Clinical Characteristics and Current Treatment of Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is a multifactorial degeneration of photoreceptors and retinal pigment epithelium. The societal impact is significant, with more than 2 million individuals in the United States alone affected by advanced stages of AMD. Recent progress in our understanding of this complex disease and parallel developments in therapeutics and imaging have translated into new management paradigms in recent years. However, there are many unanswered questions, and diagnostic and prognostic precision and treatment outcomes can still be improved. In this article, we discuss the clinical features of AMD, provide correlations with modern imaging and histopathology, and present an overview of treatment strategies.

Age-related macular degeneration (AMD) is a multifactorial maculopathy characterized by late-onset progressive neurodegeneration of photoreceptors and retinal pigment epithelium (RPE) (Miller 2013). AMD is the leading cause of irreversible blindness in older individuals of industrialized nations. In the United States alone, it was estimated that more than 9 million people had AMD in 2000, of which nearly 2 million were in advanced stages (Friedman et al. 2004). These figures were projected to more than double by 2020. The World Health Organization indicates that AMD ranks third after cataract and glaucoma as a leading cause of blindness globally (WHO 2013).

AMD is typically classified into two phenotypic categories: nonneovascular (dry; nonexudative), and neovascular (wet; exudative). Non-

neovascular AMD is characterized by small, yellow, round deposits called drusen at the level of the RPE. Other changes include focal RPE hyperpigmentation and atrophy. When atrophic areas become confluent, the condition is termed geographic atrophy, which is considered an advanced stage of nonexudative AMD. Neovascular AMD is also an advanced form of AMD, and occurs when abnormal blood vessels grow beneath the neurosensory retina or RPE.

Although only 10% of patients with AMD have the neovascular form, it formerly caused ~90% of AMD-related blindness (Ferris et al. 1984). The past decade has seen revolutionary advances in the treatment of neovascular AMD with anti-vascular endothelial growth factor (VEGF) agents. Numerous basic, translational, and clinical studies are underway to further im-

Editors: Eric A. Pierce, Richard H. Masland, and Joan W. Miller
Additional Perspectives on Retinal Disorders: Genetic Approaches to Diagnosis and Treatment available at www.perspectivesinmedicine.org

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Cite this article as *Cold Spring Harb Perspect Med* 2015;5:a017178

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prove these outcomes and lessen treatment burden.

RISK FACTORS

Demographic Risk Factors

Age is the strongest risk factor for development and progression of all forms of AMD. The Eye Diseases Prevalence Research Group pooled data from seven regional population-based studies and applied the rates to the 2000 United States Census (Friedman et al. 2004). The prevalence of intermediate AMD (at least one druse 125 μ m or larger in one or both eyes) was 5.4% in 60- to 64-year old people, 7.4% in 65–69-year old people, 10.2% in 70–74-year old people, 14.1% in 75- to 79-year old people, and 23.6% in those 80 or older. The respective rates of geographic atrophy were 0.3%, 0.5%, 0.9%, 1.8%, and 6.9%. The respective rates of neovascular AMD were 0.4%, 0.6%, 1.2%, 2.2%, and 8.2%.

Advanced AMD (neovascular AMD and geographic atrophy) has been shown to be more frequent in Caucasians. In the Baltimore Eye Study (BES), 30% of bilateral blindness was caused by AMD in Caucasians, whereas none of the African Americans became bilaterally blind from AMD (Sommer et al. 1991). The Eye Diseases Prevalence Research Group pooled data from the Baltimore Eye Study, Barbados Eye Study, and the Salisbury Eye Evaluation Project, and showed that African Americans, similar to Caucasians, have a steady increase in large drusen and advanced AMD with age (Friedman et al. 2004). However, the exponential increase later in life is not observed in African Americans. Latinos appear to have high prevalence of early AMD but not advanced AMD (Varma et al. 2004), and Asians have relatively similar rates to Caucasians (Kawasaki et al. 2010).

Environmental Risk Factors

Smoking is an important modifiable risk factor for AMD. The Age-Related Eye Disease Study (AREDS) was a randomized study that examined the effects of high-dose antioxidants and zinc as a treatment for AMD. From the 4519

subjects enrolled in the risk factor analyses, the AREDS showed that those who had ever smoked had almost double the risk for neovascular AMD compared with those who had never smoked (AREDS-Study-Group 2000). The Physicians' Health Study involved 21,157 participants and showed that current smokers of 20 or more cigarettes per day had double the risk of developing AMD compared with never-smokers (Christen et al. 1996). The Nurses' Health Study analysis of 31,843 women showed similar findings (Seddon et al. 1996).

Systemic Risk Factors

The association between AMD and cardiovascular disease has been observed, but it remains equivocal whether cardiovascular disease is an independent risk factor for AMD. Some large studies have shown that carotid atherosclerotic lesions increase the risk for AMD (Vingerling et al. 1995), although others have not (Klein et al. 2013). Cerebrovascular disease overall does not seem to be a strong risk factor (Goldberg et al. 1988; Eye-Disease-Case-Control-Study-Group 1992; Klein et al. 1993; Vinding 1995; Vingerling et al. 1995). A larger number of epidemiological studies have implicated hypertension as a risk factor (Sperduto and Hiller 1986; Goldberg et al. 1988; Hyman et al. 2000; Klein et al. 2003; van Leeuwen et al. 2003) compared to those that did not (Eye-Disease-Case-Control-Study-Group 1992; Klein et al. 1993). Studies investigating gene-environment interactions may provide a better understanding of the role of cardiovascular disease in AMD (Feehan et al. 2011).

