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Avacincaptad pegol: New therapy for geographic atrophy in age-related macular degeneration

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Abstract

Geographic atrophy (GA) is still an important global health concern, especially for patients over 50 years, as it represents a late stage of dry age-related macular degeneration (AMD) and accounts for a large portion of permanent central vision loss. The pathogenesis of GA is complex and multifactorial, including oxidative stress, chronic inflammation, abnormalities in the vitamin A visual cycle and progressive dysfunction of the retinal pigment epithelium (RPE). The chronic activation of the complement system, particularly the alternative pathway, is fundamental in the degeneration of RPE cells and

photoreceptors. In addition, genetic factors, in particular genetic variants of complement regulatory genes, further increase the risk of disease and can accelerate its progression.

Until recently, treatment options were limited to antioxidant supplements based on Age-Related Eye Disease Study (AREDS and AREDS2) recommendations, which demonstrated average effectiveness in slowing disease progression. However, the emergence of medications targeting the complement system marked a turning point. Pegcetacoplan, the C3 inhibitor, and avacincaptad pegol, the C5 inhibitor, have been shown to slow down GA the progression. Although these drugs do not improve visual acuity, they change the natural course of the disease. The difference in the target of the complement cascade may influence the safety of treatment. However, there is still a need for further research to optimize treatment and individualize therapy for patients with GA.

Key words: geographic atrophy, age-related macular degeneration, avacincaptad pegol, izervay

1. Introduction

GA is the advanced stage of AMD. It is one of the main reasons of permanent loss of central vision in patients over 50 years, especially in industrialized countries [1]. The incidence of GA increases with patients' age and is now estimated to affect over 5 million people worldwide, mainly in the European population [2].

The term "geographic" describes well-demarcated atrophic lesions in the retina, which appear as visible, irregular forms that increase gradually over time. The disease process develops in the external layers of the retina, leading to a decrease in the density of choroidal vessels and causing gradual loss of cells in the RPE and photoreceptor layer [1]. First lesions often occur outside the foveal center and typically expand in its direction typically for about 1,5-2,4 years [3]. However, in some patients the disturbance in central vision may be present from the beginning of the disease.

In the early stage of the disease symptoms are often subtle. The first symptoms include deterioration of vision in low light conditions and low contrast. Patients start to notice that they need more light to read or perform precise activities [4]. As the GA progresses, scotomas appear in the central field of vision, making it difficult to recognize faces, read or drive [5]. Despite deterioration of functioning in everyday activities, visual acuity checked using the Snellen chart may remain correct for a long time, if the fovea is not yet occupied [6].

As the atrophic lesion reaches the foveal area, there is a significant decline in central vision and a noticeable limitation in patients' independence [7]. GA affects not only the visual performance, but also patients' quality of life. Due to the aging of the population, the number of patients with GA will probably increase [8]. Despite the increasing burden of the disease, effective therapeutic options have remained limited for a long time, underscoring the need for new treatment strategies. Recent advances in therapies that target parts of the complement system, such as complement C3 and C5 inhibitors, have

opened up new paths for modifying GA progression. Therefore, the aim of this review is to summarize the current knowledge on the pathophysiology of GA and to discuss new therapies that target parts of the complement system, with a particular focus on avacincaptad pegol as a new treatment option.

2. Materials and methods

2.1 Search strategy

In this review we included following keywords Boolean operators (AND/OR): “geographic atrophy”, “age-related macular degeneration”, “avacincaptad pegol” and “izervay”. In order to find suitable studies we used free text and/or MeSH keywords. Apart from searching only in electronic database, we searched through the reference lists in the suitable articles to find more studies. The last search was conducted on 21st Feb 2026. Studies, which were published before 1990, were not added to our review.

2.2 Inclusion criteria

Studies meeting all of the following criteria were included in the analysis: clinical trials, observational studies, randomized controlled trials (RCTs), experimental studies, meta-analyses, systematic reviews and narrative reviews evaluating geographic atrophy (GA) secondary to age-related macular degeneration (AMD); studies investigating the pathophysiology of GA, the role of the complement system, or therapeutic strategies targeting complement components, particularly avacincaptad pegol and pegcetacoplan; studies reporting outcomes related to GA progression, lesion growth, visual function, or treatment safety; and studies involving human subjects with GA secondary to AMD or experimental studies investigating molecular and cellular mechanisms relevant to the disease. We excluded: studies that did meet the inclusion criteria and did not report data on the outcomes.

Regulatory documents and prescribing information related to approved therapies were also considered when relevant to pharmacological characteristics and safety profiles. Case reports and conference abstracts were used only for background information and were not included as evidence in the article. Only articles published in English and after 1990 were included in the review.

