RESTORING ACCOMMODATION. *The eyedrop appears to increase lens elasticity.*

REFRACTIVE

Eyedrop Shows Promise for Presbyopia

A NOVEL ANTIOXIDANT EYEDROP shows promise of being an effective treatment for presbyopia, with a first-in-class pharmaceutical approach to addressing one of the biggest remaining refractive challenges in ophthalmology.

Unlike other potential presbyopia eyedrops on the horizon,[1] the drug (UNR844, 1.5% solution, Novartis) does not rely on the pinhole effect. Instead, it aims at directly enhancing the eye's accommodative apparatus by increasing lens deformability and elasticity.[2]

Study specifics. In a small phase 1/2 dosing and safety study, the treated patients (n = 50) showed statistically significant improvements in distance-corrected near visual acuity (DCNVA) when compared to those who received placebo drops (n = 25).[2] The improvements were detected at day 8 ($p = 0.024$) and continued to increase at every study visit thereafter, until dosing ended at day 91 ($p = 0.001$).

Outcomes. At day 91, the mean change (standard deviation [SD]) in VA was –0.159 (+0.120) LogMAR in treated eyes, versus –0.079 (+0.116) in eyes receiving placebo drops ($p = 0.007$). Improvements in DCNVA were largely sustained over the seven-month period that followed the 91 days of dosing, although there was some attenuation of the effect over time. No significant adverse ocular or systemic effects were observed in either cohort.

Mechanism of action. UNR844's active ingredient is a prodrug lipoic acid choline ester, which—when inside lens fiber cells—is metabolized into the antioxidant dihydrolipoic acid (DHLA). Inside the lens, DHLA reduces the formation of disulfide bonds between lens proteins in the aqueous humor's oxidizing environment. (During the natural progression of presbyopia, these disulfide bonds accumulate in the lens with age, stiffening it.[3]) Fewer disulfide bonds and consequent softening of the lens are thought to restore the lens' ability to accommodate.

A new era? Even though much research remains to be done—including a larger safety study and a phase 3 efficacy trial—the early results in the preliminary safety study are promising, said principal investigator Michael S. Korenfeld, MD, in private practice in Washington, Missouri. "This medication has potential for the treatment of a condition that affects pretty much everyone who lives past age 40," Dr. Korenfeld said.

Unanswered questions. Among the questions about UNR844 that remain to be answered are whether daily dosing beyond 91 days would increase the improvements seen in the current study, Dr. Korenfeld said.

Researchers also will need to develop a way to stabilize UNR844 for commercial use. "This is an antioxidant drug that is vulnerable in a way that most drugs are not. If it is exposed to oxygen, it loses its potency," Dr. Korenfeld said. "So in order to maintain full potency, Novartis will have to maintain the formulation in a reduced state in a world full of oxygen. This indeed will be tricky." —*Linda Roach*

1 Grzybowski A et al. *Asia Pac J Ophthalmol* (Phila). 2020;9(3):226-233.
2 Korenfeld MS et al. *Eye* (Lond). Published online Jan. 29, 2021.
3 Garner WH, Garner MH. *Invest Ophthalmol Vis Sci.* 2016;57(6):2851-63.

Relevant financial disclosures: Dr. Korenfeld—Encore Vision: S; Novartis: C,S; Orasis: C.

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RETINA

Smartphone-Based App Helps Monitor Progression

DURING THE PANDEMIC LOCKDOWN, ophthalmologists at the Singapore National Eye Centre (SNEC) found that some patients with retinal diseases could successfully use a smartphone-based app to monitor their eyes for signs of progression.[1]

Timely detection. The 732 participants in the SNEC study tested themselves at home for signs of metamorphopsia with the FDA-approved Alleye smartphone app (Oculocare Medical). The app requires the patient to perform a series of dot-alignment hyperacuity tasks on the phone screen.[2]

Researchers viewed test results on a dedicated monitoring portal to identify a loss in hyperacuity (considered a "trigger event"), which may precede symptomatic visual deterioration, so the patient could be brought into the clinic for follow-up. The patients had diagnoses of diabetic macular edema, wet or dry age-related macular degeneration, diabetic retinopathy, or retinal vein occlusion.

