

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Effects of Pupillary Dilation in PAC Suspects With Cataract

January 2021

Anatomic changes caused by visually significant cataract (VSC) may predispose patients with primary angle-closure (PAC) to rises in intraocular pressure (IOP) and acute angle closure during pupillary dilation. Safety studies of pharmacologic dilation in this population are lacking, as is research on dynamic changes in IOP and anterior chamber structures beyond one hour after cataract surgery. To fill the void, Zhao et al. looked at these parameters with swept-source optical coherence tomography (SS-OCT) in PAC suspects admitted for cataract surgery. They found no cases of acute PAC and a low risk of IOP elevation.

This prospective study was conducted at Shanghai General Hospital. PAC suspects with VSC and no prior laser or intraocular surgery underwent a standardized eye exam, biometry, and SS-OCT before pupillary dilation with 0.5% tropicamide and 0.5% phenylephrine hydrochloride. IOP measurements and SS-OCT were repeated at one, four, and six hours after dilation (PDH1, PDH4, and PDH6, respectively). Main outcome measures were changes in IOP and SS-OCT parameters.

The study included 78 patients (78 eyes); mean age was 71 years, and 74% were female. Most patients completed the PDH1 and PDH4 assessments

(100% and 85%, respectively). The mean IOP increased from 14.8 ± 2.6 mm Hg at baseline to 15.5 ± 3.5 mm Hg at PDH1 ($p = .03$) but fell to 14.9 ± 3.1 mm Hg by PDH4 ($p = .09$). The IOP increase was ≥ 5 mm Hg at PDH1 and PDH4 in four patients (5.13%) and three patients (3.85%), respectively, and was ≥ 8 mm Hg in two patients (2.56%) and one patient (1.28%), respectively. By PDH6, no patient's IOP was elevated ≥ 5 mm Hg. No episodes of acute PAC were reported during the observation period. Lens vault and iris volume declined from baseline to PDH1 and were sustained to PDH4. Other SS-OCT measurements were found to be significantly increased at both assessments. At PDH1, the only factor that was negatively linked to IOP elevation level was increased anterior chamber depth ($p = .003$).

According to the authors, the low risk for IOP spike in this cohort may relate to relaxation of the ciliary muscle, leading to posterior displacement of the lens-iris diaphragm and deepening of the anterior chamber. They urged further study of anterior chamber structures to elucidate the mechanism of dilation-related IOP changes in PAC suspects and to identify related risk factors.



Brolucizumab Outcomes at 96 Weeks

January 2021

Brolucizumab, a novel VEGF inhibitor with an extended dosing schedule, is under evaluation as a treatment for neovascular age-related macular degeneration (AMD). In the phase 3 HAWK and HARRIER studies, brolucizumab showed noninferior efficacy and safety relative to aflibercept at the 48-week

mark. Continuing this work, Dugel et al. noted persistence of these favorable outcomes to week 96. In addition, gains in best-corrected visual acuity (BCVA) were comparable for the two agents, and anatomic outcomes were better with brolucizumab.

In the original research, treatment-naïve eyes with wet AMD were assigned randomly (1:1:1) to receive either brolucizumab 3 mg ($n = 358$), brolucizumab 6 mg ($n = 360$), or aflibercept 2 mg ($n = 360$) in HAWK and 1:1 to brolucizumab 6 mg ($n = 370$) or aflibercept 2 mg ($n = 369$) in HARRIER. After three loading doses, brolucizumab was given every 12 weeks (q12w), with a switch to every eight weeks (q8w) based on disease activity assessments. Aflibercept was dosed q8w throughout.

