# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

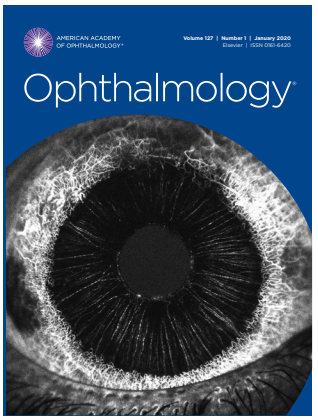
## *Ophthalmology*

Selected by Stephen D. McLeod, MD

### Topical Cenegermin for Neurotrophic Keratopathy

January 2020

**Pflugfelder et al.** evaluated the efficacy and safety of topical cenegermin in patients with neurotrophic keratopathy. They found that, when compared to vehicle, the drug was more effective at reducing lesion size and led to fewer events indicating disease progression. Moreover, cenegermin was well tolerated; most adverse effects were local, mild, and transient.




This double-masked, vehicle-controlled trial included 48 patients treated at 11 study sites in the United States. Participants were assigned randomly (1:1) to receive topical cenegermin 20 µg/mL or vehicle eye drops. Six drops were administered daily for eight weeks, and follow-up continued through 24 weeks. The primary end point was healing of the neurotrophic lesion (persistent epithelial defect or corneal ulcer) by week 8. Masked central readers measured neurotrophic lesions from clinical photographs and then assessed corneal healing status conventionally (<0.5 mm of fluorescein staining in greatest dimension of lesion area) as well as conservatively (0-mm lesion staining and no other residual staining).

Secondary outcomes included corneal healing at four weeks of treatment and overall changes in lesion size, disease progression events, visual acuity, and corneal sensitivity from baseline to week 8.

The conventional assessment showed significant differences at week 8, as 70% of the active-treatment arm and 29% of the vehicle arm had less than 0.5 mm of lesion staining ($p = .006$). With regard to the conservative assessment at week 8, 65% of the cenegermin group and 17% of those who received vehicle had 0 mm of lesion staining and no other staining residually ($p < .001$). Conservative evaluation also revealed significant between-group differences at week 4 (key secondary end point). Cenegermin produced significant reductions in lesion size and disease progression rates throughout treatment and was well tolerated. Most adverse events were mild, local, and resolved rapidly.

The authors concluded that cenegermin 0.002% ophthalmic solution represents a safe noninvasive option to treat neurotrophic keratopathy. They added that it "can become part of the treatment algorithm for this often difficult to manage disease with a high need for targeted and effective pharmacotherapies." More research is warranted to define the pathologic processes modulated by cenegermin.

### Brolucizumab for Neovascular AMD

January 2020

In two similarly designed phase 3 trials (HAWK and HARRIER), **Dugel et al.** compared the efficacy and safety of brolucizumab and aflibercept for treatment of neovascular age-related macular degeneration. The findings of both studies indicate that brolucizumab is noninferior to aflibercept in terms of visual function at week 48. Anatomic outcomes were better with brolucizumab, and overall safety was comparable for the two treatments.

Both studies were double-masked, active-controlled trials, with a combined enrollment of 1,817 patients. All patients had untreated active choroidal neovascularization caused by age-related macular degeneration (AMD) in the study eye.

Participants were assigned randomly to receive intravitreal brolucizumab (3 mg or 6 mg) or aflibercept (2 mg). After three monthly injections (loading dosage), brolucizumab-treated eyes received an injection every 12 weeks (q12w), which was adjusted to every eight weeks (q8w) if disease activity persisted. Aflibercept-treated eyes received q8w dosing.

The primary hypothesis of the study was noninferiority of brolucizumab in best-corrected visual acuity (BCVA)

mean change from baseline to week 48 (margin: 4 letters). Other key end points were the anatomic outcomes and the proportion of patients who maintained q12w dosing of brolucizumab through week 48.

Forty-eight weeks after treatment was begun, each arm of brolucizumab showed noninferiority to aflibercept in BCVA change from baseline: least squares (LS) mean in the HAWK study was +6.6 (6 mg) and +6.1 (3 mg) letters with brolucizumab versus +6.8 letters with aflibercept. In the HARRIER study, LS mean values were +6.9 letters for brolucizumab (6 mg) versus +7.6 letters for aflibercept. The p value was <.001 for all comparisons of brolucizumab and aflibercept. More than 50% of eyes treated with 6 mg of brolucizumab were maintained on q12w dosing through week 48 (56% in HAWK, 51% in HARRIER).

