Progress of clinical therapies for dry age-related macular degeneration

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Abstract

● Dry age-related macular degeneration (AMD) is a progressive blinding disease that currently affects millions of people worldwide with no successful treatment available. Significant research efforts are currently underway to develop therapies aimed at slowing the progression of this disease or, more notably, reversing it. Here the therapies which have reached clinical trial for treatment of dry AMD were reviewed. A thorough search of PubMed, Embase, and Clinicaltrials.gov has led to a comprehensive collection of the most recent strategies being evaluated. This review also endeavors to assess the status and future directions of therapeutics for this debilitating condition.

● KEYWORDS: dry age-related macular degeneration; age-related macular degeneration; drug therapy

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in adults over 50 years of age[1]. This is particularly worrying as the portion of the population in this age range is rapidly increasing. In fact, the number of people in the United States aged 65y and older is expected to reach 82.7 million by 2050[2], more than doubling 2005 levels[3]. More relevantly, a study designed to model AMD prevalence over time predicted that the number of early AMD cases may increase from 9.1 million in 2010 to 17.8 million in 2050[4], highlighting the urgency for continued research efforts to address the unmet needs of these patients. There are two forms of AMD, the dry (non-exudative) and wet (exudative) types. Wet AMD occurs when the choroid layer of the retina develops neovascularization. These new vessels are not as robust as well-established vasculature and, thus, become leaky to fluids, blood, and lipids which can penetrate the layers of the retina causing scar tissue and decreased cellular function. On the other hand, dry AMD is characterized by drusen deposition, pigment change and, in advanced stages, geographic atrophy of the macula[5]. Geographic atrophy occurs when the layers of the macula become progressively thinner and less functioning. Due to the known molecular mechanisms that underlie wet AMD, there are several FDA-approved therapies to treat this form of the disease, whereas, dry AMD has no approved therapies[5]. This is particularly concerning considering that the dry form of AMD is the most common type and accounts for more than 90% of diagnosed cases[6].

This review article will focus on clinical therapies being developed for the treatment of dry AMD, as this is the area most in need of treatment options for patients. Only therapies that have been at least evaluated in clinical trials will be discussed.

DRY AGE-RELATED MACULAR DEGENERATION THERAPIES

As progress in research provides new insight on mechanisms underlying the pathogenesis of dry AMD and uncovers new possible disease targets, a wide variety of potential therapeutic options are being developed.

Cell Based Therapies Cell based therapies are generally divided into two types: stem cell-based and non-stem cell-based therapies. Both types of therapies take advantage of the immune-privileged environment of the subretinal space as a target, though they aim to affect this space via different mechanisms. Stem cell-based therapies aim at replacing degenerated retinal pigment epithelium (RPE) cells by delivering healthy RPE cells into the subretinal space to preserve the health and function of the remaining photoreceptors and possibly support damaged light-sensitive cells to a return of function. The non-stem cell-based therapies,
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on the other hand, introduce cells that will release protective factors that are lacking in the extracellular environment to support photoreceptor survival and function. Aspects of cell therapy still actively researched are the optimal timing of transplantation, cell type to be targeted (choroidal endothelium, RPE, photoreceptors), and transplant product (encapsulated cell therapy, RPE with scaffold vs without scaffold) to name a few. The concerns with stem cell-based therapies include immune rejection, differentiation into undesired cell types, damage to surrounding tissues, and tumor formation. This section will look at cell-based therapies currently being trialed. Ocata Therapeutics (now acquired by Astellas Pharma) studied a stem cell-based therapy utilizing human embryonic stem cells (hESC)-derived RPE. This trial employed the first generation of hESC-derived RPE cell line named MA09-hRPE. The Phase I/II study aimed at ascertaining the safety of subretinal transplantation of MA09-hRPE in a total of 18 patients (9 with Stargardt’s macular dystrophy and 9 with atrophic AMD). There were three dose treatments assessed (50,000, 100,000, and 150,000 cells). No evidence was found on adverse events such as proliferation, rejection, or serious ocular or systemic safety issues related to the transplanted cells. However, there were adverse events associated with vitreoretinal surgery and immunosuppression, one instance of which was a case of endophthalmitis. Seventy-two percent (13 of 18) of subjects had increased subretinal pigmentation consistent with transplanted RPE at the atrophic area border. At one-year post-treatment, visual function was improved in ten eyes, improved or remained stable in seven eyes, and worsened as a result of natural disease progression rather than a complication of the SCOTS procedure. Of the implanted eyes (9 with Stargardt’s macular dystrophy and 9 with atrophic AMD), 20 of 32 eyes experienced visual acuity improvements, there was a high rate of retinal perforation and detachment. Approximately 17% (6/35 subjects) experienced retinal detachments and 37% (13/35 subjects) experienced retinal perforations. This high rate of adverse events was largely attributed to the eye surgery and surgical delivery system, with only 15% of adverse events related to palucorcel (and these were also considered reasonably related to the surgery or delivery system). Due to this high rate of adverse events the Phase I/IIa study was suspended.