The early visual gains in both studies were maintained through week 96. In HAWK, changes in BCVA (least squares [LS] mean \pm standard error) from baseline to week 96 were 5.6 ± 0.79 and 5.9

± 0.78 letters for brolucizumab 3 mg and 6 mg, respectively, and 5.3 ± 0.78 letters for aflibercept. In HARRIER, the changes were 6.1 ± 0.73 letters with brolucizumab 6 mg and 6.6 ± 0.73 letters with aflibercept. Reductions in central subfield thickness were greater with brolucizumab 6 mg than with aflibercept: LS mean, $-174.8 \mu\text{m}$ vs. $-148.7 \mu\text{m}$ ($p = .0115$), respectively, in HAWK and $-197.7 \mu\text{m}$ vs. $-155.1 \mu\text{m}$ ($p < .0001$), respectively, in HARRIER. At week 96 of HAWK, intraretinal and/or subretinal fluid was present in significantly fewer eyes treated with brolucizumab (31% [$p = .0688$] with 3 mg and 24% [$p = .0002$] with 6 mg) than with aflibercept (37%); in HARRIER, fluid was present in 24% of eyes treated with brolucizumab 6 mg ($p < .0001$) and in 39% of aflibercept-treated eyes. The probability of maintaining a q12w regimen for brolucizumab 6 mg at last disease assessment was 45.4% in HAWK and 38.6% in HARRIER. Overall, brolucizumab was well tolerated.

These longer-term outcomes suggest that brolucizumab may improve disease control while lightening the treatment burden of neovascular AMD.

OCT Retinal Thickness Map Detects HCQ Retinopathy

January 2021

Kim et al. used a retinal thickness deviation map, generated from swept-source optical coherence tomography (SS-OCT) images, to screen for hydroxychloroquine (HCQ) retinopathy. In their retrospective study of more than 2,300 eyes, the deviation map was highly sensitive and specific for detecting retinopathy.

This study included 1,192 Korean patients with a history of HCQ treatment. There were 881 patients (1,723 eyes) in the discovery set and 311 patients (591 eyes) in the validation set. Participants were screened for retinal toxicity using SS-OCT, fundus autofluorescence, and standard automated perimetry. The authors' scan was a $12 \times 9\text{-mm}^2$ macular volume SS-OCT; built-in software generated the retinal thickness deviation map. Abnormality was indicated by yellow or

red pixels on the map that corresponded to $<5\%$ and $<1\%$ of the normative level, respectively. All abnormal findings were evaluated. Diagnostic criteria were derived from the discovery set and verified by the validation set. Outcome measures were the rate and pattern of abnormalities and the sensitivity and specificity of diagnostic criteria.

The map for eyes with HCQ retinopathy displayed abnormal patterns in the pericentral ring (36%), the parafoveal ring (6.1%), or in both rings (34.2%). Other observed patterns were a central island (13.2%) and whole macular thinning (10.5%). The diagnostic criterion of " ≥ 5 contiguous red pixels showing one of these five characteristic patterns in both eyes" had the best sensitivity and specificity in both datasets (range, 87.5% to 100%). In eyes with HCQ retinopathy, the area of abnormality on the map correlated strongly with mean deviation ($p < .001$) and pattern standard deviation ($p < .001$) on the Humphrey 30-2 test.

This type of map could hasten objective assessment of HCQ retinopathy, as it doesn't require morphologic evaluation of the outer retina. It also may aid screening for other conditions that involve retinal thinning.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Return to the OR After Vitrectomy for Vitreous Opacities

January 2021

In an analysis of data from the IRIS (Intelligent Research in Sight) Registry, Rubino et al. investigated the rate of return to the operating room following vitrectomy surgery for vitreous opacities. They found a 3.7% rate of return for ophthalmic procedures other than cataract surgery—and of these, most were for retinal detachment repair.

For this retrospective study, the researchers identified 50,836 eyes that underwent vitrectomy surgery for vitreous opacities from 2013 to 2017. After they adjusted for and eliminated eyes that also had other surgical retinal disease codes linked to the same surg-

ery, the dataset comprised 17,615 eyes that had only a vitreous opacity code alongside the initial vitrectomy. (Relevant codes from both ICD-9-CM and ICD-10-CM were used.)

Of these 17,615 eyes, 2,830 (16.1%) returned within one year for an additional surgical procedure, with 2,187 (12.4%) returning for cataract surgery and 643 (3.7%) returning for another procedure. In 457 eyes (2.6%), this additional procedure involved repair of a retinal detachment; other noncataract procedures included vitrectomy with panretinal or focal laser and vitrectomy for macular hole repair.

