

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

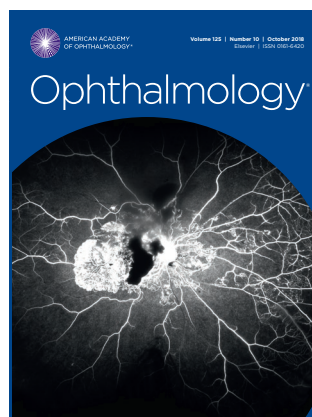
Selected by Stephen D. McLeod, MD

Emixustat for Geographic Atrophy Secondary to AMD

October 2018

Rosenfeld et al. evaluated the use of emixustat hydrochloride in the management of geographic atrophy (GA). They found that emixustat did not reduce the growth rate of GA—and that the most common adverse events were ocular in nature and likely attributable to the drug's mechanism of action.

Enrollees (N = 508) had GA secondary to age-related macular degeneration (AMD), total GA area ranging from 1.25 to 18 mm², and a visual acuity score of at least 35 letters. Participants were assigned randomly (1:1:1:1) to receive placebo or emixustat (2.5, 5, or 10 mg) administered orally, once daily, for 24 months. Evaluations were conducted from screening through month 25. The primary efficacy endpoint was the mean annual growth rate of total GA area, which was measured from fundus autofluorescence images at a central reading center. Also measured was the change from baseline in normal luminance best-corrected visual acuity (NL-BCVA). Safety and tolerability were determined by documenting adverse effects, measuring vital signs, and reviewing findings from lab tests and physical exams.



The study was completed by 320 patients (63%). Demographics and baseline characteristics were comparable among the 4 groups. During the study, average GA growth rates were similar with placebo and emixustat (placebo: 1.69 mm² per year; emixustat groups: 1.69-1.84 mm² per year). Changes in NL-BCVA also were comparable among the study groups. Subjects whose low luminance deficit (LLD) was larger at baseline (≥ 20 letters) had faster GA growth during the 24-month treatment period. No meaningful association was observed between GA growth rate and the risk-allele status of the AMD-associated single-nucleotide polymorphisms that were tested.

The most common adverse events in patients treated with emixustat were delayed dark adaptation (55%), chromatopsia (18%), visual impairment (15%), and erythropsia (15%).

The authors noted that this research sheds further light on the natural history of GA and confirms previously observed links between certain baseline traits and the rate of GA growth. Even though emixustat was not effective in their study, robust safety data were gained that may be relevant to other indications for emixustat.

Topical Ocular Glucocorticoids Cause Adrenal Suppression in Infants

October 2018

Bangsgaard et al. assessed adrenal suppression among infants who received topical ocular glucocorticoids (GCs) following surgery for congenital cataract. They found that two-thirds of their study population experienced this adverse effect, which correlated strongly with high cumulative doses.

This retrospective, consecutive case series included patients under 2 years of age who underwent surgery at Copenhagen University Hospital in Denmark. The surgical procedure and GC dosing protocol were standard. The authors reviewed patients' records and documented outcomes, GC dose per kg of body weight, and the timing of a standard corticotropin (adrenocorticotropic hormone) stimulation test. The main outcome measure was the incidence of adrenal suppression among infants who were tested for it during GC treatment.

Of the 26 infants who underwent the surgery, 15 (58%) received the corticotropin stimulation test while on GC treatment. Ten (67%) of the 15 infants had adrenal suppression, and the degree of suppression varied widely. Two of these displayed obvious clinical signs of Cushing syndrome, and another had signs of Addisonian crisis while under general anesthesia. Adrenal suppression was treated with hydrocortisone replacement therapy. In the 5 days preceding testing, cumulative GC doses per body

weight were significantly higher for the patients with suppressed adrenal function. Recovery of adrenal function occurred after a median of 3.1 months (range, 2.3 months to 2.3 years).

Eleven (42%) of the 26 infants were tested later, at a median of 21 days (range, 6–89 days) after cessation of GC treatment. All test results were normal at that time.

