J Med Sci 2017;37(4):121-129
DOI: 10.4103/jmedsci.jmedsci_115_16

REVIEW ARTICLE

Overview of Clinical Trials for Dry Age-related Macular Degeneration

Wen-Sheng Cheng[1,3], Da-Wen Lu[2], Chiao-Hsi Chiang[3,4], Charn-Jung Chang[3]

[1]Graduate Institute of Medical Sciences, National Defense Medical Center, [2]Department of Ophthalmology, Tri-Service General Hospital, National Defense Medical Center, [3]School of Pharmacy, National Defense Medical Center, [4]Genuine Chemical Pharmaceutical Co., Ltd, Taoyuan, Taipei, Taiwan, Republic of China

The overall goal of treating age-related macular degeneration (AMD) is to target the underlying cause of the disease and prevent, or at least slow down, the loss of vision, which requires the preservation of the choroid, retinal pigment epithelium (RPE), and photoreceptors. At present, there is no proven drug treatment for dry AMD; however, the cessation of smoking and treatments based on the age-related eye diseases study vitamin formula combined with a healthy diet are considered the only options for slowing disease progression. A number of pharmaceutical agents are currently under evaluation for the treatment of dry AMD using strategies such as reduction RPE and photoreceptor loss, neuroprotection, visual cycle modulators, suppression of inflammation, prevention of oxidative damage, and choroidal perfusion enhancers. The hope is that some of these therapies will achieve significant improvement to current management and prevent future loss of vision in this devastating eye condition.

Key words: Age-related macular degeneration, retinal pigment epithelium, photoreceptors, age-related eye disease study, choroidal perfusion enhancers

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among individuals over the age of 65 in industrialized countries. It affects 30–50 million people worldwide. Of these, 1.5 million people have wet macular degeneration with 600,000 new cases diagnosed per year.[1] This disease can be divided into two basic subtypes [Figure 1].[2] Wet or neovascular AMD (10% of cases) is the growth of new blood vessels from the choroid under macular vision, leading to rapid blindness. The other type, nonexudative or dry AMD (90% of cases), is the much more insidious subtype, in which vision slowly decreases over many years due to loss of photoreceptors and development of geographic atrophy (GA). The cause of AMD is multifactorial resulting from a combination of genetic and environmental risk factors. Cellular dysfunction and apoptosis probably play a key role in understanding the pathogenesis of AMD.[3] The vast majority of AMD patients have the dry form of the disease, characterized by a constellation of clinical features, including drusen, pigment abnormalities (focal hyper- or hypopigmentation of the retinal pigment epithelium [RPE]), and GA of the macula.[4] As defined by the age-related eye disease study (AREDS), the severity of AMD can be classified into three categories: early, intermediate, and advanced.[5]

The current management of AMD can be divided into two categories: first, antivasoendothelial growth factor (anti-VEGF) intravitreal injection for wet AMD; second, antioxidant vitamins for dry AMD. Anti-VEGF medications must be used relatively early in the disease process, before scar formation has occurred. These medications have the potential to increase the risk of thromboembolic events in an already susceptible population. Intravitreal injection, regardless of the drug used, has well-documented risks including bacterial endophthalmitis, cataract formation, hemorrhage, and retinal detachment.[6] While antiangiogenic therapies such as ranibizumab (lucentis, genentech/roche), aflibercept (eylea, regeneron/bayer), and bevacizumab (avastin, genentech/roche) have revolutionized the care of patients with neovascular AMD, there is no evidence to suggest that these antiangiogenic

Received: November 12, 2016; Revised: March 03, 2017; Accepted: May 09, 2017
Corresponding Author: Dr. Charn-Jung Chang, School of Pharmacy, National Defense Medical Center, Taipei, Taiwan, Republic of China. Tel: 886-2-87923100; Fax: 886-2-8798-3169. E-mail: michael0938@hotmail.com

How to cite this article: Cheng WS, Lu DW, Chiang CH, Chang CJ. Overview of clinical trials for dry age-related macular degeneration. J Med Sci 2017;37:121-9.

