Novel therapeutic interventions for age-related macular degeneration

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Abstract

Age-related macular degeneration (AMD) is the leading cause of vision loss in the elderly, with a major negative impact on quality of life. It is expected that AMD prevalence would rise as the world population ages, necessitating the development of viable therapies. This article presents the most recent advances in AMD treatment, with a focus on innovative techniques that hold the promise of improving results for older patients. The potential applications of stem cell therapy, gene therapy, anti-VEGF drugs, and novel drug delivery systems to address the challenges of AMD treatment in elderly patients are highlighted. There is a pressing need to educate and stimulate future research and therapeutic practice with the goal of conserving vision and improving the quality of life for older persons.

Keywords: Macular degeneration, anti-VEGF, vision

1. Introduction

In the last two decades, maculopathies—specifically, age-related macular degeneration (AMD) have become increasingly significant as causes of permanent vision impairment and blindness due to rising life expectancy and population aging, in general. The medium-advanced and late stages of AMD, a progressive chronic disease of the central retina, are primarily responsible for vision loss. The causes include the loss of retinal pigment epithelium cells, closure of the choriocapillaris in eyes with geographic atrophy, and/or scar formation in the macular region in conjunction with choroidal neovascularization in the foveal region (1,2). Early stages of AMD are characterized by drusen and depigmentation of retinal pigment epithelium (RPE) cells. Different forms of drusen are linked to varying levels of risk for AMD. It progresses from early to intermediate and severe stages due to increasing drusen and degradation of RPE cells, resulting in pigmentary alterations and aberrant new blood vessels (3,4).

The primary non-modifiable environmental risk factor for AMD is aging. Ethnicity and gender are also significant non-modifiable risk factors. While there are no significant differences in the frequencies of drusen between white and non-white populations, research has shown that white females are more likely than black individuals to develop severe, late forms of AMD (5). Other environmental risk factors associated with AMD include smoking, higher body mass index, cardiovascular disease, high fat diet with restricted anti-oxidant compounds (e.g. zinc oxide, vitamins A, C, and E) and an unhealthy lifestyle (6). It is more common as people age and projections show that by 2040, 288 million people will be affected by this disease [7]. AMD has a substantial negative influence on aged individuals and can result in blindness and irreversible vision loss, making it a serious global public health concern (7-9). Various stages of progression of AMD starting from early to neovascular stage are depicted in figure 1.

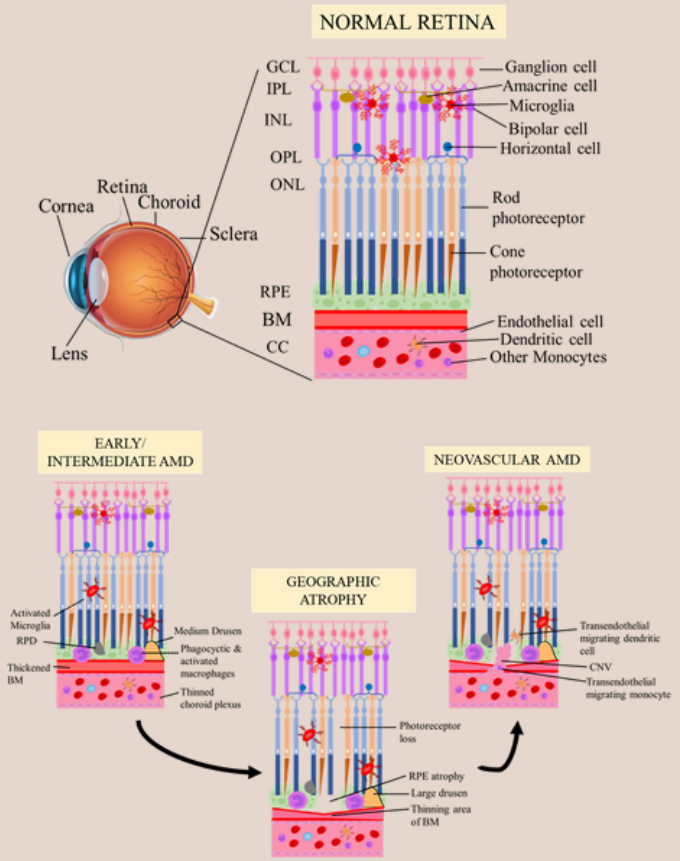

Figure 1. Various stages of age-related macular degeneration (AMD), adapted from [59]

