Age-related macular degeneration: diagnosis and management

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Background: Age-related macular degeneration (AMD) is a leading cause of blind registration in Western Europe and the third leading cause of blindness worldwide.

Methods: The management of AMD is discussed with a review of current and new treatments.

Results: Although there is no treatment for advanced dry AMD (geographic atrophy), there have been considerable advances in the management of neovascular AMD (nAMD). Established therapies for nAMD include laser photocoagulation and photodynamic therapy (PDT), but these have largely been superseded by agents which block the action of vascular endothelial growth factor (anti-VEGF agents). Current preventative strategies involve cessation of smoking and use of specific nutritional supplements to reduce the risk of developing nAMD.

Conclusions: There have been exciting advances in the treatment of nAMD and increased understanding of the genetics and pathogenic mechanisms involved will hopefully lead to the development of new therapies in the future.

Keywords: age-related macular degeneration/treatment/diagnosis/prophylaxis

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness and visual disability in patients aged ≥60 years in Europe and North America.¹ Worldwide, AMD is the third leading cause of blindness, behind cataract and glaucoma, causing 8.7% of all legal blindness.² The clinical spectrum of AMD encompasses drusen, hyperplasia of the retinal pigment epithelium (RPE), geographic atrophy and choroidal neovascularization (CNV). These changes affect the macula of the retina and subsequently may affect central or reading visual acuity.

AMD has been classified in one of the two ways. It can be divided into two broad clinical categories depending on whether there is a
presence of abnormal neovascularization: neovascular (synonymous with exudative or wet) and dry AMD. A second classification is used depending on the extent of visual impairment; late AMD, which includes neovascular AMD and an advanced dry form called geographic atrophy and early AMD that includes all other forms (Fig. 1). Early (dry) AMD is more prevalent than neovascular AMD in the UK and USA. However, patients with neovascular AMD account for $\sim$75% of cases of severe visual impairment secondary to AMD.$^3$

Patients with early (dry) AMD consisting of drusen and hyperplasia of the RPE may have no visual difficulties (Fig. 2). A minority of patients with early (dry) AMD may progress to geographic atrophy. Geographic atrophy is gradually progressive, and may involve the centre of the fovea causing central visual loss (Fig. 3). Geographic atrophy accounts for $\sim$25% of patients with severe visual loss secondary to AMD.$^3$

It is believed that the changes in Bruch’s membrane and RPE that occur in dry AMD may give rise to a state where blood vessels may sprout off existing choriocapillaris (pro-angiogenic state). These vessels then break through the normal level of Bruch’s membrane into the sub-RPE or sub-retinal spaces. Neovascular AMD is defined by the development of CNV. The patient will often report a sudden worsening of their central vision, often with distortion. Clinically, the CNV produces haemorrhage, exudative retinal detachment or serous or haemorrhagic pigment epithelial detachments (Fig. 4). In end-stage disease, this results in a fibrovascular or atrophic macular scar and subsequent permanent damage to the central vision.

![Fig. 1 Classification of age-related macular degeneration.](image_url)
Fig. 2 Fundus photograph showing an eye with drusen and RPE hyperplasia.

Fig. 3 Fundus photograph showing an eye with advanced geographic atrophy (dry AMD).
Prevalence/demographics

Friedman et al.\(^4\) found that AMD occurs in patients over the age of \(~55\) years. Prevalence increases substantially with increasing age. They also estimated that AMD affects \(>1.75\) million individuals aged \(\geq 40\) years in the USA. Owing to the rapidly ageing population, this figure is projected to rise to almost \(3\) million by 2020. Furthermore, \(~10–15\%\) of patients with AMD have severe loss of central vision.

The prevalence of AMD varies between racial groups with higher prevalence in European-descended populations. Pooled data from three large epidemiological studies showed that drusen were strongly age-related in the black population, and that sight-threatening AMD was less prevalent than in a white population.\(^4\) Hispanic and Latin American populations seem to have a lower incidence of advanced and neovascular AMD than European-descended white populations.\(^1,5\) There is little data available on other population groups.

Risk factors for the development of AMD

There have been a number of studies investigating risk factors for the development of AMD. However, there have been conflicting results for
many risk factors in different study populations. The only consistently positive associations are smoking and a genetic component.

**Smoking**
There is a strong epidemiological association between smoking and the development of advanced AMD. Current smokers have an increased risk of developing dry and neovascular AMD relative to non-smokers with an odds ratio (OR) of 2.83 and 2.35, respectively. Past smokers have an OR of 2.80 and 1.82, respectively, when compared with non-smokers. Cigarette smoking confers an increased risk of developing AMD in addition to known genetic associations (see Genetics section). The benefit of smoking cessation to prevent second eye disease has not been evaluated.