While these rates of reoperation are in line with results from other studies, the authors cautioned that the risks and possibilities of additional surgeries should be carefully considered and discussed with patients. (*Also see related commentary by Jerry Sebag, MD, in the same issue.*) —Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Minimally Invasive Surgery for Intraconal Orbital Tumors

January 2021

Caballero-García et al. set out to assess the efficacy of 360-degree minimally invasive endoscopic surgery for orbital intraconal tumors. They observed immediate and long-term favorable morphologic and aesthetic results.

For this retrospective case series, the researchers included 22 adults (mean age, 52.3 ± 11 years). The patients received endonasal surgery or anterior orbitotomy with full endoscopic visualization during a five-year period at a clinic in Cuba. For each patient, the authors identified and classified the relationship between the tumor and the optic nerve: Type I lesions were upper medial to the optic nerve; type II lesions were lower medial; type III lesions were lower lateral; type IV lesions were upper lateral; and type V lesions were centrally located and originated in the optic nerve itself or its sheath.

An endonasal surgical approach was used for type I and II lesions. Type III

and IV lesions had endoscopic anterior orbitotomy. For type V lesions, the surgical approach depended on the amount of space between the rectus muscles.

Proptosis was present in 19 of the 22 patients, and visual loss was present in three patients. Cavernous hemangioma was the most common diagnosis (72.7%), followed by orbital sheet meningioma (9.1%). The most frequent tumor locations were types II and IV. Total resection was achieved in all but one patient. All patients with visual loss regained normal visual function after surgery, and orbital proptosis resolved in all 19 patients.

Cavernous hemangiomas are ideal lesions for minimally invasive techniques because of their low flow, encapsulated nature, and ease of extracapsular dissection. However, the authors cautioned about the disadvantages of endoscopy, including the long learning curve and challenges in patient selection. Although the minimally invasive procedure can be safe and effective in some patients with orbital intraconal tumors, larger studies are needed.

RVO Raises the Risk of Dementia

January 2021

Retinal vascular defects are associated with brain-related changes in patients with dementia, but evidence of a link between retinal vein occlusion (RVO) and dementia risk is limited. To explore this possibility, Nam et al. looked at data from South Korea and found a significant association between RVO and elevated risk of all-cause dementia, Alzheimer disease (AD), and vascular dementia (VD).

Data were gathered from the South Korean National Health Insurance Service, which covers approximately 97% of the South Korean population. Individuals who were diagnosed with RVO from 2006 to 2010 and who had a health exam in 2009 or 2010 were eligible for inclusion. Patients were monitored for the development of dementia through December 2016; the mean follow-up time was 6.6 years. Individuals under 40 years of age and those with missing data were excluded

IRIS Registry Snapshot: Switching Anti-VEGF Drugs in DME

Diabetic macular edema (DME) is a leading cause of vision loss in patients with diabetic retinopathy and can appear at any stage of the disease. Current treatment involves intravitreal injections of anti-VEGF agents; ophthalmologists typically start with one drug and switch to a different agent when the clinical response is suboptimal.

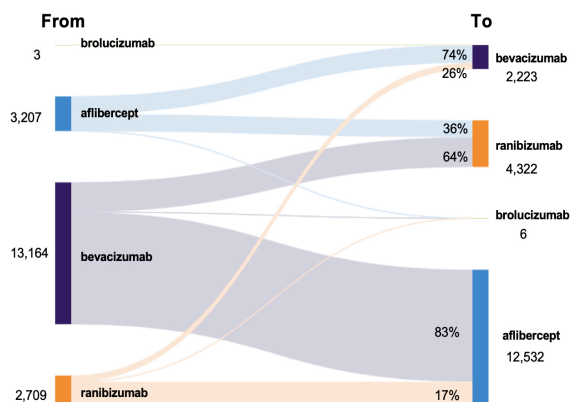
Verana Health assessed switching patterns by analyzing statistically de-identified electronic health record data from the Academy's IRIS (Intelligent Research in Sight) Registry. A switcher was defined as an eye that had at least three injections of one agent and then had a different agent at a subsequent visit. Eyes without specified laterality were excluded.

