Age-related macular degeneration

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Age-related macular degeneration is a leading cause of visual impairment and severe vision loss. Clinically, it is classified as early-stage (medium-sized drusen and retinal pigmentary changes) to late-stage (neovascular and atrophic). Age-related macular degeneration is a multifactorial disorder, with dysregulation in the complement, lipid, angiogenic, inflammatory, and extracellular matrix pathways implicated in its pathogenesis. More than 50 genetic susceptibility loci have been identified, of which the most important are in the *CFH* and *ARMS2* genes. The major non-genetic risk factors are smoking and low dietary intake of antioxidants (zinc and carotenoids). Progression from early-stage to late-stage disease can be slowed with high-dose zinc and antioxidant vitamin supplements. Intravitreal anti-vascular endothelial growth factor therapy (eg, ranibizumab, aflibercept, or bevacizumab) is highly effective at treating neovascular age-related macular degeneration, and has markedly decreased the prevalence of visual impairment in populations worldwide. Currently, no proven therapies for atrophic disease are available, but several agents are being investigated in clinical trials. Future progress is likely to be from improved efforts in prevention and risk-factor modification, personalised medicine targeting specific pathways, newer anti-vascular endothelial growth factor agents or other agents, and regenerative therapies.

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Introduction

Age-related macular degeneration (AMD) is a disease that affects the macular region of the retina, causing progressive loss of central vision.[1,2] Early-stage AMD includes clinical signs such as drusen and abnormalities of the retinal pigment epithelium. Late-stage AMD can be neovascular (also known as wet or exudative) or non-neovascular (known as atrophic, dry, or non-exudative). Late AMD results in loss of central visual acuity, leading to severe and permanent visual impairment and legal blindness, which has a major impact on quality of life and functional independence. By 2020, the number of people with AMD globally is expected to be around 200 million, increasing to nearly 300 million by 2040,[3] thus posing a major public health problem with substantial socioeconomic implications. Although AMD remains the third leading cause of severe irreversible vision loss worldwide, legal blindness and visual impairment have decreased in incidence since the introduction of treatments targeting vascular endothelial growth factor (VEGF).[1,2,4]

Diagnosis, classification, and symptoms

AMD was traditionally diagnosed on the basis of clinical examination or assessment of colour fundus photographs. During the past two decades, spectral-domain optical coherence tomography and fundus autofluorescence imaging have been used to detect lesions, with improved resolution. Fluorescein angiography remains a useful modality to detect choroidal neovascularisation (to confirm the presence of neovascular AMD) and its location and activity (indicated by the extent of dye leakage). Optical coherence tomography angiography has emerged as a non-invasive approach that requires no dye. This method detects the presence of choroidal vascular networks seen in choroidal neovascularisation, but does not detect leakage, and will have an increasingly important role in the future.[5–7] Use of multimodal imaging provides complementary information about AMD.

AMD has several classification systems (table 1).[8–12] Population studies have traditionally classified AMD into early and late stages, whereas clinic-based studies and trials frequently use the Age-Related Eye Diseases Study (AREDS) severity scale[11] and its simplified version,[12] which was validated in a population study (figure 1).[13] To use the AREDS simplified severity scale, one risk factor is assigned for each eye with large drusen, one risk factor is assigned for each eye with pigment abnormalities, and one risk factor is assigned if neither eye has large drusen and both eyes have medium (intermediate) drusen (appendix). More specific classifications are also available. In the Beckman classification,[9] the presence of small (<63 μm diameter), hard drusen (or drupelets) is regarded as a sign of normal ageing rather than of AMD. Thus, early AMD is defined by the presence of medium-sized drusen (63–125 μm) or retinal pigmentary changes (hyperpigmentation or hypopigmentation) in the macular region, or both; and intermediate AMD is defined as the presence of extensive medium drusen or at least one large druse, or both.[9] Early AMD stages according to traditional classifications include the presence of early or intermediate AMD according to the Beckman classification. Late AMD is defined by the presence of signs indicating either neovascular or atrophic AMD.[9]

Early AMD is often asymptomatic. Some patients notice mild central distortion, particularly when reading, and

Search strategy and selection criteria

We systematically searched PubMed and Medline databases from Jan 1, 1980, to June 30, 2017, using the search terms "macular degeneration", "choroidal neovascularisation", "geographic atrophy", "drusen", "age-related maculopathy", "AMD", and "ARMD". Relevant articles in English (or English translations) were retrieved and reviewed. Reference lists of reviews and original research articles were also searched to identify relevant studies.

See Online for appendix

	Definition
Epidemiological classification (Wisconsin grading)[10]	
Early AMD	Large (≥125 μm) drusen or retinal pseudodrusen, or pigmentary abnormalities
Late AMD	Neovascular AMD or geographic atrophy
Basic clinical classification[8]*	
No ageing changes	No drusen and no pigment abnormalities
Normal ageing changes	Only small drusen ≤63 μm and no pigment abnormalities
Early AMD	Medium drusen >63 μm and ≤125 μm, and no pigment abnormalities
Intermediate AMD	Large drusen >125 μm or any pigment abnormalities
Late AMD	Neovascular AMD or geographic atrophy
AREDS simplified severity scale points[12]†	
0	No large drusen (>125 μm) or pigment changes in either eye
1	Large drusen or pigment changes in one eye only
2	Large drusen and pigment changes in one eye only; or large drusen or pigment changes in both eyes; or neovascular AMD or geographic atrophy in one eye
3	Large drusen and pigment changes in one eye; and large drusen or pigment changes in the fellow eye
4	Large drusen and pigment changes in both eyes

AMD=age-related macular degeneration. AREDS=Age-Related Eye Diseases Study. *Definition is based on the worse eye. †An eye with late AMD has a score of 2.

