# Age-related macular degeneration

Age-related macular degeneration is a primary degenerative disorder of the macula in people aged 55 years or above. It is the single largest cause of irreversible visual loss in the developed world, and in the UK alone an estimated quarter of a million people are blind as a result of age-related macular degeneration (Ferris et al, 2013). The two forms of age-related macular degeneration, geographic atrophy (dry) and exudative (wet) age-related macular degeneration, account for two-thirds of all registrations for visual impairment in the UK. An estimated 26 000 patients are diagnosed with 'wet' age-related macular degeneration every year. This article reviews the pathophysiology of age-related macular degeneration, its main clinical manifestations and current treatment options.

## Pathophysiology

Age-related macular degeneration can be divided into two main pathological entities, dry and wet (*Figure 1*). In its early stages, dry age-related macular degeneration is characterized by the accumulation of drusen or yellow lipid deposits beneath the retinal pigment epithelium and within the Bruch's membrane of the retina. On fundus examination, these drusen are visible as pale yellow deposits on the retinal surface. These may be accompanied by areas of focal hyper- or hypopigmentation, which reflect degenerative changes within the retina. Drusen and retinal pigment epithelium irregularities correlate poorly with visual symptoms, and vision may be preserved until the onset of geographic atrophy. Clinically, geographic atrophy manifests itself as well-defined areas of retinal thinning with scalloped margins through which underlying choroidal vessels may become visible.

A proportion of patients (up to 18%) with these early changes may also progress to wet age-related macular degeneration. In particular, the presence of large drusen (>125 microns in diameter) and pigment abnormalities in either eye give the highest cumulative risk of progression to wet age-related macular degeneration.

In exudative or neovascular wet age-related macular degeneration there is accumulation of intraretinal fluid as a consequence of the formation of pathological blood vessels in the choroid (choroidal neovascularization). These abnormal vessels allow leakage of blood contents and are associated with thickening of the retina or the formation of cystic spaces within the retina (*Figures 2a* and *b*). These pathological changes in turn cause misalignment of photoreceptors and hence degenerative changes with eventual cell death and fibrosis. Clinically, wet age-related macular degeneration is characterized by haemorrhages, exudates and macular thickening as a result of oedema. If left untreated, wet age-related macular degeneration eventually leads to a fibrotic lesion known as a disciform scar (*Figure 3*).

Risk factors for age-related macular degeneration include increasing age, smoking and a positive family history. Poor diet, low vitamin intake, previous cataract surgery (Wang et al, 2003) and light damage to the retina, especially in the ultraviolet range (Taylor et al, 1990), have all been suggested as potential risk factors for macular degeneration, with some surgeons advocating the use of ultraviolet filters in intraocular implants at the time of cataract surgery. However, these are largely unproven and remain a matter for debate.

## Clinical features

In the presence of drusen only, subtle changes in contrast sensitivity, colour vision, central visual field and dark adaptation have been described. However, patients are generally asymptomatic with little or no visual loss and the condition may only be detected on routine eye testing or on screening with an Amsler grid. With progressive geographic atrophy (*Figure 4*), patients may report a

Figure 1. Pathophysiology of age-related macular degeneration (AMD).

