New approaches and potential treatments for dry age-related macular degeneration

Novas abordagens e tratamentos potenciais da forma seca da degeneração macular relacionada à idade

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ABSTRACT

Emerging treatments for dry age-related macular degeneration (AMD) and geographic atrophy focus on two strategies that target components involved in physiopathological pathways: prevention of photoreceptors and retinal pigment epithelium loss (neuroprotection induction, oxidative damage prevention, and visual cycle modification) and suppression of inflammation. Neuroprotective drugs, such as ciliary neurotrophic factor, brimonidine tartrate, tandospirone, and anti-amyloid β antibodies, aim to prevent apoptosis of retinal cells. Oxidative stress and depletion of essential micronutrients are targeted by the Age-Related Eye Disease Study (AREDS) formulation. Visual cycle modulators reduce the activity of the photoreceptors and retinal accumulation of toxic fluorophores and lipofuscin. Eyes with dry age-related macular degeneration present chronic inflammation and potential treatments include corticosteroid and complement inhibition. We review the current concepts and rationale of dry age-related macular degeneration treatment that will most likely include a combination of drugs targeting different pathways involved in the development and progression of age-related macular degeneration.

Keywords: Macular degeneration/drug therapy; Retina; Retinal pigment epithelium; Inflammation; Complement activation

RESUMO

Os novos tratamentos para a forma seca da degeneração macular relacionada à idade (DMRI) e da atrofia geográfica têm sido baseados em duas estratégias que abordam componentes envolvidos nos mecanismos fisiopatológicos da doença: prevenção da perda de fotorreceptores e células do epitélio pigmentado da retina (indução de neuroproteção, diminuição do dano oxidativo e modificação do ciclo visual) e supressão da inflamação. As drogas neuroprotetoras visam evitar a apoptose das células retinianas, como o fator neurotrófico ciliar, o tartarato de brimonidina, a tandosporina e anticorpos antiamiloide β. A redução do dano oxidativo e a complementação de micronutrientes essenciais são os objetivos da fórmula AREDS. Os modificadores do ciclo visual reduzem a atividade dos fotorreceptores e o acúmulo de fluoróforos tóxicos e lipofuscina na retina. Olhos com a forma seca da degeneração macular relacionada à idade apresentam inflamação crônica e os novos tratamentos incluem corticosteroides e inibidores do sistema complemento. Neste artigo, revisamos o estágio atual do tratamento da forma seca da degeneração macular relacionada à idade que provavelmente será feito através da combinação de drogas que agem em diferentes componentes envolvidos no aparecimento e na progressão da degeneração macular relacionada à idade.

Descritores: *Degeneração macular/quimioterapia; Retina; Epitélio pigmentado da retina; Inflamação; Ativação do complemento*

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people aged over 50 and its prevalence increases exponentially after the age of 70[1,2]. Although neovascular AMD is the most damaging form of the disease, dry AMD accounts for approximately 90% of all cases. Geographic atrophy (GA), the advanced non-neovascular form of AMD, accounts for 35% of all cases of late-stage AMD and 20% of legal blindness attributable to AMD[3]. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents has revolutionized the treatment and prognosis of neovascular AMD. However, dry AMD treatment still remains a challenge. Currently, the only approved treatment for dry AMD is the use of Age-Related Eye Disease Study (AREDS)-based vitamin supplements, which does not halt the vision loss but lowers the risk of developing advanced stages of AMD (either geographic atrophy or neovascular AMD) and reduces visual loss in people at risk for the disease. In addition, the AREDS formula does not prevent GA from forming or progressing[4,5].

Over the last years, a significant amount of research has been focusing on the physiopathology of dry AMD and new treatment approaches. However, research has been hampered by some issues, such as the multifactorial nature of dry AMD, its complex physiopathology, the lack of an animal model for dry AMD, and the lack of in vitro systems for testing new drugs.

