

ADVANCES IN THERAPY FOR DRY AMD

Numerous approaches to treatment of dry AMD are under development.

BY ARON SHAPIRO



Among the multitude of age-related conditions we face is age-related macular degeneration (AMD). The risk of AMD increases directly with age, and AMD is more common in white Americans and others of European descent, affecting more than 14% of those older than 80 years in this population.¹ If left untreated, AMD

can progress from the early dry stage to the wet form and eventually to irreversible blindness.²

Certain precautions can help mitigate the progression of AMD. Because obesity can increase the risk of AMD progression, good nutrition (including leafy vegetables, fruits, and foods rich in omega-3 fatty acids), and weight control are suggested, along with nutritional supplementation.³ The multicenter, randomized, controlled AREDS clinical trial found that oral supplementation with a combination of antioxidants and zinc in patients with intermediate or advanced AMD in one eye reduced by 25% the risk of developing advanced AMD in the other eye over the next 5 years.⁴ Avoiding smoking, controlling blood pressure, minimizing exposure to ultraviolet and harmful blue light, and attending periodic eye examinations can all contribute to decreasing progression of this disease.³

Although these precautionary measures can help to decelerate AMD progression, often some form of therapy is ultimately required. This article describes therapeutic options in development that could pave the way for more effective management of dry AMD.

DRY AMD DEVELOPMENT AND PROGRESSION

Cellular damage that accompanies aging often causes incomplete phagocytosis and breakdown of the outer segments of retinal pigment epithelium (RPE) cells. This can result in a buildup of the waste product lipofuscin in RPE cell granules. Lipofuscin is composed of membrane phospholipids, membrane proteins, visual cycle proteins, lipid-protein complexes, and retinoids. N-retinylidene-N-retinylethanolamine (A2E), one of the main chromophores residing in the lipofuscin granules, is responsible for lipofuscin-mediated phototoxicity.⁵⁻⁷

Phospholipids of plasma membranes are rich in docosahexaenoic acid (DHA), a multisaturated omega-3 lipid acid.

When eyes are exposed to sunlight in an environment rich in oxygen, DHA combines with phosphatidylethanolamine PE (PE-DHA) or phosphatidylcholine (PC-DHA) and by peroxidation splits into carbonic fragments, which, when combined with protein, make up carboxyethylpyrrole-protein adducts (CEPs). CEPs play a role in the inflammatory process associated with AMD.⁷⁻⁹

Malondialdehyde (MDA) is another molecule involved in AMD progression. Complement factor H binds MDA and can block MDA-induced proinflammatory effects.¹⁰

During the visual cycle, a reaction between all-trans-retinal and membrane phospholipids causes the release of A2E, the photosensitization of which leads to the production of reactive oxygen species (ROS). This excessive oxidative stress can result in RPE cell dysfunction and, ultimately, apoptotic cell death.^{5,9,11,12}

The development of drusen, or yellow amorphous deposits in the space in between RPE and Bruch membrane, signals AMD progression. Drusen may be nodular (hard and discrete) due to a focal thickening of the RPE basement membrane or may be limited in separation of the RPE basement membrane from the Bruch membrane.⁷

The disease can then progress into geographic atrophy (GA), a devastating complication of dry AMD. Drusen-associated GA can result in severe irreversible central vision loss due to the formation of dense scotomas, resulting in deficits in reading and other visual tasks. The decline in vision may be minor in the early stages if the foveas are spared, but later with central involvement it becomes severe. Visual acuity as measured on eye charts does not correlate well with GA lesions or progression, prompting the development of alternative end points for clinical research to test therapeutic agents.^{7,13}

THERAPEUTIC STRATEGIES IN DEVELOPMENT

No treatment options for dry AMD are currently in the market, and patients are usually advised to follow the precautionary measures outlined above to help slow disease progression. Many companies and researchers are developing products to target dry AMD progression by exploiting a variety of modes of action. The table "Therapeutics Under Clinical Development for Dry AMD/GA" outlines small

molecules, cell therapies, devices, and aptamers/peptides/antibodies in development for dry AMD treatment.