2.3 Study selection

Articles were selected based on title, abstract and keywords, then after reading full text of studies, probably matching the criteria. Ten reviewers conducted the independent study selection via PubMed Central, Google Scholar and ResearchGate to find articles that meet the inclusion criteria mentioned above in the text.

3. Pathomechanism of geographic atrophy

Development of GA, the advanced stage of AMD, is the consequence of long-term impact of metabolic, oxidative and environmental factors, which gradually disturb homeostasis

of the RPE [9]. Chronic stress, aging and smoking promote extracellular deposits to increase between RPE and Bruch's membrane [10]. These deposits, called drusen, consist of proteins, lipids, β -amyloid deposits, cellular debris, apolipoproteins, zinc ions and iron. Their presence, especially large and soft ones without distinct borders, is associated with an increased risk of disease progression [11]. Moreover, lipofuscin accumulates with age in the RPE cells, which reflects the impairment of lysosomal capacity and increase of oxidative stress. Photosensitizing characteristics of some lipofuscin components leads to creating reactive oxygen species (ROS), increasing the cellular damage. Simultaneously, activation of inflammatory pathways, induced by genetic and environmental factors, strengthen chronic inflammation that promote RPE atrophy and photoreceptor degeneration [12].

3.1 Vitamin A visual cycle

The key element for proper functioning of the retina is vitamin A visual cycle, responsible for regeneration of 11-cis-retinal. After the absorption of photon, 11-cis-retinal isomerizes to the all-trans form, which leads to phototransduction cascade and generates an electrical signal [13]. Retinoids circulate between photoreceptors and RPE in different chemical forms, and their transport, esterification, accumulation and re-isomerization require precise coordinated enzymatic reactions. Part of the retinaldehyde can react with phosphatidylethanolamine forming adducts, which further convert into dimeric vitamin A products such as N-retinylidene-N-retinylethanolamine (A2E) [14]. These compounds deposit as lipofuscin granules in the RPE, acting cytotoxically and destabilizing the functions of lysosomes. Excessive accumulation of these products disturbs the balance between regeneration and elimination of toxins, which may be the cause of RPE atrophy and AMD [15].

3.2 Genes connected to GA

Susceptibility to late stage of AMD, especially GA, is dependent on the complex integration of numerous genetic variants including inflammatory, lipid and angiogenic pathways as well as mechanisms maintaining homeostasis. Genetic variants, which affect the complementary system such as CFH, CFI, C3, C2/CFB and C9, change the activity of the complementary cascade, affecting both the initiation of the convertase and the formation of the MAC [16]. Variant p.Tyr402His (rs1061170) in CFH gene located on 1q31.3 locus has an important role in impairing the ability of factor H to bind cell surface components and inflammatory proteins, resulting in chronic, local complement activation within the retina. Less common variant p.Arg1210Cys, also in CFH gene, further confirms the key role of the inefficient regulation of the alternative complement pathway in the pathogenesis of AMD [17].

Another relevant region connected with AMD risk are ARMS2 and HTRA1 on 10q26 locus. ARMS2 is involved in the regulation of complement activation, by interacting with properdin and affecting C3b opsonization [18]. HTRA1 encodes a serine protease involved in extracellular matrix remodeling and modulation of signaling pathways such

as TGF- β and Wnt. Overexpression of HTRA1 in RPE is observed, for instance in oxidative stress, and is connected to accumulation of abnormal subretinal deposits, intensification of inflammatory process and disorders of vascular architecture [19]. Moreover HTRA1 interacts with matrix proteins, such as EFEMP1 and fibronectin, which promote the formation of drusen-like structures and secondary complement activation [20].

Apart from genes associated with immune response, an important role is also played by variants affecting lipid metabolism (including APOE, LIPC, CETP), the organization and stability of the extracellular matrix (COL8A1, COL10A1, TIMP3, ADAMTS9), DNA repair processes and cell survival (RAD51B, TNFRSF10A) and the regulation of angiogenesis (VEGFA, TGFBR1) [10]. Moreover, some loci show different significance depending on the clinical type, for instance variant near MMP9 is strongly connected to exudative form than with GA [21].

3.3 The complement pathway

Activation of complement cascade is one of the main mechanisms of the innate immune system involved in the development of GA. Chronic, low-level activation of this cascade within the retina promotes a presence of persistent inflammation and progressive degeneration of RPE and photoreceptors. The complement system includes not less than 30 plasma and membrane proteins, the interaction of which leads to opsonization, chemotaxis of inflammatory cells and elimination of damaged cells [22]. There are three ways in which it can be activated. The classic one is initiated by immune complexes, the lectin one is dependent on polysaccharides recognition and alternative one which is spontaneously triggered by antigens on foreign pathogen [23].

