

## The Royal College of Ophthalmologists Guidelines on AMD: Executive Summary

This article has been corrected since Advance Online Publication and a corrigendum is also printed in this issue

Age-related macular degeneration (AMD) is a common condition in older adults. Since publication of the last guidelines in 2009, new data have emerged on the management of AMD and novel solutions have been tested to meet the ongoing challenge of AMD service demands. Thus, there are compelling reasons to update the College guidelines on AMD. This is a summary of the guidelines. The full guidelines are available at <http://www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines>

The purposes of the guidelines are to set the standards for best practice, to educate medical trainees, to inform patients, carers, and consumer organisations, to act as a benchmark for service planning by providers, to guide commissioners, and to set national standards for audit.

### Classification and epidemiology

Early AMD is characterised by drusen  $\geq 63 \mu\text{m}$  diameter and hyper- or hypo-pigmentation. A proportion of eyes with early AMD progress to late AMD, that is, exudative AMD or geographic atrophy (GA). In exudative AMD, also termed neovascular AMD (nvAMD), new blood vessels develop which in the vast majority of cases have their origin in the choroid, which subsequently invade the retina (choroidal neovascularisation, CNV). In some cases, the vessels may arise in the retina, retinal angiomatous proliferation (RAP), before anastomosing with choroidal vessels. In other cases, the vascular abnormality may be contained within the choroid: idiopathic polypoidal choroidopathy (IPC). Regardless of the origin and/or the location of the neovascular complex, the vessels are abnormal and allow blood constituents to leak out, causing anatomical disruption, cell loss and eventually fibrosis. GA is a sharply demarcated area of partial or complete depigmentation reflecting atrophy of the retinal pigment epithelium.

A number of classification systems exist but often these have limited applicability in clinical settings. The pragmatic 4-stage grading system validated in the Age-Related Eye Disease Study (AREDS) is therefore advocated.<sup>1</sup> Three ocular factors predict the progression of AMD: the presence of large drusen ( $> 125 \mu\text{m}$ , which approximates the size of a normal retinal vein at the disc margin), retinal pigment epithelial abnormalities, and the presence of late AMD in one eye.<sup>2</sup>

In the United Kingdom, the prevalence of late AMD has been estimated as 4.8% (95% CI 3.4–6.6%) in those over 65 years and 12.2% (95% CI 8.8–16.3%) in those aged 80 years or more.<sup>3</sup> In the United Kingdom, an estimated quarter of a million adults suffer blindness due to this condition.<sup>4</sup>

The natural history of advanced AMD is one of unremitting central visual loss. A longitudinal study of GA found that 31% suffered a three-line loss in acuity within 2 years of diagnosis and that this had increased to 53% at 4 years.<sup>5</sup> A meta-analysis of high-quality trials on

nvAMD for which data were available on natural history found that the proportion of patients who developed severe vision loss ( $> 6$  lines) from baseline increased from 21.3% at 6 months to 41.9% at 3 years.<sup>6</sup> Vision-related quality of life has been shown to decline significantly as early AMD progresses to late AMD over a 15-year follow-up.<sup>7</sup>

### Diagnosis

Exudative AMD usually presents with sudden loss or distortion of central vision, but patients may be unaware of the symptoms when the event occurs in the first eye. Fundus fluorescein angiography (FFA) is the gold standard to diagnose CNV due to AMD. Optical coherence tomography (OCT) is excellent at detecting leakage from abnormal vessels. Dynamic high-speed indocyanine green angiography (ICG) is useful to delineate the choroidal circulation more clearly than FFA.

The presentation of GA may be insidious and may be detected on routine optometric examination. If GA is bilateral, patients typically complain of difficulties in reading initially small print and eventually larger print. Fundus autofluorescence (FAF) gives an indication of the health of the RPE. FAF with spectral domain OCT can reveal areas of GA, which may not be clinically visible on biomicroscopy.<sup>8</sup>

Macular lesions potentially mimicking AMD include diabetic maculopathy, high myopia, inflammatory CNV, central serous chorioretinopathy, and macular telangiectasia, whereas pattern dystrophies can mimic GA.

### Risk factors

Many strong risk mediators for AMD exist that include increasing age, current smoking, and family history.<sup>9</sup> Nutrition has been the subject of great interest, and decreased serum, dietary, and retinal levels of carotenoids have been associated with an increased risk of AMD in some but not all observational studies. AREDS found a reduced risk (adjusted odds ratio 0.72; 99% CIs 0.52–0.98) of progression to advanced AMD in those with at least early AMD (or advanced AMD in their other eye) with antioxidant vitamins C and E, zinc, and beta-carotene.<sup>10</sup> However, the beta-carotene component of the AREDS formulation has been associated with an increased risk of lung cancer in smokers and is therefore not recommended in current smokers. In AREDS2, it was found that elimination of beta-carotene was as safe and effective in terms of risk of AMD progression.<sup>11</sup> In AREDS2, addition to the AREDS formulation of lutein and zeaxanthin, or of omega-3 long-chain polyunsaturated fatty acids, or both, also had no apparent effect on risk of AMD progression. A systematic review of prospective studies of dietary intake found no evidence that diets high in antioxidant vitamins prevent AMD.<sup>12,13</sup> Although there is insufficient evidence to prescribe dietary supplements routinely in patients with AMD or for the prevention of AMD, eating a diet rich in leafy green vegetables and fresh fruit is recommended.

