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The Peril of Macular Degeneration: A Challenge to Vision

Makula Dejenerasyonu Tehlikesi: Görme İçin Bir Zorluk

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ABSTRACT

Age-related macular degeneration (ArMD) significantly contributes to the prevalence of blindness on a global scale. ArMD has emerged as the third most prevalent cause of vision impairment worldwide with the substantial increase in the elderly population. The key variables contributing to geographical atrophy (GA) and neovascular ArMD are ArMD, key forms of ArMD, both leading to significant vision impairment in older persons. GA is also known as late-stage macular degeneration. Cigarette smoking, dietary components, cardiovascular diseases, inherited markers, genes that control angiogenic pathways, lipids, and complement were shown to be important risk factors. In the last two decades, numerous studies have demonstrated that the percentage of macular degeneration cases has decreased. This may be attributed to the introduction of novel approaches to diagnosis and treatment. This review comprehensively explores ArMD, covering recent developments and classifications. It covers diagnosis methods, grading systems, and prevention strategies. It highlights advancements in treatment, including ankyrin repeat proteins, gene therapy via recombinant adeno-associated virus, and offering promising avenues for ArMD management.

Keywords: Age-related macular degeneration, vascular endothelial growth factor, geographic atrophy, scaffold, 3D bioprinting

ÖZ

Yaşa bağlı makula dejenerasyonu (ArMD), küresel ölçekte körlüğün yaygınlığına önemli ölçüde katkıda bulunur. Yaşlı nüfusun önemli ölçüde artmasıyla ArMD, dünya çapında görme bozukluğunun üçüncü en yaygın nedeni olarak ortaya çıkmıştır. Coğrafi atrofi (GA) ve neovasküler ArMD'ye katkıda bulunan temel değişkenler, her ikisi de yaşlı kişilerde önemli görme bozukluğuna yol açan ArMD'nin temel formları olan ArMD'dir. GA, geç evre makula dejenerasyonu olarak da bilinir. Sigara içmek, diyet bileşenleri, kardiyovasküler hastalıklar, kalıtsal belirteçler, anjiyojenik yolları kontrol eden genler, lipitler ve tamamlayıcının önemli risk faktörleri olduğu gösterilmiştir. Son yirmi yılda, çok sayıda çalışma makula dejenerasyonu vakalarının yüzdesinin azaldığını göstermiştir. Bu, tanı ve tedaviye yönelik yeni yaklaşımların getirilmesine bağlanabilir. Bu inceleme, son gelişmeleri ve sınıflandırmaları kapsayarak ArMD'yi kapsamlı bir şekilde incelemektedir. Tanı yöntemlerini, derecelendirme sistemlerini ve önleme stratejilerini kapsamaktadır. Ankrin tekrar proteinleri, rekombinant adeno-ilişkili virüs yoluyla gen terapisi ve ArMD yönetimi için umut verici yollar sunulması da dahil olmak üzere tedavi alanındaki ilerlemeleri vurgulamaktadır.

Anahtar Sözcükler: Yaşa bağlı maküler dejenerasyon, vasküler endotelyal büyüme faktörü, coğrafi atrofi, iskele, 3D biyobaskı