At week 16, before any variations in treatment exposure, disease activity was more common with aflibercept than with brolucizumab 6 mg (HAWK: 34.5% vs. 24.0%, p = .001; HARRIER: 32.2% vs. 22.7% p = .002). Reductions in central subfield thickness from baseline to week 48 were greater with brolucizumab 6 mg than with aflibercept in HAWK (LS mean, –172.8 µm vs. –143.7 µm; p = .001) and in HARRIER (LS mean, –193.8 µm vs. –143.9 µm; p < .001). Anatomic retinal fluid outcomes favored brolucizumab. Overall, adverse event rates were similar for the study drugs.

The authors noted that the forthcoming 96-week data will provide further insight into the efficacy and safety of brolucizumab (q12w and q8w) relative to aflibercept (q8w).

### Hydrus Versus iStent as Standalone Treatment for OAG

January 2020

**Ahmed et al.** hypothesized that a single Hydrus microstent would result in lower intraocular pressure (IOP) and reduced need for glaucoma medication in patients with open-angle glaucoma (OAG) compared to a pair of iStent devices. They found that the Hydrus resulted in a higher rate of surgical success and less need for glaucoma medication. The safety profiles of the two devices were similar.

For this prospective randomized study, the researchers included 152 patients (152 eyes) who were between 45 and 84 years old. All participants had OAG, a Shaffer angle of grade III or IV, best-corrected visual acuity (BCVA) of 20/30 or better, and IOP of 23 to 39 mm Hg after washout of hypotensive medications.

Study eyes were assigned randomly (1:1) to undergo standalone microinvasive glaucoma surgery (MIGS) consisting of one Hydrus or two iStents. Follow-up exams were performed on day 1, week 1, and months 1, 3, 6, and 12 following surgery. Outcomes of interest were between- and within-group differences in IOP and number of glaucoma medications at 12 months. Complete surgical success was defined as freedom from repeat glaucoma surgery, IOP ≤18 mm Hg, and no need for glaucoma medication. Safety measures included frequency of surgical complications, changes in VA, abnormal slit-lamp findings, and adverse events. The study groups were well matched in terms of baseline demographics, glaucoma status, medication use, and baseline IOP.

Twelve months of follow-up was completed by 148 patients (97.4%). At this point, the complete success rate was better for the Hydrus device compared to two iStents (30.1% vs. 9.3%; p < .001). The Hydrus also was associated with reduced need for glaucoma medication (p = .004); more Hydrus subjects were completely free of such medication by month 12 (p = .0057). Secondary glaucoma surgery was required for two eyes in the iStent group (3.9%) and none in the Hydrus group. Two eyes treated with Hydrus and one treated with iStent had BCVA loss of 2 lines or more.

The authors acknowledged the limitations of unmasked postoperative examinations but conclude that these findings suggest that trabecular MIGS devices may play an important role in managing IOP and reducing the need for hypotensive medication.

*—Summaries by Lynda Seminara*

## *Ophthalmology Retina*

Selected by Andrew P. Schachat, MD

### AREDS2: Long-Term VA Following Anti-VEGF

January 2020

**Keenan et al.** set out to analyze best-corrected visual acuity (BCVA) outcomes of patients with wet age-related macular degeneration (AMD) after intravitreal injections of anti-VEGF drugs. They found that mean BCVA decreased by about 1.5 to 2 letters per year—and that, at five years, BCVA was 20/40 or better in approximately 50% of eyes and 20/200 or worse in 14%.

This study is Report No. 19 of the Age-Related Eye Disease Study 2 (AREDS2). A total of 986 AREDS2 participants (1,105 eyes) met the inclusion criteria (no late AMD, BCVA 20/100 or better, and no previous anti-VEGF injections).

All participants received at least one anti-VEGF injection during follow-up; decisions regarding treatment were made by local ophthalmologists during normal clinical care.

