Review

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Advancements in the treatment of geographic atrophy: focus on pegcetacoplan in age-related macular degeneration

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Abstract

Geographic atrophy (GA) is a progressive form of age-related macular degeneration characterized by the degeneration of retinal pigment epithelial cells and photoreceptor death. The dysregulation of the complement cascade has been implicated in GA progression. This review provides a comprehensive overview of the pathophysiology of age-related macular degeneration and GA, discusses current therapeutic options, and focuses on the recent breakthrough drug, pegcetacoplan (SYFOVRE). Pegcetacoplan is a complement inhibitor that selectively targets the C3 complement protein, effectively modulating complement activation. Clinical trials, including the OAKS and DERBY studies, have demonstrated the efficacy of SYFOVRE in reducing the growth of GA lesions compared to placebo. The FDA approval of SYFOVRE as the first and only definitive therapy for GA marks a significant milestone in the management of this debilitating condition. The review also explores potential future treatment strategies, including immune-modulating agents and ocular gene therapy. While SYFOVRE offers new hope for GA patients, further research is needed to evaluate its long-term benefits, safety profile, and optimal treatment regimens.

Keywords: geographic atrophy, age-related macular degeneration, retinal pigment epithelium, photoreceptor death, complement cascade, pegcetacoplan, SYFOVRE

Introduction

Age-related macular degeneration (AMD) is the leading cause of progressive central vision loss in developed countries[1]. The estimated global prevalence of AMD in 2021 was 8.7%[2] and in 2020 it was found that over 11 million individuals in the U.S. along with over 190 million worldwide were affected by AMD[3]. Furthermore, the incidence of AMD is expected to rise because of the aging population[2].

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HIGHLIGHTS

- Age-related macular degeneration (AMD) is a prevalent condition causing central vision loss.
- Genetic factors play a role in the development and progression of AMD.
- AMD is characterized by pathological changes in the macula, leading to impairment of central vision.
- Dry AMD is the predominant subtype, which can progress to neovascular AMD.
- Pegcetacoplan (SYFOVRE) is a breakthrough treatment for geographic atrophy in AMD, targeting the complement cascade.
- Clinical trials have shown that pegcetacoplan effectively reduces geographic atrophy lesion growth.
- Other treatment options for AMD include immune-modulating agents, neuroprotective agents, visual cycle inhibitors, and ocular gene therapy.
- Ongoing research aims to further advance the management of AMD and explore new treatment strategies.

AMD is characterized by pathological alterations occurring in the inner retinal layers of the macula and the adjacent vasculature, leading to the impairment of central vision[4]. The degeneration can be characterized as an intensified manifestation of retinal aging when compared to the natural deterioration of retinal function seen in older individuals[5]. The risk of developing AMD is influenced by variations in more than 30 genes[4]. These genes are involved in various biological processes such as

the complement pathway, lipid metabolism, DNA repair, collagen production, protein binding, and cell signaling. Among these genes, those responsible for encoding complement factor H (CFH) and ARMS/HTRA proteins are strongly linked to the development and progression of AMD[6].

Drusen, which is the buildup of retinal deposits, is a significant clinical characteristic observed in AMD and could serve as an initial indication of the 'dry' form of the disease[4]. Early dry AMD is marked by the presence of soft Drusen and alterations in various components including Bruch's membrane, choriocapillaris, retinal pigment epithelium (RPE), and photoreceptors. In contrast, the distinguishing attributes of advanced dry AMD include geographic atrophy (GA), detachment of epithelial pigment, development of subretinal neovascularization, occurrence of hemorrhage, and formation of fibrous scars[1]. The occurrence of early AMD was found to be 8% in individuals aged 45 years or older, whereas the rate for late AMD was only 0.4%[2].

Dry AMD is the prevailing morphological subtype, and it has the potential to advance into 'wet' or neovascular AMD. In this condition, the formation of choroidal neovascular membranes (CNV) in the central area can result in bleeding and leakage of fluid into the retina, leading to significant visual impairment[4]. Approximately 10% of individuals with AMD are affected by this specific type, which is responsible for roughly 90% of the instances where the disease leads to severe vision loss[7].

GA secondary to AMD is characterized by the appearance of well-defined atrophic lesions in the outer retina. These lesions are caused by the loss of photoreceptors, RPE, and the underlying choriocapillaris, ultimately leading to permanent visual impairment[8,9]. Various imaging techniques directly capture the visualized presence and advancement of GA lesions. The perifoveal macula is usually where these lesions initially appear, with the foveal center being unaffected at first. However, as time passes, the lesions often grow and merge, eventually encompassing the fovea. While the rate of progression of GA can vary significantly among patients, emerging evidence indicates that certain features might play a crucial role in predicting the advancement of the disease and its outcomes[8].