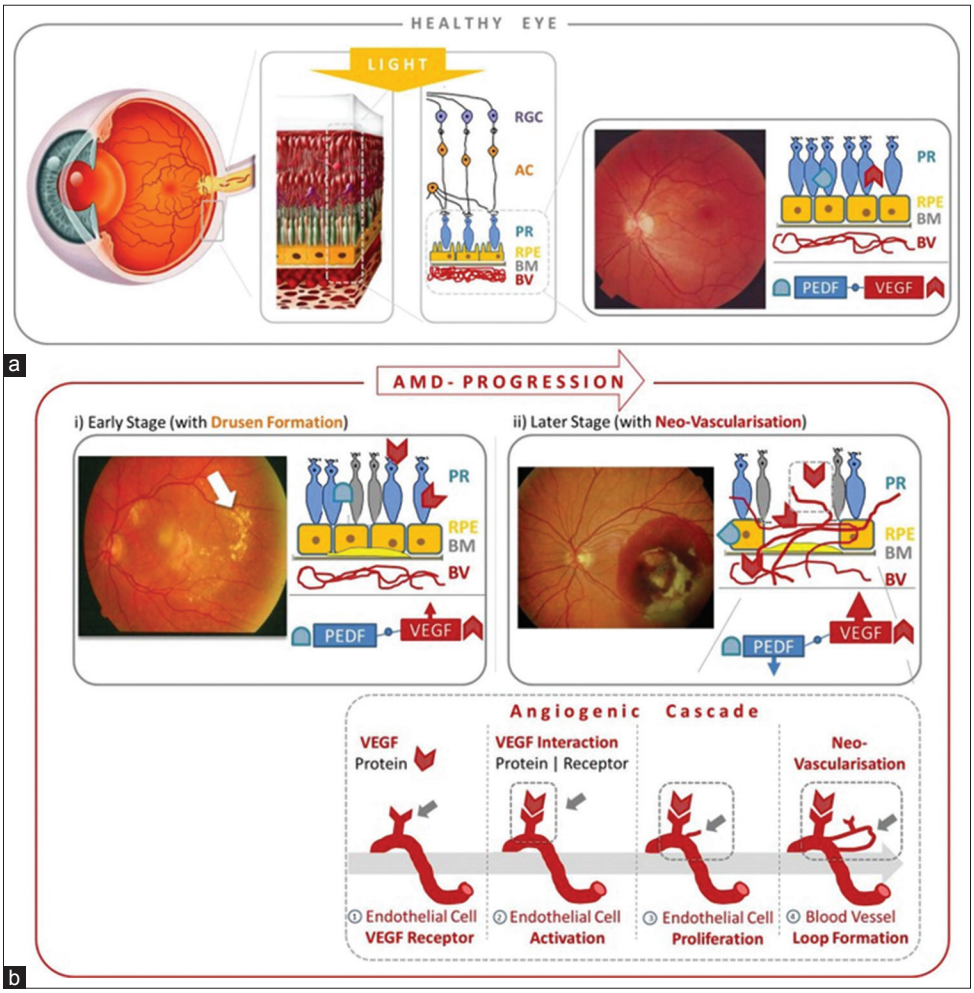

Figure 1: Illustration of the AMD progression. (a) Sketch of a healthy eye with intact morphology (RGC: retinal ganglion cells; AC: amakrin cells; PR: photoreceptors; RPE: Retinal pigment epithelium cells; BM: Bruch's membrane; BV: Blood vessels). (b) Demonstration of AMD progression: (i) Early/intermediate stage with drusen (accumulation of lipid and protein wastes in droplets) formation (light yellow) and (ii) later stage with neovascularization increased by vasoendothelial growth factor and vasoendothelial growth factor receptor interaction. An imbalance of the intraocular protein composition promotes new blood vessel formation in case of vasoendothelial growth factor dominance

drugs have any beneficial or detrimental effect on the underlying degenerative process known as dry AMD. Even under the best of circumstances when eyes with wet AMD are treated and converted back to dry AMD, the dry AMD will most likely progress over time to central GA and vision loss. New therapeutics clinical trials are being developed for both of these diseases using novel technologies, formulations, and different modes of administration.

CURRENT TREATMENT OPTIONS FOR DRY AGE-RELATED MACULAR DEGENERATION

In the past decade, the AREDS, a multicenter, randomized, controlled clinical trial demonstrated that oral supplementation using a combination of Vitamin C, Vitamin E, beta-carotene, zinc oxide, and cupric oxide in patients with intermediate or advanced AMD in one eye reduced the relative risk of developing advanced AMD in the other eye by 25%.[7] The relative risk of vision loss of three or more lines was reduced by 19%. The AREDS did not show a statistically significant benefit of the vitamin formulation for either the development of new GA or for involvement of the fovea in eyes with preexisting atrophy.[7] In part, this result may be due to the paucity of patients with GA in the study. The study also showed that patients who took the beta-carotene version of the AREDS formula and who were former smokers had an increased risk of developing lung cancer.[8] The AREDS2 is underway to determine the effect of other vitamin supplements, such as lutein, zeaxanthin, and omega-3 polyunsaturated fatty acids [Table 1], to see whether this combination can further

slow the progression of vision loss from dry AMD.[8] A number of proposed in the Complications of AMD Prevention Trial, did not demonstrate clinically significant reduction of vision loss in patients with large drusen.[9] The goal of treating dry AMD is to target the underlying cause of the disease and prevent. This approach has been hampered by two major issues. First, there are no reliable *in vitro* systems for testing the efficacy of any drug for dry AMD, and no true animal model exists for AMD. The only model that may be useful for potential drug testing is the naturally occurring monkey colonies that have been found to develop drusen. The second issue that has hampered drug development is the uncertainty surrounding the best molecular pathway to target for dry AMD treatment.

