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Review Article

Emerging Pharmacological Targets for Treatment of Dry Age-related Macular Degeneration and Geographical Atrophy

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Abstract

Age-related macular degeneration (AMD) is difficult to treat and causes visual impairment worldwide, especially for dry AMD. The aging phenomenon can affect macular function, manifesting as blurred central vision. There are two types of AMD: dry and wet. By 2040, some variants of AMD are estimated to affect 288 million people globally. Although wet (exudative) AMD accounts for 10% of all AMD cases, it also contributes to 90% of the cases of patients with vision loss. Therapeutic options for wet age-related macular degeneration have expanded during the last few years. The therapeutic strategies mainly rely on anti-vascular endothelial growth factor (anti-VEGF) drugs and photodynamic therapy (PDT), though the treatment approaches for dry AMD are limited to dietary supplementation to delay progression. Moreover, clinical trials with potential candidate molecules for wet AMD exceed those for dry AMD. Although the disease is not rare, there are few therapeutic targets in the pipeline for dry AMD, and these targets may serve as promising pharmacotherapeutic options in the future. The current review sheds light on successes and failures of the existing novel drug molecules and potential targets for treating dry AMD in clinical trials registered at the Clinical Trials.gov registry run by the United States Food and Drug Administration (U.S. FDA) some of which are published in relevant journals.

Introduction

Age-related macular degeneration (AMD) is one of the critical causes of vision loss and visual disability in the elderly population in developed countries.[1,2] Dry AMD contributes to 10% of vision loss cases and is categorized into early, intermediate, and late stages, depending on the presence of hyper or hypopigmentation with drusen within the macula.[3] Late dry AMD, also known as geographical atrophy, and wet AMD, characterized by choroidal neovascularization, are both advanced forms of age-related macular degeneration (AMD). Geographical atrophy or advanced/late-stage of dry AMD has been named due to the appearance of map-like lesions in the macula on performing the ocular examination. The macular retinal lesions develop due to the degeneration of photoreceptor cells and supporting retinal pigment epithelial tissues, which may take years to develop, and the patient may appear asymptomatic. However, at the late stage of geographical atrophy, the patients develop sudden and severe visual disabilities.[4] The pathophysiology behind the dry AMD is drusen formation (insoluble lipid-laden cellular debris deposits between Bruch's membrane and Retinal Pigment Epithelium, RPE), a post-inflammatory process. During the process, complement and cytokines are involved, leading to atrophy in the macular retinal pigment epithelium, usually associated with the degeneration of the photoreceptors that clinically manifest as central blurring of vision in the affected eye.[5,6] Once dry AMD progresses to the advanced or late stage (geographical atrophy), there is no effective treatment to prevent vision loss or repair damaged photoreceptors. The existing treatment targeting the inflammatory complement and cytokine pathways may benefit patients by delaying the disease pro-

Keywords: Age related macular degeneration; Geographical atrophy; Choroidal neovascularization; Photoreceptors; Retinal Pigment Epithelium; Pipeline drugs; Clinical trials.

Abbreviations: A2E, N-retinylidene-N-retinylethanolamine; AAV2, adeno-associated viral vector; ADMSC, adipose tissue derived mesenchymal stem cells; ARMD/AMD, age-related macular degeneration; ATP, Adenosine Tri Phosphate; BCVA, best corrected visual acuity; CF1, complement factor 1; CTNF, ciliary neurotrophic factor; Da, Daltons; DDS, drug delivery system; DHA, docosahexanoic acid; ECT, encapsulated cell technology; FAF, fundus autofluorescence photography; GA, geographical atrophy; HESC, human embryonic stem cells; HT1A, hydroxytryptamine 1A receptor; IOP, intra ocular pressure; LCPUFA, long chain poly-unsaturated fatty acid; LDL, low-density lipoprotein; mf-ERG, modified Electro-retinogram; MIRA-1, Multicenter investigation of Rheopheresis for Age-related macular degeneration; OCT, optical coherence tomography; PBM, photobiomodulation therapy; PLGA, Poly Lactic-co-Glycolic Acid; RBP, retinol binding protein; RCT, randomised controlled trials; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