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INTRODUCTION

Age-related macular degeneration (ArMD) is a long-lasting eye ailment that significantly contributes to permanent blindness in the geriatric population globally. The condition has grown due to the significant increase in life expectancy worldwide. The macula is a distinct rounded area in the central part of the back of the eye, measuring about 5.5 mm in diameter. It is positioned roughly 0.53-0.8 mm below the center of the optic disc. The center of the macula contains a small central depression known as the fovea centralis. The macula contains a high concentration of cone photoreceptors and is the region with the greatest visual acuity. The fovea is responsible for the sharp and detailed central vision. The macula is particularly vulnerable to damage caused by direct exposure to light. As a result, it is the primary cause of significant and gradual vision deterioration in individuals aged 55 and above (1). In ArMD, the macula undergoes changes in its deeper retinal layers and the surrounding blood vessels, resulting in a decline in central vision. The impact on the quality of life of the aged population will be severe, resulting in a considerable monetary and social challenge in health care. The phenomenon of aging is rapidly emerging as a looming epidemic on a, especially in highly industrialized and affluent nations. According to the United States of America (USA) projections, individuals aged 61 and beyond are expected to triple, reaching an estimated 2 billion. Similarly, the population of individuals aged 81 and above would also increase, surging five times by 2060, (2,3). This age group would make up 33% of the population in the industrialized world. The significant shift in the population's age distribution is a cause for concern due to the rise of health issues closely linked to aging (4). Our literature analysis provides a clear explanation of the factors that increase the risk of ArMD, the different stages of the disease, and the methods used for diagnosis and treatment. The prevalence of ArMD is 7.45% among Asians, 13.44% among Europeans, and 7.61% among individuals of African descent (5). Asia, with its population accounting for over 50% of the global population, is projected to experience 113 million cases of ArMD by the year 2040 (1). A study conducted in Germany revealed a 23% rise in early ArMD patients and a 36% increase in late ArMD cases over a 15-year period from 2002 to 2017 (6). The United States had a prevalence of 18.34 million cases of early-stage ArMD among individuals aged 40 and above in 2019, accounting for 11.64% of the population. The frequency of late-stage ArMD was 1.49 million, which accounted for 0.94% of the population. ArMD is responsible for 55.6% of cases of visual impairment and 23.9% of cases of blindness among Caucasian persons in the USA. Approximately 11 million people worldwide experience visual loss and blindness as a result of advanced macular degeneration. The World Health Organization reports that the majority of individuals with visual impairment and blindness are over the age of 50 (7). Approximately 8 million cases of vision deficiency and blindness can be attributed to ArMD, which is more prevalent in high-income nations. According to a study conducted in 2015, ArMD was responsible for blindness in 5.8% of blind individuals worldwide, making it the fourth most prevalent cause. It was the third most significant factor leading to moderate to severe vision impairment (MSVI), impacting 3.9% of persons with visual impairments. Recently, the application of treatment techniques has increased, such as the direct administration of vascular endothelial growth factor (VEGF) inhibitors via ocular injections, which has significantly reduced the likelihood of blindness. However, no notable decrease in the occurrence of MSVI was observed (8-10). Although there have been significant advancements in precautionary treatments, the number of primary-stage ArMD cases is projected to increase rapidly due to the expanding growth of the geriatric population; the estimated rise in ArMD blindness might be two to three times higher without treatment. This review article comprehensively explores ArMD, covering recent developments and classifications. It covers diagnosis methods, grading systems, and preclusion strategies. It highlights advancements in treatment, including developed ankyrin repeat proteins (DARP), gene therapy via recombinant adeno-associated virus, and scaffold-based retinal implants, offering promising avenues for ArMD management.

ArMD Categories and Classifications

Several grading systems are available to categorize ArMD for diagnostic and prognostic purposes. Two primary forms of ArMD are typically distinguished: dry ArMD and Wet ArMD. They can be divided into phases and subclasses according to their progress and ocular symptoms (11). Dry ArMD, or non-exudative macular degeneration, is characterized by drusen, which are small yellow deposits between the retinal pigment epithelium (RPE) and Bruch's membrane (BrM). The initial signs of macular degeneration are the extracellular deposits, which can vary in size and density. ArMD is primarily classified into early, middle, and advanced stages. Early-stage ArMD typically exhibits no noticeable symptoms and is mostly diagnosed through a clinical eye examination. Stage 1 of ArMD is characterized by typical age-related changes, including drusen smaller than 63 µm, commonly known as drupelets, and no abnormalities in pigmentation (12). In early ArMD (second stage), drusen have a diameter ranging from 63 to 124 µm and do not cause any irregularities in the RPE cells. Intermediate ArMD is characterized by large drusen measuring at least 125 µm in diameter, together with accompanying abnormalities in the RPE (13). Drusen are frequently accompanied by changes in the RPE, leading to localized areas of reduced or increased pigmentation. The RPE pigmentary changes serve as indicators for more severe phases, and hence have a role in possible vision loss. A widely used grading system employed by numerous scholars and clinicians defines the progressive stage of dry ArMD by the presence of geographical atrophy (GA), characterized by the degeneration of the choriocapillaris and the permanent photoreceptor cell depletion (14). The range of ArMD includes the neo-vascular form, often known as the exudative or wet type of ArMD. This form is characterized by the fast growth of new blood vessels into the sub-RPE or sub-retinal locations. Choroidal neovascularization (CNV) enlargement results in the emergence of atypical blood vessels, which may lead to bleeding and have significant consequences such as the detachment of the RPE, ultimately causing rapid vision deterioration (15). Uncommon serous pigment epithelial detachment (PED) may cause substantial vision impairment. This process occurs when fluid accumulates in the spaces underneath the retina, causing the RPE to rupture and degeneration of. The progression of degeneration and cellular demise in ArMD is characterized by a gradual pace, typically devoid of any discernible symptoms during the initial phases. Macular morphology is commonly used to evaluate clinical symptoms, while genetic biomarkers are not widely employed for disease screening. Valid functional endpoints are necessary for accurately assessing

visual changes in ArMD, in addition to the physical manifestations observed in the macula.