CLINICAL TRIAL ENDPOINTS IN AGE-RELATED MACULAR DEGENERATION

The most obvious study endpoint for AMD therapies would be the reservation of visual acuity (VA); however, studies using VA as an endpoint would take many years to complete due to the slow progression of the disease. To decrease the time required to show a benefit from a drug, surrogate endpoints have been developed that might indicate a positive outcome without waiting the years required to show VA benefit. These surrogate endpoints include slowing or eliminating the progression of dry AMD to wet AMD, reducing the treatment interval and burden for patients with wet AMD undergoing anti-VEGF therapy, eliminating or reducing the drusen burden in the macula, and slowing the enlargement rate of GA. The area of drusen in the macula can be measured using color fundus photography (CFP) and has already been used as an endpoint in the laser-to-drusen trials. The change in drusen autofluorescence characteristics in response to pharmacotherapy is a novel clinical trial endpoint that has been explored previously. Another clinical trial endpoint would incorporate spectral-domain optical coherence tomography (SD-OCT) as a way to reliably and reproducibly identify drusen in the macula and provide truly automated volume and area quantification. This strategy is currently being tested in clinical trials. However, based on a symposium held in Washington, DC, and sponsored by the National Eye Institute and the Food and Drug Administration (FDA), the most likely surrogate clinical trial endpoint is to assess a drug's effects on the growth of GA since GA is a feature of dry AMD that would affect vision by being associated with the loss of photoreceptors, RPE, and choriocapillaris.[9] The next most attractive endpoint involves the quantitative assessment of drusen, which are the best identified using CFP and SD-OCT. No one knows the best clinical trial endpoint for studying any of the emerging treatment; however, slowing the growth rate of GA has become the most appealing option. These modalities include CFP, fluorescein angiography, fundus autofluorescence, SD-OCT, and dark adaptation.

Table 1: Age-related eye disease study 2 and age-related eye disease study formula

Supplements	Amount (QD)		Comments (percentage DV*)
	AREDS2	AREDS	
Vitamin C	500 mg	500 mg	840
Vitamin E	400 IU	400 IU	1340
Zinc	80 mg	80 mg	540
Copper	2 mg	2 mg	100
Beta-carotene	X	15 mg	**
Lutein	10 mg	X	**
Zeaxanthin	2 mg	X	**

*Percentage DV based on a 2000-calorie diet, **DV not established. DV=Daily value; AREDS2=Age-related eye disease study 2; AREDS=Age-related eye disease study

PRECLINICAL AND CLINICAL TRIALS OF DRUGS IN DEVELOPMENT FOR DRY AGE-RELATED MACULAR DEGENERATION

Over the past decades, treatment options have focused on slowing the pathological progression of dry AMD to wet AMD and several clinical trial checkpoints have been considered to test the different treatment strategies. These strategies include (a) choroidal perfusion enhancers; (b) neuroprotection; (c) reduction of toxic byproducts; (d) visual cycle modulation; (e) suppression of inflammation; (f) stem cell replacement [Figure 2].[10]

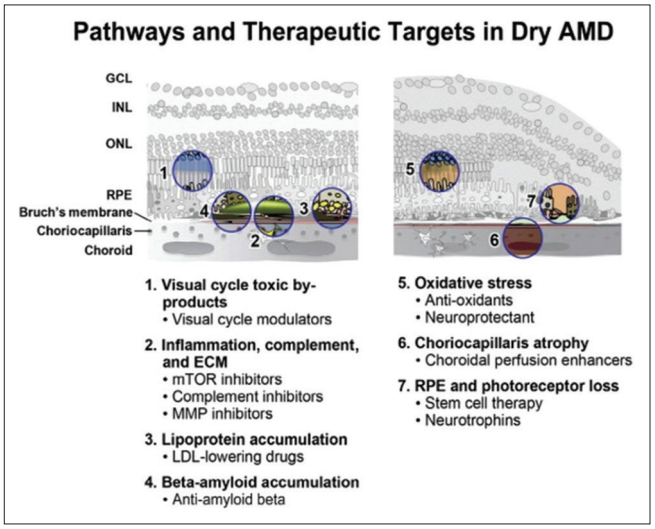

Figure 2: The pathways and therapeutics targets in dry age-related macular degeneration, up-to-date; mainly, clinical trial for dry AMD had been done by visual cycle toxic by-products (lipoprotein, β-amyloid etc.), inflammation, oxidative stress, choriocapillaries atrophy, and retinal pigment epithelium and photoreceptor loss

Improve choroidal circulation and protect against ischemia

It has been seen that blood flow through RPE/ choroid complex is reduced in patients of AMD. The blood flow reduction has been found in patients with increasing severity of AMD. Thus, the drugs which improve choroidal circulation and protect against ischemia may promote survival of photoreceptors and the RPE [Table 2].[11] Trimetazidine is a drug currently used for the treatment of angina pectoris. It improves myocardial glucose utilization by stopping fatty acid metabolism, and it is considered to have cytoprotective effects in ischemic conditions.[12] An ongoing multicenter, randomized, placebo-controlled study in Europe is investigating the off-label use of trimetazidine (Vastarel MR, 35 mg tablet) and the primary goal of this study is to slow the conversion of dry AMD to wet AMD. Other uses for this drug include the treatment of vertigo, tinnitus, and vision loss and visual field loss due to vascular causes.