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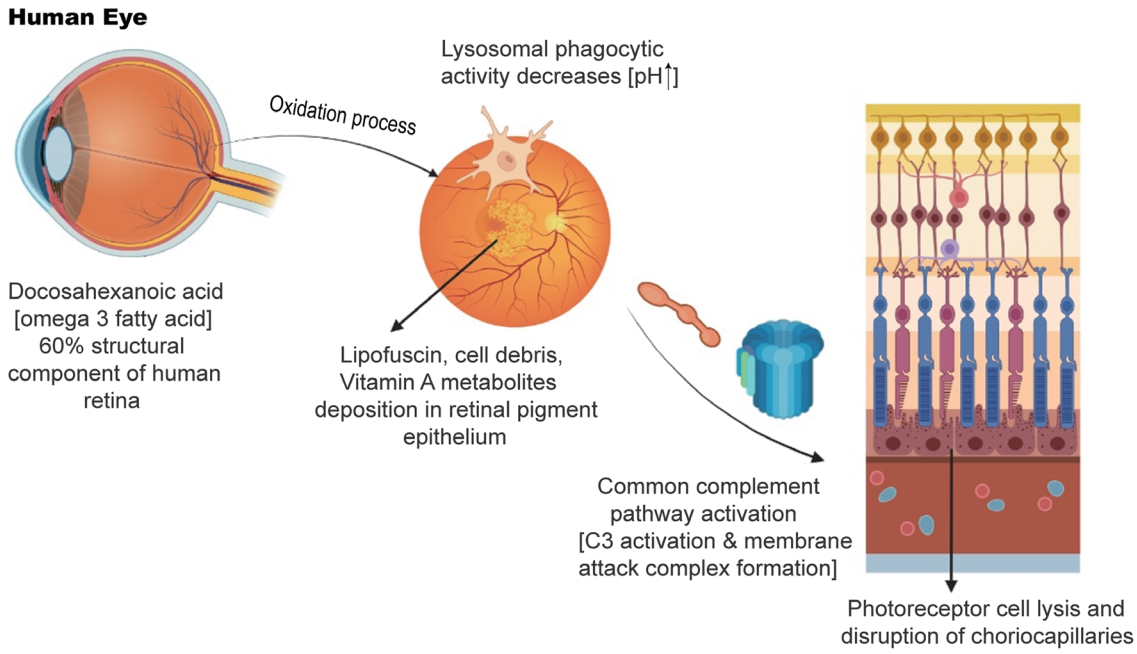

Fig. 1. Pathogenesis of dry age related macular degeneration and geographical atrophy. A2E, N-retinylidene-N-retinylethanolamine; GA, geographical atrophy; RPE, retinal pigment epithelium (created with www.BioRender.com).

gression.[7] Our review mainly focuses on all pipeline drugs tested under clinical trials registered at the U.S. FDA-run Clinical Trials.gov registry some of which are published in the relevant journals to understand the potential therapeutic targets and their mechanisms for treating dry AMD or Geographical Atrophy.

Pathogenesis of dry AMD

The pathogenesis of dry AMD is mediated by cytokines and complement pathway activation. However, various unexplained trigger factors contribute to the disease development and need further evaluation. Docosahexaenoic acid (DHA) constitutes almost 60% polyunsaturated fatty acid of the structural framework of the human retina, especially in the RPE, and is involved in the pathogenesis of dry AMD.[8] Human retina is the ocular interface exposed constantly most of the time to light and oxygen due to excess oxygen demand by RPE cells. Peroxidation of DHA leads to the formation of lipofuscin (yellow-brown pigment) that tends to accumulate in the RPE, which is non-degradable in the RPE cellular lysosomes.[9] Therefore, an increase in the lysosomal pH impairs the phagosomal activity of lysosomal enzymes in the RPE. Subsequently, there is deposition of cellular debris, lipofuscin, and vitamin A metabolites (A2-E) in the RPE layer of the retina, which activates the complement pathway to activate complement C3.[10] C3 protein, an essential component for amplification of the complement pathways, is cleaved to membrane attack complex (cytotoxic component) that induces cell lysis and subsequently destroys photoreceptors and choriocapillaries progressing to GA. GA is a chronic progressive macular degeneration and can manifest as late-stage dry AMD.[11] Diagrammatic representation of the AMD and GA pathogenesis and pharmacological intervention is provided in Figures 1 and 2 respectively. Recent studies in a mouse macular degeneration model have shown that immunotherapies targeting the beta-amyloid plaques in Alzheimer's disease can improve the clearance of amyloid deposited in the retina and electroretinogram deficits, suggesting that beta amyloids deposits are crucial for the pathogenesis of dry AMD.[12]

Pipeline drugs for dry AMD

The treatment armamentarium for wet AMD is exhaustive.[13] There is no approved drug for treating dry AMD or GA globally, and there remains an unmet need for developing drugs in this therapeutic area. Few drugs in the pipeline are undergoing clinical trials that have shown promising results in delaying the progression of dry AMD by their neuroprotective effect on photoreceptors and RPE.[14] Hence, understanding and exploring more therapeutic targets for treating dry AMD and GA is vital.