Table 1: **Definitions and classification scales for AMD**

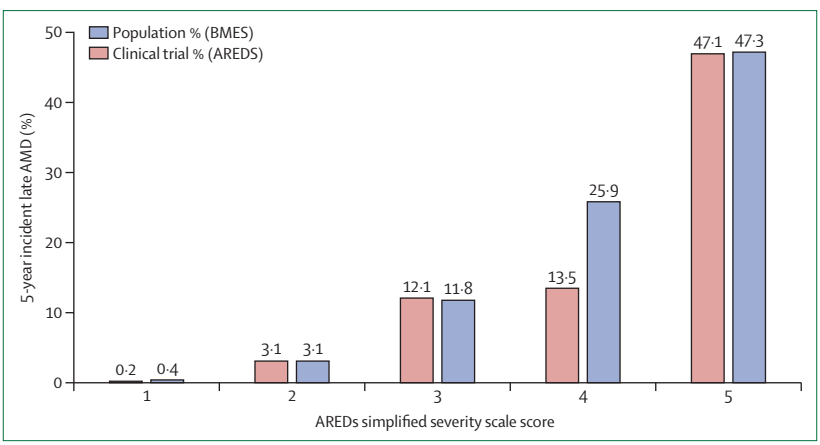

Figure 1: **5-year incidence of late AMD by AREDS simplified severity scale score in a population-based study and a clinical trial**

BMES (a population-based study) and AREDS (a clinical trial) showed remarkable concordance of 5-year incidence stratified by AREDS simplified severity scale score, supporting the validity of the scale. Reproduced from Liew et al,[13] by permission of the American Academy of Ophthalmology. AMD=age-related macular degeneration. BMES=Blue Mountains Eye Study. AREDS=Age-Related Eye Diseases Study.

reduced reading ability with low luminance. Late AMD affects central vision and can progress rapidly (in weeks or months) in the neovascular form, and more slowly (in years or decades) in the atrophic form. The earliest symptoms of AMD include distorted vision when reading, driving, or watching television, and a dark or grey patch (scotoma) in the central vision, with difficulty recognising faces. If only one eye is affected, symptoms might not be apparent until the good eye is occluded.

Neovascular AMD is characterised by the choroidal neovascularisation complex, which incorporates several typical lesions: presence of fluid or retinal haemorrhage (which can be intraretinal, subretinal, or below the retinal pigment epithelium), retinal pigment epithelial detachments, hard exudate, or subretinal fibrous scar tissue. Multimodal imaging, particularly with optical coherence tomography, shows these manifestations clearly and provides information on the size, location, and extent of drusen, as well as the presence and activity of choroidal neovascularisation (figure 2).

Atrophic AMD is also termed geographic atrophy and includes outer retinal thinning. Geographic atrophy can be unifocal or multifocal, and can surround but spare the central macula. Geographic atrophy progresses at a rate of around 2 mm²/year on average, but this rate varies considerably.[14] Multimodal imaging is especially useful to detect and monitor the progression of geographic atrophy because lesion borders and extent can be quantified with greater precision using fundus autofluorescence imaging and spectral-domain optical coherence tomography (figure 3).[14] Optical coherence tomography technology continues to improve, and new algorithms could provide better anatomical endpoints for clinical trials assessing new therapies for retarding the progression of geographic atrophy.

Reticular pseudodrusen might be a risk factor for the development or progression of geographic atrophy and, to a lesser extent, neovascular AMD in the same eye.[15,16] The nature of reticular pseudodrusen is debatable.[17] This sign is best visualised on multimodal imaging, appearing as dot-like or reticular (net-like) aggregations on near-infrared imaging or colour photography, more prominently in blue light. On optical coherence tomography scans, reticular pseudodrusen appear as hyper-reflective foci in the subretinal space above the retinal pigment epithelium (hence the term pseudodrusen).

Epidemiology, prevalence, incidence, and risk factors

Three large, population-based studies—the Blue Mountains Eye Study (BMES), Beaver Dam Eye Study