The chronic activation of alternative pathway and local classical pathway, activated by C1q, are involved in the development of GA. With age, deposition of C1q in the retina increases, which may increase tissue damage under conditions of oxidative stress [24]. The creation of the multi-subunit complexes, which are called C3 and C5 convertases, is the main goal of the pathway initiation, as they act on their corresponding proteins [25]. Fission of C3 leads to formation of fragments with strong pro-inflammatory (C3a) and opsonizing (C3b) effects. Products of activation C3 and C5 were found within drusen and subretinal space in patients with AMD, which confirms local complement activity [24]. C3a and C5a, acting through their receptor in the microglia and macrophages, support recruitment inflammatory cells into the subretinal space and disturbances of lysosomal homeostasis in the RPE [26].

Factor B, crucial for alternative pathway, after binding with C3b and proteolysis by factor D forms C3 convertase (C3bBb), which is responsible for further amplification of the reaction. Patients with AMD are prone to have elevated levels of factor B activation fragments in the vitreous body, Bruch's membrane and choroid [27]. Activation of C5 convertase by the C3b influences C5 to create C5a and C5b, which after activation of next complement components initiate formation of membrane attack complex (MAC, C5b-9) [28]. Overaccumulation of MAC in the RPE may result in damage in the membrane and

cell lysis. In physiological conditions this process is inhibited by regulatory proteins, such as complement factor H (CFH), complement factor I (CFI) and CD59, which limit the formation of convertase and polymerization of C9 [28].

Furthermore, RPE dysfunction and damage to the blood-retina barrier are also important elements of GA pathophysiology, as it allows the complement components to penetrate from the systemic circulation into the subretinal space, making it vulnerable to MAC [29]. During animal research on mice it has been emphasized that both excessive activation and complete absence of selected components or receptors, such as C3, C3aR and C5aR, of regulation of this cascade, resulting in photoreceptor loss, Bruch's membrane thickening and increased inflammation. This shows, that complement plays an important role in maintaining tissue homeostasis [30, 31].

3.4 Oxidative stress

One of the most documented and easily modified risk factors of AMD is smoking, which is estimated to be responsible for a great portion of cases in the older population. Cigarette smoke consists many compounds with strong pro-oxidant potential, including hydroquinone (HQ), which increase the formation of ROS and oxidative damage to retinal cells [32]. However, oxidative stress in the retina is a multifactorial phenomenon, as it is caused not only by smoking, but also aging and chronic exposure to light [33]. The action of these factors promotes damage to mitochondrial DNA (mtDNA), oxidation of proteins and lipids and damage in the structural integrity of mitochondria, which leads to their dysfunction [34].

Additionally, photoreceptors rely mainly on glycolysis for their metabolism and produce significant amounts of lactate, which is used by the RPE as a substrate for oxidative phosphorylation [35]. During chronic, oxidative stress RPE cells intensify glycolysis, what disrupts their supporting function and secondarily impairs photoreceptor homeostasis. These changes are associated with abnormal formation of proteins important for maintaining structure and function of mitochondria, such as translocase of the outer mitochondrial membrane 20 (TOMM20) or subunits of the respiratory chain, which further deepens the energy deficit in the retina [36].

Development of pathogenesis of AMD is also affected by retinoic acid receptor-related orphan receptor alpha (ROR α), which participates in the regulation of inflammatory pathways and lipid and lipoprotein metabolism [37]. It inhibits pathway of NF- κ B, which limits the expression of pro-inflammatory mediators triggered by TNF- α , such as IL-6, IL-8 or COX-2 [38]. Furthermore, certain variants of the ROR α gene are connected with an increased risk of AMD [39]. Moreover, ROR α can also modulate pathological neovascularization process within the RPE complex/choroid, so it may promote progression to the exudative form of AMD [40].

4. Treatment of GA

4.1 Supplementation

Supplementation in GA and generally in a “dry” form of AMD is limited and unclear. Most of the evidence is from large clinical trials such as Age-Related Eye Disease Study and its continuation AREDS2, which analyzed the effect of vitamin supplementation in the progression of neovascular AMD and GA. Systematic reviews showed that formula with antioxidant vitamins, such as vitamin C, E and beta-carotene, zinc can slightly slow down the progression of the disease and reduce the risk of progression to advanced stages of AMD, including GA. The effect is especially noticeable in patients with more advanced AMD. Adding to the formula lutein and zeaxanthin in AREDS2 can slightly reduce risk of progression to the GA vs placebo, but the quality of the evidence is low and the benefits are not clear. During trials supplements were generally well-tolerated, but most of the studies were too small to reliably assess rare side effects. Some ingredients, such as beta-carotene, may be associated with risks for specific groups, for instance increase risk of lung cancer in smokers [41].

