

# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## Ophthalmology

### Fluorometholone for Protecting the Ocular Surface in Dry Eye

January 2016

In this double-masked trial, **Pinto-Fraga et al.** evaluated the clinical efficacy of the topical corticosteroid fluorometholone (FML) in dry eye disease (DED) and examined whether it could protect the ocular surface against exposure to adverse environments. They found that, indeed, FML was effective in reducing DED signs and preventing exacerbation caused by desiccating stress.

This study consisted of 4 visits by 41 DED patients over a 22-day period. All patients were randomly selected to receive 1 drop 4 times daily of either topical 0.1% FML or topical polyvinyl alcohol (PA) for 22 days. The researchers assessed corneal and conjunctival staining, conjunctival hyperemia, tear film breakup time (TBUT), tear osmolarity, and Symptom Assessment in Dry Eye scores at 4 time points: at baseline, on day 21 before and after 2-hour exposure to an adverse environment (counted as 2 visits), and on day 22.

The researchers found that after 21 days of treatment, the FML group had greater improvements in corneal and conjunctival staining, hyperemia, and TBUT than the PA group. The FML group also showed no significant changes in

staining and hyperemia after exposure to adverse conditions, whereas the PA group experienced significant worsening in these variables. Further, the percentage of patients with at least a 1-grade increase in corneal staining was significantly higher in the PA group after exposure.

The researchers concluded that, based on these results, FML therapy could be a suitable prophylactic approach for DED patients who expect to experience an environmental stress.

### Outcomes of Cataract Surgery in Uveitic Eyes

January 2016

**Sen et al.** assessed the visual outcomes of cataract surgery for patients in the Multicenter Uveitis Steroid Treatment (MUST) trial. They found that the surgery substantially improved vision,

whether the uveitis was being treated with an intraocular steroid implant or with standard systemic therapy.

This prospective cohort study included 117 eyes from 82 patients who underwent cataract surgery during follow-up in the MUST

trial—a clinical study comparing a fluocinolone implant with systemic corticosteroids and immunosuppres-

sive medications for the treatment of noninfectious uveitis. Visual outcomes were evaluated at 3, 6, and 9 months after cataract surgery.

Of the 117 eyes, 28 (24%) received systemic therapy and 89 (76%) received an implant. The researchers found no significant difference in visual acuity (VA) improvement between the treatment groups. For all eyes, VA increased by 23 letters from the preoperative visit to the 3-month visit and remained stable through 9 months of follow-up. African-American race, longer duration of uveitis, and hypotony were all associated with worse preoperative VA but did not affect postsurgical recovery.

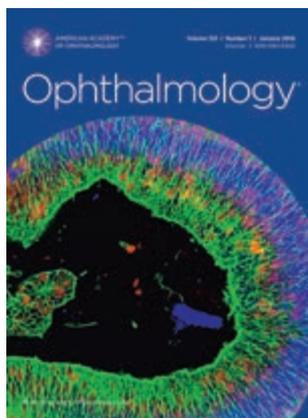
Because a large majority of eyes showed an improvement in VA, the researchers were limited in their ability to perform multivariate analyses of risk factors related to VA.

### Safety of E10030 and Ranibizumab for AMD

January 2016

**Jaffe et al.** assessed the combination of E10030 (Fovista), a platelet-derived growth factor, and the anti-VEGF agent ranibizumab to treat age-related macular degeneration (AMD). They found that the therapy was safe and well tolerated, with no evidence of systemic or ocular toxicity.

For this phase 1 clinical trial, the researchers enrolled 23 patients aged 50 years or older who had a diagnosis of AMD. Part 1 of the study included 15 patients. Three received a single intravitreal E10030 (0.03 mg) injection and



then a subsequent intravitreal ranibizumab (0.5 mg) injection at weeks 2, 6, and 10. Once the safety of the combination doses was established, 12 additional patients then received E10030 (0.03, 0.3, 1.5, or 3.0 mg) in combination with ranibizumab (0.5 mg) at day 0 and months 1 and 2. Part 2 then consisted of 8 additional patients who received E10030 (0.3, 1.5, or 3.0 mg) with ranibizumab (0.5 mg) at day 0 and months 1 and 2. The primary outcome measure for the trial was safety at week 12.

All doses of E10030 administered with ranibizumab were well tolerated, and no dose-limiting toxicities or relevant safety events were noted. Mean change in visual acuity for the combination therapy was a gain of 14 letters, and 59% of participants gained at least 15 letters from baseline at week 12. On fluorescein angiography at week 12, there was an 85.5% mean reduction from baseline in choroidal neovascularization size. In addition, optical coherence tomography at week 12 showed a mean decrease in center point thickness and central subfield thickness of 38.9% and 33.7%, respectively.