The primary outcome measures were mean refracted BCVA and the proportions of eyes with BCVA of 20/40 or better and 20/200 or worse. An exploratory outcome measure was the mean number of anti-VEGF injections, as reported by the treating ophthalmologists.

All told, 977 of the 986 participants (99.1%) had at least one post-treatment visit. During the study, the percentage of eyes with a BCVA of 20/40 or better declined from 59.3% at the first annual study visit after the first injection to 49.7% by the fifth annual exam. In contrast, the percentage of eyes with a BCVA of 20/200 or worse rose from 5.5% to 14.4% during the same time period.

The mean annual numbers of injections per eye were 2.9 during year 1 and 3.9, 3.3, 3.1, and 3.0 in the succeeding years of the study. Patients received a mixture of ranibizumab, bevacizumab, and, in fewer cases, aflibercept injections; in addition, they were treated under several dosing regimens (including treat-and-extend,

fixed interval, and as-needed).

The authors noted that although the treating ophthalmologists were making decisions outside of a randomized clinical trial protocol, the participants were part of the AREDS2 cohort. Thus, this study does not fully represent a real-world setting. Nonetheless, the data may be useful in assessing the long-term effects of anti-VEGF treatment for wet AMD, they said.

*—Summary by Jean Shaw*

## American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

### Predictors of Successful Outcome for Malignant Glaucoma

January 2020

**Thompson et al.** set out to identify factors linked to favorable outcomes of malignant glaucoma. They found that earlier vitrectomy may shorten recovery time and that Nd:YAG laser hyaloidotomy and oral carbonic anhydrase inhibitors may be the most ideal methods to reduce intraocular pressure (IOP). Maximum improvement in IOP and best visual acuity (BVA) may lag behind anatomic resolution.

This retrospective study included 64 eyes (55 patients) with malignant glaucoma treated at the same facility. Data from medical records were collected, including anatomic details, IOP, and BVA. Of the 64 eyes, 56 (87.5%) required surgery. Data analysis indicated that vitrectomy was more likely to be successful in eyes that had previously undergone fewer than three incisional surgeries, were treated with fewer than three topical glaucoma medications, or had IOP ≤30 mm Hg (all $p < .05$). If vitrectomy was performed within 30 days of the malignant glaucoma diagnosis, the time to recovery of anatomy, BVA, and IOP was faster (all $p < .05$). IOP reductions were greater for patients who received oral carbonic anhydrase inhibitors ($p = .016$, underwent Nd:YAG laser hyaloidotomy ($p = .007$), or had no history of malignant glaucoma ($p = .007$).

Resolution of anatomy occurred much faster than maximal improvement in IOP or BVA (both $p < .001$); and treatment with an oral carbonic anhydrase inhibitor hastened anatomic recovery ($p = .01$). Improvement in BVA was significantly faster for men and African Americans (both $p < .05$). Eyes that had chamber reformation in the clinic achieved maximum IOP reduction more quickly ($p < .002$). Trabeculectomy before diagnosis of the malignancy predicted prolonged recovery of anatomy, BVA, and IOP (all $p < .05$). Surgical reconstruction of the anterior chamber at the time of pars plana and/or anterior vitrectomy had no significant effect on recovery. Vitrectomy (either type) was more likely to be successful in eyes with better glaucoma control before the malignancy. The degree of improvement in IOP, BVA, or the number of glaucoma medications did not differ according to whether the condition was managed medically or surgically.

Trabeculectomy may slow recovery from malignant glaucoma, but anatomic resolution may be swifter with oral carbonic anhydrase inhibitors, and IOP may be optimized by clinic-based reformation of the anterior chamber. The authors recommend pooling data from multiple institutions to better gauge the effectiveness of methods to manage malignant glaucoma.

### VR Headsets May Be Safe for Young Children

January 2020

Safety warnings that come with virtual reality (VR) 3D binocular headsets state that their use is banned for children under 13 years of age. However, quantitative studies of the effects of these headsets on children are lacking. **Tychsen and Foeller** performed a study in 4- to 10-year-olds and found no meaningful adverse effect on visuomotor function. After use of the device, participants had no significant postural instability or maladaptation of the vestibulo-ocular reflex.

