


LITERATURE REVIEW

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Diagnosis and Therapy of Age-Related Macular Degeneration

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ABSTRACT

Age-related macular degeneration (AMD) is one of the leading causes of central vision loss in older adults and is becoming an increasingly important health problem in aging populations. This disease involves complex interactions among oxidative stress, chronic inflammation, retinal pigment epithelium dysfunction, changes in Bruch's membrane, complement system dysregulation, and genetic factors. Diagnostic advances in retinal imaging, particularly optical coherence tomography (OCT), and a better understanding of morphological and molecular biomarkers have expanded clinicians' ability to recognize disease course, assess progression risk, and evaluate treatment response. From a therapeutic perspective, AMD management includes AREDS2-based nutritional supplementation in selected cases, anti-vascular endothelial growth factor (anti-VEGF) therapy for the neovascular form, and the development of new approaches such as gene therapy and long-term drug delivery systems. This review briefly discusses the diagnostic and therapeutic aspects of AMD to support evidence-based understanding and clinical practice. Early recognition and appropriate management are important for preserving vision and guiding patient care.

Keywords: Age-related macular degeneration, antioxidant vitamins, AREDS2, lutein, nutritional supplementation, zeaxanthin.

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INTRODUCTION

One of the leading causes of central vision loss in older adults is age-related macular degeneration, or AMD.[1] AMD is a degenerative disease of the macula that causes progressive decline in central visual acuity in older adults. Clinically, it is divided into the atrophic/non-exudative (dry) form, including geographic atrophy, and the neovascular/exudative (wet) form with choroidal neovascularization.[1] Dry AMD usually progresses slowly, whereas wet AMD is rapid and destructive and is responsible for severe blindness in the majority of cases. This disease affects the macula, a small area of the retina that plays an important role in detailed vision, such as when reading or recognizing faces.

MAIN REVIEW

Risk Factors

The main risk factors include age, a history of smoking, dyslipidemia/metabolic disorders, light exposure, a diet low in carotenoids, and genetic predisposition (CFH, ARMS2/HTRA1, C3).[2] AMD results from the interaction of chronic oxidative stress in the RPE/photoreceptors, mitochondrial and autophagic dysfunction, lipofuscin/A2E accumulation, thickening and dysfunction of Bruch's membrane, inflammasome activation (NLRP3), and dysregulation of the complement pathway (C3a, C5a, MAC), with a strong contribution from CFH/C3/ARMS2-HTRA1 polymorphisms.[1,3] Individuals with genetic variants such as CFH Y402H or ARMS2 A69S have a relatively higher risk of developing AMD, even at a younger age.[2,4] These mutations accelerate complement activation, disrupt the binding of inhibitory factors on the surface of Bruch's membrane, and facilitate the inflammatory process.[5]

Prevalence

The prevalence of AMD increases with age, especially in individuals over 60 years of age.[5–7] Based on projections by Lee, *et al*., the number of people with AMD globally is expected to rise sharply by 2050 as life expectancy increases, becoming a continuously growing global public health burden.[5,8] Epidemiological projections estimate a surge in cases through 2040–2050.[9] AMD is currently not only a challenge in ophthalmology, but has also become a public health problem.

Pathophysiology

The degenerative process in Age-Related Macular Degeneration (AMD) cannot be seen as solely as a consequence of aging. The pathogenesis of AMD involves various complex interactions among oxidative stress, chronic inflammation, mitochondrial dysfunction, and immune system abnormalities. Research shows that chronic oxidative stress in photoreceptors and the RPE triggers the accumulation of toxic lipofuscin and A2E.[5] These toxic compounds trigger lysosomal damage, impaired autophagy, and chronic activation of the complement system. This condition causes the Bruch's membrane layer to thicken and fill with debris, so it fails to function as a medium for metabolite exchange between the choroid and the retina.[5]

A series of complex biological changes contributes to central retinal tissue damage. One of these is degeneration of the retinal pigment epithelium (RPE), which gradually undergoes multifactorial dysfunction, including lipofuscin accumulation and chronic oxidative stress.[3,10,11]

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In wet AMD, tissue hypoxia promotes VEGF expression and choroidal angiogenesis; the VEGF–PEDF imbalance exacerbates leakage, edema, and hemorrhage. Morphologically, intermediate AMD is characterized by large drusen and/or AMD-associated pigmentary abnormalities (> 125 μm), pigment abnormalities, and RPE changes, whereas the advanced stage includes geographic atrophy or CNV (choroidal neovascularization).[1,2]

AMD is classified into two main forms of clinical manifestation, namely the atrophic (dry) form and the neovascular (wet) form. The atrophic (dry) form is slow but progressive, whereas the neovascular (wet) form is rapid and destructive. Although data show that only approximately 10%–15% of patients with AMD develop the neovascular form, this form is responsible for most cases of severe vision loss.[3]

In general, the initial symptoms may be subtle or vague, ranging from mild visual distortion to sudden loss of central vision, particularly in the neovascular form. Drusen, as subretinal deposits that accumulate between Bruch's membrane and the RPE, are an early sign of AMD. Their main components include cholesterol esters, complement proteins, and metabolic debris that interfere with nutrient and waste exchange between the retina and the choroid.[5] Not only does their quantity increase, but the molecular quality of their constituents also shows a tendency to stimulate local immune responses and low-grade chronic inflammation.[6–8,13]