It is important that studies involving stem cell-based therapies are approached in a manner that is safe and ethical for patients. The potential of stem cell therapies increasingly raised hope in patients awaiting for a treatment, some clinics began offering the promise of stem cell-assisted regeneration without going through the sanctioned channels of the FDA. This in turn generated much controversy in both the biomedical and general communities. Could unregulated stem cell-based treatments provide benefit to patients not approved for clinical trials? Possibly. Could it unnecessarily endanger patients desperate for a treatment? Probably. These questions are at the root of the controversy and came to full light with the SCOTS (Stem Cell Ophthalmology Treatment Study) study. The study reported fairly promising results of autologous bone marrow-derived stem cells injected intravitreally as a potential therapy for dry AMD: after the treatment, 20 of 32 eyes experienced improvement in visual acuity averaging 27.6% on logMAR and ranging from 2.5% to 44.6% with a high statistical significance of P≤0.001. Of the eyes treated, another 11 had visual acuity that remained stable and one had visual acuity that worsened as a result of natural disease progression rather than a complication of the SCOTS procedure. However, other clinical trials (in London and Japan) that are researching stem cell-derived RPE implantation but these studies occurred in patients with exudative AMD. Finally, a new trial is investigating autologous induced pluripotent stem cell (iPSCs)-derived RPE. Sponsored by the National Eye Institute, this Phase I/IIa clinical trial will assess the safety and feasibility of subretinal transplantation of iPSC-derived RPE grown as a monolayer on a biodegradable poly lactic-co-glycolic acid (PLGA) scaffold in patients with geographic atrophy. This trial is currently recruiting.
several patients receiving such autologous stem cell therapies as part of this or similar studies, have come forward claiming severe vision loss as a result of the treatment. In fact, in an article published in *The New England Journal of Medicine*, three patients who received intravitreal injections of autologous adipose tissue-derived “stem cells” reported vision loss to a visual acuity ranging from 20/200 to no light perception (before injection visual acuity was 20/30 to 20/200) \[16\]. Large concern remains that, without rigorous oversight of clinical trials, patients may continue to receive unregulated therapies that puts them at risk of severe complications and unethical medical care.

**Complement Inhibition**

Research has shown that the complement system plays a key role in the pathogenesis of geographic atrophy \[17-19\]. The complement system is divided into three distinct but interconnected pathways: the classical pathway, the alternative pathway, and the lectin pathway. The trigger to each pathway is unique \[19\]. The classical pathway is triggered by an antigen-antibody complex. The alternative pathway is triggered by binding to the surface of a cell or pathogen. The lectin pathway is triggered by polysaccharides that reside in bacterial surfaces. All three pathways converge at the cleavage of complement C3 and C5 and the formation of the membrane attack complex (MAC) leading to pathogen cell death \[18\]. Several complement system proteins, complement regulatory proteins and activators, have been identified as components of drusen associated to AMD. In addition, genetic studies described highly significant statistical associations between AMD and variants of several complement-associated genes (complement factor H, complement factor B, complement component 3, etc) \[19\]. Complement inhibition appears as a potential therapy, though without important challenges including necessity of regular -often frequent- dosing, delivery of therapy to targeted area, and method of delivery, among others. Several new therapies being investigated that target a component of the complement system will be reviewed in this section.