In this article, we will review dry AMD emerging treatments that have basically focused on two strategies: prevention of photoreceptors and retinal pigment epithelium (RPE) cells loss, and suppression of inflammation. The former can be achieved by neuroprotection induction, oxidative damage prevention, and visual cycle modification (Table 1). Before getting into details on the drugs under research, the physiopathology of dry AMD will be presented.

Dry AMD and geographic atrophy pathogenesis

The processes involved in dry AMD and GA pathogenesis are not completely understood. Current investigations suggest that oxidation and inflammation play important roles in the pathogenesis of the diseases.

Docosahexaenoic acid (DHA) is an omega-3 fatty acid that is a primary structural component of the human retina, comprising 60% of the polyunsaturated fatty acids in the retina. It is the most oxidizable fatty acid in the body and is found in the membrane of the outer segment of the photoreceptors[6]. The human macula has a lifelong exposure to light and very high oxygen consumption. This microenvironment is highly permissive for the oxidative damage of reactive oxygen to DHA. DHA peroxidation generates lipofuscin, a yellow-brown pigment that represents undigested material from the oxidation of DHA. Lipofuscin cannot be degraded by the lysosomes

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Table 1. New drugs in the pipeline for the treatment of dry AMD and GA

Drug and mechanism of action	Route of administration	Manufacturer
Prevention of photoreceptors and retinal pigment epithelim (RPE) loss		
Neuroprotection		
CNTF (NT-501)	Intravitreal implant (ECT)	Neurotech Pharmaceuticals
Brimonidine tartrate	Intravitreal implant	Allergan, Inc.
Tandospirone	Topical	Alcon Laboratories, Inc.
Anti-amyloid β antibody		
Glatiramer acetate	Subcutaneous	Teva Pharmaceuticals
RN6G	Intravenous	Pfizer, Inc.
Oxidative damage prevention		
AREDS formulation		Bausch & Lomb, Inc.
Visual cycle modulators		
Fenretinide	Oral	ReVision Therapeutics
ACU-4429	Oral	Acucela, Inc.
Suppression of inflammation		
Corticosteroid		
Fluocinolone acetonide	Intravitreal implant	Alimera Sciences
Complement system inhibition		
POT-4	Intravitreal injection	Potentia Pharmaceuticals
Eculizumab	Intravenous	Alexion Pharmaceuticals
ARC1905	Intravitreal injection	Ophthotech Corp.
FCFD4514S	Intravitreal injection	Genentech, Inc.

in the retinal pigment epithelium (RPE) and accumulates within it, increasing RPE lysosomal pH. Continuous lipofuscin formation along with pH change interfere with proper lysosomal enzymes function and impair their phagosomal activity[7]. With time, RPE becomes overwhelmed with cellular debris and vitamin A metabolites, such as A2-E (a toxic vitamin A dimer). When present in excessive levels, lipofuscin and A2-E damage photoreceptors and choriocapillaris, leading to geographic atrophy[8].

Besides being toxic to the RPE, A2-E has also been shown to activate the complement cascade[9,10]. Complement system is part of the immune system called the innate immune system. It consists of many small proteins in the blood and is a potent mechanism of host defense against pathogens and abnormal cells. Its activation leads to an inflammatory response, therefore it must be tightly regulated.

There are 3 pathways of complement activation (classical, lectin, and alternative pathways) that converge into a final common pathway, when a protein named factor C3 is generated. Ultimately, factor C3 cleavage results in formation of the membrane attack complex, the cytotoxic component of the complement system that causes cell lysis (Figure 1). Factor C3 plays an important role in an amplification loop of complement system activation.

Complement factor H (CFH) is a circulating protein that inhibits directly or indirectly the three complement activation pathways. It downregulates the system and prevents it from getting out of control. In patients with early and late AMD, many CFH polymorphisms have been described[11]. With abnormal CFH, complement system downregulation is defective and excess inflammation may result. Additionally, histological analysis of drusen revealed the presence of complement factors and the terminal membrane attack complex[12]. It is still unknown whether those complement factors are systemically or locally produced in the retina[13]. Regardless of its origin, the retina with dry AMD presents with chronic subclinical local inflammation that may trigger and/or sustain the damaging process[14,15].