Bruch's membrane progressively thickens due to abnormal deposits resulting from the degradation of both proteins and lipids. Over time, this structure loses not only its flexibility but also its functional ability to support nutrient diffusion and retinal waste excretion. The result is a dysfunctional metabolic environment that gradually triggers RPE cell death.[5–7]

Autophagic dysfunction and mitochondrial damage initiate structural abnormalities in the RPE. Impaired autophagy causes oxidized protein accumulation, while mitochondrial damage disrupts ATP production and worsens oxidative stress, promoting RPE cell apoptosis.[3,7,8,11] Accumulation of A2E, a toxic bisretinoid compound formed from the visual cycle, has also been shown to damage lysosomes and increase sensitivity to blue light, thereby worsening retinal damage.[5,8]

Activation of the innate immune system also accelerates disease progression. Activation of the NLRP3 inflammasome in the RPE by the accumulation of Alu retrotransposon RNA has been shown to trigger the release of pro-inflammatory cytokines such as IL-1β and IL-18, which amplify the local inflammatory response.[5,14] This inflammation is chronic and low-grade, but is sufficient to cause gradual damage to the macular retina.

In addition to inflammation, the complement pathway contributes significantly to the pathophysiology of AMD. Activation of the alternative complement pathway, characterized by increased levels of C3a and C5a, is frequently found in the retinal tissue of patients with AMD.[9,15] Genetic polymorphisms in CFH, C3, and C9 increase susceptibility to excessive activation of this system.[2,8] The combination of genetic factors and the accumulation of complement proteins in drusen forms a cycle of immune damage that is difficult to stop. A schematic of complement pathway activation and MAC formation in AMD is shown in **Figure 1**.[16]

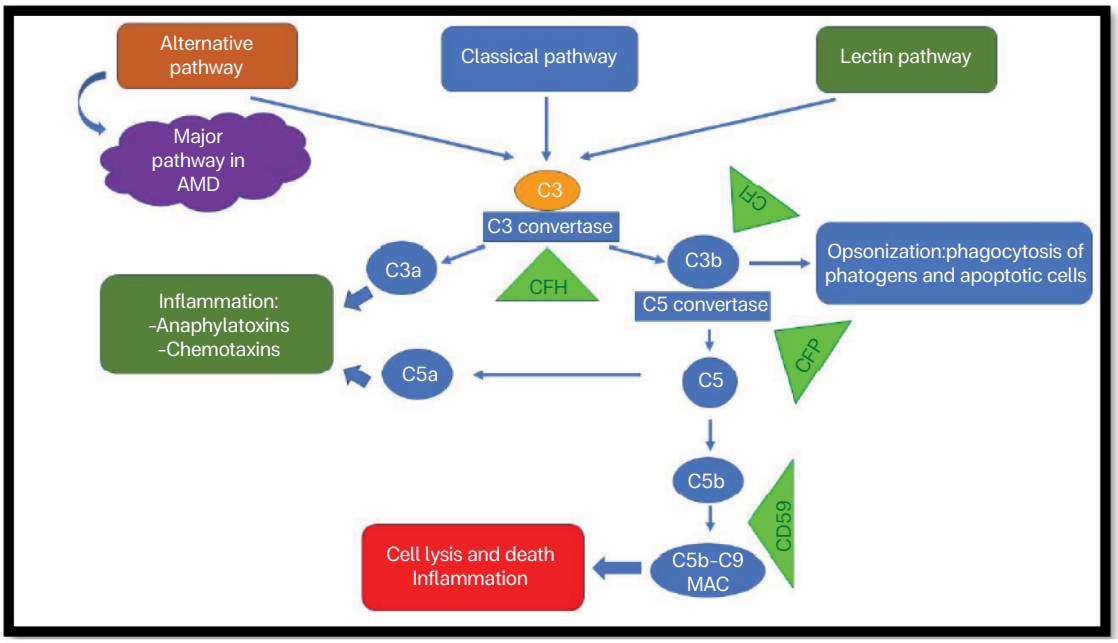


Figure 1. The three main pathways, classical, lectin, and alternative, converge on C3 activation, which then forms C3 convertase and triggers the formation of C3a and C3b. C3a and C5a act as anaphylatoxins that induce inflammation; further activation forms the C5b–C9 complex (MAC), which causes cell lysis and retinal damage. Polymorphisms in the CFH (complement factor H) gene play a role in dysregulation of this system and increase susceptibility to AMD.[16]

Abbreviations: AMD: Age-related macular degeneration; C3: Complement component 3; C5: Complement component 5; CFH: Complement factor H; CFI: Complement factor I; CFP: Complement factor properdin; CD59: Cluster of differentiation 59; MAC: Membrane attack complex.