The treatment of dry AMD is based on two disease-modifying agents: 1) Neuroprotectants for photoreceptors and RPE cells and antioxidant agents. 2) Anti-inflammatory agents, like corticosteroids and agents targeting complement activation (Fig. 2).

Neuroprotective agents

Ciliary Neurotrophic Factor (CNTF, NT-501) (Neurotech Pharmaceuticals)

CNTF has been tried and tested as a treatment for dry AMD and GA. CNTF can retard further damage to the photoreceptor cells in degenerative macular diseases, such as AMD and retinitis pigmentosa. Delivering drugs from the systemic circulation across the blood-retinal barrier is a big challenge to reaching the neurosensory retina. With the advent of Encapsulated Cell Technology (ECT), sustained release of therapeutic agents across the blood-retinal barrier has become convenient. However, the dose-dependent increase in retinal thickness has been observed by optical coherence tomography (OCT) over four months. CTNF delivered by encapsulated cell technology effectively delayed the progression of GA, especially for those with 20/63 or bet-

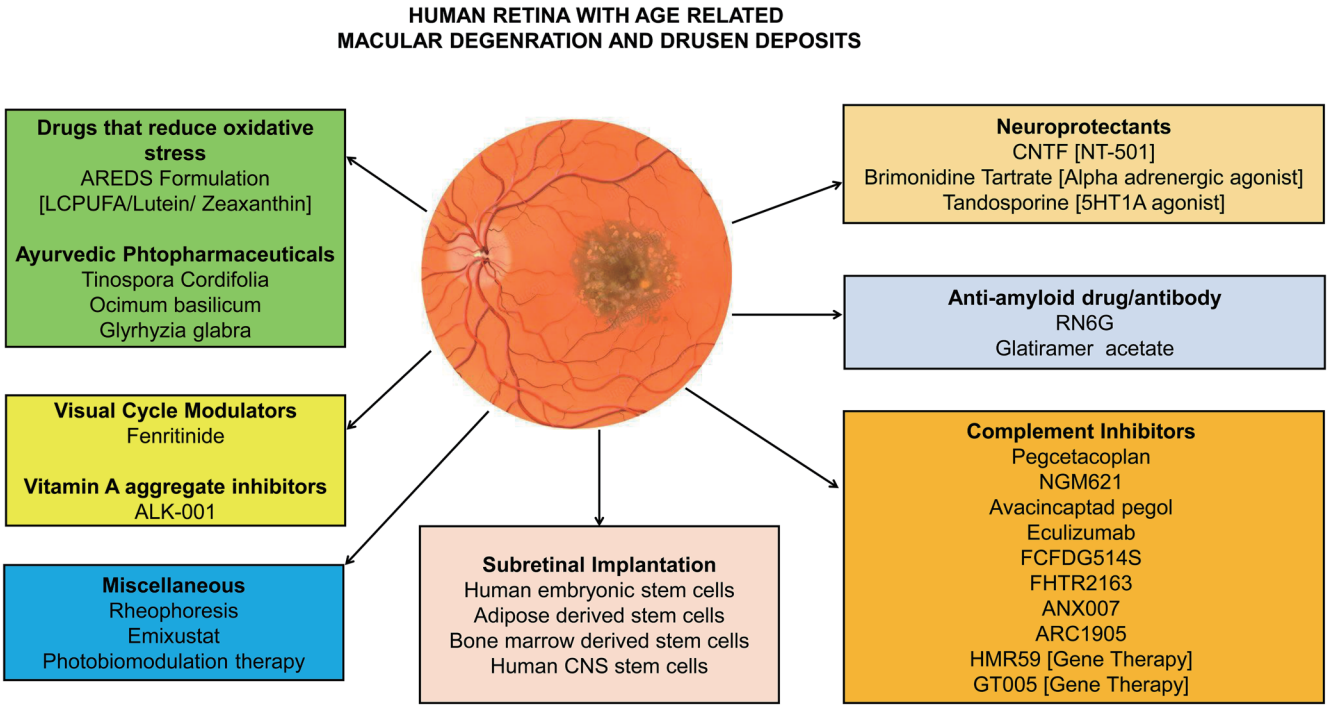

Fig. 2. Pipeline investigational drugs for dry age related macular degeneration and geographical atrophy. 5HT1A, Serotonin receptor agonist; AREDS, age related eye disease studies; CNS, central nervous system; CNTF, Ciliary Neurotropic Factors; LCPUFA, long chain polyunsaturated fatty acid.