Chronic local inflammation has also been found in other degenerative diseases characterized by accumulation of debris that can no longer be eliminated by the usual routes, such as atherosclerosis[16] and Alzheimer disease[17]. Some components, like vitronectin and amyloid β, present in deposits found in those diseases, have also been shown in retinal drusen from eyes with AMD[12,18]. It is postulated that the presence of such debris triggers a local inflammatory response that can activate the immune system[19-22]. The inflammatory cells chronically present in that microenvironment release cytokines that attract more inflammatory cells. These cells extend their processes through the Bruch's membrane and basal lamina, making them thicken and creating a drusen inflammatory core. Over time, these changes may lead to impaired diffusion of waste products from hormones and nutrients to the RPE, including oxygen and vitamin A[7,23].

Treatment approaches for dry AMD and geographic atrophy

Although the complete pathological mechanisms underlying dry AMD have not been completely understood, new pharmacological treatments have emerged over the last years. Different approaches will be presented according to the different strategies and pharmacological targeting of components involved in dry AMD physiopathological pathways.

1. Prevention of photoreceptors and RPE cells loss

One of the focused strategies is the prevention of photoreceptors and RPE cells loss, which include neuroprotection induction, oxidative damage prevention, and visual cycle modification.

1.1 Neuroprotection induction

Neuroprotective drugs aim to preserve macular function by preventing apoptosis of viable RPE cells and photoreceptors. The main drugs under investigation will be described: Ciliary neurotrophic factor (CNTF), brimonidine tartrate, tandospirone, and anti-amyloid β antibodies.

- Ciliary neurotrophic factor (CNTF) is a potent neurotrophic factor that slows down loss of photoreceptors in various animal models of retinal degeneration[24-27], and there are evidences

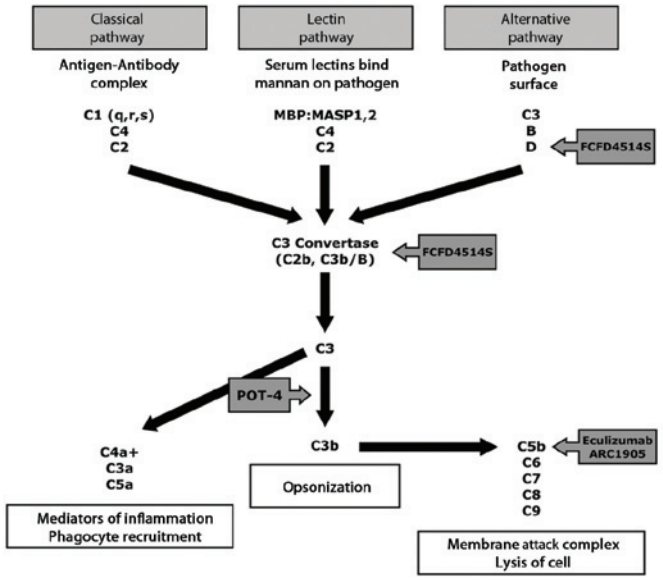

Figure 1. The three pathways of complement system activation (classical, lectin, and alternative pathways). In arrowed boxes are therapeutic agents currently investigated in clinical trials.

of its efficacy in human retinitis pigmentosa[28]. NT-501 (Neurotech Pharmaceuticals, USA) is an intravitreal sustained-release device made of a semipermeable polymer outer membrane which contains an internal yarn scaffold that supports live human cells (encapsulated cell technology, ECT). In this case, the cells are genetically engineered to produce human CNTF. ECT implants are distinct from other drug delivery implants in that they do not primarily store drug but rather produce the therapeutic drug to be delivered in situ. The implant is 6 mm long with 1 mm diameter, is inserted into the vitreous and releases CNTF in two different output rates for a year or longer: 5 and 20 ng/day[26,28,29].

