Treatment of Age-Related Macular Degeneration

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ABSTRACT

Aging macular degeneration (AMD) is a leading reason for irreversible loss of vision, particularly in the elderly. This review takes into account current management options for AMD, both traditional and emerging approaches, to offer an overview of effective management. A qualitative literature review from 2019 to 2024 was conducted with Google Scholar and PubMed using the keywords "AMD treatment." Peer-reviewed publications regarding intravitreal injections and experimental treatments were accessed. The review highlights the effectiveness of intravitreal injections of VEGF inhibitors as the standard treatment for the exudative form of AMD. There are no effective treatments, though, for late-stage dry AMD. In particular, technological strides in cloud computing and artificial intelligence (AI) have promised early diagnosis and treatment planning. The review explains the significance of continued research into treatment of dry AMD. In conclusion, while great leaps have been made in the therapy of exudative AMD using VEGF inhibitors and early detection using AI, more studies and collaboration between healthcare providers must be undertaken to develop effective therapies for dry AMD and optimize patient outcomes.

Keywords: age-related macular degeneration; AMD treatment; VEGF inhibitors; artificial intelligence, macula dystrophy

INTRODUCTION

In general, AMD or age-related macular degeneration is perhaps the most important cause of vision loss that is irreversible in people aged 55 and older and it largely influences activities such as recognizing faces and driving among others[1]. The disease targets the macula, which is an important part of the retina as it is responsible for central vision that is sharp. Basically, AMD progresses through four stages from early signs such as small drusen to more advanced stages that are characterized by geographic atrophy (GA) or neovascular AMD (nAMD). In addition, advanced AMD can further be categorized into GA or dry AMD and wet AMD with the latter having a number of subtypes such as CNV or choroidal neovascularization and polypoidal choroidal vasculopathy (PCV)[2]. Different unique challenges are presented by each subtype, specifically about prognosis and treatment.

The international burden of AMD is increasing and it is mainly due to the aging populations. For example, by 2040, the number of AMD cases is expected to increase to 288 million with Asians having the highest share because of their large population[3]. The prevalence of AMD and its management are further complicated by ethnic and regional differences. AMD, for example, is more common among Europeans with the rate being 12.33% than Asians and Africans with their rates being 7.38% and 7.53%[4]. For personalizing treatment, it is quite important to understand these demographic changes and differences.

In the last 15 years, VEGF therapies have changed the treatment of AMD, specifically for nAMD[5]. These therapies have significantly improved the preservation of vision and quality of life for millions of patients. It is shown by clinical trials that more than 95% of patients tend to maintain baseline visual acuity after two years of treatment and up to 40% experience improvement in the vision[5]. However, outcomes in the real world often lag behind the results of clinical trials. Some challenges range from high rates of treatment discontinuation to fewer injections with many patients stopping the therapy prematurely[6].

In spite of the positive effect of anti-VEGF therapies, there are still gaps in AMD management and these range from chronicity of the disease and adherence to the treatment to the need for new therapies capable of extending the intervals between doses. Different investigational approaches like continuous systems for drug delivery and gene therapy have potential but they definitely need more research. This article is aimed at showing the current state of treatment of AMD with a focus on gaps in the literature.

REVIEW OF THE LITERATURE

In the paper of[7], the therapeutic value of anti-VEGF agents like ranibizumab and aflibercept in nAMD treatment is highlighted. The therapy has significantly altered the quality of life in patients with retarding disease progression and prevention against loss of vision. However, the study also presents some of the challenges, such as the incomplete response in some patients, diminished efficacy with time, and intravitreal injection burden on both patients and caregivers. More recent treatments, such as designed ankyrin repeat proteins (DARPins), are promising as they can ensure compliance with reduced injections.

Alternatively, the study by[8] distinguishes between the neovascular and atrophic forms of AMD. While the neovascular form of AMD produces the most serious visual loss, it is present in a lower proportion of AMD patients. The article points to the role of several risk factors including age, heredity, and smoking, of which smoking is most modifiable. Early identification by imaging techniques such as OCT and early treatment with anti-VEGF agents are shown to improve the prognosis of neovascular AMD. The study also notes the benefits of antioxidant supplements like those utilized in the AREDS2 trial for intermediate or advanced AMD but offer less benefit in the early stages.

