# Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

## *Ophthalmology*

Selected by Stephen D. McLeod, MD

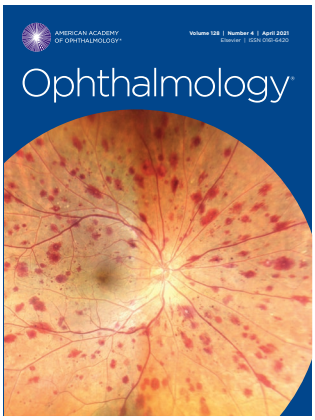
### Uveitic Edema Often Relapses After Steroid Treatment

May 2021

**Tomkins-Netzer et al.** conducted longitudinal follow-up of patients with uveitic macular edema enrolled in the Multicenter Uveitis Steroid Treatment (MUST) trial. They found that seven years after treatment, 43% of patients experienced at least one episode of relapse, suggesting the need for ongoing monitoring with OCT.

The MUST study included 177 patients (248 eyes) with a mean age of 52 years. OCT measurements were obtained at baseline and annually thereafter, and visual acuity (VA) was measured at each visit. Macular edema was defined as a center macular thickness (CMT) of ≥240 µm on time-domain OCT or equivalent. Resolution of edema was defined as normalization of CMT on OCT. Relapse denoted an increase in CMT to ≥240 µm detected in an eye with previous resolution. Main outcome measures were VA and resolution of macular edema or relapse.

Information on short-acting regional corticosteroid treatment was available for 227 eyes. Of these, 40% received at least one corticosteroid injection. The overall injection rate was 0.53 per eye year. The cumulative percentage of macular edema resolution at any point during the seven years of follow-up was 94%. Presence of epiretinal membrane on OCT was linked to lower likelihood of edema resolution (hazard ratio [HR], 0.74; p = .05).




Among 177 eyes with resolution of edema, the cumulative percentage of relapse within seven years was 43%. Eyes with resolved edema gained a mean of 6.24 letters (p < .001). Eyes without resolution of edema had no gain in vision (mean change, –1.30 letters; p = .065). Eyes that developed macular edema during the year (incident or relapsed) lost a mean of 8.65 letters (p < .001).

When given sufficient time and treatment, nearly all uveitic macular edema resolves, even though episodes of relapse are common, the authors said. Because VA was superior for eyes with resolved edema, they suggest that inflammation control and edema resolution may be visually relevant treatment goals.

### Gene Therapy for LHON

May 2021

**Newman et al.** evaluated gene therapy as an early intervention for Leber hereditary optic neuropathy (LHON). The primary efficacy end point was not achieved, with equivalent improvement in visual acuity (VA) observed in both treatment and control eyes.

For this phase 3 trial, the researchers enrolled patients with the m.11778G>A mitochondrial DNA mutation who experienced vision loss within six months of LHON onset. The right eye of each patient was assigned randomly to receive one injection of rAAV2/*2-ND4* (9 × 1010 viral genomes in 90 µL) or one sham injection. The left eye was given the other treatment. The primary end point was a clinically significant difference (–0.3 logMAR; 15 letters) in BCVA from baseline to week 48. Follow-up continued to week 96.

The efficacy analysis included 38 patients (mean age, 36.8 years; 82% male). The mean duration of vision loss at treatment was 3.6 months (active) and 3.9 months (sham). Mean baseline logMAR BCVA (standard deviation [SD]) was 1.31 SD and 1.26 SD, respectively. At week 48, the difference in BCVA change from baseline between active and sham treatments was –0.01 logMAR (p = .89). Initially, mean BCVA declined in both groups, reaching the worst levels at week 24, followed by a plateau phase until week 48, and then improvement of 10 and 9 ETDRS letters, respectively, from the plateau level to week 96. At final follow-up, vision outcomes were comparable for both groups of eyes. Treatment was well tolerated.