MC-1101 (MacuCLEAR) is a topically administered eye drop because its active pharmaceutical ingredient has been used for decades as a systemic antihypertensive agent in the clinic, it is qualified for 505 (b)(2) status and fast track eligibility. It has been shown to increase choroidal blood flow in ocular hypertensive rabbit models measured with colored microsphere technique and to facilitate retinal function recovery following ischemic insult in rat eyes as measured with electroretinography b-waves. It works by increasing ocular blood flow in the choroidal blood vessels, thus preventing the rupture of Bruch membrane [Figure 3].[13] This approach would more efficiently return the visual cells to normal function and would be more effective than using various agents to suppress the production of numerous metabolic wastes. A phase I/proof of concept, open-label, placebo controlled study, in which healthy volunteers and patients with early dry AMD self-administered MC1101 to the front of the eye using the VersiDoser™ ophthalmic delivery system (Mystic Pharmaceuticals, Austin, TX) over 3 days, has been completed. In this study, 31 individuals (11 AMD patients and twenty healthy control patients) aged 50–89 were treated contralaterally with MC-1101 and placebo and dosed a total of seven times over 3 days. MC-1101 was found to be safe and well tolerated; no significant safety-related issues were reported in October 2009 (NCT01013376). Mild and transitory ocular hyperemia was the most common treatment related. A phase 2/3 vehicle-controlled, double-masked, single-center study comprised sixty patients and primary outcome measures were visual function and primary efficacy assessment by adaptation methodology up to 24 months; secondary outcome measures included safety and tolerability up to 24 months. The phase 2/3 trial (aged 50–85) is recruiting over the course of April 2016 in USA (NCT02127463).[11]

Table 2: Drugs to preserve photoreceptors and the retinal pigment epithelium

Drugs	Mechanism of action	Sponsor	Trial subjects	Clinical phase	Clinical trial identifier
Trimetazidine	Anti-ischemic agent with cytoprotective effects (oral)	Institut de Recherches internationales Servier	Drusen in study eye, wet AMD in follow eye	Phase III	ISRCTN99532788 (completed - not published)
MC-1101	Increase choroidal blood flow (topical)	MacuCLEAR	Dry AMD	Phase II/III	NCT02127463 (ongoing)
NT-501:encapsulated CNTF	Neuroprotection: rescues photoreceptors from degeneration (intravitreal)	Neurotech Pharmaceuticals	Geographic atrophy	Phase II	NCT00447954 (completed at April, 2011)
Brimonidine tartrate	Neuroprotection: alpha-2 adrenergic receptor agonist (intravitreal)	Allergan	Geographic atrophy	Phase II	NCT00658619 (completed at March, 2013)
Tandospirone (AL-8309B)	Neuroprotection: 5-HT1A receptor agonists (selective serotonin 1A receptor agonist) (topical)	Alcon	Geographic atrophy	Phase III	NCT00890097 (terminated at June 2014)
RN6G	Neuroprotection: binds and eliminates amyloid β (IV)	Pfizer	Geographic atrophy	Phase I	NCT00877032 (completed - not published at March, 2015) NCT01003691 (completed at March, 2013)
GSK 933776	Neuroprotection: binds and eliminates amyloid β (INF)	GSK	Geographic atrophy	Phase II	NCT01342926 (ongoing)
Fenretinide	Visual cycle inhibitors: Retinol analog inhibits binding of retinol (oral)	Sirion Therapeutics	Geographic atrophy	Phase II	NCT00429936 (completed at June 2010)
Emixustat HCl (ACU-4429)	Visual cycle inhibitors: Nonretinoid inhibits isomerization of retinol (oral)	Acucela	Geographic atrophy	Phase II Phase II/III	NCT01002950 (completed at Feb, 2014)
SEATTLE					NCT01802866 (ongoing)

CNTF=Ciliary neurotrophic factor; IV=Intravenous; AMD=Age-related macular degeneration; INF=Interferon; GSK=GlaxoSmithKline

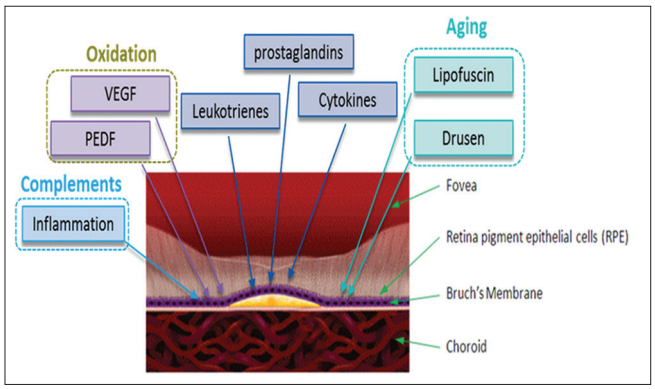

Figure 3: Summary of how restoration of choroidal blood flow (CBF) prevents progression of AMD. CBF is resumed and metabolic wastes are excreted, the visual disturbances would be halted and/or reversed. The oxidative stress can induce cell death by causing mtDNA damage in the RPR cells. Clinical, the loss of RPE cells signifies an important change of early AMD. Also the RPE cells are reduced and neovascular growth factors (VEGF, PEDF etc.) by the aged. The rich proteinaceous composition of drusen is made of complement regulators, amyloid-β (Aβ), and oxidation by-products. The secreted inflammasome effector cytokines, IL-1β and IL-18, exert cytotoxic effects on RPE cells