4.2 Complement inhibitors

4.2.1 Pegcetacoplan

Pegcetacoplan is the complement inhibitor affecting the C3 protein, which is the central point of all three pathways of complement cascade activation [42]. By acting on C3, pegcetacoplan blocks the formation of such inflammatory mediators as C3a, C3b, C5a, and the membrane attack complex (MAC). This mechanism allows it to reduce inflammation and retinal tissue damage. Because C3 is the convergence point of the classical, lectin, and alternative pathways, inhibition at this level results in inhibition of complement activation [42]. Thus, it plays an important role in the pathogenesis of GA. Intravitreal medication under the name Syfovre was approved by the Food and Drug Administration (FDA) in February 2023 as one of the first therapies dedicated for GA treatment. The recommended dosing regimen includes monthly or bimonthly intravitreal injections, which allows for long-term inhibition of complement activity in the retinal microenvironment [43]. In phase II FILLY trial in 2020 and then in two phase III OAKS and DERBY clinical trials, the rate of atrophic lesion enlargement has slowed down, indicating the efficacy of pegcetacoplan. In the first one, the GA growth was reduced by 29% if drug was taken once a month or 20% if it was administered once every two months. Results from the other two trials after 18 month, during which the drug was administered analogously to the study described above, GA growth was reduced by 23% and 18% [44-45]. Moreover, there may be a protective effect of the pegcetacoplan on the retina nearby the atrophy area. Some analyses also show that treatment may reduce the formation of new atrophic lesions outside existing areas, resulting in a possible protective effect on adjacent retinal tissue [46]. The treatment is associated with some side effects, including eye discomfort, which is the most common, and vitreous floaters. In some patients there has been reported an increased incidence of conversion to neovascular

AMD, which requires a careful ophthalmological monitoring and, if necessary, the initiation of anti-VEGF therapy. Serious complications typical of intravitreal injection, such as increase in intraocular pressure or retinal detachments, are less common [47].

4.2.2 Lampalizumab

Lampalizumab is one of the first treatment targeting the complement system, which was studied in the treatment of GA in AMD. It is a humanized monoclonal antibody targeted against factor D, which is one of the factors in the activation of the alternative pathway of the complement system. Inhibition of this factor leads to inhibition of creating the C3-convertase complex in the alternative pathway of complement activation. As a result it should reduce the chronic inflammatory activation observed in the retina of patients with AMD [48].

In the phase II MAHALO study [48] it was observed that in patients treated with lampalizumab the progression of geographic atrophy was slower, especially in the subgroup of patients with specific genetic variants related to the regulation of the complement system, such as mutation in CFI gene. These results led to the initiation of two large phase III clinical trials – CHROMA and SPECTRI [49].

However in both phase III clinical trials the effect of lampalizumab on the rate of growth of GA lesions compared to placebo had not statistically significant difference. As a result to the lack of effectiveness further development of this drug has been completed. Despite the therapeutic failure, studies on lampalizumab have played an important role in development of knowledge about the pathogenesis of AMD and have confirmed the importance of the complement system as a potential therapeutic target in GA [48,49].

4.3 Emerging therapies

4.3.1 Photobiomodulation

Photobiomodulation (PBM) is the therapeutic strategy in AMD, which goal is to adjust the mitochondrial function of retinal cells by using the low-intensity light, especially in the red and near infrared wavelength range. Described exposure to such light leads to absorption of energy through cytochrome oxidase in mitochondria, which increases the production of ATP, supports cellular functions and reduces oxidative stress. These processes are the basis of the potential therapeutic effects of PBM in GA [50]. The clinical trial called **LIGHTSITE** I and III used multi-length light (590, 660 and 850 nm) and observed improvement in anatomical and functional parameters and a reduction in the risk of progression to GA vs to placebo [51]. There are no clear clinical effects in slowing the progression of GA, although small visual acuity or drusen volume occasionally occur. Moreover, the quality of the data is hampered by small group sizes and potential study bias. Therefore, there is still need for larger, well-designed studies to confirm the real effectiveness of PBM as a therapy in GA [50].