## *American Journal of Ophthalmology*

### **Iris-Sutured Posterior Chamber IOLs in Children**

January 2016

Shah et al. reported the long-term outcomes and complications of iris-sutured posterior chamber intraocular lenses (PCIOLs) in a pediatric population. Iris-sutured IOLs have been used as an alternative to transsclerally sutured IOLs to correct aphakia in children. Because dislocation of these IOLs occurs frequently, however, the procedure should be considered with caution in this group.

This retrospective interventional case series involved 12 consecutive patients (17 eyes) who received a foldable iris-sutured PCIOL between September 2004 and September 2007. Of the 17 eyes, 6 (35%) had hereditary or idiopathic ectopia lentis, 5 (29%) had Marfan syndrome, 2 (12%) were aphakic after pars plana vitrectomy,

and 4 (24%) were aphakic after trauma. Mean age at surgery was 7.2 years, and average follow-up was 4.7 years.

Dislocation of the PCIOL occurred in 7 eyes at an average of 12.1 months after surgery, and 2 patients had a second dislocation. The rate of dislocation was higher in patients with a history of ectopia lentis due to Marfan syndrome, idiopathic causes, or hereditary causes than in patients with other causes of aphakia (71% vs. 29%). The authors commented that although this difference was not statistically significant, it was clinically significant. Mean visual acuity improved in 12 of 17 patients (71%). One eye of a Marfan patient sustained a retinal detachment 8 months after dislocation of the PCIOL, and 1 patient experienced iris capture of the PCIOL after surgery.

The authors concluded that although this technique improves VA in the majority of patients, ophthalmologists should be aware that the dislocation rate is 50% in eyes followed for more than 1 year.

### **Geo-Epidemiology of AMD**

January 2016

Reibaldi et al. studied the demographic, geographic, and race-related factors that account for variability in prevalence rates of age-related macular degeneration (AMD) using a systematic review, meta-regression, and decision-tree analysis. The strongest correlations they identified were with race and sun exposure.

A systematic literature review identified population-based studies on the prevalence of AMD published before May 2014. The researchers included only those studies that took place in a spatially explicit geographic area that could be geolocalized and that used retinal photographs and standardized grading classifications. Information on latitude and longitude data (geolocalization) and the mean annual exposure to sunlight (insolation) were obtained for each of the areas surveyed. Age-standardized prevalence rates across studies were estimated using the direct standardization method. Correlations between the prevalence of

AMD and longitude and latitude were obtained by regression analysis. The researchers further investigated other relevant factors and potential associations through Bayesian meta-regression and conditional-inference decision trees.

After multiple analyses, the researchers observed significant correlations between insolation, latitude, longitude, age, and race and the prevalence rates of early and late AMD. Proximity to the equator and insolation were inversely correlated with prevalence of AMD. Decision-tree analysis identified that the most important predictive variable was race for early AMD and insolation for late AMD. In terms of race, people of European ancestry had higher rates of early AMD than Asians; they also had higher rates of both early and late AMD than people of African ancestry.

### **Photodynamic Therapy for Choroidal Metastasis**

January 2016

In a retrospective interventional case series, Ghodasra and Demirci assessed the effectiveness of photodynamic therapy (PDT) in the management of choroidal metastasis. They concluded that PDT might be an effective therapeutic option in selected cases.

Patients with choroidal metastasis treated with PDT at a single institution were reviewed. PDT was applied with verteporfin at a dose of 6 mg/m<sup>2</sup> body surface area and a 689-nm diode laser for 83 seconds. Twenty-one tumors in 13 eyes of 10 patients were included. Eight tumors were treated with a single session of PDT, 11 tumors received 2 sessions, 1 tumor received 3 sessions, and 1 tumor received 5 sessions.

At the end of a mean follow-up of 12 months, 9 eyes (69%) had stable or improved visual acuity, while 4 eyes (31%) had decreased visual acuity. Mean logMAR change in visual acuity was -0.09. Seventeen of 21 tumors (81%) were flat at last follow-up. The mean decrease in ultrasound-measured thickness was 0.83 mm, while the decrease in thickness, as measured by enhanced depth imaging optical coherence tomography, was 400 μm.

Eighteen tumors (86%) had complete resolution of subretinal fluid. There were no PDT-related complications.

## **JAMA Ophthalmology**

### **Vision-Related Activities and Quality of Life in Glaucoma**

December 2015

Ekici et al. examined the relationships between clinical visual assessments, vision-related performance (VRP), and subjective vision-related quality of life (VRQoL) in a large, prospective cohort study. The strongest correlation they found was between contrast sensitivity and the ability to perform vision-related activities.

