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Dry AMD treatments promising

Potential agents take several different paths in terms of their therapeutic benefit

By Liz Meszaros

Reviewed by David S. Boyer, MD

Philadelphia—Potential treatments for the management of dry age-related macular degeneration (AMD) are numerous, but so far, studies still are ongoing as to their therapeutic benefit, said David S. Boyer, MD, here at the Macula 2011 and Atlantic Coast Retina Club meeting of the Wills Eye Institute.



Dr. Boyer

These promising agents fall into several categories, including those that offer

neuroprotection, reduction in byproduct accumulation, visual cycle modulation, and suppression of inflammation.

“Currently, the only approved treatment of dry AMD is the use of vitamins based upon the results of the Age-Related Eye Disease Study (AREDS) that showed a reduction of both a loss of visual acuity and of progression of dry AMD,” said Dr. Boyer, who is with Retina Vitreous Associates Medical Group, Los Angeles, and a clinical professor of ophthalmology, University of Southern California/Keck School of Medicine, Los Angeles. “Patients with geographic atrophy, however, did not seem to have a reduction in formation or progression.”

Neuroprotective agents

Several neuroprotective agents currently are under investigation for the treatment of dry AMD. Among them are NT-501, brimonidine tartrate, and topical tansospirone.

■ NT-501 (Neurotech) consists of encapsulated human retinal pigment epithelium

Take-Home Message

Neuroprotection, reduced byproduct accumulation, visual cycle modulation, and inflammation suppression are all paths that may lead to the same end—a successful treatment for dry age-related macular degeneration (AMD). There is no deficit in the potential number of pharmacologic agents currently under investigation as possible treatments for dry AMD, but the final results are not in yet.

(RPE) cells genetically modified to secrete ciliary neurotrophic factor (CNTF). CNTF is a growth factor capable of rescuing dying photoreceptors and protecting them from degeneration. It has been shown to inhibit photoreceptor apoptosis in an animal model of retinal degeneration.

Using encapsulated cell technology that permits CNTF-producing transfected RPE cells to be implanted into the vitreous cavity, this agent has a sustained-release platform that produces CNTF for a year or longer. The phase II study is completed and data analysis did not show a statistically significant decrease in growth of the geographic atrophy. However, it did show a trend toward improvement in both macular volume measurements and vision in patients with good beginning visual acuity, compared with control or low dose, Dr. Boyer said.

Other neuroprotective agents currently under investigation for dry AMD include a brimonidine tartrate intravitreal implant (Allergan) and topical tansospirone (Alcon Laboratories).

■ Brimonidine tartrate is an alpha-2 adrenergic receptor agonist that has been found to be neuroprotective in a variety of animal experiments. It is injected intravitreally using the same injector as the long-acting dexamethasone implant. It is currently in phase II trials to compare the use of 200 or 400 µg, with the other eye as a control.

■ Tansospirone (AL-8309B) is a selective serotonin 1A agonist that has been shown to be neuroprotective in animal models. This drug appears to provide a dose-dependent protection of photoreceptors and RPE cells from photo-oxidative stress. The ongoing GATE trial has more than 500 participants.

Reduce byproduct accumulation

Amyloid beta has been discovered in pathologic studies of drusen. Based on this observation, several compounds that reduce the accumulation of amyloid beta are being studied. Two currently under investigation include glatiramer acetate and RN6G (PF-4382923) a humanized monoclonal antibody versus ABeta40 and ABeta42.

Glatiramer acetate (Copaxone, Teva Pharmaceutical Industries) is a treatment approved by the FDA to treat multiple sclerosis. This agent may reduce drusen over a period of 3 or 4 months when patients are treated with weekly injections. Its effects may be neuroprotective, and currently, several small studies are under way to examine this as a potential treatment.

Visual cycle modulators

Another potential strategy for the treatment of dry AMD is to interfere with the normal visual cycle and preserve vision by decreasing





ing the accumulation of toxic metabolites, including lipofuscin and A2E.

“Essentially, what visual cycle modulators do is slow down the activity of the rods and reduce the metabolic load on the cones,” Dr. Boyer said. “If we can do this, we will slow down the visual cycle, and reduce the accumulation of these toxins, A2E and lipofuscin, to prevent cell damage and eventual cell loss.”

‘Dry AMD is a uniquely human disease with no good animal models. Many [studies of] strategies targeting different aspects of the problem are currently under way, and [we hope] results from phase II trials will give us future treatments to aid our patients.’

David S. Boyer, MD

To this end, fenretinide (RT-101, ReVision Therapeutics) is being investigated. Fenretinide works to bind retinal-binding protein in the circulation.

“This complex is small and excreted by the kidneys, thereby reducing the amount of retinol binding protein available to bind with retinol. In turn, this prevents the uptake of retinol by the RPE, thereby down-regulating photoreceptor metabolism. The phase II study investigating fenretinide for the treatment of geographic atrophy has just released 2-year results. The most significant finding was the reduction in the formation of choroidal neovascularization in both the low- and high-dose groups compared [with] placebo. A phase III trial is being planned,” Dr. Boyer said.

Down-regulation of photoreceptor activ-

ity also is being investigated using an oral agent (ACU-4429, Acucela). ACU-4429 is a small nonretinoid molecule that functions as 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 toxic fluorophores (A2E) and lipofuscin. An ongoing phase I study has shown

that ACU-4429 is safe and well tolerated in healthy volunteers. A phase II study for treatment of dry AMD currently is being planned.

Suppression of inflammation

Suppression of inflammation may play a role in the formation of drusen, progression of geographic atrophy, and conversion of dry to wet AMD. Three broad categories of drugs are being studied: glucocorticoids, complement inhibitors, and sirolimus.

The most exciting approach—and the one that has received the most research interest—is inhibition of the complement system, Dr. Boyer said. Of the three main pathways of the complement system (classical, lectin, alternative), the alternative pathway has created the biggest interest. Drusen contain both C-5 and membrane at-

tack complex (C5b-9); if these components can be reduced, drusen and the potential to convert to wet AMD may be improved.

The complement pathway is being blocked at different points in the cascade by different drugs. Currently, blocking factor D, adding factor H, blocking C-3, C-3a, C5, and C5a are all being studied.

POT-4 (Potentia), a compstatin derivative that inhibits complement component 3, involves an intravitreal deposit of a cyclic peptide of 13 amino acids and recently completed phase I trials. It was found to be safe and demonstrated definite biologic activity in the higher doses. A phase II trial is under way.

Eculizumab (Soliris, Alexion) is the first FDA-approved complement inhibitor for the treatment of paroxysmal nocturnal hemoglobinuria. It is a humanized IgG antibody administered intravenously that acts against complement component 5. It is currently in an ongoing phase II trial at Bascom Palmer Eye Institute under the guidance of Philip J. Rosenfeld, MD, PhD.

“Dry AMD is a uniquely human disease with no good animal models,” Dr. Boyer said. “Many [studies of] strategies targeting different aspects of the problem are currently under way, and [we hope] results from phase II trials will give us future treatments to aid our patients.” **OT**

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