4.3.2 Gene therapy

Overactivation of the complement system is one of the main causes of GA, that is why gene therapy focuses mainly on the modulation of this system. One of the investigated approaches is increasing the expression of proteins inhibiting formation of membrane attacking complex (MAC) [52]. CD59, a protein anchored in the cell membrane by glycosylphosphatidylinositol (GPI), is blocking C9 from building into C5b-8 complex and therefore limits cytotoxic effect of MAC. HMR59 (AAVCAGsCD59), developed by Hemera Biosciences, uses administered adeno-associated virus 2 (AAV2) administered intravitreally to provide CD59 in soluble form. In clinical trial phase I HMR-1001 progression of GA was reduced by 23%, although 27% of patients experienced mild vitritis and uveitis, which needed anti-inflammatory therapy for 6-8 weeks [53].

Alternative strategy is increasing complement factor I (CFI), which inhibits activation of C3. GT005 therapy uses recombinant non-replicating AAV vector, which encodes human CFI. It was developed by Gyroscope Therapeutics to be administered subretinally. In the trial phase I/II FOCUS level of CFI increased up to 122% and a decrease of about 46% in the concentration of key C3 degradation proteins linked to complement system activation vs baseline values. Next trials, such as EXPLORE and HORIZON, ended prematurely due to failure to meet efficacy endpoints [53].

4.3.3 Stem cell therapy

Stem cell therapy is one of the newest and most innovative directions of research on the treatment of GA. Its' main goal is to replace the damaged cells of the RPE, which degeneration is one of the main causes of disease progression. This approach uses various stem cell sources, such as embryonic stem cells and induced pluripotent stem cells (iPSCs), which can differentiate into RPE cells. Once the appropriate cells are collected, they are transplanted into the subretinal space, where they have the potential to integrate with the existing retinal structure and support photoreceptor function. Preclinical studies have shown that transplanted RPE cells can survive in the retinal environment and partially restore the protective functions of metabolism and photoreceptors. However stem cell therapy is still in the early stage of development and requires further research on safety, long-term durability of the therapeutic effect and the potential risk of complications, such as immune response or uncontrolled cell proliferation [54].

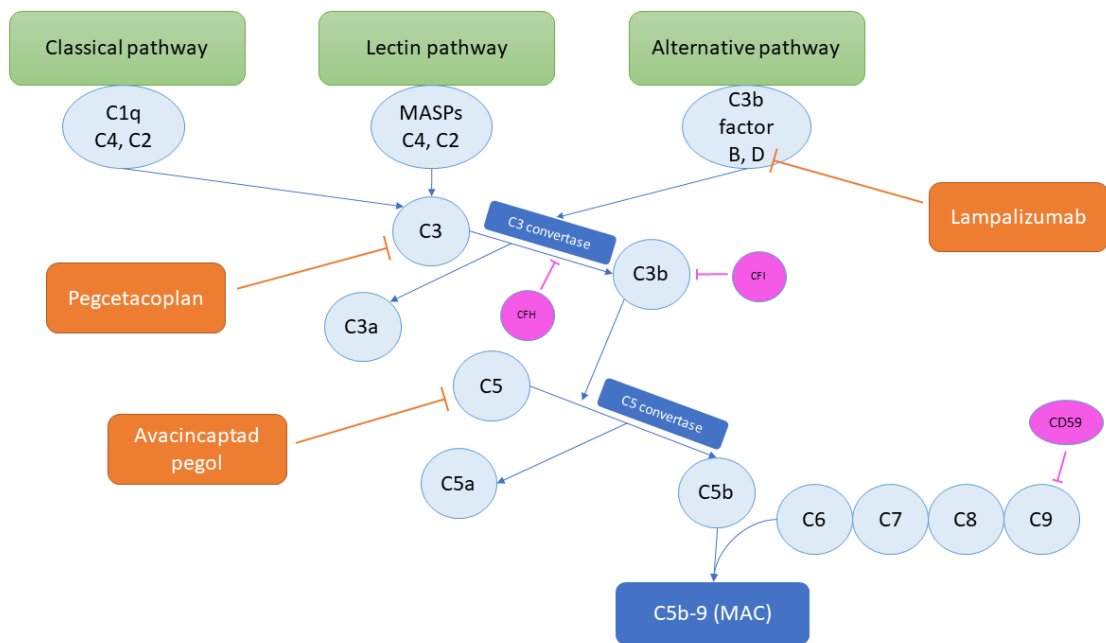


Figure 1. Complement activation pathways and mechanism of action of avacincaptad pegol, pegcetacoplan and lampalizumab.

5. Avacincaptad pegol

5.1 Characteristics of Avacincaptad pegol

Avacincaptad pegol, registered in USA under the name Izervay, is a pegylated RNA aptamer that is a selective inhibitor of the C5 component of the complement system. It was developed for the treatment of GA secondary to AMD. This medication is administered in the form of intravitreal injections and was approved based on the results of phase 2/3 clinical trials (GATHER1 and GATHER2), which showed its effectiveness in slowing down the progression of retinal atrophy [55].

