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Review Article

Ophthalmology Section

# Treatment Paradigms in Age-Related Macular Degeneration: A Narrative Review Bridging Innovations in Dry and Wet AMD

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## ABSTRACT

Age-related Macular Degeneration (AMD) is still the largest cause of vision loss in the elderly globally, with two distinct clinical forms: dry (non exudative) and neovascular or wet (exudative) AMD. Dry AMD advances slowly and is characterised by drusen and Geographic Atrophy (GA), whereas wet AMD is distinguished by Choroidal Neovascularisation (CNV) and frequently results in fast and severe vision impairment. In recent years, there has been substantial progress in recognising and managing both forms. This comprehensive analysis looks at existing therapy options as well as emerging developments in AMD treatment. For dry AMD, dietary supplements, lifestyle changes and experimental treatments such as complement inhibitors and neuroprotective chemicals are considered. In the area of wet AMD, anti-vascular endothelial growth factor medications such as Ranibizumab, Aflibercept and Brolucizumab remain the cornerstone of therapy. Newer agents, such as Faricimab and port delivery systems, offer longer dose intervals and promise better patient compliance. Furthermore, the function of gene therapy, stem cell transplantation, as well as sustained drug delivery systems is highlighted as emerging frontiers in AMD treatment. The review also looks at how these developments affect visual results, treatment burden and quality of life. Despite recent treatment advances, unmet needs remain, notably in avoiding the advancement of dry AMD and managing refractory instances of neovascular AMD.

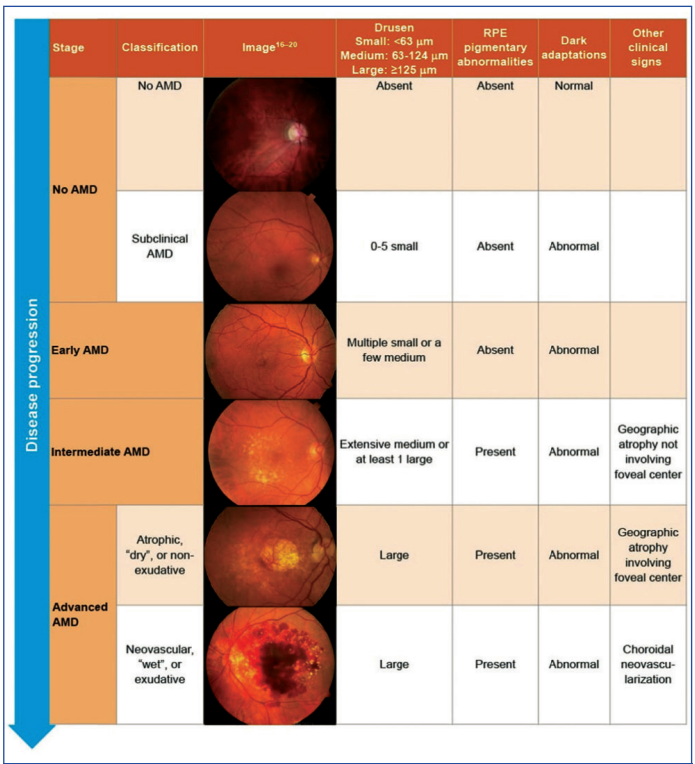

**Keywords:** Anti-vascular endothelial growth factor, Complement inhibitors, Gene therapy, Retinal diseases, Vision loss

## INTRODUCTION

Age-related Macular Degeneration (AMD) remains a multifactorial disorder and one of the largest causes of permanent blindness in the senior population, with an estimated 288 million afflicted people by 2040 [1,2]. Its gradual and irreversible nature results in a considerable social economic burden and increasing health resource utilisation [3,4]. Furthermore, aging is the primary risk factor for AMD; so, as life expectancy rises, this burden will inevitably increase in the near future.