Best-corrected visual acuity (BCVA) assesses the capacity to see retinal features at a specific distance after correcting refractive defects. It is commonly used as a reliable indicator to monitor the decline in vision and, consequently, the impact on life (16). The result of the gradual and continuous decline of eyesight, lasting for several months to years. The eye is suitable for implementing advanced therapy medicinal products (ATMPs) based on genes, tissues, or cells. The compact size of the organ is suitable for effective therapy with a minimal amount of ATMPs (17). The segmented anatomical structure can restrict the spread of therapeutic drugs to regions that are not intended to be targeted. Presently, expanding an ATMP for ocular diseases can facilitate innovation. It can reveal innovative therapy approaches for previously considered untreatable eye diseases (17). Cell therapy is being developed as a treatment for ArMD using the immune-privileged property seen in the sub-retinal area. Potential approaches include either regenerating or fixing the impaired RPE cells, or introducing cells that have a beneficial influence on the function and survival of photoreceptors via paracrine signaling. The primary focus of this research is to identify the most effective transplantation targets, including RPE, photoreceptors, and choroidal endothelial cells. The optimal time and techniques for administering these transplants are currently being explored. Much research has investigated the efficacy of administering cell-based therapy directly into the eye's vitreous fluid, but the findings have been inconsistent. In laboratory conditions, delivering cells to the back part of the eye by directly injecting cell suspensions or cultivated cells under the retina in laboratory conditions is also a promising strategy. Administering RPE cells in a suspended condition has many disadvantages, including the loss of their unique qualities, the formation of rosettes, and the migration of cells. These issues are absent in implants that use scaffolds. Implanting viable RPE cells onto precisely designed biomimetic scaffolds has the potential to accurately replicate the structure of natural tissues and assist in the recovery of visual capabilities (18). An optimal scaffold should be non-immunogenic, display exceptional mechanical strength, and be adequately thin to facilitate the passage of nutrients and metabolites between the retina and choriocapillaris. Through a scaffold-based method, cells may attain and sustain basal and apical polarization using tight junctions before implantation (19). Transplantations using different scaffolds have shown increased cell viability and better arrangement of RPE cell populations. To transport RPE-scaffold materials to the subretinal region, it is necessary to employ meticulously developed tools to minimize any potential damage. The SMAD family member 3 pathway has been observed to alter the phenotypic behavior of RPE cells, leading to the creation of scars through microglia on different scaffolds (20). In addition, some scaffolds have yet to be tested in living organisms, and it can be difficult to control the variability between different batches and the biomechanical properties of these scaffolds. An important obstacle in retinal tissue engineering (TE) is the establishment of suitable neuronal influences between the RPE implant and its adjacent cellular milieu. Advancements in biomaterials science and stem cell research, as well as knowledge gathered from clinical trials, may aid in overcoming the difficulties related to creating high-quality cell therapy medical products for ArMD (21).

Diagnosis

A dilated fundus examination is recommended for individuals aged 55 or older to detect macular degeneration. To analyze ArMD, the assessor should observe the presence of drusen deposits, pigmentary abnormalities, GA, bleeding, exudation of fluid, formation of scars, and development of fibrosis (22). The distribution, dimensions, and abundance of drusen are all factors that need to be considered. A comprehensive eye examination is conducted to eliminate the possibility of any simultaneous ocular pathological conditions. While the examination is important for disease staging, several imaging modalities are increasingly essential for connecting inspection findings and guiding therapy (23). Significant progress has been made in retinal imaging techniques. Preferential hyperacuity perimetry (PHP) quantifies the intensity of visual irregularities, such as metamorphopsia and scotoma, that occur in the middle 15° of the visual field. This is assessed using the very acute visual ability known as hyperacuity. PHP has shown an appreciable sensitivity (83%) and specificity (88%) in properly distinguishing between recent-onset CNV and intermediate phases of ArMD. In addition, PHP has been suggested to assess the efficacy of photodynamic and anti-VEGF therapy in treating neovascular nArMD (24,25). Traditionally, fluorescein angiography (FA) has been the established method for detecting CNV in ArMD. A patient's vein is injected with fluorescein dye, and images of the chorioretinal circulation are captured over an extended period. This invasive imaging technique may be used to detect the presence of leaks from different types of neovascular lesions. Indocyanine green angiography (ICG) may be used in certain situations. Indocyanine green dye is used in ICG procedures to evaluate the blood circulation in the choroid and identify hidden CNV problems. Optical coherence tomography (OCT), a frequently used noninvasive method, has significantly revolutionized the understanding and management of ArMD. It provides a thorough depiction of the various strata of the retina (26). OCT employs light to provide a precise image of the 10 layers of the retina and the underlying choroid. This method has similarities with ultrasonography in its ability to accurately identify the specific layers impacted by ArMD. The photographs aid the clinician in providing a more precise representation of the disease stage and CNV activity while facilitating the differentiation between wet ArMD and dry ArMD. OCT may be used to assess the effectiveness of therapy over time and provide insights for future treatment decisions. OCT imaging can accurately detect the presence of fluid in both the retina and underneath layers, a characteristic feature of wet ArMD. OCT angiography, sometimes called OCT angiography (OCT-A), is a modern imaging technique. OCT-A is an advanced technology that improves the ability to see the choroid's complex circulation system without invasive treatments (27). This approach aids in understanding the changes that occur in the small blood vessels of neovascular ArMD (nArMD) when abnormal new blood vessels are growing in the choroid (CNV lesions). Furthermore, OCT-A can promptly identify the development of fresh blood vessels, allowing for more comprehensive monitoring and, if needed, faster intervention. OCT-A has supplanted FA and ICG in the majority of clinical situations. Nevertheless, OCT lacks the sensitivity to detect first indications or identify individuals with a higher likelihood of ArMD. This is due to its subpar spatial resolution and insufficient intrinsic information about the retinal and RPE cells as well as the