The neovascular form of AMD (wet AMD) shows additional complexity through pathological angiogenesis. Hypoxia from RPE dysfunction and choroidal capillary degeneration triggers VEGF (vascular endothelial growth factor) expression, which then causes abnormal new blood vessels to grow from the choroid toward the retina.[3,15] These vessels tend to be fragile and leaky, causing subretinal hemorrhage, edema, and the formation of fibrotic tissue that impairs visual acuity.[3]

At the same time, decreased expression of antiangiogenic molecules such as pigment epithelium-derived factor (PEDF) further worsens this angiogenic imbalance. In addition, patients with AMD also show susceptibility to rupture of newly formed blood vessels, resulting in the complication of vitreous hemorrhage.[3,17]

Biochemical changes in drusen and Bruch's membrane indicate involvement of stress proteins, inflammatory molecules, and oxidized lipids, which create a retinal tissue environment unfavorable for photoreceptor cell survival.[5,18,19] This condition demonstrates the complexity of AMD, which involves interactions among metabolic dysfunction, oxidative stress, immune dysregulation, and changes in the extracellular microstructure.

Changes in choroidal microcirculation have also been reported, even before the clinical manifestations of AMD become apparent. Reduced choroidal perfusion, the formation of avascular zones, and increased vascular resistance indicate that retinal ischemia also contributes to the pathogenesis of this disease.[20,21]

AMD cannot be interpreted merely as a passive degenerative process. Instead, AMD results from of active interactions among structural tissue instability, oxidative insult, chronic inflammation, and genetic predisposition. The deeper the understanding of these pathways, the greater the opportunities to intervene in disease progression more precisely and individually.

Morphology and Histopathology

The morphological characteristics of AMD include drusen, irregular pigmentation, and geographic retinal atrophy. These findings characterize early-stage AMD.[11] The main lesions involve the outer retinal complex: RPE–Bruch's membrane–photoreceptors–choriocapillaris. Large soft drusen, basal laminar deposits (BlamD), and basal linear deposits (BlinD) interfere with nutrient/waste transport and become precursors of progression. Geographic atrophy shows loss of the RPE and photoreceptors as well as changes in the choriocapillaris. In wet AMD, sub-RPE/subretinal fibrovascular membranes, fibrin/erythrocytes, and subfoveal scar tissue are present. However, in some cases, clear clinical changes appear only after chronic histological damage has occurred. Therefore, it is very important to reconsider the role of retinal histopathological examination in the early diagnostic stages of AMD. Microscopic examination of the retina shows that debris accumulation between the retinal pigment epithelium (RPE) and Bruch's membrane plays a significant role in retinal metabolic dysfunction.[5]

The histopathological lesions of AMD, in both the dry and wet forms, reflect the gradual disintegration of the outer retinal complex. In general, the affected retinal layers include the retinal pigment epithelium (RPE), Bruch's membrane, photoreceptors, and superficial choroidal capillaries. The histopathological process does not proceed linearly, but passes through cycles of damage, compensation, and tissue reorganization.[17] **Figure 2** shows the orientation of the retinal layers, particularly the relationship among the RPE, Bruch's membrane, and photoreceptors.[22]

In non-exudative AMD, drusen are often the most prominent histological finding. Drusen are classically located between the RPE and Bruch's membrane and appear as yellowish round deposits on microscopic fundus examination. The size and consistency of drusen are used to distinguish normal retinal aging from pathological AMD. Soft drusen larger than 125 μm with indistinct borders are more frequently found in patients with highly progressive AMD.[5,18,19] In advanced stages, geographic atrophy is seen and is histopathologically characterized by complete loss of the RPE and photoreceptor layers in specific areas of the retina. These areas usually allow direct visualization of the choroid, indicating multilayer retinal damage. Structural changes such as loss of the choriocapillaris and erosion of the intercapillary pillars of Bruch's membrane are also found.[5,18,19]

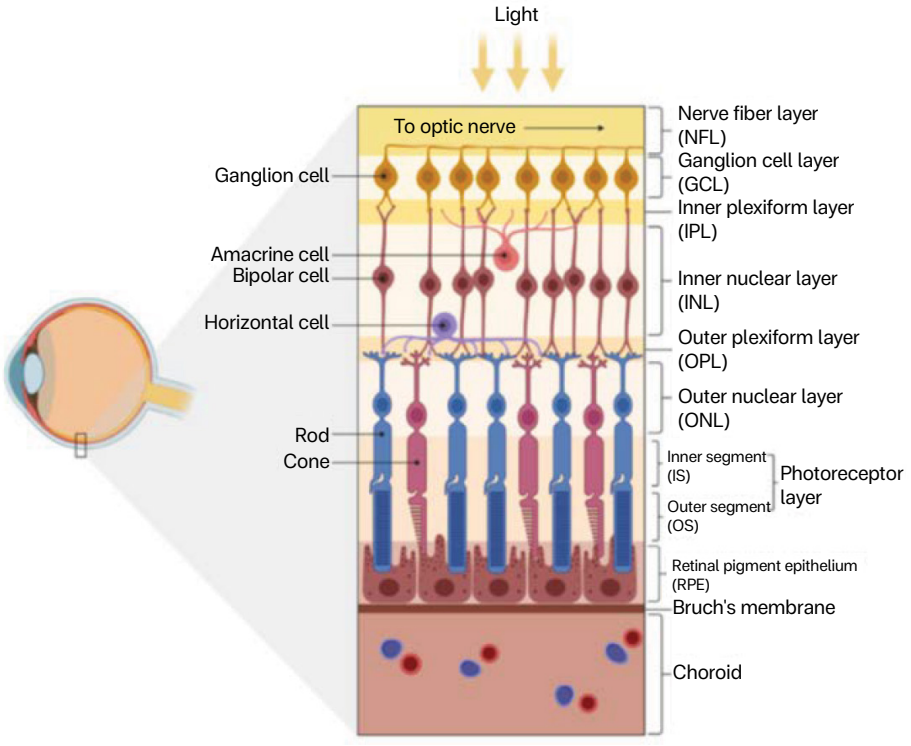


Figure 2. Retinal structure.[22]