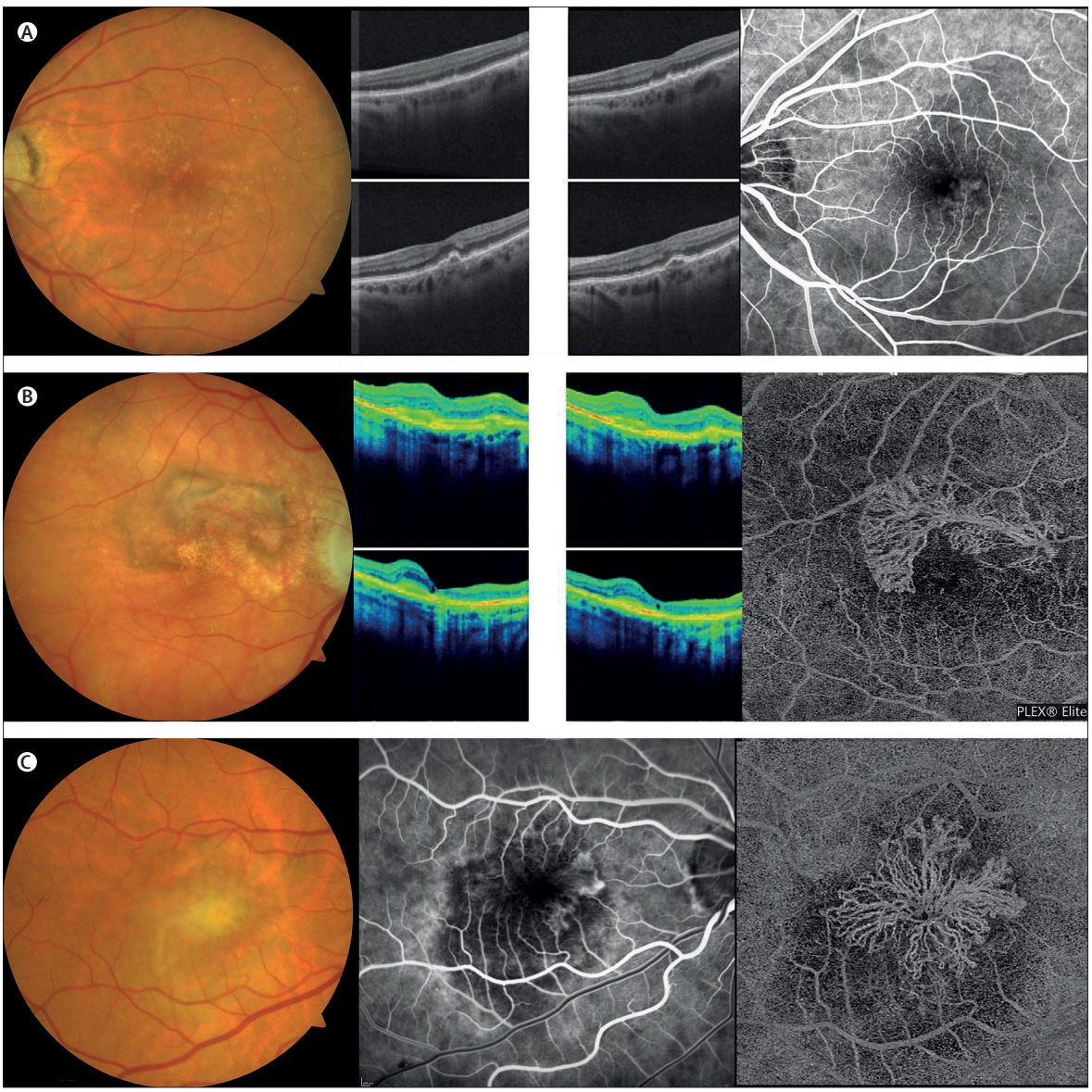

Figure 2: **Multimodal imaging of AMD**
(A) Large soft drusen on colour photography (left), spectral-domain optical coherence tomography (middle), and fluorescein angiography (right). (B) Recent-onset neovascular AMD on colour photography (left), spectral-domain optical coherence tomography (middle), and optical coherence tomography angiography showing appearance of choroidal new vessels (right). (C) Longer-standing neovascular AMD with fibrous scar on colour photography (left), fluorescein angiography (middle), and optical coherence tomography angiography showing Medusa-like appearance of choroidal new vessels (right). AMD=age-related macular degeneration.

(BDES), and Rotterdam Study (RS)—have provided individual and pooled data on AMD prevalence and incidence in white populations.[10]

Many risk factors have been identified for AMD. Age is by far the strongest risk factor, with nearly all late AMD cases occurring in people older than 60 years. The estimated prevalence of late AMD in the three large population-based studies was 0·2% (10 of 4797 participants) for people aged 55–64 years, and increased to 13·1% (68 of 521) for people more than 85 years of age.[18] BMES showed the 15-year incidence was 22·7% (462 of 2036) for early AMD and 6·8% (165 of 2421) for late AMD.[19] AMD incidence was greater in women than in men for all age groups. Meta-analysed data from 14 population-based cohort studies in the European Eye Epidemiology consortium[20] showed that overall prevalence was 13·2% for early AMD and 3·0% for late AMD for people aged 70 years or older. This pattern was similar to those recorded in BDES, in which the 5-year incidence of AMD was 60% lower for each successive generation, as defined by year of birth (1901–24, 1925–45, 1946–64, and 1965–84).[21]

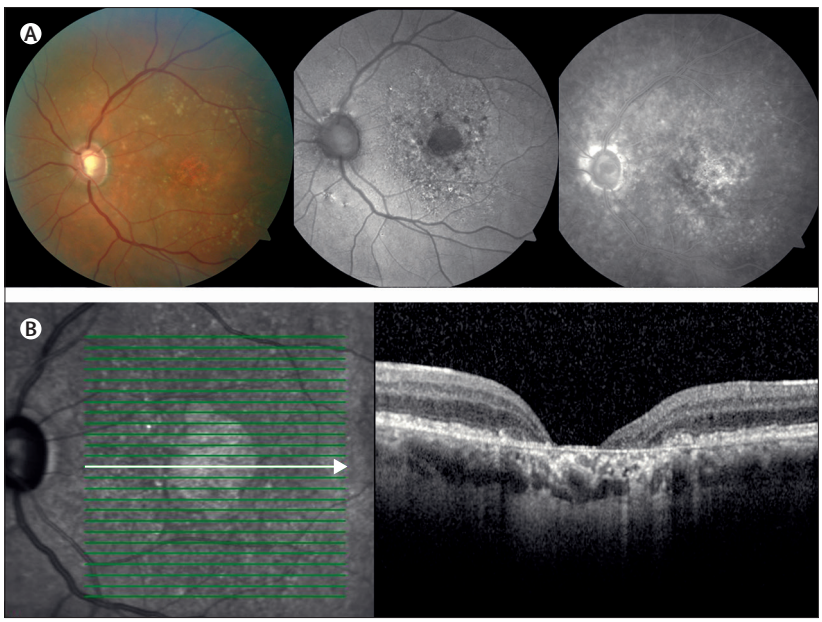

Figure 3: **Multimodal imaging of geographic atrophy**
(A) Large soft drusen surrounding an area of geographic atrophy on colour fundus photography (left), fundus autofluorescence imaging (middle), and fluorescein angiography (right). (B) Near-infrared imaging (left) and optical coherence tomography (right) of geographic atrophy.