microvasculature (28,29). Hence, innovative diagnostic methods are being developed to enhance accuracy for detecting distinct indications of disease progression. The present focus of research is on adaptive optics retinal imaging, which offers improved resolution and the ability to distinguish detailed outlines of microstructural features in microvasculature, retinal nerve fibers, and photoreceptor cells. Resonance raman spectroscopy is a highly capable technique that accurately quantifies the concentrations of carotenoids and xanthophylls in the macular area of the human retina (30).

Grading of Age-related Macular Degeneration

Multiple grading methods are available to categorize ArMD for analytical purposes and prognosis determination. Two primary forms of ArMD are often distinguished: dry ArMD and wet ArMD. Figure 1 represents symptoms of macular degeneration.

Both may further be classified by the ocular symptoms and course of the disease, which are used to categorize it into subclasses and stages. Dry ArMD, sometimes called non-exudative macular degeneration, is distinguished by the presence of drusen. Drusen are small yellow deposits located in the space between the RPE and BrM (31). The early signs of macular degeneration are extracellular deposits, which can vary in size and density. ArMD is primarily classified into early, middle, and advanced stages. The initial stage of ArMD typically lacks noticeable symptoms and is mostly identified through a clinical eye examination. Stage 1 of ArMD is characterized by typical aging changes with drusen size smaller than 63 µm, known as drupelets, and no pigment abnormalities. In early ArMD (second stage), drusen have a diameter ranging from 63 to 124 µm and do not cause any irregularities in the RPE cells. Intermediate ArMD is characterized by large drusen measuring at least 125 µm in diameter, along with accompanying abnormalities in the RPE (32).

Drusen are frequently accompanied by changes in the RPE, leading to localized areas of reduced or increased pigmentation. The presence of RPE pigmentary alterations indicates advancing to more severe stages and hence plays a role in the possibility of visual impairment. A widely used grading system defines the advanced stage of dry ArMD as the presence of GA, described by the choriocapillaris degeneration, and the gradual, irreversible damage to the cells responsible for detecting light, known as photoreceptor cells (33). The spectrum of ArMD includes the neovascular variant, referred to as the exudative or wet variation of ArMD. This type is distinguished by the rapid proliferation of new blood vessels in the sub-RPE or subretinal regions. CNV enlargement results in the leakage of aberrant arteries, potentially leading to bleeding and severe consequences such as the detachment of the RPE, ultimately culminating in rapid vision loss. While uncommon, severe PED has the potential to cause substantial vision impairment. This disorder occurs when fluid accumulates in the spaces under the retina, causing the RPE to rupture and the outer retina to degenerate (34). The progression of disintegration and cellular demise in ArMD is characterized by a gradual, progression, typically devoid of any discernible symptoms during the initial phases. Evaluating clinical symptoms usually involves the examination of macular morphology, and using genetic indicators for disease screening is not a common practice. Valid functional endpoints are necessary for accurately assessing visual changes in ArMD, in addition to the physical signs observed in the macula. BCVA is a measure of the capacity to see details of an object at a exact distance after correcting refractive abnormalities. It is often used as a reliable indicator to track the decline of vision and its impact on quality of life (35). The result of the non-neovascular type is a gradual but consistent decline in eyesight, lasting several months, to years. Initially, the presence of drusen alone was the clinical indication; however, the distinctive structural features were linked to the swift advancement to the advanced stages of ArMD. The nonexudative type ultimately results in irreversible deformation of the RPE and GA. However, when exudative alterations occur, there is a sudden decline in visual potential, posing a significant threat to the individual's quality of life within weeks (36). Regardless of the specific form, if either atrophic or exudative changes impact the fovea, it may lead to significant visual impairment due to central vision loss. Figure 2 shows fundus photography (top) and its corresponding spectral domain optical

