Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Anti-VEGF for ROP: Impact on Developmental Outcomes for the Eye and Brain

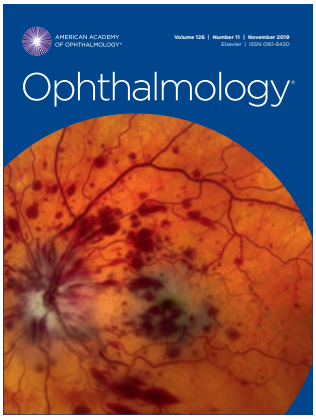
November 2019

Fan et al. looked at ocular and neurodevelopment outcomes for toddlers born prematurely who had received intravitreal injections of bevacizumab for type 1 retinopathy of prematurity (ROP). Their findings support the growing trend of using anti-VEGF drugs to manage ROP.

This prospective case-controlled study was conducted from June 2014 to January 2019 at Chang Gung Memorial Hospital in Taiwan. The final analysis set included 148 patients (85 boys, 63 girls), grouped as follows: premature infants without ROP (group 0; n = 79), premature infants with ROP whose condition regressed spontaneously without treatment (group 1; n = 31), and premature infants with ROP who were treated with a single intravitreal injection of bevacizumab (group 2; n = 38).

Patients in all three groups received follow-up, and their ocular developmental and neurodevelopmental outcomes were compared when they were 1 to 3 years old. Ocular evaluation included cycloplegic refractometry, axial length, and Cardiff acuity. Neurodevelopment was assessed with the Bayley Scales of Infant and Toddler Development (third edition).

The mean age at evaluation was 1.49 years. As expected, gestational age (GA), birth weight, and Apgar scores were significantly higher in group 0. There were no significant differences between groups 1 and 2 in demographics or systemic risk factors, except for younger GA in group 2. Cylindrical power was significantly larger in groups 1 and 2 compared with group 0. Relative to group 0, the spherical equivalent in group 2 was significantly more myopic, and Cardiff acuity was much poorer. Groups 1 and 2 were comparable in refractive status, axial length, and Cardiff acuity.



There were no meaningful differences in neurodevelopment between any of the three groups (after adjusting for GA and systemic risk factors), including the risk of poor neurodevelopmental outcomes.

The researchers noted that two previous retrospective studies raised concerns about neurodevelopmental outcomes for infants with ROP treated with bevacizumab. Although this study demonstrated no such disadvantage, the authors acknowledged that their sample size may have been inadequate for detecting small but clinically significant differences. *(Also see related commentary by Susan M. Carden, MBBS, PhD, in the same issue.)*

Cataract Surgery, Surgeon Volume, and VA Results

November 2019

The association between higher cataract surgery volume and lower complication rates is well recognized. However, data are limited on the relationship between case volume and visual outcomes. **Cox et al.** aimed to build on existing evidence by exploring potential correlations. Using a large database, they found that the work of higher-volume cataract surgeons performing phacoemulsification resulted in slightly improved visual acuity (VA) outcomes and lower complication rates.

For this study, the researchers included 35,880 eyes that received small-incision cataract surgery (SICS) or phacoemulsification with intended IOL placement. All surgeries were performed in 2015 at the Aravind Eye Hospital in Madurai, India. Bivariate linear regression with random effects was used to assess each eye's uncorrected VA (UCVA) at follow-up relative to surgeon case volume and to other demographic and case factors. Factors with a p value below 0.20 on bivariate regression were included in random-effects multivariate regression modeling. The primary objective was to assess relationships between surgeon case volume and patients' visual outcomes after cataract surgery. Secondary objectives included exploring potential correlations between other case characteristics

and VA outcomes and between case volume and complication rates.

The operations were performed by 69 surgeons; individual case volume for 2015 ranged from 76 to 2,900. In general, higher case volume was independently associated with a statistically significant (but clinically modest) improvement in UCVA after phacoemulsification but not after SICS. However, this effect appeared to plateau at a caseload of approximately 350 cases per year. The favorable UCVA trend was not observed for surgeons who performed between 1,501 and 2,000 cases per year; their patients' visual outcomes were worse than for other surgeon groups, except the lowest-volume cohorts. Higher case volume was associated with significantly lower complication rates with phacoemulsification as well as with SICS. Younger patient age was independently linked to better visual outcomes and lower complication rates with both procedures.

Greater surgeon experience correlated with lower complication rates for phacoemulsification but not for SICS. Level of experience did not correlate with VA outcomes.