**Genetics**
Both Beaver Dam and Rotterdam studies found an increased risk of AMD developing in relatives of affected individuals. The OR for a sibling of an affected individual developing neovascular AMD after 5-year follow-up in the Beaver Dam study was 10.3. In the Rotterdam study, there was an OR of 6.6 for signs of early AMD in the offspring of affected individuals when compared with offspring of non-affected individuals.

Three studies have found an association between a polymorphism in complement factor \( H \) (a control protein involved in the regulation of the alternative pathway of the complement cascade) and AMD. The relative risk of developing AMD with the common polymorphism \( T \rightarrow C \) substitution in exon 9 of the complement factor \( H \) gene is about 2.3–2.7 for heterozygotes and 3.5–7.4 for homozygotes. This finding has been subsequently supported by findings in other population groups. Another member of the complement system, factor B, has also been shown to have both high-risk and protective variants associated with the development of AMD. A third gene (LOC387715) found on chromosome 10, whose gene product has a function yet to be fully elucidated, has an independent effect on AMD almost as strong as that of the Factor H gene. Interestingly, both the high-risk variants of Factor H and LOC387715 interact with cigarette smoking to confer an increased risk of developing AMD than each factor alone. These exciting discoveries should lead to improved understanding of the pathogenesis of AMD and the development of novel therapies.
Natural history

Approximately 90% of the white population aged $\geq 40$ years will have one or two small hard drusen ($< 63 \, \mu m$ in diameter) in the macula of either eye. There is almost no risk of progression to advanced AMD in these eyes. However, in eyes with $> 8$ small hard drusen (Fig. 2), there is a 2–3-fold increased risk of developing large soft drusen ($\geq 125 \, \mu m$ in diameter, where $125 \, \mu m$ is approximately the width of a retinal vein at the optic nerve head) and pigmentary changes after 10 years. Large soft drusen are associated with a 6–7-fold increased risk of progression to advanced AMD. Large numbers of small hard drusen are also associated with progression to geographic atrophy. Patients with neovascular AMD in one eye have an $\sim 50\%$ risk of second eye CNV at 7 years follow-up.\footnote{3,53}

Diagnosis

History

Patients usually present with distortion, blurring or a scotoma (black or grey patch) in their central vision, which is rapid in onset in neovascular AMD and more gradually progressive in geographic atrophy. Patients with dry AMD in both eyes or unilateral neovascular AMD may be asymptomatic or just complain of mild distortion in their vision and be detected as an incidental finding at a routine optometric assessment. Patients with vision loss from late AMD (defined as presence of CNV or GA) in both eyes can develop visual hallucinations (Charles Bonnet syndrome). Visual hallucinations may be unformed (coloured lights or patterns) or formed (animals, people and scenes). Many patients will not volunteer these symptoms unless directly asked.

Clinical examination

Patients with drusen and mild pigmentary changes alone may have a visual acuity within the normal range. Patients with late AMD usually have reduced visual acuity in the affected eye. An area of central distortion or scotoma may be mapped out by the patient on an Amsler grid. Examination of the fundus, preferably using a stereoscopic viewing method (slit-lamp biomicroscopy), shows the presence of drusen, pigmentary, exudative, haemorrhagic or atrophic changes affecting the macula. Non-stereoscopic examination (direct ophthalmoscopy or fundal photography) may miss retinal thickening or elevation due to neovascular AMD.
Additional tests
Fluorescein angiography is used to confirm the presence and nature of neovascular AMD. Sodium fluorescein dye is injected intravenously. Fundus photographs are then taken through a barrier filter as the fluorescein dye fills the choroidal and retinal circulations. CNV can be defined either by its anatomical location relative to the centre of the fovea or by its filling characteristics. Treatment is often determined based on an understanding of these two angiographic findings. ‘Classic’ CNV membranes fill with dye in the arterial phase, are well defined and leak fluorescein dye beyond the borders in later shots. Lesions that leak in a less clearly demarcated pattern in later shots, but not in the early shots, are termed ‘occult’ lesions. CNV may be predominantly classic (greater than 50% classic component) or minimally classic (50% or less classic component). Currently, the determination of the type of neovascular AMD is essential in order to assess the suitability for treatment modalities such as laser photocoagulation and photodynamic therapy (PDT), but pharmacologic therapies (anti-VEGF agents) are effective in treating all subtypes of CNV.

Lesions are also divided into extrafoveal, juxtafoveal or subfoveal types depending on their location. The location of the lesion influences treatment options.

- Extrafoveal lesions: 200–2500 µm from the fovea
- Juxtafoveal lesions: 1–199 µm from the fovea
- Subfoveal lesions involve the centre of the fovea.

Optical coherence tomography may also be a useful adjunctive diagnostic tool. This device produces a cross-sectional image through the retina, RPE and choroid, and can measure macular thickness and the tissue plane of fluid collections. This can be helpful in determining the presence of pigment epithelial detachments and in patients with allergy to sodium fluorescein.

