Age related macular degeneration, as the term implies, affects older adults and accounts for about half of all vision impairment or blind registrations in the developed world. Its prevalence is increasing with the global demographic shift towards an ageing society. The two vision threatening manifestations of age related macular degeneration occur either as a consequence of neovascularisation, which causes an acute exudative pathology, or from cell loss due to geographic atrophy. Both neovascular age related macular degeneration and geographic atrophy result in reduced central vision with loss of visual discrimination necessary for reading, driving, and recognising faces. The main aims of treatment are either to prevent the progression of early disease or to treat the manifestations of advanced disease if these do occur. This review examines the pathogenesis of age related macular degeneration and recent advances in its management.

What is macular degeneration?

The macula is the central area of the fundus of the eye that is easily seen on ophthalmoscopy and comprises a region bounded by the optic nerve and the superior and inferior retinal vascular arcades (fig 1A). A large range of inherited and acquired conditions fall into the category of macular degeneration. This review focuses only on the most common, age related macular degeneration. Early age related macular degeneration is present when a spectrum of changes is observed in the ageing eye before the onset of overt loss of vision. These changes include drusen, which are focal yellowish coloured deposits, and alterations in the pigmentation (hypopigmentation and hyperpigmentation) of the macula. The term late age related macular degeneration is applied when neovascularisation and or geographic atrophy are observed. The commonly used term ‘dry macular degeneration’ is potentially confusing.
since it is used to signify the presence of drusen, pigmentary irregularities, or both, as well as geographic atrophy. The terms early and late macular degeneration are preferable.

What do we know about the pathogenesis of age related macular degeneration?

The molecular pathways leading to age related macular degeneration remain to be elucidated. The retina and its pigmented epithelium are unique among body tissues in their constant exposure to light energy and high oxygen concentrations, both of which are potent sources of free radicals—therefore, it has been suggested that the cumulative effects of oxidative stress over a lifetime may be the initiating stimulus for macular degeneration. Concordant with this hypothesis are the findings of epidemiological studies, which show that cigarette smoking and a high lifetime exposure to sunlight are risk factors. One recent cross sectional population based study in the European Union found that people with low levels of antioxidants in their serum combined with high cumulative lifetime sunlight exposure had a two fold increased risk of developing late macular degeneration.

More recently, consistent associations between the clinical spectrum of age related macular degeneration and polymorphisms in genes encoding proteins involved in immune regulation have been observed and provide additional insights into how this condition may develop. Carriage of at-risk alleles at multiple complement loci confer additive risks and, when combined with information on lifestyle factors such as smoking, can account for as much as 80% of the risk.

What is the natural history of macular degeneration?

Early macular degeneration can progress to late manifestations with sight loss in a proportion of people. The risk of progression is highly variable and depends on the severity and extent of the features of early macular degeneration. The age related eye diseases study has quantified this risk and showed that people with small drusen in both eyes have a very low risk of progression—between 0.4% and 3.0% over five years. However, if large drusen and pigmentary abnormalities are present in both eyes this risk increases to around 47.3%. Initially, geographic atrophy develops as focal areas of depigmentation. Eventually these coalesce or expand to involve the central macula causing progressive worsening of vision to legal blindness. Neovascular complications on the other hand have a more acute onset with sudden development of central blurring and distortion. Left untreated the area of neovascularisation expands rapidly and a large fibrous scar develops in the macula. A recent meta-analysis of data from several controlled clinical trials showed that within three years of the onset of neovascularisation more than half of untreated eyes will have a level of vision of 20/200 (Snellen 6/60) or worse, which is within the WHO definition of severe visual impairment. When both eyes are affected with late stage age related macular degeneration sight can be markedly reduced and tasks that require visual discrimination, such as reading, driving, and recognising faces become difficult.

How is the diagnosis made?

Since the presence of small areas of geographic atrophy is compatible with good vision, the diagnosis is often incidental during attendance at regular eye examinations. Patients who develop neovascular disease will usually complain of central distortion and blurring in the affected eye. When late neovascular disease affects only one eye, however, the condition may be an incidental finding. The diagnosis is usually evident on clinical examination and fundus photography (fig 1). If neovascularisation is present, fluorescein angiography, a method for examining the intraocular vascular beds, reveals the abnormal blood vessels which often leak profusely (fig 1D).

Optical coherence tomography is now used to image the retina and the retinal pigment epithelium non-invasively. It has provided a rapid method of assessing the macular tissues (fig 2). The tomograms provide cross sectional views of the macula and abnormal tissue such as the choroidal neovascular membrane can be seen. The extent and severity of the exudative response, which causes separation of the tissue layers, may be visualised. When geographic atrophy is present, thinning of the macular tissues is seen but without separation of the layers. Thus tomography can be helpful in distinguishing neovascularisation and particularly in monitoring the therapeutic response.
What are the principles of management?
The principles of management can be broadly divided into prevention in the early stages and treatment to ameliorate symptoms if late stage complications develop.

Preventing progression
Research into the prevention of age related macular degeneration has focused on risk factors that exacerbate oxidative stress or interventions that ameliorate their effects, such as supplementation with antioxidant vitamins, particularly the macular carotenoids lutein and zeaxanthin. Stopping cigarette smoking is recommended since its adverse association with late age related macular degeneration is unequivocal.