CLINICAL FEATURES

Normal Aging

The macula undergoes a spectrum of subclinical changes in the normally aging eye. In a subset of individuals, these changes progress to more pathologically significant findings and manifest clinically as AMD (Zarbin 2004). Healthy young maculae normally have a sharp foveal light reflex on biomicroscopy, caused by the concave shape of the fovea. As the macula

ages, this reflex becomes blunted, possibly owing to the decrease in photoreceptor density, shallowing of the foveal pit, and enlargement of the capillary-free zone (Laatikainen and Larinkari 1977). Several small, well-defined drusen will usually be present in the elderly (Klein et al. 1992). Irregularity of the RPE also causes a stippled background of varying degrees.

Morphologic changes are abundant in the normally aging macula. The photoreceptor drop-out during aging is mostly caused by loss of rods (Curcio et al. 1993); foveal cone density appears to remain constant until beyond the ninth decade (Feeney-Burns et al. 1990; Curcio et al. 1993). The outer segments of the rods become disorganized and may accumulate at the apices of the RPE (Feeney-Burns et al. 1990).

The RPE is vulnerable to age-related changes because it is a nonreplicating tissue. For the entire lifespan of the eye, it continually engulfs photoreceptor discs and material from surrounding photoreceptors and RPE cells; it also undergoes autophagy of its cellular contents. Undigested material remains as lipofuscin, a granular lipid-containing pigment containing a mixture of fluorescent cellular byproducts, which exponentially increases with aging (Feeney-Burns et al. 1980). As lipofuscin accumulates in the RPE, cytoplasmic space and metabolic capacity become limited, and the RPE deteriorates over time (Panda-Jonas et al. 1996).

The basal infoldings of the RPE are also reduced from striated cuticular or basal laminar deposits (BLamD) that start to accumulate between the RPE basal plasma membrane and the underlying basement membrane. BLamD are uniformly seen by the seventh decade of life (Sarks 1976) and are composed of lipoproteins and amyloid β . They are considered normal aging changes if they are focal lesions (Miller 2013). Clinically, early forms of BLamD can appear as small, well-circumscribed, “hard” drusen. They may have a translucent appearance if clustered together and viewed with retroillumination on biomicroscopy for middle-aged individuals. However, BLamD are often not directly visible on clinical funduscopy and represent more of a histopathologic finding. An eye with early BLamD typically has a normal clinical

Clinical Features and Treatments for AMD

fundus appearance. BLamD are distinct from basal linear deposits (BLinD), which are specific histopathologic findings of AMD. Whereas BLamD accumulate between the RPE plasma membrane and the RPE basement membrane (in the sub-RPE space), BLinD are located deeper beneath the RPE basement membrane at the level of Bruch’s membrane (Miller 2013).

Early and Intermediate AMD

The aforementioned morphologic changes of the aging fundus are clinically benign. There are several features that characterize the tipping point toward the pathologic state of AMD. In AMD with RPE degeneration, the patchy BLamD seen in normal aging develop an overlying layer of a diffuse, thick, amorphous, hyalinized material, which can become nodular elevations (Bressler et al. 1994). Clinical correlation of this late form of BLamD has not been accurately established, but its presence can be inferred by pigmentary changes (Sarks et al. 2007). Focal areas of hyperpigmentation correlate histologically with RPE hypertrophy and pigmented cells that migrate to the sub-RPE and sub-retinal space. These pigmented cells may also migrate into the outer nuclear layer, and represent compromised RPE cells that can no longer support photoreceptors.

BLinD form layers of membranous debris within Bruch’s membrane, between the RPE basement membrane and the inner collagenous layer. BLinD are thought to be primarily composed of lipoprotein particles (Sarks et al. 1980). These layers accumulate and clinically appear as soft drusen that are characteristic of AMD (Fig. 1) (Sarks et al. 2007). Multilayered BLinD cause a separation of the RPE from Bruch’s membrane, and blood, serous fluid, and choroidal neovascular membranes can make their way into this space. However, BLinD can also accumulate as focal aggregations of basal mounds between the RPE basement membrane and plasma membrane (Sarks et al. 1988). BLinD do not manifest as drusen in this type of accumulation, but may cause pigmentary changes and primary geographic atrophy without drusen on clinical examination (Sarks et al. 2007).

Figure 1. Color fundus photograph of drusen in non-neovascular age-related macular degeneration. There are small ($<63\ \mu\text{m}$, green arrow), intermediate ($63\text{--}124\ \mu\text{m}$, yellow arrow), and large ($\geq 125\ \mu\text{m}$ [average diameter of retinal venule at the optic disc margin], red arrow) drusen.

Reticular Pseudodrusen

Reticular pseudodrusen (or subretinal drusenoid deposits) represent a subphenotype of AMD that was first identified on blue-light (red-free) fundus photography (Mimoun et al. 1990). They clinically appear as yellowish, faint, interlacing networks that most commonly occur along the arcades, and do not fluoresce on fluorescein angiography. Fluorescein sodium is a yellow, synthetic salt dye. Its molecules excite when exposed to blue light (wavelengths 485–500 nm), and emit a green light (520–535 nm) as it returns to its original state. For retinal imaging, fluorescein is injected intravenously, and serial fundus photographs or videos are taken using a green filter.

