

Journal Highlights

NEW FINDINGS FROM *OPHTHALMOLOGY*, *AJO*, AND *JAMA OPHTHALMOLOGY*

Ophthalmology

Selected by Stephen D. McLeod, MD

hCECs for Endothelial Failure: Five-Year Results

April 2021

Building on their previous investigations of cultured human corneal endothelial cells (hCECs) to manage endothelial failure, Numa et al. evaluated long-term postoperative results of the first clinical trial in humans. They found that normal corneal endothelial function was restored in 10 of 11 eyes by the five-year mark, and no serious adverse reactions occurred.

This prospective observational study included 11 patients (11 eyes) with a pseudophakic endothelial failure condition (e.g., Fuchs endothelial corneal dystrophy or corneal edema). All eyes had been implanted with a posterior chamber IOL.

The researchers' novel procedure involves simultaneous injection of cultured hCEC cells supplemented with a Rho-associated protein kinase inhibitor to promote CEC engraftment. After injection, follow-up occurred at weeks 1, 4, 12, and 24 during the first year and annually thereafter. The primary outcome was the change in central corneal

endothelial cell density (ECD) following therapy. Other outcome measures were corneal thickness, best-corrected visual acuity (BCVA), and intraocular pressure (IOP) during follow-up.

Within five years of the procedure, normal corneal endothelial function was restored in 10 of the 11 eyes. The mean (standard deviation) value for central corneal ECD was 1,257 (467) cells/mm². BCVA improved significantly in 10 eyes; mean log-MAR values at baseline and five years were 0.876 and 0.046, respectively. No major adverse effects occurred.

The authors describe their approach as “a paradigm shift in corneal regenerative medicine, with potential clinical application to patients worldwide.” They added that therapeutic outcomes could be enhanced by further improving the biological quality of cultured

hCECs and learning more about efficacy across a wide range of conditions.

Avacincaptad Pegol for GA

April 2021

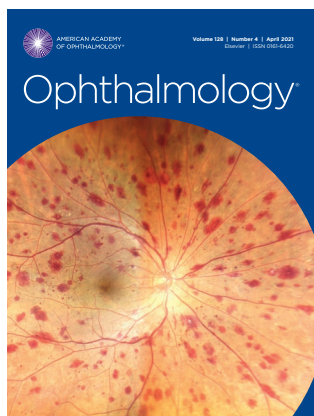
Jaffe et al. conducted a phase 2/3 pivotal study of the safety and efficacy of intravitreal avacincaptad pegol for geographic atrophy (GA) associated with age-related macular degeneration (AMD). They found that 2- and 4-mg dosing regimens of the drug slowed GA progression significantly in comparison to sham treatment. Moreover,

the safety profiles were favorable.

For this two-part study, the researchers included 286 patients with GA secondary to AMD (mean age, 78.2 years). The main efficacy measure was mean rate of change in GA, determined from fundus autofluorescence imaging at baseline and months 6 and 12 of treatment. Injections were administered monthly. In part 1 of the study, 77 patients were assigned randomly (1:1:1) to one of three groups: avacincaptad pegol 1 mg, avacincaptad pegol 2 mg, or sham control. Part 2 consisted of 209 patients randomized (1:2:2) to receive avacincaptad pegol 2 mg, avacincaptad pegol 4 mg, or sham. Due to the drug's viscosity, the 4-mg dose was divided into two intravitreal injections of 2 mg. For uniformity, the avacincaptad pegol 2-mg group also received a sham administration during each treatment, and the sham group was given two sham injections.

Both the 2-mg and 4-mg doses of avacincaptad pegol met the primary efficacy end point. GA growth (by square-root transformation) through month 12 was 27.4% ($p = .0072$) and 27.8% ($p = .0051$), respectively, compared with growth in the sham groups. Avacincaptad pegol was well tolerated overall; there were no drug-related adverse events (AEs) or serious ocular AEs.

A phase 3 confirmatory trial is underway. Given the similar efficacy of the 2- and 4-mg regimens, and the need for just one injection with 2-mg treatment, the higher dose was excluded from the phase 3 trial.