This study meticulously dissects the pathophysiology of AMD and GA, with a specific focus on the dysregulation of the complement cascade, a central player in disease progression. By comprehensively elucidating SYFOVRE's mechanism of action and its clinical efficacy, this study aims to equip clinicians, researchers, and patients with a profound understanding of GA and the groundbreaking treatment option SYFOVRE, ultimately enhancing patient care and outcomes. This understanding is instrumental in advancing AMD therapeutics and ultimately enhancing the quality of life for patients grappling with this visually debilitating condition.

Materials and methods

Literature search and data sources

A comprehensive literature search was performed utilizing multiple electronic databases, including PubMed, Embase, Scopus, and the Cochrane Library. The objective was to identify pertinent studies related to GA in AMD. The search encompassed studies published up to the most recent available date in the respective databases.

Inclusion and exclusion criteria

Inclusion criteria were clearly defined to ensure the relevance of the studies selected for analysis. Studies meeting the following criteria were included: investigations focusing on GA secondary to AMD, clinical trials, observational studies, reviews, and other relevant articles reporting on the pathophysiology, treatment, or management of GA in AMD, and studies published in the English language.

On the other hand, exclusion criteria were established to filter out irrelevant or redundant studies. Studies meeting the following criteria were excluded: studies unrelated to GA or AMD, studies not published in English, and duplicate publications or redundant data.

Search terms

The search terms were meticulously selected and refined, incorporating a blend of Medical Subject Headings (MeSH) and pertinent keywords. A range of search terms was employed, including 'geographic atrophy', 'age-related macular degeneration', 'retinal pigment epithelium', 'photoreceptor death', 'complement cascade', 'pegcetacoplan', 'SYFOVRE', 'treatment', 'pathophysiology', and 'clinical trials'. These search terms were strategically combined and adapted for each specific database to ensure an optimal and inclusive retrieval of relevant studies.

Results and discussion

Pathophysiology of AMD and GA

The advanced stages of AMD can be observed in two distinct forms, namely GA and neovascular AMD (nAMD), and both forms can coexist[10]. This coexistence may be due to the shared risk factors between the two forms[11]. The ultimate cause of vision loss in both forms is related to the dysfunction of photoreceptors[12]. In GA, vision loss occurs because of the deterioration of the RPE, accompanied by the loss of the choriocapillaris. On the other hand, in CNV, new blood vessels grow from the choriocapillaris beneath the layer of the RPE. These vessels can leak, leading to hemorrhage and exudation. If left untreated, this process can result in scarring[3] (Table 1).

Pathophysiologically, AMD can be described as a disturbance in the typical balance-maintaining processes of the retina, which occurs due to an intensified reaction associated with aging[14]. The most well-established risk factor for AMD is getting older, and one element of the natural aging process involves the buildup of harmful metabolic waste substances like reactive oxygen species[15]. The retina is especially vulnerable to oxidative stress due to its high metabolic demand, abundant oxygen supply, presence of photosensitizers and polyunsaturated fatty acids, and constant exposure to light[15]. Smoking, a known risk factor for AMD, exacerbates oxidative stress by generating reactive oxygen species, reducing antioxidant levels, inducing hypoxia (oxygen deprivation), and decreasing blood flow to the choroid[10,16,17]. These combined effects contribute to the development of AMD by promoting chronic inflammation and tissue destruction in localized areas. This ultimately leads to the death of retinal pigment epithelial cells, resulting in GA, and in some cases, serves as a trigger for abnormal blood vessel growth associated with

Table 1

Classification of age-related macular degeneration: clinical characteristics and imaging findings[13]

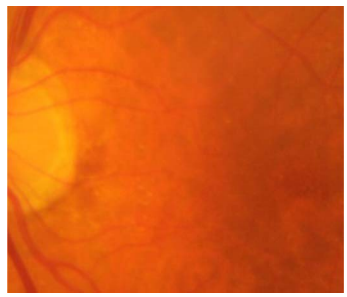
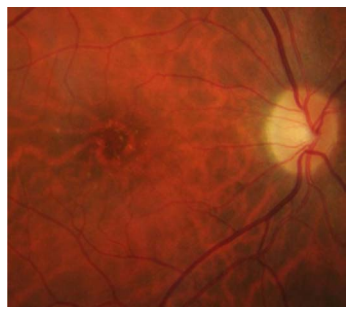
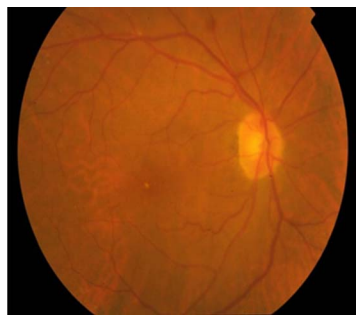
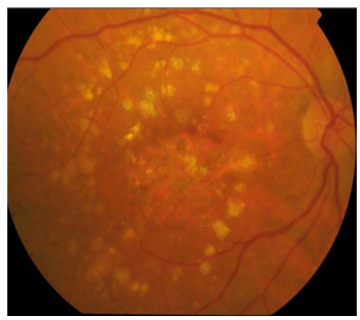
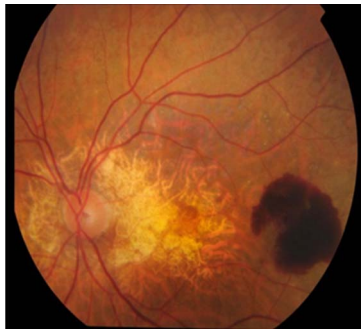
Disease stage	Clinical characteristics	Imaging findings
No abnormal findings	No aging changes: absence of drusen no pigmentary abnormalities age-related changes: drupelets only (small Drusen ≤ 63 μm). No pigmentary abnormalities	
Early AMD	Medium-sized Drusen > 63 μm and ≤ 125 μm No pigmentary abnormalities	
Intermediate AMD	Large Drusen > 125 μm and/or pigmentary abnormalities	
Advanced AMD	Lesions from geographic atrophy	