Differential diagnosis of CNV
CNV can occur secondary to other disease processes that alter the integrity of the Bruch’s membrane/RPE complex, such as pathological myopia (short-sightedness greater than −6 dioptres). Myopic patients can develop atrophic or neovascular changes that are similar to AMD, but may appear at a younger age and have a different natural history and response to treatment. Some inflammatory eye diseases result in CNV, but there are usually signs of active or previous uveitis that would not be present in AMD. Some inherited macular dystrophies may look similar to dry AMD. However, these are usually very symmetrical, there may be a family history and onset is usually at an earlier age.
Management

If neovascular AMD is present, the type and location of CNV must be determined by fluorescein angiography, ideally within a few days of onset of symptoms, as treatment options and response to treatment and subsequently final visual outcome are better in early disease. For this reason, at risk patients with known dry AMD are asked to regularly check the vision in the fellow eye using an Amsler grid or similar target and to seek urgent ophthalmic review if they develop new visual symptoms. Table 1 gives an overview of treatments for neovascular AMD and there is more detailed discussion below.

At present, there is no proven treatment for patients with dry AMD progressing to atrophy, although the cessation of smoking and the use of high-dose antioxidant vitamins may reduce the risk of CNV developing (see below).

Conventional laser treatment

Argon laser photocoagulation can be used to ablate the area of active CNV in patients with neovascular AMD. The Macular Photocoagulation study established that laser photocoagulation prevented severe loss of vision (loss of six or more lines of visual acuity) in extrafoveal CNV secondary to AMD.19 This randomized, controlled trial (RCT) terminated recruitment to the extrafoveal arm at 18 months as 60% of untreated eyes but only 25% of treated eyes had severe visual loss.19 A 5-year follow-up data showed that 64% of untreated eyes developed severe visual loss compared with 46% of treated eyes at 5 years.20 However, there is a 54% recurrence rate at 5 years after treatment. Approximately 75% of recurrences occur within the first year.

Patients with juxtafoveal CNV fared less well than extrafoveal CNV. At 5-year follow-up, 55% of treated patients had experienced severe visual loss compared with 65% controls.21 A sub-group analysis found that classic CNV without an occult component benefited from treatment and that juxtafoveal lesions with an occult component did not benefit from laser photocoagulation.

Patients with treated subfoveal CNV were less likely to have severe visual loss at 4-year follow-up than untreated eyes (23 versus 45%).22 However, this treatment is rarely performed as there is a significant risk of immediate worsening of vision in treated patients (20% chance of severe visual loss within 3 months in the treated group versus 11% of controls) and there are now available other treatments for subfoveal lesions.

Only a minority (13% in a series by Freund et al.) of patients presenting with neovascular AMD fulfil the treatment criteria for argon
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Trial name</th>
<th>Trial method</th>
<th>CNV Lesion Type</th>
<th>Number in trial (eyes)</th>
<th>Total follow-up (years)</th>
<th>Visual outcome</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Argon laser photocoagulation</td>
<td>MPS</td>
<td>RCT</td>
<td>New subfoveal</td>
<td>77</td>
<td>83</td>
<td>4</td>
<td>SVL 22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Juxtafoveal</td>
<td>138</td>
<td>138</td>
<td>5</td>
<td>SVL 52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extrafoveal</td>
<td>119</td>
<td>117</td>
<td>5</td>
<td>SVL 46%</td>
</tr>
<tr>
<td>PDT</td>
<td>TAP</td>
<td>RCT</td>
<td>All subfoveal with some classic component</td>
<td>402</td>
<td>207</td>
<td>2</td>
<td>MVL or better in 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Predominately classic</td>
<td>159</td>
<td>83</td>
<td>2</td>
<td>SVL, 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimally classic</td>
<td>202</td>
<td>104</td>
<td>2</td>
<td>MVL, 46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classic, no occult</td>
<td>93</td>
<td>49</td>
<td>2</td>
<td>MVL, 26%</td>
</tr>
<tr>
<td>VIP</td>
<td>RCT</td>
<td>Subfoveal occult no classic CNV</td>
<td>166</td>
<td>92</td>
<td>2</td>
<td>MVL in 55%</td>
<td>MVL in 68%</td>
</tr>
<tr>
<td>Pegaptanib (Macugen®)</td>
<td>VISION</td>
<td>RCT</td>
<td>Subfoveal classic and occult</td>
<td>890 (3 subgroups with different doses)</td>
<td>296</td>
<td>1</td>
<td>SVL 10% with 0.3 mg dose</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis®)</td>
<td>MARINA</td>
<td>RCT</td>
<td>Subfoveal occult/ minimally classic</td>
<td>240 (0.5 mg subgroup)</td>
<td>238</td>
<td>2</td>
<td>90% lost &lt; 15 letters</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33% gained ≥ 15 letters</td>
<td>4% gained ≥ 15 letters</td>
</tr>
<tr>
<td>ANCHOR</td>
<td>RCT</td>
<td>Subfoveal predominantly classic</td>
<td>140 (0.5 mg subgroup)</td>
<td>143 PDT treated</td>
<td>1</td>
<td>96% lost &lt; 15 letters</td>
<td>64% lost &lt; 15 letters</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>40% gained ≥ 15 letters</td>
<td>6% gained ≥ 15 letters</td>
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Continued
<table>
<thead>
<tr>
<th>Treatment</th>
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<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>Spaide et al.</td>
<td>PCS</td>
<td>Subfoveal CNV</td>
<td>266</td>
<td>0</td>
<td>Variable (2 month data available for 222 eyes)</td>
<td>31% had visual improvement at 2-month follow-up</td>
</tr>
<tr>
<td>Intravitreal TCA (single dose)</td>
<td>Gillies et al.</td>
<td>RCT</td>
<td>Subfoveal CNV with any classic component</td>
<td>73</td>
<td>70</td>
<td>1</td>
<td>SVL 35%</td>
</tr>
<tr>
<td>PDT plus intravitreal TCA 25 mg</td>
<td>Augustin et al.</td>
<td>PCS</td>
<td>All CNV</td>
<td>184 (148 subfoveal, 19 juxta-, 17 extra)</td>
<td>0</td>
<td>Variable</td>
<td>Mean visual acuity improved by 1.22 Snellen lines</td>
</tr>
<tr>
<td>Anecortave acetate (15 mg dose)</td>
<td>D’Amico et al.</td>
<td>RCT</td>
<td>Subfoveal CNV (25 eyes with predominately classic CNV)</td>
<td>33 eyes</td>
<td>30 eyes</td>
<td>1</td>
<td>79% lost &lt;15 letters</td>
</tr>
<tr>
<td>Anecortave acetate</td>
<td>Slakter et al.</td>
<td>RCT</td>
<td>Subfoveal predominantly classic</td>
<td>263</td>
<td>267</td>
<td>1</td>
<td>3% SVL</td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular translocation</td>
<td>Aisenbrey et al.</td>
<td>PCS</td>
<td>Subfoveal CNV</td>
<td>90</td>
<td>0</td>
<td>1</td>
<td>27% increased BCVA by ≥15 letters</td>
</tr>
<tr>
<td>Limited macular translocation</td>
<td>Fujii et al.</td>
<td>RCS</td>
<td></td>
<td>86</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

