Recent advances in the treatment of age-related macular degeneration

Loss of central vision with age-related macular degeneration (ARMD) is a devastating reality for 8% of adults aged over 65 years in the UK,¹ but new therapies with the potential to halt and improve visual loss have emerged. As a result, the NHS faces some difficult choices in terms of provision of and access to treatments.

ARMD is thought to be a group of genetically- and environmentally-determined retinal degenerative diseases: in ARMD there is an age-related dysfunction of the retinal pigment epithelial cells, which are essential for photoreceptor metabolism and removal of waste products. Dysfunctional cells accumulate undigested waste, which is clinically evident as focal yellow subretinal clumps, termed drusen. Drusen are the herald of ARMD, and large or numerous drusen are poor prognostic factors for future visual loss.² The disruption of photoreceptor metabolism eventually causes areas of retinal atrophy: the macula, the 'high definition' central point of the retina with the highest density of photoreceptors, is consequently more susceptible to this progressive dysfunction.

In the majority of patients, ARMD occurs as atrophic or 'dry' macular degeneration. This is a relatively slow process, and at the present time there is no effective treatment. In the remaining patients with 'wet' or neovascular disease there is aberrant growth of choroidal blood vessels beneath the dysfunctional retina: haemorrhage and oedema from these neovascular membranes causes sudden central visual loss. Retinal angiography is needed to identify and classify the membranes as 'classic' well-defined lesions or amorphous 'occult' membranes, as the classification has an impact on the treatments available. A current estimate of the incidence of wet ARMD in the UK is around 21 000 new cases each year.³

Patients with ARMD who need referral to ophthalmic services present to their primary care provider or optometrist with gradual visual loss, or more urgently with sudden central visual loss. The Royal College of Ophthalmologists recommends that this

'urgent' group should undergo retinal angiography and assessment for possible treatment within 2 weeks of visual loss.^{3,4} To improve the efficiency of the patient journey, and in this era of practice-based commissioning, there is an argument that optometrists should make direct referrals to ophthalmology services where necessary. Optometrists also play a vital screening role in the detection of the asymptomatic age-related maculopathy (drusen and focal retinal pigment epithelial changes) precedent to symptomatic ARMD.

Detection of the earlier changes is important as there is evidence that intervention at this stage can alter progression; for example, patients can be advised to stop smoking. Although ARMD has a multifactorial aetiology, with a recently discovered HTRA1 gene polymorphism⁵ (and no doubt more genetic associations to come), smoking is the significant avoidable risk factor for developing ARMD:² smokers are 3.6 times more likely to develop ARMD than those who have never smoked.

The Age-Related Eye Disease Study (AREDS) demonstrated that a combination of high doses of vitamins C and E, beta-carotene, and zinc reduces the risk of second-eye progression in patients with significant visual loss from wet ARMD.⁶ Beta-carotene is contraindicated in smokers because of the increased risk of small cell lung cancer,⁶ while long-term vitamin E should be used with caution in patients with cardiovascular disease because of a possible increased risk of heart failure.⁷ A number of formulations are available with or without these contentious ingredients; as yet there is no proven benefit for the wider group of patients with ARMD, but all patients should be advised to eat a balanced diet.

As there is no known effective treatment for dry ARMD, adequate social support and visual rehabilitation is essential. For example, patients can be referred by the ophthalmologist to low visual aid clinics, for training in the use of magnifying glasses or eccentric viewing techniques. If necessary, patients with ARMD can also be formally

registered as visually impaired. Ancillary organisations, such as the Royal National Institute for the Blind, Macular Disease Society, and Sight Savers, can also provide invaluable support for patients with ARMD. Depression rates among this vulnerable group are as high as 30%, and severity of depression is not always linked to severity of visual loss.⁸

Interventional research has centred on wet ARMD and anti-angiogenesis either through direct obliteration of neovascular membranes or inhibition of pro-angiogenic cytokines, such as vascular endothelial growth factor (VEGF).