The authors advocate using the lowest possible dose of topical ocular GCs for the shortest period needed to control inflammation postoperatively. They also advise systematic assessment of adrenal function when standard GC protocols are utilized, along with careful evaluation of other dosing regimens. (Also see related commentary by Scott R. Lambert, MD, in the same issue.)

Prolonged Reading Worsens Dry Eye Symptoms

October 2018

Karakus et al. studied the effects of prolonged silent reading on tear film and ocular surface parameters. They found that symptoms of dry eye disease (DED) provoked by everyday tasks, such as reading for pleasure or work, often go undetected during clinical testing.

This prospective observational study included 177 patients with DED and 34 normal controls, all of whom were at least 50 years old. After symptom evaluation with the Ocular Surface Disease Index (OSDI) questionnaire, the following tests were performed in consecutive order: automated noninvasive tear breakup time (TBUT), surface asymmetry and regularity indexes, Schirmer test (without anesthesia), corneal staining using fluorescein, and conjunctival staining using lissamine green. The participants then completed a standardized validated task consisting of reading a 7,200-word story for at least 30 minutes.

The same tests were repeated after the reading exercise, and the researchers documented differences in the 2 sets of test results.

After the reading task, all test results were poorer in both study groups, except for the surface asymmetry index. The worsening was significant for corneal

and conjunctival staining in the DED group and for corneal staining in the control group.

At baseline, OSDI correlated only with scores for corneal staining and conjunctival staining. Among the measurements taken after reading, baseline OSDI correlated with TBUT and with scores for corneal staining and conjunctival staining. Changes in TBUT and Schirmer test findings correlated strongly with their respective baseline values, indicating that patients with greater tear film instability and lower aqueous tear secretion are more susceptible to worsening symptoms after reading. Worsening corneal staining results correlated with the baseline conjunctival staining values and surface regularity index.

The authors advocate use of the OSDI for more precise quantification of dry eye symptoms, particularly in clinical studies involving treatment comparisons. They also suggest that patients' dry eye symptoms be quantified after a period of silent reading, rather than at rest. (Also see related commentary by Saaeha Rauz, PhD, FRCOphth, in the same issue.)

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

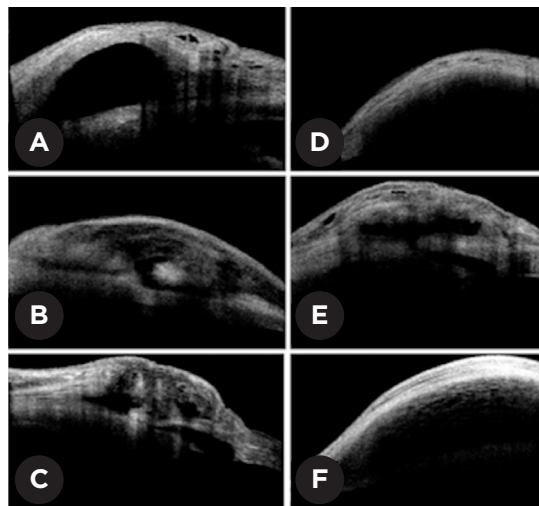
Selected by Henry D. Jampel, MD, MHS

Ologen Implant After Trabeculectomy

September/October 2018

Does the biodegradable collagen matrix implant (Ologen) further the success of trabeculectomy? Findings from the first randomized controlled trial to address this question indicate that it does not.

Sen et al. set out to compare the success of trabeculectomy performed with and without the Ologen implant, which is being investigated as a substitute or an adjunct for antimetabolites such as mitomycin C (MMC).



BLEB ANALYSIS. All images on the left are of patients who received MMC alone; images on the right are of those who received MMC and the Ologen implant. No side effects linked to the implant were noted.

For this study, the researchers recruited 50 patients (50 eyes), all of whom were Asians from north India, and assigned them to undergo either trabeculectomy with low-dose MMC (1 mg/mL, administered for 1 minute) alone or trabeculectomy plus low-dose MMC and the Ologen implant. The primary outcome was the percentage reduction in intraocular pressure (IOP); secondary outcomes included the percentage of patients achieving absolute and qualified success for IOP <15 mm Hg and <18 mm Hg; the postoperative need for glaucoma medications; and the rate of postsurgical complications.