Although the primary end point of this study was not met, bilateral improvement of VA occurred, which has been observed but is inconsistent with the typical natural history of visual outcomes of LHON. These findings

have implications for the design of future neuro-ophthalmologic trials of gene therapy, said the authors. *(Also see related commentary by John J. Chen, MD, PhD, in the same issue.)*

### Autologous Retinal Transplantation for Macular Holes

May 2021

The advent of autologous retinal transplantation (ART) has generated new ways of managing macular holes (MHs). Building on a pilot study showing success of ART for MH closure in the hands of different surgeons, **Moysidis et al.** investigated real-world outcomes. They found closure rates of 89% for MH and 95% for MHs with rhegmatogenous retinal detachment (MH-RRD). Moreover, the gains in visual acuity (VA) were substantial.

The goal of this multicenter study was to explore anatomic and functional outcomes for patients with MHs treated by ART. A worldwide open invitation for case contributions was announced at scientific meetings, through societies, and by email. Participating surgeons shared details on consecutive cases via a standardized data-collection form.

Altogether, 33 vitreoretinal surgeons contributed a total of 130 cases treated from 2017-2019. The mean maximum MH diameter was 1,470 µm, mean minimum diameter was 840 µm, and mean axial length was 24.6 mm. All patients underwent pars plana vitrectomy and ART, with intraoperative variables modified appropriately by the surgeon. OCT images were graded by two masked reviewers. Main outcomes were MH closure rate, VA, integrity of external limiting membrane and ellipsoid zone band, and alignment of neurosensory layers (ANL).

The mean age of the patients was 63 years. The indication for ART was primary MH in 27%, refractory MH in 58%, and MH-RRD in 15%. Mean VA improved from 1.37 ± 0.12 logMAR preoperatively to 1.05 ± 0.09 postoperatively (mean follow-up, 8.6 months). Closure rates were 89% for MH (78.5% complete; 10% small eccentric defect) and 95% for MH-RRD (68.4% complete; 26.3% small eccentric defect). VA improved by 3 or more lines in 43% of eyes and by 5 or more in 29%. Reconstitution of ANL ($p = .01$) and the ellipsoid band ($p = .02$) led to better visual outcomes. Dislocation of the ART graft occurred in five cases (3.8%). There were five cases of post-op retinal detachment (3.8%) and one case of endophthalmitis (0.77%).

*—Summaries by Lynda Seminara*

## Ophthalmology Retina

Selected by Andrew P. Schachat, MD

### SD-OCT Features That Precede New-Onset GA

May 2021

Using spectral-domain (SD) OCT, **Pasricha et al.** sought to identify precursor features of new geographic atrophy (GA) prior to onset. They found that early photoreceptor changes and drusen accumulation herald the evolution to GA, as early as four years before GA is diagnosed, suggesting an early anatomic end point in trials of late-stage atrophic age-related macular degeneration (AMD).

For this retrospective study, the researchers analyzed SD-OCT images and color photographs from 488 patients (488 eyes) with intermediate AMD at baseline. During the study's seven-year time frame, 62 eyes with sufficient image quality developed new-onset GA during year 2 and thereafter.

The area of new-onset GA and one size-matched control region in the same eye were separately segmented, and corresponding spatial volumes on SD-OCT images were defined at the GA incident year as well as at two, three, and four years prior to GA onset. Differences in SD-OCT features between paired precursor regions were evaluated through matched-pairs analyses. The main outcome measure was localized SD-OCT features two years before GA development.

Results showed that, at two, three, and four years before onset, the GA precursor regions had greater drusen volume than did the paired control regions ($p = .01$, $p = 003$, and $p = .003$, respectively). At two and three years before GA onset, the precursor regions were associated with the presence of hypertransmission, hyperreflective foci, SD-OCT–refractive drusen substructures, and loss or disruption of the photoreceptor zone, ellipsoid zone, and retinal pigment epithelium. At four years before onset, the precursor regions were associated with photoreceptor zone thinning and interdigitation zone loss.

These changes may correspond to biologically active sites in atrophy pathogenesis, the authors said, and they called for further studies on SD-OCT features and the molecular pathogenesis of AMD. *(Also see related commentary by Robyn Guymer, MD, in the same issue.)* *—Summary by Jean Shaw*

## Ophthalmology Science

Selected by Emily Y. Chew, MD

### Teleophthalmology: Home VA Test?

March/April 2021

Although the pandemic has furthered the expansion of teleophthalmology, the inability to remotely assess visual acuity (VA) continues to present a challenge. **Siktberg et al.** hypothesized that a home VA test, using a printed ETDRS chart, would be equivalent to an in-office ETDRS test performed in the clinic by a trained technician. They found that the home test was equivalent.