Spontaneous progression of AMD from early to intermediate and advanced stages of disease is documented in[9]. While anti-VEGF therapy is important in the management of neovascular AMD, the

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study highlights the significant gap in treatments for atrophic AMD, against which no effective treatment is available. The study calls for accurate risk stratification and early diagnosis, along with improved treatments. Gene therapy, as in[10], can be one such solution. ADVM-022 is a vector that can encode aflibercept and suppress VEGF long-term in a single dose, reducing treatment burden significantly compared to traditional anti-VEGF therapies.

The focus shifts to dry AMD in[11], for which there is no definite treatment. While anti-VEGF treatments have transformed the management of neovascular AMD, no such advance has been made for dry AMD. The study reviews existing and developing therapeutic approaches to slow dry AMD development, including antioxidative treatments and cell treatments. While first-phase trials have been promising, the study admits that further study needs to be done before these therapies are applied in the clinical setting.

Study[12] also looks in more detail at the critical role of anti-VEGF agents in treating neovascular AMD. While these therapies strongly improve vision preservation, repeated intravitreal injections that may be required place a heavy burden on patients. This has led to suboptimal outcomes or discontinuation in a few instances. New dosing regimens, such as "treat-and-extend" or as-needed therapy, have been established to reduce the number of injections without loss of efficacy, but further innovation is needed to improve outcomes in nonresponders to current therapies.

In addition[1], it also discusses the complexity of AMD as a disease that is both genetically and metabolically determined. Although anti-VEGF therapy is still the first line of treatment for wet AMD, newer medicines and emerging treatments like induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) therapy have the potential to transform AMD management, particularly in patients who are intolerant or nonresponsive to current therapies. Long-term effects of anti-VEGF treatments are considered in[13] , where the evidence is provided that certain morphological features, like intraretinal fluid (IRF), predict poor vision outcomes independently. Evidence suggests that treatments targeting these features can inhibit disease progression and improve long-term vision

While anti-VEGF treatments work for neovascular AMD[14], points out that there are no effective treatments for dry AMD, which is accompanied by retinal cell degeneration. The study promotes the use of systems biology in deciphering the disease's complex nature. Researchers will employ both genomic and clinical data to identify biomarkers, define disease mechanisms, and track response to therapy. Personalized medicine approaches can transform therapy outcomes by providing precise predictions regarding disease progression and therapeutic response.

With advancing treatment[12], identifies the shift from previous therapies, such as laser photocoagulation, to newer anti-VEGF drugs such as ranibizumab and aflibercept. While these treatments have improved patient care, further work remains in the optimization of dosing regimens and off-label use. Technologies like deep learning algorithms, which are discussed in[1], have the potential to improve the accuracy of AMD diagnosis and treatment planning. Alongside, ongoing clinical trials of emerging medications and RPE cell therapies derived from iPSCs have the potential to provide more lasting cures with fewer side effects in the long run.

To this end[14], also highlights precision medicine in managing dry AMD. Personalized computer models would help clinicians make accurate predictions about the progression of disease and treatment outcomes. Such biomarker-based simulations would also track the effectiveness of preventive treatments for avoiding vision loss. This approach mirrors advancements in other complex diseases, and future directions for AMD research are suggested. New advances in artificial intelligence (AI) shown by[15] have the potential to diagnose and treat AMD. AI models, such as convolutional neural networks (CNNs), have been able to detect AMD with more than 90% accuracy, offering a feasible solution for distant diagnosis and treatment planning.

Finally[16], provides an overview of the impact of AMD globally, stating the condition is responsible for about 9% of global blindness, though more frequencies exist in developed countries like Germany. AMD progresses through three phases: early, intermediate, and advanced. While early AMD usually occurs without symptoms, subsequent stages can result in severe central vision loss. The research emphasizes that although the treatment for exudative AMD, e.g., intravitreal VEGF inhibitors, has shown enhanced patient benefits, the dry type of AMD continues to be non-treatable, which reflects the importance of research in this direction. Likewise[17], emphasizes the irreversibility of vision impairment due to AMD, supporting the necessity of multidisciplinary treatment for the disease, especially among anticoagulation therapy patients.