At 12 months' follow-up, 22 eyes remained in the MMC group, and 23 remained in the MMC–Ologen group. In the MMC group, IOP was 25.96 ± 4.82 mm Hg preoperatively and dropped to 11.33 ± 3.81 mm Hg postoperatively. In comparison, preoperative IOP in the MMC–Ologen group was 26.32 ± 4.27 mm Hg; this dropped to 14.35 ± 3.34 mm Hg postoperatively. Greater IOP reduction was noted in the MMC group at the 6- and 12-month marks (56.9% and 55%, respectively) than in the MMC–Ologen group (47.1% and 44.2%). When an IOP of ≤ 15 mm Hg was considered as the definition of success, cumulative success was achieved in 86.5% of MMC eyes

and in 73.9% of MMC–Ologen eyes.

Medication outcomes were similar between the 2 groups at the 12-month mark—17 of the 22 remaining patients in the MMC group were off glaucoma medications at this point, versus 18 of the 23 in the MMC–Ologen group. Similarly, no significant differences were noted between the 2 groups in terms of complication rates.

The authors stated that, given the homogenous nature of their patient population, the implant should be evaluated in a more heterogenous population with different ethnicities represented. Nonetheless, they said, despite the theoretical advantages of the implant, it appears to offer no practical advantage. —*Summary by Jean Shaw*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Macular Atrophy in Wet AMD

October 2018

Domalpally et al. investigated the prevalence of macular retinal pigment epithelial atrophy in eyes with recently diagnosed neovascular age-related macular degeneration (AMD). In addition, they assessed imaging characteristics in 3 groups of patients: 1) those with macular atrophy before the onset of choroidal neovascularization (CNV), 2) those with macular atrophy concomitant to CNV diagnosis, and 3) those who developed macular atrophy during follow-up of CNV. They found that macular atrophy is common in neovascular AMD and often can be attributed to preexisting geographic atrophy (GA). In addition, they found that the presence of macular atrophy is an indicator of poor visual prognosis.

For this cohort study, the researchers evaluated participants of the AREDS2 FAF (Age-Related Eye Disease Study 2 fundus autofluorescence) ancillary study. AREDS2 FAF included 2,509 participants (4,328 eyes) at risk of developing advanced AMD. Color photographs and FAF images were evaluated in those who developed CNV. The main outcome measures were the incidence and enlargement rate of macular atrophy and visual acuity (VA) changes in

eyes with incident CNV.

Over 4 years, incident CNV developed in 334 of the 4,328 eyes. Of these, 137 eyes (41%) had macular atrophy at the event visit (defined as the point at which CNV was identified by the image reading center)—and of those 137 eyes, half had preexisting GA. Of the 197 eyes (59%) that did not have macular atrophy at the event visit, 49 developed it during follow-up.

The mean area of macular atrophy was largest in eyes with preexisting GA and CNV, and macular atrophy involved the center of the macula in over two-thirds of all eyes. With regard to VA, by 3 years of follow-up, eyes with macular atrophy had lost a mean of 10.9 letters, while those without it had lost a mean of 3.7 letters. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

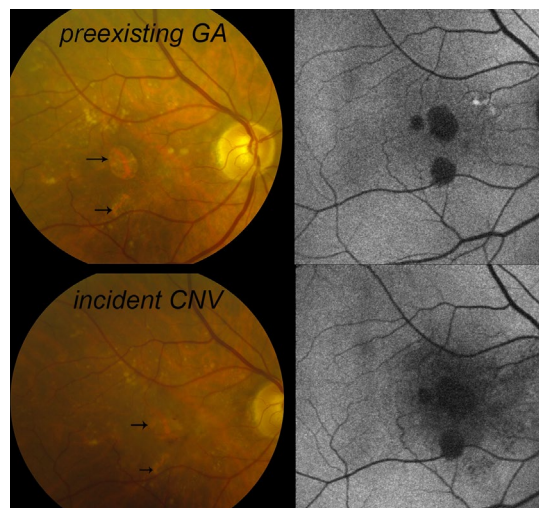
Povidone-Iodine Plus Dexamethasone for Adenoviral Conjunctivitis

October 2018

There are currently no approved medications for treating adenoviral conjunctivitis. Pepose et al. found a promising option in a topical ophthalmic suspension of povidone-iodine (PVP-I) 0.6% and dexamethasone 0.1%.