Avacincaptad pegol belongs to a class of biological drugs that target elements of the complement cascade. Due to the fact, that this medicine is structurally a pegylated RNA aptamer, its stability in the intraocular environment is increased and the half-life of local action is prolonged [56].

RNA aptamers are short, single-stranded nucleic acid molecules capable of binding specific target proteins with high affinity and specificity. In the case of avacincaptad pegol, pegylation improves pharmacokinetic stability and prolongs the residence time of the drug in the vitreous cavity, allowing for sustained complement inhibition after intravitreal administration [56].

5.2 Pharmacokinetics and Clinical Efficacy

The mechanism of action is based on selective binding C5, which unables its proteolytic cleavage into C5a and C5b and simultaneously inhibits formation of MAC. This allows for the inhibition of the final stage of complement activation while preserving the earlier

elements of the cascade. Moreover, such action may reduce systemic risk of immunosuppression in comparison to inhibitors targeting C3 [56].

By preventing the production of C5a, a strong proinflammatory mediator, and the formation of the MAC, avacincaptad pegol reduces complement-induced inflammatory damage to the retina. This mechanism is particularly important in GA, where chronic complement activation results in the progressive degeneration of RPE cells and photoreceptors [56].

The complement system makes a significant contribution to the development of AMD, especially the atrophic form, where chronic activation of the alternative pathway leads to deposition of degradation products in Bruch's membrane and causes chronic inflammation in the macula. The clinical trial GATHER1 demonstrated that monthly administration of avacincaptad pegol significantly reduces the growth rate of GA versus placebo. Furthermore, after 12 months reduction in GA progression of about 27-30% was observed, depending on the dose [55].

The GATHER1 study was a randomized, double-blind, placebo-controlled clinical trial evaluating the efficacy and safety of intravitreal avacincaptad pegol in patients with GA secondary to AMD. The study demonstrated a statistically significant reduction in the rate of GA lesion enlargement compared with the control group. This confirms the therapeutic potential of selective complement inhibition in this disease [55].

Although there is no significant improvement in visual acuity, the blockage of C5 modifies the natural history of GA. The long-term 18-month analysis of the GATHER1 study confirmed the persistence of the therapeutic effect with an acceptable safety profile [57]. In another phase 3 trial, named GATHER2, also showed a reduction in the rate of growth of retinal atrophy lesions in patients treated with avacincaptad pegol compared with placebo [58].

Moreover, results from the phase 3 GATHER2 study further confirmed the efficacy of avacincaptad pegol, which shows a significant reduction in lesion growth in GA after 12 months of treatment. These findings provide additional clinical evidence supporting the efficacy of complement C5 inhibition as a therapeutic strategy, which can modify the course of the disease [58].

Due to intravitreal administration avacincaptad pegol shows minimal systemic exposure. Moreover, plasma concentrations are low or undetectable, which limit the potential for systemic effects related to complement inhibition [56]. Pegylation of the molecule prolongs its stability in the vitreous body and enables monthly administration. This medicine is not metabolized by liver enzymes, but as an aptamer undergoes gradual nuclease degradation into smaller oligonucleotide fragments [59].

5.3 Adverse effects

Avacincaptad pegol has been observed to be a rather well-tolerated drug. Side effects are mainly connected to intravitreal injection procedure, such as endophthalmitis, increased

intraocular pressure, uveitis or retinal detachment. Other commonly reported adverse events include conjunctival bleeding, vitreous floaters, and transient ocular discomfort following injection. An increased incidence of AMD development was also observed during clinical trials, which is potentially related to disturbance of balance between inflammatory and angiogenic factors after C5 inhibition. In particular, some patients progress to neovascular AMD during treatment, which may require additional treatment with anti-VEGF drugs. This risk requires patients to be monitored and, in the event of complications, administering anti-VEGF therapy [55].

5.4 Interactions between avacincaptad pegol and other medications

Interactions between other medications, which are clinically significant are unlikely, due to minimal systemic exposure. However, patients receiving systemic complement inhibitors should be careful due to the possibility of additive immunosuppressive effects [56].