Neuroprotection

These drugs with neuroprotective properties are being investigated as treatments for dry AMD: an implanted encapsulated cell technology (NT-501, Neurotech); intravitreal brimonidine tartrate (Allergan); and topical tandospirone (AL-8309B; Alcon) [Table 2].

NT-501 is a ciliary neurotrophic factor (CNTF), a neuroprotective cytokine that prevents photoreceptor degeneration. It is one of the most powerful retinal neuroprotective agents known. CNTF prevents the loss of the outer nuclear layer. In an animal model, eyes implanted with polymer membrane capsules that secreted CNTF had a marked increase in the thickness of the outer nuclear layer compared with fellow untreated eyes. The device was evaluated in a phase 2 double-masked, sham-controlled study in 51 patients randomized 2:1:1; 24 patients received a high-dose implant, 12 patients received a low-dose implant, and 12 received placebo in a sham procedure.[14] The endpoint was VA at 12 months. Secondary endpoints included macular thickness/volume on OCT and lesion size. There was, however, no difference in progression of GA with the implant compared with sham. This study has been completed at April 2011.[11]

Brimonidine tartrate, an alpha-2 adrenergic receptor agonist, has been shown to be neuroprotective of retinal ganglion cells, bipolar cells, and photoreceptors in numerous animal models of nerve insult including ischemia, ocular hypertension, phototoxicity, and partial optic nerve crush. In this sustained-release formulation, brimonidine is being evaluated in a phase 2 trial in patients with bilateral GA. The implant, containing either 200 μg or 400 μg of drug, is inserted in one eye, and the fellow eye serves as control. The primary outcome measure is a comparison of treated and untreated eyes. The results have not been announced in March 2013.

Tandospirone**,** a topical selective serotonin 1A agonist, is approved and marketed in Japan, as an antidepressant. It has demonstrated neuroprotection in animal models, showing dose-dependent protection of photoreceptors and RPE cells from severe photooxidative stress. A phase 2 trial called geographic atrophy treatment evaluation has enrolled 540 patients, equally randomized to placebo, low dose and high dose of tandospirone. The trial result has been terminated at June 2014.[11]

Reduction of byproduct accumulation

These substances using this strategy are being assessed: intravenous RN6G (PF-4382923, Pfizer), antiamyloid beta (Aβ) antibody, and GSK 933776 (Glaxo Smith Kline) [Table 2].

RN6G (Pfizer) is a humanized monoclonal antibody against both Aβ40 and Aβ42. Administered intravenously, it binds and sequesters Aβ species in the retinal periphery, reducing the pool of toxic species in the macula and preventing the accumulation of Aβ40 and Aβ42, which have been implicated in neurodegenerative disorders. Pfizer has completed a phase 1 safety trial of the compound. A phase 2 study is planned, in which 45 subjects with dry AMD will be treated with escalating doses monthly for 6 months. The phase 1 study is completed and the phase 2 has been terminated at November 2015 (NCT00877032, NCT01577381).[11,15]

GSK 933776 is a humanized monoclonal antibody against amyloid beta, which is given by an intravenous infusion into the blood. The phase 1 study has been completed in patients with advanced AMD at July 2014 and the phase 2 study evaluating 6 monthly doses on the growth of GA is currently underway (NCT02033668, NCT01342926).[16]

Visual cycle modulators

Visual cycle modulators have received considerable attention in ophthalmology lately. There are two in development for the treatment of dry AMD, oral fenretinide (RT-101; ReVision Therapeutics; Sirion), and oral ACU-4429 (Acucela) [Table 2]. Visual cycle modulation essentially "slows down" the activity of the rods and reduces the metabolic load on the cones. It is hoped that, in doing this, these compounds can slow the deterioration that accompanies aging, reduces the accumulation of toxic fluorophores: bis-retinoid N-retinylidene-N-retinylethanolamine (A2E) and lipofuscin, and prevents the loss of photoreceptors and RPE cells.