During Singapore's lockdown in early 2020, when routine appointments were postponed, the app showed trigger events in 33 patients, seven of whom were called in for exams after a telephone consultation. Of these, five subsequently proved to have clinically verified disease progression. When the remaining 26 patients were examined at rescheduled appointments, 20 were found to have no disease progression.

FOLLOW-UP? *Home testing flagged a subset of patients who needed in-person exams.*

"We believe that such self-monitoring mobile apps, if correctly paired with an education effort [and robust follow-up], represent a novel model of

GLAUCOMA

No Consensus on Best Uses of OCTA

OCT ANGIOGRAPHY (OCTA) HAS THE POTENTIAL TO transform glaucoma diagnosis and predict glaucomatous damage. However, the emerging technology is not ready for clinical practice in glaucoma, according to an *Ophthalmic Technology Assessment* (*OTA*) from the Academy.[1]

"The current literature does not support the routine use of OCTA in the diagnosis of glaucoma at this time," said Darrell WuDunn, MD, PhD, at the University of Florida College of Medicine in Jacksonville and lead author of the *OTA*.

What the literature tells us. A search of peer-reviewed literature yielded 60 articles that met the predefined inclusion criteria of the *OTA*. Most studies focused on OCTA measures of the optic nerve head and superficial peripapillary microvasculature. Others considered OCTA measures of macular microvasculature and peripapillary deep-layer microvasculature dropout. Researchers also looked at the association of peripapillary vessel density and macular density with visual fields (VFs) and with structural OCT parameters.

Findings included the following:

- Most studies detected significant correlation between glaucoma severity and degree of vessel density loss.
- Several studies found moderate to strong correlations or associations between OCTA vessel density and VF defects.
- Many found moderate correlation between the peripapillary OCTA parameters and structural OCT parameters, both overall and in sectors, in glaucomatous eyes.
- Peripapillary OCTA showed better ability than macular OCTA to differentiate glaucomatous and normal eyes.
- The peripapillary choroidal network may be a surrogate marker for optic nerve head circulation, and abnormalities in the choroidal microvasculature may correlate with glaucomatous optic nerve damage.

Validating the technology. "I was impressed with how well OCTA vessel density correlated with traditional structural and functional measures," said Dr. WuDunn, adding that this finding reassured him of the technology's validity. Even so, there is no consensus on OCTA's best applications, despite its potential utility.

One impediment to moving forward with OCTA is a lack of interpretive software, Dr. WuDunn said. "For example, not all devices provide a vessel density measurement for different sectors or retinal layers." What's more, he added, "most lack a normative database, which would enable clinicians to assess whether a macular or peripapillary OCTA image is abnormal."

Looking ahead. Once analysis software and normative databases become available, Dr. WuDunn predicted that OCTA will have a role to play. "I anticipate that peripapillary OCTA will become most useful in distinguishing glaucoma suspects from healthy persons, and macular OCTA will be most effective in monitoring severe glaucoma." *—Miriam Karmel*

1 WuDunn D et al. *Ophthalmology*. Published online Feb. 22, 2021.

Relevant financial disclosures: Dr. WuDunn—Allergan: S.

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care that should be adopted," said study leader Kelvin Y. Chong Teo, MBBS, MMed (Ophth), at the Singapore Eye Research Institute and the Duke-NUS academic clinical program. Such a model of care could help limit the number of "arbitrary monitoring visits" that are often of low yield, he noted.

Imperfect rollout. Because of the unanticipated COVID-19 lockdown, patients who agreed to enroll in this self-monitoring initiative did not have the recommended face-to-face instruction on how to use the app. This may be why only 43% of the participants complied with the request that they test their affected eyes twice a week, the researchers said. When the 33 participants were questioned about their trigger events, 15 had not tested their eyes as often as prescribed, six had been testing the wrong eye, and five reported having trouble using the test.

Looking ahead. Despite these difficulties, Dr. Teo said, the study outcomes hint at how a properly implemented self-monitoring system might benefit certain patients.

"What we found, unsurprisingly, was that younger patients or those who had family support were more likely to sign up and be adherent to the program," he said. Other patients who participated actively were those who had poor vision in one eye. "We postulate that they were more fastidious in monitoring their vision in their good eye and hence more adherent," he noted.