2. Pathophysiology of AMD

Macular degeneration associated with aging (AMD) is a multifactorial illness influenced by genetic, environmental, and age-related factors. Internal and external environmental factors, in addition to genetic determinants, have a substantial impact on the development of AMD (10). Photoreceptors, RPE, and the choriocapillaris are all dysfunctional and degenerated in AMD, and a complex interplay between oxidative stress, inflammation, and decreased metabolic activity are all important factors in this pathophysiology (11, 12). Changes in proteostasis, malfunctioning mitochondria, and dysregulation of the extracellular matrix are among the many interrelated factors that contribute to drusen development and RPE failure, aggravating the course of the illness (13-16). Growth factors like as vascular endothelial growth factor –A (VEGF-A) play a role in choroidal neovascularization, which further complicates the pathophysiology of AMD as depicted in figure 2 (17). Understanding these fundamental mechanisms is critical for designing targeted treatments and personalized medicine approaches for AMD patients, given the wide range of variables that contribute to disease progression.

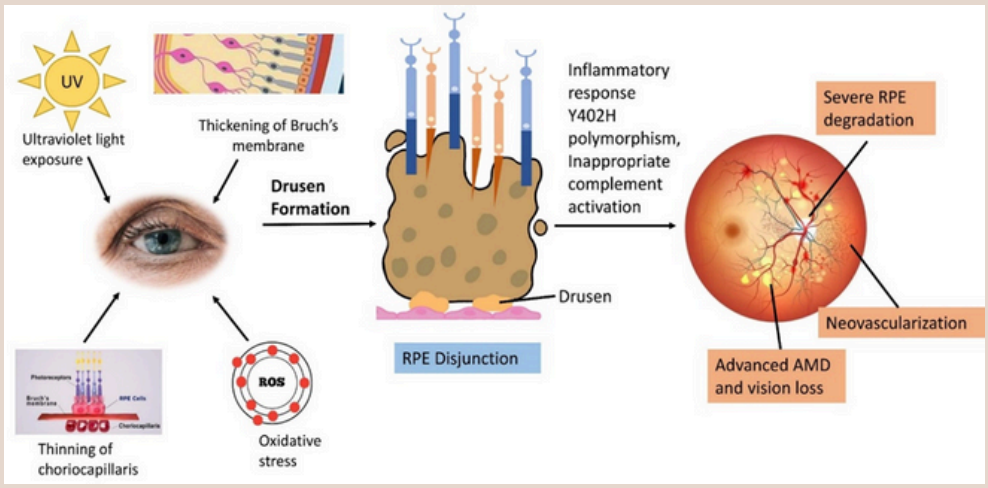

Figure 2. Pathogenesis of AMD

3. Types of AMD: Differentiation between dry and wet AMD

AMD manifests in two distinct forms: non-neovascular AMD, or dry AMD, and neovascular AMD, or wet AMD. A characteristic of wet AMD is unusual choroidal neovascularization, which causes bleeding, edema, and fibrosis as well as fast central vision loss (18,19). Conversely, dry AMD is characterized by a steady decline in vision due to progressive loss of photoreceptor cells and geographic atrophy (18). The distinction between the two types of AMD is essential for choosing the best course of treatment. Wet AMD is typically treated with anti-VEGF agents to inhibit neoangiogenesis, whereas dry AMD is still difficult to treat, though complement cascade inhibitors and gene therapy that targets pathological angiogenesis are promising approaches (20). Novel drugs with sustained pharmacological activity have been developed recently for the treatment of wet AMD, while ongoing trials are looking into various inhibitors, gene therapies, and cell-based medicines for the management of dry AMD (21). Difference in both dry and wet form of AMD is clearly depicted in figure 3. Deep neural network-based automated classification techniques have produced encouraging results in precisely differentiating between dry and wet AMD for timely intervention (22).