CNV, choroidal neovascularization; MPS, Macular Photocoagulation Study; RCT, randomized controlled trial; SVL, severe visual loss (loss of six or more lines of visual acuity); MVL, moderate visual loss; RR, relative risk; PDT, photodynamic therapy; TAP, Treatment of Age-Related Macular degeneration with Photodynamic Therapy Study; VIP, Verteporfin in Photodynamic Therapy Study; VISION VEGF, Inhibition Study in Ocular Neovascularization; MARINA, Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD (presented but not published); ANCHOR, ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD (presented but not published); TCA, triamcinolone acetonide; BCVA, best corrected visual acuity; PCS, prospective case series; RCS, retrospective case series.
laser therapy. Current recommendations are that conventional laser treatment is an option for patients with extrafoveal CNV or juxtafoveal classic no-occult CNV where the lesion is outside the foveal avascular zone or juxtafoveal classic no-occult CNV when PDT is unavailable. Patients are counselled that they will have a dense scotoma in the location of the treatment but that the aim of the treatment is to preserve central vision and minimize the final size of the scotoma. However, newer treatment options (anti-VEGF agents) avoid scotoma and offer the prospect of visual improvement.

**PDT with Verteporfin**

PDT utilizes a 10-min intravenous infusion of Verteporfin (a photosensitising drug) followed by application of a diode laser (689 nm) to the affected area in the retina 15 min after the start of the infusion. Light is absorbed by the photosensitizer molecules, which causes an oxidation process in lipid membranes and proteins. This leads to disruption of cellular structures and subsequent thrombosis and vascular occlusion in active CNV. Verteporfin is relatively contraindicated in patients with liver disease or a history of porphyria. Patients should avoid sunlight exposure for 48 h after treatment.

A systematic review of two RCTs, the Treatment of AMD with Photodynamic therapy (TAP) Study and Verteporfin in Photodynamic Therapy (VIP) Study, found that PDT with Verteporfin significantly reduced the risk of moderate and severe visual loss at 24 months compared with placebo (moderate visual loss: OR, 0.77; severe visual loss: OR, 0.62) in eyes with subfoveal CNV measuring ≤5400 μm caused by AMD. Two-year follow-up data showed that 77% of eyes with 100% classic lesions lost less than 15 letters after PDT treatment compared with 31% in the placebo group. Two-year follow-up data for predominately classic lesions showed 59% of eyes lost less than 15 letters of visual acuity compared with 31% of the placebo group. Patients with 100% occult lesions respond relatively well to PDT treatment (51% of treated patients lost <15 letters versus 25% controls at 2 years). A controversial sub-group analysis found maximal benefit in smaller lesions and those with poor initial vision. Patients with minimally classic lesions or occult classic CNV were not shown to benefit from PDT in randomized trials. Most practitioners would not use PDT for these indications and would instead treat with available anti-VEGF agents (see later section).