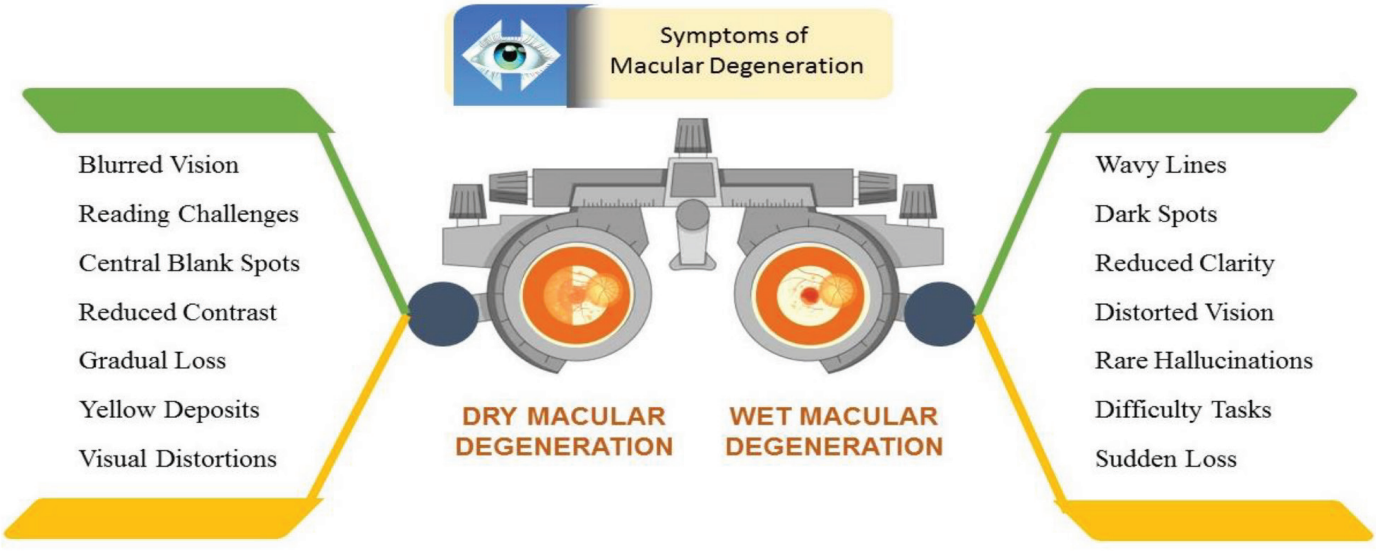

Figure 1. Symptoms of macular degeneration.

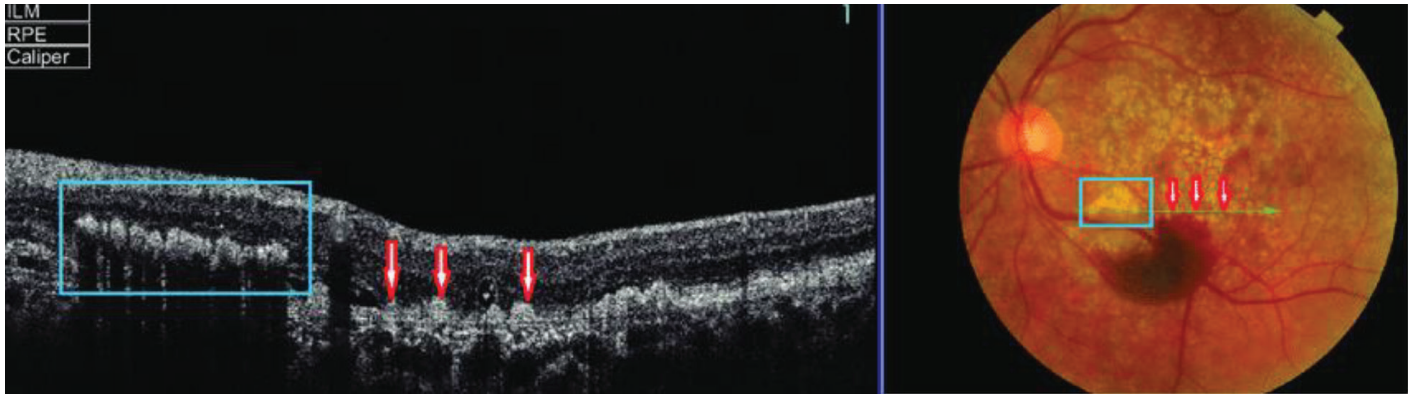

Figure 2. The fundus image on the right displays two distinct types of deposits: exudates (shown by the blue rectangle) and drusen (highlighted by the red arrow) in the patient's left eye, who has wet ArMD. The width of the B-scan line in the fundus image is equivalent to that of the B-scan SD-OCT image on the left. ArMD refers to ArMD, whereas SD-OCT stands for spectral domain optical coherence tomography (37).

