Prevention and treatment of age-related macular degeneration

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Age-related macular degeneration (AMD) is a degenerative change of the central area of the retina (macula) in people aged 55 years and above and is the leading cause of irreversible sight loss in the developed world.

The management of AMD has been transformed over the last decade with the introduction of anti-vascular endothelial growth factor (anti-VEGF) agents. Early treatment of neovascular or ‘wet’ AMD results in better visual outcomes and GPs play a critical role in the early identification and prompt referral of patients with this condition. This article will describe clinical aspects of AMD, prevention, current treatments and management of visual loss.

What is AMD?

AMD is a disease of metabolic dysfunction within the aging retina. Lipid and protein material accumulates beneath the retinal pigment epithelium (RPE) and within Bruch’s membrane (see Figure 1). Focal collections of lipid material are seen as ‘drusen’ on examination of the retina and morphological alteration of the RPE causes hyper- and hypopigmentation (see Figure 2). These changes form part of ‘dry’ AMD. As AMD progresses, the breakdown of light-sensitive cells leads to one or more areas of well-demarcated depigmented (atrophic) RPE, described as ‘geographic atrophy’ (see Figure 3).

In some patients, disordered local anatomy and biochemistry leads to hypoxia and stimulation of new blood vessel growth through the release of angiogenic growth factors (including VEGF). These abnormal blood vessels, known as a choroidal neovascular membrane, lie beneath and within the retina and can easily bleed and leak blood constituents.

Figure 1. Optical coherence tomography (OCT) scans demonstrating the layers of the retina at the fovea in cross-section. The top image [a] shows healthy retina. In the lower image [b], the usually smooth profile of the retinal pigment epithelium and Bruch’s membrane is irregular due to drusen.
How is AMD classified?

AMD is commonly described as ‘dry’ or ‘wet’ (neovascular). Wet AMD may be further subdivided based on fluorescein angiogram and occasionally indocyanine green angiography appearances into classic, occult, retinal angiomatous proliferation and choroidal polyps. There are multiple classification systems of AMD, but the Age-Related Eye Disease Study (AREDS) system has a practical application in the prescription of prophylactic vitamins (see Table 1).

Which patient groups are most susceptible?

Nonmodifiable risk factors for AMD are age and genetics, while the most consistent modifiable risk factor is smoking. Patients of increasing age, current smokers and those with a family history of the condition are therefore most susceptible to the disease.

There is inconsistent evidence for an association between AMD and long-sightedness, iris colour, dietary carotenoids (which make up macular pigment), alcohol intake, omega-3 and -6 fatty acid intake, obesity, hypertension, cardiovascular disease, diabetes, cataract surgery, sunlight exposure, gender and race.

What are the signs and symptoms of AMD?

AMD may be asymptomatic in the early stages and is often identified incidentally at a routine optometry review.

In dry AMD, patients typically describe gradual onset blurred central vision, whereas in wet AMD the onset is more rapid over days to weeks. Patients with AMD may complain of difficulty reading or of missing letters in words. Subtler symptoms include impaired light-dark adaptation (the patient may describe a central dark patch in the visual field that clears within a few minutes as they adapt) and loss of contrast sensitivity. Metamorphopsia, the perception of distorted vision (“straight lines look wavy”), is suggestive of wet AMD. Charles Bonnet syndrome, in which patients report formed visual hallucinations, may occur in patients with severe loss of vision.

Visual acuity may be normal in early and wet AMD, but deteriorates with progression of the disease. Dilated examination of the retina may reveal drusen, retinal pigmentary changes and atrophy at the macula in dry AMD. Retinal haemorrhage and subretinal fluid are seen in addition to dry changes in wet AMD.

Retinal imaging techniques

Ocular coherence tomography (OCT) scanning is a noninvasive imaging technique that provides a cross-sectional 3D image of the retina and can detect intraretinal and subretinal fluid in wet AMD (see Figure 4).

Fundus fluorescein angiography (FFA) is used to confirm the diagnosis and establish the angiographic subtype of wet AMD. To perform FFA, fluorescein dye is injected into a peripheral vein and a series of retinal images is taken. FFA may be combined with indocyanine green angiography where more detailed images of the choroidal vasculature are required. This is particularly helpful for detecting choroidal polyps and retinal angiomatous proliferation, which are subtypes of wet AMD.

OCT angiography is a new imaging technique that uses OCT technology to visualise the retinal and choroidal vascula-
Age-related macular degeneration

The treatment options
NICE has published technology appraisal guidance supporting the use of specific anti-VEGF therapies in AMD and is expected to publish full guidelines on the condition in August 2017. The Royal College of Ophthalmologists published guidelines on AMD management in 2013.

Dry AMD
Treatment of dry AMD remains limited. Specific vitamin supplementation is recommended in patients with intermediate or advanced AMD based on the AREDS trial. This randomised-controlled trial showed that the risk of progression from intermediate to advanced AMD was reduced by around 25 per cent in participants who took zinc and antioxidant supplements.

AREDS was followed by the AREDS2 trial, which showed there was no detriment when beta-carotene was omitted. Beta-carotene was therefore removed from the recommended formulation (see Box 1) as it can increase the risk of lung cancer in smokers. The benefit of supplementation in early AMD remains unproven.