ter vision at baseline. However, the study failed to demonstrate any improvement in macular lesion size in GA cases.[15–18]

Brimonidine Tartrate (Allergan, Inc)

Brimonidine has neuroprotective action due to its alpha-adrenergic activity and has been shown to retard retinal degeneration and protect RPE and photoreceptors in rodent studies. A phase IIA study has reported that brimonidine can lower intraocular pressure (IOP) when injected into the eye (through Ozurdex-like intravitreal implant) and inhibit the progression of GA in dry AMD. Brimonidine is implanted through pars plana in the vitreous humor of GA patients every six months, reducing the frequency of injections and maintaining therapeutic drug levels in the retina. Like the Ozurdex dexamethasone implant, brimonidine can be delivered by the Novadur solid polymer drug delivery system made of PLGA intravitreal solid polymer matrix that slowly degrades to lactic acid and glycolic acid with no residues left in the eye. The trial used first-generation brimonidine DDS tartrate in 22-gauge implants at doses of 132 and 264 micrometers. At the end of 12 months, there was a 19% and 28% reduction in the lesion growth rate compared with the placebo. The BEACON Phase IIB trial is ongoing and tests the second generation of brimonidine DDS that delivers more drug to the retina, i.e., a dose of 400 micrometers of free base brimonidine in a 25 gauge implant.[19,20]

Tandospirone (Alcon Laboratories, Inc.)

Tandospirone (AL-8309B) is a serotonin receptor (5-HT1A) agonist and has been approved for the treatment of depressive illness. However, it also possesses a neuroprotective effect on the photoreceptor and retinal pigment cells. The GATE study is a randomized phase III, multicenter clinical trial (N = 768) to investigate the safety and efficacy of Tandospirone in patients with GA secondary to AMD. The patients were treated with AL-8309B ophthalmic solution at varying concentration i.e 1.0%, 1.75%, or a vehicle control as topical eye drops twice daily for 30–36 months. Unfortunately, AL-8309B treatment did not significantly change the annualized GA lesion size (1.73, 1.76, and 1.71 mm^2 for the AL-8309B 1.0%, 1.75%, and vehicle group, respectively, though not associated with any safety concern.[21]

Anti-amyloid beta antibody

Glatiramer acetate (Copaxone, Teva Pharmaceuticals, Israel)

Glatiramer acetate has been used to treat multiple sclerosis due to its immunomodulatory action. This drug can suppress T cells and reduce retinal microglial cytotoxicity induced by beta-amyloid plaques. It has been shown to reduce the drusen area in patients with dry AMD compared to the sham treatment.[22–24]

RN6G (Pfizer, Inc, USA)

RN6G is a humanized monoclonal antibody against beta-amyloid plaques and disseminates the amyloid concentration in the periphery of the retina, reducing macular toxicity. In rodent models of AMD, treatment with RN6G decreases amyloid plaque deposits in the retina. However, the trial of RN6G (NCT01577381) was terminated for lack of efficacy, and the trial of GSK933776 also failed to show any benefit of treatment.[25]

Reducing oxidative stress

AREDS (Age-Related Eye Disease Studies) formulation (Bausch & Lomb, Inc.)

In AREDS2 cognition function testing RCT (factorial design),

there was no significant difference in the scores observed in participants treated with long-chain poly-unsaturated fatty acid supplements (LCPUFA) 1 gram or lutein (10 mg)/zeaxanthin (2 mg) when compared with those treated with standard of care only. All study participants were provided standard care therapy as a micronutrient formulation containing zinc, vitamin C, vitamin E, and beta carotene. Although it reduced the risk of vision loss by 19% in patients with pre-existing intermittent/ advanced AMD, it failed to show any apparent benefit in early AMD. The lutein and zeaxanthin components of the formulation are known to have anti-inflammatory and antioxidant properties and hence may exert a neuroprotective effect on the retinal pigment epithelium.[26,27]

Visual cycle modulators

Fenretinide (ReVision Therapeutics)