Of the 202,532 treated eyes with DME, 19,083 (94.2%) were switched to another anti-VEGF drug between Jan. 1, 2016, and Dec. 31, 2019. Of these, 65.7% were switched to aflibercept.

Aflibercept and ranibizumab net gained 9,325 and 1,613 eyes, respectively, whereas bevacizumab lost 10,941 eyes to switching.

Aflibercept and ranibizumab gained most of their switches from bevacizumab (83.1% and 63.7%, respectively).

Note: The Academy has partnered with Verana Health to curate and analyze IRIS Registry data.



SANKEY DIAGRAM. Switching patterns of anti-VEGF agents in DME.

from the study.

Overall, 46,259 people qualified for enrollment in the RVO group. A comparison group of 138,777 individuals without RVO, matched for age, sex, and systolic blood pressure, also received monitoring through 2016. Diagnoses of all dementia categories were established from standard ICD-10 and antidementia prescription codes. Demographic and lifestyle factors were determined from patient responses to questionnaires. Three multivariate Cox proportional hazard regression models were applied: unadjusted; adjusted for age and sex; and adjusted for age, sex, and health/lifestyle variables.

The mean age in both study groups at baseline was 63.4 ± 10.1 years. There were no significant between-group differences in gender distribution or

systolic blood pressure. Kaplan-Meier curves demonstrated greater likelihood of dementia development in the RVO group (log-rank $p < .001$). After adjustment for all confounding variables, the risk of all-cause dementia was greater in the RVO group relative to the comparison group (hazard ratio [HR]: 1.16; 95% confidence interval [CI]: 1.12-1.21), as were the risk of AD (HR: 1.15; 95% CI: 1.12-1.20) and VD (HR: 1.24; 95% CI: 1.12-1.37).

In this study, RVO was significantly associated with all categories of dementia (even in the absence of hypertension) and thus may be a risk factor for dementia. To the authors' knowledge, their study is the first large-scale longitudinal investigation of the relationship between RVO and dementia.

—Summaries by Lynda Seminara

Sensory Impairment Is Linked to Perceived Discrimination

December 2020

Perceived discrimination is a psychosocial stressor linked to adverse health outcomes. In a study of adults older than 50 years of age, Shakarchi et al. assessed whether visual impairment (VI), hearing impairment (HI), or the combination of VI and HI are associated with perceived discrimination. They found that perceived levels of discrimination were higher for individuals with impaired vision or hearing than for those without impairment—and highest for those with dual sensory impairment (DSI).

For this cross-sectional analysis, the researchers used data from the Health and Retirement Study, which included noninstitutionalized adults aged 51 and older. In 2006 and 2008 surveys, participants were asked to rate their vision and hearing—while wearing spectacles and/or hearing aids, if applicable—as poor, fair, good, very good, or excellent.

For this study, sensory impairment was defined as poor or fair ability and was categorized as VI alone, HI alone, DSI, or no impairment. Perceived discrimination was assessed with the validated Williams questionnaire. Responses were converted to a score reflecting the frequency of discrimination, ranging from zero (never) to 5 (almost daily). Linear regression models were used to estimate differences in discrimination scores by sensory category, with adjustments for age, sex, race, ethnicity, and other variables. Analyses were weighted to account for design complexity and differential nonresponse to the survey.

When the sample was weighted to represent the U.S. population, the authors noted that 11.7% of 13,092 individuals had VI alone, 13.1% had HI alone, and 7.9% had DSI. In the fully adjusted model, those with VI alone (β [change in discrimination score] = 0.07), HI alone (β = 0.07), and DSI (β = 0.23) perceived greater

discrimination than those with neither type of sensory impairment. The perceived degree of discrimination was highest for the DSI group.

The authors affirmed that their findings offer insight into the psychosocial effect of sensory deficits. They emphasized the need to identify and address the reasons for such discrimination.