Treating symptoms
Once neovascular age related macular degeneration has manifested, monotherapy with an anti-vascular endothelial growth factor drug (administered into the vitreous) is the current standard of care. Using biological medicines for the management of neovascular disease and has resulted in a shift away from laser based treatments that were more usually used in previous decades, such as ablation of the area of neovascularisation with thermal laser or induction of vascular thrombosis by photodynamic therapy. Laser treatments were effective compared with natural history in restricted subgroups of patients.15 16 Effectiveness was limited by the recurrence of neovascularisation and most treated patients experienced a moderate loss of vision (defined as a fall of three or more lines of vision on the ETDRS chart) over a two year period. Therefore, the finding that pegaptanib sodium, an aptamer that selectively inhibits vascular endothelial growth factor 165, was effective in reducing vision loss and could be applied across all subgroups of neovascular age related macular degeneration was greeted with enthusiasm.17

Pegaptanib sodium was almost immediately displaced by bevacizumab, a full length humanised monoclonal antibody against vascular endothelial growth factor.18 Bevacizumab was approved initially for the treatment of metastatic colorectal cancer. Soon after, ranibizumab, an antibody fragment, was shown to be highly effective in several controlled clinical trials. The 12 month results from these trials19 20 indicated that up to a third of those treated with ranibizumab will have improved visual acuity, few patients will have progressed to moderate vision loss, and on average visual acuity is improved by two lines. Retinal imaging with optical coherence tomography before and after intravitreal administration of anti-vascular endothelial growth factor treatment shows marked reduction of intraretinal and subretinal fluid, often with spectacular and rapid apposition of the retinal layers and restoration of the anatomical contours (figure 2). This morphological restitution is often accompanied by improvements in visual acuity of the order of three to four lines on the ETDRS chart. Bevacizumab was reported to be safe for administration into the vitreous gel of the eye, with reductions in the exudative manifestations and improvements in acuity similar to those seen with ranibizumab, and it has since become the most used anti-vascular endothelial growth factor agents worldwide.21 Bevacizumab remains unlicensed but
**WHAT DO CURRENT GUIDELINES RECOMMEND?**

Subsequent to the technology appraisal and issue of guidance by the National Institute for Health and Clinical Excellence, ranibizumab has been widely adopted as the treatment of choice for subfoveal neovascular age related macular degeneration in the UK. However, the high cost of ranibizumab, along with the positive clinical experience with bevacizumab, has resulted in the majority of patients in the United States and other countries being treated with the latter drug.

In the UK, updated guidelines for the management and treatment of neovascular age related macular degeneration have been published by the Royal College of Ophthalmologists, but the clinical algorithm shown in figure 4 reflects the worldwide pattern of use of anti-vascular endothelial growth factor therapy.

**WHAT CAN CURRENT TREATMENT ACHIEVE?**

The ultimate treatment goal when neovascular age related macular degeneration has already supervened is to achieve perfect central vision with normal or near normal foveal and macular anatomy. Complete cessation of exudation can result in good apposition of the tissue layers but most patients report difficulty with reading small print and other visually demanding tasks even when tissue contours have been restored. High resolution optical coherence tomography scans obtained after anti-vascular endothelial growth factor treatment show persistent abnormalities of the outer retina even though the tissues appear to be fluid free. In cases where atrophy and fibrosis have already occurred, considerable impairment of central visual function can remain despite the achievement of a fluid free macula.

Although thermal laser photocoagulation and photodynamic therapy are less effective than ranibizumab they remain useful under specific clinical settings.

**WHAT RESEARCH IS ONGOING?**

The fusion protein of binding domains from human vascular endothelial growth factor receptors 1 and 2 is a new treatment that showed highly promising findings in terms of improved retinal morphology and visual acuity in phase 1 dose seeking trials. Its affinity for vascular endothelial growth factor is 200 times greater than that of ranibizumab, and because it remains in the vitreous for longer than ranibizumab it could achieve a similar efficacy with longer re-treatment intervals. Results of a head to head comparison of vascular endothelial growth factor TRAP and ranibizumab are expected towards the end of 2010.

Physical adjunctive treatments combined with ranibizumab are also being investigated. Although some pilot studies suggested marked reductions in the need for re-treatment with the combination of ranibizumab and physical adjunctive therapies, randomised controlled trials have not shown benefit in terms of a reduced need for re-treatment or improved visual outcome at 12 months when compared with ranibizumab monotherapy. A further approach involves focused macular irradiation using strontium 90 brachytherapy combined with an anti-vascular endothelial growth factor drug. Preliminary findings from small randomised pilot studies with 12 months of follow-up suggest functional outcomes similar to those seen in the ranibizumab monotherapy trials but achieved...
QUESTIONS FOR FUTURE RESEARCH

- Do gene-environment and gene-nutrient interactions alter the risk of age related macular degeneration?
- Do genetic factors determine morphological responsiveness to vascular endothelial growth factor inhibition?
- Can visual outcomes in neovascular age related macular degeneration be improved through adjunctive treatment with neurotrophic agents?
- What are the optimum screening strategies for identification of people at highest risk of developing late stage age related macular degeneration?

Future research

Several distinct therapeutic approaches to prevention are being investigated. These include injection of oxidative stress and interference with the visual cycle, but the most exciting development is the use of immune modulation and immunomodulators as a range of new therapeutic agents. Since drusen almost always precede the development of geographic atrophy, immunomodulatory drugs can be administered to eyes with early macular degeneration without overt functional loss. Glatiramer acetate is one such drug and a small observational study has shown marked reductions in drusen size and area within 12 weeks of intraocular administration. Other treatments include POT-4 (Potential pharmaceuticals Louisville, Kentucky) and eculizumab (Alexion Pharmaceuticals, Cheshire, Connecticut). These drugs and others are inhibitors of complement activation that prevent formation of the membrane attack complex or other inflammatory mediators, thus targeting the pathways that lead to early and late age related macular degeneration.

If the promise of new treatments is realised there is huge potential for maintaining good eyesight and quality of life in older adults.

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