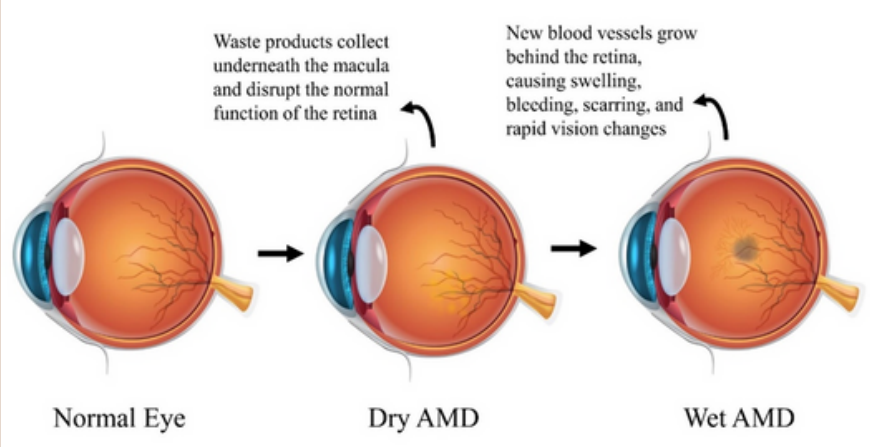

Figure 3. Difference between dry AMD and wet AMD, adapted from [60]

4. Current therapeutic approaches

4.1. Anti-VEGF therapy

Neurovascular age-related macular degeneration (nAMD) is largely treated with anti-VEGF therapy, which inhibits abnormal angiogenesis in the eye by targeting vascular endothelial growth factor (VEGF) (23,24). The visual results of individuals with nAMD have been shown to improve with approved medications such ranibizumab, aflibercept, and brolucizumab; however, the requirement for frequent injections presents a significant financial and medical burden (23, 25). Investigational therapeutics that are intended to lessen treatment burden and enhance outcomes include long-acting drugs like Abicipar and Brolucizumab, as well as sustained-release drugs and genetic therapies for prolonged VEGF suppression (26,27). Though anti-VEGF drugs already on the market have transformed the way that AMD is treated, there is still work to be done in lengthening treatment durations and developing novel techniques to improve patient adherence and results.

4.2. Laser therapy

Laser therapy is one of the most promising another therapy used in treatment of AMD. It includes various procedures such as photodynamic therapy (PDT), transpupillary thermotherapy (TTT), and laser photocoagulation (28). Conventionally laser photocoagulation was associated with incidental retinal damage but introduction of newer techniques such as subthreshold retinal laser therapy has reduced the associated side-effects (29). Furthermore, femtosecond lasers have been created to treat AMD by precisely focusing on damaged tissue and initiating a reaction that kills the tissue (30,31). Due to the frequency of recurrent lesions, these treatments are not always helpful for every patient and have a limited ability to stop the progression of the disease (29). However, in contrast to standard care, gene-editing and stem-cell therapies provide a more aggressive and perhaps more effective means of treating genetically induced AMD, with greater specificity, efficacy, and less frequent administration (32). Thus, new medicines including gene and stem cell therapy may offer more tailored and effective treatment for this chronic ocular illness, even though laser therapy may be beneficial in some AMD patients (33).

4.3. Photodynamic therapy

In photodynamic treatment (PDT), photosensitizers are activated by certain light wavelengths, which results in the production of reactive oxygen species and ultimately cell death (34-38). PDT has previously been used in conjunction with verteporfin to target choroidal neovascularization (CNV) in the context of AMD (39,40). However, the focus of PDT for AMD has turned to other chorioretinal illnesses like central serous chorioretinopathy and polypoidal choroidal vasculopathy after the introduction of anti-vascular endothelial growth factor (VEGF) therapy (41,42). PDT is a useful substitute for anti-VEGF therapy in circumstances where anti-VEGF therapy is not effective or when there are contraindications since it provides advantages including selective vascular occlusion and decreased collateral damage (40).

Nevertheless, PDT's applicability is limited to surface treatments due to factors like reduced light penetration, inadequate photosensitizer excitation, and possible side effects (36). Owing to difficulties with light, tissue oxygenation, and photosensitizer qualities, PDT is not widely used in clinical settings, despite its encouraging qualities such as low systemic toxicity and selectivity for light-accessible malignancies (38). The goal of ongoing developments in PDT techniques is to get over these obstacles and improve the therapeutic potential of PDT for diseases like AMD (34, 38). These developments include nanotechnology-based systems, biomodulation, and greater specificity.