A global meta-analysis[3] showed an almost two-times higher prevalence of early and any AMD in European white people compared with Asian people (11·2% *vs* 6·8% for early AMD; 12·3% *vs* 7·4% for any AMD). Early, late, and all AMD were also more prevalent in European white than in African people (11·2% *vs* 7·1% for early AMD; 0·5% *vs* 0·3% for late AMD; 12·3% *vs* 7·5% for all AMD), with no differences in prevalence found between Asian and African populations. European white people had a higher prevalence of geographic atrophy (1·11%) than did African (0·14%), Asian (0·21%), and Hispanic people (0·16%). The prevalence of neovascular AMD, however, was similar in all ethnic groups, with a pooled prevalence of 0·46%.[3]

AMD risk is influenced by non-genetic and environmental factors, such as smoking and diet.[22] Smoking is the strongest (and only agreed upon) modifiable risk factor for AMD, and has been consistently associated with a two-times increased risk for developing late AMD (odds ratios 1·8–3·0), and around a 10-year-younger age at onset.[18,23] Other factors with less robust evidence for their influence on AMD risk include sunlight exposure, iris colour,[18] and alcohol consumption.[24] Inflammatory mediators, measured in the form of C-reactive protein and other markers, are elevated in AMD.[25,26] The possible risks of cataract surgery in eyes with early AMD are uncertain; a Cochrane review[27] showed insufficient evidence to support cataract surgery as a risk factor for late AMD.

Cardiovascular disease risk factors, such as hypertension and hyperlipidaemia, have also been inconsistently associated with AMD risk.[28] Elevated serum lipids were associated with increased risk of intermediate AMD in some studies[29] but not in others.[30]

Implications of AMD

AMD has widespread effects on quality of life. Studies show that patients with AMD report greater life stress, lower satisfaction, lower activity levels, and increased depression than do similarly aged people without AMD.[31] When treatment outcomes do not meet expectations, depression is prevalent, even among patients who have received anti-VEGF treatment.[32] Reported health-related quality of life was similar or lower in patients with AMD than in those with other serious chronic health conditions.[33]

AMD has been associated with increased risk of functional disability in older adults.[34] BMES showed that, compared with participants with no AMD, participants with AMD (of any stage) had a roughly two-times higher risk of negative effects on activities of daily living.[34] AMD is linked to an increased risk of falls and other injuries.[35] Several studies suggest a direct association between vision loss in AMD and number of falls.[35]

AMD increases the risk of cognitive impairment, including Alzheimer's disease.[36] Some studies reported that AMD, especially atrophic AMD, is independently associated with cognitive impairment.[36] A Taiwanese study found that atrophic AMD was independently associated with an increased risk of subsequent Alzheimer's disease or dementia,[37] although this association was not observed in a UK-based study.[38] Several studies have investigated whether AMD patients are at increased risk of death, particularly cardiovascular mortality, but findings have been inconsistent.[39] A ten-study meta-analysis found that late AMD was associated with a 20% increase in all-cause mortality and a 46% increase in cardiovascular mortality.[39]

Genetics

AMD is a multifactorial disorder with a strong genetic component.[40] Discovery of genetic loci associated with AMD was one of the first major successes to come from genome-wide association studies.[40] Since then, large such studies have been done by international consortia for AMD.[41,42] By 2017, 52 common and rare variants at 34 genetic loci had been identified to be independently associated with late AMD on the basis of 16 144 cases of late AMD and 17 832 controls.[43]

The presence of very rare coding variants (frequency <0·1%) in complement factor H (*CFH*), complement factor I (*CFI*), and TIMP metallopeptidase inhibitor 3 (*TIMP3*) suggests causal roles for these genes in AMD pathogenesis.[43] The complement pathway (CFH, CFI, C2, CFB, and C3) is mainly implicated,[44] followed by the age-related maculopathy susceptibility 2 (*ARMS2*) locus, which does not yet have an identified gene product.[45] *TIMP3* encodes a matrix metalloproteinase inhibitor that is involved in regulating the degradation of

the extracellular matrix and is implicated in ageing and Sorsby fundus dystrophy.[46] Altogether, the 52 variants explained 27·2% of disease variability, and more than half the genomic heritability of AMD.[43]

Discovery of these genetic variants has led to formulation of genetic risk scores to help predict the risk of developing late AMD. Risk scores that included age, sex, smoking, and early AMD phenotypes had large area under the receiver operating curve values (0·85–0·91).[47–49] In a study by Buitendijk and colleagues,[49] the cumulative incidence of late AMD, depending on age alone, peaked at less than 20%; however, with the addition of genetic and environmental risk scores, cumulative risk could be further refined from virtually 0% to more than 65% for those with the highest risk scores (appendix). However, the American Academy of Ophthalmology advises against routine predictive genetic testing for AMD because potential ethical, legal, and societal risks outweigh potential benefits.[50]

Several gene–environment interactions for AMD have been reported. Smoking increases AMD risk for all genotypes of *CFH*, *ARMS2*, and HtrA serine peptidase 1 (*HTRA1*).[2,51,52] In monozygotic twins discordant for AMD signs, twins with more advanced AMD had greater exposure to smoking than twins with less advanced AMD.[53]

Pathogenesis of AMD

The characteristic lesions of AMD are drusen, which are visible clinically in both the macula and retinal periphery. Colour fundus photography and clinical examination can be used to document drusen according to their size as hard (or small), medium (>63 μm), or large (>125 μm).[54] Another form, compound drusen, can exist in the retinal periphery, but its implications are unclear.[55] On histology and electron microscopy, drusen, particularly large drusen, correspond to basal linear deposits that contain membranous material and are located between the basement membrane of the retinal pigment epithelium and the inner collagenous layer of Bruch's membrane.[56]

Drusen consist of various components, including neutral lipids with esterified and unesterified cholesterol (>40% of volume),[57] more than 129 different proteins[55]—including TIMP3, vitronectin, β-amyloid, apolipoproteins (E, B, A-I, C-I, and C-II), and proteins involved in complement regulation—and zinc and iron ions.[58]