Fenretinide (Sirion) conducted a phase 2 study with 246 patients with GA. The medication was an oral daily soft gel capsule given with the evening meal. Patients were randomized 1:1:1-100 mg, 300 mg, and placebo. It was a 2-year study, with interim analysis after 1 year. The medication slowed GA growth in 43% of patients, but this was only evident in a subgroup analysis, the results were not statistically significant, and no phase 3 study is planned.[17]

ACU-4429 is a small molecule, given orally, that acts selectively on the rod photoreceptors. Rods are the major source of A2E, and 90% of the photoreceptor cells are rods. This compound inhibits Rpe65 in the visual cycle and thereby reduces the buildup of 11-cis retinol and slows down the rod visual cycle [Figure 4]. The phase 2/3 trial SEATTLE is a randomized, double-masked, placebo-controlled, multicenter safety and efficacy study in patients with dry AMD/GA. There are three planned escalating dose levels of ACU-4429 (2.5, 5 and 10 mg) versus placebo (0 mg) orally QD. The pill is given at night due to problems with night vision. The dosing is once-a-day over 2 years. The study, which is currently ongoing, is expected to enroll approximately 440 patients.[18]

Suppression of inflammation

Suppression of inflammation in dry AMD is being investigated with a number of approaches, including suppressor T-cells, glucocorticoid treatment, and complement inhibition [Table 3].

Glatiramer acetate (Copaxone, Teva Pharmaceutical Industries) can suppress T-cell and downregulate inflammatory cytokines, to reduce Aβ-induced retinal microglial cytotoxicity and allow a neuroprotective phenotype of microglia to form. The drug has been approved by the US FDA for the treatment of multiple sclerosis. The study found that, the percentage of convex drusen that shrank or disappeared after 12 weeks of treatment was significantly higher in the glatiramer-treated group (27.8%) in comparison with the sham-treated group (6.8%; $P = 0.008$).[18] The trial has been suspended recruitment at 2013.[11]

Glucocorticoids, an extended release of polyimide tube containing 180 mg fluocinolone acetonide implant (Iluvien, Alimera Sciences, Alpharetta, GA), that is, FDA approved for the treatment of posterior noninfectious uveitis is being investigated in a phase 2 clinical trial in 40 patients with bilateral GA. The primary outcome measure will be the difference in GA enlargement between the treated eyes at high (0.5 mg/day) or a low (0.2 mg/day) dose and the untreated fellow eyes as a control. The results of this trial have not been released.

Complement inhibition – the complement system is part of the innate immune system. It helps defend the body from infection and modulate immune and inflammatory responses. Genetic association studies using different populations have

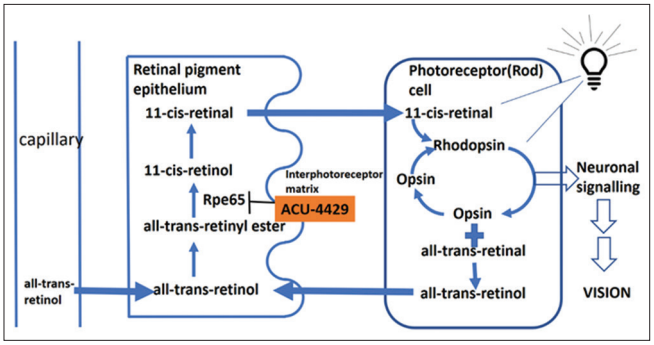

Figure 4: ACU-4429 inhibits Rpe65 in the visual cycle, reducing buildup of 11-cis retinol and slowing the rod visual cycle. RPE cells phagocytose the oxidized tips of photoreceptors outer segments (POS) for the recycling of 11-cis retinal as part of the visual cycle. With age, the recycling capacity of RPE cells decreases significantly. As a result lipofuscin, a lipid peroxidation by-product accumulates in the RPE. ACU-4429, a small nonretinoid molecule, is a modulator of the isomerase (RPE65) required for the conversion of all-trans-retinol to 11-cis-retinal in the RPE. By modulating isomerization, ACU-4429 slows the visual cycle in rod photoreceptors and decreases the accumulation of retinal toxic by-products such as N-retinylidene-N-retinylethanolamine (A2E)

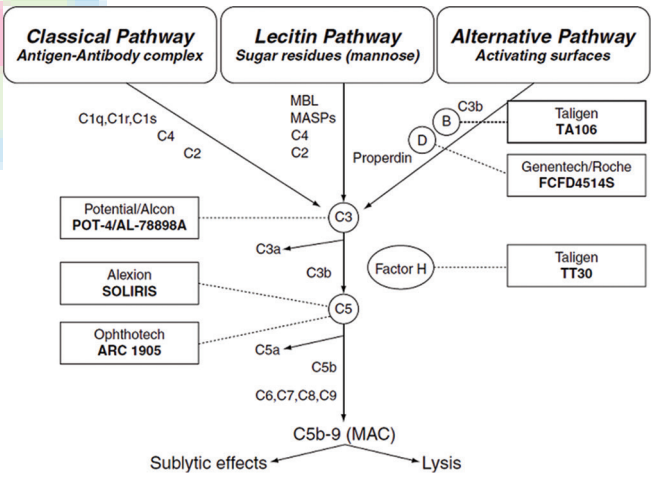

Figure 5: The complement pathway and drugs that modulate complement activation. A number of strategies for modulating the complement system are now being explored for the treatment of age- related macular degeneration. These include, in general, approaches that block various effector molecules, such as C3, C5, factor B, and factor D and an approach that reestablishes control and homeostasis of the system by augmentation the pathway with the protective form of complement factor H. This figure depicts 5 potential targets within the complement pathway that are being considered for therapeutic intervention: TA 106, which inhibits factor B; FCFD4514S, which inhibits factor D; POT-4/AL-78898A, which inhibits the system at the level of C3; SOLIRIS and ARC1905, which inhibits the system at the level of C5. All these inhibitors should prevent formation of the MAC and C5a. The target protein for each drug is encircled. Drugs and manufacture are listed in boxes with a dashed line connecting between the drug and its target protein in the complement cascade. MAC: Membrane attack complex, MBL: Mannose-binding lectin, MASPs: MBL-associated serine proteases