Visual Outcomes of Children With Optic Neuritis

December 2020

Since optic neuritis (ON) is uncommon in children, little data exist on outcomes, related conditions, and neuroimaging hallmarks. Pineles et al. prospectively studied visual outcomes for children with ON to gain insight and improve counseling of families. Although the number of participants was shy of the group's goal, improvement occurred in most of the children. Concomitant neurologic autoimmune diagnoses were common among participants in the study group.

This pilot study took place from September 2016 to July 2018 and included 23 centers in the United States and Canada that specialize in pediatric ophthalmology or neuro-ophthalmology. Inclusion criteria were presentation of the first ON episode within two weeks of symptom onset and at least one of the following features in the affected eye: distance high-contrast visual acuity (HCVA) deficit of at least 0.2 logMAR below age-based norm, diminished color vision, abnormal visual field, or optic disc swelling. Children with any preexisting ocular abnormality were excluded. The main outcome measures were monocular HCVA and low-contrast VA six months after onset of ON. Other outcomes were findings of neuroimaging, associated diagnoses, and specific antibodies.

Although the researchers hoped that 100 children would be enrolled during the two-year period, only 44 qualified for participation (age range, 3–15 years). Of these, 40 (91%) were treated with corticosteroids; the remainder received no medication during the study. ON was bilateral in 16 patients (36%). Magnetic resonance imaging showed

white-matter lesions in 23 children (52%); eight of these patients had myelin oligodendrocyte glycoprotein–associated demyelination, seven had acute disseminated encephalomyelitis, five had multiple sclerosis, and three had neuromyelitis optica.

Baseline HCVA was worse in younger participants (<10 years of age), those with neurologic autoimmune conditions or white-matter lesions, and patients who were neither White nor Hispanic. The baseline mean HCVA of 0.95 logMAR (20/200) improved to 0.12 logMAR (20/25) by six months. The mean distance low-contrast VA of 1.49 logMAR (20/640) at baseline improved to 0.73 logMAR (20/100) by six months. There were no meaningful relationships between baseline factors and HCVA improvement.

The rarity of ON in children may warrant different inclusion criteria and wider enrollment windows to attain adequate sample sizes for treatment trials, the authors noted. (*Also see related commentary by Dan Milea, MD, PhD, in the same issue.*)

Vitamin D3, Omega-3 Fatty Acids, and AMD Risk

December 2020

Christen et al. explored the effect of daily supplementation with vitamin D3 and marine omega-3 fatty acids on the risk and progression of age-related macular degeneration (AMD). They found that neither individual supplement nor the combination of the two influenced AMD incidence or progression.

This study, known as VITAL-AMD, was an ancillary analysis of the placebo-controlled VITAL study. Patients (mean age, 67 years) with and without AMD at baseline were randomized to receive one of four daily treatments: 2,000 IU of vitamin D3 (cholecalciferol) plus placebo, 1 g of omega-3 fatty acids (fish oil) plus placebo, the combination of both nutrients, or a placebo capsule of each. The primary outcome measure was composite AMD events, defined as cases of AMD that occurred during the study plus cases of progression to advanced disease in those with

AMD at baseline. Between-group differences were determined from hazard ratios (HRs).

Of the 25,871 patients included in the analysis, approximately half were women, and 71% self-identified as non-Hispanic White. The median time of treatment and follow-up was 5.3 years. During this period, AMD events occurred in 324 patients: 285 were incident cases and 39 involved disease progression. Among patients who took vitamin D3 (alone or with fish oil), 163 experienced an AMD event, compared with 161 patients who received placebo D3 (HR, 1.02). Of the patients who supplemented with fish oil (alone or with vitamin D3), 157 AMD events occurred, compared with 167 events in the corresponding placebo group (HR, 0.94). The HRs and 95% confidence intervals determined for treatment versus placebo indicated no significant differences in risk. Moreover, no between-group differences were observed from assessments of secondary endpoints by type of AMD event (incident AMD vs. progression) or by incident cases of visually significant or advanced AMD in those without AMD at baseline. (Also see related commentary by Robert N. Frank, MD, in the same issue.)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Diagnosing Pediatric Orbital Cellulitis: CT or rMRI?