Table 1

(Continued)

Disease stage	Clinical characteristics	Imaging findings
	Lesions from neovascular AMD	

neovascular AMD (nAMD) through the activity of vascular endothelial growth factor (VEGF)[18].

On the molecular scale, the disease is shaped by the occurrence of various risk factors. These factors lead to specific events that characterize the disease, such as the buildup of lipids and protein beneath the RPE cells[18,19]. Other contributing factors include oxidative stress, lipid metabolism, extracellular matrix biology, inflammation, abnormalities in the complement cascade, and other immune responses, all of which play a role in the development and progression of the disease[20]. Inflammation and impairment of RPE cells can occur when complement proteins, such as C3 and C5, buildup on or close to them. This process can initiate inflammatory reactions and worsen the dysfunction of RPE cells. It is worth noting that a sizable number of genetic risk variations associated with AMD are concentrated in genes related to the alternative pathway of the complement system. Moreover, AMD patients often show elevated levels of complement activation products[21].

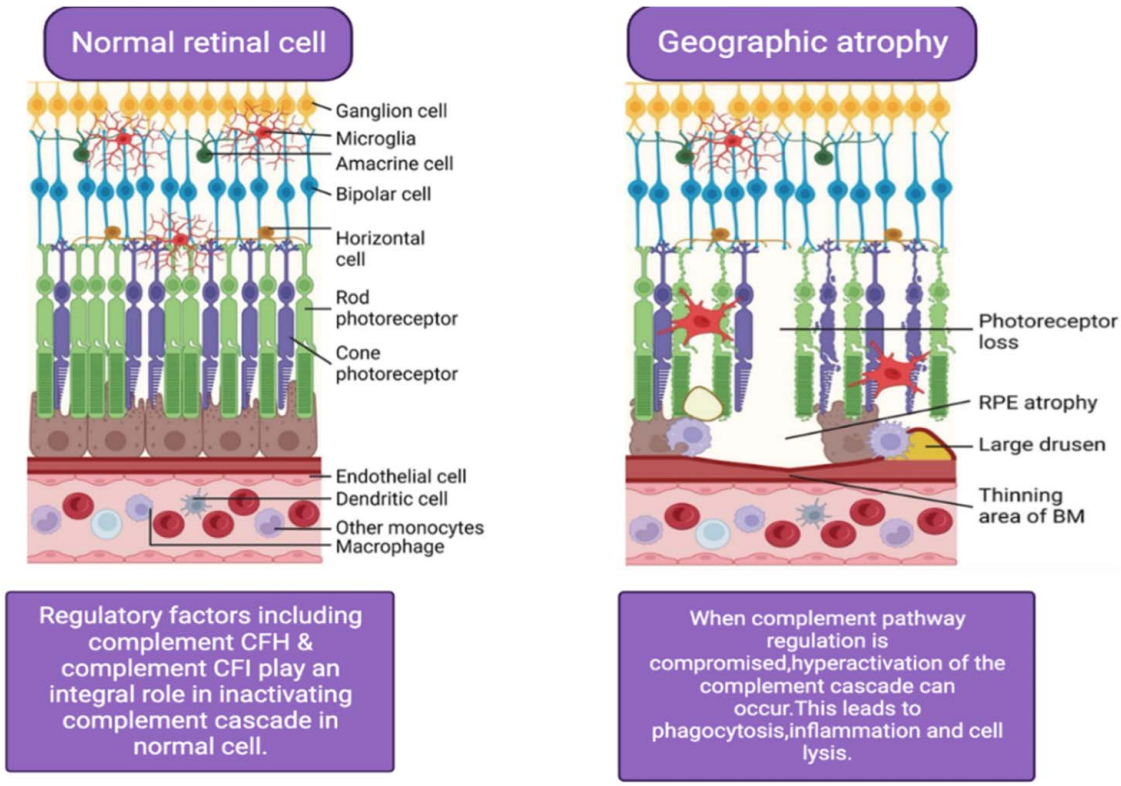


Figure 1. Pathophysiology of geographic atrophy[25].