The findings may help to inform the design and workflow of ophthalmology clinics, said the authors. This might have particular relevance in countries with a large burden of cataract-related visual impairment and a high patient-to-surgeon ratio. *(Also see related commentary by Robert J. Campbell, MD, MSc, in the same issue.)*

Outcomes of Nd:YAG Laser for Floaters

November 2019

Vitreous floaters can be addressed with the Nd:YAG laser, but research with objective structural and functional outcomes is lacking. **Nguyen et al.** conducted a retrospective comparative study of eyes with floaters and found that those treated with the Nd:YAG laser had reduced vitreous density but similar visual function as those that were untreated. Because the vision of some treated eyes was superior to that of untreated eyes, a prospective randomized study with uniform laser treatment parameters would be helpful, the authors said.

The study included 132 eyes (132 subjects; mean age, 56 years); 97 had vitreous floaters and 35 were unaffected. Of the 97 with floaters, 38 previously received Nd:YAG laser treatment; the other 59 had been evaluated but not treated and served as controls. Of the 38 treated patients, 25 were unhappy with their result and were seeking vitrectomy; the remaining 13 were satisfied with their result and remained under observation only. These two groups were comparable in age and visual acuity.

Visual acuity (VA) was measured with standard Snellen charts, and contrast sensitivity function (CSF) was assessed with the Freiburg Acuity Contrast Test. Statistical analyses included the Fisher's exact test to compare prevalence of pseudophakia, posterior vitreous detachment, and myopia. Multivariable linear regression was used to explore differences between the study groups, after adjusting for confounders.

Compared to untreated patients with floaters, patients treated with Nd:YAG laser had a 23% reduction in vitreous echodensity—but had comparable well-being, VA, and CSF.

The objective measures of CSF testing and quantitative ultrasonography yielded no differences in well-being or VA between Nd:YAG-treated patients and untreated controls.

However, these tests did show improvement in echodensity that was unrelated to well-being. The authors noted that this difference may relate to selection bias, because most patients who presented were unhappy with their Nd:YAG outcome.

The results indicate that many patients who receive Nd:YAG therapy for floaters remain symptomatic and seek further treatment. The authors suggest that future studies explore whether certain types of floaters are more responsive than others to laser treatment. They favor prospective randomized studies, with uniform protocols, focused on quantitative measures of quality of life and objective assessment of structural outcomes.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

U.K. Report: Resource Use for Geographic Atrophy

November 2019

Chakravarthy et al. used a large clinical dataset to estimate the use of eye care resources among patients with geographic atrophy (GA). They found that resource use is highest among those with GA in one eye and choroidal neovascularization (CNV) in the other.

For this retrospective analysis, the researchers collected data from 10 National Health Service clinical sites in the United Kingdom on patients with GA or early/intermediate age-related macular degeneration (AMD). Patients were seen between October 2000 and February 2016.

Patients were sorted into four subgroups: 1) Those with GA in both eyes (GA:GA), 2) those with GA in one eye and CNV in the fellow eye (GA:CNV), 3) those with GA in one eye and AMD in the fellow eye (GA:AMD), and 4) those with AMD in both eyes (AMD:AMD). Primary outcomes were the median number of visits that took place during the first two years after diagnosis of GA or AMD and the cost of clinical tests performed during these visits.

The researchers evaluated data on 7,159 patients. Results were as follows:

- Those in the AMD:AMD subgroup (n = 6,079) had a median of 2 visits and a cost of £184 during the two-year period following diagnosis.
- Patients in the GA:GA subgroup (n = 442) had a median of 3 visits and a cost of £277.
- Patients in the GA:AMD subgroup (n = 283) had a median of 4 visits and a cost of £369.
- Those in the GA:CNV subgroup (n = 355) had a median of 15 visits and a cost of £1,581.

With regard to clinical monitoring, the authors noted variations among testing strategies. For instance, while patients in the GA:CNV subgroup were commonly evaluated via optical coherence tomography, those in the other subgroups were not.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Retinal Changes That Precede DR in Type 1 Diabetes

November 2019

Few studies have focused on the initial retinal changes in children who have type 1 diabetes without diabetic retinopathy (DR). **Inanc et al.** sought to determine whether the abnormal glucose metabolism that occurs in type 1 disease affects the microcirculation of children with the disease. They compared their findings with those for healthy children and noted that diabetic eyes without clinically detectable DR had alterations in the acircularity index (AI), perimeter, and foveal density of parafoveal capillaries in the deep capillary plexus, which preceded enlargement of the foveal avascular zone (FAZ). These parameters might serve as imaging biomarkers to define early DR, the researchers said.