Basal laminar deposits, another type of retinal deposit associated with AMD, are found between the basement membrane of the retinal pigment epithelium and its plasma membrane, and consist of basement membrane proteins and long-spacing collagen.[55,59] These two types of deposit might reflect different retinal pigment epithelium responses to cellular stress, resulting in the major manifestations of early AMD lesions: drusen and retinal pigmentary abnormalities.[59]

Regarding neovascular AMD, subtypes of choroidal neovascularisation are classified according to the site of suspected invasion into the retina.[60] Type 1 neovascularisation arises when choroidal neovascularisation proliferation occurs below the retinal pigment epithelium, and corresponds to an occult choroidal neovascularisation with a poorly defined pattern of leakage on fluorescein angiography. Type 2 neovascularisation refers to choroidal neovascularisation proliferation above the retinal pigment epithelium in the subretinal space, and corresponds to classic choroidal neovascularisation with intense fluorescein leakage. Type 3 neovascularisation (or retinal angiomatous proliferation) occurs when the retinal circulation is involved, with an anastomosis between the choroidal and retinal circulations.[61–63] A further subclassification of type 1 choroidal neovascularisation known as polypoidal choroidal vasculopathy, which has a large aneurysmal component, is observed more commonly in African and Asian people,[3,64] with a reported frequency of 22% to 62% among people with AMD in Asian populations (two-times to four-times higher than that in European populations [8–13%]).[64]

Geographic atrophy, another late manifestation of AMD, is characterised by loss of retinal pigment epithelial cells, overlying photoreceptors, and underlying choroidal capillaries.[65] Histological studies suggest that, in geographic atrophy, atrophy of the retinal pigment epithelium takes place first, followed by degeneration of the choriocapillaris.[65]

Prevention and delay of AMD progression

In the AREDS[66] large multicentre clinical trial, treatment with a combined supplement containing high doses of zinc and antioxidants (ascorbic acid [vitamin C], vitamin E, β carotene, and copper) reduced the risk of progression to advanced AMD by around 25% (odds ratio 0·72, 95% CI 0·52–0·98) after an average 6·3-year follow-up. In the follow-up study (AREDS2),[51,67] in which the carotenoids lutein and zeaxanthin were added to the AREDS formula, people in the lowest quintile in terms of dietary lutein and zeaxanthin intake benefited most from the addition of these carotenoids, with around 10% reduced risk of progression to advanced AMD. Furthermore, when β carotene was replaced with lutein, the incremental benefit increased to 18%, probably because of reduced competitive carotenoid absorption. Therefore, lutein and zeaxanthin were considered a better addition to the AREDS supplement than β carotene, also allowing the potential increased risk of lung cancer from β carotene in past smokers to be avoided.[51] A large meta-analysis[68] also showed that high dietary intake of lutein and zeaxanthin was useful in reducing late AMD risk.

BMES[69] provided evidence of a protective role for fish and ω-3 fatty acids. Evidence of a linear association between increasing fish consumption and reduced AMD risk was also shown in a meta-analysis.[70] By contrast, AREDS2[71] showed no net benefit of ω-3 fatty acid supplementation, and a systematic review[72] concluded no

	Treatment	Control	Follow-up duration (years)	Mean change in visual acuity (ETDRS test letters)	
				Treatment group	Control group
Neovascular AMD					
Macugen[74]	Pegaptanib 1 mg every 6 weeks	Sham injection every 6 weeks	1	37% maintained or gained ≥0 letters	23% maintained or gained ≥0 letters
MARINA[75]	Ranibizumab 0·5 mg monthly	Sham injection monthly	1	+7·2	−10·4
ANCHOR[76]	Ranibizumab 0·5 mg monthly plus sham photodynamic therapy	Sham injection monthly plus verteporfin photodynamic therapy	1	+11·3	−9·5
VIEW 1[77]	Aflibercept 2 mg every 2 months	Ranibizumab 0·5 mg monthly	1	+7·9	+8·1
VIEW 2[77]	Aflibercept 2 mg every 2 months	Ranibizumab 0·5 mg monthly	1	+8·9	+9·4
CATT[78]	Bevacizumab 1·25 mg monthly	Ranibizumab 0·5 mg monthly	1	+7·8	+8·8
IVAN[79]	Bevacizumab 1·25 mg monthly	Ranibizumab 0·5 mg monthly	2	+4·1	+4·9
GEFAL[80]	Bevacizumab 0·5 mg monthly for 3 months, then as required	Ranibizumab 0·5 mg monthly for 3 months, then as required	1	+4·8	+2·9
BRAMD[81]	Bevacizumab 1·25 mg monthly	Ranibizumab 0·5 mg monthly	1	+5·1	+6·4
HARBOR[82]	Ranibizumab 0·5 mg monthly for 3 months, then as required	Ranibizumab 0·5 mg monthly	2	+7·9	+9·1
TREX[83]	Ranibizumab 0·5 mg monthly for at least 3 months until disease is inactive, then extension per protocol	Ranibizumab 0·5 mg monthly	1	+10·5	+9·2
LUCAS[84]	Bevacizumab 1·25 mg monthly until disease is inactive, then extension by 2 weeks up to a maximum of 12 weeks	Ranibizumab 0·5 mg monthly until inactive, then extension by 2 weeks up to a maximum of 12 weeks	1	+7·9	+8·2
AURORA[85]	Conbercept 2 mg monthly for 3 months, then monthly or as required	Conbercept 0·5 mg monthly for 3 months, then monthly or as required	1	+15·4	+9·3
OPH1002[86]	Pegpleranib 1·5 mg plus ranibizumab 0·5 mg monthly	Ranibizumab 0·5 mg monthly	1	+10·7	+9·8
OPH1003[86]	Pegpleranib 1·5 mg plus ranibizumab 0·5 mg monthly	Ranibizumab 0·5 mg monthly	1	+9·9	+10·4
HAWK[87]	Brolucizumab 6 mg monthly for 3 months, then every 2 or 3 months as required	Aflibercept 2 mg monthly for 3 months, then every 2 months	1	Non-inferiority endpoint reached	Not published
HARRIER[87]	Brolucizumab 6 mg monthly for 3 months, then every 2 or 3 months as required	Aflibercept 2 mg monthly for 3 months, then every 2 months	1	Non-inferiority endpoint reached	Not published
Pazopanib[88]	Pazopanib 10 mg/mL topical eye drops 2–4 times a day plus ranibizumab as required	Ranibizumab 0·5 mg monthly	1	+0·3 to +1·8	+1·4
Atrophic AMD					
MAHALO[89]	Lampalizumab 10 mg monthly	Sham injection monthly	1	20% reduction in GA growth; 44% reduction in those with *CFI* risk allele; −3·3 letters	−4·9 letters
GATE[90]	Tandospirone 1·75% topical ocular drop twice daily	Vehicle topical eye drops twice daily	30 months	1·76-mm² growth in GA	1·76-mm² growth in GA
COMPLETE[91]	Eculizumab 900 mg intravenous infusion weekly for 4 weeks, followed by 1200 mg every 2 weeks until week 24	Normal saline intravenous infusion weekly for 4 weeks, followed by 1200 mg every 2 weeks until week 24	1 year	+0·37-mm growth in mean square root of GA	+0·37-mm growth in mean square root of GA