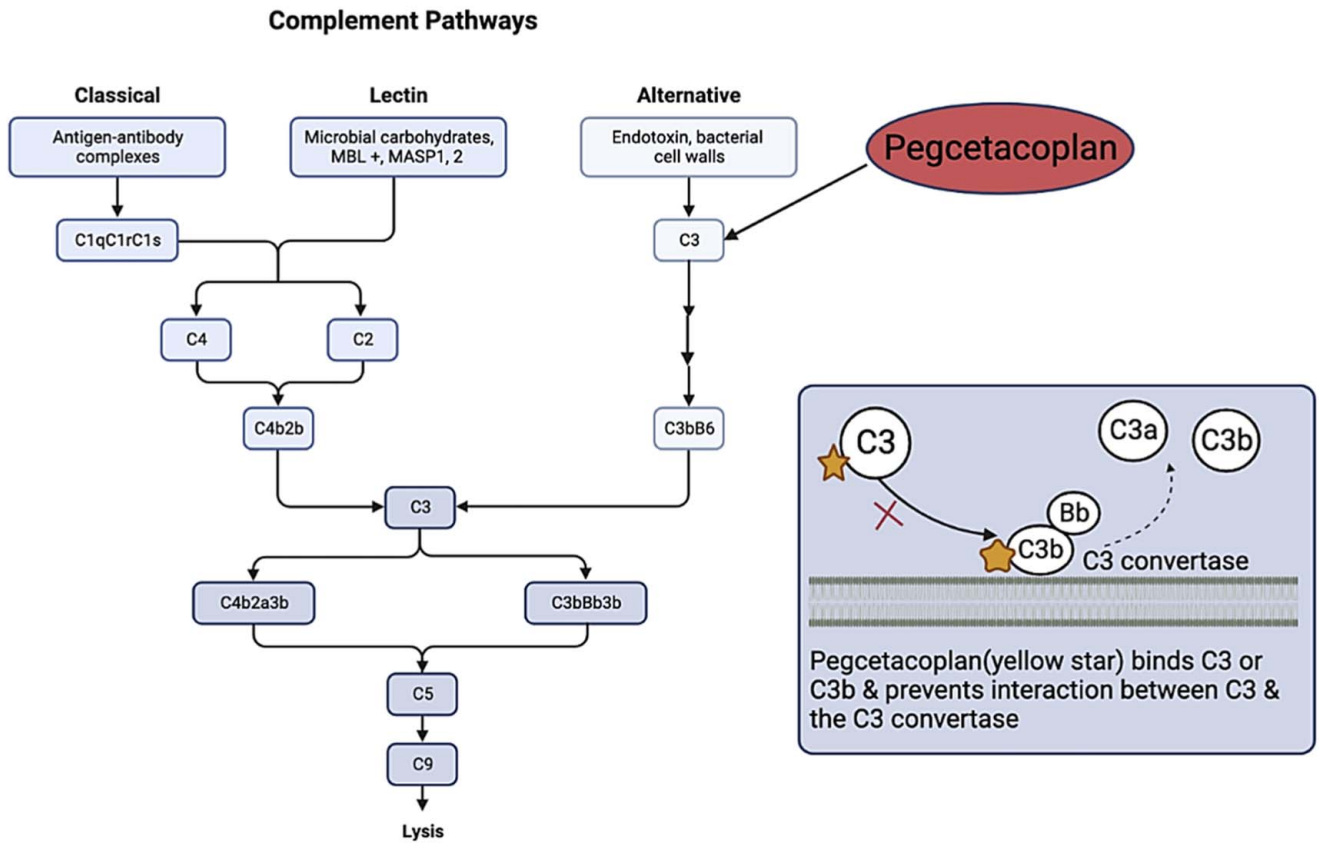


Figure 2. Role of complement cascade overactivation in geographic atrophy progression[25].

GA occurs as a result of RPE and photoreceptor death[22]. In the initial stages of the disease, lipids accumulate in Bruch's membrane, potentially due to the RPE's inability to effectively handle cellular waste linked to the turnover of outer segments. Findings from studies on Drusen, which are characteristic of the disease, indicate that they consist of lipid, amyloid, complement factors, and other cellular elements[23], which are observed in the initial and middle phases of AMD, are considered the distinctive characteristic of the retina[24] (Fig. 1).