The researchers studied 161 patients with moderate-stage glaucoma recruited from May 2012 to May 2014 in an ongoing prospective, 4-year longitudinal observational study. This report includes cross-sectional results from the baseline visit. Patients received a complete ocular examination, automated visual field (VF) test, and an optical coherence tomographic scan. Contrast sensitivity was measured with the Pelli-Robson and the Spaeth-Richman Contrast Sensitivity (SPARCS) tests. VRP was determined by the Compressed Assessment of Ability Related to Vision (CAARV) test. VRQoL was assessed by the National Eye Institute Visual Function Questionnaire 25 and a modified Glaucoma Symptom Scale (MGSS).

The strongest correlation was found between SPARCS score in the better eye and total CAARV score. The CAARV score also correlated with the Pelli-Robson score, VF mean deviation, and visual acuity (VA) in the better eye. There were more correlations between contrast sensitivity tests and VF mean deviation with VRQoL measurements than with other clinical measures (VA, intraocular pressure, Disc Damage Likelihood Scale, and mean retinal nerve fiber layer [RNFL] thickness). The MGSS scores were lower (worse) in women compared with men ( $p = .01$  for the better eye,  $p = .05$  for the worse eye, and  $p = .03$  for both eyes). Structural measures such as RNFL thickness

were generally not informative with respect to VRP or VRQoL.

The authors concluded that contrast sensitivity tests and VF mean deviation were associated with both objective measures of the ability to act and subjective measurements of VRQoL. The strongest correlation was between the SPARCS score (contrast sensitivity) in the better eye and total CAARV score. The authors noted that the results of this study were limited by the patient population and apply only within the bounds of the tested cohort.

### **Myopia, Birth Order, and Educational Exposure**

December 2015

Visual impairment due to myopia is an important public health issue. A prior analysis of population-based cohorts aged 15 to 22 years had found that myopia and high myopia were approximately 10% more common in first-born compared with later-born children. Guggenheim et al. examined whether that association was also present in an earlier generation and, if so, whether it was attenuated after adjusting for educational exposure. The latter question was based on the hypothesis that there was less parental investment in the education of later-born children.

The researchers evaluated a cross-sectional study of United Kingdom Biobank participants recruited from 2006 to 2010. Analysis was restricted to participants aged 40 to 69 years who had a vision assessment, self-reported white ethnicity, and no history of eye disorders ( $n = 89,120$ ). Myopia and high myopia were defined as autorefraction of  $-0.75$  D or less and  $-6.00$  D or less, respectively.

Two models were used to analyze odds ratios (ORs) for myopia and high myopia by birth order using logistic regression and adjusting for age and sex (model 1) or adjusting for age, sex, and highest educational level (model 2). In model 1, birth order was associated with both myopia and high myopia. The risk for myopia became progressively lower for later birth orders, suggesting a dose response. In model 2 (adjusted for education), the effect sizes

were attenuated by approximately 25% for both myopia and high myopia, and the apparent dose response for successive births was no longer seen.

These data suggest that the association between birth order and myopia is not due to a new environmental factor in the last 30 to 40 years. The attenuated effect size after adjustment for educational exposure supports the concept of reduced parental investment in education of children with later birth orders, conferring a relative protection from myopia.

### **3-D Graphical Method for Displaying IOL Calculations**

December 2015

Calculating the most accurate power of the intraocular lens (IOL) is a critical factor in optimizing patient outcomes after cataract surgery. Ladas et al. developed a graphical method for displaying IOL calculation formulas in 3 dimensions, and they describe how they incorporated information from several existing IOL formulas to create a “super formula.”

They used a numerical computing environment to create 3-D renderings, or “surfaces,” of the Hoffer Q, Holladay I, Holladay I with Koch adjustment, Haigis, and SRK/T formulas. These surfaces then were analyzed to determine where the IOL powers calculated by each formula differed by more than 0.5, 1.0, and 1.5 D. Next, a “super surface” was rendered that incorporated the ideal portions from 4 of the 5 formulas to generate a super formula. Last, IOL power values for a set of 100 eyes from consecutive patients at an eye institute were calculated using the 5 formulas and the super formula.

In these eyes, the super formula localized to the correct portion of the super surface 100% of the time and thus chose the most appropriate IOL power. The individual formulas deviated from the optimal super formula IOL power values by more than 0.5 D 30% of the time with Hoffer Q, 16% with Holladay I, 22% with Holladay I with Koch adjustment, 48% with Haigis, and 24% with SRK/T. The authors concluded that their method represents IOL

formulas in 3 dimensions. Further, they state that the IOL super formula incorporates the ideal segments from each of the existing formulas and provides an algorithm for choosing the optimal IOL formula for an individual eye. The authors suggest that this method may broaden the conceptual understanding of IOL calculations and stimulate further research.

