Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

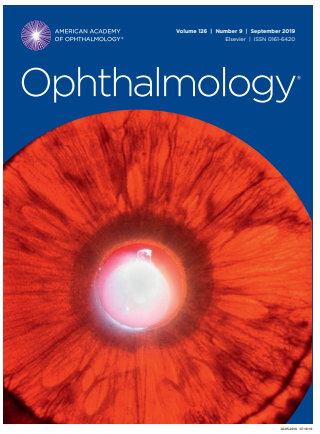
Ophthalmology

Selected by Stephen D. McLeod, MD

Primary SLT: Efficacy, Safety, and Predictors of Success

September 2019

In a post hoc analysis of the multicenter Laser in Glaucoma and Ocular Hypertension (LiGHT) study, **Garg et al.** looked at the efficacy and safety of selective laser trabeculoplasty (SLT) compared to topical medication in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) who had not been treated previously. They found SLT to be effective and safe as the sole initial therapy: Disease control was achieved for nearly 75% of eyes. Overall efficacy outcomes were superior for the OHT group. Predictors of attainment of drop-free maintenance of targeted intraocular pressure (IOP) were total SLT power and early IOP reduction.



In the LiGHT study, patients with OAG or OHT were assigned randomly to receive SLT (355 patients; 611 eyes) or topical medication (362 patients; 622 eyes). All patients needed IOP lowering of at least 20%, and each was treated to his or her predefined target. Outcome measures were early absolute IOP lowering by month 2 and achievement of drop-free disease control. The latter was defined as meeting target IOP without disease progression and without need for drops in the 36 months following SLT. The researchers also assessed disease control after single initial SLT, potential predictors of treatment success, and the incidence of procedure-related complications.

The findings suggest that SLT is comparable to topical treatment for attaining early IOP lowering, which was more pronounced in the OHT group. The greater effect seen in the OHT group was expected given the higher IOP in this arm at baseline. Early IOP lowering from primary SLT correlated positively with baseline IOP ($p < .001$). Among the eyes available for analysis at 36 months, nearly 74.6% of those treated with SLT had drop-free control at this point; 58.2% of eyes achieved this from a single trabeculoplasty. Total SLT power and two-month IOP were found to predict 36-month drop-free control from a single procedure. Six eyes (six patients) had an immediate spike in IOP after the treatment (>5 mm Hg from pretreatment IOP), one of whom required medical attention.

Although this research was exploratory in nature, it supports the utility and safety of SLT for treatment-naive OAG and OHT. Larger studies are needed to substantiate the results.

VN Gene Therapy for Inherited Retinal Dystrophy Linked to *RPE65* Mutation

September 2019

Maguire et al. looked at the efficacy, durability, and safety of voretigene neparvovec-rzyl (VN) adeno-associated viral vector–based gene therapy for inherited retinal dystrophy (IRD) caused by *RPE65* mutation. They reported findings of a phase 1 follow-on study (year 4) and a phase 3 open-label, randomized controlled trial (year 2), which suggest that the treatment effect lasts at least four years. The safety profile in their study was consistent with that of vitrectomy and subretinal injection procedures; no deleterious immune responses occurred.

This investigation included 40 patients who received 1.5×1011 vector genomes of VN in at least one eye (phase 1, n = 11; phase 3, n = 29 [20 with original intervention, nine with control/intervention]). The investigators documented outcomes of subretinal VN injection into the second eye of phase 1 subjects and into both eyes of phase 3 subjects.

Endpoints common to both studies included full-field light sensitivity threshold (FST) testing and changes in performance on the multiluminance mobility test (MLMT) within the illuminance range evaluated. Safety was assessed by adverse-event reporting, lab results, and findings of ophthalmic and physical examinations.

For phase 1 subjects, the mean change in MLMT lux score was 2.4 at

four years posttreatment versus 2.6 at year 1. Among phase 3 participants, the mean score change was 1.9 at year 2 versus 1.9 at year 1 in original intervention subjects, and 2.1 at one year among control/intervention subjects. In general, all three groups maintained improvement in FST, denoting light-sensitivity improvement of more than 2 $\log_{10}$ (cd.s/m^2) at year 1 and at subsequent follow-up visits for participating patients. The safety profile resembled that of vitrectomy and the subretinal injection procedure. There were no adverse immune responses.