Currently, an important element of GA therapy is the comparison of avacincaptad pegol with pegcetacoplan. Syfovre, as mentioned above, acts higher in the complement cascade than Izervay, blocking the central component C3 and in the consequence inhibiting formation of C3a and activation of C5 [60]. Difference between inhibiting C3 and C5 has important practical implications. Inhibition of C3 may more effectively reducing chronic inflammatory activation, but simultaneously is associated with a greater risk of disturbance in physiological opsonization and antibacterial immunity. In contrast, selective inhibition of C5, as in the case of avacincaptad pegol, allows to keep functions of C3b in opsonization and removal of immune complexes, potentially reducing the risk of systemic infections. Meta-analysis comparing complement inhibitors in GA demonstrated that both C3 and C5 inhibitors effectively reduce the rate of atrophy progression, with different safety profiles [61].

Studies with pegcetacoplan showed reduction in GA progression of about 16-22% depending on dosing schedule [60], while in the GATHER studies avacincaptad pegol the reduction effect reached 27-30% [55]. However, there is no study with direct comparison between these two medications conducted within head-to-head study, therefore methodological differences may influence the interpretation of efficacy. The choice of the therapy depend on individual patient needs, such as the rate of GA progression, the risk of developing neovascularization and concomitant diseases.

5.5 Administration and dosing

Avacincaptad pegol is administered as an intravitreal injection under sterile ophthalmic conditions. The recommended dosing regimen involves monthly injections, which allows for continuous inhibition of complement activation in the retinal environment. Intravitreal administration allows for direct delivery of the drug to the site of pathology, maintaining high local concentrations in the vitreous and retina and minimizing systemic exposure.

As with other intravitreal therapies, there should be a careful patient selection and regular ophthalmological monitoring to detect potential complications and evaluate treatment response during long-term therapy [55].

Drug	Complement target	Key clinical trials	GA reduction	Approval status
Pegcetacoplan	C3	FILLY (phase II), OAKS and DERBY (phase III)	16–23%	FDA 2023
Avacincaptad pegol	C5	GATHER1 (phase II/III), GATHER2 (phase III)	27–30%	FDA 2023
Lampalizumab	Factor D	MAHALO (phase II), CHROMA and SPECTRI (phase III)	None	Failed phase III

Table 1. Comparison of complement inhibitors in geographic atrophy.

6. Discussion

6.1 Clinical implications

The development of complement inhibitors represents a significant advance in the treatment of GA secondary to age-related macular degeneration. Therapies such as avacincaptad pegol offer the first pharmacological option that can slow the progression of retinal atrophy, thereby modifying the natural course of the disease. Although these treatments do not restore lost vision or improve visual acuity, they can delay the progression of atrophic lesions and preserve functional retinal tissue for a longer time. In clinical practice, the decision about starting treatment should be made by the clinician after considering several factors, such as the rate of disease progression, lesion location, patient's comorbidities, and the potential risk of complications related to treatment, such as transformation to wet AMD. Individualized treatment strategies and careful patient monitoring remain important to optimizing the best therapeutic outcomes.

6.2 Clinical decision making

In clinical practice, the decision to start treatment with complement inhibitor therapy in patients with GA requires careful assessment of many factors. The location and size of the atrophic lesion matter, as treatment may be more beneficial in patients with extrafoveal lesions who still have some central vision. The rate of lesion growth observed in previous imaging studies, such as fundus autofluorescence or optical coherence tomography, can also help to identify patients with higher risk of faster disease progression, who would benefit the most from treatment.

Another important factor is the potential risk of complications caused by treatment, such as the possibility of conversion to neovascular AMD, which was reported in clinical trials with complement inhibitors. Therefore, regular ophthalmologic monitoring is essential during therapy, as it allows to detect neovascular changes in the early stages and, if necessary, start anti-VEGF therapy as soon as possible. The decision to start therapy should be made individually and jointly by the physician and the patient, after a discussion of the expected benefits and potential risks.

6.3 Real-world evidence

Although randomized clinical trials such as GATHER1, GATHER2, OAKS, and DERBY have provided strong evidence supporting the efficacy of complement inhibitors in slowing the progression of GA, the availability of clinical trial data remains limited. The populations included in clinical trials are often carefully selected and may not fully represent the broader patient population encountered in clinical practice. Real-world studies will therefore be essential to assess the long-term efficacy and safety of these therapies beyond controlled clinical trials. Such studies can provide valuable information on treatment adherence, the incidence of adverse events, and the impact of treatments on visual function and quality of life over longer follow-up periods.

6.4 Safety and data gaps

Although avacincaptad pegol has demonstrated a beneficial safety profile in clinical trials, there are still some safety concerns about it. Most reported side events are related to the intravitreal injection procedure itself, including endophthalmitis, increased intraocular pressure, and intraocular inflammation. Furthermore, some studies have observed an increased number of cases of progression to wet AMD, suggesting that complement inhibition may create the imbalance between inflammatory and angiogenic pathways in the retina. Despite promising short and medium term safety results, long term safety data are still limited. Moreover, there is still need for more head to head clinical trials comparing avacincaptad pegol with other complement inhibitors, such as pegcetacoplan, which limits the ability to determine the appropriate therapeutic approach.