Intensive doses of statins, such as atorvastatin (Lipitor, Pfizer), rosuvastatin calcium (Crestor, AstraZeneca), and simvastatin (Zocor, Merck), were found to potentially clear the lipid debris that can lead to vision impairment in a subset of AMD patients studied in an early stage clinical trial. Additionally, controlling lipid cholesterol levels may be helpful in maintaining vision.⁵

Visual cycle modulators such as emixustat HCl (Acucela) function by reducing the toxic accumulation of A2E during the visual cycle, potentially slowing the progression of AMD. This is brought about by targeting RPE65 isomerase, a key enzyme for the isomerization process of all-trans-retinol to 11-cis-retinol.⁶

Inhibition of the complement system has been studied as a therapeutic approach, as local inflammation and complement activation are implicated in drusen formation.

A number of agents targeting the complement system are in development. Lampalizumab (Genentech) is a monoclonal antibody fragment targeting complement factor D.⁷ APL2 (Apellis Pharmaceuticals) is designed to broadly inhibit complement C3.⁸ LFG 316 (Novartis) is an antibody against the C5 portion of the complement pathway.⁹ Zimura (Ophthotech Corporation) is a chemically synthesized aptamer that inhibits complement factor C5.¹⁰

GSK933776 (GlaxoSmithKline) is a humanized mouse IgG1 monoclonal antibody directed against the N-terminus of the A β peptide in drusen, with the aim of reducing the pool of toxic species in the retina. Its Fc region has been engineered to reduce FC-receptor binding and complement activation to weaken the antibody's effector function and minimize the risk of side effects.¹¹

Restoration of choroidal blood flow is the proposed method of action of MC-1101 (MacuClear), using a combination of vasodilation, antiinflammation, and antioxidant properties; this could help to maintain the integrity of RPE cells and the Bruch membrane, thus preventing dry AMD from progressing to the wet form.^{12,13}

Some centers are exploring the repurposing of existing drugs for the treatment of AMD. Researchers at the University of Virginia are exploring whether the tetracycline antibiotic doxycycline, under development as Oracea, could help prevent photoreceptor cell loss and slow the progression of dry AMD.¹⁴ Researchers at the University of California, San Francisco are investigating whether the anti-hyperglycemic drug metformin can slow DNA damage by reducing levels of ROS, thereby minimizing GA progression in patients with AMD.¹⁵

Stem cell transplantation is another treatment modality being explored by numerous investigators. It is hoped that transplanted stem cells could help to regenerate the damaged RPE layer. Investigations under way include the following:

- subretinal transplantation of human neural stem cells (HuCNS-SC; StemCells Inc.)¹⁶;
- human embryonic stem cell (hESC)-derived RPE cells (MA09-hRPE; Ocata Therapeutics - Astellas Pharma US)¹⁷;
- subretinal administration of human umbilical tissue-derived cells (CNTO 2476; Janssen Research & Development) using the iTrack Model 275 microcatheter (iScience Interventional)¹⁸;
- hESC-derived RPE cells seeded on a polymeric substrate, sized to cover a substantial portion of the macula (CPCB-RPE1; Regenerative Patch Technologies)¹⁹;
- RPE cells derived from allogenic hESCs, transplanted subretinally (OpRegen; Cell Cure Neurosciences)²⁰;
- induced pluripotent stem cell (iPSC)-derived RPE cells (Moorfields Eye Hospital NHS Foundation Trust) that meets regulatory requirements for human transplantation²¹; and
- autologous bone marrow-derived stem cells (Retina Associates of South Florida and MD Stem Cells).²²

DEVICES

Several devices are also under development for the treatment of dry AMD. The photobiomodulation treatment protocol of the LT300 Light Delivery System (LumiThera) uses exposure to low levels of laser light or to light-emitting diodes emitting visible or near infrared light applied to the eye tissue to stimulate cellular processes, potentially leading to beneficial clinical effects.²³

Other devices exploit electrical stimulation in different ways. The Argus II (Second Sight Medical Products) bypasses defunct retinal cells and stimulates the remaining viable cells, inducing visual perception by converting images captured by a miniature video camera mounted on a patient's glasses into a series of small electrical pulses. These signals are transmitted wirelessly to an array of electrodes implanted on the surface of the retina. The pulses are intended to stimulate the retina's remaining cells, resulting in the perception of patterns of light in the brain. The patient then learns to interpret these visual patterns, thereby regaining some visual function. The system is controlled by software and is upgradeable, which may provide improved performance as new algorithms are developed and tested.²⁴