Bruch's membrane cannot be overlooked in the structural pathogenesis of AMD. Changes in this membrane may take the form of diffuse thickening, deposition of hyaline material, or lipoprotein accumulation in the form of basal laminar deposits (BlamD) and basal linear deposits (BlinD). BlamD is found between the RPE and the basal lamina, whereas BlinD tends to occupy the inner to outer collagenous zones of Bruch's membrane. These findings may be precursors of soft drusen.[23,24]

These deposits are not only structural markers but also impair transport of substances between the retina and the choroid, triggering hypoxia in RPE cells. In this hypoxic environment, the expression of angiogenic factors such as VEGF increases, paving the way for the formation of choroidal neovascularization.[23–25]

Meanwhile, RPE cell atrophy does not occur suddenly; cellular pleomorphism, increased intercellular distance, and decreased retinal pigment epithelial density have been observed. As atrophy progresses, tissue thinning and migration of RPE cells into deeper retinal layers occur in response to pathological environmental stress.[15,18,20]

Another change that warrants attention is the infiltration of inflammatory cells such as macrophages, plasma cells, and occasionally multinucleated giant cells. Their presence is often found together with large drusen, geographic atrophy, or subretinal neovascularization. Studies have shown the deposition of complement proteins such as C3 and C5b-9 at the sites of drusen and Bruch's membrane, indicating the involvement of the innate immune system.[26,27]

The histological features of wet AMD show vascular invasion from the choroid into the subretinal or sub-RPE space, characterized by fibrovascular membrane formation **(Figure 3).** Neovascular endothelial cells are accompanied by fibrin, erythrocytes, leukocytes, and matrix components such as fibronectin and collagen. At an advanced stage, subfoveal scar tissue forms and becomes the main cause of permanent vision loss.[15,25]

Ancillary Examinations

Although histopathology provides an important basis for understanding AMD, these findings can only be confirmed postmortem. Therefore, technologies such as optical coherence tomography (OCT) have become a bridge for the noninvasive visualization of histopathological lesions. OCT images can demonstrate outer retinal tubulation or displacement of the RPE layer that correlates directly with photoreceptor loss. Various characteristic structural biomarkers of AMD identified by OCT are shown in **Figure 4A–C**.[28]

OCT biomarkers, particularly intraretinal and subretinal fluid, help clinicians assess disease activity, monitor treatment response, and individualize anti-VEGF treatment intervals in neovascular AMD. Current treatment options include ranibizumab, aflibercept, brolucizumab, and faricimab. Recent advances include high-dose aflibercept (8 mg) and faricimab, a bispecific antibody that targets both VEGF-A and angiopoietin-2. In the PULSAR trial, aflibercept 8 mg administered every 12 or 16 weeks after loading achieved non-inferior visual acuity gains compared with aflibercept 2 mg every 8 weeks. Similarly, the TENAYA and LUCERNE trials demonstrated non-inferior visual outcomes with faricimab administered at intervals of up to 16 weeks.[25,29] OCT is used not only for diagnosis but also for risk stratification and longitudinal evaluation of patients.[28]

Over the past two decades, molecular approaches to age-related macular degeneration (AMD) have advanced significantly. The results of various genome-wide association studies (GWAS) have drawn attention to several major genes that play roles in the pathogenesis of AMD. This involves not only one pathway, but a collection of complex and interconnected biological pathways, ranging from the complement system to angiogenesis and from oxidative stress to lipid metabolism.[30,31]

Recent studies have revealed that genetic polymorphisms play an important role in determining individual risk. One of the most consistently identified variants is Y402H