For this prospective cohort study, the researchers enrolled 108 patients (209 eyes) who had scheduled in-person eye examinations at the Vanderbilt Eye Institute. Participants were between 19 and 83 years old (mean, 52 years) and had a documented prior BCVA better than 20/200 in both eyes. None of the exams involved postsurgical checkups, and all participants spoke English as their primary language.

For part 1 of the study, participants were electronically sent a PDF document consisting of instructions and an ETDRS vision chart calibrated for 5 feet. The patients completed this test at home. For part 2, during the in-person appointment, a trained ophthalmic technician measured the patients' VA, using a standard ETDRS chart cali-

brated for 4 meters. The technician also administered a survey on the ease of self-testing at home. The primary outcome was the mean adjusted letter score difference between the two tests. Secondary outcomes included responses to the survey questions.

The mean ETDRS letter scores at home and in the clinic were 75 ± 11 letters (20/32 Snellen equivalent) and 79 ± 11 letters (20/26), respectively. The difference in letter score was 3.9 ± 5.8 letters (90% confidence interval [CI], 3.1-4.7 letters). The mean adjusted VA letter score difference was 4.1 letters (90% CI, 3.2-4.9 letters). As these values were within the study's prespecified 7-letter equivalence margin, the home test was considered equivalent to the clinic test in this cohort.

With regard to ease of use, 98% of the participants agreed or strongly agreed that the test was easy to set up and perform. Fewer than 5% of participants reported any barriers to use, such as access to technology and clarity of instructions.

The authors noted that patients who are familiar with and have access to computers may have been more likely to participate. In addition, non–English speaking patients and those whose VA was worse than 20/200 were excluded, thus limiting the generalizability of the findings. Ideally, future studies would test the validity of a VA test in other patient populations, the authors said. They added that the test should not be used to replace an in-person assessment when that is indicated but rather used to delay well visits or as a tool that enhances the value of teleophthalmology visits. —*Summary by Jean Shaw*

## *American Journal of Ophthalmology*

Selected by Richard K. Parrish II, MD

### Choroidal Features May Predict GA Progression

May 2021

**Shi et al.** looked at eyes with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) to determine if changes in choriocapillaris perfusion and other choroidal parameters could be used to predict disease progression. They found significant correlation between GA enlargement rates and choriocapillaris flow deficits from the entire scan region, including the area immediately adjacent to the GA.

For this review of prospective observational research involving swept-source OCT angiography (SS-OCTA), the researchers included 38 eyes of 27 patients with GA secondary to nonexudative AMD.

The average age of the patients was 81 years, and 52% were women. Patients received follow-up for roughly 12 months (range, 10.4-13.2 months). SS-OCTA imaging was performed at baseline and the annual end point. Changes in mean choroidal thickness and choroidal vascularity index (CVI) were analyzed for potential correlation with the annual square root enlargement rate of GA.

The mean ± standard deviation (SD) area of GA was 4.98 ± 1.76 $mm^2$ at baseline and 6.52 ± 2.16 $mm^2$ approximately one year later. The mean ± SD square root enlargement rate of GA was 0.31 ± 0.15 mm/year. Neither foveal involvement nor reticular pseudodrusen contributed any significant difference to the GA enlargement rate. Moreover, there were no significant differences in findings for multifocal and unifocal GA lesions. Using the global threshold method, choriocapillaris flow deficit percentage values in each region were correlated strongly with the annual square root enlargement rates of GA. There were no meaningful differences in the rate of prediction between regions. The only choroidal parameter with a significant relationship to the annual square root enlargement rate of GA was CVI measurement inside the GA region ($p = .03$).