Patients usually require a course of treatment at three monthly intervals (mean number of treatments is 5 over 2 years). There is an ~1% risk of sudden permanent worsening of the vision following the treatment with PDT (5% in patients with occult lesions).
**Anti-angiogenic drugs**

There is currently extensive research into modulating the angiogenic response in AMD.

**Anti-vascular endothelial growth factor**

There is extensive *in vitro* and *in vivo* evidence that VEGF is implicated in retinal angiogenesis and vascular permeability. There has been intense laboratory and clinical research in this area, and researchers have developed agents that block VEGF activity some of which are already in clinical use:

1. **Pegaptanib Sodium (Macugen®)**

Pegaptanib (Macugen®, Eyetech Pharmaceuticals, NY, USA) is a selective anti-VEGF oligonucleotide conjugated with a polyethylene glycol that binds to the major human soluble VEGF isoform (VEGF165). A phase III RCT comparing intravitreal doses of 0.3, 1.0 and 3.0 mg and sham injection showed that with six weekly injections over a 48-week period there was a significant reduction in moderate visual loss (<15 letters lost) at 54 weeks follow-up. In the 0.3 mg treatment group, there was a statistically significant increase in the proportion of patients with stable vision with 70% losing <15 letters versus 55% in the sham treatment group (*P* < 0.001). Side-effects included endophthalmitis (0.16%), lens trauma (0.7%) and retinal detachment (0.6%). Pegaptanib has now been licensed for clinical use in the USA and Europe.

2. **Ranibizumab (Lucentis®)**

A recombinant anti-VEGF monoclonal antibody fragment that binds to all isoforms of VEGF-A (Ranibizumab, Lucentis®; Genentech, CA, USA) has been developed. Recent published Phase III data show a benefit from treatment for all lesion types and sizes with ranibizumab with repeated four weekly intravitreal injections. The ANCHOR study randomized 423 patients with predominantly classic neovascular AMD to monthly injections of Lucentis® at two different doses or to conventional treatment with verteporfin PDT. The 12-month results showed 94.3% of patients treated with 0.3 mg Lucentis® and 96.4% treated with 0.5 mg lost <15 letters on visual acuity testing compared with 64.3% in the PDT-treated group. In addition, visual acuity improved by ≥15 letters in 35.7% of the 0.3 mg Lucentis®-treated group and 40.3% of the 0.5 mg-treated group with only 5.6% of PDT-treated patients improving vision. The average visual acuity change was a gain of 8.5 letters in the 0.3-mg group and 11.3 letters in the 0.5-mg group compared with a decrease of 9.5 letters in the PDT-treated group at 12 months. The MARINA study randomized 716 patients with minimally classic or occult neovascular AMD to monthly injections of Lucentis® at two different doses or to sham treatment. The 24-month results showed 92% of patients treated with 0.3 mg Lucentis® and 90% treated with 0.5 mg lost fewer than 15 letters on visual acuity testing compared with 52.9% in the sham-treated group. In addition, visual acuity improved by ≥15 letters in
26.1% of the 0.3 mg Lucentis®-treated group and 33.3% of the 0.5-mg treated group compared with only 3.8% of sham injection group. The average visual acuity change was a gain of 5.4 letters in the 0.3-mg group and 6.6 letters in the 0.5-mg group compared with a decrease of 14.9 letters in the sham injection group at 24 months. The risk of endophthalmitis in the two studies was 1.4% over 2 years (0.05% per intravitreal injection). Further studies have investigated the efficacy of as required ranibizumab intravitreal injections in treating neovascular AMD in order to explore the possibility of reducing the number of intravitreal treatments while maintaining efficacy. The PIER study was a prospective, multicentre, randomized, controlled trial of 184 patients with subfoveal CNV due to AMD received either ranibizumab (0.3 or 0.5 mg) or sham treatment once a month for 3 months and followed by doses every once every 3 months for a total of 24 months in a 1:1:1 ratio. At the 12 months, patients with quarterly treatment gained a mean of 2.9 ETDRS letters (0.3 mg group) or 4.3 letters (0.5 mg group) compared with a mean loss of 8.7 letters for the sham group with 12% (0.3 mg group) and 13% (0.5 mg group) gaining 15 letters or more. This study suggests that the efficacy of ranibizumab is reduced if given as a quarterly treatment. The results from the PrONTO study, which was a prospective open-label interventional case series of neovascular AMD patients with subfoveal CNV treated with three consecutive monthly intravitreal injections of ranibizumab (0.5 mg) with further injections if clinically indicated, support this treatment strategy. At month 12, the mean visual acuity improved by 9.3 letters ($P < 0.001$) and the mean OCT central retinal thickness decreased by 178 μm ($P < 0.001$). Visual acuity improved 15 or more letters in 35% of patients. These visual acuity and OCT outcomes were achieved with an average of 5.6 injections over 12 months. This small study suggests visual acuity outcomes similar to the Phase III clinical studies, may be achieved with fewer intravitreal injections.