Imaging with optical coherence tomography (OCT), particularly spectral domain OCT (SD-OCT) has been shown to be effective at detecting reticular pseudodrusen. OCT is a noncontact imaging apparatus that projects infrared light onto the retina and detects back-scattered light, which is converted into high-resolution cross-sectional images that can be reconstructed into three dimensional thickness maps. SD-OCT systems have scanning rates of 20,000–40,000 axial scans per sec, with axial resolution of $5\ \mu\text{m}$. Hyperreflective materials

include the nerve fiber layer, plexiform layers, RPE, and blood, whereas the nuclear layers, photoreceptors, and fluid appear hyporeflexive. In patients with AMD, intraretinal fluid, subretinal fluid, and pigment epithelial detachments can be visualized with exquisite detail not previously possible with biomicroscopy.

SD-OCT imaging of reticular pseudodrusen shows numerous drusenoid deposits above the RPE in the subretinal space (Fig. 2) (Schmitz-Valckenberg et al. 2010; Zweifel et al. 2010). This is contrary to previous histopathologic studies that localized the changes to the choroid. The origin of these lesions remains unclear, but may represent direct photoreceptor damage. Reticular pseudodrusen were initially associated with neovascular AMD (Arnold et al. 1995; Cohen et al. 2007), but recent studies show that they also represent a risk factor for progression to geographic atrophy (Klein et al. 2008b; Pumariega et al. 2011).

Geographic Atrophy

Geographic atrophy is a late manifestation of nonneovascular AMD and is clinically characterized by a sharply delineated area of depigmentation revealing the underlying choroidal vasculature (Fig. 3). Most cases of geographic atrophy develop in areas previously noted to have large drusen. The life cycle of long-standing drusen is commonly characterized by the initial development of hyperpigmentation, followed by hypopigmentation as the drusen regress, and finally geographic atrophy (Klein et al. 2008a). In the AREDS, sites that developed geographic atrophy were preceded by drusen in 100%, large drusen in 96%, confluent drusen in 94%, hyperpigmentation in 96%, hypopigmentation in 82%, and refractile bodies in 23% of patients. The time of progression to geographic atrophy varied from 5.9 yr for confluent drusen to 2.5 yr for hypopigmentation or refractile bodies. The spread of atrophy can progress around the fovea in a continuous ring or in several patches perifoveally. Geographic atrophy usually does not affect the center of vision (fixation) until later stages.

Geographic atrophy on fluorescein angiography appears as sharply demarcated areas of

Figure 2. Multimodal imaging of reticular pseudodrusen (arrows). (A) Color fundus photograph showing yellowish interlacing networks that extend to the vascular arcades. (B) Red-free fundus photography most clearly demonstrates the pseudodrusen as bright spots and the interlacing networks that appear hyporeflective. (C) Fundus autofluorescence shows that the lesions are hypoauteofluorescent. (D) Spectral-domain optical coherence tomography demonstrates that the pseudodrusen are located between the retina and retinal pigment epithelium (RPE), rather than the sub-RPE localization of typical drusen.

hyperfluorescence during the transit phase because of transmission from the underlying choroidal vasculature. On SD-OCT, areas of geographic atrophy are characterized by loss of the external limiting membrane, inner/outer segment junction (or ellipsoid zone), and the RPE-Bruch's membrane complex. Because of the lack of RPE, there is often enhancement of the underlying choroidal reflectivity.

Fundus autofluorescence has been popularized as an accurate tool for monitoring the progression of geographic atrophy (Fig. 3). Autofluorescence refers to light-emitting properties of certain tissues in their natural state. The main fluorophore of RPE lipofuscin is A2E, a pyridinium bisretinoid conjugate containing two vitamin A aldehyde molecules and one ethanolamine molecule. Lipofuscin can respond to excitation by wavelengths 300–500 nm, with emission of 620–630 nm. Autofluorescence can be captured with a fundus camera equipped with the appropriate filters or more commonly

now with a scanning laser ophthalmoscope. Lesions with increased lipofuscin result in hyperautofluorescence, and a decrease of lipofuscin or absence of RPE results in hypoauteofluorescence. In geographic atrophy, the atrophic areas appear as sharply demarcated areas of loss of autofluorescence, corresponding to areas of RPE loss and therefore lack of lipofuscin. Studies have demonstrated that hyperautofluorescence of the junction between atrophic and nonatrophic areas is predictive of subsequent enlargement of the geographic atrophy, and that patches of hyperautofluorescence in the posterior pole precede new areas of atrophy (Holz et al. 2001; Schmitz-Valckenberg et al. 2006). This is thought to be from lipofuscin overload in dysfunctional RPE cells.

Neovascular AMD

Choroidal neovascularization (CNV) is the defining characteristic of neovascular AMD. The

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Figure 3. Geographic atrophy in advanced nonneovascular age-related macular degeneration. (A) Color fundus photograph of central geographic atrophy. (B) The corresponding fundus autofluorescence delineates the kidney-shaped area of atrophy as hypoautofluorescent (dark). However, it also shows that the surrounding clinically normal-appearing retina is hyperautofluorescent, which indicates an accumulation of lipofuscin. (C) Over the course of the next 6 years, the geographic atrophy gradually extends to the areas that were hyperautofluorescent in (B). (Reprinted, with permission, from Schmitz-Valckenberg et al. 2009.)

