IN THE UK it is estimated that over a quarter of a million adults suffer blindness due to age-related macular degeneration (AMD).

The disease generally affects central vision so patients have difficulty reading or recognising faces but because they retain peripheral vision they are usually able to navigate and maintain their mobility.

Readers might find a quick reminder of retinal structure helpful in understanding AMD (see Panel 1, p384).

What is AMD?
AMD is the term applied to changes in the eye, characterised by extensive drusen and pigmentary abnormalities, in people aged over 50 years.

Drusen are accumulations of lipid material below the retinal pigment epithelium and within the Bruch’s membrane, appearing as yellow spots on the retina. Pigmentary abnormalities of the macula can be hypopigmentation or hyperpigmentation.

These changes do not automatically lead to central vision loss but a number of people with these signs will go on to develop severe central vision loss.

Loss of vision occurs either as a result of “geographic atrophy”, which is a feature of dry AMD, or the growth of blood vessels into subretinal space (neovascularisation), which is a feature of wet AMD (unlike normal vessels, the new vessels are leaky — see later), or both.

Geographic atrophy is a sharply demarcated area of partial or complete depigmentation, caused by atrophy of the retinal pigment epithelium.

Most patients (80 per cent) with AMD have the dry type. Severe sight loss is associated with the wet type. However dry AMD can easily convert to wet AMD and the distinction is not always clear.

In neovascular disease new blood vessels from the choroid breach the Bruch’s membrane. This process is thought to be under the control of vascular endothelial growth factor A (VEGF-A), a pro-angiogenic growth factor which also increases vascular permeability.

These new vessels allow blood constituents to leak out, resulting in the separation of Bruch’s membrane, retinal pigment epithelium and the retina and a thickening of the retina due to fluid accumulation. This eventually results in degenerative changes in the photoreceptors and fibrosis.

There are many classifications of AMD but the one developed and used in the Age Related Eye Disease Study (AREDS)1 is increasingly used (see Panel 2, p385).

Not all patients with early signs of AMD progress to advanced disease. Patients with small drusen in both eyes have a 0.4–3 per cent risk of progressing over
five years. If large drusen and pigment abnormalities are present, however, the risk increases to around 47 per cent.

**What patients experience**

Symptoms are purely visual and depend on the type of AMD.

**Difficulty reading**

Initially, geographic atrophy starts as points of depigmentation. These coalesce to include the central macula, leading to a progressive worsening of vision and, in some cases, to severe visual impairment. However, if only one eye is affected the patient may not be aware of any visual impairment and dry AMD is sometimes only diagnosed by chance during an ophthalmic examination. If both eyes are affected the patient may complain of difficulty reading — especially small print. Sight loss in dry AMD is usually slow and insidious.

**Wavy lines and a dark spot**

Where neovascularisation occurs onset of symptoms is acute, with blurring of vision and distortion. Lines may become crooked or wavy and some patients notice a dark spot in the centre of their vision. If the second eye becomes affected the patient will suddenly complain that he or she is unable to read, see fine detail or drive. If left untreated the neovascularisation will expand rapidly, leading to a large scar and severe visual impairment.

**Charles Bonnet syndrome**

Many patients with macular degeneration suffer from visual hallucinations (eg, repeated patterns or flashes of light, odd shapes). These usually disappear after 18 months but can last longer. If not warned about hallucinations patients can believe they are developing a serious psychiatric illness and sometimes are too afraid to discuss it with their family or GP.

**Risk factors**

The exact cause of AMD is unknown, but it is proposed that macular degeneration results from the cumulative effects of oxidative stress.

The retina and the retinal pigment epithelium have a high exposure to light and oxygen, both of which can potentiate the formation of free radicals. Smoking and genetics are major risk factors and have a synergistic effect.

Smokers have a two- to three-fold increased risk of developing AMD and there is a dose-response relationship with pack-years of smoking.

Race appears to have some bearing on incidence. For example, incidence of AMD is higher in white people than in black people.