METHODOLOGY

A qualitative design is used in this study and a systematic search is carried out across several databases ranging from Google Scholar to PubMed for finding peer-reviewed studies between 2019 and 2024[18]. Different search terms such as "AMD treatment " and "VEGF inhibitors" were used for collecting a range of articles. Studies were prioritized by this review that focused on diagnostic methods and treatments[19]. It should be noted that there was a focus on including peer-reviewed articles that were in English and related to AMD treatments. Moreover, different articles that focused on clinical trials and experimental approaches were also included[20]. It should be noted that data was analyzed by going through results and conclusions deeply and this approach offered a detailed understanding of the developments in AMD care[21]. In addition to it, all the relevant ethical guidelines were considered and adhered to while carrying out this research. Since this study does not really involve human participants, the ethical

DISCUSSION

Guidelines regarding their inclusion were not considered. However, in this study, it has been ensured that the authors and owners of the information are given credit to through proper citations. Moreover, the actual references have been given in the section of references.

It is important to note that there are many studies that focus on both traditional and new therapies for managing AMD. For example[7], talks about the success of anti-VEGF therapies such ranibizumab and aflibercept for the treatment of wet AMD (Table 1). These treatments help in slowing down the disease but they come with challenges. For example, some patients do not really respond well and the treatments become less effective over time, and injections are needed frequently, which can be tiring for both patients and their caregivers. Different new treatments such as DARPins may offer a better option because they tend to last longer and need fewer injections. The wet and dry forms of AMD are compared by[7] and the wet form is determined to cause more severe loss of vision but affects fewer people than the dry form. Basically, early detection with the use of OCT is important for managing wet AMD and antioxidant supplements may help some patients with advanced AMD even though they are not effective in the early stages.

It is explained by[9] how AMD progresses from early to more severe stages and while anti-VEGF therapy is important for treating wet

Table 1. Medicines and Techniques

Study	Treatment/Medicine	Details
[7]	Anti-VEGF Therapy (Ranibizumab, Aflibercept)	Improves prognosis for neovascular AMD but has challenges like incomplete responses for different patients and decreasing effectiveness over time, and inconvenience of frequent injections. Due to it, many patients consider leaving the therapy over time.
[7]	DARPins (Designed Ankyrin Repeat Proteins)	New therapy with higher durability and needs fewer injections compared to other methods, which improves compliance.
[8]	Anti-VEGF Agents	Emphasized for early detection and quick treatment of neovascular AMD for better outcomes.
[8]	Antioxidant Supplements (AREDS2 Trial)	Beneficial for intermediate or advanced AMD with fewer benefits for earlier stages. Ineffecitve results for people in the early stages of AMD.
[9]	Anti-VEGF Therapy	Remains important for neovascular AMD but lacks effective treatments for atrophic AMD.
[10]	Gene Therapy (ADVM-022)	A single administration offers long-term VEGF inhibition, which decreases the treatment burden.
[11]	Antioxidative Drugs and Cell-Based Treatments	Early-phase trials for dry AMD show potential but need further research for clinical implementation.
[12]	Anti-VEGF Agents	"Treat-and-extend" and as-needed regimens aimed at decreasing injection frequency while maintaining efficacy.
[1]	iPSC-Derived RPE Therapy	Innovative approach for patients who do not tolerate or respond to current treatments. In case of tolerance to the existing treatments, iPSC-derived RPE therapy proves to be quite effective.
[1]	Anti-VEGF Therapy	Main treatment for wet AMD and offers some promising results compared to traditional methods. The author highlighted this therapy along with new-generation drugs.
[13]	Anti-VEGF Agents	Long-term analysis shows the need for therapies that focus on pathological features like intraretinal fluid (IRF) and lesion size for the better treatment of AMD in an effective manner.
[14]	Precision Medicine	Systems biology approach for dry AMD that uses genomic and clinical data to develop personalized treatments.
[14]	Predictive Models	The authors focused on the use of biomarkers for monitoring treatment effectiveness and decreasing risks of complications.
[14]	Anti-VEGF Agents	Progress in improving dosing strategies and exploring off-label options.
[15]	AI-Based Diagnosis and Treatment	CNNs trained on OCT images get over 90% detection accuracy and help with telemedicine for AMD diagnosis and treatment.
[16]	Anti-VEGF Inhibitors	Intravitreal injections for neovascular AMD with an emphasis on resource-intensive nature of treatment and need for collaboration between stakeholders.
[17]	Anti-VEGF Therapy	Highlights the irreversible nature of vision loss in AMD and calls for a multidisciplinary approach to management, especially with anticoagulation therapy.