CNV grows through breaks in Bruch's membrane and expands beneath the RPE (type I CNV), or between the RPE and photoreceptors (type II CNV). The incompetent endothelial cells of the new vasculature cause fluid leakage and accumulation of proteins and lipids. The new friable vessels are also prone to hemorrhage. Type I CNV typically manifests clinically as a fibrovascular retinal pigment epithelial detachment (PED). The typical clinical appearance of type II CNV is a gray-green lesion beneath the retina with overlying retinal thickening. Subretinal and intraretinal fluid, lipid exudates, and subretinal hemorrhage may accompany both types of CNV.

Fluorescein angiography is the gold standard for diagnosing CNV. Angiography can provide valuable data in distinguishing CNV from other potential causes of retinal edema such as diabetic macular edema and pseudophakic cys-

toid macular edema. The angiographic term "classic" CNV refers to a well-demarcated area of hyperfluorescence that manifests in the early phases of the angiography. In the intermediate and late phases, there is typically intense leakage from the lesion (Fig. 4A–C). This pattern correlates with type II CNV. "Occult" (type I) CNV has two patterns: (1) fibrovascular PEDs or (2) leakage from an undetermined source, characterized by an ill-defined focus of choroidal leakage without identifiable classic CNV or fibrovascular PED (Fig. 4D–F).

PEDs are focal areas that appear as elevations of the RPE on bimicroscopy. Visual acuity is relatively preserved compared with neurosensory detachments, as long as there is no overlying neurosensory detachment. There are several different types of PED: fibrovascular, drusenoid, and serous. Fibrovascular PEDs are associated with underlying CNV, whereas drusenoid PEDs are not, and serous PEDs may be seen in both scenarios.

Fibrovascular PEDs demonstrate early mottled or granular hyperfluorescence on fluorescein angiography with mild late leakage. Fibrovascular PEDs may be associated with blood. Hemorrhage localized to the sub-RPE space of the PED will appear as dark greenish-red elevations, but the blood may also track into the subretinal space and, rarely, into the vitreous. Patients with predominantly hemorrhagic PEDs often present with poor visual acuity (Bressler et al. 2004).

Drusenoid PEDs are slowly enlarging; shallow elevations of the RPE with scalloped borders that are thought to develop from the coalescence of soft drusen. They have better short-term visual outcomes compared to the other types of PEDs (Hartnett et al. 1992), but 42% of eyes with drusenoid PEDs eventually progressed to either geographic atrophy or neovascular AMD by 5 yr in the AREDS, with associated decline in vision (Cukras et al. 2010). On fluorescein angiography, there is delayed, gradual, mild staining deep to the RPE with no leakage, and drusenoid PEDs do not become intensely fluorescent as do serous PEDs. Compared with fibrovascular PEDs, drusenoid PEDs are smaller, shallower, and have irregular borders.

Figure 4. Classic and occult choroidal neovascularization (CNV) in neovascular age-related macular degeneration. (A) Color fundus photograph shows a greenish lesion deep to the retina (arrow). (B) Fluorescein angiography shows a focal well-demarcated hyperfluorescence of the CNV that leaks in later (C) frames. There are also scattered drusen that also appear bright. (D) Color fundus photograph shows drusen, pigmentary changes, and a diffusely mottled appearance of the retinal pigment epithelium. Fluorescein angiography demonstrates an ill-defined area of hyperfluorescence (E) that leaks diffusely in mid to late frames (F).

Serous PEDs are sharply demarcated, dome-shaped RPE elevations. Fluorescein pools in the lesions briskly, uniformly, and intensely, without leakage. These lesions may interfere with visualization of underlying CNV on fluorescein angiography. OCT and indocyanine green angiography (see section on Polypoidal Choroidal Vasculopathy) may be useful adjunctive tools in such cases. The natural history of all types of PEDs involves eventual collapse. Geographic atrophy can develop after the collapse of PEDs, especially with large drusenoid PEDs. Tears of the RPE may mimic geographic atrophy, but the former is usually characterized by fluid overlying the tear and intense hyperfluorescence on fluorescein angiography.

OCT, especially SD-OCT, provides detailed anatomical characterization of eyes with neovascular AMD. The ease and speed of acquiring the images has made it the most frequently used imaging modality to follow AMD patients. CNV appears as hyperreflective membranes deep to the RPE or in the subretinal space with associated intraretinal or subretinal fluid. Three-di-

mensional OCT reconstructions of CNV lesions have been shown to correlate with fluorescein findings (Malamos et al. 2009). One study showed that fluorescein angiography is superior to time-domain OCT in detecting new-onset CNV (Do et al. 2012), but it is not yet known whether this holds true with the higher-resolution SD-OCT (Khurana et al. 2010).

SD-OCT allows high-resolution imaging of the exudative fluid associated with CNV (Sayanagi et al. 2009). PEDs appear as elevation of the RPE from Bruch's membrane. Serous PEDs appear dome-shaped, with homogeneously hyporeflective material (optically empty) and good visualization of the underlying choroidal structures. Drusenoid PEDs typically have smooth surface contours with homogeneously hyperreflective material within the PED. Fibrovascular PEDs can have surfaces that are either smooth or irregular, and have heterogeneous material within the PED (Fig. 5). OCT software algorithms are under development to allow automated classification of the type of PED (Lee et al. 2012a).

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Figure 5. Spectral-domain optical coherence tomography of a central fibrovascular pigment epithelial detachment (white arrow) with overlying subretinal fluid (red arrow). The inner-segment/outer-segment junction of the photoreceptors (white arrowheads) has become disrupted in the area overlying the lesion (red arrowheads).