ArMD: Age-related macular degeneration, SD-OCT: Spectral domain optical coherence tomography

coherence tomography (SD-OCT) image (bottom), demonstrating a B-scan of the two different types of deposit: exudates (blue square) and drusen (red arrow).

Preclusion

Lutein and zeaxanthin, which are isomers, are the primary components of the macular pigment in the human retina. Their attention is concentrated on the foveal area. The primary role is to safeguard the photoreceptor's membrane system from harm caused by light and radiation (38). The Age-Related Eye Disease Study (AREDS) identified a 25% reduction in progressive ArMD and formulated specific guidelines for using vitamin supplements. Dietary supplements mostly consist of zinc, vitamin C, vitamin E, lutein, and zeaxanthin. Due to the increased susceptibility to lung cancer in those who smoke beta-carotene was replaced with lutein and zeaxanthin in the AREDS formulation. Supplementation is recommended for those who have intermediate ArMD or early ArMD in one eye and severe ArMD in the other eye. Nevertheless, there is a lack of scientific evidence to support its efficacy in treating early ArMD in both eyes. Supplementation is not recommended for preventing ArMD in the general population or for those with a verified family history of the illness. The case-control study on eye illness also showed a 40% decrease in the probability of advanced AMD, in those who took more than 6 mg of carotenoid daily (39). Current research focuses on a scleral iontophoresis device that delivers liquid carotenoid formulations directly into the retina (40). Patients, particularly those with early ArMD in one or both eyes, should implement essential modifications to their lifestyle. Aside from weight reduction and smoking cessation, these alterations may require adjusting one's dietary intake to include antioxidant-rich foods and fish containing omega-3 and omega-6 fatty acids. The lipid profile and blood pressure are two modifiable risk factors. Although the research on the correlation between exposure to ultra-violet radiation and the development of ArMD remains inconclusive, it is worth considering minimizing sun exposure as a possible lifestyle modification.

Treatment of Age-related Macular Degeneration

Anti-VEGF Refers to Drugs or Treatments That Target VGEF

Before the development of potent anti-VEGF medications, other treatments were used for ocular treatment of wet ArMD. The initial therapies for nArMD, such as photodynamic treatment, angiostatic steroids, irradiation, and laser photocoagulation, successfully prevented significant vision impairment resulting from nArMD. Nevertheless, they failed to provide substantial improvements regarding visual function (41). Anti-VEGF drugs function by directly interacting with either VEGF or VEGF receptors. These drugs have outperformed all previous treatment methods, improving visual clarity. Currently, it is the most favored treatment for wet ArMD. Unfortunately, no preventive or therapeutic measures are now available for this condition (42). The current intravitreal VEGF inhibitors include ranibizumab, bevacizumab, aflibercept, and brolucizumab. The recommended intervals for administering ranibizumab and bevacizumab are four to eight weeks. Aflibercept is delivered every 12 weeks, and brolucizumab is given every 8 to 12 weeks. "Pro re nata (PRN)" and "treat and extend" are two different distinct dosage strategies for anti-VEGF therapy. The procedures begin by delivering a predetermined monthly dose for three months. The decision to provide or delay as-needed (PRN) medication is made weekly, based on the OCT results indicating either active exudation, or stability. Despite the lack of disease activity, the treat-and-extend protocol method requires administering intravitreal injections every visit. If the retinal fluid is shown to be suppressed or eliminated on OCT, the interval between visits is extended by a preset duration. If fluid reoccurrences, the drug is delivered, and the frequency of visits is decreased (43).

Developed Ankyrin Repeat Proteins

DARP molecules are derived from ankyrin repeat proteins, prevalent binding proteins in the human genome. Abicipar polyethylene glycol (Pegol) is a 34-kilodalton recombinant protein that has undergone polyethylene glycol modification. Currently, research is being conducted to evaluate the therapeutic potential of this

medication for diabetic macular edema and nArMD. It has shown strong inhibitory effects on VEGF-A (44). Abicipar has a reduced molecular weight, a 90-fold higher binding affinity for human VEGF-A165, and almost double the duration of effect inside the eye, compared to ranibizumab. The phase 2 research of the Registration, Evaluation, Authorization and Restriction of Chemicals program found that abicipar, when given in doses of either 1 or 2 mg, exhibited a long-lasting impact that was comparable to ranibizumab at a dose of 0.5 mg (45). This benefit was shown in terms of the mean enhancement in BCVA and the decrease in central retinal thickness. The research did not uncover any safety concerns. The phase 3 Sequoia and Cedar investigations demonstrated that receiving six to eight administrations of abicipar had better visual outcomes than receiving 13 administrations of ranibizumab at week 52. The abicipar regimens, administered either every eight weeks and twelve weeks, were more effective than monthly ranibizumab in achieving consistent visual acuity. All abicipar dosage frequencies maintained visual benefits in the ensuing year, as reported in the first year. Phase 2b MAPLE research evaluated the safety and effectiveness of abicipar, utilizing an innovative manufacturing technology. The goal was to decrease the presence of pollutants that can cause inflammation in the formulation. The results indicated no endophthalmitis or retinal vasculitis sequelae, and the incidence of severe intraocular infections was 1.6% (46).