AMD=age-related macular degeneration. ETDRS=Early Treatment Diabetic Retinopathy Study. GA=geographic atrophy. CFI=complement factor I.

Table 2: **Outcomes of major treatment trials of late AMD**

benefit of increasing dietary ω-3 fatty acids in terms of preventing or slowing AMD progression.

Treatment of neovascular AMD

Anti-VEGF agents

Effective treatment for neovascular AMD is based on inhibition of the angiogenic protein VEGF, which is produced in the retina and induced by hypoxia and other conditions. VEGF increases retinal vascular permeability and promotes neovascularisation.[73] The first anti-VEGF drug to be used in trials for neovascular AMD was pegaptanib sodium, an aptamer that binds $VEGF_{165}$ and larger isoforms[74] (table 2). Ranibizumab is an antibody fragment that also binds all VEGFA isoforms, and was used in the key phase III trials MARINA[75] (for occult choroidal neovascularisation; compared with sham injections) and ANCHOR[76] (for classic choroidal neovascularisation; compared with verteporfin photodynamic therapy) that led to widespread use of ranibizumab for treatment of neovascular AMD (table 2).

Bevacizumab, which binds all isoforms of VEGFA and is approved for the treatment of metastatic colon cancer, was initially introduced as intravenous therapy for AMD,[92] and subsequently used off-label as an intravitreal injection.[93]

The Comparison of Age-Related Macular Degeneration Treatment Trials (CATT)[78] in the USA compared ranibizumab and bevacizumab for the treatment of neovascular AMD, and showed similar visual acuity outcomes for the two drugs. The Inhibition of VEGF in Age-Related Choroidal Neovascularisation (IVAN) trial[79] in the UK showed similar outcomes to CATT, which were also confirmed in subsequent trials[80,81,84] (table 2) and a Cochrane systematic review.[94] Clinicians worldwide continue to treat AMD with off-label bevacizumab, which is a small fraction of the cost of ranibizumab and appears to have equivalent effectiveness.

Aflibercept is a recombinant protein that includes binding domains of VEGF receptors 1 and 2, and is the most recent major new molecule to be used clinically worldwide. Aflibercept blocks all VEGFA isoforms and VEGFB, and blocks placental growth factor (although the potential benefit of this blockade is still unclear). The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) trials[77] showed that intravitreal aflibercept, given 2-monthly after loading, was non-inferior to monthly ranibizumab for both visual acuity gains and fluid resolution (table 2). In different optical coherence tomography compartments (intraretinal, subretinal, sub-retinal pigment epithelium), 4-weekly aflibercept achieved fluid resolution in a slightly higher proportion of patients than 8-weekly aflibercept by 1 year.[95] This finding matches the clinical observation that most (but not all) patients managed with aflibercept can be extended to 2-monthly injections.

Dosing regimens

The best maintenance regimen to use after initial loading phases of anti-VEGF therapy has been debated. Although the early MARINA[75] and ANCHOR[76] trials suggested that monthly anti-VEGF treatment was necessary to maintain vision, the CATT[78] and IVAN[79] studies showed that monthly treatment was associated with only slightly better outcomes than aggressive as-required regimens that necessitated seven to eight injections in the first year. Later trials of ranibizumab established optimum outcomes for as-required regimens, with gains of 7·9 letters at 2 years from an average 13·3 injections[82] (table 2). This study also showed that, although most patients had a good response by 3 months, around one in eight patients were late responders.[96]

Besides monthly and as-required approaches, treat-and-extend regimens, which merge scheduled treatment with flexibility of treatment intervals based on both visual and anatomic outcomes, have been popularised (table 2), and have now become standard for anti-VEGF therapy in neovascular AMD in many countries, including the USA and Australia.[83,97] The Lucentis Compared to Avastin Study (LUCAS)[98] used a treat-and-extend regimen, reporting good 2-year outcomes with use of eight to nine injections per year (table 2). Treat-and-extend regimens[99] are beginning to replace the as-required regimens typically used in the UK[97] and elsewhere, following reports of poor long-term outcomes from as-required regimens in different countries.[100] In long-term follow-up of 65 patients from pivotal neovascular AMD trials, visual acuity in 24 patients (37%) was reduced to 6/60 or worse by 7 years.[101] In the CATT study,[102] after 5 years, this proportion was 20%, and mean visual acuity had fallen to three letters lower than at baseline.