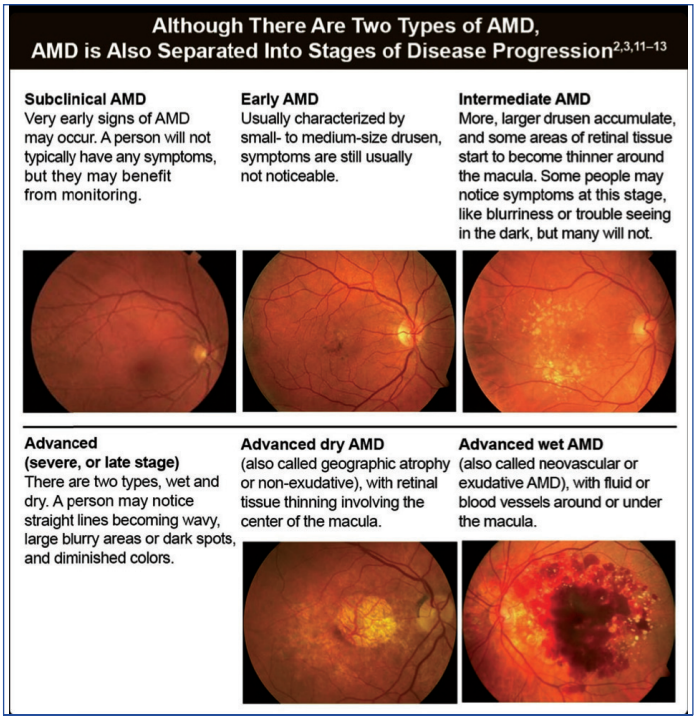
A macula is an annular region with a diameter of 5.5 mm with a centre placed 17° (4.0-5.0 mm) temporal and 0.53-0.8 mm inferior towards the centre of the optic disc. The fovea centralis is the tiny central pit in the human eye made up of closely packed cones. Sharp centre vision is due to the fovea and this fovea is encircled by the parafovea belt along with the perifoveal outer area. Macular degeneration happens as the macula deteriorates, because the illness progresses with age, it is commonly known as AMD [5].

The AMD may be categorised into four phases. The first stage is typical aging changes, with just tiny drusen and no pigment abnormalities. At this stage, the drusen diameter is less than 63 µm. In the subsequent stage (early AMD), there are a few intermediate drusen with diameters > 63 µm and ≤124 µm that lacks Retinal Pigment Epithelium (RPE) cell anomalies. Stage 3 includes widespread, moderate AMD, at least one big drusen (diameter ≥125 µm) and RPE abnormalities [6]. Stage 4, also referred to as advanced AMD, is associated with GA of fovea or other age-related and features of neovascular macular degeneration, leading to vision loss. Liew demonstrated the reliability of the Age-related Eye Disease Study (AREDS) reduced severity scale [Table/Fig 1a,b] [7]. Early AMD causes the lowest visual impairment, which is frequently accompanied by impaired reading skills, visual distortion and a black or grey area in centre vision. Extensive/ moderate vitreous wart membranes and uneven pigmentation are hallmarks of mid-term AMD. The central vision of individuals with severe AMD is considerably impacted [8].




**[Table/Fig-1a]:** The stages and classification of AMD ranges from sub-clinical to advanced.

Clinically, advanced AMD is classified into two types: dry AMD and wet AMD, in addition to disciform scar, which is the last stage. Dry AMD, commonly known as GA, does not cause blood as well as serum leakage [9]. It is distinguished by symmetrical eyes, impaired vision, disorganised macular pigmentation in both eyes, the absence of foveal reflex and variable posterior poles containing yellowish white drusen between Bruch's membrane (BrM) as well as RPE. Some advanced individuals have map-like atrophy of the posterior retina.




**[Table/Fig-1b]:** Various stages of AMD based on the progression of disease.

Wet AMD may be classified into two types: CNV and Polypoidal Choroidal Vasculopathy (PCV) that entails blood or serum leakage. At the moment, it is unclear if PCV corresponds to wet AMD. On the one hand, PCV and CNV vary in clinical features and epidemiology. On the other hand, PCV as well as CNV share environmental and genetic risk factors [10]. Patients having wet AMD experienced faster loss of visual acuity than those with dry AMD. Most people with wet AMD develop symptoms in one eye initially and the symptoms in the second eye may not appear for some time. Choroidal capillaries in CNV develop into RPE and BrM lesions, causing CNV. Because the structure of neovascularisation is imperfect, it causes a series of pathological alterations like exudation, haemorrhage and scarring, all of which contribute to central vision loss. PCV is more frequent among Asians [11]. PCV has a more consistent clinical course and better visual results than CNV, hence it has been defined as a distinct clinical entity [10]. In PCV, polypoid neovascularisation from the choroid layer can pass across the BrM but not through the RPE layer. PCV can be classified into types I and II based on the form of the lesions. Type I had an aberrant Branching Vascular Network (BVN) and polypoid lesions towards the end of the vascular network. Type II polypoid lesions were solitary or aggregated, with no evident BVN/fine reticular veins. This syndrome may result in subsequent sub-retinal or sub-macular haemorrhage [12].