### Sjögren Syndrome and Risk of Visual and Corneal Problems

May 2021

**Singh et al.** explored risk factors for severe visual impairment (VI) and corneal complications among patients with Sjögren syndrome. They found that severe VI was more common with older age, corneal involvement, lower Schirmer test scores, and the presence of glaucoma or cataract. Scleritis was the strongest risk factor for corneal perforation or ulceration.

In this study, the authors analyzed data for patients with primary or secondary Sjögren treated consecutively during an eight-year period. They conducted multivariate analyses and calculated odds ratios (OR) to determine the greatest baseline risk factors for severe VI (defined as BCVA better than 20/200) and for vision-threatening corneal complications (defined as ulceration or perforation).

The study population included 919 patients (1,838 eyes). Of these, 285 patients (31%) had primary Sjögren, and 634 (69%) had secondary disease. Most were female (82.2%), and the median age was 50 years.

Cases of Sjögren were diagnosed according to criteria of the American College of Rheumatology. The most common cause of secondary disease was rheumatoid arthritis (98.1%), followed by systemic lupus erythematosus (0.79%), psoriasis (0.79%), and scleroderma (0.6%).

Ten percent of eyes had severe VI at presentation, and 2.5% had corneal complications at that time. Baseline factors found to independently increase the risk of severe VI were the presence of corneal scarring ($p < .00001$; OR, 3.00) or corneal ulceration ($p < .00001$; OR, 12.96), low Schirmer values ($p = .0084$; OR, 0.93), concurrent cataract ($p = .0036$; OR, 2.4) or glaucoma ($p = .04$; OR, 4.09), and age older than 40 years ($p = .005$; OR, 1.02).

The greatest risk factors for corneal complications were presence of scleritis ($p < .0001$, OR, 8.9) and diagnosis of secondary Sjögren ($p = .009$; OR, 2.94). Among eyes with both scleritis and corneal ulceration, the ulcer was central in two eyes and peripheral in five eyes. Retinal pathology was more common with primary Sjögren ($p = .03$) and consisted mostly of macular degeneration and hypertensive changes. There was one case of low-grade non-Hodgkin orbital lymphoma, which occurred in a patient with primary Sjögren.

—*Summaries by Lynda Seminara*

## *JAMA Ophthalmology*

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

### Incidence of CRAO in Korea

April 2021

**Kim et al.** assessed recent trends in the incidence rates of central retinal artery occlusion (CRAO) in Korea. They found a decrease in the incidence of the condition, particularly among women, people younger than 65 years, and those born after 1930. This may reflect the development of a national health care system and the overall improvement in the management of chronic diseases, notably cardiovascular disease.

For this study, the researchers used data from the Korean National Health Insurance Service from Jan. 1, 2002, to Dec. 31, 2015. Unadjusted CRAO incidence rates were calculated using the number of identified CRAO cases and the corresponding midyear population. Standardized incidence rates were calculated based on the 2015 census population, and weighted mean annual incidence rates with 95% confidence intervals (CIs) were computed.

The researchers identified 9,892 individuals (out of a population of 50 million residents) who were diagnosed with CRAO during the study period. The mean age of those with CRAO was 62.4 years, and 5,884 (59.5%) were men. The researchers were not able to identify any patients with incident CRAO who also had giant cell arteritis, which may indicate that no patients had both conditions—or that diagnoses were either missed or miscoded.

The mean standard incidence rates of CRAO, as expressed in cases per 100,000 person-years, were 2.0 cases among the entire population (95% CI, 1.97-2.04 cases), 2.43 cases for men (95% CI, 2.37-2.49 cases), and 1.61 cases for women (95% CI, 1.57-1.66 cases). The highest incidence rate was observed among those between 80 and 84 years of age—in this age group, the overall rate was 9.84 cases (95% confidence interval [CI], 9.10-10.60 cases), with an incidence rate of 13.74 cases for men (95% CI, 12.16-15.32 cases) and 8.04 cases for women (95% CI, 7.21-8.86 cases).

During the study period, the incidence rate decreased (annual percentage change [APC], –3.46%), and this trend was more evident among women (APC, –4.56%) than in men (APC, –2.90%). In addition, the decrease was greater in those younger than 65 years (APC, –6.80%) than in those older than age 65 (APC, –0.57%). Among those born after 1930, the researchers observed a decrease in the CRAO incidence rate over time in every age group. The same decreasing trend did not occur among those born before 1930.