## ROUNDUP OF OTHER JOURNALS

### Using Stem Cells to Reverse Inherited Eye Defects

*Investigative Ophthalmology & Visual Science*  
2015;56(12):7214-7223

Cystinosis is a degenerative hereditary disorder caused by a deficiency in cystinosisin, which is encoded by the *CTNS* gene; this disease affects the eyes and the kidneys. In eyes, it can lead to crystal accumulation in the cornea and ultimately photophobia and blindness. Rocca et al. examined whether hematopoietic stem and progenitor cells (HSPCs) can help prevent crystal deposits from forming in the cornea in a mouse model. HSPCs have previously been shown to rescue the kidneys of transgenic *Ctns*<sup>-/-</sup> mice in this disease.

For this study, wild-type HSPCs from the bone marrow of transgenic DsRed mice were isolated and transplanted into the tails of *Ctns*<sup>-/-</sup> mice. A year later, the location and function of the HSPCs in the transplanted mice were analyzed by vivo confocal and fluorescence microscopy, quantitative reverse transcription polymerase chain reaction, mass spectrometry, and histology.

The researchers detected engraftment-derived HSPCs in the cornea, sclera, ciliary body, retina, choroid, and lens of *Ctns*<sup>-/-</sup> mice. They also found that in mice with high levels of cell engraftment, a single transplantation of the wild-type HSPCs prevented ocular pathology. This included substantial decreases in corneal cystine crystals, restoration of normal corneal thickness, and reduction in intraocular pressure.

The researchers called for additional

studies to determine whether similar benefits can be achieved in humans, especially if HSPCs are delivered directly within the eye.

### A New Approach to Restoring Lens Transparency in Cataracts

*Science*  
2015;350(6261):674-677

Cataracts occur when crystallins, a major protein component of the lens, begin to aggregate from accumulated damage. Makley et al. investigated whether pharmacological chaperones—small molecules that bind and stabilize the native state of a protein—can halt this aggregation and provide a nonsurgical therapy for treating cataracts.

Using a screening method that tracks the effect of ligands on protein unfolding, the researchers identified several compounds that stabilized the soluble form of  $\alpha$ -crystallins and reversed their accumulation. In proof-of-concept studies, one of these compounds improved lens transparency in mice with hereditary cataracts and partially restored protein solubility in lenses of aged mice and humans.

In an accompanying commentary, Quinlan (pp 636-637) discusses the practical implications of this research. He noted that, because of studies such as this, the protein aggregation that accompanies the development of cataracts no longer needs to be seen as an end point. Further, he suggested that the discovery and identification of sterols that improve lens transparency may lead to the development of new pharmaceuticals to treat conditions such as cataract and presbyopia.

### Propranolol in the Treatment of Infantile Hemangiomas

*British Journal of Dermatology*  
Published online Oct. 16, 2015

Because oral propranolol is widely prescribed as a first-line treatment for infantile hemangioma (IH), Wedgeworth et al. set out to establish patterns of use for this beta-blocker to help in developing treatment guidelines and designing future intervention studies.

As part of the Propranolol in the

Treatment of Complicated Haemangiomas (PITCH) Taskforce, the researchers collected data in 8 European countries on 1,096 patients who were treated for an IH with oral propranolol. Of these patients, 76.1% were female; and 92.8% had a focal IH, while the remainder had a segmental, multifocal, or indeterminate pattern.

The main indications for treatment with propranolol included periocular location with a threat to vision (29.3%), risk of cosmetic disfigurement (21.1%), and ulceration and bleeding (20.6%). In 69.2% of cases, the patients were titrated up to a daily maintenance regimen, which, in a large majority, consisted of 2 mg/kg per day. The median length of treatment was 32 weeks, and most patients (91.4%) had a good or excellent response to treatment. However, the researchers did not find a significant relationship between treatment response and duration of treatment. In addition, although there was a trend toward higher efficacy with larger doses, there was no significant difference in positive responses between those children taking either more or less than the 2 mg/kg dosage.

The median age at treatment cessation was 56 weeks, and rebound growth occurred in 14.1% of patients. Side effects, including sleep disturbances and cold peripheries, occurred in 19.6%. The risk of experiencing such an event doubled for children on a dose of more than 2 mg/kg per day.

The researchers concluded that the optimum dosage remains to be determined. They called for a more adequately powered randomized, controlled trial to compare dose regimens and their effects. ●

*Ophthalmology* summaries are written by Michael Mott and edited by Susan M. MacDonald, MD. *American Journal of Ophthalmology* summaries are edited by Thomas J. Liesegang, MD. *JAMA Ophthalmology* summaries are based on authors' abstracts, as edited by senior editor(s). *Roundup of Other Journals* is written by Michael Mott and edited by Deepak P. Edward, MD.



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