

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Argon Laser Peripheral Iridoplasty for Primary Angle-Closure Glaucoma

March 2016

Narayanaswamy et al. recently assessed the effectiveness of argon laser peripheral iridoplasty (ALPI) against travoprost eyedrops in chronic primary angle-closure (PAC) and primary angle-closure glaucoma (PACG) patients. In this study, conducted at 2 tertiary care centers in Singapore, the authors found lower treatment success rates with ALPI than with travoprost.

This randomized controlled trial included 80 PAC or PACG patients who had undergone laser iridotomy but still had at least 180 degrees of persistent appositional angle closure and an intraocular pressure (IOP) of more than 21 mm Hg. Forty patients were randomized to receive 360-degree ALPI, and the remaining half received medical therapy (travoprost, 0.004%).

Participants received repeat ALPI if they had IOP reduction of less than 20% from baseline along with inadequate angle widening at the month 1 or month 3 visit. Medication was added for ALPI patients if IOP control was not achieved 4 weeks after retreatment; travoprost patients could be prescribed additional medications as needed at any follow-up visit.

The primary outcome measure was the success rate at 1 year. Complete treatment success was defined as IOP of 21 mm Hg or less without medication. Qualified success was defined as IOP of 21 mm Hg or less with additional medication, while failure was defined as IOP of more than 21 mm Hg despite the use of additional medications, or the need for glaucoma surgery.

Complete success was achieved in 35% of eyes in the ALPI group compared with 85% of eyes in the travoprost group, while qualified success was attained in 35% and 7.5%, respectively. A failure rate of 30% was seen in the ALPI group compared with 7.5% in the medication group. IOP decreased by 4.9 mm Hg in the ALPI group and by 6.1 mm Hg in the travoprost group. Although the mean angle width increased significantly in the ALPI group, it did not attain the desired Shaffer anatomic grade of 3.

The authors concluded that ALPI lacks the desired effectiveness to control IOP over the long term in eyes with chronic angle closure. They hypothesized that this was caused, at least in part, by dysfunction of the trabecular meshwork as a result of chronic iridotrabecular contact. They noted

that because all patients in their study were Asian, further studies are needed among other ethnic groups.

Ocular Complications in Patients With Noninfectious Uveitis

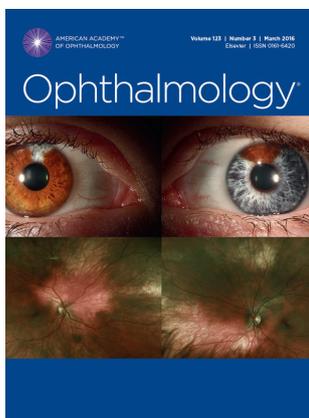
March 2016

Dick et al. compared the risk of ocular complications among patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis (NIIP-PU) and among matched controls in a retrospective analysis of a large insurance claims database. They found that NIIPPU was associated with a higher rate of several important ophthalmic conditions.

Drawing from 16.4 million insurance claims from January 1998 through March 2012, the researchers identified 1,769 uveitis patients aged 18 to 64 years who had 2 or more claims for NIIPPU diagnoses.

Uveitis cases were matched 1:1 by gender, age, region, company, employment status, and index date with controls who did not have uveitis. The mean age of cases and controls was 47 years, and 53% were women. Participants who had an ocular complication at baseline were excluded.

The study's main outcome measures included percentages of cases and controls that had ocular complications, as well as Kaplan-Meier survival analysis to estimate risk at 1, 5, and 10 years. Adjusted Cox regression analysis was used to determine hazard ratios (HRs) for each complication. The researchers found that NIIPPU cases had a higher



risk of developing any ocular complication; the 5-year risk was 66% for uveitis patients compared with 24% for controls.

More specifically, NIIPPU cases had greater 5-year risks than controls, respectively, for developing the following conditions: glaucoma (20% vs. 9%); cataract (35% vs. 13%); visual disturbance (29% vs. 9%); blindness or low vision (5% vs. 0.5%); retinal detachment (11% vs. 0.8%), and retinal disorder (28% vs. 2%).

HRs indicated greater risks of ocular complications in NIIPPU cases during the observation period: HR, 5.2 for any ocular complication; HR, 4.8 for visual disturbance; HR, 3.2 for cataract; and HR, 2.7 for glaucoma (all $p < .001$). They found that HRs were even worse for the 302 persistent uveitis cases identified in the study. They concluded that treatment initiatives are needed to reduce the visual burden of NIIPPU.