### Predicting Edema Resolution After DMEK for Fuchs

April 2021

Which patients with Fuchs dystrophy are most likely to benefit from Descemet membrane endothelial keratoplasty (DMEK)? Using Scheimpflug imaging, **Zander et al.** developed and validated a predictive model for edema resolution following DMEK. They identified five pre-op Scheimpflug parameters that may help clinicians identify ideal candidates for the procedure.

For this study, the researchers conducted a post hoc analysis of two prospective studies of patients with advanced Fuchs dystrophy. All told, 88 patients with a minimum stable follow-up of at least two months after DMEK and high-quality Scheimpflug imaging before and after surgery were identified. Development of a predictive model, using linear least absolute shrinkage and selection operator regression, was conducted in a derivation cohort of 100 eyes. This was subsequently validated in a smaller cohort of 32 eyes. The main outcome measure was decrease in central corneal thickness (CCT).

A median of 13 months after DMEK, median corneal thickness was 77 µm lower in the derivation cohort and 75 µm lower in the validation cohort. For each 10 µm of edema resolution, eyes gained 0.66 ETDRS letters in best-corrected visual acuity.

To predict edema resolution, five variables were selected by the statistical learning algorithm: two tomographic features (presence of parallel isopachs and amount of focal posterior depression) and three indicators of corneal profile and structure (anterior back scatter, posterior backscatter, and CCT). With regard to the tomographic features, eyes without any tomographic features before DMEK had more edema after surgery than those eyes with such features (mean difference, 29 µm less resolution of edema). With regard to corneal structure, the authors noted that although single measurements of CCT are not useful to detect corneal edema, CCT added to the predictive model when combined with anterior and posterior corneal backscatter.

Future studies of the model will have to show whether it improves clinical decision-making and leads to better long-term outcomes, the authors said. *(Also see related commentary by Viridian Kocaba, MD, PhD, Silke Oellerich, PhD, and Gerrit R.J. Melles, MD, PhD, in the same issue.)*

### Overminus Lens Therapy for Intermittent Exotropia

April 2021

**Chen et al.** set out to evaluate overminus spectacle therapy for the treatment of intermittent exotropia (IXT) in children between 3 and 10 years of age. They found that 12 months of overminus therapy improved distance exotropia but was associated with increased myopic shift. Moreover, the effect on distance exotropia was not maintained after treatment was discontinued.

For this trial, the researchers enrolled 386 children (mean age, 6.3 years) with IXT, a mean distance control score of 2 or worse, and a refractive error between 1 D and –6 D. The children were randomly assigned to either:

- overminus spectacle therapy (–2.5 D for 12 months, then –1.25 D for three months, followed by nonoverminus spectacles for three months), or
- nonoverminus spectacles (corrected for astigmatism, anisometropia, and myopia) worn for 18 months.

Follow-up visits took place at six, 12, 15, and 18 months. To keep participants masked, the spectacle prescription was sealed in an envelope, and lenses were

changed in both groups at the 12- and 15-month marks. The main outcome measures were the mean distance IXT control scores at 12 and 18 months. Change in refractive error from baseline to 12 months was compared between groups. At each follow-up visit, adherence with treatment was rated based on parental reports of the percentage of wear time during waking hours.

During the treatment period, spectacle wear adherence was reported as excellent (more than 75% of the time) for 149 of the 196 children in the overminus group and 144 of the 190 children in the nonoverminus group. The overall completion rate was 93% at 12 months and 86% at 18 months, with 176 of the overminus group and 155 of the nonoverminus group completing 18 months of follow-up.

At 12 months, mean distance control was better in those who wore the overminus spectacles (1.8 vs. 2.8 points; adjusted difference, –0.8; 95% confidence interval [CI], –1.0 to –0.5; $p < .001$). But by 18 months, that advantage had dissipated (2.4 points for the overminus group, vs. 2.7 for the nonoverminus group; adjusted difference, –0.2; 95% CI, –0.5 to 0.04; $p = .09$). Moreover, those in the overminus group were more likely to have a myopic shift at 12 months: Thirty-three of 189 (17%) children in this group had a shift greater than 1 D from baseline, versus two of 169 (1%) children in the nonoverminus group.