This cross-sectional prospective study included 60 patients with well-controlled diabetes and clinically undetectable DR as well as 57 age-matched controls. Optical coherence tomography angiography (OCTA) was performed, and various parameters were measured, including FAZ area, nonflow area, superficial and deep vessel density, FAZ perimeter, FAZ AI, and foveal density in the 300 µm (FD-300) surrounding the FAZ. The authors looked at the findings for these parameters in relation to the duration of diabetes and the level of glycated hemoglobin (HbA_{1c}).

Differences in mean values between the patients and control children were significant for FAZ perimeter ($p < .001$), AI ($p = .001$), and FD-300 ($p = .009$). Significant differences between these groups also were noted for vessel density in the deep superior hemiparafovea, deep temporal parafovea, and deep superior parafoveal zones ($p = .008$, $p = .015$, and $p = .005$, respectively). There were no meaningful correlations between OCTA findings and disease duration or HbA_{1c} levels.

These findings imply that defects in retinal microcirculation and irregularities at the FAZ margin can occur before DR becomes clinically apparent. The observed changes in FD-300, AI, FAZ perimeter, and vessel density of the parafoveal capillaries in the deep capillary plexus precede enlargement of the FAZ. The authors recommend further investigation of the role of OCTA in disease detection and treatment guidance for children with type 1 diabetes.

Vismodegib for Basal Cell Carcinoma

November 2019

Basal cell carcinoma (BCC), the most common skin cancer, accounts for 90% of malignant tumors of the eyelid. **Eiger-Moscovich et al.** looked at the effectiveness of vismodegib, a Hedgehog pathway inhibitor, for treating orbital and advanced periocular BCC. They found that treatment according to an individualized maximally tolerated dose achieved responses similar to those achieved in the pivotal ERIVANCE study. The authors emphasized that longer-term studies are needed to gauge prognosis.

This retrospective series included 21 patients (median age, 76 years; 16 men) with biopsy-proven periocular BCC (n = 6) or orbital BCC (n = 15). In most cases, treatment was given for five to seven months, at the usual dosage of 150 mg per day, followed by an intermission. If deterioration was observed, treatment was resumed. The aim was to customize each patient's treatment to the maximally tolerated dose. Some patients received a partial dose to minimize adverse events such as hepatotoxicity.

The median duration of vismodegib treatment was nine months. The median follow-up period was 17 months after treatment cessation. The clinical response was complete in 10 patients, partial in 10 others, and stable in one patient. No patient had progressive disease (defined as an increase in tumor size of >20%). Among the complete responders, two were still being treated and eight had finished treatment at the time of this report. Five of the eight maintained their complete response by 16 months; the other three had recurrence within eight months.

Treatment response did not seem affected by orbital involvement or tumor stage. Nearly all treatment-related adverse reactions were low grade; the most common were muscle spasm (76%) and dysgeusia (57%). The only grade 3/4 adverse event was hepatotoxicity (10%). Eight patients discontinued treatment due to side effects. Five patients died, most from reasons that appeared unrelated to vismodegib. However, one death (from sepsis) may have been related to treatment.

To the authors' knowledge, this is the largest study of vismodegib therapy for locally advanced periocular BCC. Response rates to maximally tolerated doses were comparable to those with the ERIVANCE protocol, yet the optimal treatment protocol remains unknown, and longer studies are needed.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Driving at Night: Do Yellow-Tinted Lenses Improve Vision?

October 2019

Advertising claims for yellow-tinted lenses state that they improve night vision by reducing glare and eyestrain. But in a study that involved simulating nighttime driving conditions, **Hwang et al.** found that donning the lenses did not improve participants' ability to detect pedestrians. The findings indicate that yellow lenses do not live up to product claims and that more work is needed to address nighttime driving challenges such as headlight glare (HLG).

For this single-center cohort study, the researchers enrolled 22 adults, all of whom had normal visual acuity. For the main experiment, 12 participants (mean age, 28 years) were assessed under nighttime conditions for their ability to see and respond to a pedestrian wearing a dark navy-blue shirt. The remaining 10 participants were evaluated for their ability to detect and respond to a pedestrian wearing an

orange shirt—and these 10 were divided into two groups, one of younger (n = 6; mean age, 27 years) and another of older (n = 4; mean age, 70 years) participants.

The researchers developed a simulator that replicates the HLG from oncoming cars. Each participant "drove" scripted night-driving scenarios four times (once with each of the three commercially available glasses with yellow lenses and once with clear glasses); the HLG simulator was turned on or off for each scenario. Before starting the initial scenario, each participant took at least one introductory drive to become acquainted with the driving simulator environment and the experiment's tasks. The main outcome measure was response time for the critical task of detecting a pedestrian. (The pedestrians were portrayed as either walking alongside the road or attempting to cross the road.)