VN was approved by the FDA in 2017 and represents the first authorized pharmacologic treatment for this type of IRD. The pooled results from these studies demonstrate the favorable benefit-risk profile of this gene therapy.

Observation is ongoing and will provide greater insight into the longer-term efficacy and safety profiles. In the interim, the authors emphasized the need for accurate diagnosis of IRD by genetic testing to identify the patients most likely to benefit from this treatment and other types of gene therapy. *(See also related commentary by Stephen H. Tsang, MD, PhD, in the same issue.)*

Nanotechnology Delivers Cyclosporine for Dry Eye Disease

September 2019

Although cyclosporine ophthalmic emulsion 0.05% can increase tear production in patients with dry eye disease (DED), the hydrophobic nature of this drug limits its aqueous solubility in traditional preparations. Nanomiceller formulations enhance the solubility of hydrophobic agents by entrapping the drug within the micelle structures, thus creating a clear aqueous solution. OTX-101 0.09% is a nanomicellar solution of cyclosporine. In nonclinical pharmacokinetic studies, cyclosporine levels in ocular tissue were higher after administration of OTX-101 0.05% than after cyclosporine ophthalmic emulsion 0.05%. **Goldberg et al.** assessed the efficacy and safety of OTX-101 in a phase 3 randomized clinical trial and found the study drug to be superior to the vehicle control.

This multicenter double-masked trial included adults with a history and clinical diagnosis of DED who had a global symptom score of at least 40 and a lissamine green conjunctival staining score of ≥3 and ≤9 in at least one eye. Eligible enrollees had a run-in period of 14 to 20 days; during this time, they received vehicle twice daily.

Patients who remained eligible at baseline (day 0) were assigned randomly to receive twice-daily OTX-101 0.09% or vehicle for 84 days (n = 371 and 373, respectively). Efficacy was judged by evaluating patients' signs and symptoms of DED and by Schirmer testing.

The primary efficacy endpoint was clinically meaningful improvement (≥10 mm) in the Schirmer test score from baseline to day 84. Safety was evaluated by documenting adverse events (AEs), monitoring visual acuity and intraocular pressure, and conducting slit-lamp, dilated ophthalmoscopy, and fundus examinations.

Schirmer scores demonstrated that the primary endpoint was achieved by day 84 in the active-treatment arm ($p < .001$ vs. vehicle). Greater improvement in corneal and conjunctival staining was seen in the treatment group. The global symptom score improved in all patients by approximately 30% with no difference between groups. OTX-101 0.09% was well tolerated, and most treatment-emergent AEs were mild. The most common ocular AE in both groups was mild stinging or burning after instillation of study medication. Differences between the OTX-101 and vehicle groups in multiple clinical signs were apparent within 28 days of starting treatment.

In summary, OTX-101 0.09% significantly improved tear production and ocular surface integrity.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

FAF Imaging and Progression of Geographic Atrophy in AMD

September 2019

Holmen et al. used fundus autofluorescence (FAF) imaging to evaluate the sequence of progression leading to geographic atrophy (GA) in patients with age-related macular degeneration (AMD). They found that GA can evolve from a variety of changes as seen on FAF. Moreover, they noted that, in most eyes, predominant hypoautofluorescence appears to be the final step before GA is visible.

This study was a post hoc analysis of images from the Age-Related Eye Disease Study 2 (AREDS2), which evaluated the impact of nutritional supplements on AMD progression. The researchers included 120 eyes (109 participants) with at least two years of FAF images. The first visit at which GA was identified on FAF was considered the incident visit. Images from incident visits were stacked and aligned over previous annual FAF images from the same eye, allowing for pixel-to-pixel correlation between images of sequential visits. Images were graded subjectively and independently by two certified graders at the University of Wisconsin Reading Center.