This multicenter, double-masked trial included 144 Indian adult patients with a positive AdenoPlus test. The researchers randomized this cohort to either PVP-I plus dexamethasone (n = 48), PVP-I alone (n = 50), or vehicle (n = 46). The 3 groups were then monitored 3, 6, and 12 days after treatment for both clinical resolution (the absence of watery conjunctival discharge and redness) and virus eradication (negative cell culture assay).

The proportion of patients with clinical resolution at the day 6 visit was 31.3% in the PVP-I–dexamethasone



COMPARISON. Color and autofluorescence images showing GA (top) in an eye that developed wet AMD at the next annual visit (bottom).

group, which was significantly higher than that observed in the vehicle group (10.9%) and numerically higher compared with PVP-I alone (18.0%). The results for complete eradication of the adenovirus were similar. At day 6, the proportion of patients with a negative cell culture assay was 79.2% after treatment with PVP-I plus dexamethasone, significantly higher than with vehicle (56.5%) and numerically higher compared with PVP-I alone (62.0%).

The authors also noted minimal safety concerns with the use of PVP-I plus dexamethasone. Phase 3 studies to further evaluate the safety and efficacy of this treatment are currently underway.

Endophthalmitis Following Bilateral Same-Day Anti-VEGF Injection

October 2018

The most common indications for intravitreal anti-vascular endothelial growth factor (VEGF) therapy often require chronic treatment in both eyes. As a result, retina specialists routinely opt for bilateral same-day injections to reduce the number of office visits necessary for patients. Many clinicians, however, avoid this protocol for fear of bilateral endophthalmitis. To alleviate such concerns, Borkar et al. examined the results of more than 100,000 anti-VEGF injections and found low rates of infection.

This retrospective cohort study included a review of a private practice's records for all bilateral same-day anti-VEGF injections performed from 2012 to 2017. The researchers collected demographic information for all patients as well as information relating to presentation examination, culture data, and visual outcomes.

During the 5-year span, the practice performed 101,932 bilateral same-day injections for 5,890 patients during 50,966 office visits. The number of these injections increased from approximately 870 injections per month in 2012 to 2,300 in 2017. Neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) were the most common indications for treatment. The most common agent used for neovascular AMD was ranibizumab. Aflibercept was the most common drug used for DME.

In total, the authors identified 28 cases (0.027%) of unilateral endophthalmitis—approximately 1 in 3,700 injections—and found no instances of bilateral endophthalmitis. No patient experienced more than a single occurrence.

These results, the authors noted, demonstrate the safety of bilateral same-day anti-VEGF injections when extreme caution is taken to prevent infection—a finding that is especially important as the number of patients requiring anti-VEGF treatment continues to grow. —*Summaries by Mike Mott*

JAMA Ophthalmology

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

Cataract Surgery and the Rate of Traffic Accidents

September 2018

Cataracts are a leading cause of impaired vision worldwide. But do they increase the risk of serious traffic accidents? In a population-based study, **Schlenker et al.** examined the records of >500,000 patients and found that cataract surgery was associated with a reduced rate of hospital visits due to a traffic crash when the cataract surgery patient was the driver.

This study included Canadian patients 65 years and older who underwent their first cataract surgery between 2006 and 2016. Each patient's record was tracked for up to 5 years after cataract surgery. The researchers excluded those patients who had cataract surgery combined with retina, glaucoma, or cornea surgery because of uncertain visual recovery.