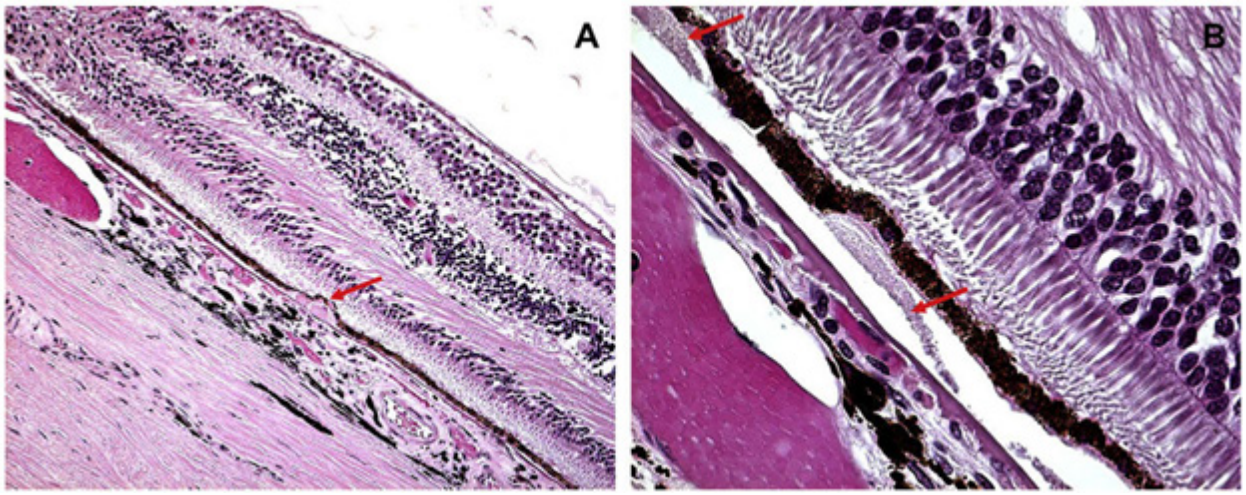


Figure 3. Retinal histopathology in wet (neovascular) AMD. Panels A and B show the formation of a fibrovascular membrane that penetrates Bruch's membrane and the retinal pigment epithelium (RPE), with invasion of blood vessels from the choroid into the subretinal space (red arrows). This structure is often accompanied by hemorrhage and edema and is a major cause of marked decline in central visual acuity.[32]



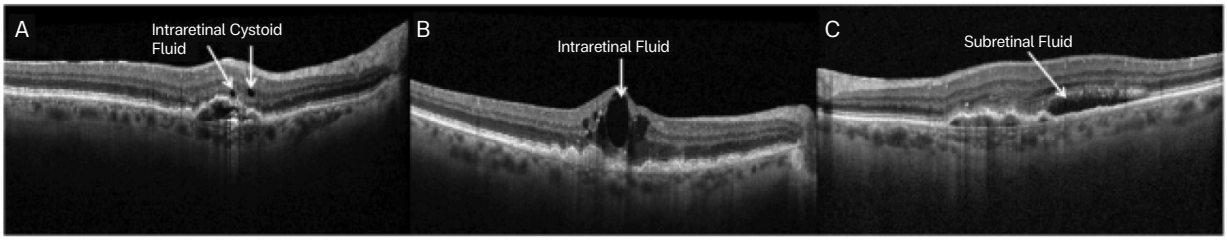


Figure 4. Optical Coherence Tomography (OCT) shows various retinal biomarkers characteristic of age-related macular degeneration (AMD). (A) Intraretinal cystoid fluid appears as small fluid-filled spaces within the retinal layers, indicating impaired vascular permeability and a response to metabolic stress. (B) Visualization of intraretinal fluid with compression of the retinal structures due to fluid accumulation, often found in the neovascular form of AMD and is associated with visual prognosis. (C) Subretinal fluid appears as fluid accumulation between the neurosensory retina and the retinal pigment epithelium (RPE), reflecting choroidal neovascular activity.[33]

in Complement Factor H (CFH), which significantly increases the risk of AMD, particularly the dry and neovascular forms.[34] In addition to CFH, other genes such as C2, CFB, CFI, and C3 have also been shown to contribute to dysregulation of the alternative complement pathway, indicating the direct involvement of innate immunity in the retinas of patients with AMD.[26,27]

Two other equally important genes, ARMS2 and HTRA1, are located on chromosome 10q26 and show a strong association with AMD progression. Although there is still debate as to whether ARMS2 or HTRA1 is the causal gene, the rs10490924 variant in ARMS2 has consistently been associated with a high risk of both geographic atrophy and neovascular AMD.[4]

On the other hand, angiogenesis is a major process in wet AMD; therefore, the role of the VEGFA (vascular endothelial growth factor A) gene is central. Increased VEGFA expression, whether due to local hypoxia or immune stimulation, promotes the formation of new blood vessels from the choroid toward the retina, a process known as choroidal neovascularization (CNV).[35] In addition to VEGFA, the TGFBR1 gene has also been reported to modulate the angiogenic response in AMD, particularly in relation to extracellular matrix regulation.[36]

Understanding these molecular pathways opens new opportunities for gene-based therapy. Several current clinical trials are evaluating the efficacy of AAV (adeno-associated virus) vectors to produce long-term expression of anti-VEGF proteins directly from retinal cells. One of these is ADVM-022, which encodes intraocular aflibercept, while GT005 targets expression of Complement Factor I (CFI) to reset the complement pathway.[1,34–36]

Several transcriptomic studies also show increased expression of inflammatory genes such as IL1B, IL18, and TNF in the retinal tissue of patients with AMD.[30,31] Chronic microinflammation occurring through NLRP3 inflammasome activation and IL-1β release is known to contribute to RPE cell death and AMD progression.[1]

In addition to inflammatory and angiogenic pathways, lipid metabolism has also begun to receive attention. Genes such as CETP, LIPC, ABCA1, and APOE play roles in cholesterol transport and deposition and have been associated with drusen formation. Protective variants of APOE ε2 have been reported to have a protective effect against the development of AMD.[1,18,19]

Various molecular biomarkers are now being identified in body fluids such as plasma and vitreous fluid. Inflammatory biomarkers such as CRP, IL-6, and IL-18, as well as angiogenic markers such as VEGF and PlGF, have shown correlations with AMD progression and response to anti-VEGF therapy.[25,35]