Gene Therapy Using Recombinant Adeno-associated Virus

Recombinant adeno-associated virus (RAAV) vectors provide long-term treatment for ArMD by inducing recipient cells to create chemical substances that inhibit VEGF. The phase 1 experiment on nArMD confirmed the safety of a single subretinal injection of an RAAV particle that carries the gene, named Fms Related Receptor Tyrosine Kinase 1 (FLT1). This transcript includes a naturally occurring chemical that hinders the activity of VEGF. The presence of sFLT-1 (soluble FLT-1) was mostly seen in the specific tissue and did not negatively affect the eyes or the whole body (47). The clinical study lasted for 52 weeks and included 32 patients who were randomly allocated to receive ranibizumab PRN (with or without subretinal RAAV). No notable disparities were seen between the groups regarding BCVA or center point thickness when using the sFLT-1 gene therapy. The researchers found a minimal level of efficacy in terms of improvements in BCVA and a decrease in fluid levels over the three-year monitoring period of the phase 1/2b study. The researchers observed that the true impact of RAAV and sFLT-1 may have been concealed due to the limited number of participants. They also noted that the trial initially aimed to assess safety and included patients who had received previous treatments (48).

Thermal Laser Photocoagulation

Thermal laser photocoagulation is a medical procedure that uses a laser to coagulate or clot blood vessels to treat certain conditions. The continuous-wave thermal laser photocoagulation might prevent the accumulation of drusen deposits in the outer layers of the retina prior to the availability of anti-VEGF drugs for treating neovascular non-arteritic anterior ischemic optic neuropathy (49). However, further clinical trial findings revealed that removing drusen by laser-induced methods could not effectively prevent the progression of advanced ArMD. In addition, laser photocoagulation often leads to a reduction in BCVA and the formation of scars. Researchers have just developed an innovative laser method that produces short bursts of light.

Clustered Regularly Interspaced Short Palindromic Repeats-Associated Protein 9 (Cas9)

Cas9 is a protein associated with Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). The CRISPR-Cas9 enzyme operates by cleaving DNA strands in a manner analogous to molecular scissors (50). Researchers are now evaluating the feasibility of using a CRISPR-Cas9 method, delivered by an AAV vector, to permanently decrease the levels of VEGF in the RPE layer of eyes affected with nArMD. This approach aims to decrease angiogenesis in the eyes. The concept of eliminating the need for periodic anti-VEGF injections is attractive. This technique resulted in a 26% decrease in VEGF-A levels and a 31% inhibition of CNV in a mouse model of laser-induced CNV (51). In contrast to intravitreal therapeutic techniques, CRISPR can be utilized to selectively target certain types of cells, reducing the probability of systemic side effects. While the CRISPR technique has potential as a treatment for nArMD, it is crucial to thoroughly evaluate it due to the susceptibility of CRISPR-based genome editing to unforeseen outcomes, and its irreversible nature (52).

Brimonidine

Brimonidine has alpha-2 adrenergic agonist properties, demonstrating cytoprotective and neuroprotective benefits in cultured cells and animal models. In a phase 2 trial to assess the effectiveness of brimonidine as a drug delivery system, a biodegradable implant was inserted into the eye to halt the progression of GA. Participants were given one of two doses of brimonidine, either 132 μg or 264 μg, instead of a placebo. By the time the participants reached 12 months, the group that received a larger dosage implant experienced a 28% drop in GA growth compared to the group that received a placebo (53). Before commencing clinical trials, it is necessary to conduct a more thorough evaluation of the features of this chemical taking into account the differences seen among species. In dry ArMD, drugs need to be administered topically to the posterior part of the eye (54). Achieving this task using eye drop formulations is a challenge. Recent investigations involving initial and early-stage clinical studies have shown that using these cells as a substitute for RPE has led to excellent safety profiles and potential effectiveness. Findings from preclinical studies suggest that reestablishing photoreceptors can reinstate visual capability, even when the outer retina has completely deteriorated.