The Nova Oculus (The Eye Machine Canada) uses externally applied microcurrent electrical stimulation to administer precise amounts of electrical current. A battery-operated device delivers low-intensity electricity that increases blood flow to the surrounding tissue. As a result, the area being treated is better nourished, more oxygen gets to the tissue, and waste products are more efficiently removed.²⁵

The Rheohemapheresis device (University Hospital Hradec Kralove) is designed to improve microcirculation

TABLE. THERAPEUTICS UNDER CLINICAL DEVELOPMENT FOR DRY AMD/GA

MOA	Product	Sponsor	Indication	Phase	Mode of Delivery
Small Molecules					
visual cycle modulator	Emixustat HCl	Acucela	GA/dry AMD	2b/3	oral daily tablet
modulating choroidal blood flow	MC-1101	Macular	dry AMD	2/3	topical, twice daily
tetracycline antibiotic 40 mg doxycycline	Oracea	University of Virginia	GA/dry AMD	2/3	daily oral capsules
antioxidant; slows DNA damage, reduces ROS levels	metformin	University of California San Francisco	nondiabetic GA/ dry AMD	2	daily oral tablets
Aptamers/Peptides/Antibodies					
mAb fragment for complement factor D	lampalizumab	Genentech	GA/advanced AMD	3	intravitreal injection
inhibition of complement C3	APL-2	Apellis Pharmaceuticals	GA/AMD	2	intravitreal injection
antibody for C5 complement	LFG 316	Novartis	GA/AMD	2	intravitreal injection
aptamer; inhibits complement Factor C5	Zimura	Ophthotech	GA/dry AMD	2/3	monthly intravitreal injection
Hu-mAb for A β peptide	GSK933776	GlaxoSmithKline	retinal amyloidosis/GA/ dry AMD	2a	intravenous infusion
Cell Therapies					
stem cell transplantation	Hu-CNS SC	StemCells Inc.	GA/advanced dry AMD	1/2	subretinal transplantation
hESC-derived RPE cells	MA09-hRPE	Ocata Therapeutics - Astellas Pharma	advanced dry AMD	1/2	subretinal transplantation
Human umbilical tissue–derived cells	CNTO 2476	Janssen Research & Development	GA/AMD	1/2a	subretinal administration
hESC-derived RPE cells seeded on polymeric substrate	CPCB-RPE1	Regenerative Patch Technologies	advanced dry AMD	1/2	subretinal implantation
hESC-derived RPE cells	OpRegen	Cell Cure Neurosciences	advanced AMD	1/2	subretinal transplantation
patient-derived iPSC transplantation	iPSC-derived RPE cells	Moorfields Eye Hospital NHS Foundation Trust	wet and dry AMD	observational study	transplantation
autologous bone marrow–derived stem	BMSC- SCOTS study	Retina Associates of South Florida and MD Stem Cells	AMD	interventional study	sub-Tenon injection
Devices					
photobiomodulation or low light level therapy	LumiThera LT 300 light delivery system	LumiThera	vision loss associated with AMD	interventional study	light exposure
electrical stimulation	Argus II System	Second Sight Medical Products	late-stage AMD	1	implantable visual retinal prosthesis
transpalpebral microcurrent electrical stimulation	Nova Oculus	The Eye Machine Canada	vision loss associated with dry AMD	interventional study	externally applied microcurrent electrical stimulation
electrophysiologic methods (double plasma filtration or cascade filtration)	rheohema- pheresis	University Hospital Hradec Kralove	high-risk dry AMD	4	cascade filtration
Abbreviations: AMD, age-related macular degeneration; GA, geographic atrophy; hESC, human embryonic stem cell; iPSC induced pluripotent stem cell; mAb, monoclonal antibody; MOA, mechanism of action; ROS, reactive oxygen species; RPE, retinal pigment epithelium					

in order to halt the activity of dry AMD. The technique is based on constant flow separation of plasma through a cell separator and secondary filtration of plasma through a hollow-fiber membrane.²⁶

CONCLUSION

No currently available treatments can prevent vision loss in individuals with advanced AMD. Appropriate nutritional supplementation may delay or prevent the development of AMD. Numerous therapeutic options for dry AMD are under development. ■

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Aron Shapiro

- vice president of retina at Ora, an ophthalmic clinical research and product development firm, in Andover, Mass.
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