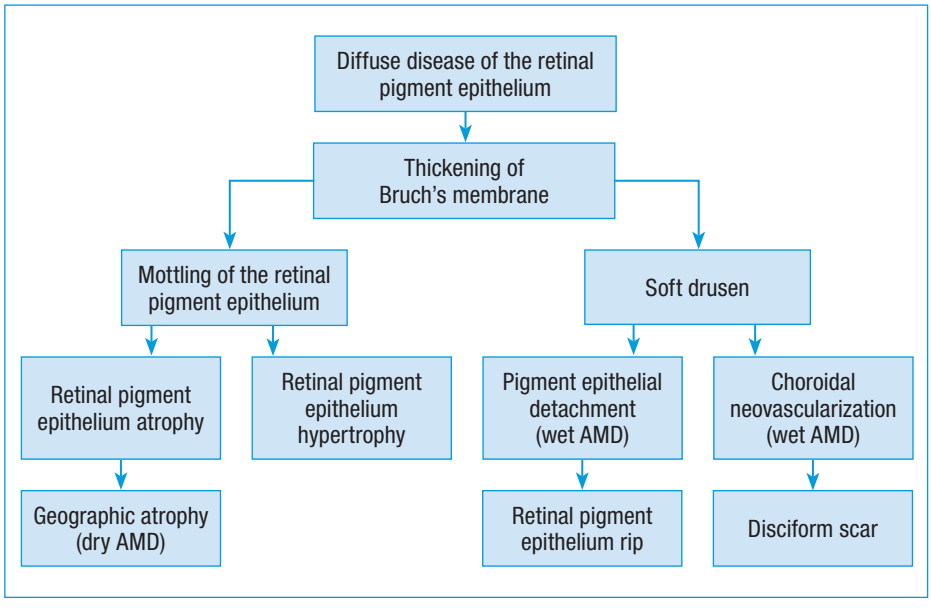


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Figure 2. **a.** Colour fundus photograph of wet age-related macular degeneration. Haemorrhages and white exudates can be seen in the macula region.

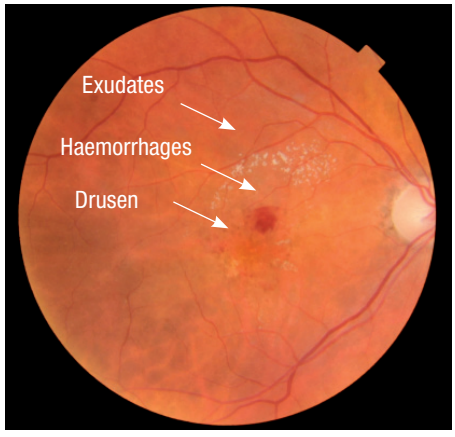
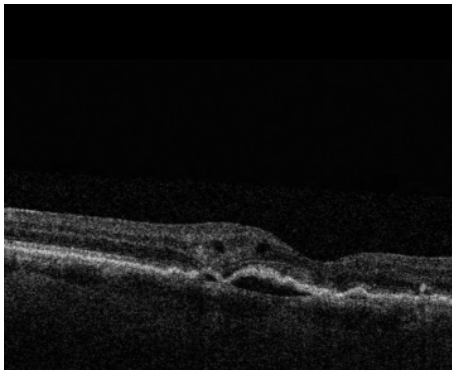



Figure 2. **b.** Optical coherence tomogram image of wet age-related macular degeneration. The 'trough' seen represents normal foveal architecture. The separation of layers in the middle represents sub-retinal and intra-retinal fluid in between the layers.



gradual decrease in central visual acuity and patchy loss of central visual fields (scotomas), all of which tend to occur over many years or even decades.

In contrast, patients with wet age-related macular degeneration present with acute symptoms of central blurring, distortion of images (metamorphopsia) and scotoma. Suspected wet age-related macular degeneration warrants an urgent referral to the ophthalmologist for investigation and treatment.

## Investigations

Optical coherence tomography and fundus fluorescein angiography are the main investigations in patients with wet age-related macular degeneration.

Optical coherence tomography enables detailed imaging of the retina and its constituent layers. It uses the principle of laser interferometry in which infrared rays 'scan' the surface profile to obtain a reflectivity pattern. By comparing the reflected beam with a reference beam of known time delay and intensity, a surface profile pattern can be built based on the interference between the two beams. Optical coherence tomography scanning allows for the precise detection of subtle fluid accumulation within or under the retina or retinal pigment epithelium that is not normally possible with ophthalmoscopy. By measuring the thickness of the retinal layers it enables monitoring of disease activity and response to treatment. A major advantage of optical coherence tomography scanning is that it is quick and non-invasive and is readily available in most high-street optometrists, thus enabling rapid diagnosis.

Retinal thickening or oedema on optical coherence tomography may be caused by conditions other than age-related macular degeneration, such as diabetic retinopathy, central serous retinopathy and retinal macroaneurysms. Fundus fluorescein angiogram represents a useful confirmatory test in all suspected cases of wet age-related macular degeneration. Fundus fluorescein angiography involves the intravenous administration of a contrast agent, fluorescein isothiocyanate, followed by fundus photography over 5–10 minutes. Fundus fluorescein angiography allows anatomical localization and characterization of the choroidal neovascularization lesion.