Dr. Teo said the SNEC continues to use self-monitoring initiatives to augment care for patients with retinal diseases. "Such initiatives should not shortchange interactions between physician and patient. Instead, they can serve to allow for a more tailored level of care, where patients are able to access care when they require it."

—Linda Roach

1 Chong Teo KY. *Ophthalmol Retina.* Published online Feb. 18, 2021.

2 Schmid MK et al. *Eye* (Lond). 2019;33(10): 1584-1589.

Relevant financial disclosures: Dr. Teo—Bayer: L; Novartis: L; Topcon: L.

CORNEA

Acanthamoeba Keratitis: Beware Misdiagnosis

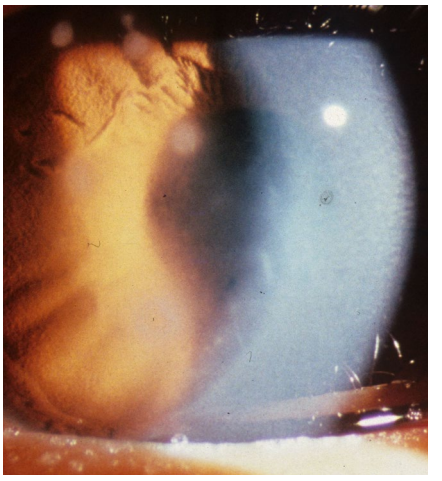
CASES OF ATYPICAL KERATITIS require a high degree of suspicion for *Acanthamoeba* keratitis (AK) and prompt referral for *Acanthamoeba* cultures, particularly in contact lens wearers, according to a study conducted at Wilmer Eye Institute in Baltimore.[1] Because of delayed or inaccurate diagnoses prior to referral, several patients in this study required PK, and the average final visual acuity (VA) of those receiving a late diagnosis was 20/240.

Easy to misdiagnose. This retrospective study included all patients (n = 43; 45 eyes) with culture-positive AK seen at Wilmer between 2012 and 2019. The patients' mean age was 41 years, and they had been symptomatic for a mean of 52.6 days (range, 6-231). Before referral, 17 (37.8%) and nine (20%) eyes were misdiagnosed with herpetic and bacterial keratitis, respectively. An additional 13 (29%) received no initial diagnosis.

Risk factors and symptoms. Contact lens use was the strongest risk factor for AK, with nearly all eyes affected (95.6%). Notably, only five eyes (11%) presented with the classic ring infiltrate of AK.

Although 37 (82%) eyes were affected by pain or discomfort, only half had severe pain. "AK is typically characterized by pain out of proportion to findings," suggesting that ophthalmologists should not rely solely on pain as a criterion, said Fasika A. Woreta, MD, MPH. Other common presenting symptoms included photophobia and blurred vision, and diffuse, multifocal, or deep infiltrate was present in roughly one-third of the patients.

Outcomes. At presentation, mean VA was 20/224 in those diagnosed within 28 days of symptom onset and 20/296 in those diagnosed more than 28 days after onset. At the final visit, VA was 20/92 in the early diagnosis group and 20/240 in the late diagnosis group.



NOT CLEAR-CUT. *Classic symptoms of* Acanthamoeba *keratitis—including severe pain—may not be present, potentially leading to an initial misdiagnosis.*

The benefit of early diagnosis in this study did not reach statistical significance, possibly due to insufficient sample size. However, the trend was toward statistical significance, as late diagnoses yielded worse VA outcomes, Dr. Woreta noted.

PK was necessary in five eyes (11%). Although none of these eyes had the classic ring infiltrate, two presented with diffuse infiltrate. Three of the five were misdiagnosed with either bacterial or herpetic keratitis.

Need for easier testing. One reason for delayed diagnosis may be a lack of access to diagnostic testing and culturing outside of tertiary care centers. To that end, coauthor Nakul Shekhawat, MD, MPH, proposed development of a rapid polymerase chain reaction test or slide preparation that can be administered in clinicians' offices. In the meantime, Dr. Woreta recommended that all contact lens wearers with any form of atypical keratitis be referred to tertiary centers for AK cultures "before making a presumed diagnosis of herpes keratitis, which can mimic AK."

—Miriam Karmel

1 Shah YS et al. *Acta Ophthalmol.* Published online Feb. 14, 2021.

Relevant financial disclosures—Dr. Shekhawat: NEI: S. Dr. Woreta: None.

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.