Recent studies have identified polymorphism of the complement factor H (CFH) gene and LOC387715/HtrA1 genes as risk factors. CFH, a major inhibitor of the complement system, is synthesised within the macula and is present in drusen. HtrA1 is an ortholog of transforming growth factor β, which is involved in the induction of VEGF secretion.

Other factors, such as iris colour and sunlight exposure, have been investigated but the evidence is conflicting and inconclusive. However wearing sunglasses with 100 per cent protection against UVA and UVB in bright sunlight would seem prudent.

**Dietary factors and advice**

Interest has focused on whether foods high in antioxidant micronutrients reduce oxidative stress and protect against AMD. In AREDS, patients were graded into four categories (see Panel 1) and received placebo, zinc alone, antioxidants alone or a zinc-antioxidants combination containing:

- Ascorbic acid 500mg
- Vitamin E 400IU
- Beta-carotene 15mg
- Zinc 80mg
- Copper 2mg

Reduction in incidence was only statistically significant in patients within categories 3 and 4 taking the combined therapy.

However, pharmacists should also be aware that two studies have shown that smokers taking beta-carotene may be at increased risk of lung cancer and another study had indicated that vitamin E supplementation is associated with an increased risk of heart failure in patients with diabetes or vascular disease.

Macular pigmentation is composed of two carotenoids, lutein and zeaxanthin. These are found in green leafy vegetables and eggs, and some trials suggest that higher dietary intake of these nutrients may decrease the risk of developing AMD. Other studies have indicated that omega-3 fatty acids (docosahexaenoic acid; DHA) and eicosapentaenoic acid (EPA) may also be protective. AREDS 2 is a 4,000 participant five-year controlled trial (2008–13) investigating the protective effect of lutein, zeaxanthin and the omega-3 fatty acids.

Many supplements are marketed for AMD but not all contain the formulation used in the AREDS trial for which there is the best evidence. It is important that smokers take a beta-carotene-free product. Most ophthalmologists generally advise dietary changes rather than supplements.

**Diagnosis**

AMD is usually evident on clinical examination and fundus photography. The clinician will see either areas of pallor with sharply defined scallop edges or an exudative macular lesion.

---

**Key points**

- Age-related macular degeneration, particularly the wet type, can cause severe vision loss.
- Stopping smoking decreases the risk of developing AMD.
- Some trials indicate that certain nutrients may protect against AMD. These include antioxidants, lutein, zeaxanthin and omega-3 fatty acids.
- Dry AMD can rapidly progress to wet AMD so patients with worsening vision should seek urgent appointment.
- Treatment for wet AMD includes laser therapy, surgery, photodynamic therapy (verteporfin) and anti-VEGF agents. There is no treatment for dry AMD.
Fundus fluorescein angiography (FFA) is the gold standard for diagnosing choroidal neovascularisation in AMD. For the procedure 3–5ml of 10 or 20 per cent fluorescein is injected into a suitable peripheral vein and a sequence of images is taken with a digital camera over 10 minutes to identify abnormal blood vessels and leakages. The main side effects of the fluorescein are nausea, vomiting, syncope, pruritus and a temporary yellowing of the skin. Serious side effects (eg, anaphylaxis and cardiac arrest) are rare but a crash trolley should be available.

Indocyanine green (contraindicated in patients with iodine allergies) is occasionally used to visualise the choroidal circulation.

Optical coherence tomography (OCT), which allows non-invasive visualisation of the retina, is used for monitoring retinal oedema and response to treatment.

**Treatments**

There are no specific treatments for dry AMD. Patients should be encouraged to stop smoking and to eat a diet rich in green leafy vegetables, eggs and a portion of oily fish once a week. They should be advised to seek an urgent appointment if there is any deterioration in vision.

Wet AMD can be treated and it is estimated that 26,000 patients per year in the UK have wet AMD eligible for treatment, including laser therapy, surgery and pharmacotherapy.

Laser treatment (to destroy abnormal blood vessels) is only suitable for a few patients and has limitations — it causes scarring and the disease tends to recur. Surgery (eg, macular translocation) is outside the scope of this article and not generally recommended.