5. Novel therapeutic interventions

5.1. Gene therapy

Gene therapy for AMD entails delivering therapeutic genes to specific tissues in order to overcome the difficulties of regular intravitreal injections. It employs a variety of strategies, including gene replenishment, gene editing, splicing modification, and gene expression suppression (43). Various delivery routes, including as intravitreal, suprachoroidal, and subretinal, are used, each having its own set of advantages and disadvantages in terms of transgene delivery, immunogenicity, and collateral effects (44). Recent applications, such ABBV-RGX-314, ixo-vec, and 4D-150, use adeno-associated viral vectors to express anti-VEGF medicines and have shown promising outcomes in clinical trials (45). The approach aims to sustain the delivery of therapeutic proteins, primarily leading to reduced treatment frequency and improved visual outcomes (46). However, limitations such as immunogenicity, safety concerns and route of administration requires additional sophistication in vector creation and delivery approaches to improve safety and efficacy (47), which can be substantially ensured by the use of adequate in vitro models (43).

5.2. Stem cell therapy

Stem cells, used in regenerative therapy, are undifferentiated or partially differentiated cells that can transform into several types of cells and proliferate endlessly to produce more of the same stem cell and thus establishes the normal physiology in diseased state. Stem cell therapy plays a significant role in the treatment of AMD. Sources of stem cells include non-ocular-derived stem cells such embryonic stem cells and induced pluripotent stem cells, as well as ocular-derived progenitor cells like retinal progenitor cells (48). Various stem cell types, such as mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs), have been shown in numerous studies to have the capacity to replace damaged retinal cells (49-51). In particular, preclinical research has demonstrated the safety and effectiveness of using iPSCs to create autologous cell replacement therapy for AMD (52). Due to its high specificity and efficacy, stem cell therapies are a significant substitute for conventional anti-VEGF injections, lowering the frequency of administration and logistics-related issues (53).

5.3. RNA-based therapies

The ability of RNA-based medicines to target the underlying genetic causes of AMD confers significant benefits in its therapy. These medicines include messenger RNA (mRNA) vaccines and antisense oligonucleotides (AONs) which target the genetic defects associated with retinal failure (54). RNA-based therapies modify expression of the genes associated with VEGF-A which is a crucial element in AMD progression, particularly in wet AMD, and hence aids in its treatment (55,56). This approach serves as

more targeted and effective treatment for AMD that will benefit patients' eyesight and provide better results. It confronts several obstacles as it is a relatively new and underdeveloped area of research. Cost-effective mass production, minimizing off-target effects and effective delivery to target tissues are some of the major obstacles that need to be worked upon for this approached to be used as primary line of defense against AMD (57). The therapeutic potential of RNA-based drugs is being increased despite these obstacles, providing fresh hope for the treatment of AMD and other disorders, owing to developments in intracellular trafficking techniques and an increasing understanding of RNA functions (58).

6. Conclusion

The rapidly evolving treatment choices for AMD has led to its better and more individualized treatment, especially for older patients. There is no reasonable medication available for dry AMD, on the other hand wet AMD has traditionally been treated primarily with anti-VEGF medicine, however this requires a time-consuming regular injection regime. Current treatment modalities primarily include anti-VEGF injections, laser therapy, and PDT which has certain limitations associated with them. Sustained-release devices, gene therapies, and long-acting pharmaceuticals are some of the approaches to negate the limitations linked to conventional therapies and enhance patient compliance. PDT has its unique role when other approaches render ineffective. Gene therapy showcases high potential in AMD treatment owing to its ability of genetic modification. Similarly, stem cell therapy promises most effective treatment by replacing damaged cells with newly proliferated cells. Another novel strategy to treat the underlying genetic problems of AMD is the development of RNA-based therapeutics, such as mRNA vaccinations. Although obstacles must be addressed, these treatments have the potential to dramatically alter AMD treatment. All things considered, these developments are opening doors for less taxing and more efficient treatment alternatives, which will enhance the lives of AMD patients.

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