Wet AMD
NICE currently recommends the anti-VEGF agents ranibizumab (Lucentis) or aflibercept (Eylea) for use in subfoveal choroidal neovascular membranes (see Table 2). Patients may be treated if they have a visual acuity of 6/12 to 6/96 and there is no permanent structural damage to the fovea. These agents improve vision in around a third of patients, the majority will maintain their visual acuity and around 10 per cent will not respond to therapy. Bevacizumab (Avastin) is an anti-VEGF agent that was developed for use in colorectal carcinoma. It is cheaper than the other anti-VEGF agents but is unlicensed for use in AMD. It is sometimes used ‘off label’.

These drugs are administered as an intravitreal injection under topical local anaesthetic. This takes place as a day case in a hospital or community unit, often by nurses or trained allied health-

Figure 4. Colour fundus photographs and ocular coherence tomography (OCT) scans of a right eye before anti-VEGF treatment [a], and after anti-VEGF treatment [b]. There is resolution of the macular haemorrhages and subretinal fluid
**500mg vitamin C**
**400IU vitamin E**
**80mg zinc oxide**
**2mg copper**
**± lutein and zeaxanthin**

**Box 1.** Currently recommended dietary supplementation for patients with intermediate or advanced age-related macular degeneration

Care professionals. Clinical trials administered monthly injections for 24 months. In the NHS, injections are usually administered monthly for three months. After this, treatments are either given every month as a PRN (when required) regimen or as part of a treat and extend regimen, treating monthly until stable and then extending the treatment interval each time the patient is stable up to an injection once every three months. Treatment is then withdrawn after a period of stability or treatment failure.

Potentially serious adverse events occur in <0.1% of intravitreal injections and include endophthalmitis, retinal detachment and cataract. Systemic anti-VEGF agents confer an increased risk of events classified as arterial thromboembolism (ATE), including myocardial infarction and stroke. There may be a small increased risk of these events in patients who receive intravitreal anti-VEGF agents. The MARINA trial demonstrated an ATE rate of 4.6% in recipients of ranibizumab versus 3.8% in recipients of a sham injection at 24 months; however, this was not statistically significant.\(^\text{10}\)

Photodynamic therapy is rarely used but is an option in patients with choroidal polyps.

**What is the GP’s role in management?**

The rapid onset of central distortion in an older adult should be considered AMD until proven otherwise. GPs ought to make an urgent referral to a local optometry or hospital retina service, depending on local structuring of services. The Royal College of Ophthalmologists has developed a “Wet AMD rapid access referral” form for optometrists and GPs.\(^\text{15}\)

GPs may provide advice on how to slow progression of the disease. Patients who smoke should be supported in smoking cessation. Patients should be advised to eat a diet rich in dark green leafy vegetables and on the benefits of vitamin supplementation in intermediate and advanced AMD.

Complications of intravitreal injections are rare but potentially sight threatening.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mode of action</th>
<th>Key relevant trials</th>
<th>NICE approved?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td>Humanised Fab fragment of a monoclonal antibody that binds to and inhibits the action of all isoforms of VEGF-A</td>
<td>MARINA(^\text{10}) ANCHOR(^\text{11}) (superiority studies against sham injection)</td>
<td>Yes</td>
</tr>
<tr>
<td>Afiblercept (Eylea)</td>
<td>Fusion protein that inhibits all isoforms of VEGF-A and placental growth factor</td>
<td>VIEW1/VIEW2(^\text{12}) (noninferiority studies against ranibizumab)</td>
<td>Yes</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Humanised full-length monoclonal antibody derived from the same antibody as ranibizumab. Likely to bind to all the same isoforms of VEGF-A as ranibizumab, but with a different affinity</td>
<td>CATT(^\text{13}) IVAN(^\text{14}) (noninferiority studies against ranibizumab)</td>
<td>No</td>
</tr>
</tbody>
</table>

**Table 2.** Properties of antiangiogenic therapies for wet age-related macular degeneration


**References**


Declaration of interests
None to declare.

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POEMs

Single-dose dexamethasone an option for acute adult asthma

Clinical question:
Is a single dose of dexamethasone as effective as five days of prednisone for acute exacerbations of asthma?

Bottom line:
A single dose of 12mg dexamethasone, which has a longer duration of action than prednisone, is almost as effective as five days of 60mg prednisone for the prevention of relapse in adults with acute asthma treated in a emergency department. It is a reasonable option for treatment in the emergency department, given its fewer side-effects. In this study, patients who received the single dose also took placebo for four days; further research is needed to determine whether patients are comfortable with taking just a single dose. (LOE = 2b)

Reference:


Synopsis:
These investigators enrolled 456 adults younger than 56 years who presented with acute asthma to an emergency department and required at least one treatment with a beta-agonist. The patients were randomly assigned, using concealed allocation, to receive treatment with prednisone 60mg daily for five days or a single dose of dexamethasone 12mg followed by four days of placebo. Treatment was started in the emergency department.

Of the 456 people initially enrolled, 376 could be evaluated; 16 were admitted before leaving the emergency department and 73 could not be contacted (more in the dexamethasone group). Over the subsequent two weeks, 12.1% of the dexamethasone group and 9.8% of prednisone group had a relapse that required additional treatment (difference 2.3%; 95% CI -4.1% to 8.6%). This difference did not meet the researchers’ threshold for noninferiority of 8%, meaning that treatment with dexamethasone was slightly less effective. The hospitalisation rate was low (3%) and did not differ between treatment groups. Side-effects were more common in the prednisone group.

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