Figure 3. Colour fundus photograph of a disciform scar.

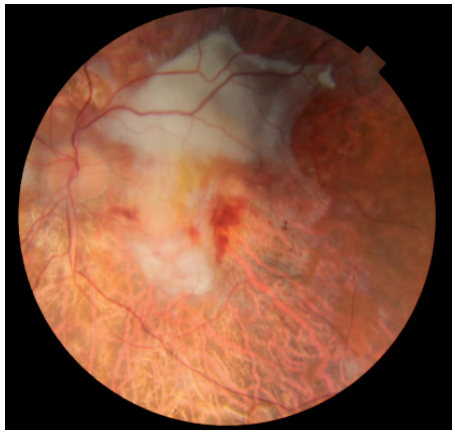
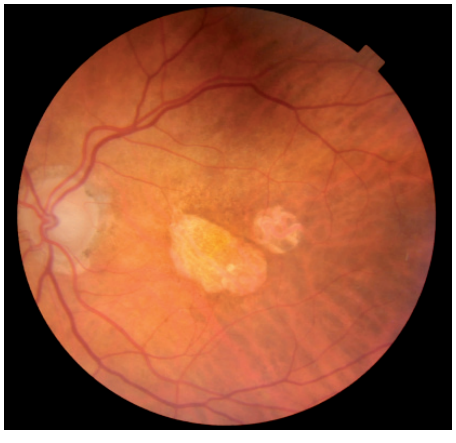


Figure 4. Colour fundus photograph of geographic atrophy.



## Treatment options

### Wet age-related macular degeneration

The development of anti-vascular endothelial growth factors (anti-VEGF) has revolutionized the treatment of wet age-related macular degeneration in the last decade and these have superseded other treatment modalities such as laser photocoagulation or photodynamic therapy.

Ranibizumab (Lucentis) is a humanized Fab fragment of a monoclonal antibody that binds to and inhibits the action of VEGF-A. The MARINA trial showed that with monthly intraocular injections of ranibizumab, visual acuity was improved in patients receiving ranibizumab 0.5 mg. Mean visual acuity increased by 7.2 letters on a LogMAR chart at 12 months *vs* a decrease of 10.4 letters with sham injections ($P<0.001$). The ANCHOR trial showed that ranibizumab injections were superior to photodynamic therapy in visual outcomes, and had a similar safety profile (Brown et al, 2006). Ranibizumab was approved by the National Institute for Clinical Excellence in 2008 for use in patients with wet age-related macular degeneration with visual acuities between 6/12 and 6/96, where the area affected by age-related macular degeneration measures 12 disc areas or less and where there is evidence of recent disease progression, such as haemorrhage or recent changes in visual acuity.

Long-term studies have now shown that at about 7 years from initiation of treatment with ranibizumab, approximately one third of patients demonstrated good visual outcomes, whereas an equal proportion had poor outcomes. Even after successful treatment, patients with wet age-related macular degeneration remained at risk of significant visual loss at a late stage in their treatment (Rofagha et al, 2013).

## KEY POINTS

- Age-related macular degeneration is the largest cause of irreversible blindness in the world.
- Age-related macular degeneration can be divided into two main entities: a 'dry' form, and a 'wet' (exudative) form.
- Dry age-related macular degeneration is characterized by deposition of lipid deposits called drusen in Bruch's membrane, pigment epithelial disturbances and by geographic atrophy.
- Wet age-related macular degeneration is characterized by retinal haemorrhages, exudates, intra-retinal, sub-retinal or sub-retinal pigment epithelium fluid and oedema from a choroidal neovascular membrane.
- Some patients with dry age-related macular degeneration will show conversion to wet age-related macular degeneration.
- Anti-vascular endothelial growth factor injections are the mainstay of treatment for wet age-related macular degeneration. There is currently no treatment for dry age-related macular degeneration, but vitamin supplementation has been shown to marginally slow its progression.

Aflibercept (Eylea) is a more recent addition to the anti-VEGF armamentarium. It is a fusion protein that inhibits all forms of VEGF-A. Two large studies, VIEW1 and VIEW2, have shown aflibercept to be non-inferior to ranibizumab in terms of functional outcomes and with no adverse safety profile (Heier et al, 2012). It has the theoretical advantage of requiring fewer injections and fewer clinic visits than ranibizumab.