Several studies are designed to target the C5 component of the complement pathway. A Phase II clinical trial investigated intravitreal injections of LFG316 (a human IgG1 that targets C5 to inhibit the complement system) in subjects with geographic atrophy. The study consisted of 158 participants and was divided into 2 parts. Part A evaluated the safety and efficacy of multiple 5 mg/50 µL doses of intravitreal LFG316 against sham every 28d for 505 days; whereas Part B evaluated the safety and pharmacokinetics of a single intravitreal dose of 10 mg/100 µL of LFG316 \[20\]. At the conclusion of the clinical trial, the intravitreal LFG316 showed a tolerable safety profile but no improvement in either visual acuity or in preventing progression of geographic atrophy lesion. Another intravitreal C5 inhibitor, Zimura (avacincaptad pegol), sponsored by Iveric Bio, was studied in a Phase Ib randomized, controlled trial and met its prespecified primary endpoint of reducing the mean rate of geographic atrophy. The mean rate of geographic atrophy growth reduction over a year in the 2 mg group (compared to sham) was 27.38% (P=0.0072). In the 4 mg group, the percentage was 27.81% (P=0.0051) \[21\]. There were no reported adverse events and the trial will be moving into Phase 3.

Lampalizumab, a humanized monoclonal antibody, targets and inhibits complement factor D. Complement factor D is an enzyme that is the rate-limiting step in activation of the alternative complement pathway \[22-23\]. A Phase II trial of lampalizumab suggested that it reduced the rate of geographic atrophy enlargement leading to a twin Phase III double-masked, randomized, sham controlled clinical trials (Chroma and Spectri) that enrolled subjects across 275 sites in 23 countries for a total of 1881 subjects \[24\]. These trials studied the safety and efficacy of an intravitreal injection of 10 mg of lampalizumab every 4 to 6wk versus sham injections. The results of these identical Phase III trials did not show a reduction in lesion progression compared to the sham treatment over 48wk.

Pegcetacoplan (APL-2 sponsored by Apellis Pharmaceuticals) inhibits C3, acting at the convergence point of all three complement pathways and thus inhibiting all of them. A Phase II trial (entitled FILLY) enrolled 246 subjects from 43 international sites and randomly assigned them to one of four cohorts with the goal of a 2:2:1:1 structure (15 mg intravitreal APL-2 monthly (n=86), 15 mg intravitreal APL-2 every other month (EOM; n=79), sham monthly (n=41), and sham EOM (n=40)) \[25\]. Treatment occurred for a total of 12mo with a 6-month follow-up observation. Results at 12mo showed 29% lower rate of geographic atrophy lesion growth in subjects who received APL-2 every month compared to sham (P=0.008) and a 20% lower rate in subjects who received APL-2 EOM (P=0.067). The study analysis showed the effect was most prominent in the last 6mo of treatment, with slow growth of the lesion by 47% (P<0.001) in monthly APL-2 and by 33% (P=0.01) in EOM group compared to sham \[25\], during this time-period. The secondary endpoint of change in BCVA showed no difference between groups. Adverse events were noted, including endophthalmitis in 2 subjects in the monthly APL-2 group and one subject in the EOM group. Another adverse event described was increased incidence of exudation (20.9% in monthly and 8.9% in EOM) compared to sham counterparts (1.2%). This exudation was responsive to standard-of-care treatment. Subjects that had a history of choroidal neovascularization (CNV) in the fellow eye developed exudative AMD at higher rates compared to sham (36.1% (13/36 subjects) in monthly, 17.9% (5/28 subjects) in
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EOM, and 0 in sham). For subjects without a history of CNV, exudative AMD developed in 10% (5/50 subjects) in monthly, 3.9% (2/51 subjects) in EOM, and 1.9% (1/52) in sham25]. Based on this risk/benefit profile, two 30-month, Phase III, multicenter, randomized, double-masked, sham-injected controlled studies (DERBY and OAKS) are in progress to determine safety and efficacy of multiple intravitreal APL-2 injections in subjects with geographic atrophy related to AMD. In these Phase III trials, 600 internationally recruited patients will be randomized into 4 arms: APL-2 15 mg monthly for 24mo, APL-2 15 mg EOM for 24mo, and two corresponding sham groups26–27.