The researchers found no significant difference in response time with the various yellow lenses for any experimental condition—and no benefit when compared with clear lenses. Among younger drivers, the impact of HLG was more pronounced with the simulation involving the navy-wearing pedestrian. In the simulation involving the orange-wearing pedestrian, older drivers were significantly slower to respond than were younger participants (1.5 seconds vs. 0.3 seconds, respectively).

Thus, yellow lenses did not appear to improve drivers' ability to detect pedestrians at night or to reduce problems with HLG. These findings challenge the notion of recommending the lenses to patients who have poor nighttime vision. *(See also related commentary by Robert W. Massof, PhD, in the same issue.)*

The High Costs of Rx Waste

October 2019

Tauber et al. looked at the effect of unused pharmaceuticals related to phacoemulsification surgery and found the financial and environmental burdens to be high, particularly for discarded eyedrops.

For this descriptive qualitative study, the authors included four surgical sites in the northeastern United States: a private ambulatory care center, a private tertiary care center, a federally run medical center for veterans, and a private outpatient facility. Pricing and other data for use of services and pharmaceuticals were obtained for each facility. The volume or weight of medications remaining after routine phacoemulsification procedures (without vitreous loss or other complications) was measured. From these data, the mean costs of medications were calculated per case and per month. Environmental effects were estimated by economic models of input-output lifecycle assessment.

Primary outcomes were the cost of unused pharmaceutical products (in U.S. dollars) and the potential carbon footprint of cataract surgery, as evaluated in the kilogram equivalents of carbon emissions (carbon dioxide [CO_2-e]), air pollution (fine particulate matter emissions of ≤10 μm in diameter [PM_{10}-e]), and eutrophication potential (nitrogen [N-e]).

A total of 116 unique drugs were assessed among the four centers. A cumulative mean 83,070 mL of 183,304 mL per month (45.3%) of pharmaceuticals were unused by weight or volume. (Unmeasured medications were assumed to have no excess left over.)

The annual cost of unused products per site was approximately $195,200. The product type with the greatest amount of waste was eyedrops (65.7% by volume), followed by systemic drugs (59.9%) and injections (24.8%). With regard to pollution, monthly unused products at the ambulatory care center (65.9% by volume), tertiary care center (21.3%), federal medical center (38.5%), and outpatient facility (56.8%) resulted in unnecessary potential emissions of 2,135, 2,498, 418, and 711 kg CO_2-e per month, respectively. Unnecessary potential air pollution among the sites varied from 0.8 to 4.5 kg PM_{10}-e per month, and unnecessary eutrophication potential ranged from 0.07 to 0.42 kg N-e per month.

If these findings can be substantiated and shown to be generalizable in the United States or elsewhere, efforts to reduce such costs may be of value, said the authors. Larger-scale, multicenter studies should be helpful for understanding the full extent and effects of unused pharmaceuticals. Of note in this study: The surgeons and OR staff were not involved in data reporting or analysis, but they were aware of the nature of the study, which may have influenced their use of materials and led to underestimation of the total waste. *(See also related commentary by Paul Lee, MD, JD, in the same issue.)*

GCA and Race: Is There a Correlation?

October 2019

Giant cell arteritis (GCA) is the most common vasculitis in adults and is linked to high rates of morbidity and mortality. Although its incidence in white populations has been studied extensively, little is known about its preponderance in other racial or ethnic groups. **Gruener et al.** explored the racial incidences of biopsy-proven GCA in a tertiary care facility that serves a substantial black population. They observed a similar rate of GCA in black and white patients.

For this study, the authors identified all patients who underwent temporal artery biopsy (TAB) from July 2007 through September 2017 at the Wilmer Eye Institute in Baltimore. Self-reported data on race, sex, and age were tallied and compared with data for all other patients attending the hospital during the same period. Main outcomes were the estimated rates of biopsy-proven GCA among blacks and whites.

Of the 586 patients who underwent TAB (mean age, 70.5 years; 423 [72.2%] women), 167 (28.5%) were black, 382 (65.2%) were white, and 37 (6.3%) were of other or unknown race. Crude annual incidence rates for biopsy-proven GCA were 2.9 per 100,000 blacks and 4.2 per 100,000 whites. Population-adjusted age- and sex-standardized incidence rates were 3.1 and 3.6 per 100,000 black and white patients, respectively (p = .70). The female-to-male incidence ratio was 1.9 (p = .03). The white-to-black incidence ratio was not significant (1.2; p = .66).