The mean age of the 559,546 patients was 76 years, and 58% were women. Almost no patient had received a medical warning from his or her physician regarding fitness to operate a vehicle noted in the record. A total of 4,680 traffic crashes occurred during the baseline interval, and 1,200 traffic crashes took place during the follow-up after cataract surgery. This reduction represented 0.22 fewer crashes per 1,000 patient-years when the patient was the driver. No reduction in crashes was observed in other secondary outcomes, including traffic accidents in which the patient was a passenger or pedestrian. With regard to patient subgroups, the researchers found that patients who were younger, were male, had more emergency visits in general, and had more frequent outpatient physician visits were at greater risk of traffic crashes when driving.

These results suggest that improvements in vision following cataract surgery are associated with decreased driving risks. The researchers also noted postsurgery crash rates were highest in the first month, perhaps owing to uncorrected refractive error, adapting to recovery, or overconfidence—a finding that should inform postsurgery physician counseling.

Enhanced Screening Model for Retinopathy of Prematurity

September 2018

Current screening criteria for retinopathy of prematurity (ROP) are predominantly based on birth weight (BW) and gestational age (GA) and have low predictive value for identifying infants who are at risk for severe cases. To improve ROP screening specificity and sensitivity, **Binenbaum et al.** proposed a new set of criteria combining BW, GA,

and postnatal weight gain.

The retrospective Postnatal Growth and ROP Study included 6-year data on 7,483 premature infants from the United States and Canada who were examined for ROP and had a known ROP outcome. The researchers developed a hybrid predictive model to apply to this data, which combined common BW and GA thresholds with a comparison with expected growth from infants without ROP, an assessment of multiple growth intervals, and a consideration of nonphysiological weight gain.

Their final model consisted of the following 6 screening criteria:

- a BW of <1,051 g;
- a GA of <28 weeks;
- a weight gain of <120 g during days 10-19 after birth, <180 g during days 20-29, or <170 g during days 30-39; and
- hydrocephalus diagnosed on brain imaging study.

Applied in this fashion to the 6-year data, the researchers' model accurately predicted 459 of 459 infants with type 1 ROP, 466 of 472 with type 2 ROP, and 524 of 524 treated for ROP. It also reduced the number of unnecessary examinations by 2,269.

According to the authors, these criteria predict the development of severe ROP with a greater specificity and sensitivity than do current screening methods. And because the model uses routinely collected data and requires minimal calculation, it would have a minimal impact on workflow in neonatal intensive care units.

The Influence of Visual Impairment on Cognitive Function

September 2018

Worsening vision and declining cognitive function are common among the elderly. To better understand the relationship between the 2 conditions, **Zheng et al.** conducted a population-based study of older U.S. adults and found that visual impairment might have a substantially large influence on declining mental abilities.

For this study, the researchers evaluated 2,520 adults aged 65 to 84 in 4 rounds across a 4-year period. Outcome

measures included visual acuity (VA) via Early Treatment Diabetic Retinopathy Study (ETDRS) charts and cognitive status via the Mini-Mental State Examination (MMSE).

Both VA and MMSE scores worsened over time. The average biannual decline of VA was 0.022 logMAR, and the average annual decline in VA was 0.011 logMAR—an annual loss of less than 1 letter on the ETDRS acuity chart, or roughly 1 line over 8 years. For the MMSE score, the average biannual decline was -0.59 .

The researchers also looked at the VA and MMSE relationship longitudinally and found that the rate of worsening VA was associated with the rate of declining MMSE score: For example, VA in the previous rounds of examination were associated with MMSE scores in subsequent rounds, and vice versa. However, the impact of VA on the MMSE scores was larger and stronger than the reverse, demonstrating that vision is likely the driving force in this dynamic relationship.

This longitudinal association between vision and cognitive function suggests that maintaining good vision could be an important strategy for minimizing age-related cognitive change. (Also see related commentary by Paul J. Foster, PhD, FRCS (Ed), Sharon Y.L. Chua, PhD, and Axel Petzold, MD, PhD, in the same issue.)