**Verteporfin**

Verteporfin (Visudyne) is the basis of photodynamic therapy. Verteporfin is a porphyrin sensitisser, preferentially taken up by rapidly proliferating endothelial cells. Given by intravenous infusion over 10 minutes, it is activated by laser light directed to the choroidal neovascularisation lesion at a single spot. This generates an oxygen singlet which causes damage to the vascular endothelial cells and thrombotic occlusion of the blood vessels within the lesion. Patients should be evaluated every three months and retreatment given in the event of recurrent choroidal neovascularisation leakage (licensed for up to four treatments per year).

The National Institute for Health and Clinical Excellence only approved it for patients with totally classic lesions (a subset of wet AMD). In addition, its use has fallen with the launch of ranibizumab because although photodynamic therapy reduces the risk of moderate to severe visual loss, most patients still lose vision and improvements are unusual. Verteporfin is reserved for patients in whom intravitreal injections are contraindicated (eg, past history of retinal detachment) or unacceptable.

**Anti-VEGF agents**

Currently there are two licensed and one unlicensed anti-VEGF-A agents used in the treatment of wet AMD. All have to be given by intravitreal injection. These injections run the risk of causing endophthalmitis (sight threatening infection), retinal detachment, uveitis and traumatic lens injury. They also increase the incidence of cataract formation.

The Royal College of Ophthalmologists recommends continual treatment of AMD with anti-VEGF agents if there is persistent evidence of lesion activity, the lesion continues to respond to treatment and there are no contraindications to further treatment. Treatment could last two years or more. There are, however, unanswered questions, such as how long patients should be monitored.

**Pegaptanib**

Pegaptanib (Macugen) was the first anti-VEGF-A agent launched. It binds to VEGF-A isoform 165. It is used every six weeks. Although there have been no head to head trials with ranibizumab, the latter appears to be the more efficacious — NICE does not recommend pegaptanib for the treatment of AMD.

**Ranibizumab**

Ranibizumab (Lucentis®) is the Fab portion of a monoclonal antibody that binds to all four isoforms of VEGF-A and therefore prevents it binding to its receptor. The full monoclonal antibody (bevacizumab — see later) was initially thought to be too large to penetrate the inner membrane of the retina and so the ranibizumab fragment was developed.

Treatment with ranibizumab is recommended by NICE for patients with AMD who have experienced recent progression of the disease and who also have no permanent damage of the fovea, a limited lesion size and a specified visual acuity.

The cost of ranibizumab beyond 14 injections per eye is currently met by the manufacturer under the ranibizumab repayment scheme. In the UK ranibizumab is licensed for three initial consecutive monthly injections and then patients are reviewed every month. They receive another dose if there are any signs of disease progression.

In two landmark clinical trials (ANCHOR and MARINA), a significant number of patients were found to gain more than 15 letters on the ETDRS (Early Treatment Diabetic Retinopathy Study) scale which was measured at 24 months. In both trials the patients in the ranibizumab arm received a monthly injection for two years.

The PrONTO study had a dosing schedule more in line with UK practice where, after their initial three doses, patients are given further doses as needed. Although the results were on a par with the landmark trials the number of patients was small. However the recently published Comparison of AMD Treatments Trial (CATT®) demonstrates that similar results are seen with monthly and when-required ranibizumab injections.

Due to the number of patients with AMD and the need for them to be assessed monthly for two to four years most ophthalmic departments are struggling with capacity issues. Various trials are investigating whether patients can be monitored less frequently.

**Panel 2: Disease Description**

<table>
<thead>
<tr>
<th>No AMD (category 1)</th>
<th>None or very few small drusen &lt;63μm in diameter.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early AMD (category 2)</td>
<td>Any or all of the following:</td>
</tr>
<tr>
<td></td>
<td>Multiple small drusen</td>
</tr>
<tr>
<td></td>
<td>Few intermediate drusen 63–124μm in diameter</td>
</tr>
<tr>
<td></td>
<td>Retinal pigment epithelium abnormalities</td>
</tr>
<tr>
<td>Intermediate AMD (category 3)</td>
<td>Any or all of the following:</td>
</tr>
<tr>
<td></td>
<td>Extensive intermediate drusen and at least one large druse (&gt;125μm)</td>
</tr>
<tr>
<td></td>
<td>Geographic atrophy not involving the centre of the fovea</td>
</tr>
<tr>
<td>Advanced AMD (category 4)</td>
<td>Geographic atrophy involving the fovea or any features of neovascularisation (eg, new vessels in the retina or subretina, haemorrhage, exudate), or both</td>
</tr>
</tbody>
</table>