Within this context, AMD can no longer be understood simply as a degenerative disease caused solely by advanced age. Genetic factors also play a very important role. Variations in the CFH, ARMS2/HTRA1, and C3 genes are known to increase susceptibility to the development of AMD.[2] In genome-wide association studies (GWAS), CFH and C3 variants are strongly associated with uncontrolled activation of the complement pathway, particularly in patients with the neovascular form.[2,5]

Optical coherence tomography (OCT) maps structural biomarkers such as intraretinal/subretinal fluid, PED, SHRM, and outer retinal tubulation, guiding treatment decisions and evaluation of the response to anti-VEGF therapy.[33,37] Molecular profiles (VEGF/PlGF, CRP, IL-6/IL-18) and genetic profiles (CFH, ARMS2/HTRA1) serve as risk indicators and have potential for personalization, although they are not yet standard for AREDS2 selection.

It should also be noted that advances in molecular technology have changed the paradigm of AMD diagnosis and classification. Examinations such as immunohistochemistry, protein expression through Western Blot, and polymerase chain reaction (PCR) are now used to detect specific biomarkers associated with disease progression. Meanwhile, Optical Coherence Tomography (OCT) enables noninvasive visualization of structural retinal biomarkers such as pigment epithelial detachment (PED), subretinal hyperreflective material (SHRM), and intraretinal fluid.[3,6,7,11,13,37]

Management

Based on the large Age-Related Eye Disease Study (AREDS) and AREDS2 clinical trials conducted by the National Eye Institute, a combination of certain antioxidants and minerals can reduce the risk of AMD progression to late AMD.[7,37,38] AREDS2, which is a modification of the original AREDS formulation, replaced beta-carotene with lutein and zeaxanthin for safety reasons in smokers and evaluated the additional benefit of omega-3 fatty acids.[1,16]

The original AREDS formulation consisted of vitamin C (500 mg), vitamin E (400 IU),





beta-carotene (15 mg), zinc oxide (80 mg), and copper oxide (2 mg). This formulation reduced the risk of progression to late AMD by up to 25% over 5 years in patients with intermediate to advanced stages.[21] However, because beta-carotene was associated with an increased risk of lung cancer in smokers, AREDS2 modified the formulation by replacing it with lutein (10 mg) and zeaxanthin (2 mg).[22] The AREDS2 study also added omega-3 fatty acids (DHA and EPA), but these components did not provide a significant additional benefit in reducing AMD progression.[9,21] Evidence from the AREDS2 study showed that the new formulation remained effective in reducing the risk of progression to late AMD without increasing the risk of lung cancer and even showed slightly better statistical results, particularly in the subgroup with low dietary carotenoid intake.[9]

AREDS2 (n > 4,000) showed that replacing beta-carotene with lutein/zeaxanthin remained effective in reducing the risk of progression to late AMD; the relative benefit was more pronounced in individuals with low carotenoid intake and avoided the risk of lung cancer in smokers.[23] The addition of omega-3 did not provide an additional benefit for progression.[21]

Biological Mechanisms of AREDS2

The main mechanisms of the AREDS2 components are their antioxidant effects and stabilization of retinal cell membranes. Lutein and zeaxanthin are carotenoids concentrated in the macula and function as blue-light filters and free-radical neutralizers. Zinc and copper support the activity of antioxidant enzymes such as superoxide dismutase. Vitamins C and E work synergistically to reduce oxidative stress in the retinal pigment epithelium (RPE) and photoreceptors. This reduction in oxidative stress is believed to delay cellular dysfunction and drusen accumulation, which are characteristic of dry AMD.[23,39]

AREDS2 primarily reduces oxidative stress and stabilizes retinal cell membranes. Macular carotenoids (lutein/zeaxanthin) act as blue-spectrum filters and radical quenchers; vitamins C/E work synergistically; zinc/copper support superoxide dismutase and other antioxidant pathways, delaying RPE dysfunction and drusen accumulation.[39]

The AREDS2 formulation is generally safe. Beta-carotene is avoided in smokers/former smokers and is replaced by lutein/zeaxanthin. High doses of zinc may cause gastrointestinal complaints/mineral imbalance, and copper is supplemented to prevent copper-deficiency anemia. Monitoring of tolerance is recommended in older patients receiving polypharmacy.[8,9,21]

Clinical Indications, Safety, and Administration Practice

Main indication: intermediate-stage AMD based on findings of large drusen/pigment abnormalities and/or GA without active neovascularization. It is not recommended for primary prevention in the general population without AMD and is not a therapy for active wet AMD. Continuous daily administration according to the AREDS2 formulation; periodically evaluate of retinal structure with OCT and counsel on a diet rich in natural carotenoids (green/yellow vegetables).[21,40]

Clinical Evidence for the Application of AREDS2

AREDS2 involved more than 4,000 patients with AMD. The main results showed that supplementation with lutein and zeaxanthin as replacements for beta-carotene can reduce the risk of progression to late AMD by up to 18%. This formulation is most effective in patients with intermediate-stage disease or geographic atrophy without active neovascularization.[21]