Scaffold-Based Retinal Implants

Despite the immense potential of cell and gene therapies, their successful implementation in clinical practice faces major obstacles. TE provides an alternative method for treating ArMD by creating TE products (TEP) that may replace damaged RPE and restore its functioning. This effectively stops the course of the sickness (55). TE for the regeneration of RPE necessitates scaffolds with certain characteristics that facilitate cellular connections, development, and specialization while simultaneously inhibiting unwanted immunological reactions and inflammation from the host. Creating a three-dimensional framework with appropriate structural characteristics and bioactivity is necessary to achieve this objective. This crucial scaffold should be able to imitate the biological role of

the natural extracellular matrix in certain tissues, providing structural reinforcement and serving as a temporary matrix. Scaffolds may be infused with various cell types, such as stem cells, progenitor cells, differentiated cells, or can be directly implanted to accelerate functional tissue regeneration in regions that are not functioning properly (56). It is crucial to methodically include scaffold properties and their regulatory functions in scaffold design to effectively enhance tissue regeneration at the implantation site.

Advances for ArMD Treatment

Central vision loss caused by ArMD affects the individual's capacity to read, drive, recognize individuals, and perform essential everyday tasks. The phenotypic presentation of the infection exhibits considerable variation, from initial or midway ArMD with few symptoms to late-stage disease that can result in visual distortion and reduced center visual acuity. Scotomas refer to regions in the visual field with partial or total absence of vision. Total loss of central vision refers to the full lack of vision in the center area of the visual field (3). By using multimodal imaging techniques to examine the ultrastructure of the retina, retinal imaging professionals can now assess the severity of the disease and identify ArMD at an early stage with greater precision. Conducting a comprehensive fundus assessment in patients without symptoms to identify drusen is becoming recognized as a screening technique. The visual results of individuals with advanced neovascular ArMD have improved due to the advancement of anti-VEGF medications targeting VEGF. The efficacy of anti-VEGF medication varies across individuals and does not guarantee favorable outcomes for every patient (43). In addition, the effectiveness of the therapy tends to decrease with time, and the need for frequent injections places a considerable burden on the healthcare system, both for patients seeking medical care and those responsible for administering it. The human retina is an intricate tissue that plays a vital role in the visual and central nervous systems. Due to the lack of a natural reservoir of stem cells in the retina, any damage to retinal cells, particularly photoreceptor cells, results in irreversible vision loss. ArMD is a medical condition defined by the progressive deterioration of the retina. Therapeutic interventions are available for the neovascular type to prevent ArMD and halt the progression of the illness. Advanced therapies are a developing area of study that aims to provide cell and gene-based treatments for degenerative diseases like ArMD, with the potential to provide a cure. Various treatments based on cellular and genetic methods are presently undergoing clinical trials to treat ArMD and GA. Scaffold-based approaches for managing retinal degenerative diseases have shown promise as an avenue to impede or delay the progression of ArMD. Nevertheless, this approach necessitates the utilization of noxious organic solvents during the processing stage, which can detrimentally impact the survival of cells (18). 3D-bioprinting is a scaffold construction technology that offers several advantages over freeze drying. It has superior physical qualities, promotes better cell adhesion, and allows for precise enhanced mechanical characteristics by regulating scaffold microstructures. However, to achieve ideal mechanical and porous building features in 3D bioprinting, it is necessary to perform multi-objective optimizations (20). These optimizations involve identifying suitable printing settings such as print speed, pressure, stacking, and spacing, and determining the appropriate material composition, namely the ratio of cells to bioink. This necessitates a significant amount of time dedicated to conducting lengthy experiments, which requires substantial resources (56).

CONCLUSION

ArMD's central vision loss impairs reading, driving, recognizing people, and daily duties. Intermediate or early-stage ArMD illness may exhibit few symptoms. Still, advanced-stage disease may result in visual distortion, decreased central visual acuity, scotomas, and complete loss of central vision. Using several imaging techniques simultaneously, which capture precise pictures of the retina's inner structure, allows retinal imaging experts to can assess the disease's severity and discover ArMD sooner and correctly. Medical experts prefer optical coherence tomography for diagnosis; however, screening asymptomatic fundus for drusen is becoming increasingly popular. Lutein, other vitamins, and carotenoids have prevented severe ArMD progression. However, not all patients benefit from anti-VEGF treatment. Its effectiveness decreases with time, and repeated injections burden the healthcare system, including those who get medical treatment and those who provide care. Research is carried out to alleviate this load, enhance VEGF inhibition, and create gene and regenerative therapies. Unfortunately, patients with severe ArMD have few GA therapy options. Raising awareness and decreasing ArMD's harmful effects require public education on modifiable risk factors and beneficial supplements.

Footnotes

Authorship Contributions

Concept: N.R., S.R., P.M., Design: S.R., V.B.A., Supervision: S.R., Resources: P.M., Material: V.B.A., Data Collection or Processing: N.R., P.M., Analysis or Interpretation: S.R., M.S., V.B.A., Literature Search: N.R., V.B.A., Writing: N.R., S.R., M.S., P.M., V.B.A., Critical Review: P.M.

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