# DISCUSSION

## Epidemiology

The prevalence of AMD is growing, with ethnic and geographic variations. With the world's population aging, the number of AMD patients was projected to reach 196 million by 2020 and 288 million by 2040 [13,14]. AMD is more prevalent in whites compared to blacks [15,16]. The prevalence of AMD was 12.33% in Europe, 7.38% in Asia and 7.53% in Africa [13].

## General Causative Factors

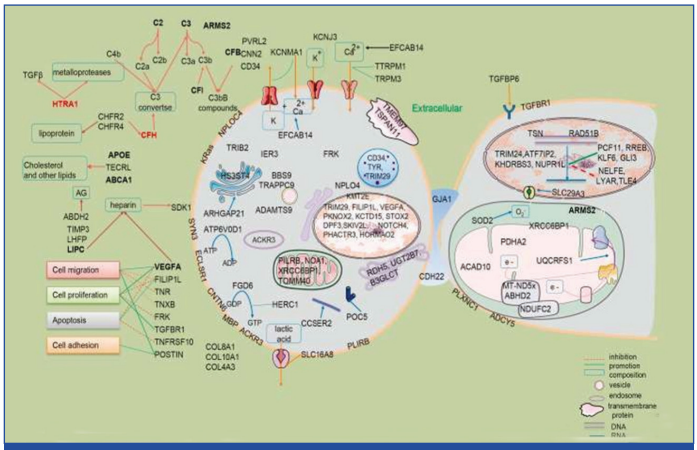
There are various risk factors for AMD, including age, race, blood pressure and lifestyle. The blue iris is more susceptible to acquire AMD compared to the brown iris [17]. Systemic risk factors for AMD include cardiovascular disease and atherosclerosis. Diabetic Retinopathy (DR), High-density Lipoprotein (HDL), obesity and high systolic blood pressure all raise the incidence of AMD in diabetic individuals [18]. Klein R et al., also found that baseline blood cystatin C levels were related with the risk of early AMD and wet AMD [19]. According to studies, smoking and excessive drinking increase the risk of AMD. Lutein and zeaxanthin can lower the risk of AMD, while vitamins C, E, D and zinc oxide may delay the onset of AMD. Increased fish intake can lessen the incidence of AMD, whereas Docosahexaenoic Acid (DHA) and Eicosapentaenoic acid (EPA) may delay its onset. Furthermore, taking a lunch break is connected with a decreased risk of developing advanced AMD. People who were divorced or separated were threefold more likely to suffer from advanced AMD than those who were married [20].

## Genetics and Environment

Some AMD-related genes and environmental variables (smoking) interact to impact the prevalence and progression of AMD. Smoking altered Complement Factor H (CFH) and Complement Component 3 (C3) binding, decreased CFH levels in plasma and altered CFH binding capacity to C3b via the rs1061170 variation [21]. As a result, smokers with rs1061170 have a higher risk of AMD. Smoking raises the risk for all persons with the HTRA1 genotype [22,23]. AREDS found a strong relationship between CFH 402H and Body Mass Index (BMI). The Blue Mountains Eye Study (BMES) discovered that increasing fish diet in CFH 402Y carriers had a greater protective impact against late AMD. Consumption of antioxidant foods also decreased the incidence of early AMD in patients with a high genetic risk for the CFH and HTRA1 loci. Similar to CFH variations, having both HTRA1 mutations and greater C-reactive protein levels raises the risk of AMD [24,25].