Unlike other common diseases, AMD is relatively unusual in that several genes of large effect have been reported to alter the risk in a large fraction of patients. At present, the utility of commercially available genetic

testing kits for estimated risk of developing AMD is uncertain.

### Treatment

Historically laser ablation of CNV was the only treatment option. Laser treatment can no longer be justified for most cases of nvAMD, although might still be considered for lesions well away from the fovea, thereby avoiding the time investment, risks, and cost associated with anti-vascular endothelial growth factor (VEGF) agents.<sup>14</sup>

Photodynamic therapy with verteporfin (vPDT) is no longer justified as monotherapy for nvAMD. vPDT is recommended only in patients with IPC, performed within 1–2 weeks of FFA and then as required 3 monthly.<sup>15</sup> Patients should be advised to avoid direct sunlight exposure for 2 days following treatment. Severe vision loss can occur immediately after vPDT in 1–4% of patients, and this may be permanent in a small proportion of cases. Idiosyncratic back pain occurs in 1–2% of patients, which resolves when the infusion is stopped.

Steroids have been used in nvAMD, but current evidence does not support their use either as monotherapy or in combination with other treatment modalities.<sup>16</sup> Submacular surgery has been attempted in nvAMD, but there is no evidence of a visual benefit and a significantly increased risk of cataract and retinal detachment following surgery.<sup>17</sup> Radiotherapy is another treatment modality that has been suggested, but a Cochrane review in 2010 reported no benefit.<sup>18</sup> However, newer evidence on the efficacy and safety of radiotherapy is expected as several clinical trials are ongoing.

VEGF-A is a pro-angiogenic growth factor that also stimulates vascular permeability and has a major role in the pathology of CNV. Anti-VEGF therapies are now the mainstay of treatment of nvAMD. All lesion types of nvAMD benefit from treatment with anti-VEGF therapy, although IPC lesions respond best to vPDT monotherapy or in combination with intravitreal injections of anti-VEGF. Pegaptanib sodium (Macugen, Eyetech/Pfizer) was the first to be approved but now has no role in the management of nvAMD. Ranibizumab (Lucentis, Genentech Inc./Novartis) is a humanised Fab fragment of a monoclonal antibody that binds to and inhibits the action of all isoforms of VEGF-A. Two pivotal clinical trials established the superior efficacy of ranibizumab over vPDT or observation only.<sup>19,20</sup> Aflibercept (Eylea, Bayer) is a fusion protein that inhibits all isoforms of VEGF-A as well as placental growth factor thought to contribute to the pathogenic effects of CNV. Two-monthly aflibercept has been shown to be non-inferior to monthly ranibizumab for nvAMD.<sup>21</sup> Aflibercept was referred to NICE in February 2012 and is now recommended for nvAMD (TA294). Other comparative effectiveness trials have tested bevacizumab *vs* ranibizumab and have provided strong evidence of equivalence of visual outcomes regardless of the drug used.<sup>22,23</sup> Currently, ranibizumab and aflibercept carry a label for intraocular administration for nvAMD. As bevacizumab seems to have similar efficacy to ranibizumab, its ‘off-label’ status should be clearly stated before its use in patients. The European Medicines

Authority suggests an approach that is ‘patient-centric’, treating on as-needed basis.<sup>24</sup> This approach is more likely to avoid undertreatment or overtreatment. Present knowledge does not allow accurate prediction of which patients are at risk of recurrence of neovascular activity. Systemic safety has been a concern given the physiological role of VEGF. A meta-analysis of recent trials showed a small excess of serious adverse events (SAEs) with bevacizumab compared with ranibizumab, with an odds ratio of 0.75 (95% CIs 0.61–0.92). The most common organ system involved was the gastrointestinal tract, and the incidence of SAEs was greater for those treated with prn bevacizumab compared with the mandatory monthly group.

The role of combination treatments, including anti-VEGF agents with vPDT and steroids, is not established. The current College guidelines provide recommendations for the delivery of treatment, criteria for initiation of therapy, continuation of therapy, or temporary cessation and termination of treatment, and details on the method of intravitreal drug delivery. In particular, a multidisciplinary approach is central to patient management. Patients should be advised regarding the potential complications of intravitreal injections and the need for monitoring every 4–8 weeks, depending on the anti-VEGF used, continued for up to and beyond 2 years. Further research is required into appropriate duration and optimal regimen in terms of frequency of injections. It still remains to be seen whether less-frequent dosing of licensed anti-VEGF agents than that used in the pivotal trials will achieve the same visual benefit.