All precursor images were classified as either 1) minimal change autofluorescence, 2) predominant hypoautofluorescence (decreased autofluorescence), 3) predominant hyperautofluorescence (increased autofluorescence), or 4) mixed autofluorescence. Main outcome measures were GA area and rate of enlargement.

At 1.0 mm^2, the mean area of incident visit GA on FAF was significantly smaller than the mean area of incident GA and baseline GA previously described in clinical trials. The mean enlargement rate of incident GA was 0.97 mm^2 per year. Although precursor lesion classification was not associated with the area of incident GA, it was associated with enlargement rate, and minimal-change autofluorescence lesions were linked to faster enlargement rates.

Among all types of precursor lesions, predominant hypoautofluorescence lesions were the most common: Three years before GA developed, they accounted for 42% of precursor lesions; this percentage grew to 81% one year before GA developed.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

DM Rupture Alone Does Not Produce Hydrops in Keratoconic Eyes

September 2019

Parker et al. set out to evaluate the long-held assumption that eyes with keratoconus develop corneal hydrops when the Descemet membrane (DM) breaks. In a two-center retrospective study, the investigators found that no patient had hydrops after DM endothelial keratoplasty (DMEK; in which the DM is selectively replaced). In contrast, hydrops occurred in every patient in whom the posterior corneal stroma and DM were inadvertently punctured during Bowman layer (BL) transplantation. These results discredit DM breakdown alone as the cause of corneal edema in keratoconus.

The authors hypothesized that if DM rupture is the sole reason for corneal hydrops in keratoconus, then edema should result from loss of membrane integrity, regardless of whether the DM break occurred alone or in conjunction with perforation of other corneal layers. To test this, they evaluated outcomes for 15 patients: 10 patients (16 eyes) with comorbid Fuchs endothelial corneal dystrophy and keratoconus who underwent DMEK and five patients (five eyes) with keratoconus who had inadvertent piercing of the posterior corneal stroma and DM during surgery to transplant the BL.

To determine which patients experienced hydrops, the authors reviewed data from slit-lamp biomicroscopy and anterior segment optical coherence tomography conducted intraoperatively and in the early post-op period. They found no evidence of fluid accumulation in any eye treated with DMEK, even though the procedure involves resection of the DM and, in four of the 16 eyes, led to partial or near-total detachment of the donor DM graft postoperatively. In contrast, hydrops developed immediately in all five eyes that had inadvertent perforation of the posterior stroma and DM.

For more than a century, circumstantial evidence has suggested that hydrops in keratoconic eyes is caused by disruption of DM integrity. Advances in lamellar keratoplasty have enabled precise manipulation and excision of the DM, which has led to re-evaluation of the conventional model.

The authors concluded that a defect in the DM is not sufficient to produce hydrops in keratoconus; an accompanying disruption in the posterior corneal stroma would be necessary for the edema to occur. Therefore, they suggested that researchers consider addressing the posterior corneal stroma in future efforts to prevent or treat keratoconic hydrops.

Telemedicine for Management of Wet AMD

September 2019

The success of anti-VEGF pharmacotherapy has revolutionized the management of exudative age-related macular degeneration (AMD), but the need for frequent injections has caused substantial medical and social burdens. To address these issues, the Mayo Clinic in Rochester, Minnesota, established a practice model in which stable patients with wet AMD who had to travel a considerable distance could be managed by one of two local ophthalmologists, under the guidance of a retina specialist in Rochester. **Starr et al.** reported the clinic's experience with electronic communication between the clinicians and concluded that the telemedicine system proved effective for managing patients with exudative AMD.

For this study, the authors reviewed medical records of all patients who received electronic consultation for the management of exudative AMD at the clinic from September 2015 through August 2017, which included monthly anti-VEGF injections. E-consults were conducted by the retina specialist, and office exams were done by a comprehensive ophthalmologist, who also provided follow-up care. Collected data included the specialist's recommendations for intravitreal agent, interval between injections, number of injections, and follow-up schedule.

