs to be continued remains uncertain, as the underlying disease, and hence the stimulus for new blood vessel growth, has not been addressed by these new treatments.

Prior to ranibizumab becoming available, clinicians were already using a related drug, bevacizumab (the full length monoclonal antibody to VEGF derived from the same mouse monoclonal antibody as ranibizumab), to treat wet AMD. Bevacizumab is only approved for use in treating metastatic colon cancer. Although there have been no randomised controlled trials evaluating bevacizumab in the treatment of wet AMD, several uncontrolled case series have reported short-term efficacy and safety similar to ranibizumab.^{7,8} Off-label use of bevacizumab continues around the world, including in Australia, due to its much cheaper cost compared with ranibizumab.

No prospective randomised studies comparing ranibizumab and bevacizumab have taken place, although there are plans for such a trial through the US National Eye Institute. Until the results of such

EDITORIALS

a comparative trial are forthcoming, government and the community face a dilemma of whether to approve and subsidise the well studied but expensive drug ranibizumab, or to delay that decision and therefore condone the off-label use of a drug that has not been submitted to the rigours of a randomised clinical trial nor studied to the extent that we expect before a new drug is introduced.

Despite these advances in treatment, our knowledge about the underlying mechanisms and pathogenesis of AMD is still lacking. To date, cessation of smoking remains the most important intervention to reduce the risk of AMD and its progression, especially the wet form. There is still no specific treatment for dry AMD, which leads to a slower, but still significant, loss of vision. Also, our ability to predict and prevent progression of early AMD to the visually devastating complications of late AMD is limited. Achieving this would truly represent a major advance in the treatment of AMD. The recent explosion in publications reporting significant gene associations with AMD may prove a major step in helping us achieve this ultimate aim.^{9,10}

Competing interests

I am on the medical advisory boards of two drug companies, Novartis Pharmaceuticals and Pfizer, that produce anti-VEGF drugs for the treatment of AMD. I am also principal investigator on numerous clinical trials of anti-VEGF agents, including ranibizumab, and the Centre for Eye Research Australia receives funding from Novartis, Pfizer, Alcon and Allergan to cover the costs of these clinical trials. These companies had no role in the preparation of this manuscript.

Author details

Robyn H Guymer, MB BS, PhD, FRANZCO, Director of Clinical Research

Centre for Eye Research Australia, University of Melbourne, Melbourne, VIC.

Correspondence: rhg@unimelb.edu.au

References

- 1 Taylor HR, Keeffe JE, Vu HTV, et al. Vision loss in Australia. *Med J Aust* 2005; 182: 565-568.
- 2 Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1995; 102: 1450-1460.
- 3 Taylor HR, Pezzullo ML, Keeffe JE. The economic impact and cost of visual impairment in Australia. *Br J Ophthalmol* 2006; 90: 272-275.
- 4 Leung DW, Cachianes G, Kuang WJ, et al. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science* 1989; 246: 1306-1309.
- 5 Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355: 1419-1431.
- 6 Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355: 1432-1444.
- 7 Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularisation secondary to age-related macular degeneration. *Retina* 2006; 26: 383-390.
- 8 Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006; 113: 363-372.
- 9 Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci U S A* 2005; 102: 7227-7232.
- 10 Yang Z, Camp NJ, Sun H, et al. A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. *Science* 2006; 314: 992-993. □