Treatment for non-neovascular AMD is limited and consists mainly of counselling, smoking cessation, rehabilitation, and prescription of AREDS-style vitamins to reduce the risk of progression in those expected to benefit. Clinical trials of novel therapies are now taking place but are not currently available in clinical practice. Intraocular optical aids, such as the Implantable Telescope (IMT) prosthesis (Vision-Care Ophthalmic Technologies, Saratoga, CA, USA), may have a role in some,<sup>25</sup> although careful pre-operative planning is necessary.

Patients with a new diagnosis of AMD must be treated with empathy. Ideally new patients with AMD should not have to wait more than 1 week from referral to clinic and not more than 1 week from clinic to treatment if needed. They should be given information on their diagnosis, risk factors for progression, prognosis, treatment options, registration, if needed, and on supporting literature such as visual rehabilitation and low-vision services, and patient-support organisations. The staff in secondary care should be aware of the impact of diagnosis on patients, and senior ophthalmological oversight should be embedded in quality systems.

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## References

- 1 Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmology* 2000; **107**: 2224–2232.
- 2 Klein R, Klein BE, Knudtson MD, Meuer SM, Swift M, Gangnon RE. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Ophthalmology* 2007; **114**: 253–262.
- 3 Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol* 2012; **96**: 752–756.
- 4 Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? *Br J Ophthalmol* 2003; **87**: 312–317.
- 5 Sunness JS, Gonzalez-Baron J, Applegate CA, Bressler NM, Tian Y, Hawkins B *et al.* Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology* 1999; **106**: 1768–1779.
- 6 Wong TY, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R *et al.* The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology* 2008; **115**: 116–126.
- 7 Coleman AL, Yu F, Ensrud KE, Stone KL, Cauley JA, Pedula KL *et al.* Impact of age-related macular degeneration on vision-specific quality of life: Follow-up from the 10-year and 15-year visits of the Study of Osteoporotic Fractures. *Am J Ophthalmol* 2010; **150**: 683–691.
- 8 Forte R, Querques G, Querques L, Massamba N, Le Tien V, Souied EH *et al.* Multimodal imaging of dry age-related macular degeneration. *Acta Ophthalmol* 2012; **90**: e281–e287.
- 9 Chakravarthy U, Querques G, Querques L, Massamba N, Le Tien V, Souied EH. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol* 2010; **10**: 31.
- 10 Age-Related Eye Disease Study Research, G. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001; **119**: 1417–1436.
- 11 Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA* 2013; **309**: 2005–2015.
- 12 Chong EW, Wong TY, Kreis AJ, Simpson JA, Guymer RH. Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *Br Med J* 2007; **335**: 755.
- 13 Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database Syst Rev* 2012; **11**: CD000254.
- 14 Shah AM, Bressler NM, Jampol LM. Does laser still have a role in the management of retinal vascular and neovascular diseases? *Am J Ophthalmol* 2011; **152**: 332–339. e331.
- 15 Koh A, Lee WK, Chen LJ, Chen SJ, Hashad Y, Kim H *et al.* EVEREST study: efficacy and safety of verteporfin photodynamic therapy in combination with ranibizumab or alone versus ranibizumab monotherapy in patients with symptomatic macular polypoidal choroidal vasculopathy. *Retina* 2012; **32**: 1453–1464.
- 16 Becerra EM, Morescalchi F, Gandolfo F, Danzi P, Nascimbeni G, Arcidiacono B *et al.* Clinical evidence of intravitreal triamcinolone acetonide in the management of age-related macular degeneration. *Curr Drug Targets* 2011; **12**: 149–172.
- 17 Giansanti F, Eandi CM, Virgili G. Submacular surgery for choroidal neovascularisation secondary to age-related macular degeneration. *Cochrane Database Syst Rev* 2009; **15**: CD006931.
- 18 Evans JR, Sivagnanavel V, Chong V. Radiotherapy for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2010, (5): Art. No. CD004004; doi:10.1002/14651858.CD004004.pub3.
- 19 Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP *et al.* Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1432–1444.
- 20 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY *et al.* Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006; **355**: 1419–1431.
- 21 Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD *et al.* Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012; **119**: 2537–2548.
- 22 Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA *et al.* Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet* 2013; **382**: 1258–1267.
- 23 Comparison of Age-related Macular Degeneration Treatments Trials Research Group Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ *et al.* Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012; **119**: 1388–1398.
- 24 Brand CS. Management of retinal vascular diseases: a patient-centric approach. *Eye* 2012; **26**(Suppl 2): S1–16.
- 25 Brown GC, Brown MM, Lieske HB, Lieske PA, Brown KS, Lane SS. Comparative effectiveness and cost-effectiveness of the implantable miniature telescope. *Ophthalmology* 2011; **118**: 1834–1843.

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