**Gene Therapy** Gene therapy is designed to replace a deficient or non-functioning protein to stop or reverse a disease process. As an organ, the eye is particularly amenable to gene therapy as it is small, transparent, and has a ready control in the other eye. The small size of the eye necessitates less genetic vector for treatment and as an enclosed organ it limits systemic spread of therapeutic agent28. As a transparent organ, the eye allows delivery of therapy to the exact target and many noninvasive methods to follow-up outcome measures through exam and imaging. Also, as mentioned earlier, the eye is a generally immune-privileged environment that limits immune response to genetic therapies. Gene therapy, being a one-time administration, is appealing in terms of patient compliance. Choosing the optimal viral vector, however, requires careful consideration of cloning capacity, safety, and tissue tropism. Adeno-associated viral vectors are most often used in gene therapy for ophthalmic diseases due to low pathogenicity, prolonged expression profile and ability to transduce multiple cell types29. Another important aspect being evaluated is the method of delivery of the vector (pars plana vitrectomy, intravitreal injection, retinotomy, or via the choroid). The following describes undergoing gene therapy trials.

A gene therapy currently being investigated is AAVCAGsCD59 sponsored by Hemera Biosciences. AAVCAGsCD59 is engineered to cause normal retinal cells to increase expression of a soluble form of CD59. The soluble recombinant version of naturally occurring CD59 is designed to protect retinal cells responsible for vision by inhibiting the MAC, the terminal step of complement-mediated cell lysis29. In the Phase I, multicenter, dose-escalating, safety and tolerability study, subjects with advanced dry AMD with geographic atrophy were given an intravitreal injection of AAVCAGsCD5929. This trial lasted 26wk with an additional 18-month follow-up for safety evaluation. This trial has been completed, and results are still awaited. A multicenter Phase II trial of AAVCAGsCD59 is already planned. Subjects with advanced AMD with geographic atrophy will be randomized in a 1:1:1 ratio comparing intravitreal high vs low dose of AAVCAGsCD59 vs sham injection with a 24-month follow-up to evaluate safety and reduction in geographic atrophy lesion growth30]. The trial is listed as not yet recruiting.

Gyroscope Therapeutics is sponsoring several trials for GT005. GT005 is a recombinant non-replicating adeno-associated vector therapy that encodes a human complement factor to balance an overactive complement system by increasing production of complement factor I protein31. FOCUS is the first of these trials: a Phase I/II multicenter study that evaluates the safety, dose response, and efficacy of two doses of GT005 via a single subretinal injection in subjects with macular atrophy due to AMD31. Subjects are then followed for 48wk. This trial is currently in progress and recruiting, with an estimated enrollment of 35 subjects. Over the last several months, Gyroscope Therapeutic has released plans for two other Phase II clinical trials. EXPLORE is a Phase II, outcomes assessor-masked, multicenter, randomized study to evaluate safety and efficacy of two doses of GT005 administered as a single subretinal injection in subjects with GA secondary to AMD32. There is an 8-week screening period and then subjects are followed for 48wk. This study is currently in progress and recruiting, with an estimated enrollment of 75 subjects. The Phase II trial HORIZON, has been recently initiated and will be conducted analogously to the EXPLORE trial, estimating enrollment of 180 participants33.

**Visual Cycle Modulators** Visual cycle modulators are a class of non-retinoid, small molecule compounds that target various enzymes that participate on the phototransduction cascade in the visual cycle34. During the phototransduction cascade, photoreceptors have a high metabolic demand that leads to increased metabolic waste and potentially inflammatory byproducts. These byproducts are thought to accumulate and lead to inflammation, which has been theorized to contribute to the development of geographic atrophy. The goal, therefore, of modulating the visual cycle is to reduce inflammation and mitigate the process that may lead to geographic atrophy. Visual cycle modulators with oral route of administration are appealing to patients, but the downside of these treatments is that dark adaptation and low-light vision can be adversely affected by modulating the visual cycle. This section will review two visual cycle modulators being assessed.

