

# News in Review

COMMENTARY AND PERSPECTIVE

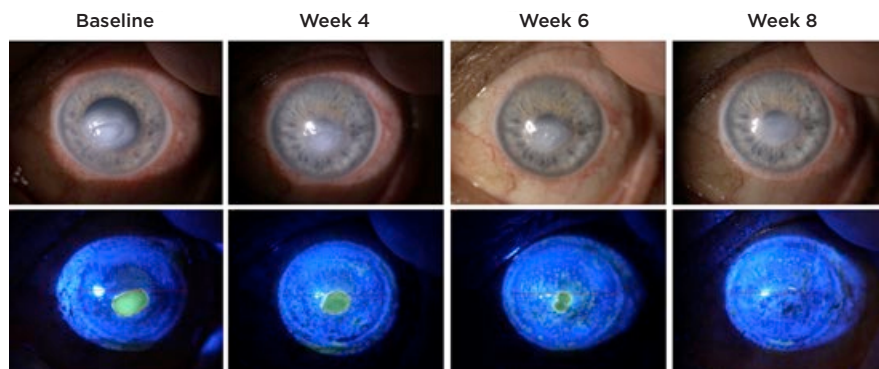
## CORNEA

### First-in-Class Rx for Neurotrophic Keratitis

**A RECOMBINANT FORM OF HUMAN** nerve growth factor (rhNGF) has become the first FDA-approved drug for the treatment of neurotrophic keratitis (NK), a degenerative disease of the corneal epithelium that results from loss of corneal sensation.<sup>1</sup> The drug—cenegermin (Oxervate, Dompé)—represents 2 additional firsts: It is the first application of an rhNGF as a drug and the first topical biologic medication approved in ophthalmology. It may become available in the United States early next year.

**Urgent need.** With NK, trigeminal nerve damage originates in the eye or the brain because of factors ranging from herpes eye infection to brain surgery, said Harminder S. Dua, FRCS, FRCOphth, PhD, at the University of Nottingham in the United Kingdom. Independently or simultaneously, NK then impairs sensory and trophic functions, including blinking, secretion of tears, and the nutritional health of corneal cells.<sup>2</sup> Although NK affects fewer than 5 in 10,000 people, its impact can be severe, ranging from corneal thinning, ulceration, and perforation to visual impairment or blindness.<sup>3</sup>

**Alleviating the damage.** Cenegermin was evaluated in 2 studies involving a total of 151 patients. Treatment involved 8 weeks of cenegermin eyedrops, delivered 8 times a day. Across both



**EFFICACY.** This patient received cenegermin for NK. Photographs taken under diffuse white light (top) and cobalt-blue light (bottom).

studies, 70% of patients treated with the drug experienced complete corneal healing, versus 28% in the control groups. Adverse reactions included eye pain and inflammation, ocular hyperemia, and tearing. After 1 year, about 80% of those who were successfully treated remained free of disease.<sup>3</sup>

“The studies were quite promising, but it was difficult to believe this was really possible until I saw it myself,” said Prof. Dua, who has now successfully treated 3 patients with severe cases of NK. Previously, he said, “We had supportive treatments such as lubricating drops, eye patching, autologous serum drops, tarsorrhaphy, and amniotic membrane patches. But we had nothing to treat the underlying disease.”

**A neural revival.** Because rhNGF is involved in the development, maintenance, and survival of nerve cells, cenegermin has the ability to address the root cause of NK and restore corneal integrity. “It revitalizes the nerves’ ability to secrete neuropeptides that support the health and regeneration of the corneal epithelium and the keratocytes of the stroma,” said Prof. Dua.

Prior to treatment, corneal sensation was as low as 5 mm in his patients with NK, with 60 mm representing normal sensation, he said. “After treatment with

Oxervate eyedrops, we’ve seen corneal sensation return to 50 mm. In addition, we can observe nerve regeneration using in vivo confocal microscopy. Although the new nerves are more coiled and tortuous, their sprouting in the cornea is very exciting.”