Subretinal fluid on SD-OCT appears as darkly hyporeflective spaces beneath the retina, and intraretinal fluid commonly presents as hyporeflective cystic spaces within the retina. Degenerative cystic changes can be seen in long-standing disease, but these findings do not signify active exudation. These cystic lesions are often sharply demarcated and static. Outer retinal tubulation is another finding in advanced AMD, consisting of round or ovoid, relatively hyporeflective spaces with hyperreflective borders (Fig. 6) (Zweifel et al. 2009). These structures are thought to represent cross sections of tubular branches of degenerating photoreceptors. It is important to recognize degenerative cysts and outer retinal tubulation, because these findings may be misinterpreted as active intraretinal fluid and may prompt unnecessary treatment.

The end-stage result of neovascular AMD is a subretinal, fibrovascular, disciform scar that causes deterioration of the overlying sensory retina. Disciform scars usually appear white to yellow and may have areas of hyperpigmentation caused by RPE hyperplasia. Depending on the extent of RPE hyperplasia within the scar, angiography may show staining or blockage. These fibrovascular scars may continue to grow, with new neovascularization along the borders of the lesions. The late-stage appearance can be very variable. Some heavily pigmented,

elevated scars may mimic choroidal tumors, whereas others may develop substantial lipid deposition to mimic Coats' disease and rarely, massive exudation of fluid may cause a large serous retinal detachment.

Polypoidal Choroidal Vasculopathy

Polypoidal choroidal vasculopathy (PCV) is proposed to be a variant of type I CNV (Imamura et al. 2010). Abnormal tubular and polyp-shaped vascular channels deep to the RPE characterize PCV. It is generally seen in Asian, Hispanic, and black populations. One study from Japan showed that approximately half of patients with neovascular AMD had PCV (Maruko et al. 2007). It is now recognized that PCV also affects white populations, albeit to a lesser degree (Imamura et al. 2010). PCV occurs more often in younger patients, may not always be associated with drusen, and often contains a hemorrhagic component. Large polyps may be visible on clinical examination, but funduscopy,

Figure 6. Outer retinal tubulation (arrows) and degenerative cystic cavities (arrowheads) located above a fibrovascular scar. The “en face” optical coherence tomography (OCT) demonstrates that the tubulations form a branching network. The corresponding B-scan OCT (inset) shows the tubulations as round and ovoid hyporeflective spaces with a ring of hyperreflectivity, and the degenerative cysts as sharply demarcated cavities. (Adapted, with permission, from Wolff et al. 2012.)

Figure 7. Polypoidal choroidal vasculopathy. (A) Color fundus photograph showing two pigment epithelial detachments (PED; arrows) with circinate exudation and subretinal fluid. (B) Indocyanine green angiography showing hyperfluorescent polypoidal lesions in the choroidal vasculature (arrow). (C) The corresponding spectral domain optical coherence tomography shows the subretinal fluid (arrows) and elevation of the retinal pigment epithelium (asterisk). (Adapted, with permission, from Yonekawa 2013.)

OCT, and fluorescein angiography are often not able to distinguish PCV from typical AMD. Indocyanine green (ICG) angiography is the definitive method to image the polypoidal vascular structures in the choroid (Fig. 7).

ICG angiography uses a high-molecular weight dye with infrared emission (830–840 nm). A confocal laser applies an infrared 790 nm light beam and photographs/video are taken similarly to fluorescein angiography. The ICG dye has strong protein-binding properties, and the large size of the ICG-protein complexes reduces the amount of extravasation from the choriocapillaris, which allows superior visualization of the choroidal circulation. Compared with the visible light used for fluorescein, the infrared spectrum allows deeper penetration through the retina and RPE, as well as through media opacities such as cataract and hemorrhage.

Retinal Angiomatous Proliferation

Retinal angiomatous proliferation is another variant of neovascular AMD that is characterized by intraretinal neovascularization. Other

names for this entity include “retinal angiomatous lesion,” “deep retinal vascular anomalous complex,” “retinal anastomosis to the lesion,” “retinal vascular anomalous complex,” “retinal choroidal anastomosis,” and “type III neovascularization” (Yannuzzi et al. 2001; Freund et al. 2008). As the multiple names suggest, there is much debate over its pathogenesis and natural history. Yannuzzi and colleagues introduced the most commonly used term “retinal angiomatous proliferation (RAP)” in 2001 to describe a neovascular process that originated within the neurosensory retina (Yannuzzi et al. 2001). The intraretinal neovascularization was then thought to extend posteriorly into the subretinal space, create a PED, and merge with underlying type I CNV. Gass and colleagues proposed an alternative theory in 2003, describing a process in which the initial pathologic stimulus is an occult type I CNV with associated superficial retinal hemorrhages between the outer retinal capillaries and the CNV (Gass et al. 2003). This was thought to be followed by choroidal-retinal anastomoses, resulting in a “piggy-back” type II CNV overlying the type I CNV.