In a UK-based multicentre study of around 93 000 injections for neovascular AMD in 11 000 patients,[100,103] after 2 years of as-required treatment, visual acuity had increased to 56 letters (baseline 55 letters, Snellen equivalent acuity of 6/21), and fell to a mean of 53 letters (–2 letters below baseline) by 3 years.[100] Number of ranibizumab injections decreased from a mean of 5·7 in year 1 to 3·7 in years 2 and 3, and baseline visual acuity was a crucial predictor of outcomes.[100] 16% of eyes assessed in the study were second-treated eyes, which typically started treatment with better baseline visual acuity (average 65 letters, Snellen equivalent 6/15, close to driving-standard vision), and maintained better vision than first-treated eyes for at least 3 years.[103] Second-eye involvement occurred in around 14% of patients per year for fellow eyes with a visual acuity of 6/60 or better at baseline; for eyes with 6/18 or better baseline vision, second-eye involvement was 50% by 3 years. The data also suggest that neovascular AMD should be detected rapidly, when vision is still fairly good, because presenting vision is the strongest predictor of final vision. Undertreatment of fellow eyes with neovascular AMD is a predictor of further vision decline.[104]

Population impact

Following the introduction of anti-VEGF therapy, the incidence of AMD-related blindness has fallen dramatically (by around 50%) in Denmark and Scotland.[105,106] The UK AMD Electronic Medical Record System (EMR) Users Group reported the cumulative incidence of new blindness (worse than 6/60 in the treated eye) in patients receiving as-required anti-VEGF therapy as 5% at 1 year, 9% at 2 years, 12% at 3 years, and 16% at 4 years.[107] These values were substantially lower than those previously reported in a study of the natural history of untreated neovascular AMD,[108] in which over 75% of eyes not blind at baseline developed new blindness within 3 years. The AMD EMR Users Group study[107] also found that the cumulative incidence of new visual impairment was 30% at 1 year, 41% at 2 years, 49% at 3 years, and 54% at 4 years, suggesting considerable scope for improvement in outcomes.

Real-world studies indicate that relative undertreatment of neovascular AMD is very frequent. The AURA

Study[109] of 2227 patients estimated that at least 5·1 ranibizumab injections were needed to maintain visual acuity from baseline to year 1, and that 8·3 injections were needed to maintain visual acuity from years 1 to 2. Overall, the mean number of injections given in year 1 was 5·4, but only 4·5 were given in year 2. Thus, the injection number needed to maintain acuity was higher than that typically administered in AURA. Gillies and colleagues[110] reported a real-world comparison between ranibizumab and aflibercept in treatment-naive patients with neovascular AMD, with similar baseline characteristics and relatively good starting vision (n=197 eyes per treatment group). The mean numbers of injections (8·1 for ranibizumab and 8·0 for aflibercept) and visits to the clinic (9·6 and 9·5) were similar in both groups, as were 1-year gains (+3·7 letters and +4·3 letters).

Treatments for subtypes of neovascular AMD

The seminal anti-VEGF trials for AMD were done in patients with occult (MARINA)[75] and classic (ANCHOR)[76] choroidal neovascularisation lesions. Although anti-VEGF therapy is clearly effective for choroidal neovascularisation, there is less strong evidence for its efficacy in other subtypes of AMD, such as polypoidal choroidal vasculopathy[64] and retinal angiomatous proliferation.[62]

The 12-month findings from trials of therapy for polypoidal choroidal vasculopathy might clarify these issues. The EVEREST I[111] and II[112] trials compared ranibizumab monotherapy with ranibizumab combined with verteporfin photodynamic therapy, and found similar visual acuity outcomes, but better anatomical outcomes in terms of a higher proportion of eyes with complete regression of polyps (combination therapy 78% [14 of 18 patients] *vs* monotherapy 29% [6 of 21]) and fluid-free retina in patients who received the combination therapy. By contrast, the PLANET study[113] found that aflibercept monotherapy was non-inferior to aflibercept combined with rescue photodynamic therapy in terms of vision gained (+10·7 letters for monotherapy and +10·8 letters for combination therapy at 12 months) and inactive polyps (81·7% [116 participants] and 88·9% [136]). The PLANET study[114] also showed improvements in visual (+10·7 letters) or functional outcomes in more than 85% of participants who were treated with intravitreal aflibercept injection monotherapy, with no signs of leakage from polypoidal lesions in more than 80%. The addition of photodynamic therapy to intravitreal aflibercept injection did not confer additional benefits in visual outcomes; however, as only a few participants met the criteria of a suboptimal response to receive photodynamic therapy, the benefit of adding photodynamic therapy for polypoidal choroidal vasculopathy cannot be established from this trial.[114]

Safety

The systemic and ocular safety of anti-VEGF agents has been much investigated. For ranibizumab, which has been trialled more than other agents, a 2014 systematic review and meta-analysis of randomised trials found no relationship with mortality, but a possible relationship between more intensive treatment and risk of systemic vascular events.[115] A US Medicare beneficiary data linkage study reported no increased risk of acute myocardial infarction, stroke, or all-cause mortality from ranibizumab use.[116] In terms of ocular safety, post-injection infection (endophthalmitis) was rare (1 per 1700 injections), occurring in 11 (<1%) of 1185 patients in the CATT study.[117]

Treatment of atrophic AMD

Atrophic AMD (geographic atrophy) is estimated to account for 20% of legal blindness (20/200 [Snellen equivalent 6/60] or worse in the better eye) in the USA.[118] When affecting the foveal centre, geographic atrophy typically impairs driving vision as well as the ability to read and to recognise faces. However, visual acuity does not correlate well with the extent of geographic atrophy because the fovea can be spared or surrounded for extended periods.[13] Therefore, use of traditional visual acuity as an endpoint in clinical trials can be problematic, as the study duration could be prohibitively long because of the relatively slow growth of geographic atrophy lesions, particularly in the early stages. Alternative clinical endpoints are being explored, including improved reading indices,[119] geographic atrophy growth defined by fundus autofluorescence imaging, optical coherence tomography indices, and composite endpoints based on multimodal imaging.[120]