**Challenges ahead.** Cenegermin requires frequent instillation. But NK patients may take that in stride, as many of them have already been using multiple drops several times a day, said Prof. Dua. A bigger challenge may be the weekly visits to the pharmacy, where drops must be frozen and released a batch at a time and then kept in the patient’s refrigerator for no longer than 7 days.

“Another challenge is the cost of 2 months of treatment,” said Prof. Dua. In the United Kingdom, where clinicians have had access to the drug since 2017, that cost is about £11,000 to £12,000, he said. U.S. pricing has yet to be determined. —Annie Stuart

1 Voelker R. *JAMA*. 2018;320(13):1309.

2 Dua HS et al. *Prog Retin Eye Res*. 2018;66:107-131.

3 Bonini S et al. *Ophthalmology*. 2018;125(9):1332-1343.

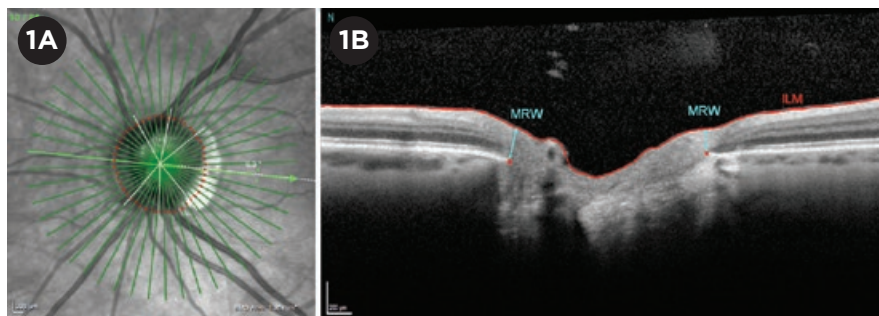
Relevant financial disclosures—Prof. Dua: Dompé: C.

## OTA Outlines SD-OCT Benefits

**CAN SPECTRAL-DOMAIN OPTICAL coherence tomography (SD-OCT) help clinicians detect structural glaucomatous damage and the changes associated with the diagnosis of glaucoma? Yes and yes, according to an Academy *Ophthalmic Technology Assessment (OTA)*.<sup>1</sup>**

“Classic structural changes associated with glaucoma can be detected in the retinal nerve fiber layer, the macula, and the optic nerve with SD-OCT technology,” said Teresa C. Chen, MD, at Harvard Medical School in Boston. She called SD-OCT “a useful tool in the management of glaucoma patients.”

**Expansion in knowledge.** The literature review began where the previous imaging *OTA* left off—February 2006—and concluded in April



**CONFIRMATION.** Radial scan (1A) and corresponding SD-OCT image (1B). In this imaging example, SD-OCT was used to rule out glaucoma in myopic eyes. MRW = minimum rim width; ILM = internal limiting membrane.

2018. During that time, 708 articles on the use of SD-OCT to help clinicians detect changes in eyes diagnosed with glaucoma appeared in the literature. Of those, 74 met inclusion criteria, with 2 identified as level I, and 57 as level II. The remaining 15 articles were not used in the analysis.

**Expansion in technology.** “Most clinical practices have transitioned from the older 2-D time-domain OCT

machines to the newer 3-D SD-OCT machines,” Dr. Chen said. In the studies evaluated in the *OTA*, the Cirrus High-Definition OCT (Carl Zeiss Meditec) was the most commonly studied machine, followed by the RTVue-100 (Optovue), the Spectralis SD-OCT (Heidelberg Engineering), and the 3D OCT-1000 and 3D OCT-2000 (Topcon).