A synthetic retinoid can be used orally as a chemoprotective drug against prostate cancer and in women at risk of developing breast cancer. It also has antineoplastic, chemoprotective, pro-apoptotic, anti-inflammatory, and anti-angiogenic properties, and its side effects include mild to moderate drying of mucosal membranes with a delay in dark adaptation. Fenretinide can reduce the accumulation of lipofuscin and retinol-derived toxins in an animal model of Stargardt disease. Fenretinide reduces the circulating levels of retinol and its carrier protein, retinol-binding protein (RBP). As A2E and related toxins are derived from retinol, reducing circulating RBP-retinol levels can decrease retinol-derived toxins in the eye.[28,29] A phase 2 study with 100 and 300 mg of fenretinide was investigated. The interim results revealed that at 24 months, the 300 mg fenretinide group exhibited approximately 40% reduction in the progression of GA compared to the placebo group.[30,31]

Subretinal implantation of stem cells derived from different sources

Human Embryonic Stem Cells (HESC)

Stem cell therapy may provide a safe and promising treatment for retinal diseases. The technology to derive RPEs from hESCs has been developed. A Phase I/IIa clinical study in patients diagnosed with advanced dry AMD and GA (NCT02286089) by subretinal injection of 50–200 k OpRegen cells with immunosuppressive therapy for three months post-implantation. Based on interim Phase I/IIa results of 3 cohorts of 12 patients each, the therapy was well tolerated. Adverse events included the formation of mild epiretinal membranes (ERM), with one being successfully peeled two months after therapy while one patient experienced retinal detachment. OCT confirmed the continued presence of retinal pigment cells transplanted. Dosing in cohort 4 is still ongoing.[32,33]

Adipose-derived stem cell implantation

There are case reports to evaluate the safety of subretinal implantation with adipose tissue-derived mesenchymal stem cell (ADMSC) in advanced stages of retinitis pigmentosa (RP), with one out of 11 patients experiencing choroidal neovascular membrane and five patients having epiretinal membrane at and around the implantation site, respectively. Many studies have investigated the efficacy of this intervention in different types of degenerative macular diseases. Among the published prospective case series, one of the Phase 2 studies assessed the safety and efficacy of suprachoroidal Adipose Tissue-Derived Mesenchymal Stem Cell (ADMSC) in patients suffering from dry AMD and observed an improvement in visual acuity and visual field.[34,35]

Bone marrow-derived stem cell implantation

Few studies have evaluated the role of bone marrow-derived stem cells in treating advanced dry AMD using multifocal electroretinogram (mf-ERG) and fundus autofluorescence imaging. There is no significant improvement in median log MAR BCVA between the test and control groups at the 6-month follow-up. Multifocal Electroretinogram, however, revealed significant improvement in amplitude and implicit time in the intervention group, while there was a significant decrease noted in the greatest linear dimension (GLD) of GA in the eyes receiving stem cells (6.78 ± 2.60 mm at baseline to 6.56 ± 2.59 mm at six months, $p = 0.021$) while there was no such improvement noticed in the control group.[36]

Human CNS stem cells (Hu CNS-SC)

The Phase 1/2 study by StemCells, Inc. United States (NCT01632527) tested the efficacy of surgical implantation with human CNS Stem cells (Hu CNS-SC) in the subretinal space of patients with GA without choroidal neovascularization. However, this study did not report the results yet.[37]

Potential drugs and gene therapies targeting the complement system

The details of drugs affecting the various components of the complement pathway and route of administration are provided in Table 1.

C3 complement system inhibitors

Pegcetacoplan (Apellis Pharmaceuticals)

It is a protein drug approved to treat paroxysmal nocturnal hemoglobinuria in adults. Pegcetacoplan functions and acts as a pegylated C3 inhibitor. In the Phase 2 FILLY study, intravitreal injections with 15 mg pegcetacoplan monthly for 12 months significantly inhibited the growth rate of GA lesions by 29% compared with the sham therapy. This was further confirmed by the Phase 3 OAKS study (N = 637 patients) that revealed that monthly injections with 15 mg/0.1 mL pegcetacoplan for 12 months significantly reduced GA lesion growth by 22% compared with the sham therapy. Treatment with the same dose of pegcetacoplan every other month significantly reduced GA lesion growth by 16%. Another confirmatory Phase 3 study of DERBY (621 patients) did not meet the primary endpoint. In the pooled analysis of all Phase 3 trials, pegcetacoplan has a greater effect on eyes with extrafoveal lesions at baseline, decreasing GA lesion growth by 26% for monthly regimen and 23% with every-other-month injections with accepted tolerability profile. However, the pooled safety data of these Phase 3 trials have shown three cases with infectious endophthalmitis (0.047% risk per injection), 13 cases with intraocular inflammation (0.21% risk per injection), and no retinal vasculitis or vascular occlusion. The pooled data also revealed that pegcetacoplan treatment was associated with a dose-dependent increase in new-onset wet AMD with a rate of 6.0% in the monthly cohort, 4.1% in the every-other-month cohort, and 2.4% in the sham group.[38,39]