NT-501 was evaluated in a phase 2 clinical trial that enrolled 51 patients with GA secondary to AMD[29]. Patients were randomized to 3 groups (low and high dose of CNTF, or sham injection) and were followed up for 1 year. At 12 months, patients who received the low- and high-dose implants presented a significant increase in retinal thickness that may reflect increased photoreceptors metabolic activity or an increased number of photoreceptors. CNTF appeared to preserve visual acuity and a mean 0.8-letter gain was present in the high-dose group vs a mean 9.7-letter loss in the combined low-dose and sham groups. However, CNTF had no apparent effect on the progression of GA. Interestingly, no visual acuity loss occurred in eyes with 20/63 or better baseline vision when treated with high-dose implants. A phase 3 study is planned.

- Brimonidine tartrate (Allergan Inc., USA) is an alpha-2 adrenergic receptor agonist. These receptors are present in the mammalian retina[30] and brimonidine tartrate has been shown to protect retinal ganglion cells, bipolar cells, and photoreceptors in numerous models of experimental nerve injury, including retina ischemia, ocular hypertension, retinal phototoxicity, and partial optic nerve crush[31-33]. Brimonidine tartrate works as a neuroprotectant activating some pathways inside and outside cells, such as increasing the expression of basic fibroblast growth factor mRNA, a cytokine that delays apoptosis, increases the expression of proteins that regulate mitochondrial membrane permeability and inhibit apoptosis[34], and suppresses the accumulation of glutamate that causes neuronal cell death[35]. Brimonidine tartrate is delivered by a sustained-release biodegradable implant that is injected into the vitreous through a 22-gauge needle with the same applicator system used to deliver dexamethasone (Ozurdex; Allergan Inc., USA).

A 2-year phase 2 clinical trial evaluating the brimonidine implant in patients with GA is under way. Patients were randomized to 3 treatment groups to receive the implant at 200 or 400 µg, or sham treatment (ClinicalTrials.gov number, NCT00658619). A second implant will be injected 6 months after the first one. Results of this study are still pending.

- Tandospirone (Alcon Laboratories Inc., USA) is a selective serotonin 1A agonist that is used as anxiolytic and antidepressant. In an animal model, it has been shown to protect photoreceptors and RPE cells from photo-oxidative stress by decreasing microglia activation/recruitment and complement deposition in the outer retinax[36]. A 1-year phase 2 clinical trial including patients with GA is ongoing and two doses of topical tandospirone are being tested (ClinicalTrials.gov number, NCT00890097).
- Anti-amyloid β antibodies reduce the accumulation of amyloid β, a toxic byproduct which deposit is found in drusen and in patients with GA. Amyloid β is believed to be an important component of local inflammatory reaction that may contribute to the etiology of dry AMD. Two drugs using this strategy are being tested: Glatiramer acetate and RN6G.

Glatiramer acetate (Copaxone; Teva Pharmaceutical, Israel) is an immunomodulatory drug currently used to treat multiple sclerosis. Its mechanism of action is not fully elucidated but there are evidences that it suppresses T-cells, downregulates inflammatory cytokines, reduces amyloid β-induced retinal microglial cytotoxicity, and allows a neuroprotective phenotype of microglia to form[37]. The analysis of the drusen in patients with Alzheimer disease treated with glatiramer acetate showed that the drug reduces drusen area[38]. Specifically in patients with dry AMD, glatiramer acetate shrank or eliminate more drusen than did sham treatment[39].

RN6G (Pfizer Inc., USA) is a humanized monoclonal antibody against amyloid β that binds and sequesters amyloid β in the retinal periphery, reducing the pool of toxic species available in the macula and preventing its accumulation. In a mouse model of AMD, RN6G is administered systemically and has been shown to reduce amyloid β deposits in the retina. In addition, RN6G preserves animals retinal function and maintains normal RPE morphology[40]. Phase 1 clinical trial has been completed and a phase 2 study is planned, in which AMD patients will be treated monthly for 6 months.