Is 10-2 Testing Needed for Early VF Loss?

April 2021

The notion that testing the central visual field (VF) may give better diagnostic information than full-field testing begs the question of whether the 10-2 test should be done in addition to, or instead of, the 24-2 test. West et al. compared the ability of these tests to detect abnormal VFs in patients with early glaucomatous damage. Their analysis, which included just the 12 central locations of 24-2 perimetry to ensure fair comparison, showed little evidence that 10-2 testing could identify damage not detected by 24-2 testing.

This prospective observational study included eyes of patients with open-angle glaucoma (n = 97) and healthy controls (n = 65). The median mean deviation of the 97 glaucomatous eyes was -2.31 dB. All patients underwent 10-2 and 24-2 VF testing. The criteria used to compare test performance were total deviation (TD) and pattern deviation (PD) analyses at the 5% and 2% levels. Also analyzed were two pairs of follow-up tests, each performed four months apart. For equitable comparison of the methods, only the 12 central locations of the 24-2 test were included in the analyses. Main outcomes were area under the receiver operating characteristic curve (AUC), sensitivity at identically matched specificity for each criterion, overlap of abnormal VFs with both tests, and replicability of the findings in two subsequent evaluations.

The AUC comparison revealed no significant difference for any of the specified criteria. The values ranged from 0.91 to 0.94 for the 10-2 test and from 0.88 to 0.93 for the 24-2 test. At matched specificity, the 24-2 test was significantly more sensitive for all criteria except PD at 5%. Among patients with an abnormal field detected by either test, 60% to 86% exhibited the abnormality with both tests. Within each quadrant, concordance was even better (70% to 87%). Reproducibility occurred in more than half the cases. The best repeatability was for TD at the 5% level (70% of patients); the poorest was for PD at 5% (55% of patients).

The authors recognize that 10-2 testing may be a valuable follow-up tool for advanced cases of glaucoma. However, the results of this study suggest that it may be unnecessary in early-stage glaucoma. Yet contradictions abound, and there is evidence that 10-2 tests detect abnormalities missed by 24-2 testing. Some investigators are modifying the 24-2 test to include more test sites in the central VF, but published data are sparse. Given the limited resources of many facilities and the need for frequent reliable testing to effectively monitor progression, the authors suggest reserving the 10-2 test for patients at high risk of progression in the central VF.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Diabetes Control and POAG Progression

March/April 2021

Although diabetes has been proposed as a risk factor for glaucoma, objective evidence of the impact of poorly controlled diabetes on glaucoma progression is lacking. Johnson et al. investigated whether diabetes control had an effect on functional and cellular measures of glaucoma development. They found no significant association.

For this retrospective cohort study, the researchers evaluated data on 222 patients (351 eyes). At baseline, 167 eyes (47.6%) had primary open-angle glaucoma (POAG), and 184 eyes (52.4%) were glaucoma suspects. All patients had concomitant type 2 diabetes, and their mean baseline age was 62.5 ± 10.2 years. During follow-up of 6.9 ± 5.1 years, the participants had an average of 4.8 standard automated perimetry (SAP) tests (range, 2-28); 3.6 spectral-domain optical coherence tomography (SD-OCT) scans of the retinal nerve fiber layer (RNFL; range, 2-10); and 8.3 tests of glycated hemoglobin (HbA1c; range, 2-21).

As a proxy for diabetes control, the researchers used three distinct HbA1c measurements: mean, peak, and fluc-

tuating HbA1c. The main outcome measures were the rates of change in SAP test results and RNFL thickness over time. Use of metformin, a widely prescribed diabetes medication, was also evaluated.

Results of the analysis showed that the mean rate of SAP change was -0.19 ± 0.20 dB per year, and the rate of RNFL loss was -0.83 ± 0.51 μ m per year. After adjusting for confounding factors, the three HbA1c assessments were not found to be significantly associated with glaucoma progression over time. In addition, no association between metformin use and glaucoma status was observed. —Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Submacular Hemorrhage and Timing of Anti-VEGF Therapy

April 2021

More retina physicians are employing a treat-and-extend anti-VEGF regimen for their patients with age-related macular degeneration (AMD)—but do prolonged dosing intervals raise the risk of large submacular hemorrhages (SMHs)? Matsunaga et al. set out to characterize the timing of large SMHs in patients with wet AMD. They found that treat-and-extend regimens do not seem to be associated with large SMHs in these patients, and they suggest that a mechanism other than loss of effective VEGF inhibition may play a role.