In an extension phase of this study, the researchers are collecting data on change in refractive error and axial length at 24 and 36 months. *(Also see related commentary by Boon Long Quah, MBBS, MMed, in the same issue.)*

*—Summaries by Jean Shaw*

## Other Journals

Selected by Prem S. Subramanian, MD, PhD

### Impact of Foveal Factors on Retinal Detachment Repair

*Eye*
Published online Jan. 29, 2021

Many pre-op factors have been shown to contribute to visual acuity (VA) results after treatment of retinal detachment (RDs), including symptom duration, baseline VA, and detachment height. **Hostovsky et al.** explored whether foveal features may have a similar correlation with post-op VA after macula-off RD repair. They found that foveal changes play a significant role in the pathogenesis of lost vision in such detachments, particularly those that are high and thus have greater tangential tension in the foveal region.

For this study, the authors reviewed medical records of 47 consecutive patients with a macula-off RD who presented during a two-month period. All had spectral-domain (SD) OCT imaging preoperatively. Parameters used to assess the fovea included RD height (measured manually), intraretinal morphologic changes, and foveal and subretinal pathologic features such as epiretinal membrane and macular hole (MH). All OCT findings were evaluated by Dr. Hostovsky, who was masked to the clinical data.

The majority (44 of 47) of affected eyes could be imaged by SD-OCT and were entered into the study. Six patients had MHs. Repair procedures were pneumatic retinopexy (n = 22), pars plana vitrectomy (n = 17), and scleral buckle (n = 5). All patients with MH received pneumatic retinopexy. According to univariate analysis, final visual outcomes correlated strongly with detachment height, symptom duration, and the presence of MH or epiretinal membrane ($p = .001$, .003 and .03, respectively). Also significant was the relationship between MH presence and RD height. Per multiple regression analysis, the only factor of these with a meaningful correlation to final VA was the presence of MH ($p = .003$) or epiretinal membrane ($p = .007$). Another significant relationship to final VA in multivariable analyses was success of the first surgery ($p = .006$).

The authors noted that the proportion of MHs, plus the correlation between MH and detachment height, may imply that elevated tension in the fovea of patients with high macula-off detachment leads to poorer visual outcomes after repair. The elevated tangential traction on the foveal region could cause MHs, said the authors.

### Heads-Up Display Improves Comfort for Cataract Surgeons

*Clinical Ophthalmology*
2021:15;347-356

Although heads-up digital visualization systems have improved neck and back comfort for ophthalmic surgeons in small studies, the designs and conditions of those investigations did not mirror real-world conditions. **Weinstock et al.** performed a larger study to better understand surgeons' perceptions of the heads-up display (HUD) versus conventional microscopes in the operating room. They found that most participants preferred HUD.

For this study, the researchers distributed a three-part online survey to cataract surgeons with HUD experience. Part 1 collected surgeon-specific variables, such as musculoskeletal health history and HUD usage factors. Part 2 comprised the validated electronic version of the Nordic Musculoskeletal Questionnaire, which addresses pain-related issues in the neck, upper back, lower back, and shoulders in the preceding 12 months. Part 3 used customized questions that elicited the surgeons' preferences for HUD or standard operating microscopes. A multivariable model was developed to identify variables that predict improvement of pain.

The analysis set included 64 surgeons. Of these, 37 were posterior segment only, 25 were anterior segment only, and two reported experience in both areas. The surgeons had practiced a mean of 14.9 years, and the mean time of HUD use was 2.3 years. Most surgeons "agreed" or "strongly agreed" that HUD reduced the severity (64%) and frequency (63%) of their pain, led to improved posture (73%), and improved their overall comfort (77%). Of those who experienced headaches or other pain/discomfort while operating, 44% and 82% (respectively) noted improvement in those conditions after implementing HUD.

The odds of pain attenuation since HUD introduction was 5.12 times higher for those who used HUD in at least half of their cases.

*—Summaries by Lynda Seminara*