Role of complement cascade overactivation in GA progression: mechanisms and implications in AMD

In the past 20 years, there has been significant interest in understanding how immune dysfunction, particularly the inappropriate activation of the complement cascade, contributes to the development of AMD. The complement cascade consists of three components: the classical pathway, the mannose-binding lectin pathway, and the alternative pathway. Each pathway has a unique role in immune function and is activated through different mechanisms. These three pathways ultimately merge into a final pathway when complement factor C3 is cleaved into C3a and C3b, triggering phagocytosis, inflammation, the formation of a membrane attack complex (MAC), and ultimately cell death[26]. The alternative pathway, in particular, has been associated with the development of AMD, as the majority of identified risk alleles are regulators of this pathway[27]. Immunocytochemical evidence provided by Johnson *et al.* supported the hypothesis that immune complexes may contribute to the formation of Drusen. The presence of various components of the complement system, such as C3, C5, and C9, was detected in Drusen of patients with AMD. Furthermore, multiple studies have demonstrated that Drusen deposits contain lipids, proteins, and complement products, strongly suggesting an overactive complement system as a significant factor in the development of the disease. Complement C3, complement factor F, complement factor H (CFH), and MAC were identified in both Drusen and AMD lesions. Additionally, elevated levels of C3, C3d, Bb, and C5a were found in the plasma of AMD patients. These findings, particularly the dysregulation of the alternative pathway leading to increased C3 turnover, suggest a prominent pathogenic role in AMD[28].

In the mouse model of CNV caused by lasers, the process of immunolabeling has revealed the presence of C3a and C5a substances near and within the RPE cells shortly after the laser-induced injury. It is noteworthy that Nozaki *et al.*[29], in their study, discovered that C3a and C5a stimulated the production of VEGF specifically in the RPE cells. Aberrant blood vessel formation, known as abnormal angiogenesis, is controlled by a protein called VEGF and is crucial in the progression of CNV in advanced neovascular AMD. The typical blood flow in the retina relies on VEGF to maintain a healthy network of blood vessels in both the choroid and retina[6]. These microvascular insults suggest both an ischemic and an inflammatory component influencing the pathophysiology of the disease (Fig. 2).

Current treatment options for GA in AMD

The loss of vision due to AMD can have a substantial influence on quality of life and can worsen the age-related health issues and comorbidities of the elderly[4]. AMD and its associated diagnostic and therapeutic procedures were also linked to high medical expenses[21]. With an aging population and a spike in the prevalence of GA secondary to AMD, imperative treatment is desperately needed to minimize both individual and socio-economic burdens. Treatment for GA has remained elusive even though there have been numerous studies to discuss potential treatment options and the methods that are available at present aim to only stall the progression of the disease.

The ARED studies established that taking the AREDS2 supplements daily slowed down the loss of central vision in people with intermediate or late AMD[30]. These supplements are composed of specific amounts of certain vitamins and minerals including Vitamin C (500 mg), Vitamin E (400IU), Cupric oxide (2 mg), Lutein (10 mg), Zeaxanthin (2 mg), and Zinc oxide (80 mg) and may be prescribed by some medical practitioners for GA[31]. Additionally, lifestyle changes are advised for all patients with AMD. These include the incorporation of antioxidant-rich foods in the diet, cessation of smoking, weight loss, blood pressure, and lipid control[4].

Visual rehabilitation is one approach to help people adapt to life with low vision. It encompasses numerous services that help to enhance low vision including prescription eyewear, visual aids like magnifying glasses, and learning skills to better manage everyday activities[22]. A recent study concluded that the implantation of the Scharioth macula lens in the better-seeing eye of GA patients followed by visual rehabilitation enhanced near vision and alleviated mental health signs related to vision[32]. According to another study, visual training in patients with AMD leads to improvements in fixation stability, reading speed, and visual acuity[24].

Patients with bilateral, end-stage AMD may be candidates for the surgical replacement of their lens with the implantable miniature telescope[33]. This device makes use of the fact that AMD usually causes loss of central vision, leaving peripheral vision intact. The implantable miniature telescope magnifies the images in the central visual field and focuses them onto the healthy peripheral retina[33,34]. It is implanted unilaterally and eliminates peripheral vision in that eye, causing complete dependence on the contralateral eye for peripheral vision[33,34]. It is noteworthy that the patient should be willing to undergo preoperative and postoperative visual training to determine eligibility and to teach techniques for using the device, respectively[35].

Pegcetacoplan (SYFOVRE): A breakthrough treatment for GA in AMD

Pegcetacoplan is a medication that was first approved by the FDA in May 2021 to be given as a subcutaneous infusion for the treatment of patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)[36]. In February 2023, intravitreal Pegcetacoplan injection (SYFOVRE) was authorized by the FDA as the first and only definitive therapy for GA[37].

Mechanism of action of pegcetacoplan

Pegcetacoplan is a complement inhibitor and selectively targets the C3 complement protein. An important factor in the pathophysiology of AMD is the disordered functioning of the complement system and so, due to its position upstream of all key effectors and the convergence of all 3 complement activation pathways over it, C3 is a desirable target in AMD[38]. Pegcetacoplan binds to C3 and C3b which not only hinders the cleavage of C3 into C3a and C3b but also blocks the formation of downstream mediators of the complement cascade[39].