For this retrospective case series, the researchers included 42 patients (42 eyes) who had a large SMH resulting from wet AMD and were selected to undergo pars plana vitrectomy with subretinal tissue plasminogen activator. Mean age was 82 ± 9.9 years, and 60% of the patients were taking anticoagulation or antiplatelet medications. All patients received intravitreal injections of one or more of three anti-VEGF drugs (aflibercept, bevacizumab, and ranibizumab) in a treat-and-extend fashion. The main outcome measures included the timing of SMH in relation to the last anti-VEGF injection and treatment status at the time of SMH.

When their SMH occurred, 19 (45%)

of the patients were stable, 15 (36%) were treatment-naïve, five (12%) were on a recently extended anti-VEGF dosing regimen, and three (7%) were on a shortened anti-VEGF regimen. The average treatment interval at the time the hemorrhage occurred was 6.8 weeks, with an average of 13.2 total injections (median, 7; range, 1-37) before SMH. The average time between last injection and SMH was 29 days (range, 5-62 days), and SMH was more likely to occur within 30 days of an anti-VEGF injection than after 30 days ($p < .001$).

The authors noted that this study's limitations include its selection for patients who had large SMHs and underwent surgical intervention. Thus, the findings may not apply to smaller subretinal hemorrhages or to those not affecting the fovea. They noted that large, controlled studies are needed to further assess the risks of SMH in AMD and to shed light on its underlying mechanisms. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Use of Adaptive Optics for Pseudoxanthoma Elasticum

April 2021

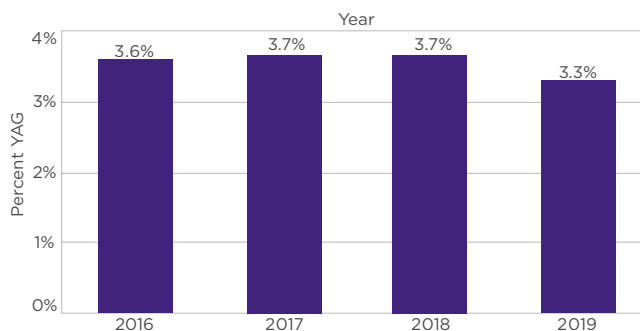
Typical ocular findings of pseudoxanthoma elasticum (PXE), a rare progressive disorder, are peau d'orange, angioid streaks, and optic nerve drusen. Although conventional imaging has been helpful for detecting retinopathy associated with PXE, further work is needed to characterize the condition's ocular abnormalities. To this end, **Murro et al.** applied a multimodal approach, including flood-illumination adaptive optics (AO), to specifically explore retinal features of patients with PXE. They observed three distinct types of angioid streaks, as well as tiny crystalline bodies that were not detected by standard retinal imaging techniques.

For this retrospective series, the authors reviewed records on 21 eyes of 18 patients (mean age, 37 years; range, 14-66) with PXE. Demographic and clinical data were gathered, along with results of imaging tests (color,

IRIS Registry Snapshot: YAG Capsulotomies

Analyzing statistically de-identified electronic health record (EHR) data from the Academy's IRIS Registry, Verana Health determined the rate of Nd:YAG capsulotomies performed within six

months of cataract surgeries in the United States from 2016 through 2019. The study included 7,548,726 total cataract surgeries in 4,537,122 unique patients. As shown in the chart, the rate remained stable over time.



Note: The Academy has partnered with Verana Health (www.veranahealth.com) to curate and analyze IRIS Registry data.

infrared, and autofluorescence fundus imaging; optical coherence tomography scans; and AO exams).