Table 3: Drugs to suppress inflammation

Drugs	Mechanism of action	Sponsor	Trial subjects	Clinical phase	Clinical trial identifier
POT-4/AL-78898A	Inhibits complement component 3 (intravitreal)	Potentia/alcon	Wet AMD Advanced neovascular lesions	Phase I	NCT00473928 (completed at March, 2010)
ARC1905	Aptamer against complement component 5 (intravitreal)	Ophthotech	Geographic atrophy and/or drusen	Phase I	NCT00935883 (completed at November, 2013)
Eculizumab	Monoclonal Antibody against complement component 5 (IV)	Alexion	Geographic atrophy and/drusen	Phase II	NCT00935883 (completed at January, 2015)
FCFD4514S	Fab derived from a monoclonal antibody against complement factor D (intravitreal)	Genetech/Roche	Geographic atrophy	Phase I	NCT00973011 (completed at February, 2012)
Glatiramer acetate (Copaxone, Teva)	Induces glatiramer acetate-specific suppressor T-cells and downregulates inflammatory cytolines (subcutaneous)	Kaplan Medical Center New York Eye and Ear Infirmary	Drusen	Phase II, III Phase I	NCT00466076 (unknown April, 2007) NCT00541333 (suspended at May 2013)
Fluocinolone acetonide (iluvien)	Glucocorticoid-mediated Suppression of inflammation (intravitreal)	Alimera sciences	Geographic atrophy	Phase II	NCT00695318 (terminated at May 2015)
LFG 316	Inhibits complement component 5 (intravitreal)	Novartis	Geographic atrophy Dry AMD	Phase II	NCT01527500 (completed at December, 2015)
TA 106	Antigen-binding fragment from a monoclonal antibody against complement factor B	Taligen Therapeutics	Dry AMD	Preclinical	None

IV=Intravenous; AMD=Age-related macular degeneration

shown that inflammation appears to be the driving force behind AMD.[19] In 2005, four groups identified a genetic polymorphism in complement factor H which was associated with an increased risk of developing AMD. These genetic association studies confirmed previous histopathological studies that implicated complement proteins in the pathogenesis of AMD [Figure 5]. The following medicines target different stages in the complement pathway: Eculizumab, Aptamer (C5 inhibition); POT-4 (C3 inhibition); antifactor D; LFG 316 (C5 inhibition) [Table 3].

Eculizumab (alexion) is the first FDA-approved complement inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria. It is a humanized IgG antibody against C5. It is currently administered by intravenous (systemic) infusion. It works by preventing lysis of red blood cells and the formation of membrane attack complex. The phase 2 study had been completed, but it did not demonstrate decreased drusen volume or prevent GA growth in two separate cohorts (NCT00935883).[11,20]

Aptamer (ARC1905, Ophthotech) is given by intravitreal to eye, but the phase I study had been completed at November, 2013 (NCT00950638).[11]

POT-4, now known as AL-78898A (Alcon), is a cyclic peptide that irreversibly binds to C3 to inhibit complement pathways and prevent membrane attack complex formation. It forms a gel when injected into the vitreous. The phase 2 study evaluated 12 monthly doses on the progression of GA at March 2010. The results have not yet been released (NCT00476928).[21]

Antifactor D fab/lampalizumab (genentech/roche) is a humanized monoclonal antibody fragment targeting complement factor D. It is designed to inhibit complement activation and chronic inflammation in tissues. The phase 1/2 clinical trial (MAHALO) evaluated antifactor D for GA associated with dry AMD. The complement inhibitor lampalizumab reduces disease progression by 20% and by 44% in a biomarker-defined subset, according to results from the MAHALO study. Of the biomarkers were identified, patients with complement factor I showed a protective response to the medication in preventing disease progression. These data were presented at the 2013 American Academy of Ophthalmology subspecialty day meeting. A phase 3 study is planned.[11,20]

LFG 316 (Novartis) is an antibody against the C5 portion of the complement pathway. A long-acting delivery system is in preclinical development.[21] It is administered by intravitreal injection. The phase 1 study has been completed in patients with advanced AMD, GA, or choroidal neovascularization. The phase 2 study is currently ongoing, evaluating 6 monthly doses on the growth of GA. This study has been completed at December 2015.[11]

Stem cell replacement

Another potential therapy is the delivery of stem cells. Two of the companies currently pursuing this therapy are advanced cell technology (ACT) and Janssen Biotech (JandJ and I-science) (CNTO 2476).