Additional data show that the protective effect of AREDS2 is more pronounced in patients with low dietary levels of lutein and zeaxanthin. In addition, patients with a history of smoking or active smokers should not consume beta-carotene because of the increased carcinogenic risk.[21]

Personalization of Therapy

Several studies show that response to AREDS2 may be influenced by genetic variation, particularly polymorphisms in the CFH and ARMS2 genes. However, meta-analyses show that although these variants affect the risk of AMD, the effectiveness of AREDS2 remains consistent in most genetic subpopulations, so this supplement continues to be generally recommended.[21]

Other Therapies for AMD (Particularly the Neovascular Form)

In wet AMD, anti-VEGF agents (ranibizumab, aflibercept, brolucizumab, faricimab) remain the mainstay; treat-and-extend/PRN regimens balance visit burden and clinical outcomes. Combination PDT is beneficial in certain phenotypes (polypoidal).[41] AAV-based gene therapies (e.g., ADVM-022, RGX-314) and long-term delivery systems are being developed to reduce injection frequency. AREDS2 complements rather than replaces these therapies. In some cases, response to anti-VEGF therapies such as ranibizumab, aflibercept, or brolucizumab is determined by specific biomarkers visible on OCT images.[10,29,30,37,41]

From a therapeutic perspective, anti-VEGF therapy has revolutionized the management of neovascular AMD. Molecules such as aflibercept and brolucizumab are designed to neutralize excessive VEGF-A, thereby suppressing neovascular growth and reducing vascular leakage.[39] However, responses to therapy are not always the same. Long-term studies have found that the occurrence of vitreous hemorrhage (VH) can significantly reduce the visual effect of therapy. Interestingly, younger patients with large submacular hemorrhages have a higher risk of developing VH complications after anti-VEGF monotherapy.[3]

Meanwhile, therapies based on gene editing and regenerative medicine, such as RPE cell transplantation and saponin therapy for Bruch's membrane rejuvenation, are currently receiving attention.[5] New pharmacological approaches targeting matrix metalloproteinase (MMP) activation to improve the permeability of Bruch's membrane are also being explored preclinically. By restoring nutrient diffusion and retinal waste elimination, these approaches are expected to slow the progression of dry AMD.[5]

The main challenge in the treatment of age-related macular degeneration (AMD), particularly the neovascular or exudative form, no longer lies solely in treatment effectiveness. It also lies in long-term sustainability, patient adaptability to treatment protocols, and the potential for personalizing therapeutic interventions based on specific





biomarkers. Anti-vascular endothelial growth factor (anti-VEGF) has been the mainstay of nAMD therapy for more than a decade. Agents such as ranibizumab, aflibercept, and brolucizumab have shown significant efficacy in reducing the rate of vision loss, although the need for repeated injections remains a burden that has not been fully resolved. The mechanism by which brolucizumab binds to VEGF-A and inhibits VEGFR-1/-2 interactions, thereby suppressing CNV, is summarized in **Figure 5**.[11]

Pegaptanib became the first anti-VEGF agent approved by the FDA in 2004, followed by ranibizumab in 2006 and aflibercept in 2011, through the MARINA, ANCHOR, and VIEW 1–2 studies, respectively.[41] The combination of effectiveness and safety profiles formed the basis for the broad clinical acceptance of these drugs. However, the high requirement for intravitreal injections, up to eight times per year, has encouraged the exploration of new strategies, such as treat-and-extend and pro re nata (PRN) regimens, which are better adapted to individual patient responses.[42]

Over time, the treatment framework has also increasingly shifted toward a precision approach. Several gene and molecular therapy candidates have been developed, including RGX-314 and Ixo-vec, which are designed to express anti-VEGF proteins over a prolonged period, thereby reducing the need for repeated injections.[43] Furthermore, molecules such as 4D-150 even combine anti-VEGF protein expression with a VEGF-C-inhibiting miRNA, opening opportunities for dual-target therapy.[43]

From a combination-therapy perspective, photodynamic therapy (PDT) with verteporfin remains relevant in cases of polypoidal choroidal vasculopathy, particularly when combined with an anti-VEGF agent such as ranibizumab. Data show that this combination increases polyp regression and reduces the need for injections.[41] In addition, bispecific antibodies such as faricimab, which simultaneously targets VEGF-A and angiopoietin-2, have shown promising efficacy and have recently been approved for clinical use. The architecture of the AAV-based ADVM-022 vector encoding aflibercept for long-term expression in the retina is shown in **Figure 6**.[44]

Future directions in AMD therapy also emphasize developing long-term drug delivery systems. Port delivery systems and depot injections, such as those tested with nanoparticle-based sunitinib (GB-102), offer reduced injection frequency while maintaining therapeutic effectiveness for several months.[44]

Nevertheless, there remains a group of patients who are nonresponsive to anti-VEGF therapy. For this group, experimental approaches such as UBX1325, an inhibitor of anti-apoptotic proteins, and Wnt agonists such as Restoret (EYE103) are being evaluated in clinical studies.[42] Research is also directed toward RNA-based therapies, including small interfering RNA and antisense oligonucleotides, which offer potential for the treatment of specific genetic mutations.