**Results.** “Though different machines have different scan protocols

## Video-Oculography for Assessing Concussive Injury

**DESPITE THE CURRENT USE OF BRAIN IMAGING AND neurocognitive assessment, the optimal diagnosis and treatment of concussive injuries have long been hampered by a lack of objective testing. That might soon change, as researchers have identified a group of oculomotor, vestibular, and reaction time (OVRT) metrics associated with both acute and chronic concussion.<sup>1</sup>**

**Testing protocol.** Drawing on 50 high school-aged athletes clinically diagnosed with a sports-related concussion and 170 control students, the study team used a video nystagmography device that combines eye tracking, stimulation, and analysis to assess OVRT function.

Tests were conducted in dim light with the students seated in front of a white reflective screen over a broad range of postconcussion times, from 1 day to 1 year after injury. Full-field stimuli were created by a rotating projector. Other visual stimuli were projected by a 650-nm laser onto the display surface.

**A potential biomarker.** “We found multiple deficits in the concussion population compared with the controls,” said Kevin M. Kelly, MD, PhD, a neurologist at Allegheny General Hospital in Pittsburgh. “These included alterations in smooth pursuit tracking, delays

in smooth pursuit initiation, delayed reaction times, and dramatically impaired response during optokinetic nystagmus tests.”

Optokinetic nystagmus (OKN) gain was the only metric that remained significantly impaired more than 3 weeks following injury. This suggests not only that concussions can induce oculomotor deficits beyond the initial phases of recovery, but also that OKN might serve as a potential biomarker of protracted healing from traumatic brain injury.

**Therapeutic importance.** Because linear regression models were able to distinguish between concussed students and controls with high accuracy, the research team believes that OVRT metrics could serve as a diagnostic aid for general clinical use.

“These results indicate that OVRT tests can be used as a reliable adjunctive tool in the diagnosis of concussion,” said Dr. Kelly. “And given the potential for OVRT measurements to shift over the course of recovery, they might also provide the practitioner with objective assessments regarding the utility and efficacy of therapeutic approaches—such as medications and physical therapy—for treating traumatic brain injury.”

—Mike Mott

1 Kelly KM et al. *J Head Trauma Rehabil*. Published online Sept. 18, 2018.

**Relevant financial disclosures**—Dr. Kelly: U.S. Department of Defense: S; Neuro Kinetics: S.

and different software packages, all can detect the same classic pattern of structural changes noted in glaucoma—superior and inferior thinning,” said Dr. Chen. Findings from the *OTA* include the following:

- All instruments were capable of detecting damage to the retinal nerve fiber layer (RNFL), macula, and optic nerve in patients with preperimetric and perimetric glaucoma.
- RNFL was the most commonly studied single parameter, followed by the macula and optic nerve.
- All instruments can detect the same typical pattern of glaucomatous RNFL loss that affects primarily the inferior, inferior temporal, superior, and superior temporal regions of the optic nerve.
- The best disc parameters for detecting glaucomatous nerve damage are global rim area, inferior rim area, and vertical cup-to-disc ratio.
- Newer reference-plane independent optic nerve parameters may have the same or better detection capability when compared with older reference-plane dependent disc parameters.

**Bottom line.** The *OTA* does caution clinicians to be aware of factors that may influence test results, including “testing artifacts, false positives, false negatives, refractive error . . . and normal aging changes.” But overall, “SD-OCT machines allow for better axial resolutions, faster acquisition speeds, better scan quality, and better reproducibility, all of which affords us better information to care for our patients,” Dr. Chen said. —*Miriam Karmel*

1 Chen TC et al. *Ophthalmology*. 2018;125(11):1817-1827.

Relevant financial disclosures—Dr. Chen: None.

## INFECTION CONTROL

# Eye Exams Linked to NICU Infections

### OPHTHALMOLOGISTS ARE WELL

aware of the need for infection control measures when performing direct-contact exams. But a recent epidemiological investigation of an adenovirus

outbreak in a Pennsylvania neonatal intensive care unit (NICU) highlights the critical need for rigorous infection-control protocols even with indirect eye exams.