Bevacizumab (Avastin) is a humanized full-length antibody derived from the same monoclonal antibody as ranibizumab. Originally developed as a chemotherapy agent for bowel cancer, its beneficial effects in the eye were discovered accidentally before the licensing of ranibizumab (Rosenfield et al, 2006). A Cochrane review found that ranibizumab and bevacizumab have comparable efficacy and safety profiles when used in the eye (Moja et al, 2014). As a vial of bevacizumab can be aliquoted into smaller doses for direct ocular administration (a process known as compounding), it is up to 20 times cheaper and hence more cost-effective than ranibizumab or aflibercept. The use of off-label bevacizumab is common in the United States and parts of Europe, especially among self-pay patients.

At a cost of £244 million, ranibizumab was the second most expensive drug in the NHS in 2014 (Hawkes, 2014) and a switch from ranibizumab or aflibercept to bevacizumab could potentially lead to savings for the NHS of several hundred millions of pounds annually. Cost-effiency studies have shown that ranibizumab is less cost-effective than bevacizumab and produces little to no gain in quality-adjusted life years but is associated with a significant increase in cost (Dakin et al, 2014). However, despite recent pressure from clinical commissioning groups, the use of bevacizumab for ocular conditions in the NHS continues to remain highly controversial (Cohen, 2015).

### Dry age-related macular degeneration

Treatment options for dry age-related macular degeneration are currently limited. Lampalizumab is a monoclonal antibody that binds to complement factor D, thus inhibiting the alternative pathway of the complement cascade, which has been implicated in the development of dry age-related macular degeneration. A phase II trial showed that it reduced the progression of geographic atrophy by 20.4% against sham at 18 months (Williams, 2013). Phase III trials are currently ongoing.

Patients with early age-related macular degeneration should be advised to stop smoking as this is a major risk factor.

Vitamin supplementation with high-dose antioxidants and minerals with a proprietary formula called AREDS (500 mg vitamin C, 400 mg IU vitamin E, 15 mg beta-carotene, 80 mg zinc and 2 mg copper) has been shown to delay the progression to wet age-related macular degeneration by 25% in patients who have lost vision in one eye from wet age-related macular degeneration and have early age-related macular degeneration in the other eye (Age-Related Eye Disease Study Research Group, 2001). Particular care needs to be taken to ensure patients stop smoking, as the beta-carotene in the formulation has been associated with an increased risk of lung cancer in smokers. The more recent AREDS2 study (Age-Related Eye Disease Study 2 Research Group, 2013) showed that omega-3 fatty acids do not offer any increased benefit, but that substituting beta-carotene with lutein and zeaxanthin (carotenoids which are found in green leafy vegetables like spinach, broccoli and cabbage) might offer equal protection but without the additional risk associated with smoking.

## Rehabilitation

Patients with significant sight loss are referred to the low vision aid services for support. Advice on adequate task lighting and the provision of optical aids and magnifiers may help to optimize residual visual function.

Patients with dry age-related macular degeneration may have impaired reading ability despite reasonably preserved distance visual acuity. For such patients, low vision aids such as magnifiers and computers with enhanced contrast settings may help in improving functional vision. Patients with loss of foveal vision as a result of macular degeneration may develop another preferential retinal locus of vision in lieu of the fovea, which can be enhanced using biofeedback and training.

Intra-ocular optical aids and implants have also been suggested as surgical treatments. The implantable miniature telescope works by enlarging the retinal image centrally, thus partly overcoming any scotoma centrally (Singer et al, 2012). The IOL-VIP system consists of a combination of lenses inserted into the eye which, via a prismatic effect, causes eccentric fixation on a preserved area of retina (Orzalesi et al, 2007).

Some patients with advanced age-related macular degeneration may develop visual hallucinations (Charles–Bonnet syndrome). These patients need reassurance that Charles–Bonnet syndrome often improves after 18 months although in some cases it may persist for years.

Patients with very significant sight impairment can be registered as being sight impaired or severely sight impaired. The benefits of visual impairment certification include access to help from social services, disability living allowance, free sight tests and low vision aids. **BJHM**

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