Clinical trials and FDA approval of SYFOVRE for the treatment of GA:

The OAKS and DERBY studies were two Phase III studies to determine the safety and effectiveness of SYFOVRE for the treatment of GA[40]. In these studies, 1258 patients with GA, either with or without sub-foveal involvement, were randomly chosen and studied for 24 months. Of these 1258 patients, in a 2:2:1:1 ratio, 839 were administered SYFOVRE at 15 mg/0.1 ml monthly ($n=419$) or every other month (EOM) ($n=420$) and 419 a placebo monthly ($n=208$) or EOM ($n=211$). Fundus autofluorescence was used to measure the change in the total area of GA lesions from baseline and this was used as a parameter to evaluate the findings of these studies[41]. In both studies, there was an overall reduction in the growth rate of GA lesions compared to placebo. There was also an increased efficacy of the drug over time since the reduction in GA lesion growth at 18–24 months when given SYFOVRE monthly and EOM was 30 and 24%, respectively, which was considerably higher than that seen at 0–6 months which was 13% when given SYFOVRE monthly and 12% when given EOM[42] results of these studies are summarized in Table 2.

The results of the DERBY and OAKS clinical studies at 12 and 18 months and the Phase II FILLY clinical study at 12 months led Apellis Pharmaceuticals, in June 2022, to set forth a New Drug Application (NDA) to the FDA for the approval of SYFOVRE as a treatment for GA. It was accepted and was subjected to priority review in July of the same year. To further solidify its application, Apellis provided data from DERBY and OAKS at 24 months in November 2022 which eventually led to the FDA's authorization of SYFOVRE in February 2023[40].

In these trials, the use of SYFOVRE was most frequently associated with wet AMD, ocular discomfort, vitreous floaters, and conjunctival hemorrhage, all of which occurred at an incidence of greater than 5%. Furthermore, as with any intravitreal injection, endophthalmitis, retinal detachments, and increases in intraocular pressure were reported but in less than 1% of the participants only[43].

Mode of administration, clinical applications, and side effects

SYFOVRE (Pegcetacoplan injection) is an aseptic, clear, translucent to light yellow aqueous solution in a single-dose vial for intravitreal use. Each vial allows for the delivery of 0.1 ml of a solution containing 15 mg Pegcetacoplan, trehalose dihydrate (5.95 mg), glacial acetic acid (0.0895 mg), and sodium acetate trihydrate (0.0353 mg)[31]. In terms of pharmacology, SYFOVRE is a complement inhibitor that directs at the central protein of the complement cascade called C3.

The complement cascade safeguards the body against infections by killing infectious and injured cells, but severe diseases related to the cascade can occur when the cascade over activates and exterminates normal cells. SYFOVRE acts by regulating the

Table 2
Summary of clinical trials evaluating the efficacy of pegcetacoplan (SYFOVRE) in geographic atrophy: OAKS and DERBY Trials[41]

Clinical trial	Type of clinical trial	Total number of participants	Trial assessment	Trial Duration	Results
OAKS	multicenter, randomized, double-masked Phase 3	637	Change from baseline in the rate of GA lesion area growth measured by FAF	24 months	Slowed growth by: 22% – when taken monthly 17% – when taken EOM
DERBY	multicenter, randomized, double-masked Phase 3	621	Change from baseline in the rate of GA lesion area growth measured by FAF	24 months	Slowed growth by: 18% when taken monthly 17% when taken EOM

body's immune system and the origination and expansion of many diseases[33]. It bisects the C3 fragments and controls the C3-mediated extravascular hemolysis. The cleavage of C3 is supervened by obstruction of the complete complement cascade as it serves as a point of convergence for all complement pathways[44].

The SYFOVRE injection is administered into the vitreous cavity of the eye immediately after the dosage has been prepared by a qualified physician. Also, the dosage is to be administered every 25 to 60 days[37]. The intraocular pressure of the patient should be checked before the administration and should be lowered with topical β-adrenergic antagonists when necessary[45]. Before administration, numbing medicine for pain and antibiotics are administered prophylactically to deal with any infection that may arise during the procedure[39].

SYFOVRE can cause some side effects[46,7]. The most common reported so far is eye discomfort about 13% of patients reported[46]. The next important side effect is wet AMD, seen in 12% of patients, which shows symptoms such as vision distortion and deterioration[46,47]. About 10% of patients have complained about floaters[46]. 4–6% might have a vitreous detachment[46]. Furthermore, 8% could experience redness and swelling of the eye[46].

Future prospects in the treatment of GA: advancements and promising strategies

The knowledge of the key role that complement cascade activation plays in AMD has led to several therapeutic options that target the complement cascade. There are several emerging treatment strategies being investigated that hold promise for managing or potentially slowing down the progression of GA.

Immune-modulating agents

The primary role of immune-modulating agents is to restore or balance the immune response in such immune-related disorders.