6.5 Limitations

This review has many limitations that should be considered. First, as a narrative review, it does not follow the rigorous methodology of a systematic review or meta-analysis, which can effect in potential selection bias in the literature included to the article. Second, the available clinical evidence on avacincaptad pegol is still relatively limited and comes primarily from a small number of randomized clinical trials, mainly from the GATHER1 and GATHER2 trials. Furthermore, many of the studies included in the review focused on surrogate anatomical outcomes, such as the rate of growth of geographic atrophic lesions, rather than on functional visual outcomes. Another limitation is the heterogeneity of the available studies, including differences in study design, patient's populations, duration of follow-up, and outcome measures, which may make it difficult to directly compare therapeutic strategies that target different components of the complement cascade.

6.6 Future research directions

Although there is a significant progress in the development of therapies targeted at parts of the complement system, many important cases, such as the optimal treatment of geographic atrophy, are not resolved yet. Future research should focus on the long-term clinical outcomes associated with complement inhibition, especially with regard to the sustained efficacy and safety of avacincaptad pegol over longer treatment periods. Most of the currently available data come from clinical trials with relatively short follow-up, so

longer, real-world studies are needed to determine whether the observed slowing of GA progression translates into significant long term preservation of visual function and quality of life.

Another important line of research is the direct comparison of different complement inhibitors, such as avacincaptad pegol and pegcetacoplan. Currently, there are no randomized, head-to-head clinical trials, making it difficult to determine the relative benefits of inhibiting different components of the complement cascade. Such studies could provide valuable information on the optimal therapeutic target within the complement pathway and help clinicians select the most appropriate treatment strategy for individual patients.

Future studies should also explore the potential role of biomarkers, such as genetic variants related to complement regulations, as predictors of treatment response. A better understanding of factors, which are specific for the patient that influence disease progression and therapeutic effectiveness can facilitate the development of personalized treatments. Furthermore, advances in retinal imaging techniques, such as high-resolution optical coherence tomography and artificial intelligence, which is based on image analysis, can enable earlier detection of disease progression and more accurate monitoring of treatment outcomes.

The development of combination therapies that target multiple pathogenic mechanisms involved in GA, such as complement activation, oxidative stress, mitochondrial dysfunction, and inflammatory pathways, represents another promising area of research. Integrating pharmacological therapies with new strategies, such as gene therapy or photobiomodulation may further improve the prognosis of patients with this progressive and currently incurable retinal disease.

7. Conclusions

GA is an important clinical challenge due to progressive and irreversible cause of retinal damage. Complex pathogenesis of the disease includes cooperation of genetic, inflammatory and oxidative factors, what complicates to create an effective therapy. The main reason of GA development is chronic activation of complement system, which is currently the target of new therapeutic strategies. The use of C3 and C5 inhibitory is the a breakthrough in treatment of this form of AMD. This therapies decelerate the rate of growth of atrophy lesions. Although they modify the natural course of the disease, they do not improve visual acuity. Differences in mechanism of action of C3 and C5 inhibitors result in different safety profiles and requirement for individualized treatment selection. Furthermore, other methods, such as photobiomodulation and gene therapies, are being developed and may complement current treatment options in the future. Further progress in understanding the pathmechanisms of GA is significant for developing more effective and personalized therapeutic strategies.

Abbreviations

A2E	-				N-retinylidene-N-retinylethanolamine
AAV2	-	Administered		adeno-associated	virus 2
AMD					Age-related macular degeneration
AREDS/AREDS 2					Age-Related Eye Disease Study/ Age-Related Eye Disease Study 2
CFH	-		Complement		factor H
CFI	-		Complement		factor I
FDA	-	Food	and	Drug	Administration
GA	-			Geographic	atrophy
GPI		-			Glycosylphosphatidylinositol
HQ					Hydroquinone
iPSCs	-	induced		pluripotent	stem cells
MAC	-		Membrane		attacking complex
mtDNA		-		Mitochondrial	DNA
PBM			-		Photobiomodulation
ROR α	-	Retinoic acid	receptor-related	orphan	receptor alpha
ROS	-		Reactive		oxygen species
RPE	-		Retinal		pigment epithelial
TOMM20					Translocase of the outer mitochondrial membrane 20

Disclosure

Author Contributions

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Validation, J.K., D.S., K.K.;
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