Emixustat hydrochloride, or ACU-4429, modulates the visual cycle by inhibition of the enzyme isomerohydrolase, RPE6535. The Phase IIb/III clinical trial, entitled SEATTLE (Safety and Efficacy Assessment Treatment Trials of Emixustat hydrochloride), was a multicenter, randomized, double-masked, dose-ranging study that compared ACU-4429 to placebo in patients with geographically atrophic dry AMD35. In this trial 508 subjects were randomized (1:1:1:1) to arms given emixustat 2.5, 5, 10 mg, or placebo daily for 2y.
The results of the trial however showed that emixustat did not reduce the growth rate of geographic atrophy, and the most common adverse events were delayed dark adaptation (55%), chromatopsia (18%), visual impairment (15%), and erythropsia (15%)\[36\]. Another visual cycle modulator currently being studied is ALK-001. ALK-001 is a modified form of vitamin A that forms toxic vitamin A dimers more slowly than natural vitamin A. Accumulation of high levels of vitamin A dimers in the RPE is thought to induce retinal toxicity and contribute to the development and/or progression of AMD\[36\]. Currently, a Phase III, multicenter, randomized, double-masked, parallel-group, placebo-controlled study is investigating the safety and efficacy of ALK-001 in subjects with geographic atrophy secondary to AMD\[36\]. The study is currently recruiting and aims to have 300 participants.

**Neuroprotection** Neuroprotection aims to stop progressive cellular damage and necrosis in AMD by utilizing cytoprotective and neuroprotective agents to enhance resilience of neuroretinal tissue against cellular injury. There are various strategies being investigated to achieve neuroprotection, such as, reducing oxidative injury, inhibiting cell death and apoptosis, and adding neurotrophic factors. The following will examine therapies being explored to convey neuroprotective properties to neuroretinal tissue.

Elamipretide is a tetrapeptide drug designed to reverse mitochondrial dysfunction by improving ATP production, restoring mitochondrial membrane potential and normal calcium influx, and reducing superoxide generation\[37\]. It is theorized that this mitochondrial dysfunction can lead to cell death and geographic atrophy in dry AMD. The ReCLAIM-1 Phase I clinical trial was an open-label, single-center trial to evaluate safety and tolerability of elamipretide in 40 subjects with either noncentral geographic atrophy or high-risk drusen without geographic atrophy\[38\]. The subjects received 40 mg elamipretide subcutaneous injection daily for 12wk. The results at 24wk showed that the group with noncentral geographic atrophy had a mean increase in BCVA of 4.6±5.1 letters from baseline (P=0.003) and a mean increase in low-luminance visual acuity (LLVA) of 5.4±7.9 letters from baseline (P=0.025). There was also found to be a mean increase in low-luminance reading acuity of logMAR -0.52±0.75 (P<0.017), though BCVA had no significant change. The growth rate of the lesion (mean change in square root area 0.13±0.14 mm by OCT) was shown to be less than that of 24-week growth rate observed in placebo control arms. In the high-risk drusen group at 24wk, there was a mean increase in BCVA of 3.6±6.4 letters from baseline (P=0.025) and mean increase in LLVA of 5.6±7.8 letters from baseline (P=0.006). There was also an increase in BCVA of logMAR -0.11±0.15 (P=0.005) and an increase in low-luminance reading acuity of logMAR -0.28±0.17 (P=0.0001)\[37\]. These results demonstrated that elamipretide was well tolerated in patients with dry AMD, and that elamipretide may also slow geographic atrophy progression. The ReCLAIM-2 trial is a Phase II, randomized, double-masked, placebo-controlled study to evaluate the safety and efficacy of elamipretide in subjects with AMD with noncentral geographic atrophy\[39\]. An estimated 180 subjects will be randomized 2:1 to receive 40 mg elamipretide via subcutaneous injection or placebo injection daily for up to 48wk with a 4-week follow-up. The trial is currently recruiting and results are awaited.