### Adenovirus outbreak.

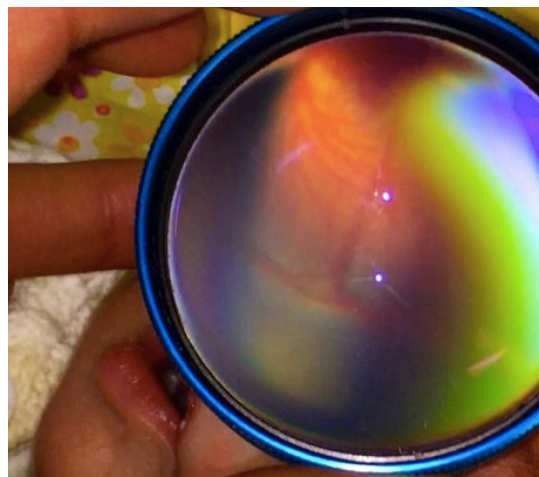
During routine microbiologic surveillance, the Department of Infection Prevention and Control at the Children’s Hospital of Philadelphia (CHOP) discovered adenovirus-positive respiratory specimens in their NICU patients in August 2016.<sup>1</sup> Their epidemiologic investigation included detailed review of neonates’ medical records, interviews with staff, and direct observation of clinical practices.

**Connection with eye exams.** Next-generation sequencing of the virus strain definitively linked the outbreak cases with ophthalmic equipment used by the providers. Real-time polymerase chain reaction (PCR) and genome sequencing found adenovirus serotype-3 DNA on 2 indirect ophthalmoscopes and 2 handheld lenses used during routine, weekly screening for retinopathy of prematurity (ROP).

**Neonatal outcomes.** Out of 43 neonates tested for ROP in August 2016, 23 tested positive for the adenovirus. Of these 23 cases, all had respiratory symptoms, 12 needed additional respiratory support, 5 developed pneumonia, and 11 had ocular symptoms. Four neonates died; of these, 3 had underlying serious conditions prior to infection. All 23 had received an ophthalmological exam during “ROP rounds” within 14 days of onset.

**Adult outcomes.** Nine adults (6 employees, 3 parents) were affected by the outbreak. All had conjunctivitis symptoms and either had provided care to or had direct contact with the infants.

**Infection control.** The investigation found that 2 providers, each using a handheld lens and indirect ophthalmoscope, moved bedside to bedside around the NICU, carrying their equipment by hand or in a pocket. Observa-



**INFECTION RISK.** Adenovirus was transmitted via handheld lenses and indirect ophthalmoscopes during routine ROP screening.

tion revealed a lack of standard hygiene practices, inconsistent handwashing, and limited glove use with this shared equipment.

The NICU then instituted stricter infection control protocols, including isolation, heightened vigilance of hand hygiene and use of gloves, daily staff screening for symptoms, and environmental disinfection. The NICU was able to contain the outbreak; no secondary transmission occurred with this vulnerable, high-risk population.

**Looking ahead.** As the outbreak has triggered legal action, CHOP officials declined to comment. But Kimberly A. Drenser, MD, PhD, at Beaumont Eye Institute in Royal Oak, Michigan, pointed out, “For premature infants, the risk of exposure is high, since they receive eye exams weekly and the ophthalmologists aren’t regular NICU staff. It’s much harder to control infection with outside staff coming in to do bedside exams.”

As a result, Dr. Drenser added, “more NICUs are moving toward digital teleophthalmology exams for ROP. NICU staff take infants’ photos and an outside reader evaluates them.”

—*Rebecca Taylor*

1 Sammons JS et al. *Ophthalmology*. Published online Sept. 1, 2018.

Relevant financial disclosures—Dr. Drenser: None.

See the financial disclosure key, page 8. For full disclosures, including category descriptions, view this News in Review at [aao.org/eyenet](http://aao.org/eyenet).