Photodynamic therapy has been recommended by the National Institute for Clinical Excellence (NICE) for the treatment of predominantly 'classic' wet ARMD in patients with visual acuities no worse than 6/60: verteporfin (Visudyne®, Novartis) is injected intravenously, binds to the subretinal neovascular membrane, and is laser activated, which releases destructive free radicals and results in significantly reduced visual loss progression.⁹ There are an estimated 7000 patients eligible for treatment with verteporfin based on the NICE criteria,⁴ which has recently been broadened in some primary care trusts. Photodynamic therapy focuses on the membrane rather than the underlying angiogenic molecular environment, so there is reduction in efficacy over time.

The emergent anti-angiogenic pharmacotherapies deal with the molecular environment, specifically VEGF, so the potential advantage over photodynamic therapy is broader efficacy in a number of lesion subtypes and less destruction of 'normal' tissue. These treatments all require intraocular injections with a low associated risk of intraocular infection or haemorrhage. Despite the fact that multiple treatments are often required, patient-based surveys have consistently shown that these invasive treatments confer an improved quality of life.¹⁰

Pegaptanib sodium (Macugen®, Pfizer) significantly reduces the progression to

severe visual loss in wet ARMD by 50% at 1 year.¹¹ Macugen is under NICE evaluation and is available on a trial basis at selected UK centres. Ranibizumab (Lucentis®, Novartis), which is also under NICE evaluation, has been shown to prevent visual loss in 95% of patients and, remarkably, improves visual acuity in 35%.¹² Bevacizumab (Avastin®, Roche), previously approved for the treatment of metastatic colorectal carcinoma, has been used increasingly since 2005 in the treatment of wet ARMD, but is not licensed for intraocular use. The progenitor to Lucentis®, and marketed by the same company in the US (Genetech), the larger Avastin molecule, was thought unlikely to cross retinal layers, but has been shown to cross diseased retinæ with encouraging results and low rate of adverse events.¹³

Recent estimates suggest that there may be 21 000 new cases of wet ARMD eligible for these new drugs each year, compared with 7000 patients eligible for photodynamic therapy.⁴ The significant advantage of Avastin is its low cost: £3 compared to over £1000 per treatment for the specifically-designed Lucentis®. However, the implications for the NHS are significant, not only in terms of the financial cost of the drug, but also trained personnel and infrastructure. A recent cost analysis of ARMD therapies estimated the total 2-year costs for treatment at approximately €1400/£1000 for Avastin®, €7600/£5600 for Visudyne®, €18 600/£13 900 for Macugen®, and €45 900/£34 200 for Lucentis®.¹⁰

Anti-angiogenic steroids such as anecortave acetate (Retaane®, Alcon) and squalamine lactate (Evizon™, Genaera Corporation) have also been shown to reduce neovascularisation.^{14,15} Further studies are underway.

NICE aimed to complete its consultation on Lucentis® and Macugen® by early 2008, but has no plans to evaluate Avastin®. The presumed reason for this oversight has been the accepted dogma that NICE is unable to evaluate 'off-label' medicines, as they do not receive the relevant drug referrals from the Department of Health and the Medicines and Healthcare products Regulatory Agency. A Department of Health spokesperson recently stated that their 'hands were tied' with regards to referring Avastin® to NICE for evaluation.¹⁶ This is not

supported by published guidelines on NICE recommendations which state that 'use outside a licensed indication may be recommended'.¹⁷ Genetech has expressed worries regarding the sterility of Avastin® packaging as the reason why they are not applying for a license for the intraocular use of the much cheaper drug,¹⁸ despite strong support for the intra-ocular use of Avastin® from the American Academy of Ophthalmology.¹⁹ As such, clinicians wishing to use Avastin are faced with ethical questions surrounding off-label drug prescription and conventional evidence-based drug consultation. There is now growing pressure on NICE from professional and patient lobbies to evaluate Avastin® for wet ARMD.

In the short-term future, treatments targeting ageing by encouraging the dispersal of accumulating waste products show promise, and retinal stem cell transplants provide hope for millions of patients blinded by diseases such as macular degeneration. Viral vector gene therapy also holds great potential.

The challenge ahead lies in the health economics of access to these drugs and the other emerging treatments, but the future is indeed brighter for our patients.

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