During the study period, 200 e-consults were performed (for 83 eyes of 59 patients), 198 of which were completed. The mean age of patients at the time of e-consult was 82.3 ± 7.3 years, and the mean follow-up period was 2.4 ± 0.81 years. The mean distance from the patient's home to the retina specialist was 70 ± 44 miles. Visual acuity was stable throughout the study period, and no patient was lost to follow-up. Only 14 consults (7%) did not comply with the recommendations of the specialist. In most cases, this was due to scheduling errors/conflicts or to comorbidities that resulted in missed appointments.

The authors concluded that, in select patients and settings, telemedicine may be a viable option for screening and managing patients with wet AMD. They emphasized that a successful retina telemedicine service requires support from a large health system network with excellent communication and the ability to share electronic data seamlessly.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Ambient Light, IOL Choice, and the Circadian Clock

August 2019

Chellappa et al. explored the effects of IOL choice on the functioning of the circadian system, cognitive function, and sleep regulation in older adults. They found that optimizing spectral light transmission in cataract surgery patients appears to minimize adverse age-related effects in all three areas.

This cross-sectional study was performed at the Centre for Chronobiology of the University of Basel and included 13 adults who had undergone cataract surgery (mean age, 69.9 years) and 16 healthy controls (mean age, 63.6 years). Eight of the cataract patients had received a blue-blocking (BB) IOL; the other five had received an IOL that blocked ultraviolet [UV] light only.

The study consisted of 1) an ambulatory segment lasting approximately three weeks, in which participants'

sleep-wake cycles were assessed, which was followed by 2) an in-laboratory segment.

The in-lab portion began with 3.5 hours of dim-dark adaptation, immediately followed by two hours of evening light exposure to either blue-enriched or non–blue-enriched light. This was followed by 30 minutes of dim light exposure, eight hours of sleep opportunity, and two hours of morning dim light. This protocol was used three times for each patient, with one-week intervals between sessions.

The authors analyzed salivary melatonin levels, cognitive test findings, sleep structure, and electroencephalographic activity to explore possible links between lens replacement and markers of circadian rhythms, cognitive performance, and sleep regulation.

Compared with controls, patients with IOLs had an attenuated increase in melatonin levels during light exposure (mean increases: 23.3% in the BB group and 19.1% in the UV group; $p < .001$ vs. controls). Improvement in cognitive function, indexed by sustained attention performance, was better for the UV-blocking IOL group (mean, 276.9 ms) than the BB IOL group (mean, 348.3 ms) during light exposure and after sleep.

The increase in slow-wave sleep was higher for the UV group (mean increase, 13%) than for controls (mean increase, 5.2%). Frontal non-REM slow-wave activity during the sleep cycle was greater in the UV group than in the BB group (mean, 79.9 $\mu V^2/Hz$ vs. 53.2 $\mu V^2/Hz$).

These empirical data from stringently controlled lab conditions suggest that optimizing spectral light transmission in patients who undergo cataract surgery may have a beneficial effect on circadian rhythms, cognition, and sleep. *(Also see related commentary by Line Kessel, MD, PhD, FEBO, and Michael Larson, MD, DMSc, in the same issue.)*

Israeli Education System and Myopia Risk

August 2019

In a large population-based study of adolescent males in Israel, **Bez et al.** looked for correlations between the type of education system and the preponderance of myopia. They found that ultra-Orthodox education is associated with the highest odds of both myopia and high myopia.

For this nationwide study, the researchers evaluated 22,823 young Israeli men (mean age, 17.7 years) who were candidates for military service, had participated in the military draft board in 2013, and had undergone medical and visual assessments.

Participants had studied in one of the three predominant Israeli education systems: secular, Orthodox Judaism, or ultra-Orthodox Judaism.

The main outcome measure was the odds ratio (OR) for associations between the type of education system and the prevalence and severity of myopia. Myopia severity was classified as low (−0.50 to −2.99 D), moderate (−3.00 to −5.99 D), or high (−6.00 D or more). Statistical methods included univariable logistic regression (to assess links between myopia and independent variables and covariates), the $\chi 2$ test (for categorical variables), one-way analysis of variance (for continuous variables), and multivariable logistic regression (to estimate associations between education systems and myopia severity).