3. Bevacizumab (Avastin®)

Initially developed for use in oncology (licensed for use in colorectal cancer), bevacizumab (Avastin®) has been increasingly used as an intravitreal injection to treat neovascular AMD. Bevacizumab is a full-length, humanized, monoclonal antibody binding all forms of VEGF-A. Several published case series have suggested efficacy similar to that of Lucentis®, but as yet there have been no prospective, randomized, controlled trials published. The largest retrospective case series of 266 eyes with follow-up of 2 months (data available for 222 eyes) showed visual acuity improvement in 31.1% with a statistically significant reduction in mean central macular thickness. The evidence for the efficacy of intravitreal bevacizumab in treating neovascular AMD is from interventional case series with no reports from multi-centre, randomized, controlled trials. However, despite the availability of a licensed alternative treatment (ranibizumab), there is widespread, worldwide ‘off-label’ use of bevacizumab for this indication as Lucentis, is significantly more expensive than Avastin and as Avastin was available prior to the licensing of Lucentis. This has given rise
to the highly unusual situation of a drug (Avastin) used for an unlicensed indication despite robust clinical trials supporting the safety and efficacy of a licensed alternative (Lucentis) in treating wet AMD.

Intravitreal VEGF inhibitors appear to be relatively free from systemic side-effects and complications although systemic VEGF-A inhibition may predispose to thrombo-embolic complications and an excess risk of thrombo-embolic complications was reported in the first year of follow-up in the ranubizumab (Lucentis®) randomized, controlled trials which diminished in the second year of follow-up. The SAILOR (Safety Assessment of Intravitreal Lucentis for AMD) study is an ongoing phase IIIb study with patients randomized to 0.3 or 0.5 mg of Lucentis. A planned interim safety analysis from this study reported a higher risk of cerebrovascular accidents in the 0.5 mg group (1.2%) compared with the 0.3 mg group (0.3%). The results of further clinical trials are awaited, and other VEGF or VEGF receptor blocking drugs are also under development.

Selected treatments still undergoing evaluation

**Transpupillary thermotherapy**

Transpupillary thermotherapy (TTT) involves the use of a long-pulse diode laser (810 nm) to occlude CNV. A formal RCT (TTT4CNV Trial) did not show any benefit in treating subfoveal occult CNV secondary to AMD compared with sham (presented at ARVO Annual Meeting 2005 by Reichel et al.).

**Steroids**

A number of different steroids have been evaluated and different delivery vehicles including depot preparations are in development. However, published data are limited to triamcinolone acetonide and anecortave acetate.

**Triamcinolone**

Triamcinolone acetonide is a glucocorticoid and if injected into the vitreous, it may have an effect for up to ~4–6 months. A RCT to evaluate a single dose of 4 mg intravitreal triamcinolone acetonide versus placebo in the treatment of 151 eyes with CNV with a classic component found no difference in risk of severe visual loss between treatment and control groups at 1 year. A number of small, non-randomized trials have been performed using repeated doses of triamcinolone 25 mg; however, there is no robust data to show a benefit over natural history. Currently, no good RCT data exist to support its use yet either alone or in combination with other therapies although there is a suggestion of enhanced efficacy in combination with PDT.
Several RCTs are ongoing, including one using a preservative free version of triamcinolone that may have less associated ocular morbidity and combination with other treatment.

Anecortave acetate
Anecortave acetate is a synthetic angiostatic steroid that has no glucocorticoid activity and a good ocular safety profile. It prevents vascular growth by inhibiting proteases necessary for endothelial cell migration. A RCT of 128 patients investigated the use of six monthly juxtascleral (injection into the tissue plane between the Tenon’s sheath and sclera rather than into the vitreous cavity) injection of anecortave acetate at 3, 15 and 30 mg doses versus placebo. At 1-year follow-up, patients in the 15 mg treatment group did significantly better than the control group in mean change from baseline visual acuity ($P = 0.01$), stabilization of visual acuity ($P = 0.03$) and prevention of severe visual loss ($P = 0.02$). There were no significant safety issues. A phase III equivalency study between 15 mg anecortave against PDT did not reach its primary endpoint of equivalency despite similar outcomes between the two groups (see Table 1). The authors felt that the outcome of anecortave was limited by reflux during delivery and further trials are ongoing with modification of the delivery technique. Anecortave has received a license for use in neovascular AMD in Australia in 2006.

Medical treatments not shown to be beneficial by RCTs

Radiotherapy
Low doses of ionizing radiation can inhibit vascular endothelial cell proliferation in vitro and prevent angiogenesis in vivo. A systematic review of 11 trials of teletherapy (external beam radiotherapy) found great variability in the treatment methods and was unable to draw any firm conclusions about the efficacy of radiotherapy.