With AO, the authors detected photoreceptors within angioid streaks and identified three types of streaks: "crack" (type 1), "band" (type 2), and "hypopigmented" (type 3). Type 1 was found in eight eyes and resembled a well-defined jagged hyporeflective fissure. Type 2 was seen in 12 eyes; these bands looked similar to the cracks (type 1) but were larger. Type 3 defects, noted in three eyes, were characterized by small, short, ill-defined streaks and diffuse hyper-reflectivity. Dark spots were present on these streaks and were most evident at the boundaries. Comet lesions appeared hyper-reflective and round on AO imaging. In all eyes, the cone mosaic was less pronounced within streaks than in nearby areas.

This work demonstrates that some PXE-related retinal anomalies may be undetectable with standard imaging. The authors recognize that their series is small; however, the rarity of PXE poses challenges to developing large studies.

AADI Placement in Children: Which Quadrant Is Best?

April 2021

In eyes with refractory glaucoma, glaucoma drainage devices typically

are placed in the superotemporal (ST) or inferonasal (IN) quadrant. Placement in either location appears equally safe and effective in adults, but little is known of the relationship between shunt location and outcomes in children. **Puthuran et al.** studied placement of an Aurolab aqueous drainage implant (AADI) in pediatric eyes with refractory glaucoma. They found that procedures in the ST quadrant led to lower intraocular pressure (IOP), reduced need for IOP-lowering medications postoperatively, and were safer overall than were IN-quadrant procedures.

Patients eligible for inclusion were under 19 years of age and had received an AADI at Aravind Eye Hospital (Madurai, India) during a six-year period. Placement location was determined by the amount of scarring and conjunctival mobility. Cumulative success was defined as IOP ≤ 21 mm Hg or IOP reduction of $\geq 20\%$ below baseline at two consecutive visits occurring more than three months postoperatively. Failure was considered inadequate IOP reduction, persistent hypotony, loss of light perception, or reoperation for glaucoma or a complication of the procedure.

Overall, the medical records of 144 eyes were reviewed (144 patients; mean age, 10.1 years). Shunts were placed in the IN quadrant in 33% and

the ST quadrant in 67%. Baseline IOP and corneal diameter were higher for the IN group ($p = .04$ and $p = .004$, respectively); no other differences were noted. Two years after surgery, IOP was consistently lower in the ST group (13.7 ± 6.2 mm Hg vs. 17.5 ± 7.4 mm Hg; $p = .005$), as was the number of IOP-lowering medications (0.8 ± 0.9 vs. 1.5 ± 1.0 ; $p = .001$). ST placement was linked to substantially less tube exposure (0% vs. 12%; $p = .05$) and greater cumulative success (65.6% vs. 50.7%; $p = .15$). Higher IOP at baseline was the sole factor significantly affecting failure, which occurred at a higher rate with IN placement, but the difference between groups was not significant.

The authors cautioned that their findings may not necessarily apply to other patient populations or drainage devices, but they suggest avoiding IN placement of AADs in children unless there are contraindications to using the ST quadrant.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Hand Sanitizer and Eye Injuries in Children

March 2021

Alcohol-based hand sanitizer (ABHS), widely used to limit SARS-CoV-2 transmission, contains ingredients that can be toxic to the eye. In France, Martin et al. tracked accidental ocular exposures to ABHS in children. They found a 7-fold increase in pediatric cases of ABHS eye exposure from 2019-2020, with some cases requiring surgery.

For this retrospective case series, a team of ophthalmologists and toxicologists retrieved epidemiologic data from the French National Database of Poisonings and a pediatric ophthalmology referral hospital in Paris. They then tallied the number of eye exposures to ABHS that occurred in children from April to August for both 2019 and 2020.

The number of ABHS exposures in 2019 was 33 (1.3% of total poison-related pediatric eye injuries); this rose to 232 cases (9.9%) in 2020. Similarly,

hospital admissions among these patients increased during the same time frame, from one child (age, 16 months) in 2019 to 16 children (mean age, 3.5 years) in 2020. Eight children had a corneal and/or conjunctival ulcer, and two of the eight required an amniotic membrane transplant.