The Orthodox educational systems require extensive reading starting in early childhood; this is most intensive in ultra-Orthodox schools. This study found that myopia was most common among the students who received ultra-Orthodox education (82.2%), followed by those with standard Orthodox education (50.3%). In contrast, myopia was present in less than 30% of students in the secular system. Compared with secular education, standard Orthodox education was linked to greater odds of myopia (OR, 2.3; $p < .001$), as was ultra-Orthodox education (OR, 9.3; $p < .001$). Compared with the secular system, the multivariable adjusted OR for high myopia was 4.6 in the standard Orthodox system ($p < .001$) and 38.5 ($p < .001$) in the ultra-Orthodox system.

These findings suggest an independent link between the structure of educational systems and the prevalence and severity of myopia and thus support the belief that near-work activities contribute to myopia development and progression.

The authors emphasized that their study is strictly observational; as a result, causal relationships cannot be inferred. They encouraged research on strategies that may minimize myopia development in students, such as reducing reading time and increasing font sizes of textbooks. *(Also see related commentary by Maria A. Woodward, MD, MSc, Lev Prasov, MD, PhD, and Paula Anne Newman-Casey, MD, MS, in the same issue.)*

Accuracy of AJCC *Cancer Staging Manual* for Conjunctival Melanoma

August 2019

Physicians who stage cancer recognize the need for collaborative data sharing and the importance of validating cancer staging systems that are used to standardize patient care. **Jain et al.** tested the accuracy of content in the eighth (2018) edition of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* for estimating mortality and metastasis rates for conjunctival melanoma. They found that the manual's content is accurate.

For this registry-based international study, the authors pooled data from 10 ophthalmic oncology centers representing 288 patients (mean age, 59.7 years) with conjunctival melanoma. The patients were diagnosed from 2001 through 2013; treatments included excision biopsy, cryotherapy, topical chemotherapy, radiation therapy, enucleation, and exenteration. Main outcome measures were metastasis rates and the five- and 10-year Kaplan-Meier mortality rates according to the clinical T (cT) categories and subcategories. Data were analyzed in 2018.

With regard to tumor category, 218 patients (75.7%) had cT1 tumors, 34 (11.8%) had cT2 disease, 15 (5.2%) had cT3 tumors, and 21 (7.3%) were classified as having cTx disease. No patients had cT4 tumors. The pathologic T category (pT) was pTis in 43 patients (14.9%), pT1 in 169 (58.7%), pT2 in 33

(11.5%), pT3 in 12 (4.2%), and pTx in 31 (10.8%).

At presentation, metastasis was noted in five patients (1.7%). During follow-up, metastasis had occurred in 24 patients (8.5%) after a median of 4.3 years (interquartile range [IQR], 2.9-6.0 years). Twenty-nine (10.1%) of the 288 patients died of a melanoma-related cause, at a median time of 5.3 years (IQR, 1.8-7.0 years). Patients with T3 disease were the only group with mortality in the first year.

The highest mortality rates were found among patients with cT2 and cT3 conjunctival melanoma, compared with those presenting with cT1 tumors. Specifically, cumulative mortality rates for patients with cT1 tumors were 0% at 1 year, 2.5% at 5 years, and 15.2% at 10 years. For patients with cT2 tumors, the mortality rates were 0% at 1 year, 28.6% at 5 years, and 43.6% at 10 years. Among those with cT3 tumors, mortality rates were 21.1% and 31.6% at 1 and 5 years, respectively (10-year data were not available).

The risk of death was higher for patients with ulcerated melanoma (hazard ratio, 7.58; p = .04).