Alpha-interferon treatment
A large RCT evaluating alpha-interferon as a treatment in wet AMD found no statistically significant benefit from treatment (three different dosages) compared with placebo over a 1-year period. Therefore, alpha-interferon is not recommended as a treatment in wet AMD.
Surgical treatments

There are a number of surgical techniques available in the management of wet AMD. These techniques are only performed by a limited number of surgeons.

Excision of choroidal neovascular membranes

This involves performing a pars plana vitrectomy then removing the CNV via a retinotomy incision. This method theoretically preserves foveal retinal photoreceptors and is suitable for occult lesions as the precise anatomical boundaries of the CNV do not need to be delineated. A multi-centre RCT of 454 eyes found no statistical difference between the treatment group and controls at 24 months. There was an increased risk of retinal detachment in the treatment group compared with controls.

Retinal pigment epithelial cell transplantation

Exogenous RPE transplantation
It is thought that the reason for poor visual acuity outcomes following CNV excision is removal of RPE cells with the excised CNV complex. This leads to choriocapillaris atrophy and subsequent loss of photoreceptor function due to ischaemia. New techniques using RPE cell transplantation aim to overcome this issue. Early studies using human foetal RPE cell transplants gave disappointing results due to the development of chronic cystoid macular oedema which affected central visual acuity.

Autologous RPE transplantation
Recent studies using autologous RPE transplantation have had more promising results. A consecutive patient case series of 53 patients with subfoveal CNV found a statistically significant improvement in reading visual acuity between the group with CNV excision and autologous RPE transplantation when compared with the group with CNV excision only. However, the complication rate is too high currently to use this approach outside research studies.

Evacuation of submacular haemorrhage

Large submacular haemorrhage secondary to wet AMD carries a poor visual prognosis due to the development of subretinal fibrosis.
Early surgical removal of haemorrhage has been advocated to prevent permanent visual loss. Mechanical removal of clot results in extensive iatrogenic damage. A large RCT investigating surgery for haemorrhagic CNV (lesions composed of >50% haemorrhage) found that there was no difference in the risk of loss of two or more lines of visual acuity at 2 years between the treatment and control groups (56% of treated cases versus 59% of controls). However, the risk of severe visual loss was less in the surgery group (36% control group versus 21% surgery group, \( P = 0.004 \)). A newer technique using tissue plasminogen activator (tPA) without the need for a vitrectomy has been described. However, the numbers of patients treated are small and no RCT has been performed. Combined evacuation of blood with retinal translocation is described below.

**Macular translocation**

This procedure aims to relocate the fovea to an adjacent area of healthy RPE in eyes with subfoveal CNV. There are two main methods for relocating the fovea.

**360° Retinotomy and macular translocation**

A pars plana vitrectomy is performed followed by a 360° retinotomy. The retina is then artificially detached, rotated around the optic nerve and re-attached. The largest case series to date presented by Aisenbrey *et al.* found that 24/90 (27%) had three or more line gain on the ETDRS chart at 12 months and that 32% had three or more line loss of vision. The complication rate was high in initially reported series (retinal detachment in 29% mainly due to proliferative vitreoretinopathy, CNV recurrence in 22% and cystoid macular oedema in 52%), but is reducing in more recent series. A recent pilot RCT comparing surgery to PDT reported a higher proportion of patients improving vision after macular translocation surgery at 1 year follow-up. Additional strabismus surgery is required and some patients have persistent diplopia. The surgery is complex and the operation is lengthy, but has potential in very selected cases to restore vision.

**Limited macular translocation**

Limited macular translocation involves a chorioscleral shortening procedure to move the fovea to a healthy area of RPE. This can be achieved by infolding or outpouching of the sclera, which creates redundancy of the retinal tissue which can then be displaced 1–2 mm. There are no RCTs of this technique. The largest retrospective case series to date reported outcomes on 102 eyes; of which, 1-year
follow-up was achieved in 86.48 This study found that 39.5% had a two or more lines of improvement in visual acuity. However, there was a 34.6% CNV recurrence rate; of which, 65% of recurrences were subfoveal and resulted in loss of visual acuity.

The arrival of anti-VEGF agents has restricted the use of surgery to selected cases in specialist centres.

**Combination therapy**

The use of anti-VEGF agents with intensive patient follow-up and repeated intravitreal injections every 4–6 weeks has led to an interest in combination therapies both to reduce retreatment rates and to improve outcomes. Numerous case series and retrospective studies have been published evaluating combination therapies in wet AMD but at present, there is no clear data on the usefulness of combination therapies although there is a suggestion of benefit from combining PDT and intravitreous triamcinolone. There are, however, several RCTs underway to investigate the role of combination therapies with the prospect of reducing the frequency of anti-VEGF therapy.