For this prospective study, the researchers included 50 children (29 boys) whose mean age was 7.2 years. Participants were required to have logMAR corrected distance visual acuity (CDVA) of 20/50 or better and stereoacuity of 800 seconds of an arc or better.

Multiple parameters were documented for each child before and after each of two sequential play sessions.

The sessions, which lasted 30 minutes each, involved a 3D flying game (Eagle Flight) that requires head movements to control flight direction (i.e., pitch, yaw, and roll axes). Each VR session was followed by testing of binocular CDVA, refractive error, binocular eye alignment (strabismus), stereoacuity, and postural stability. Visually induced motion sickness was assessed using a questionnaire. Five children also underwent before-and-after testing of visual-vestibulo-ocular reflex (V-VOR) adaptation. Any change from baseline in a visuomotor measure represented a safety concern.

Of the 50 children, 46 (92%) completed the entire study. There were no significant changes from baseline in binocular CDVA ($p = .89$), refractive error ($p = .36$), binocular eye alignment ($p = .90$), or stereoacuity ($p = .45$). Postural stability degraded 9% (on average) from baseline to 60 minutes following VR exposure ($p = .06$). From pre- to post-trial, scores on the questionnaire increased by a mean of 4.7% for all four symptom categories: fatigue ($p = .03$), head/neck discomfort ($p = .03$), eye discomfort ($p = .02$), and motion sickness ($p = .01$). V-VOR gain remained stable in the five children tested. No child who finished both sessions asked to stop the game, and most were disappointed when the play ended.

Three children (6% of participants) stopped playing in the first 10 minutes of the initial session: two girls (aged 5 and 6) and one boy (aged 7). The girls cited discomfort consistent with mild motion sickness; the boy said he was bored and the headset was uncomfortable. No child experienced aftereffects such as flashbacks in the days following the study.

The authors concluded that young children seem to tolerate immersive 3D VR play well without any noteworthy effects on visuomotor function.

*—Summaries by Lynda Seminara*

## *JAMA Ophthalmology*

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

### Impact of Secondhand Smoke on the Choroid of Children

December 2019

**Yuan et al.** assessed the relationship between choroidal thickness and secondhand smoke exposure in children between the ages of 6 and 8. They found that secondhand smoke correlates with choroidal thinning in an exposure-dependent manner.

For this study, the researchers included 1,400 patients recruited from the population-based Hong Kong Children Eye Study. All participants underwent detailed ophthalmic investigations, including measurement of choroidal thickness via swept-source optical coherence tomography. History of secondhand cigarette smoke was obtained from a questionnaire completed by parents or guardians. The correlation between choroidal thickness and exposure to secondhand smoke was assessed with multiple linear regression analyses, controlling for confounding factors.

Of the 1,400 participating children, 459 (32.8%) had been exposed to secondhand cigarette smoke. After adjustment for age, sex, body mass index, axial length, and birth weight, secondhand smoke was found to correlate with thinner choroidal parameters. When choroidal measurements were compared, those of smoke-exposed children were 8.3 µm thinner in the central subfield, 7.2 µm narrower in the inner inferior, 6.4 µm narrower in the outer inferior, 6.4 µm thinner in the inner temporal, and 7.3 µm thinner in the outer temporal.

Choroidal thinning was more common in families with multiple smokers and in homes with larger amounts of secondhand smoke. For each additional smoker, choroidal thinning increased by 7.86 µm in the central subfield, 4.51 µm in the outer superior, 6.23 µm in the inner inferior, 5.59 µm in the outer inferior, 6.06 µm in the inner nasal region, and 6.55 µm in the outer nasal region. Increasing exposure to secondhand smoke by one cigarette per day was linked to further choroidal thinning of 0.54 µm in the central subfield, 0.42 µm in the inner temporal sector, and 0.47 µm in the outer temporal sector.

Although these findings suggest that secondhand smoke is linked to choroidal thinning in children, the authors cautioned that the association does not necessarily indicate a causal effect. *(Also see related commentary by Cécile Delacourt, PhD, in the same issue.)*

### Cost-Effectiveness of Ranibizumab and PRP for Proliferative DR

December 2019

In a secondary analysis from the DRCR.net Protocol S study, **Hutton et al.** compared the cost-effectiveness of ranibizumab and panretinal photocoagulation (PRP) for patients who had proliferative diabetic retinopathy (PDR) but did not have center-involved diabetic macular edema (DME) and associated loss of visual acuity. They found that the first-line use of PRP is a more cost-effective approach for these patients.