This study suggests that the eighth edition of the AJCC *Cancer Staging Manual* is an accurate resource for staging conjunctival melanoma and for estimating metastasis and mortality rates. The findings support use of this information to guide patient care and future research. *(Also see related commentary by Bita Esmaeli, MD, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Transepithelial CXL With Iontophoresis for Keratoconus: Two-Year Outcomes

Journal of Cataract & Refractive Surgery
2019;45:992-1000

Iontophoresis is a noninvasive technique for delivering a charged substance into the corneal stroma by repulsive electromotive force. **Lombardo et al.** developed a slightly modified transepithelial iontophoresis (T-ionto) corneal cross-linking (CXL) technique and compared this procedure to standard CXL. Two years following treatment, the outcomes of T-ionto CXL were comparable to those of standard CXL for halting keratoconus progression, despite less corneal apex flattening with the new technique.

In this single-site trial, participants' eyes were assigned randomly to receive T-ionto CXL (n = 22) or standard CXL (n = 12). Outcome measures included corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), manifest refraction spherical equivalent, maximum simulated keratometry (K), corneal higher-order aberrations, central corneal thickness, and endothelial cell density. All outcomes were assessed at various intervals through 24 months post-op.

By two years, mean maximum K had flattened by –1.05 ± 1.20 D in the T-ionto CXL group (p = .07) and by –1.51 ± 0.89 D in the control group (p < .001). Two eyes that received T-ionto CXL showed maximum K steepening of >1.0 D by 24 months; this did not occur in any control eye. The mean change in CDVA was –0.08 ± 0.15 logMAR in T-ionto CXL eyes (p = .04) and –0.02 ± 0.06 logMAR in standard CXL eyes (p = .34). By 24 months, UDVA improved from 0.80 ± 0.19 logMAR to 0.48 ± 0.36 logMAR in T-ionto CXL eyes (p < .001) and from 0.65 ± 0.30 logMAR to 0.32 ± 0.29 logMAR in eyes that received standard CXL (p = .01). The average decrease in myopic defocus was significant in both groups (+0.81 D; p < .05).

There were no significant between-group differences in the various outcome measures at 24 months. Corneal higher-order aberration and endothelial cell density values did not change significantly in either group, and central corneal thickness was nearly unchanged from baseline. The cornea was clear in all 22 eyes that underwent T-ionto CXL; haze was present in two control eyes (16.66%).

In summary, the favorable outcomes observed at one year remained stable for both procedures through two years of follow-up. Standard CXL produced greater flattening of the corneal apex.

Autofocals: Gaze-Contingent Eyeglasses for Presbyopes

Science Advances
2019;5(6):eaav6187

Presbyopia, which affects a substantial percentage of aging adults, still does not have an ideal solution. Each option—from spectacles to accommodating IOLs—has drawbacks. **Padmanaban et al.** designed a correction device for presbyopia, which they called "autofocals," aimed at mimicking the natural accommodation response by combining eye tracker and depth sensor data to automatically drive focus-tunable lenses. Testing in two studies showed that autofocals outperformed traditional corrective lenses on visual acuity and refocusing ability.

The authors' wearable prototype incorporates three elements: 1) electronically controlled liquid lenses; 2) a wide field-of-view stereo depth camera; and 3) binocular eye tracking. This autofocal system can automatically adjust the focal power of the liquid lenses based on input from the eye trackers. Because just 0.5 degrees of gaze direction error in each eye tracker is enough for perceivable changes in sharpness, the authors devised a custom sensor fusion algorithm that incorporates a depth camera. The depth serves as an extra stream of information to continually adjust for errors in eye tracking.

In the first study of the experimental device (19 participants), the visual acuity achieved with autofocals at all tested distances was superior to that with monovision or progressive lenses, and contrast sensitivity was similar. For refocusing, autofocals were faster and much more accurate than progressive lenses. In the second study, 23 of 37 users considered autofocals the best device for ease of refocusing.

Overall, users preferred these eye-tracked autofocals to a previously proposed depth-tracked system, suggesting that the technology chosen for adjusting lens power may substantially affect user acceptance of focus-tunable eyewear. The comfort, convenience, and ease of use of autofocals warrant further exploration.

—Summaries by Lynda Seminara