NGM621 (NGM Biopharmaceuticals)

NGM621 is a humanized IgG1 antibody and can inhibit the enzymatic cleavage of C3. Unlike the other complement-targeting ther-

Table 1. Novel Therapies targeting complement pathway for Geographical atrophy and dry AMD

Study Drug [Pharmaceutical company name]	Complement Target	Delivery method	Current trial phase	Most Recent Trials	Study Status
Pegcetacoplan [Apellis]	C3	Intra vitreal implant [IVI]	III	OAKS, DERBY	Active, Not recruiting
NGM621 [NGM Biopharmaceuticals]	C3	Intra vitreal implant [IVI]	II	CATALINA	Active, Not recruiting
Avacincaptad pegol/Zimura [Iveric Bio]	C5	Intra vitreal implant [IVI]	III	GATHER II	Active, Not recruiting
ANX007 [Hemera]	C1q	Intra vitreal implant [IVI]	II	ARCHER	Recruiting
HMR59 [Hemera]	C9	Intra vitreal implant [IVI]	I	HMR-1001	Completed
GT005 [Gyroscope Therapeutics]	Complement Factor I	Subretinal	I/II and II	FOCUS, EXPLORE, HORIZON	Recruiting

AMD, Age related Macular Degeneration; C, Complement factor; IVI, Intravitreal injection. Clinical trials name: OAKS, DERBY, GATHER II, ARCHER, HMR-1001, FOCUS, EXPLORE, HORIZON.

apeutics for GA, NGM621 is not pegylated. In the Phase 1 trial, the agent was well tolerated with no drug-related adverse events. The Phase 2 CATALINA trial is ongoing, with approximately 320 patients enrolled. The study is designed to randomly assign patients to receive intravitreal injections of 15 mg versus sham therapy (2:1 ratio) every 4 or 8 weeks for a total of 52 weeks. The primary efficacy endpoint is the rate of change in GA lesion area measured by fundus autofluorescence (FAF) for 52 weeks.[40]

POT-4 (Potentia Pharmaceuticals, USA)

When injected intravitreally, the drug is released gradually, and it binds to C3 protein, the central component of the complement pathways known to trigger the inflammatory process.[41]

Avacincaptad pegol (Zimura, Iveric Bio)

Avacincaptad pegol is a specific inhibitor of C5 and can slow down the progression of retinal cell degeneration. Treatment with 2 mg or 4 mg Avacincaptad pegol for 12 months can reduce GA lesion growth by approximately 27% in the (Phase III GATHER 1, N = 286) clinical trial. This drug selectively inhibits C5 and has additional safety advantages. A confirmatory pivotal trial (GATHER II) is underway to evaluate the efficacy and safety of this drug.[42,43]

Eculizumab (Soliris, Alexion Pharmaceuticals, USA)

Eculizumab is a humanized IgG monoclonal antibody against C5 that prevents its cleavage into C5a and C5b during the process of complement activation. The strategic blockade of the C5 cleavage prevents the release of the downstream anaphylatoxin C5a and the formation of the cytolytic membrane attack complex (MAC). Currently, a phase II study (COMPLETE trial) is testing the efficacy and safety of intravenous infusion with eculizumab for patients with dry AMD/GA.[44]

ARC 1905 (Opthotech Corp, USA)

This aptamer selectively inhibits C5. Currently, there is an undergoing Phase 1 study (NCT 00950638).[45]

Gene therapy

HMR59 (Hemera Biosciences)

HMR59 carries the soluble form of CD59 gene in a recombinant adeno-associated viral (AAV2) vector. CD59 is a glycosylphosphatidylinositol-anchored membrane inhibitor of the membrane attack complex. Functionally, HMR59 treatment can prevent the recruitment of complement C9. The membrane attack complex is the terminal step of an activated complement cascade. A completed Phase 1 study of HMR59 investigated the dose-escalating safety and tolerability of a single intravitreal injection for GA with a total of 17 patients. There were no systemic or severe adverse events associated with HMR59 injections. Mild ocular inflammation occurred in three patients' treated eyes, including two eyes that developed vitreous inflammation that resolved after six weeks of observation and one eye that developed anterior chamber and vitreous inflammation that resolved with topical corticosteroids. Not a single patient converted to wet AMD during the 18-month follow-up period.[46]

GT005 (Gyroscope Therapeutics)

GT005 is a recombinant adenovirus-associated vector 2 (AAV2) that contains a nucleotide sequence encoding complement factor I (CFI). Subretinal injection with GT005 was designed to enable cellular transduction and induce CFI expression and secretion.