Clinically, RAP lesions are commonly characterized by intraretinal hemorrhage overlying a retinal vessel that acutely dives in toward the RPE (Fig. 8). Lesions are often located in the paramacular area. Angiomatous tissue with surrounding capillary telangiectasia and dilated perfusing arterioles or draining venules can be seen in early stages. Subretinal fluid and/or hemorrhage are seen if type II neovascularization has occurred. ICG plays an important role in distinguishing RAP from PCV and occult CNV. ICG angiography allows visualization of the anastomotic connections between the retinal and choroidal circulation characteristic of RAP. However, anastomotic connections may also be seen in end-stage neovascular AMD or disciform scarring. The visual prognosis of RAP lesions was conventionally thought to be poor, but subgroup analysis of the Verteporfin in Photodynamic Therapy (VIP) trial showed that the natural history is in fact quite variable, as in typical neovascular AMD, and the lesions responded well to photodynamic therapy (Scott and Bressler 2010).

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Figure 8. Retinal angiomatous proliferation (RAP). (A) Color fundus photograph showing focal intraretinal hemorrhage (arrow) and an underlying pigment epithelial detachment (PED) (arrowheads). There are also drusen (asterisk). (B) Fluorescein angiography shows a focal hyperfluorescence and the underlying PED. (C) Indocyanine green angiography reveals an anastomotic lesion connecting retinal vasculature (arrows). (D) Spectral-domain optical coherence tomography also shows that there is intraretinal fluid (arrowhead) in addition to the PED (white arrow). A hyperreflective focus on the surface of the PED corresponds to the RAP lesion (red arrow).

TREATMENT OF NONNEOVASCULAR AMD

AREDS was a randomized, double-masked clinical trial, which examined the effect of antioxidant and zinc supplementation on progression of AMD. (AREDS Study Group 2000; AREDS Study Group 2001). It enrolled 3640 participants who were stratified into four categories of severity. Category 1: essentially no AMD, with total drusen area less than 5 small drusen ($<63\ \mu\text{m}$); Category 2: mild AMD with multiple small drusen or single/scattered intermediate drusen ($63\text{--}124\ \mu\text{m}$), and/or pigmentary changes; Category 3: at least one large druse ($\geq 125\ \mu\text{m}$) and/or extensive intermediate drusen and/or geographic atrophy not involving the central macula; Category 4: advanced AMD in the fellow nonstudy eye. Participants were randomized to one of four treatment arms: oral daily supplementation with (1) antioxidants (vitamin C 500 mg, vitamin E 400 IU, β -carotene 15 mg), (2) zinc (zinc oxide 80 mg and copper 2 mg), (3) the combination of antioxidants and zinc, or (4) placebo.

Control patients in Category 2 had a 1.3% probability of progressing to advanced AMD in 5 yr. Category 3 had 18% likelihood, and Category 4 had 43%. The largest risk reduction was seen in Category 3 and 4 participants who were randomized to take both antioxidants and zinc (odds ratio 0.66, or 34% odds reduction; $p = 0.001$). This group also had the largest

reduction in loss of 15 letters or more with an odds ratio of 0.73 ($p = 0.008$), corresponding to a 27% risk reduction. Based on these findings, it was recommended that patients in Category 3 and 4 would benefit from antioxidant and zinc supplementation. Current and former heavy smokers were urged to take a regimen free of β -carotene, which has been shown by epidemiologic studies to increase the risk of lung cancer in smokers.

The AREDS investigators initiated AREDS 2 in 2006 (AREDS2 Study Group 2013). The goal was to determine whether adding omega-3 fatty acids (docosahexanoic acid [DHA] and its precursor eicosapentanoic acid [EPA]) and/or lutein and zeaxanthin to the original AREDS formulation would further reduce the risk of advanced AMD. 4203 participants with either bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye were randomized into four arms: (1) original AREDS, (2) AREDS + lutein 10 mg + zeaxanthin 2 mg, (3) AREDS + DHA 350 mg + EPA 650 mg, and (4) AREDS + DHA/EPA + lutein/zeaxanthin. In a secondary randomization, participants were randomized to the original AREDS formulation with or without β -carotene, and standard or lower doses of zinc.

The results (AREDS2 Study Group 2013) showed that there was no further benefit in adding DHA/EPA or lutein/zeaxanthin to the original AREDS formulation. However, it was found

that participants who took the original AREDS formulation without β -carotene but with lutein and zeaxanthin and had slightly lower rates of progression to advanced AMD, compared to those taking the original formulation with β -carotene (hazard ratio 0.82; $p = 0.02$). Therefore it was suggested that lutein/zeaxanthin could be substituted for β -carotene.

Treatments in Development

The complement pathway has been implicated in the pathogenesis of AMD and many clinical trials are under way to investigate whether complement inhibitors can slow the progression of nonneovascular AMD. Studies of a systemically administered anti-C5 antibody, eculizumab, failed to show efficacy in reducing drusen volume or progression of geographic atrophy. (Garcia Filho et al. 2014; Yehoshua et al. 2014). A Phase II sham-controlled, randomized study that enrolled 129 patients with bilateral geographic atrophy, and showed that monthly intravitreal injections of lampalizumab (antifactor D, Roche/Genentech) resulted in a 20% reduction in the rate of growth geographic atrophy at 18 mo (Regillo 2013). Of note, patients positive for a specific complement factor I polymorphism (57% of the study participants) benefited from a 44% growth reduction. Many other trials of complement inhibitors are also in progress (Miller 2013).