Brimonidine tartrate is an alpha-2 adrenergic agonist classically used for lowering intraocular pressure by topical administration in patients with glaucoma, but is being evaluated for possible neuroprotective properties based on observations from animal studies\[40-41\]. In a Phase IIa randomized clinical trial of a brimonidine delayed-delivery intravitreal implant, 119 subjects with geographic atrophy were followed over 24mo to determine safety and efficacy compared to sham. The delayed-delivery bioerodible implant is designed to release brimonidine over six months, with another implant at 6mo. Subjects were randomized to either 200 µg brimonidine implant (n=49), 400 µg brimonidine implant (n=41), or sham procedure (n=23)\[42\]. Geographic atrophy progression rate compared to sham was lower in brimonidine groups but was not statistically significant. BEACON, a Phase IIb multicenter, randomized, double-masked, parallel-assignment, trial of newly formulated 400 µg brimonidine implant vs sham procedure, consisted of 310 participants with geographic atrophy secondary to AMD. The implant was given on day 1 and replaced at 3-month intervals\[43\]. The study was stopped at interim analysis due to slow geographic atrophy lesion progression rate of about 1.6 mm2/y in enrolled subjects; nonetheless, the results demonstrated that the implant significantly reduced lesion growth at 30mo\[44\]. Due to these results of safety and efficacy, two Phase III multicenter, randomized studies of brimonidine delayed-delivery system at 200 and 400 µg doses are planned (IMAGINE and ENVISION)\[44\].

**Anti-Inflammatory Therapies** Though commonly used as broad-spectrum antibiotics at higher doses, sub-antimicrobial doses of tetracyclines can also exhibit anti-inflammatory properties\[45\]. It has been shown that these antibiotics can prevent complement activation, inhibit cytokine production through effects on microglia and T-cell activation, inhibit caspase activation, reduce reactive oxygen species, and inhibit matrix metalloproteinases involved in the breakdown of the barrier between the RPE and Bruch’s membrane\[45-46\]. This section reviews trials evaluating antibiotics and other agents for potential anti-inflammatory properties.
Doxycycline (Oracea) is currently being studied in a Phase II/III randomized, double-blind, placebo controlled clinical trial (TOGA) to evaluate the safety and efficacy of Oracea in subjects with geographic atrophy secondary to non-exudative AMD. In this trial, 286 subjects will complete a 6-month observation phase followed by a 24-month treatment phase. The subjects will be randomized in a 1:1 ratio to 40 mg doxycycline or placebo capsules taken daily for 24 mo.\(^{[47]}\). Results are awaited.

In addition to antibiotics, a new antibody treatment is also being evaluated as anti-inflammatory agent. Studies have implicated HTRA1, a serine protease gene on chromosome 10q25, as a major genetic risk factor for wet AMD\(^{[48]}\). This gene can stimulate breakdown and destruction of extracellular matrix protein leading to atrophy in retinal tissues. In order to inhibit the HTRA1 protein, FHTR2163 (also termed RG6147 and RO7171009) a humanized Fab, is being studied. The Phase I, multicenter, single-dose, dose-escalation and multiple-dose (20 mg FHTR2163) and no serious side effects were reported\(^{[50]}\). Although the final results are awaited, a Phase II trial is already recruiting. The Phase II, multicenter, randomized, single-masked, sham-controlled clinical trial (GALLEGO) is assessing safety and efficacy of intravitreal injections of RG6147 in subjects with geographic atrophy secondary to AMD\(^{[49]}\). The trial has been completed and, while final results have not been posted, according to intermediate results by Roche the therapy was found to be safe and well-tolerated at the highest dose tested (20 mg FHTR2163) and no serious side effects were reported\(^{[50]}\). Although the final results are awaited, a Phase II trial is already recruiting. The Phase II, multicenter, randomized, single-masked, sham-controlled clinical trial (GALLEGO) is assessing safety and efficacy of intravitreal injections of RG6147 in subjects with geographic atrophy secondary to AMD. The study aims to enroll 360 subjects who will be randomized to one of four arms: intravitreal RG6147 every four weeks, intravitreal RG6147 every eight weeks or a respective sham control for approximately 76 wk\(^{[51]}\). At the end of this Phase II trial, eligible subjects will have the option of enrolling in an open-label extension study with subjects receiving 20 mg RG6147 every four weeks or 20 mg RG6147 every six weeks for up to 148 wk\(^{[52]}\).

**Photobiomodulation** This potential therapy utilizes light within the spectrum of low-intensity visual light to near infrared in order to affect cellular function of retinal cells. This non-invasive treatment option works by using wavelengths of light that can be absorbed by cytochrome C oxidase in the mitochondria of retinal cells to improve cellular respiration, increased membrane potentials, and ATP production; it also leads to reduction in markers of age-related retinal inflammation, reduced free radical production and oxidative stress\(^{[53]}\). Thus, the activation of the mitochondrial respiratory chain components leads to stabilization of metabolic function and can ultimately promote cellular proliferation, in addition to, cytoprotection\(^{[54]}\). Several studies are currently underway to explore the safety and efficacy of photobiomodulation (PBM) as a treatment for dry AMD.

