Human Visual Cycle Modulation for Dry AMD

Novel oral nonretinoid treatment targets visual cycle process that creates toxic byproducts implicated in retinal diseases.

BY NANCY BOMAN, MD, PHD

The visual cycle—the process of regenerating 11-cis-retinal in the retina—produces toxic byproducts, including A2E, which are considered to be the upstream cause of nonexudative age-related macular degeneration (AMD). Designed specifically for the treatment of retinal diseases, ACU-4429 is a new chemical entity in a class of novel, nonretinoid pharmacologic compounds intended to modulate the overactivity of the visual cycle in patients with retinal degenerative diseases. ACU-4429 is being developed by Acucela Inc. (Seattle, WA) as a once-daily, oral tablet for the treatment of dry AMD. It has been granted expedited review by the US Food and Drug Administration.

AMD

AMD affects 15 million people in the United States[1] and is reported to be the fourth leading cause of blindness worldwide.[2] For the vast majority (>80%) of these patients, there are no approved medicinal therapies. With the incidence of AMD expected to double over the next 20 years as the population ages, a significant unmet medical need exists. AMD, a retinal disease that causes severe and irreversible loss of vision, is a leading cause of blindness in individuals older than 55 years. As individuals with AMD age, the disease gradually destroys the fine central vision needed to see objects clearly and to perform common daily tasks such as reading and driving. AMD occurs in two forms: wet (exudative) and dry (nonexudative). Wet AMD is characterized by the formation of abnormal blood vessels (choroidal neovascularization). These vessels can leak fluid leading to the formation of scar tissue on the macula and causing loss of central vision. Although wet AMD accounts for approximately 20% of all cases of AMD,[3] it is responsible for 90% of blindness associated with the disease. Wet AMD evolves rapidly, with a majority of patients going blind within a few years of being diagnosed.

Dry AMD occurs when the light-sensitive cells in the macula slowly break down, resulting in poor macular function and causing a gradual loss of central vision in the affected eye. Dry AMD is much more common than the wet form of the disease: approximately 80% of all people with intermediate and advanced AMD combined have the dry form of the disease. Despite the increasing prevalence of dry AMD among the aging population, there are no therapies currently approved to treat this condition.

Dry AMD is characterized by lipofuscin deposition. The accumulation of A2E, the major component of lipofuscin, causes retinal pigment epithelial cell apoptosis. A2E accumulation can be detected by fundus autofluorescence. Ophthalmologically, dry AMD is characterized by the presence of drusen and other changes in the back of the eye. Progression of dry AMD occurs in stages, referred to as early, intermediate, and advanced. The dry form can advance and cause vision loss without turning into the wet form, but it can also convert into the wet form, even before becoming late stage. There is no way to predict if or when such a conversion may occur. The dry form of AMD initially causes slightly blurred vision. The center of vision in particular may become shadowed or fuzzy, and this blurred region grows larger as the disease progresses. The vision loss AMD patients experience greatly reduces their quality of life. Patients with AMD are more likely to have difficulties performing daily tasks such as shopping, using a telephone and even doing simple housework. The condition also increases patients' risk for accidents such as hip fractures, and many patients with the disease are unable to drive. Halting or slowing the progression of AMD would help preserve vision and improve patients' quality of life.

ACU-4429 AND VISUAL CYCLE MODULATION

The pharmacologic basis for ACU-4429 as a potential therapy for dry AMD lies in the visual cycle of the eye.

The visual cycle involves a series of biochemical reactions (Figure 1) initiated by the interaction of a photon of light with the visual pigment protein rhodopsin, leading to an electrophysiological signal and resulting in visual perception. The process continues with a series of reactions resulting in regeneration of the rhodopsin molecule, completing the visual cycle. One of the biochemical steps in the visual cycle is the isomerization of all-trans-retinol to 11-cis-retinol. The isomerization process of the visual cycle is the target of modulation by ACU-4429. Because it targets RPE65 isomerase, a key enzyme in the visual cycle that is strongly expressed in the retinal pigment epithelium (RPE), ACU-4429's mechanism of action occurs specifically within the eye.

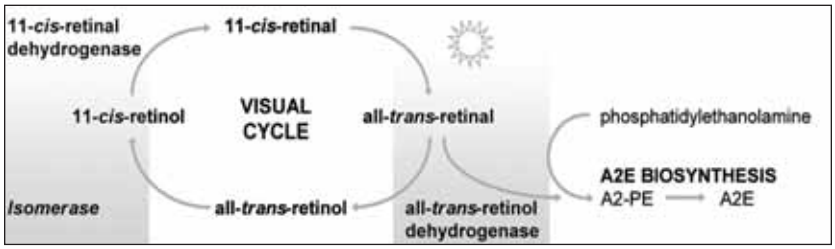

Figure 1. Visual cycle modulation mechanism of reducing A2E levels.

The pathogenesis of degeneration of the retina in dry AMD (and some other degenerative retinal diseases) is associated with generation of toxic byproducts of the visual cycle, the excess accumulation of which increases as we age and is toxic to retinal cells. Vision is initiated through the photoisomerization of rhodopsin-bound 11-cis-retinal to all-trans-retinal upon light exposure (Figure 1). Through the biochemical processes of the visual cycle, this is later re-converted to 11-cis-retinal by isomerization. All-trans-retinal has been shown to be a precursor for biosynthesis of toxic compounds such as A2E, a key component of lipofuscin accumulating in the RPE cells.[4,5] A2E exposure to light has been shown to generate phototoxic compounds that damage RPE cells.[5] A2E toxicities include free radical generation upon light exposure, detergent-like properties that can damage RPE cell membrane, inhibition of RPE lysosomes (which leads to drusen formation), and activation of complement factors, a major genetic risk factor for AMD. In preclinical models, regulating the speed of the visual cycle has been shown to reduce the rate of 11-cis-retinol formation during the visual cycle and thereby reduce the formation of all-trans-retinal and A2E accumulation, slowing or halting the progression of degenerative retinal diseases such as AMD.

ACU-4429 CLINICAL TRIALS

A recently completed phase 1 study[6] assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of a single dose of ACU-4429 in healthy volunteers 55 to 80 years of age. In the single-center, randomized, double-masked, placebo-controlled, dose-escalation study, oral administration of ACU-4429 was well tolerated. Electroretinography (ERG) tests after exposure to light flashes demonstrated a dose-dependent slowing of the b-wave amplitude recovery time over dose ranges of 10 mg to 75 mg. Additionally, data demonstrate dose-dependent suppression of b-wave amplitude using ERG, marking the first time that a nonretinoid, small molecule therapeutic has effectively targeted the visual cycle in a dose-dependent manner and suggesting that ACU-4429 may offer potential for treating dry AMD and other degenerative eye conditions. Pharmacokinetic results demonstrated that systemic exposure to ACU-4429 increased proportionately with dose, so that exposure can be easily adjusted in the clinic with increase or decrease of dose of ACU-4429. Maximal plasma concentration also increased linearly with dose. A recently completed phase 1b study assessed the safety, tolerability and pharmacokinetics of daily doses of ACU-4429 for 14 days in healthy volunteers 22 to 55 years of age. ACU-4429 was well tolerated for 14 days at doses up to 40 mg/day. ACU-4429 is currently being studied in the ENVISION (Evaluating a Novel Vision Treatment for AMD) Clarity Trial, a phase 2 clinical trial of ACU-4429 in patients with dry AMD.

SUMMARY

ACU-4429, an orally administered visual cycle modulator, is being studied in clinical trials as a potential treatment for dry AMD. ■

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