## Pathophysiology of AMD

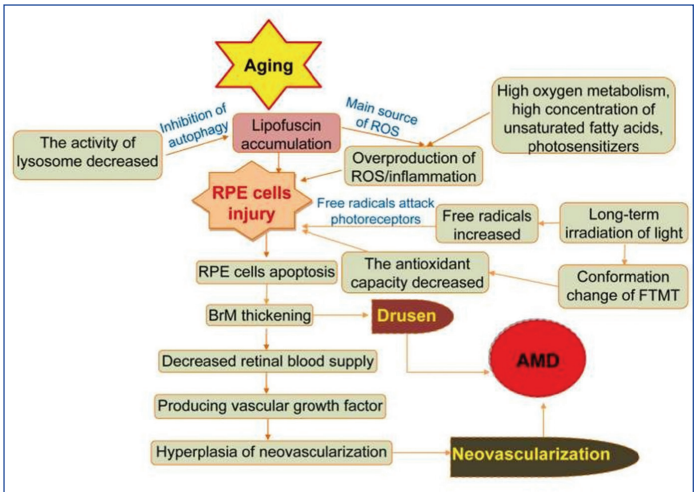
**RPE cell senescence:** A sequence of alterations triggered by the aging of RPE cells can result in AMD. The aging RPE cells disrupt the equilibrium of enzymes within the extracellular matrix of the macular region, causing them to accumulate on the BrM. Metabolites collect on the BrM, producing vitreous warts, causing damage to neighboring retinal tissues and limiting the retina's blood flow. RPE cell senescence causes immune cells to generate VEGF. Calcification, rupture and phagocytosis of the Bruch membrane create blood vessels, which eventually leads to AMD [Table/Fig-2,3] [26].




**[Table/Fig-2]:** A schematic depiction showing AMD-related genes and proteins. Some of these genes are distributed in the nucleus and take part in the regulation of transcription processes, histone methylation and so on; some are distributed in the mitochondria to engage in the electron transmission of the respiratory chain; and some are distributed in the cytoplasmic matrix as well as serve as the cytoskeleton utilised by the cytoskeleton to participate in the regulation of cellular activities. AG represents arachidonic acid glyceride [5].

## Oxidative Stress

Retina is one of the greatest oxygen-consuming tissues in the human body. The building up of oxidative stress serves a significant role in the pathophysiology of AMD [27]. The accumulated oxidative damage to RPE is primarily caused by an imbalance in the synthesis and clearance of Reactive Oxygen Species (ROS). The existence of elevated oxygen metabolism, polyunsaturated fatty acid concentrations and photosensitisers can all contribute to increased




**[Table/Fig-3]:** AMD develops with age. This graphic depicts the non genetic processes of AMD caused by RPE cell senescence, oxidative stress, haemodynamics and other factors that occur with age [5].

ROS generation in the retina [28]. Lipofuscin is the primary generator of ROS that accumulate in RPE with age, exacerbating oxidative stress within retina [29]. Preventing and treating associated disorders may aim to reduce oxidative damage. It was also subsequently discovered that the antioxidant combination had minimal effect on slowing the advancement of CNV [30].

## Metabolism of Lipid

The HDL cholesterol levels had been linked to a higher risk of AMD, but high Total Cholesterol (TC) and Low-Density Lipoprotein Cholesterol (LDL-C) were linked to a lower risk of AMD. Researchers discovered Advanced Lipid peroxidation End products (ALEs) within the lipofuscin, vitreous warts and BrM of AMD patients. The formation of advanced lipid ALEs disrupts protein stability and causes death of photoreceptors as well as RPE cells [31].

## Neovascularisation

The VEGF represents one of the primary dangers of wet AMD and it plays a significant role in the development of CNV and PCV [32]. Excessive neovascularisation can occur when vascular-promoting cytokines are overexpressed and inhibitory cytokines are downregulated. According to studies, exudative AMD patients had lower pulse amplitude and ocular blood flow than non exudative AMD patients. Thickening of the BrM may result in greater choroidal vascular resistance and a reduction in choroidal blood flow may be associated with the establishment of CNV [33]. Additionally, choroidal vitreous warts and aberrant pigmentation enhance the risk of AMD. After one eye develops to advanced AMD, the 5-year chance of developing AMD in the second eye is projected to be around 30% and 40%, that is much greater than in the general population [34].