Eculizumab (Soliris; Alexion Pharmaceuticals) is a monoclonal antibody that has been modified from a mouse antihuman C5 antibody to become humanized[48]. Eculizumab is a systemic complement factor 5 inhibitor that effectively manages to prevent MAC formation by inhibiting the cleavage of C5 into C5a and C5b[26]. Despite the hopeful potential of Eculizumab in slowing the progression of GA, the COMPLETE study (NCT00935883), a phase 2 study involving 30 patients conducted between November 2009 and March 2011, reported no significant reduction in the growth rate of GA[48]. The study was randomized and double-masked, with participants receiving either intravenous Eculizumab or a placebo[48]. The lack of observed effect could be attributed to several factors, including the small sample size, short study duration, the possibility of targeting the wrong component (C5), and the potential superior penetration of the drug when delivered directly into the eye (intravitreal) compared to the systemic route chosen in this study[48].

The MAHALO study presented encouraging findings that support further exploration of the complement pathway as a potential treatment for GA. Lampalizumab, an antibody developed by Genentech Inc. and F. Hoffmann-La Roche AG, targets complement factor D (CFD) in the alternative pathway[49]. By binding to CFD, Lampalizumab hinders the activation of the alternative complement pathway. Previous Phase 1 and 2 trials

(NCT00973011; NCT01229215) of Lampalizumab indicated no adverse effects on ocular or systemic health[49,50]. The MAHALO trial, conducted from May 2011 to April 2013, involved 129 patients and lasted for 18 months. It was a randomized study with sham injections serving as the control. Participants were divided into four groups: monthly sham injections, monthly 10 mg Lampalizumab injections, sham injections every other month, or 10 mg Lampalizumab injections every other month[49]. The primary outcome measure assessed the average change in GA lesion size, measured using autofluorescence, over 18 months. The study revealed that monthly intravitreal administration of Lampalizumab led to a 20% reduction in lesion area progression compared to the sham group. In a subgroup analysis focusing on carriers of complement factor I (CFI) risk alleles, the reduction was even more significant at 44%. Currently, Phase 3 trials for Lampalizumab, named Chroma (NCT02247479) and Spectri (NCT02247531), are underway to further investigate its efficacy[22].

Zimura (ARC 1905; Ophthotech Corp), an aptamer that targets C5 and acts against it, is presently in the phase 2/3 testing stage. The trials aim to investigate the impact of monthly injections of Zimura directly into the eye compared to a stimulated treatment on the improvement of visual acuity in individuals with nonfoveal GA. The study, which is anticipated to conclude in December 2018, plans to recruit 300 participants (NCT02686658)[22].

Pegcetacoplan (SYFOVRE), the first drug approved by the US Food and Drug Administration (FDA) for treating GA, works by inhibiting all three pathways of the complement system[51]. Its approval was granted based on promising outcomes observed in the phase 3 OAKS and DERBY trials. In these trials, the injection therapy demonstrated a reduction in lesion growth compared to a placebo treatment and showed increased effectiveness over a period of 24 weeks. The data indicated that the most significant benefit, a reduction of up to 36% in lesion growth, was observed with monthly treatment between 18 and 24 months[52].

Furthermore, the pivotal trial results revealed a favorable safety profile after ~12 000 injections. The most reported adverse reactions in patients receiving Pegcetacoplan included ocular discomfort, neovascular AMD, vitreous floaters, and conjunctival hemorrhage[52].

Avacincaptad pegol (ACP), a pegylated RNA aptamer, exhibits specific binding to complement C5, inhibiting its cleavage process and thereby decelerating the advancement of complement-mediated inflammation and cellular demise observed in GA[53]. The approval process for ACP as a new drug by the FDA is expected to be completed by August. The submission for its New Drug Application (NDA) is supported by data from the GATHER1 and GATHER2 clinical trials, which spanned a period of 12 months[54]. These trials showed that the experimental treatment was effective in reducing the average growth rate of GA by 35% or less[54].

ACP and Pegcetacoplan have shown significant reductions in the growth of GA lesions, whereas NGM621, unfortunately, did not exhibit such positive outcomes[55].

Neuroprotective agents

Neuroprotective substances have the potential to slow down the death of photoreceptor cells in patients with GA, which in turn can delay the progression of the disease. The effectiveness of these substances may depend on future evaluations of neurotrophic factors.

Brimonidine, an alpha-2 adrenergic receptor agonist, has been used for many years to lower intraocular pressure in glaucoma treatment. The effectiveness of Brimonidine was assessed in the phase 2 double-blind BEACON clinical trial, where patients with GA secondary to AMD received an intravitreal implant of Brimonidine. The trial results indicated a reduction of lesions by an average of 10% at month 24 and 12% at month 30 ($P = .017$). Moreover, Brimonidine exhibited a favorable safety profile, with no unexpected adverse events reported[53].

Visual cycle inhibitors

These inhibitors are designed to slow down or block specific enzymes or molecules involved in the visual cycle, ultimately aiming to treat or prevent certain retinal degenerative diseases.

Fenretinide, a synthetic derivative of vitamin A, indirectly targets the visual cycle in the eye by reducing retinol concentrations, thus inhibiting the visual cycle[56]. However, a phase 2 double-blind randomized placebo-controlled trial involving 246 patients compared two dosing regimens of oral fenretinide (RT-101, Sirion Therapeutics Inc) (100 mg daily, 300 mg daily) with a placebo. The trial results showed no statistically significant treatment effect on GA lesion growth at 24 months, although there was a trend toward slowing GA lesion growth[56].