Furthermore, nutritional therapy strategies such as AREDS2 supplementation continue to be maintained for preventing progression from the early stage to late AMD. However, studies show that the response to micronutrient supplements such as lutein and zeaxanthin is not modulated by major AMD risk genetic variants, so not all patients obtain equal benefits.[40]

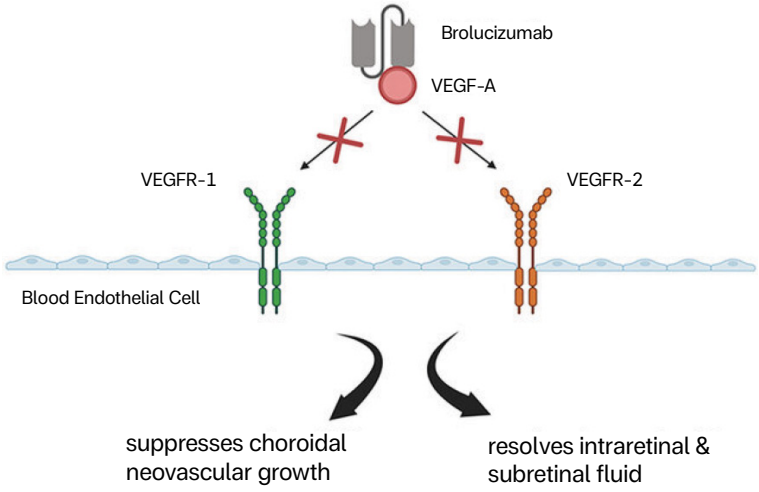


Figure 5. Mechanism of action of brolucizumab as an anti-VEGF agent. Brolucizumab binds to VEGF-A and inhibits its interaction with the VEGFR-1 and VEGFR-2 receptors on vascular endothelial cells. This mechanism suppresses choroidal neovascular growth and reduces the accumulation of intraretinal and subretinal fluid, thereby resolving macular edema and improving visual acuity.[38]
Abbreviations: VEGF-A: Vascular endothelial growth factor A; VEGFR: Vascular endothelial growth factor receptor.

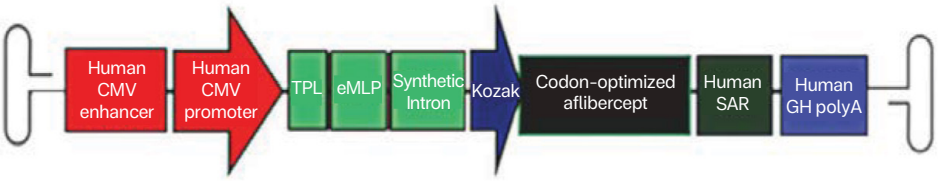


Figure 6. Genetic construction of the AAV-based ADVM-022 vector encoding aflibercept with strong regulatory elements for long-term expression in the retina. This vector is designed to reduce the frequency of intravitreal anti-VEGF injections in patients with neovascular AMD genetic vector.[34]
Abbreviations: CMV: Cytomegalovirus; TPL: Tripartite leader; eMLP: enhanced major late promoter; SAR: Scaffold attachment region; GH polyA: Growth hormone (GH) polyadenylation.

CONCLUSION

Age-related macular degeneration is a degenerative retinal disease with complex mechanisms involving oxidative stress, chronic inflammation, retinal pigment epithelium dysfunction, Bruch's membrane changes, complement system dysregulation, and genetic factors. From a diagnostic perspective, recognition of morphological and histopathological findings such as drusen, pigment changes, geographic atrophy, and





choroidal neovascularization, together with the use of noninvasive examinations such as optical coherence tomography, is very important for assessing disease stage, risk of progression, and response to therapy. Advances in molecular biomarkers have also further enriched the understanding of the course of AMD and opened opportunities for more precise assessment. From a therapeutic perspective, AMD management depends on the form and stage of the disease and includes AREDS 2 supplementation in intermediate-stage AMD, anti-VEGF therapy in the neovascular form, and the development of new approaches such as gene therapy and long-term drug delivery systems.

DECLARATIONS

Consent for Publication

This narrative review does not report original patient data, identifiable personal information, or identifiable images of individuals. Therefore, patient consent for publication is not applicable. Institutional names appear solely as author affiliations.

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Author Contributions

Reza Aditya Digambiro (RAD) contributed to the conception and scope of the review, literature selection, manuscript drafting, and revision. Husnun Amalia (HA) contributed to the interpretation of ophthalmological evidence and critically reviewed the diagnostic and therapeutic sections. Florinda Ilona (FI) and Julian Chendrasari (JC) contributed to the interpretation of morphological and histopathological findings and critically reviewed the relevant sections. All authors reviewed and approved the final manuscript and agree to be accountable for its content.

Conflict of Interest

The authors declare no financial or non-financial conflicts of interest related to this review.

Declaration on the Use of Artificial Intelligence (AI)

The authors used ChatGPT (OpenAI) to assist with literature searches, reference identification, English language editing, and the preparation of selected manuscript revisions. AI assistance included revisions concerning anti-VEGF therapies, AMD staging terminology, and publication declarations. The authors independently checked the cited sources, assessed the accuracy of scientific statements, and reviewed, verified, and approved all AI-assisted content. AI tools did not generate original patient data or conduct statistical analyses. The authors retain full responsibility for the accuracy, integrity, and final content of the manuscript.

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