Other potential therapeutic strategies in development include targeting inflammasomes, visual cycle modulation, and neuroprotection. Inflammasomes are multiprotein complexes that activate inflammatory cascades, and have been identified as potential targets for both non-neovascular (Tarallo et al. 2012) and neovascular (Doyle et al. 2012) AMD. Interrupting the photoreceptor light cycle to decrease the accumulation of A2E, a toxic component of lipofuscin, is another avenue under investigation. Early trials indicate that visual cycle modulators may have a role in slowing the progression of geographic atrophy (Kubota et al. 2012; Mata et al. 2013). Research in neuroprotection aims to identify agents that will interfere with cell death pathways and inhibit the loss of neural retina

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that is the ultimate cause of vision loss in AMD as well as many other disorders. (Trichonas et al. 2010; Wong et al. 2010; Zhang et al. 2011a; Miller 2013; Tsai 2013). Subretinal transplantation of stem cells is also being investigated as a means of regenerating RPE cells and eventually, perhaps photoreceptors as well (Schwartz et al. 2012).

TREATMENT OF NEOVASCULAR AMD

Photocoagulation

The Macular Photocoagulation Study (MPS) demonstrated the efficacy of argon photocoagulation for extrafoveal CNV (MPS Study Group 1982; MPS Study Group 1986). However, this treatment modality has been largely abandoned because of frequent recurrences and limited applicability.

Macular Surgery

Submacular surgery to directly remove neovascular membranes evolved in the 1990s as an alternative to observation or photocoagulation. The Submacular Surgery Trials showed that there was no benefit in visual outcomes in patients with subfoveal CNV treated with submacular surgery (Hawkins et al. 2004). However, treated lesions that were predominantly hemorrhagic lost less vision compared with observation (Bressler et al. 2004), although this did not translate into improved quality of life (Childs et al. 2004).

Macular translocation is a surgical procedure in which CNV is typically removed and the macula is displaced so that the fovea overlies normal RPE (Machemer and Steinhorst 1993; Ninomiya et al. 1996; de Juan et al. 1998; Lai et al. 2002; Mruthyunjaya et al. 2004). Limited macular translocation involves partially detaching the retina via injection of subretinal fluid and shifting the inferior retina downward with the help of a gas bubble to create a retinal fold. Another translocation technique involves 360° peripheral retinectomy to fully detach and rotate the entire retina. Since the emergence of pharmacological therapies, surgical techniques

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are rarely used in management of neovascular AMD.

The current primary indication for surgical intervention in neovascular AMD is management of large submacular hemorrhages. Displacement of such hemorrhage is often attempted with vitrectomy and subretinal injection of tissue plasminogen activator and intravitreal gas (Hassan et al. 1999; Hattenbach et al. 2001; Hauptert et al. 2001; Olivier et al. 2004; Singh et al. 2006). Successful pneumatic displacement with intravitreal gas injection, injections without vitrectomy and with or without tissue plasminogen activator, have also been reported (Ohji et al. 1998; Daneshvar et al. 1999; Ron et al. 2007; Mizutani et al. 2011).

Photodynamic Therapy

Photodynamic therapy (PDT) using verteporfin (Visudyne; Valeant Ophthalmics, Bridgewater, NJ) was approved by the United States Food and Drug Administration (FDA) for the treatment of neovascular AMD in 2000. PDT uses intravenously administered photosensitizing molecules that can be activated by photons in specific wavelengths, which allows photochemical damage by the generation of free radicals. An advantage over photocoagulation is the relative sparing of normal tissue, because only tissues that accumulate the photosensitizers are directly affected.

The Treatment of AMD with Photodynamic Therapy (TAP) trial was the phase III study that established the efficacy of PDT for neovascular AMD (TAP-Study-Group 1999). It randomized 609 participants with subfoveal neovascular AMD with a predominantly classic component, to verteporfin PDT or placebo. More eyes treated with PDT lost less than 15 letters of visual acuity at 12 mo (61% vs. 46%; $p < 0.001$). Eyes with predominantly classic lesions benefited the most. The benefits were sustained at two (Bressler 2001) and three years (Blumenkranz et al. 2002).

The VIP study examined verteporfin PDT for the treatment of subfoveal occult-only lesions and classic lesions with good visual acuities (VIP Study Group 2001). Eyes treated with

PDT experienced less vision loss of 15 or more letters (54% vs 67%; $p = 0.023$) at two years compared with placebo. The VIO trial also randomized patients with occult lesions to PDT or placebo, but showed only a trend favoring PDT that was not statistically significant (Kaiser 2009).

Anti-VEGF Therapy

Pegaptanib

Pegaptanib sodium (Macugen; Valeant Ophthalmics, Bridgewater, NJ) is a pegylated RNA aptamer that selectively binds VEGF₁₆₅, which is thought to be one of the primary pathologic VEGF isoforms. Pegaptanib became the first anti-VEGF agent approved by the FDA for treatment of neovascular AMD based on the VISION studies (Gragoudas et al. 2004) which demonstrated that pegaptanib 0.3 mg given intravitreally every 6 wk resulted in 70% of patients losing fewer than 15 letters of visual acuity, compared to 55% of controls ($p < 0.001$). However, use of pegaptanib has been largely replaced by the pan-VEGF-A inhibitors.

Ranibizumab

Ranibizumab (Lucentis; Genentech, South San Francisco, CA) is a humanized monoclonal Fab fragment that neutralizes all active isoforms of VEGF-A. Its efficacy was demonstrated in the ANCHOR (Brown et al. 2009) and MARINA (Rosenfeld et al. 2006) trials, and it was FDA approved for the treatment of neovascular AMD in 2006.