In the original trial, Lightsite I, LumiThera utilized it’s LT300 Light Delivery System in a double-masked, randomized, sham-controlled, parallel group study of 30 subjects with dry AMD over a period of 1 year\(^{[54]}\). The results were presented in 2018 and showed a statistically significant reduction in central drusen volume and thickness at one year (\(P=0.005\)). Subjects also demonstrated statistically significant Visual Function Questionnaire-25 (VFQ-25) composite score (mean change from BL, 7.89, \(P=0.003, 95\%\)CI: -12.61 to -3.17) and in selected Quality of Life questions\(^{[55]}\). Based on the positive results from this trial LumiThera has several other trials in the works. LIGHTSITE II is utilizing the Valeda Light Delivery System (which delivers 590, 660, and 850 nm wavelengths of light to the study eye) in a double masked, sham-controlled, parallel design, prospective trial with 96 subjects in up to 10 European centers\(^{[56]}\). The subjects are randomized 1:2 to sham vs PBM treatment, receiving 3 treatments per week for 3-5 wk and starting again at months 4 and 8. The study is currently active and not recruiting. The LIGHTSITE III trial is another double-masked, randomized, sham-controlled, parallel group, multicenter study that is assessing the safety and efficacy of the Valeda Light Delivery System in subjects with dry AMD with repeated sham or PBM treatments at several time-points throughout the 2-year study\(^{[57]}\). This study is in the recruiting phase. Finally, the ELECTROLIGHT study is a prospective pilot study to assess retinal function with electroretinogram after PBM treatment with the Valeda Light Delivery System. Subjects in the study will receive 3 PBM treatments per week for 3 wk for a total of 9 sessions and will assess multi-focal ERG function changes, visual acuity, and contrast sensitivity among other endpoints\(^{[58]}\). This study is currently recruiting.

**Prostheses** Several implanted prosthetic devices are being engineered and studied to restore vision in degenerative diseases such as dry AMD. These prosthetic devices are designed to mimic the function of lost photoreceptors and to electrically stimulate surviving retinal cells. They provoke neural activity in remaining retinal cells by detecting and converting light into electrical stimuli that can be delivered to the unaffected areas of the inner retinal neurons to evoke downstream visual pathway\(^{[59]}\). Though there are several different retinal prosthetic implants, all of them contain an image capture unit with either a microphoto diode array or an external camera, and an array of electrodes for stimulation of the inner retinal neurons to mediate the luminance of spatial information of images\(^{[60]}\). The prosthesis systems have demonstrated benefit of some visual restoration for patients. However, there are still important hurdles related to engineering of the devices and biophysical implantation...
that would generate outcomes closer to natural vision. These devices are generally classified based on the location the device is implanted: epiretinal, subretinal, suprachoroidal or inside the optic nerve head[59].

The first approved retinal prosthetic device in clinical trials was the Argus II. This device was originally studied in patients with complete blindness due to retinitis pigmentosa, showing some restoration of basic visual function that led to authorization for use of the device on the European market in 2011[63]. Subsequently, the Argus II Retinal Prosthesis System Dry AMD Feasibility study attempted to assess the device in patients with dry AMD. In this study, 5 subjects with severe dry AMD (classified as legally blind) were implanted with the prosthesis to evaluate safety of the device and surgical procedure, functioning of the system and extent of vision restoration. The device is composed of an implanted internal unit and an external unit. The external unit consists of a small camera and transmitter mounted to a pair of glasses that is connected to a video processing unit and battery worn in a belt or shoulder strap. The implanted internal unit consists of a receiving and transmitting antenna and electronics case (fixed to the sclera outside of the eye) and a 60-electrode array surgically attached epiretinally over the macula by a retinal tack; the electrode array and electronics case are connected by a metallized polymer ribbon camera that penetrates the sclera in the pars plana[62]. The results of this feasibility study demonstrated visual function in areas of geographic atrophy that showed absent visual function before implantation; reported adverse events included development of proliferative vitreoretinopathy in two patients[63].