Of note, 63 of the 232 cases of exposure in 2020 occurred in public places. This is a key detail, the authors said, as public gel dispensers are easy for children to access—and the gel typically is delivered right at the height of a small child's eyes. The authors urged caution in positioning the dispensers in public places and added that parents and caregivers should be warned about the potential danger that hand sanitizers can pose to children. (Also see related commentary by Kathryn Colby, MD, PhD, in the same issue.)

COVID's Impact on Myopia in Children

March 2021

With COVID lockdowns closing schools and keeping children confined at home, what impact is the pandemic having on the prevalence of myopia? Wang et al. set out to investigate this issue in school-age children during the early months of the COVID pandemic in China. They found that home confinement and the shift to online learning appeared to be linked to an increase in myopia in 6- to 8-year-old children.

For this prospective cross-sectional study, the researchers evaluated data from a series of photoscreenings conducted at 10 elementary schools in Feicheng, China. From 2015-2019, the screenings occurred in September; in 2020, the screenings occurred in June, after schools reopened following the COVID lockdown. All told, noncycloplegic photorefractive data were available from 194,904 tests conducted in 123,535 children aged 6 to 13 years.

From 2015-2019, the spherical equivalent refraction (SER) distribution in the children appeared to be stable, with a slight overall myopic shift. In the 2020 screening, however, a myopic shift of approximately -0.3 D was noted in the younger children (ages

6-8). In contrast, the SER differences between 2020 and the previous screenings were minimal for older children, ranging from -0.12 for 9-year-olds to -0.05 for 12- and 13-year-olds—despite the fact that the older children spent more time online in their classes (2.5 hours online per day for grades 3-6, versus 1 hour per day for grades 1-2).

The researchers hypothesize that the refractive status of younger children may be more sensitive to environmental changes that trigger myopia development, and they call for additional studies to assess the issue. In the interim, they wrote, “If home confinement is necessary, parents should control the children's screen time as much as possible and increase the allowable outdoor activity while maintaining safe social distancing.” (Also see related commentary by Caroline C.W. Klaver, MD, PhD, Jan Roelof Polling, BSc, and Clair A. Enthoven, MSc, in the same issue.)

Metformin May Reduce AMD Risk

March 2021

Metformin, widely prescribed for diabetes, has been found to lower the risk of developing several age-related diseases, including cardiovascular disease. Blitzer et al. set out to determine whether a similar protective effect could be found with regard to age-related macular degeneration (AMD). They found that it was associated with reduced odds of developing AMD, with the greatest benefit at low to moderate doses of metformin and in the absence of coexisting diabetic retinopathy (DR).

For this case-control study, the researchers used data derived from a large U.S. health insurance claims database. They identified 312,404 participants who met the case inclusion criteria for AMD and an additional 312,376 controls who were matched 1:1 based on such factors as age and the presence of anemia and/or hypertension. All participants were age 55 or older.

Patients with AMD were slightly more likely to have diabetes than were controls (26% and 25.5%, respectively). The percentage of those with hypertension (65.1%) was the same for both

groups, and the number with anemia was roughly equivalent (6.5% for those with AMD, vs. 6.4% for controls). Those with AMD were more likely to smoke (5.7%, vs. 4.9% of controls) and to have hyperlipidemia (49.6%, vs. 48.8% of controls). In addition, patients with AMD were more likely to have nonproliferative DR (3.7%, vs. 1.7% of controls) or proliferative DR (0.7%, vs. 0.4% of controls).

The use of metformin for more than two years reduced the odds of developing AMD, with an odds ratio (OR) of 0.94 (95% confidence interval [CI], 0.92-0.96; $p < .001$). This was particularly true for low to moderate doses: A dose of 1-270 g over two years had an OR of 0.91 (95% CI, 0.89-0.94); the finding was similar for doses of 271-600 g. In contrast, doses of 601-1,080 g had an OR of 0.95 (95% CI, 0.92-0.98), and doses greater than 1,080 g did not reduce AMD incidence. As for the presence or absence of DR, metformin use reduced the odds of developing AMD only in those diabetic patients who did not have DR (OR, 0.93 [95% CI, 0.91-0.95]; $p < .0001$). In contrast, patients who had diabetes and DR and were taking metformin were at greater risk of developing AMD (OR, 1.07 [95% CI, 1.01-1.15]; $p < .03$).