AMD, there are still no effective treatments for the dry form and this study highlights the need for better ways for diagnosing and treating AMD, and it points to new therapies in development. Gene therapy, which is introduced in another study[10], shows potential for treating wet AMD. Basically, ADVM-022 is a type of gene therapy that uses a virus for delivering a treatment that stops the disease from progressing. In fact, a single injection of ADVM-022 is capable of offering benefits that last long and decreasing the need for frequent treatments.

Regardless, it should be noted that dry AMD is harder to treat and[11] reviewed current treatments and shows that even though anti-VEGF therapy works for wet AMD, there are no innovations yet for dry AMD. Different approaches are being explored by researchers like using drugs that protect the retina and gene therapy, and treatments using stem cell. However, many of these therapies are still in early testing stages and it is explained by[12] that even though anti-VEGF therapies have improved the treatment of wet AMD, they still need injections frequently, which can be quite challenging for patients. For managing this, doctors are testing different schedules of treatments that decrease the number of injections while still being effective.

It is suggested by[1] that AMD is affected by several metabolic and genetic factors and new studies into drugs and stem cell treatments could offer better options for people who do not really respond to current therapies[13]. Looks at results from patients treated with anti-VEGF therapy in the long run and shows that certain changes in the eye such as fluid buildup are capable of leading to worse vision with time. It is shown by this finding that there is a need for therapies that are capable of addressing these issues. In spite of progress in managing wet AMD[14], shows that dry AMD still does not have effective treatments. Researchers are looking at new methods, including studying the genetic and protein changes of the disease for making better treatments[12] looks at how older therapies like laser treatment have been replaced by anti-VEGF agents and even though these newer treatments are more effective, there is still room for improvement in decreasing the burden of the treatment.

It is highlighted by[15] how the treatment of AMD could be improved by AI and it uses a large dataset of OCT images for training an AI system that is capable of diagnosing AMD with accuracy. This AI system is capable of helping doctors in offering treatment recommendations and allowing patients to be diagnosed remotely, which is quite useful in areas with fewer specialists. Regardless, a gap that still needs to be addressed in AMD treatment is the lack of proper solutions for dry AMD. Even though there have been advancements in treating wet AMD with therapies like anti-VEGF, these treatments do not really

work for the dry form of the disease. Dry AMD is more common but is harder to treat and there are no treatments that are currently available for stopping or slowing its progression in an effective manner. Different researchers are focusing new approaches such as AI-based systems and drugs capable of protecting the retina and gene therapy but these treatments are still in their early stages and cannot be implemented in practical settings. In the future, experimental studies should be carried out for determining which treatment is better for managing AMD with a focus on new treatments.

CONCLUSION

Overall, even though there have been major developments in the management of wet AMD, especially with different anti-VEGF therapies, there are still challenges like decreasing effectiveness over time and frequent injections. Different new approaches such as DARPins and gene therapy have the potential for more convenient and longer-lasting treatments. However, dry AMD still poses a major challenge because there are currently no effective therapies for slowing or stopping its progression. It is important to note that ongoing research in stem cell treatments and AI-based tools for diagnosis show potential for the improvement of both types of AMD in the future. However, more detailed and long-term studies that are experimental in nature are necessary for improving clinical understanding and developing more effective solutions, especially for the treatment of dry AMD.

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