While low serum CFI levels are associated with a much higher risk of AMD, an increase in intraocular CFI levels can dampen an over-activated alternative complement pathway and potentially reduce AMD progression.[47] The Phase 1/2 FOCUS study has evaluated the safety and tolerability of subretinal delivery of GT005 in patients with GA. Dose escalation in cohorts 1 to 3 have completed dosing *via* transvitreal delivery, while in the dose expansion in cohort 4, recruitment is still ongoing. Cohorts 5 to 7 will receive gene therapy through the Orbit Subretinal Delivery System (Gyroscope Therapeutics).[47] Interim results from cohorts 1 to 4 revealed that GT005 subretinal delivery was well tolerated. Compared with the baseline, there was an average increase in CFI levels by 146%. The first patient who received GT005 had a sustainable CFI increase at 84 weeks post-treatment. In addition, reductions in downstream complement biomarkers were detected. Two Phase 2 studies, EXPLORE and HORIZON, actively enroll patients to evaluate the safety and efficacy of two doses of GT005 administered as a single subretinal injection, with GA lesion growth measured by Fundus Autofluorescence Photography (FAF) at 48 weeks post-treatment as the primary efficacy endpoint.[48,49]

Factor D protein inhibition in the alterative complement pathway

FCFD4514S (Genentech Inc, USA)

FCFD4514S is a humanized monoclonal antibody against factor D protein in the alternative complement pathway and is also undergoing phase 1 study (NCT 00973011).[50]

C1Q protein inhibition of the complement pathway

ANX007 (Annexon Biosciences)

ANX007 is an antigen-binding fragment of a humanized recombinant monoclonal antibody. ANX007 can bind to the C1q component to block the downstream signaling of the classical complement cascade. Safety and efficacy data from two Phase 1 studies in primary open-angle glaucoma patients are promising. The Phase 2 ARCHER (NCT04656561) study is active and investigating the efficacy of intravitreal injections with ANX007 for GA patients. The sample size for this study is 240 individuals randomly assigned to monthly or every-other-month intravitreal injections with 5 mg ANX007 or sham therapy for 12 months, followed by 6 months in the off-treatment phase. The primary efficacy endpoint is the change in the GA lesion area.[51,52]

High-temperature requirement A1 (HTRA1) inhibition

FHTR2163 (Genentech)

FHTR2163 is an antigen-binding fragment of a humanized monoclonal antibody against the A1 protein. A single nucleotide polymorphism is associated with increased levels of HTRA1 protein, which confers a risk of dry AMD by 49.3%. In the Phase 1 study, the drug molecule was tolerated well with no dose-limiting toxicity, while currently, the Phase 2 GALLEGO study is underway to evaluate the efficacy of intravitreal injections with 20 mg FHTR2163 every 4 or 8 weeks over 76 weeks. The primary efficacy endpoint measures the GA lesion growth area from baseline to 72 weeks using fundus autofluorescence imaging.[53]

Vitamin A aggregates formation inhibitors

ALK-001 (Alkeus Pharmaceuticals)

ALK-001 is a chemically modified vitamin A and can prevent the formation of toxic vitamin A aggregates, reducing the accumulation of debris in the RPE. The results of the Phase III study are awaited and will help us to evaluate the efficacy of this potential drug molecule in inhibiting the growth rate of GA lesions.[31,54,55]

Miscellaneous therapies

Photobiomodulation therapy (PBM)

PBM is a light-based technology that stimulates bioenergetic output in targeted tissues. Selected wavelengths of light in the far red to near-infrared spectrum (500–1,000 nm) can modulate biological function through direct and indirect cellular effects on mitochondrial respiratory chain components. PBM activation of photoacceptors in the mitochondria improves the generation of adenosine triphosphate (ATP), modulates the production of intracellular signaling molecules, such as reactive oxygen species and nitric oxide, and triggers secondary effects that produce sustainable changes in cell function and viability. The beneficial cellular effects can be observed only with the appropriate selection of wavelength, dose, timing, and delivery of PBM treatment.[56]

Emixustat (ACU-4429, Acucela Inc.)