Another prosthetic system being researched in dry AMD is PRIMA, a photovoltaic subretinal wireless bionic vision system. This system consists of a camera integrated in the external component to capture visual information. The environmental information is processed by a pocket processor attached to the glasses and transmitted via a miniaturized projector that projects near infrared light onto the implant under the retina in the back of the eye. The photovoltaic cells of the implant convert this optical information into electrical stimulation to excite the nerve cells of the retina to induce visual perception[64]. Currently, there is a European and a US trial that are running simultaneously to study feasibility and safety. The PRIMA FS trial has enrolled 5 participants with atrophic dry AMD and is currently active and not recruiting. The 12-month results indicated that all 5 patients could perceive white-yellow prosthetic visual patterns with adjustable brightness within the previous scotomata, the majority had increased prosthetic acuity (with ability to recognize letters), and no adverse events were reported[65]. The PRIMA US feasibility study also has 5 participants and will be monitoring safety and performance of the device for up to 36mo[66]. This study is currently recruiting and results are awaited. There are several other retinal prosthetic devices aimed at vision restoration that are currently being researched in patients with retinitis pigmentosa.

**CONCLUSION**

Dry AMD is a debilitating retinal disease that leads to blindness, and that is affecting a rapidly increasing population facing lack of available therapeutic options. Different pathobiological targets that have been identified as possible contributors to the onset or progression of the disease are the focus of active investigation toward developing therapeutic strategies. Because different schools of thought have evidence supporting contribution of their pathobiological target on the onset or perpetuation of retinal damage in dry AMD, therapeutic approaches are varied and debated. Approaches from visual cycle modulation to gene therapy, to complement inhibition, to neuroprotection, to anti-inflammatory therapy, to cell-based treatments, to prosthetic devices, to PBM all have merit and an important role in elucidating which avenue will provide the best therapeutic treatment that is so desperately needed. With each trial we learn more about whether evidence of contribution to the pathology can be translated into a viable therapy. AMD pathogenesis is very complex and still not well understood, thus gaining a better understanding of the processes underlying this condition will be paramount in identifying successful treatments.

Continued research into improved methods to determine visual function endpoints for both, diagnosis and treatment of AMD are also critical. The most used endpoint currently is BCVA. This endpoint only assesses fine visual resolution and is not sensitive in the early stages of AMD, nor does it effectively demonstrate slowing of progression[67]. Other options that are being used in place of BCVA include contrast sensitivity, microperimetry, OCT, and fundus autofluorescence. Contrast sensitivity is better correlated to visual performance with respect to activities such as mobility and may be present in early stages of dry AMD, however like BCVA, is only a single functional measurement of visual function. Microperimetry combines traditional perimetry with real-time macular monitoring to account for eye movement instability seen when fixation is outside of the fovea. This modality provides accurate fundus-oriented sensitivity maps of the central visual field and is a valuable correlation between visual function and structural endpoints[67]. OCT yields 2D information for assessing the layers of the retina and 3D information can be constructed to compare with fundus autofluorescence. Continued development of OCT in order to assess for geographic atrophy and monitor lesion progression will ultimately lead to more widespread use of OCT and may assist in understanding the underlying
pathological mechanisms of AMD and GA\cite{68}. Fundus Autofluorescence detects the fluorescent signal produced by lipofuscin (an autofluorescent material in the RPE) to image the RPE. Some of the shortcomings of this imaging modality include the bright light imaging that may be uncomfortable for patients, the blue light that is utilized and may be harmful for patients, and the fact that it is not possible to determine extent of foveal involvement due to absorption by macular pigment\cite{69}. Not one of the methods described is without shortcomings but all have the potential to be utilized as a tool for evaluation of functional and anatomic endpoints. The future development of these and other such endpoints would help to better devise future trials, determine efficacy of therapies in clinical trials in a more accurate manner, and potentially give deeper insight into pathophysiological mechanisms of AMD. Continued advances in the technologies to image and assess AMD could allow earlier detection and better characterization of the disease stage, with the potential of rendering current therapies more effective if they can be initiated before substantial disease progression. As far as therapies, research in the future will need to continue investigating long-term safety and efficacy. Continued improvement in method of delivery, surgical approaches, side effect profile, and ease of patient compliance will be of vital importance as well.

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