**Prophylaxis**

**Nutritional supplements**

A large RCT of 3640 patients [Age-related Eye Disease Study (AREDS)] investigated four nutritional treatments for the prevention of advanced AMD (development of CNV or geographic atrophy).49 These treatments were placebo, zinc (80 mg plus copper 2 mg/daily), antioxidants (vitamin C 500 mg plus vitamin E 400 IU plus beta-carotene 15 mg/daily) and zinc plus antioxidants. Overall, it was found that compared with placebo, zinc plus antioxidants significantly reduced the proportion of patients progressing to advanced AMD (OR, 0.72; 99% CI, 0.52–0.98) or moderate visual loss (OR, 0.73; 99% CI, 0.54–0.99) over a 6-year period.

The visual benefit is greatest, and was statistically significant in people with late AMD in one eye and early AMD in the other. There is no benefit in patients with no signs of AMD or those with bilateral, advanced AMD. These high doses of zinc and anti-oxidants cannot be achieved from diet alone. There was little evidence of harm in this study although some patients developed yellowing of the skin secondary to anti-oxidant ingestion and increased admission for genitourinary complications secondary to zinc ingestion. There is good evidence from other studies that the beta-carotene component increases the risk of
lung cancer in smokers, and this treatment is currently not recommended in smokers or ex-smokers. There are currently no RCTs on other nutritional supplements such as lutein or doses of anti-oxidants other than those used in the RCT described above.

**Laser to drusen**

Two RCTs have investigated the use of laser to eyes with drusen to prevent subsequent development of advanced AMD\(^5^0,5^1,5^4\). The study by Olk *et al.*\(^5^0\) in 229 eyes found a statistically significant increase in visual acuity in eyes with drusen treated with diode laser compared with eyes with no treatment at 2 years (improvement of $\geq 2$ lines in 11% with laser versus 0% with no treatment; 95% CI, 6–25). However, a second RCT by the Choroidal Neovascularization Prevention Trial Research Group found that in the subgroup of people with unilateral drusen, laser significantly increased the incidence of CNV compared with no treatment [estimated 12-month incidence 17% with laser versus 3% with no treatment ($P < 0.05$)].\(^5^1,5^4\) In view of the increased risk of CNV, laser treatment for drusen is not currently recommended.

**Anecortave acetate**

A multi-centre RCT is currently underway to evaluate the use of juxtascleral injection of anecortave acetate as a prophylactic treatment in fellow eyes of patients with unilateral advanced wet AMD.

**Supportive measures**

**Low vision aids and eccentric fixation methods**

Treatment may or may not be possible in patients with AMD, but most will benefit from supportive measures. These include simple advice on adequate lighting in the home and for near-vision tasks. Formal assessment for low visual aids by a trained optometrist will enable the patient to optimize the use of the vision that he or she has. Closed circuit television (CCTV) aids are useful for some patients to enlarge text, but are expensive to purchase.

Some patients can be trained to use eccentric fixation in order to improve their visual acuity. This technique involves the patient looking just to one side of the object of interest rather than directly at the object. Healthier juxtafoveal retina can then be used to produce an image. No good RCTs exist to determine the effectiveness of low visual aids yet.

Formal partial-sighted or blind registration also enables patients to access social support and practical advice on modifications to the
home and the provision of other aids. Many patients also benefit from counselling either formally or informally through patient support groups.

**Implantable miniature telescope**
In addition to standard low-vision aids, newer approaches to visual rehabilitation have included the implantable miniature telescope.\(^{52}\)
This is a monocular-fixed focus telescopic device implanted into the patient's eye during cataract surgery which provides magnification of the central vision at the expense of the field of view. There have been encouraging results in clinical trials with further trials ongoing.

**Current treatment recommendations for wet AMD**
The introduction of anti-VEGF agents has revolutionized the management of wet AMD. In a rapidly changing field, our current recommendations for management include:

1. Pan-anti-VEGF blockade using ranibizumab. The use of Avastin remains controversial, but potentially very cost-effective.
2. Argon laser ablative therapy restricted to small, well-defined extra-foveal CNV.
3. The role of PDT may be in combination therapy and is subject to further study at present.
4. Surgical macular translocation may be considered in selected cases including second affected eyes not suitable for anti-VEGF therapy (including RPE.rips involving the macula).
5. Preventative measures including cessation of smoking and use of AREDS nutritional supplements.

**Summary**
AMD is an increasing health burden throughout the world and is the third commonest cause of visual impairment worldwide. There are a number of established treatment options as well as promising therapies and surgical approaches under evaluation to stabilize vision in wet AMD. It is, therefore, important that patients with symptoms of impaired central vision should be seen and assessed promptly by an ophthalmologist in order that appropriate investigations can be performed to assess suitability for treatment. All patients should also have access to supportive measures and appropriate advice on lighting, etc. The role of prophylactic treatments is also important in order to
preserve central vision. The increasing understanding of the genetics and pathogenesis of AMD may lead to the development of more specific and effective therapies in the future.

References