**Signposting**

- The Royal National Institute of Blind People (www.rnib.org.uk) provides patient information leaflets in large clear print, Braille and audio CD. It also runs a free medicines information line so that patients can listen to information leaflets (0800 198 5000).
- The Macular Disease Society website (www.maculardisease.org) has a series of information leaflets that can be printed or downloaded onto an MP3 player.
- AMD Alliance International (www.amdalliance.org/home.html) is a source of information about AMD. The website includes patient videos on living with the disease.

*Available online until 23 April 2012, www.pjonline.com*
Bevacizumab

Bevacizumab (Avastin®) is licensed for various cancers but an unlicensed product is available from special manufacturers for intravitreal use. Due to the difference in cost (£60 for a bevacizumab special), bevacizumab is widely used in the US for the treatment of AMD. In the current UK economic climate it is an attractive proposition for primary care trusts to commission its use in the treatment of AMD. However, prescribing an unlicensed product where a licensed product exists is not generally supported by the General Medical Council. In December 2011, following the first year results of CATT the Royal College of Ophthalmologists stated that in AMD both ranibizumab and bevacizumab are equally effective and have similar safety profiles, but supported the continued use of ranibizumab for AMD.9 The royal college accepts the use of bevacizumab for retinal conditions where no licensed or NICE-approved treatments are available, where patients have failed to respond to ranibizumab and where ophthalmologists wish to use anti-VEGF agents earlier than specified in the NICE guidelines. The college believes that the Medicines and Healthcare Products Regulatory Agency and NICE should produce guidelines on this.

Two large head to head trials of ranibizumab and bevacizumab are currently running to provide evidence on efficacy and safety. The IVAN trial (UK), expected to report in May and CATT (US), which has reported its first year results but has a further year to run.

In CATT, non-inferiority was reported between monthly ranibizumab and bevacizumab injections and between monthly ranibizumab and when-required ranibizumab. The results were inconclusive for regular bevacizumab versus when required bevacizumab. That patients on pro bevacizumab required more injections than those on pro ranibizumab does not support the anecdotal opinion that bevacizumab has a longer duration of action. Serious adverse effects were significantly higher in the bevacizumab group but these were scattered across a range of organ systems rather than mostly comprising arteriothrombotic events as expected.

A major shift to bevacizumab is unlikely until IVAN is published and both the GMC and the MHRA support its use. The NICE guidance on ranibizumab and pegaptanib in AMD was due for review in August 2011. It would clarify the situation if bevacizumab were included in the next review.

Developments

VEGF Trap-Eye ( aflibercept) is a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2, that binds all forms of VEGF-A. Trials suggest it is non-inferior to ranibizumab and, after initial stabilisation, the injection needs only to be given every two months. Its manufacturer Bayer has applied for marketing authorisation and it is expected to be launched (as Eylea) in the autumn.

There is research into inhibition of the neovascular process and also in combining ranibizumab with other agents (e.g., verteporfin, intravitreal steroids or radioactive intravitreal implants). See Panel 3 for more on areas of research.

Role for pharmacists

Pharmacists can provide a valuable service in educating people about AMD and supporting patients. They can encourage people to:

- Stop smoking
- Eat a diet of plenty of green leafy vegetables, eggs and oily fish
- Wear good quality sunglasses in bright light

They can also:

- Provide information and education on AMD and on Charles Bonnet syndrome (see Resources)
- Explain the issues behind the ranibizumab/bevacizumab controversy
- Signpost patient to self help groups (see p385)

References available online.

DECLARATION OF INTEREST The author has taken part on a panel on unlicensed medicines sponsored by Novartis. The fee went to the Leeds Teaching Hospital Trust.