Journal of AAPOS

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Periorbital (preseptal) cellulitis is a common infection in children presenting to emergency departments (EDs). In suspected cases, it is crucial to rule out orbital cellulitis and orbital abscess, serious conditions that place pediatric patients at risk for blindness, intracranial infection, and, possibly, death. Computed tomography (CT) of the orbit with contrast is generally indicated to distinguish periorbital and orbital cellulitis in children and is considered the diagnostic standard. However, CT scanning with contrast involves

exposure to ionizing radiation, which may increase the risk of malignancy and eye lens damage. Jain et al. looked at whether noncontrast rapid magnetic resonance imaging (rMRI) could be a reliable alternative to CT for identifying pediatric orbital cellulitis. They found that rMRI accurately diagnosed orbital cellulitis in all patients, in perfect agreement with CT findings.

For this study, the authors evaluated 14 patients (mean age, 5.9 years; range, 0.33-13 years) with suspected orbital cellulitis. The decision to obtain imaging (standard orbital CT with contrast, followed by noncontrast rMRI) was made by the attending ED provider. Thirteen patients completed the rMRI assessments. Sedation was not used for either procedure. Clinical decisions for each patient were based on CT findings.

Three experienced pediatric neuro-radiologists reviewed the rMRI images, without access to clinical information or CT results. Of the 26 orbits assessed by both CT and rMRI, three were positive for retroseptal orbital cellulitis by CT and were correctly diagnosed by rMRI as well. Agreement among the three observers was 26 of 26 for establishing the presence or absence of retroseptal cellulitis.

The authors acknowledged that rMRI imaging may be problematic in some EDs. However, the procedure has many benefits—in addition to sparing children from exposure to ionizing radiation, rMRI does not require intravenous access.

Thrombolysis for Central Retinal Artery Occlusion

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2020;40:333-345

Acute nonarteritic central retinal artery occlusion (CRAO) is an ophthalmologic and neurologic emergency with poor visual prognosis and no proven therapies. Although retinal infarction is regarded as comparable to brain infarction, and thrombolysis is a standard therapy for brain acute ischemic stroke syndromes, reperfusion therapies for acute CRAO are still controversial. Dumitrascu et al. reviewed published evidence for IV and intra-arterial (IA)

tissue plasminogen activator (tPA) in CRAO management. They found that patients with nonarteritic CRAO often did not present within the currently accepted time window for IV or IA thrombolysis, leading to poor visual outcomes.

For this study, the researchers included all reports since 1960 found in three online databases of acute IV or IA therapy with alteplase in patients with nonarteritic CRAO. Use of IV thrombolysis was reported in seven articles, involving 111 patients. Of these, 54% received IV alteplase within 4.5 hours of symptom onset.

Most patients were treated at the dose currently recommended for acute cerebral ischemia (0.9 mg/kg), with IV heparin administered concomitantly at 1,200 units per hour over five days. No hemorrhagic complications were noted when the current cerebral ischemic protocol was followed; however, symptomatic intracranial hemorrhage (ICH) occurred in one patient for whom heparin was initiated immediately after alteplase administration. Two patients had asymptomatic ICH, and another had hematuria.

Use of IA alteplase was reported in six studies, with only 13.4% of 134 patients treated within the first six hours of visual loss. Alteplase was infused continuously or in aliquots, with the dosage ranging from 8.8 mg to 80 mg. Most of these studies involved heparin administration in addition to tPA. Adverse events for IA thrombolysis were minimal and included two transient ischemic attacks, two cases of ICH, one hypertensive crisis, two groin hematomas, and 12 minor side effects that may have been unrelated to tPA treatment.

The authors emphasize that eye stroke encounters must involve expert ophthalmologic evaluation to determine the correct diagnosis and to look for ocular signs that could guide tPA administration or IA management. They also recommend that future work include investigating the effect of thrombolysis on visual outcomes, as the currently unfavorable view of the outcomes of CRAO treatment may be related to delayed time to intervention.

—Summaries by Lynda Seminara