ACT is using human embryonic stem cells (hESCs). There are two separate phase 1/2 trials to test the safety of the hESC-derived RPE cellular therapy for dry AMD and Stargardt macular dystrophy. The first study is a single uniocular subretinal infusion of MA09-hRPE cells in 1 of 4 dose levels NCT01345006). The other is a phase 1/2 a study to evaluate the safety and tolerability of MA09-hRPE cellular therapy in patients with advanced dry AMD. The study is ongoing but not recruiting participants at December 2015 (NCT01344993).[11]

CNTO 2476 uses stem cells derived from an umbilical source. The cells are delivered through subretinal injection, external approach using iTrack microcatheter, and endoscope. There is a phase 1/2 a study ongoing in GA patients, and currently, two centers are enrolling. This study is ongoing, but not recruiting participants (NCT01226628).[11]

CONCLUSION

One of the difficulties in dry AMD research is that it is a uniquely human disease with no good animal models. Despite this, valiant research efforts continue at many centers around the country and worldwide. Several different treatment strategies and clinical trial endpoints are being investigated, but it will take years before we know if any of them are successful. Regardless of whether any of these drugs prove successful, these clinical trials will produce a wealth of natural history data on the progression of dry AMD and provide us with extensive experience using several different imaging modalities to track disease progression. As we refine our clinical trial design and investigate established and novel drugs for the treatment of dry AMD, there is a good chance that a treatment breakthrough should occur within the next decade. Many clinical trials are under way, and it is to be hoped that within the next year, some of them will yield promising results and point the way toward the future therapies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Klein R, Cruickshanks KJ, Nash SD, Krantz EM, Nieto FJ, Huang GH, *et al.* The prevalence of age-related macular degeneration and associated risk factors. Arch Ophthalmol 2010;128:750-8.
2. Target AMD. Available from: http://www.targetamd.eu/scientific-background/disease-pathology/.
3. Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: The complications of age-related macular degeneration prevention trial. Ophthalmology 2006;113:1974-86.
4. Friedman DS, O'Colmain BJ, Muñoz B, Tomany SC, McCarty C, de Jong PT, *et al.* Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564-72.
5. Ferris FL, Davis MD, Clemons TE, Lee LY, Chew EY, Lindblad AS, *et al.* A simplified severity scale for age-related macular degeneration: AREDS Report No 18. Arch Ophthalmol 2005;123:1570-4.
6. AMD Alliance International. Available from: http://www.amdalliance.org/.
7. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with Vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS Report No 8. Arch Ophthalmol 2001;119:1417-36.
8. Age-Related Eye Disease Study Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA 2013;309:2005-15.
9. Ding X, Patel M, Chan CC. Molecular pathology of age-related macular degeneration. Prog Retin Eye Res 2009;28:1-18.
10. Patel HR, Hariprasad SM, Eichenbaum D. Geographic atrophy: Clinical impact and emerging treatments. Ophthalmic Surg Lasers Imaging Retina 2015;46:8-13.
11. Available from: http://www.clinicaltrials.gov.
12. Yehoshua Z, Rosenfeld PJ. Treatment Approaches for Dry AMD. Holz FG, Pauleikhoff D, Spaide RF, Bird AC, editors. Age-related Macular Degeneration. Ch. 17. Berlin, Germany: Springer; 2013. p. 263-74.
13. Chiou G. Is dry AMD treatable? A new ophthalmic solution may halt disease progression. Retina Today 2012:69-71.
14. Jaffe GJ, Tao W. A Phase 2 Study of Encapsulated CNTF-secreting Cell Implant (NT-501) in Patients with Geographic Atrophy Associated with dry AMD-18-month Results. Paper Presented At: American Society of Retina Specialists 28th Annual Meeting; Vancouver, Canada; August 28-September 1, 2010.
15. Evans JB, Syed BA. New hope for dry AMD? Nat Rev Drug Discov 2013;12:501-2.

16. Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ. Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. Retina 2013;33:498-507.
17. Kubota R, Boman NL, David R, Mallikaarjun S, Patil S, Birch D. Safety and effect on rod function of ACU-4429, a novel small-molecule visual cycle modulator. Retina 2012;32:183-8.
18. Landa G, Rosen RB, Patel A, Lima VC, Tai KW, Perez VR, *et al.* Qualitative spectral OCT/SLO analysis of Drusen change in dry age-related macular degeneration patients treated with Copaxone. J Ocul Pharmacol Ther 2011;27:77-82.
19. Gehrs KM, Jackson JR, Brown EN, Allikmets R, Hageman GS. Complement, age-related macular degeneration and a vision of the future. Arch Ophthalmol 2010;128:349-58.
20. Roe R, Boyer D. The Pipeline for Dry Macular Degeneration. Review of Ophthalmology; 2011. Available from: https://www.reviewofophthalmology.com/article/the-pipeline-for-dry-macular-degeneration.
21. Ambati J, Atkinson JP, Gelfand BD. Immunology of age-related macular degeneration. Nat Rev Immunol 2013;13:438-51.