Emixustat is a compound that targets specific enzymes involved in the visual cycle to regulate the production of visual chromophores and prevent the accumulation of harmful bis-retinoids[57]. Its primary target is the RPE-specific 65kDa protein (RPE65). As a result, emixustat indirectly reduces the activity of rod photoreceptors by decreasing the availability of rhodopsin[58]. A phase 2 study involving 72 participants investigated the effects of oral emixustat (ACU-4429) compared to a placebo. The study found a dose-dependent reversible impact on rod function, indicating the need for further research to understand its potential in treating GA[58]. Phase 2/3 studies have been conducted, but no published results are currently available[59].

Ocular gene therapy

One of the top contenders is GT005, a gene therapy based on AAV2 that aims to restore the balance of the complement system in patients. By increasing protein production, this therapy seeks to reduce inflammation in individuals.

In the FOCUS trial, which included patients with GA, three different doses of GT005 were evaluated in the phase 1/2 study. Two of the doses demonstrated a favorable safety profile, although some mild adverse events were observed in the eyes of the study participants. Ongoing trials, namely EXPLORE and HORIZON, are currently investigating the potential of this one-time subretinal injection gene therapy[60]. A different agent, known as AAVCAGsCD59, was developed to enhance the presence of CD59, a protein found on the surface of cells that inhibits the formation of MAC, thereby reducing the extent of disease-related damage and atrophy. Its Phase 1, dose-escalating HMR-1001 trial randomized 17 patients into three different arms of varying IVT dosage. The researchers observed a lower rate of GA progression in the highest-dose arm. Importantly, the treatment was well tolerated in all 3 groups[61].

Future prospect

This study sheds light on potential avenues for future research in the field of GA and AMD. Firstly, continued exploration of the complement cascade and its dysregulation in AMD is crucial. Deeper investigations into the underlying genetic, molecular, and immunological factors influencing disease onset and progression can guide the development of more targeted therapies. Future studies should prioritize long-term safety and efficacy assessments of emerging treatments like pegcetacoplan (SYFOVRE) to establish their sustained benefits. Moreover, comparative studies evaluating the effectiveness of combination therapies and personalized treatment approaches may provide valuable insights into optimizing treatment outcomes for individual patients. Furthermore, research focusing on the enhancement of early diagnostic methods and predictive markers for GA progression is essential to facilitate timely intervention and minimize irreversible vision loss. Lastly, exploring novel interventions, such as ocular gene therapy and neuroprotective agents, holds promise for altering disease trajectories and preserving visual function, necessitating further rigorous investigation to translate these potentials into clinical benefits.

Limitations

While this study aimed to provide a comprehensive overview of GA in AMD and discuss the recent breakthrough drug, pegcetacoplan (SYFOVRE), several limitations should be acknowledged. Firstly, the available literature and data were limited to publications up to the date of our last search, and new research or advancements beyond this period may not be incorporated. Secondly, despite efforts to include a diverse range of sources, potential publication bias cannot be entirely ruled out. Additionally, the focus on English language publications may introduce language bias. Moreover, the complexity of AMD and the variability in disease progression and treatment response among individuals pose inherent challenges in drawing definitive conclusions. Lastly, while the review synthesized available evidence, it does not replace the need for primary research and clinical trials, and further investigation is imperative to corroborate findings and advance the understanding and management of GA in AMD.

Conclusion

In conclusion, AMD is a prevalent and debilitating eye disease that poses a significant global health challenge, particularly in aging populations. The disease can manifest in two distinct forms: GA and neovascular AMD (nAMD), often coexisting and both leading to severe vision impairment. AMD's pathophysiology is multifaceted, involving oxidative stress, inflammation, lipid metabolism, and immune responses, with a prominent role in the complement cascade in its progression.

SYFOVRE represents a significant advancement in the treatment of GA, providing the first approved intravitreal injection specifically targeting this form of advanced dry AMD. It has revealed new possibilities for the management of GA and brings hope to patients with this debilitating condition. While it offers promising clinical outcomes, it is important to be aware of potential side effects and ongoing safety monitoring and research related to SYFOVRE. This includes monitoring real-world data and postmarketing surveillance studies to further evaluate the long-term benefits and risks of SYFOVRE in larger patient populations.

Ethics approval statement

Ethics approval was not required for this review.

Patient consent

Informed consent was not required for this review.

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None.

Author contribution

A.N., J.I., and I.A.M.: were involved in the study concept, the collection of the data, drafting, literature review, data validation, supervision, and editing of the manuscript; M.T., F.S., N.R., A.H., A.K.N., and E.K.A.: were responsible for the literature review and revising the manuscript for important intellectual content.

Conflicts of interest disclosures

There are no conflicts of interest.

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