Five-year efficacy, safety, and resource utilization data were gathered for 213 adults with PDR, and results were simulated through 10 years. Treatment protocols were intravenous ranibizumab (0.5 mg) at baseline and up to every four weeks thereafter (per a structured retreatment protocol) versus PRP at baseline. Any eye, regardless of treatment assignment, could receive ranibizumab for concomitant DME involving vision loss. Main outcomes were incremental cost-effectiveness ratios (ICERs) for each treatment among patients (including those who did have center-involved DME at baseline).

At year 5, mean costs for patients with vision-impairing DME at baseline were $22,355 for the PRP group and $40,825 for the ranibizumab group. Quality-adjusted life-years (QALYs) were 0.02 and 0.30, respectively. For patients without center-involved DME at baseline, the ICER of ranibizumab relative to PRP was $582,268/QALY at five years and $742,202/QALY at 10 years. For patients with center-involved DME at baseline, the ICERs for ranibizumab were $65,576/QALY at five years and $63,930/QALY at 10 years.

Based on these analyses, ranibizumab is likely to be cost-effective for patients with PDR and center-involved DME but unlikely to be more cost-effective than PRP for those without center-involved DME. These findings are consistent with the earlier two-year results of Protocol S.

Although a lower dose of ranibizumab (0.3 mg) is available and may help to reduce costs, the present study involved only the 0.5-mg dose. The authors acknowledged that it would be difficult to generalize the cost-effectiveness of ranibizumab to that of other anti-VEGF agents because long-term data for other drugs are lacking. A lower price point for a drug that is at least as effective as ranibizumab may render anti-VEGF therapy cost-effective for PDR treatment even if center-involved DME is absent. The authors noted that their findings may be considered with patient-specific factors when choosing a treatment for PDR. *(Also see related commentary by Steven M. Kymes, PhD, and David Vollman, MD, in the same issue.)*

### Firearm-Related Ocular Trauma in Children and Adolescents

December 2019

**Weiss et al.** evaluated the epidemiologic pattern of firearm-related ocular injuries in young people. They found that more than half of the injuries were associated with traumatic brain injury, and 12% of the injuries resulted in death.

For this retrospective analysis, the authors used records from the National Trauma Data Bank from 2008-2014. Of note, the data bank includes most U.S. trauma centers; however, it does not include emergency departments in other hospitals.

Of the 8,715 firearm-related ocular injuries leading to hospitalization during this time, 1,972 (22.6%) were in people under 21 years of age. Collected data included age, sex, race/ethnicity, injury intent, disease/injury classification codes, Injury Severity Score (ISS), Glasgow Coma Scale (GCS) score, geo-

graphic location, length of hospital stay, health insurance status, and disposition at discharge.

Results showed that most of the pediatric patients were male (85.1%) and adolescents (52.6%), with a mean age of 15.2 years. Most commonly, the injuries occurred at home (38.6%) or on the street (24.8%). The mean (standard deviation) hospital stay was 7.6 (12) days, ISS was 16 (13.1), and GCS score was 11 (5.1).

The most common ocular injuries were open wound of the eyeball (41.6%), ocular adnexa (25.5%), orbital injury or fracture (30.0%), and contusion of the eye or adnexa (21.1%). The youngest group of patients (≤4 years of age) was most likely to be injured unintentionally (odds ratio [OR], 4.41; $p < .001$) and at home (OR, 5.39; $p < .001$). The oldest group (19-21 years) had the highest odds of assault injury (OR, 2.17; $p < .001$) and injury in the street (OR, 1.61; $p < .001$).