This study has several limitations, the authors acknowledge. Nonetheless, the study results suggest that metformin may have a role in preventing or slowing the progression of AMD, and they called for future studies on the issue. (Also see related commentary by Myra B. McGuinness, MBIostat, PhD, Jessica Kasza, BSc, PhD, and Robyn H Guymer, MBBS, PhD, in the same issue.)

—Summaries by Jean Shaw

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

OAG May Not Raise the Risk of Dementia

Journal of Glaucoma

Published online Dec. 29, 2020

Although studies have shown that dementia risk is higher for people with open-angle glaucoma (OAG), the true

relationship between these diseases is still poorly understood. In a retrospective population-based study of patients with OAG, Belamkar et al. found that the 10-year probability of dementia actually was lower for these patients than for the population at large.

The study included 509 residents of Olmstead County, Minnesota; all had OAG diagnosed during a 36-year period. The cumulative risk of dementia development was calculated for these patients and compared with that of the general U.S. population. The authors used data from an earlier study in residents of the same county to identify patients with OAG, which included primary OAG, normal-tension glaucoma, pseudoexfoliative glaucoma, pigmentary glaucoma, and treated ocular hypertension. Demographic data and comorbidities were recorded. Kaplan-Meier methods were applied to estimate the cumulative risk of developing dementia or Alzheimer disease (AD), and Cox proportional hazard models were used to identify potential risk factors.

The median age of the study population was 67.5 years; the majority were white (98%) and female (59%). Dementia or AD developed in 118 (23%) of the 509 participants. AD was the predominant type of dementia ($n = 99$). The mean age at OAG diagnosis was 74.9 years for those with dementia and 65.0 years for those without dementia. The 10-year cumulative probability was 12.0% for all types of dementia and 9.9% for AD. These values are significantly lower than expected for the general U.S. population (expected incidence for both, 19.0%). Prospective studies in a more geographically and ethnically diverse population should be considered to strengthen these findings.

Younger Age Linked to Better SMILE Results

British Journal of Ophthalmology

Published online Nov. 18, 2020

Outcomes of small-incision lenticule extraction (SMILE) have been widely reported since its introduction in 2011 but have not been studied for different age groups. Primavera et al. reviewed

patient data by age group (≤ 35 years and ≥ 40 years) to explore the potential relationship between age and surgical outcomes. The authors found that while SMILE was efficient, safe, and reasonably predictable in both age groups, younger patients had better results.

Patients in this study were required to have myopia (with or without mild or moderate astigmatism), mesopic pupil < 7 mm, expected residual stromal bed under the cap of > 250 μm , pre-op central corneal thickness > 490 μm , and expected post-op mean keratometry > 35 D.

The SMILE procedures were performed by one of two experienced surgeons during a three-year period. All eyes were evaluated preoperatively and were matched between groups by preoperative refractive spherical equivalent difference of ± 0.25 D for each pair. Efficacy, safety, predictability, and astigmatic changes were assessed postoperatively at one and six months.

There were 51 eyes in each age group. By six months post-SMILE, both groups had gained lines of uncorrected as well as corrected distance visual acuity (CDVA), but the improvement in CDVA was significantly better in those ≤ 35 years of age ($p = .005$). Mean residual astigmatism was much worse in the older group ($p = .019$) despite a higher level of preoperative astigmatism in the younger group. The efficacy index for those older than 39 years was 0.86 at month 1 and 0.97 at month 6, compared with 0.97 and 1.07, respectively, for the younger patients ($p = .003$ at month 6). The safety index, calculated as loss of CDVA, for the older group was 0.93 at one month and 1.04 at six months, compared with 1.00 and 1.11, respectively, for the younger group ($p = .008$ at month 6).

Even though refractive outcomes were acceptable in older patients, this group had significantly lower indexes of efficacy and safety, poorer astigmatism reduction, and a tendency toward undercorrection. The authors suggested that the differences in outcomes may relate to the stiffening of the corneal stroma that occurs with aging.

—Summaries by Lynda Seminara