There is a conventional explanation concerning the origin and progression of AMD, known as haemodynamics, which maintains choroidal vascular dysfunction represents the root cause of AMD. Neovascular AMD refers to atherosclerotic abnormalities in the eye's blood flow. Friedman offered a new haemodynamic theory in 1997 that AMD results from a shift in choroidal blood flow induced by a rise in choroidal and scleral sclerosis [5]. Blood lipid deposition and atherosclerosis cause thickening of the vascular wall, stenosis of the vascular lumen and decreased vascular wall compliance, resulting in decreased choroidal blood flow and abnormal choroidal perfusion, leading to within insufficient perfusion of RPE cells or Bruch membrane injury, that eventually leads to AMD. Recent clinical and experimental findings support the hypothesis that choroidal haemodynamics contribute to the progression of AMD [35].

## Prevention and Treatment Modalities

Preventive programs may be the best option for management, but efforts to offer innovative drugs capable of changing the medical progression of AMD have shown to be more profitable than projected. A diet rich in antioxidants such as vitamins C and E, lutein, zeaxanthin, zinc, β-carotene and polyunsaturated fatty acids can reduce the risk of AMD [36]. More specifically, it has been shown that the Mediterranean diet is effective in the prevention of this illness. Furthermore, lifestyle improvements, including quitting smoking, as well as regular exercise, proper weight control and regular sleep of approximately eight hours each night, have been shown to be an effective strategy in lowering the chance of AMD development [37].

## Emerging Therapies for Dry AMD

The complement system, which is a component of the innate immune response, serves a significant part in the pathogenesis of dry AMD, particularly GA, the disease's severe phase. Chronic activation in the complement cascade causes RPE degradation, photoreceptor loss and gradual macula atrophy. The Food and Drug Administration (FDA) has authorised two medications for the treatment of GA: Pegcetacoplan and Avacincaptad Pegol, due to their ability to control this system.

**Pegcetacoplan (Brand: Syfovre™):** ***Mechanism:*** Pegcetacoplan inhibits complement C3. By inhibiting C3, a key component of the complement cascade, it blocks downstream effectors that cause inflammation and cell lysis in retinal tissue. Two Clinical studies suggestive of the OAKS Trial (NCT03525613) as well as the DERBY Trial (NCT03525600) completed Phase III randomised clinical studies that compared monthly and every other-month intravitreal injection. Findings: The OAKS study accomplished its primary goal, demonstrating a substantial decrease in GA lesion development (22% monthly dosage; 16% every other month). DERBY did not originally fulfil the primary goal, however post-hoc analysis found favorable findings in specific subgroups. FDA Approval was given in February 2023; the FDA approved the first therapy for GA [38].

Avacincaptad Pegol (Izervay™) is a complement C5 inhibitor that works at a later stage in the complement cascade to limit the development of the Membrane Attack Complex (MAC) while avoiding RPE apoptosis and degeneration. Clinical trials of two different studies undertaken were GATHER1 Trial (NCT02686658): A phase II/III trial that revealed a 27.4% decrease in GA lesion development after 12 months of monthly medication. GATHER2 Trial (NCT04435366): Confirmed effectiveness and safety, including a 14.3% decrease in legislation over 12 months. The FDA granted authorisation in August 2023 for the management of GA due to AMD [Table/Fig-3-6] [39].

| Disease/condition | Type | Key features | Pathophysiology / Aetiology | Treatment options |
|---|---|---|---|---|
| Dry AMD (Atrophic) | Early/Intermediate/Advanced | Drusen deposits, RPE atrophy, Geographic Atrophy (GA) | Aging, oxidative stress, lipofuscin accumulation | AREDS 2 vitamins, lifestyle changes, clinical trials |
| Wet AMD (Neovascular/ Exudative) | Advanced | Choroidal Neovascularisation (CNV), haemorrhage, fluid accumulation | VEGF-driven abnormal blood vessels | Anti-VEGF injections (e.g., ranibizumab, aflibercept) |
| Geographic Atrophy (GA) | Late Dry AMD | Progressive RPE and photoreceptor loss | Extension of dry AMD; complement pathway involvement | Pegcetacoplan (approved), gene therapy trials |
| Polypoidal Choroidal Vasculopathy (PCV) | Variant of Wet AMD | Polyp-like choroidal vessel outpouchings, sub-retinal bleeding | Abnormal inner choroidal vasculature | Anti-VEGF and photodynamic therapy |