Complement inhibition has been identified as an important potential therapeutic intervention for atrophic AMD.[121] Drugs targeting the complement pathway, such as eculizumab[91] and lampalizumab,[89] have been tested in phase 2 and phase 3 clinical trials (table 2). In the MAHALO phase II trial,[89] compared with a sham control, lampalizumab treatment led to a 20% reduction in geographic atrophy area progression, and a greater reduction of 44% in *CFI* risk-allele carriers (around half the trial sample). However, findings from the phase III trials Chroma and Spectri[122] showed that lampalizumab did not reduce geographic atrophy enlargement compared with a sham control during 48 weeks of treatment. Furthermore, in the COMPLETE study,[91] eculizumab showed no effect on geographic atrophy growth.

Other agents such as tandospirone eye drops[90] did not affect the progression of geographic atrophy (table 2). Tandospirone is a partial agonist of the serotonin (5-hydroxytryptamine) 1A receptor, a mechanism considered potentially neuroprotective in CNS injury similar to that seen in geographic atrophy.

Alternative anti-VEGF therapies

The results of trials of newer anti-VEGF therapies, including intravitreal therapy with conbercept[85] or brolucizumab,[87,123,124] have been reported for neovascular

AMD (table 2). The phase II trial[85] of conbercept suggested similar or greater visual acuity gains and similar injection frequency to that of ranibizumab in the CATT study. Brolucizumab was non-inferior to ranibizumab in phase II trials, and showed a 1-month increase in the median time to post-baseline therapy, suggesting potentially longer treatment intervals than those of ranibizumab.[123] Brolucizumab also showed greater fluid resolution than aflibercept.[87]

Strittmatter and colleagues[125] postulated that targeting platelet-derived growth factor receptors and VEGF receptors together could inhibit development of pericyte scaffolds, thus better attenuating choroidal neovascularisation. A trial series investigated whether this dual antagonism could improve neovascular AMD outcomes compared with anti-VEGF monotherapy.[88] Phase IIb trials of the platelet-derived growth factor antagonist pegpleranib[126] showed a 62% greater incremental benefit of combination therapy (pegpleranib and ranibizumab) compared with anti-VEGF monotherapy (ranibizumab alone).[127] However, two phase III trials[86,128] showed no visual or anatomical benefit of combination therapy compared with ranibizumab monotherapy (table 2).

Future directions

Practical therapeutic strategies for a complex disease such as AMD are likely to combine multiple factors, including diet, lifestyle, and improved pharmacological interventions, taking into account personalised genetic information.[129] There is increasing interest in interventions to delay the progression from early to late stages of AMD. One area of research is high-dose statin therapy, shown in some small studies to be associated with drusen regression.[130,131] Given the high lipid content of drusen, there is a reasonable biological plausibility for such a mechanism of action, and well-established treatments such as statins could easily be translated into clinical practice. However, evidence remains mixed, with a Cochrane review finding no benefit of statin use in delaying AMD progression.[132]

Gene therapies involving expression of anti-angiogenic proteins by gene delivery have been proposed for neovascular AMD to reduce intravitreal therapy, with preclinical trials done in animal models;[133] the proposed modes of administration are clinic-based intravitreal injection or operating theatre-based subretinal injections. Early data from in-human studies of chronic neovascular AMD suggested safety and early efficacy of subretinal injection of rAAV.sFLT-1, a recombinant adeno-associated viral vector encoding soluble VEGF receptor 1.[134,135] Stem-cell-based therapies, particularly for advanced atrophic AMD to potentially replace dead or dysfunctional retinal pigment epithelium with healthy retinal pigment epithelium, are currently being explored.[133,136]

Visual rehabilitation with low-vision magnifiers, including hand or stand magnifiers, spectacles, and closed circuit television, has been the principal method for helping patients with late AMD. Although these tools can be effective for correcting overall visual functioning, they are cumbersome to use and cosmetically burdensome.[137] Therefore, intraocular implants have become a potentially attractive alternative to extraocular visual aids. A 2017 review of seven types of intraocular lenses recommended for AMD patients found no single ideal lens for use in existing AMD that did not have considerable drawbacks.[137] Further independent clinical studies with long follow-up are necessary before general use of these optical devices by people with AMD.

Advances in electronic technology have made artificial vision through use of retinal prostheses feasible. Two commercial devices have been tested in multiple human clinical trials: the Argus II electronic epiretinal device (Second Sight Medical Products, CA, USA) and the Alpha-IMS electronic subretinal device (Retina Implant AG, Germany).[138,139] These devices were originally designed for patients with advanced retinitis pigmentosa, a form of inherited retinal degeneration that is generally much more severe than AMD. The prostheses provide discrimination between light and dark and, in some patients, recognition of large objects and improved visual function. The cost and longevity of these prostheses limit their use in clinical practice at present.

Conclusion

Over the past decade, major advances have been made in our understanding of the genetic basis of AMD, imaging of the pathological changes that occur, prevention of AMD progression through changes to nutrient intakes, and new therapeutic options in the form of anti-VEGF agents to treat neovascular AMD. As a result, legal blindness and visual impairment from AMD have substantially decreased in incidence. Current research is focused on developing new and longer-lasting agents for neovascular AMD and interventions to slow the progression of geographic atrophy.

Contributors

All authors contributed to the writing of the manuscript and designing of tables and figures.

Declaration of interests

PM has consulted for Novartis, Bayer, Roche, and Abbott. GL has received a travel grant for conference attendance from Bayer. BG declares no competing interests. TYW has consulted for Abbott, Bayer, Boehringer Ingelheim, Genentech, Novartis, Roche, and Santen.

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