The ANCHOR study randomized 430 participants with predominantly classic CNV to monthly 0.3 mg ranibizumab, 0.5 mg ranibizumab, or verteporfin PDT (Brown et al. 2009). The primary outcome of loss of fewer than 15 letters at 12 mo was met (94.3%, 96.4%, and 64.3%, respectively; $p < 0.001$) and sustained at 24 mo. Visual acuity improved by 15 letters or more in 35.7%, 40.3%, and 5.6%, respectively ($p < 0.001$), at 12 mo, and similarly at 24 mo. At 12 mo, the mean letters gained or lost were +8.5, +11.3, and -9.5, respectively ($p < 0.001$), and this difference was comparable at 24 mo.

The MARINA trial randomized 716 participants with minimally classic or occult CNV with evidence of recent progression to 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections (Rosenfeld et al. 2006). At 12 mo, <15 letters were lost in 94.5%, 94.6%, and 62.2% of patients, respectively ($p < 0.001$). Visual acuity improved by 15 or more letters in 24.8%, 33.8%, and 5.0% of patients, respectively ($p < 0.001$). Mean letters gained or lost were +6.5, +7.2, and -10.4, respectively ($p < 0.001$). The benefits were sustained at 24 mo.

Bevacizumab

Bevacizumab (Avastin; Genentech, South San Francisco, CA), a monoclonal anti-VEGF-A antibody, is the parent molecule of ranibizumab. It is FDA approved for the treatment of several systemic malignancies, but is used off-label as a cost-effective anti-VEGF agent for various ophthalmic conditions. The Comparison of AMD Treatment Trials (CATT) study was a federally funded, multicenter, noninferiority trial that randomized 1208 participants with neovascular AMD to receive ranibizumab or bevacizumab on either a monthly schedule or “as needed.” (Martin et al. 2011, 2012). Monthly bevacizumab and monthly ranibizumab had similar efficacies, with a mean of 8.0 and 8.5 letters gained, respectively. The as-needed schedules were also comparable, with 5.9 and 6.8 letters gained, respectively. The difference between monthly and as-needed regimens did not reach statistical significance.

Aflibercept

Aflibercept (Eylea; Regeneron, Tarrytown, NY) is a recombinant fusion protein of the ligand-binding elements of VEGF receptors 1 and 2, which are fused to the Fc portion of human IgG1. It blocks all VEGF-A isoforms, VEGF-B and placental growth factor (Browning et al. 2012; Stewart 2012). The benefit of aflibercept over previous agents is its demonstrated efficacy when given on a less frequent bimonthly injection schedule (Papadopoulos et al. 2012). Aflibercept was FDA approved in 2011 after

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the results of the VIEW 1 and VIEW 2 studies, which were two parallel phase III trials that randomized 2419 patients to 0.5 mg monthly aflibercept, 2.0 mg monthly aflibercept, 2.0 mg aflibercept every 2 mo after three initial monthly doses, or monthly 0.5 mg ranibizumab (Heier et al. 2012). All aflibercept groups were comparable to monthly ranibizumab for the primary endpoint (proportion of patients losing <15 letters at 1 yr). The letters gained and anatomic measures as seen on OCT were also comparable.

Combination Therapy

The role of PDT in treating typical neovascular AMD has become limited to refractory cases given the superior results obtained with anti-VEGF therapy. Studies investigating combination PDT and anti-VEGF therapy for AMD did not show benefit with respect to visual acuity or significant reduction in number of injections (Kaiser et al. 2012; Larsen et al. 2012).

PDT, however, still plays an important role in the treatment of PCV (Kurashige et al. 2008; Kang et al. 2013; Yamashita et al. 2013). Anti-VEGF agents can decrease the exudation associated with PCV to improve visual acuity, but often do not close the polypoidal vascular abnormalities (Gomi et al. 2008; Koizumi et al. 2011); the local photochemical damage of PDT can directly close these channels (Koh et al. 2012). Combining PDT with anti-VEGF agents appears to be an effective approach (Kim and Yu 2011; Koh et al. 2012; Lee et al. 2012b; Tomita et al. 2012). The EVEREST study randomized 61 patients with PCV to verteporfin PDT, ranibizumab 0.5 mg, or the combination, and showed that PDT with ranibizumab or PDT alone was superior to ranibizumab monotherapy in achieving polyp regression at 6 mo ($p < 0.01$) (Koh et al. 2012).

Despite the success of current pharmacotherapies for neovascular AMD, better visual results and more durable therapies remain goals to be achieved. Strategies under investigation include inhibition of platelet-derived growth factor (Boyer 2013), and other mechanisms of VEGF blockade including anti-VEGF gene therapy. (Lukason et al. 2011; Zhang et al. 2011b; Campochiaro et al. 2013).

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CONCLUDING REMARKS

Many recent advances in ophthalmology have been in the arena of AMD. From genetic studies to new imaging technology, breakthroughs in treatment, and gains in the fundamental understanding of its pathophysiology, the strides made in AMD research have prevented blindness in millions of individuals. However, better and further-reaching treatments are needed. Directions for ongoing and future research that will help achieve such treatments include more precise phenotyping of AMD utilizing modern imaging capabilities combined with genotyping, a deeper understanding of AMD pathophysiology, improved disease models, further insight into pharmacogenomic interactions, and new drug delivery technology.

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Cold Spring Harb Perspect Med 2015; doi: 10.1101/cshperspect.a017178 originally published online October 3, 2014

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