Injuries among black patients were more likely to be the result of an assault (OR, 4.53; $p < .001$); in contrast, injuries among white patients were more likely to be self-inflicted (OR, 7.1; $p < .001$). Most cases of traumatic brain injury resulted from self-inflicted harm (OR, 5.99; $p < .001$), as did most visual pathway injuries (OR, 2.86; $p < .001$). The mortality rate for inpatients was 12.2%. *(Also see related commentary by Joseph K. Canner, MHS; Joseph V. Sakran, MD, MPH, MPA, and Fasika Woreta, MD, in the same issue.)*

*—Summaries by Lynda Seminara*

## OTHER JOURNALS

Selected by Deepak P. Edward, MD

### Glaucoma Procedure Preferences: When Surgeons Adopt the Patient Role

*Eye*
2019;33(10):1577-1583

If you were the patient, which glaucoma procedure would you prefer? **Chang et al.** surveyed the members of the American Glaucoma Society (AGS) to determine which glaucoma procedure they would prefer to have performed on themselves and then compared results with those of a previous AGS survey on practice preferences for hypothetical patient vignettes.

For the present study, the authors distributed a survey electronically to AGS members, who completed it anonymously. Participants were asked to adopt the role of a patient who had open-angle glaucoma and progressive visual field loss requiring surgery. Three pre-op intraocular pressure (IOP) scenarios were given (<21, 21-26, and >26 mm Hg), and respondents were asked to choose the glaucoma procedure(s) they would prefer to receive for each IOP scenario.

Overall, 289 surgeons participated (27.4% of active/provisional AGS members). The most preferred procedures, for the three IOP ranges combined, were ab interno trabeculotomy (20.3%), Xen gel stent (18.6%), iStent with two devices (14.3%), and traditional trabeculectomy plus mitomycin C (14.1%). A significant number of participants would prefer procedures that spared the conjunctiva or did not result in bleb formation, even for the lowest pre-op IOP level. For all three IOP ranges, older surgeons were more likely than their younger counterparts to prefer traditional trabeculectomy and to have just one procedure.

### Orbital Inflammation Caused by Osteoporosis Rx

*Clinical & Experimental Ophthalmology*
Published online Oct. 15, 2019

Although ocular side effects of bisphosphonates (which are used to treat osteoporosis) are uncommon, they can affect any layer of the eye and cause conjunctivitis, scleritis, and uveitis. Most patients recover after discontinuing the medication and taking steroids. **Han and Weatherhead** described such a case, this one involving orbital inflammation after zoledronic acid infusion.

In this report, a 59-year-old woman received an IV infusion of zoledronic acid (Aclasta 5 mg) for treatment of osteoporosis. The next day, she had a headache, bilateral retro-orbital pain, and mild photosensitivity. On the second day, her upper and lower left eyelids developed redness, and she experienced eye-movement discomfort. Her physician prescribed chloramphenicol eyedrops for presumed conjunctivitis. Symptoms worsened, and diplopia occurred in all gaze positions other than primary. The patient denied a history of trauma, sinusitis, or recent fever. She has trigeminal neuralgia, for which she takes pregabalin.

When she presented to the authors, her visual acuity was 20/16 in her right eye and 20/20 in her left; her intraocular pressure was 22 and 26 mm Hg, respectively. She had marked swelling of the left periorbital region, with gross proptosis (4 mm) observed by Hertel exophthalmometry. All movement in her left eye was restricted. The left upper lid was erythematous with mild edema.

Results of Ishihara color testing were similar for both eyes, and pupillary reflexes were normal. Slit-lamp examination showed marked conjunctival chemosis, but the anterior chamber and posterior segment appeared normal. There was no sign of scleritis or uveitis. Blood test results were remarkable only for elevated C-reactive protein (29 mg/L). Extensive preseptal edema and retro-orbital fat stranding were detected by orbital computed tomography. Extraocular muscles and paranasal sinuses appeared normal.

The diagnosis of orbital inflammation secondary to zoledronic acid was made, and IV methylprednisolone (500 mg) was begun. Signs and symptoms improved within 24 hours, and treatment was switched to oral prednisone (60 mg/day, for a dose of 1 mg/kg). The follow-up exam two weeks later showed complete resolution of orbital inflammation. The full range of eye movement had returned, and proptosis had resolved. The prednisone was tapered rapidly.

Given the high prevalence of osteoporosis and the use of bisphosphonates, the authors said, it is important for clinicians to ask about medication use in patients who present with orbital inflammation.

*—Summaries by Lynda Seminara*