| | | | | |
|---|---|---|---|---|
| Retinal Angiomatous Proliferation (RAP) | Variant of Wet AMD | Intraretinal neovascularisation | Retinal vascular anomalies with secondary CNV | Anti-VEGF therapy |
| Pseudovitelliform Macular Dystrophy | AMD mimic (genetic overlap) | Yellowish lesion resembling vitelliform deposits | Mutation-related (Best1, PRPH2) or age-related mimic | Observation or anti-VEGF in rare cases of CNV |
| Central Serous Chorioretinopathy (CSC) | AMD mimic in older adults | Serous retinal detachment, often reversible | Choroidal hyperpermeability, stress, corticosteroids | Photodynamic therapy, mineralocorticoid receptor antagonists |
| Myopic CNV | Degenerative myopia complication | The CNV due to extreme thinning of retina and choroid | High myopia with Bruch's membrane rupture | Anti-VEGF injections |

**[Table/Fig-4]:** Represents the AMD-related Diseases (AMDRD).

| Nutrient | Role in AMD prevention | Major food sources |
|---|---|---|
| Lutein and Zeaxanthin | Antioxidants; filter harmful blue light; support macular health | Dark leafy greens (spinach, kale, collards), corn, eggs, zucchini, broccoli |
| Vitamin C (Ascorbic Acid) | Antioxidant; protects eye cells from oxidative stress | Citrus fruits (oranges, lemons), strawberries, bell peppers, guava, kiwi |
| Vitamin E | Protects photoreceptors from oxidative damage | Almonds, sunflower seeds, hazelnuts, vegetable oils (sunflower, wheat germ) |
| Zinc | Involved in visual pigment formation; boosts antioxidant activity | Oysters, red meat, poultry, beans, nuts, whole grains |
| Copper | Works with zinc to maintain eye health | Shellfish, nuts, seeds, whole grains, organ meats |
| Omega-3 Fatty Acids (DHA and EPA) | Reduce inflammation; support retinal structure | Fatty fish (salmon, mackerel, sardines, tuna), flaxseeds, chia seeds, walnuts |
| Beta-Carotene (Provitamin A) | Converted to vitamin A; supports photoreceptor function | Carrots, sweet potatoes, pumpkin, spinach, kale |
| Vitamin A | Essential for retinal function and night vision | Liver, eggs, fortified dairy products, orange and yellow vegetables |
| Selenium | Antioxidant synergy with Vitamin E | Brazil nuts, fish, eggs, whole grains |
| Anthocyanins | Improve circulation and reduce inflammation in the retina | Berries (blueberries, blackberries, bilberries), grapes, red cabbage |
| Flavonoids | Antioxidant and anti- inflammatory properties | Green tea, onions, apples, citrus fruits, dark chocolate |

**[Table/Fig-5]:** Summarising key nutrients that have shown protective effects against the onset or progression of AMD, along with their major food sources

| Lifestyle factor | Recommendation | Rationale/Benefit |
|---|---|---|
| Quit smoking | Complete cessation of tobacco use | Smoking is the strongest modifiable risk factor; increases oxidative stress in retina. |
| Maintain a healthy diet | Adopt a diet rich in leafy greens, fruits, fish, nuts and whole grains | Provides antioxidants, omega-3s and carotenoids that protect retinal cells. |
| Control body weight | Maintain a healthy BMI through balanced diet and exercise | Obesity is associated with inflammation and increased AMD risk. |
| Exercise regularly | At least 150 minutes of moderate aerobic activity per week | Improves blood circulation to the eyes and reduces inflammation |
| Protect eyes from Ultraviolet (UV) and blue light | Wear sunglasses with UV protection and use blue-light filters on screens | Reduces photo-oxidative damage to the macula |
| Manage chronic Conditions | Control diabetes, hypertension and cardiovascular diseases | Vascular health directly impacts retinal blood supply and function |
| Limit alcohol intake | Drink in moderation or avoid completely | Excessive alcohol contributes to nutrient depletion and oxidative stress |
| Take nutritional supplements (if needed) | Consider AREDS2 formulation for those at risk or diagnosed with AMD | Shown to slow AMD progression in clinical studies |
| Regular eye exams | Annual comprehensive eye exams for individuals over 50 or at risk | Early detection allows timely intervention and monitoring |
| Reduce screen time and Eye strain | Follow the 20-20-20 rule (every 20 minutes, look 20 feet away for 20 seconds) | Helps reduce digital eye strain and preserve long-term eye health. |
| Stay hydrated | Drink adequate water daily | Hydration helps maintain ocular surface and overall eye function |