Emixustat is a small molecule visual cycle modulator formulated as emixustat hydrochloride. This is the first oral drug that delays the retinal disease process. Emixustat was developed by British-American chemist Ian L. Scott and is undergoing Phase 3 trials for dry AMD. The toxic byproduct, N-retinylidene-N-retinylethanolamine (A2E), is a major chromophore in lipofuscin, formed from the release of all-trans-retinol within the outer segment of human photoreceptors. A2E leads to the formation of singlet oxygen radicals on exposure to high-energy light and oxygen. Emixustat hydrochloride is a synthetic small molecule non-retinoid designed to stop the visual cycle by inhibiting the formation of 11-cis-retinal. Emixustat hydrochloride binds to RPE-65 and prevents the isomerohydrolase reaction. Without 11-cis-retinal, the rod photoreceptor cells do not produce all-trans-retinol and A2E. A placebo-controlled Phase 1b RCT has shown the safety and tolerability of treatment with emixustat (5, 10, 20, 30, or 40 mg) daily for 14 days in healthy volunteers.[57,58]

Rheopheresis

AMD is considered to be mediated by the disturbance in the micro-circulation of the retina at a cellular and molecular level. Rheopheresis is a type of therapeutic plasmapheresis-like procedure that is safe and effective in treating retinal microcirculatory disorders of the retina. Rheopheresis can eliminate high molecular weight proteins from human plasma of a defined spectrum. These include many components in the blood (>25 nm or >500 kDa) that are pathophysiologically related to AMD, such as fibrinogen, LDL cholesterol, immune complexes, IgM, von Willebrand factor, and alpha 2 & beta 2 macroglobulin that are associated with increase blood viscosity. The increase in blood viscosity reduces blood flow, especially micro-circulation, with more propensity for blood erythrocytes and thrombocytes to aggregate. A series of Rheopheresis procedures at definite intervals can improve the microcirculation of the retina and help in faster recovery of retinal function. Though it is as yet an unproven therapeutic option under investigation, it has been tested in clinical trials. The most extensive study to assess the effectiveness of Rheopheresis in dry AMD is the Multicenter Investigation of Rheopheresis for

AMD (MIRA-1) trial, which leads the results. Moreover, a larger proportion of treated subjects experienced adverse events that required intervention (24.0%) compared to those receiving placebo (5.8%).[59,60]

Ayurvedic phytopharmaceuticals

Many Rasayana medicines, such as *Tinospora Cordifolia, Cantella Asiatica, Bacopa monnieri, Convolvulus pluricaulis, Ocimum basilicum L., Curcuma Longa L., Acorus Calamus, Glycyrrhiza glabra L*. mentioned in Ayurvedic literature may have a potential role in the age-related degenerative process in cells by telomere lengthening and preventing DNA damage.[61] However, their effect needs to be explored in AMD-related clinical trials.

Strengths and limitations

Our review covers all the unapproved pipeline therapies for dry AMD under investigation. The study discusses the published clinical trial results/interim results related to dry AMD. However, the study has a few limitations. Some of the interventions to treat dry AMD are still under investigation, and results are not updated in the public domain. Hence, we have not discussed these results in detail, although their mechanisms are well described as an investigational therapy. BVCA is the most common primary endpoint used in many clinical trials, but it may fail to diagnose foveal-sparing GA. Moreover, the review mainly narrates the clinical development phase, and describing all the pre-clinical development part of a new molecular/chemical entity does not fall under the scope of this review.

Future directions

GA is an irreversible or decompensated stage of dry AMD and has no successful treatment. Stem cell-based therapy (embryonic stem cell-derived and induced pluripotent stem cells) remains under investigation to rejuvenate the degraded photoreceptor cells, but it faces challenges such as immune rejection, non-desired cellular differentiation, and tumor formation. BCVA is a gold standard measure to evaluate the visual function and most accepted endpoints to test the efficacy of treatment. However, fovea-sparing GA is often missed in the early stages. Recent technologies to assess visual function, like microperimetry, color fundus photography, fundus autofluorescence, optical coherence tomography, multifocal electroretinography, low luminance visual acuity, reading speed, and contrast sensitivity, are the most sensitive methods to check the visual function, even in a patient with foveal sparing GA using the preserved BCVA. With advancing drug delivery technology, disease progression monitoring, and better safety and efficacious treatment, the treatment of armamentarium for dry AMD will expand.

Conclusions

There is a need to explore promising therapeutic targets and treatment options for dry AMD or GA. Furthermore, early and accurate diagnosis may aid in initiating treatment before disease progression. Genetics and environmental factors may also help researchers better understand the pathogenesis of dry AMD.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Conceptualization, review of literature, and manuscript drafting (MM, RM, SZ, and ST); manuscript editing and reviewing (RM). All authors have made a significant contribution to this study and have approved the submission of the final manuscript (MM, RM, SZ, and ST).

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