1.2 Oxidative damage prevention

AMD is a multifactorial disease caused by genetic predisposition, lifelong exposure to free radicals, exposure to environmental toxins, and low levels of naturally occurring antioxidants. Oxidative stress and depletion of essential micronutrients are important factors for AMD progression. Indeed, the AREDS formula (Bausch & Lomb Pharmaceuticals Inc., USA) is the first effective treatment to slow the progression of the disease for patients at high risk for developing advanced AMD.

AREDS is a multi-center, randomized clinical trial that included more than 3,000 patients over a 5-year period[4]. It was designed to evaluate the effect of high doses of antioxidants and zinc on the progression of AMD. High levels of antioxidants (vitamin C, vitamin E, and beta-carotene) and zinc significantly reduced the risk of advanced AMD and associated vision loss. AREDS showed that people at high risk of developing advanced AMD lowered their risk by about 25% when treated with the micronutrients combination. In the same high-risk group, which included people with intermediate AMD or advanced AMD in one eye but not the other eye, the nutrients reduced the risk of vision loss by about 19%. For patients who had either no AMD or early AMD, the nutrients did not provide an apparent benefit.

AREDS2 is a multicenter, randomized clinical trial designed to assess the effects of oral supplementation of macular xanthophylls

(lutein and zeaxanthin) and/or long-chain omega-3 fatty acids (DHA and EPA - eicosapentaenoic acid) on the progression to advanced AMD. These micronutrients are believed to function as antioxidants, anti-inflammatory, and anti-angiogenic agents. An additional goal of the study is to assess whether forms of the AREDS nutritional supplement with reduced zinc and/or no beta-carotene works as well as the original supplement in reducing the risk of progression to advanced AMD. Enrollment was concluded in 2008 and participants are being followed for approximately 5 years (ClinicalTrials.gov number, NCT00345176).

1.3 Visual cycle modification

Visual cycle modulators are pharmacologic compounds intended to modulate the visual cycle in patients with AMD. Visual cycle modulators essentially "slow down" the activity of the photoreceptors and reduce the metabolic load on these cells. So, these compounds may slow the deterioration by reducing the accumulation of toxic fluorophores (mainly A2-E) and lipofuscin, thereby preventing the loss of photoreceptors and RPE cells. Two drugs are currently being tested: Fenretinide and ACU-4429.

- Fenretinide (ReVision Therapeutics, USA) is a synthetic derivative of vitamin A, which after oral intake, strongly competes with vitamin A for binding to the retinol binding protein (RBP). The complex fenretinide-RBP is excreted in urine due to its relatively small size and decreases the available pool of vitamin A available for uptake at the RPE. Because A2-E biosynthesis relies ultimately on circulating vitamin A, in doing this, fenretinide inhibits the accumulation of A2-E and lipofuscin in cells of the RPE[41]. Fenretinide has been shown to have anti-angiogenic and anti-inflammatory properties[42].

A multicenter, randomized phase 2 clinical trial included 246 patients with GA followed up for 1 year who were randomized to 100 mg, 300 mg oral fenretinide, and placebo. This study showed reduction in lesion growth that correlated with reduction in RBP[43]. In addition, patients in both treatment arms presented reduced incidence of choroidal neovascularization[42].

- ACU-4429 (Acucela, Inc., USA) is a small, non-retinoid molecule that modulates RPE65, an enzyme required to convert trans-retinol to cis-retinol within the RPE. It has been shown to prevent the accumulation of A2-E in the mouse retina, thereby slowing down the visual cycle. ACU-4429 is given orally and acts selectively on the rod photoreceptors, the major source of A2-E in the retina.