Of the 573 individuals ≥50 years

of age, 92 (16.1%) had biopsy-proven GCA. Of these, 14 were black (8.4% of tested black patients) and 75 were white (19.6% of tested white patients). The authors did not consciously apply different clinical criteria or thresholds for offering or performing TAB in the study population; therefore, the higher pretest probability among whites may suggest that the link between symptoms and disease is stronger in this racial group.

Contrary to research suggesting that GCA is more common in whites and that its occurrence in blacks may be almost negligible, this study indicates that blacks and whites have a similar incidence of GCA. Therefore, the authors recommend that the clinical thresholds for diagnosing and managing GCA be the same for white and black populations. *(See also related commentary by Michael K. Yoon, MD, and Joseph F. Rizzo III, MD, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Eye Evaluation Needed in Children With Brain Tumors

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Visual impairment in children with brain tumors has received limited attention. Ophthalmologic evaluation is not required for most neuro-oncology clinical trials, and visual function is rarely monitored during or after treatment of the tumor. In a study of children with primary brain tumors, **Liu et al.** looked at patterns of referral to ophthalmology and found that more than half of the children were not referred. The authors emphasized that ophthalmologic evaluation of these patients is needed to ensure that visual function deficits are identified and managed.

For this retrospective study, the researchers included 141 children with a primary brain tumor treated at Loma Linda University Children's Hospital and Eye Institute during a five-year period. Outcomes of interest were the incidence of ophthalmic evaluation, the prevalence of abnormal ophthalmic findings, and the association of such findings with tumor characteristics.

The median age of the children was 7 years (range, 0-18 years); 52% were male. Findings showed that 73 patients (52%) did not have any formal ophthalmologic evaluation. The other 68 patients received assessment by one of four pediatric ophthalmologists and/or neuro-ophthalmologists; the total number of eye care visits for these patients was 222.

The mean five-year survival rates for patients with and without eye exams did not differ substantially (78.3% vs. 84.9%, respectively). The median time from tumor diagnosis to initial ophthalmologic evaluation was nine months (range, 0-94 months). Among the 68 examined children, 10 (15%) had visual symptoms at the time of tumor diagnosis, and 61 (90%) had abnormal findings when examined, including strabismus (60%), impaired visual acuity (54%), amblyopia (38%), papilledema (35%), visual field defects (19%), optic atrophy (18%), and keratopathy (15%). Strabismus was more common with posterior fossa tumors. Radiation therapy correlated significantly with amblyopia.

In light of these findings, the authors recommend ophthalmologic referral of children with brain tumors so that visual sequelae can be detected and vision preserved.

Making Telemedicine a Reality

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Kern et al. implemented a cloud-based referral platform for medical retina hospital eye services (HES) in the United Kingdom, which was designed to alleviate demands on ophthalmology services by improving communication between opticians and ophthalmologists. In this pilot study, the digital-first program drastically reduced the number of unnecessary referrals, decreased referral wait time, and facilitated communication between health care providers. According to the authors, the platform may serve as a foundation for implementing artificial intelligence.

For their study, the authors initially reviewed records for 103 patients treated at Moorfields Eye Hospital in London. The patients were classified into the HES referral pathway by one of 11 contributing optometrists, who used the cloud-based platform to share data with a single consultant ophthalmologist at Moorfields. The optometrists were instructed to refer all presumable retina cases via the platform. Initial triage was performed by the optometrist, and other types of referrals (e.g., glaucoma, cataract, or anterior segment conditions) were excluded and sent through the conventional general ophthalmic services pathway. The main outcome measure was the reduction of unnecessary referrals.

A review of patient data in a web-based interface showed that 54 (52%) of the 103 patients initially classified into the referral pathway did not need referral to a specialist. Fourteen patients who needed urgent treatment were identified. Usability was measured in duration for data input and review, which averaged 9.2 minutes for optometrists and 3.0 minutes for ophthalmologists. The most common diagnoses were dry age-related macular degeneration (AMD; n = 34), wet AMD (n = 9), epiretinal membranes (n = 7), and choroidal nevi (n = 7).

Data from this and other research suggest that virtual clinic settings are safe for certain ophthalmic conditions. A study of the health economic impact of cloud-based telemedicine services is being planned. Important to the success of such programs is patient satisfaction and acceptability, which should be addressed in future studies, said the authors. *—Summaries by Lynda Seminara*

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