**[Table/Fig-6]:** Lifestyle modifications to reduce AMD risk.

## Stem Cell Therapy

Stem cell therapy is a novel therapeutic option for treating dry AMD. Researchers reported the first successful transplantation of RPE cells produced from human Embryonic Stem Cells (hESC) into elderly individuals with dry AMD in 2012 [40]. They successfully transplanted cultivated hESC-RPE cells into patients and no adverse abnormalities such as teratoma or aberrant proliferation of hESC-RPE cells were noticed. Researchers created a biological patch made of RPE monolayer generated from hESC [41]. In clinical studies, the eyesight of two AMD patients with significant visual impairment was stabilised and improved. Their research indicates the feasibility as well as safety of hESC-RPE patch transplanting as a therapy for dry AMD. One downside of this method involves the fact that localised immunosuppression is required for hESC-RPE. There is no indication of abnormal proliferation, tumorigenicity, or any major ocular/systemic safety issues associated with transplanted individuals. Mandai M et al., investigated the possibility of transplanting RPE cells produced from pluripotent stem cells (IPSC) to cure AMD [42].

## Senolytic Drugs

Senolytic drugs preferentially trigger apoptosis in senescent cells, which have stopped proliferating but are metabolically active and release pro-inflammatory cytokines and proteases. Senescent RPE cells contribute to persistent inflammation, oxidative stress and tissue degradation in AMD. Senescent RPE cells in the macula emit SASP factors (e.g., IL-6, IL-8, TNF-$\alpha$), causing complement activation, photoreceptor degradation and Bruch's membrane thinning, which are essential hallmarks in dry AMD. Eliminating these cells might reduce retinal inflammation, enhance cellular function and halt disease development [43].

## Promising Senolytic Drugs

**1. BCL-xL Inhibitor: UBX1325 (Foselutoclax):** Blocks BCL-xL, a key survival pathway in senescent cells. previously used in models of diabetic retinal edema and ischemic retinopathy, UBX1325 reduced vascular leakage and abnormal neovascularisation by eliminating senescent vascular cells. Phase 1 Trials indicated a single intravitreal injection was safe and improved Best-corrected Visual Acuity (BCVA) in patients with Diabetic Macular Oedema (DME), showing up to +6 ETDRS letters gain and no significant ocular inflammation**,** while II phase demonstrated the durable vision improvement (+6.1 ETDRS letters at 18 weeks vs control) and maintenance of retinal thickness post single injection, supporting its senolytic action in human retinal disease [44]. Dasatinib+Quercetin (D+Q) is a combination known to eliminate senescent cells via tyrosine kinase inhibition and PI3K pathway modulation. Preclinical evidence showed reduced SASP and improved tissue function in aging models; while not yet tested specifically in AMD, these agents are under broader senotherapeutic exploration. Fisetin and Navitoclax where Fisetin is a natural flavonoid with anti-senescent activity and Navitoclax, another BCL-2 family inhibitor, are both effective senolytics in-vitro and in-vivo. They have potential applicability in AMD, but AMD-specific studies are pending [45].

## Innovations in Wet AMD Management

Gene Therapies: Because AMD is multifaceted and complicated, treating it presents a number of obstacles. Gene therapy therapies in AMD are designed to maintain the expression of antiangiogenic and anticomplement proteins. Because the eye is a tiny, contained microenvironment with a blood-retinal barrier, a small quantity of reagent may be injected and retain a high concentration for an extended period of time without being harmed by the immune system. Gene therapy achieves the objective of curing illnesses by inserting genetic material within patients. In AMD, AAV2 carriers with VEGF binding proteins are employed to suppress angiogenesis. AAV2-sFLT01 and AAV2-sFLT02 are fused onto human IgG1 Fc regions or methyl domains and can be utilised to reduce CNV [46]. Studies have indicated that AAV2 vector- mediated therapy is both safe and effective and might be employed as a long-term treatment for wet AMD. Additionally, viral vectors containing endostatin and angiostatin suppressed angiogenesis [47,48].