Phase 1 clinical trial showed a dose-dependent inhibition of the b wave on electroretinogram. Adverse events, including dyschromatopsia and alteration in dark adaptation, were mild and transient[44]. A phase 2 clinical trial is enrolling patients with dry AMD and GA (ClinicalTrials.gov number, NCT01002950). Patients will receive once-daily dosing over 3 months with 3 different doses of ACU-4429 or placebo.

2. Suppression of inflammation

There is a large amount of evidence that inflammation plays an important role in causing both advanced dry AMD with atrophy and choroidal neovascularization. Inflammatory elements are present in drusen, such as components of the complement system, acute-phase proteins, proteins that modulate the immune response, lipofuscin, and dendritic cells[12,14,45-50]. Therefore, it is likely that if inflammation could be reduced, progression of AMD could be slowed. This hypothesis is being investigated with a number of approaches, including corticosteroid treatment and complement inhibition.

2.1 Corticosteroids

Corticosteroids are a class of chemicals that are naturally produced in the adrenal cortex and analogues of these hormones, which are synthesized in laboratories. Corticosteroids are involved in a wide range of physiologic processes including the regulation of inflammation.

- Fluocinolone acetonide (Alimera Sciences, USA) is a potent corticosteroid that presented a neuroprotective effect in an animal model by dampening retinal neuroinflammation[51,52]. It is postulated that the sustained-release implant, which delivers fluocinolone acetonide directly into the vitreous, may suppress retinal neuroinflammation and slow the rate of retinal degeneration. The implant is inserted into the vitreous via a 25-gauge injector. A phase 2 clinical trial enrolling patients with GA is under way.

2.2 Complement system inhibitors

Several therapeutic agents involved in the complement cascade are under investigation.

- POT-4 (Potentia Pharmaceuticals, USA) is a synthetic peptide that reversibly binds complement factor C3 and inhibits activation of the complement cascade (Figure 1). POT-4 prevents cleavage of C3 into C3a and C3b, which eventually leads to the formation of the membrane attack complex. As C3 is a central component of all complement activation pathways, its inhibition shuts down all downstream complement activation that could otherwise lead to local inflammation, tissue damage, and up-regulation of angiogenic factors. POT-4 is injected directly into the vitreous and forms an intravitreal blob, which slowly releases the drug over time. Results of a phase 1 clinical trial indicate that POT-4 is safe even in high doses (ClinicalTrials.gov number, NCT00473928) and a phase 2 is being planned for the treatment of both dry and wet AMD to further define its efficacy profile.
- Eculizumab (Alexion Pharmaceuticals, USA) is a humanized IgG antibody that selectively inhibits the cleavage of C5 factor into C5a and C5b (Figure 1). Because it is a C5 inhibitor, eculizumab inhibits further downstream on the complement cascade than C3 inhibitors, thereby reducing only terminal complement activity, so the proximal functions of complement system remains intact. A phase 2 study with patients with dry AMD is under way (ClinicalTrials.gov number, NCT00935883).
- ARC1905 (Ophthotech Corp., USA) is an aptamer that is a potent and selective inhibitor of factor C5 of the complement cascade (Figure 1). The rationale is the same than that of eculizumab and a phase 1 study is under way (ClinicalTrials.gov number, NCT 00950638).
- FCFD4514S (Genentech Inc., USA) is a human monoclonal antibody that inhibits complement factor D, a protein involved in the alternative complement pathway (Figure 1). Phase 1 study is under way (ClinicalTrials.gov numbers, NCT 00973011).

CONCLUSION

Currently, the only approved treatment for dry AMD is the use of AREDS formulation. However, this multivitamin complex does not prevent AMD and its positive effects are modest as it only slows down the progression for patients at high risk for advanced AMD. Many advances in the fields of epidemiology, pathogenesis, and genetics have been produced in the last decade. Novel treatment strategies are under investigation for the treatment of dry AMD and GA, such as prevention of photoreceptors and RPE cells loss, and suppression of inflammation. In the near future, it is likely that the treatment of dry AMD will be a combination of different drugs that will target the different pathways involved in the development and progression of AMD.

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