—Summaries by Mike Mott

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Cost-Effectiveness of Intracameral Moxifloxacin

Journal of Cataract & Refractive Surgery
2018;44(8):971-978

Using recent data and different payer perspectives, Leung et al. compared adjuvant intracameral (IC) moxifloxacin plus perioperative topical antibiotic treatment against standard prophylaxis (i.e., topical antibiotics) to assess cost-effectiveness for endophthalmitis prevention after cataract surgery. They found that, despite the rising cost of IC moxifloxacin, the drug can be

cost-effective as well as cost-saving from the U.S. societal perspective. However, from the standpoint of the health care sector, the drug was cost-effective but not cost-saving.

The researchers calculated incremental cost-effectiveness ratios (ICER) and incremental cost-utility ratios (ICUR) for 2 groups of patients: 1) Those who received standard prophylaxis and 2) those who received standard prophylaxis plus IC moxifloxacin. The base case was a healthy 73-year-old man with bilateral cataracts undergoing uncomplicated first-eye surgery. Incidence and cost data were derived from results of a PubMed search in addition to Medicare reimbursement rates and average wholesale drug prices. All costs and benefits were adjusted by 3% annually and for inflation. To assess uncertainty, the authors performed deterministic and probabilistic sensitivity analyses.

Their results showed that, compared with standard prophylaxis, an adjuvant 500 μg of IC moxifloxacin (for \$20) was cost-saving from a societal standpoint in the base case. In probabilistic sensitivity analyses, all values were within the societal willingness-to-pay threshold of \$50,000 per quality-adjusted life year (QALY). Of 10,000 iterations, 6,142 (61%) were cost-saving. Although IC moxifloxacin at this price point was cost-effective from the health care sector perspective (ICUR of \$8,275 per QALY), it was cost-saving only in cases with posterior capsule tear. Adjuvant IC moxifloxacin was superior to topical antibiotics for improving QALYs.

According to this study, the price tag for 500 μg of IC moxifloxacin would need to be less than \$22.20 to achieve societal cost-saving and less than \$9.20 for health care sector cost-saving.

Low-Dose Hyaluronidase for Reduction of HA Nodules

JAMA Dermatology
2018;154(7):765-772

In the first randomized study to evaluate the issue, Alam et al. tested the effectiveness of low-dose hyaluronidase to reduce aliquots of hyaluronic acid (HA) filler that had been injected into

patients' arms. They found that very small doses permitted dissolution of minute quantities of HA filler and eliminated the need to remove the entire implant. This indicates a potential role for low-dose hyaluronidase in resolving minor asymmetries that may occur with such fillers, as can occur with injections in the periorbital area.

This study was a split-arm, parallel-group randomized trial of 72 injection sites among 9 women (mean age, 45.8 years). Aliquots of Juvéderm Ultra XC (Allergan) or Restylane-L (Galderma) were injected bilaterally into the upper inner arms of each participant. At 1, 2, and 3 weeks following the injections, each injection site received a constant volume (0.1 mL) of variable-dose hyaluronidase (1.5, 3.0, or 9.0 U per 0.1 mL) or saline control.

At both the 4-week and 4-month marks, physician assessments of filler detectability were significantly different for saline and hyaluronidase. Findings were similar for subjects' self-assessments. The areas that received 9.0 U of hyaluronidase were significantly less palpable than those that received 1.5 U. Dose dependence was more common with Restylane-L.

Although very small doses of hyaluronidase can disintegrate HA, slightly higher doses usually provide faster dissolution. Low doses may be effective if only subtle changes are needed, such as refining contour. The low-dose strategy may be more appropriate, convenient, and satisfying for certain patients.

—Summaries by Lynda Seminara

AAO 2018

ART + SCIENCE

MORE AT THE MEETING

EDITORIAL RECEPTION. Meet Henry D. Jampel, MD, MHS, editor of *Ophthalmology Glaucoma*, and Andrew P. Schachat, MD, editor of *Ophthalmology Retina*.

When: Sunday, Oct. 28, 10:00-11:00 a.m. **Where:** Resource Center, Booth 508. **Access:** Journal participants and subscribers.