## Specific Antibodies

Bispecific antibodies represent a novel therapeutic strategy in wet AMD, targeting multiple pathological pathways simultaneously to enhance efficacy and durability of treatment. Two leading candidates are [Table/Fig-7].

| Agent | Targets | Key benefits | Status | Advantages |
|---|---|---|---|---|
| Efdamrofusp Alfa (IBI302) | VEGF + Complement (C3/C5) | Non inferior BCVA slows macular atrophy | Phase II (China) | Beneficial in patients with complement dysregulation or those at higher risk of GA. Potential to delay progression to atrophic AMD. |
| Faricimab (Vabysmo™) | VEGF-A + Angiopoietin-2 | Reduced treatment frequency, improved durability | FDA Approved (2022) | Improved vascular stability and reduced inflammation. Potential to prevent retinal fluid recurrence and extend treatment intervals in stable responders. |

**[Table/Fig-7]:** Targeting multiple pathological pathways simultaneously to enhance efficacy and durability of treatment.

## Anti-VEGF Drugs and Additional anti-VEGF Treatments

Successful therapy for nAMD is based on the reduction of VEGF, an angiogenesis promoter that is produced in the retina and triggered by a variety of factors, the most common of which is hypoxia. VEGF increases retinal vascular permeability and promotes the creation of new blood vessels. The first anti-VEGF drug used in clinical trials for nAMD had been aptamer pegaptanib sodium that binds to VEGF. Ranibizumab is an antibody fragment that can bind to all VEGFA isoforms [49]. It was used in the crucial phase III studies MARINA (occult CNV) and ANCHOR (classic CNV), which resulted in the widespread use of ranibizumab for nAMD management [50,51]. Bevacizumab, another antibody that binds to all VEGFA isoforms, was initially prescribed as an intravenous therapy for AMD but was subsequently administered intravitreally off-label. The Comparison of AMD Treatment Trials (CATT) in the United States compared ranibizumab to bevacizumab in the management of nAMD and found equivalent visual acuity outcomes [52]. Globally, practitioners continue to treat this sickness off-label with bevacizumab since it is substantially less expensive than ranibizumab and appears to be as effective [53]. Aflibercept, a recombinant protein that contains the receptor-binding domains of VEGF receptors 1 and 2, is one of the most recent major new compounds to be used in clinical trials on a worldwide scale [54]. Aflibercept inhibits all VEGFA and VEGFB isoforms, as well as placental growth factors, which have yet to be regarded beneficial. The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) studies found that intravitreal aflibercept delivered biweekly after loading was equivalent to monthly ranibizumab in terms of visual acuity gains and fluid resolution. Brolucizumab also exhibited better fluid resolution than aflibercept. In research on the subject, the authors hypothesised that addressing the receptors of both Platelet-derived Growth Factor (PDGF) and VEGF in tandem may delay the formation of pericyte scaffolds, hence increasing CNV inhibition. A number of clinical trials investigated whether this dual antagonism may improve the prognosis of nAMD over anti-VEGF monotherapy [55]. In Phase IIb tests of the PDGF antagonist pegpleranib, combination treatment (pegpleranib + ranibizumab) had a 62% greater incremental impact than anti-VEGF monotherapy. Nonetheless, two phase III studies found no visual or structural benefit of combination treatment above ranibizumab therapy alone [56].

# CONCLUSION(S)

In summary, over the last few decades, significant advances have been achieved regarding our understanding of AMD prevention, diagnosis and treatment, while the findings indicate that AMD has a systemic component, with many different factors involved, including genetic, environmental, autoimmune and non autoimmune disorders. Healthy habits including regular exercise and keeping a normal lipid profile and weight, are crucial for lowering the risk of AMD. Furthermore, therapeutic options for reducing AMD should consider a number of parameters to prevent and improve medication treatments, as well as personalised genetic information. As a consequence of technological advancements and scientific developments, the incidence of AMD-related visual impairment as well as legal blindness has been significantly reduced. The present review article focusses on discovering and expanding understanding regarding the relationship between genetics and aetiology with AMD. We believe that this review will stimulate researchers and lecturers, as well as fresh conversations, to contribute to a better knowledge of AMD, which will enhance patients' visual acuity and improve their quality of life.

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