Association of Statin Use With Cataract Progression and Surgery

April 2016

Epidemiologic studies have investigated an association between statin use and the development of cataracts but have not established a definitive link. Al-Holou et al. examined this issue in a substudy within the Age-Related Eye Diseases Study 2 (AREDS2) population and found that the use of statins was associated with cataract surgery and progression of both cortical and posterior subcapsular (PSC) lens opacities.

AREDS2 involved 4,203 participants aged 50 through 85 between 2006 and 2008; the main study concluded in October 2012, after a median follow-up of 5 years. From that population, 2,771 individuals—who were bilaterally phakic at baseline, with less than 5% center subfield cortical or PSC opacity—were included in the present substudy. Statin use was self-reported at baseline.

Progression to more than 5% central opacity was the outcome for both cortical and PSC cataracts, and cataract surgery was used as a surrogate of moderate to severe lens opacity of unspecified type. Slit-lamp examination

was conducted at annual study visits, and telephone calls were made every 6 months to inquire about cataract surgery between the study visits.

Among the 2,771 participants, 1,184 (42.7%) were statin users. Statin users tended to be older, male, and former or current smokers; they also tended to have a history of diabetes and aspirin use as well as a history of cardiovascular disease and its risk factors.

In this analysis, statin users had an increased risk of cataract surgery (hazard ratio [HR], 1.90; 95% CI, 1.17-3.10), cortical lens opacity progression (HR, 1.52; 95% CI, 1.08-2.12), and PSC lens opacity progression (HR, 1.84; 95% CI, 1.25-2.71). Female statin users had an increased risk of cataract progression and cataract surgery. Statin users under the age of 75 years also had an increased risk of PSC lens opacity progression and cataract surgery.

The authors noted that AREDS2 study participants do not necessarily represent the wider population, and thus, the findings may not be generalizable. Nevertheless, the authors concluded that this study raises important questions, and given the large number of people who take these drugs, further study is needed to elucidate potential associations. Meanwhile, they said, patients should be encouraged to take statins when medically indicated and maintain regular eye examinations.

American Journal of Ophthalmology

Risk of MI and Stroke With Intravitreal Bevacizumab in AMD

March 2016

Concerns have been raised about whether intravitreal VEGF inhibitors increase the risk of myocardial infarction (MI) and stroke, but the peer-reviewed literature presents conflicting opinions. This prompted Etminan et al. to undertake a population-based study to examine the risk in patients receiving bevacizumab for age-related macular degeneration (AMD). They found that intravitreal bevacizumab did not appear to increase these cardiovascular events.

The authors used 2 cohorts of AMD patients in British Columbia, Canada, and 2 study designs: First, in a retrospective cohort study, they examined the risk of MI and stroke in patients with wet AMD who received intravitreal bevacizumab compared with those not taking VEGF inhibitors. Second, they conducted a nested case-control study among new users of intravitreal bevacizumab on the risk of MI or stroke. In both studies, a number of adjustments were applied in the analyses, including age, sex, presence of diabetes and vascular disorders, and the use of various drugs.

The retrospective cohort study included 5,644 patients who received bevacizumab and 2,564 who did not receive any anti-VEGF agent; all participants had been diagnosed with wet AMD. The rate of MI among intravitreal bevacizumab users was 11/1,000 person-years compared with 14.9/1,000 person-years in nonusers, yielding an adjusted rate ratio (RR) for MI of 0.70 (95% CI, 0.50-1.00).

The nested case-control study included 313 cases of MI with 3,130 matched controls as well as 65 cases of stroke matched with 650 corresponding controls. Several analyses were performed to investigate a possible dose-response, but no significant increase in the risk of either MI or stroke was found with either single or multiple injections of bevacizumab.

The authors concluded that, given the comparable effectiveness of bevacizumab and ranibizumab, these results will be reassuring to clinicians who choose to use off-label bevacizumab as a more cost-effective anti-VEGF therapy for their patients.

A PCR-Based Algorithm to Detect and Prevent Adenoviral Conjunctivitis Transmission

March 2016

Adenoviral conjunctivitis (AVC) can range from a mild, self-limited condition to prolonged ocular morbidity in the case of epidemic keratoconjunctivitis (EKC). At presentation, it is difficult to distinguish mild AVC from EKC or even from other causes of red eye. Kuo

et al. reported the 36-month results of a pilot program at Johns Hopkins Hospital (JHH) to reduce the transmission of EKC in the workplace through polymerase chain reaction (PCR) confirmation of adenovirus and a defined furlough protocol.

For employees with suspected conjunctivitis, the JHH algorithm consists of initial evaluation by nurse practitioners in the Occupational Health clinic who were trained by corneal specialists to recognize signs or symptoms consistent with AVC and to collect swab specimens from the inferior fornix. These swabs are submitted to a JHH laboratory for PCR testing. Employees with suspected viral conjunctivitis are evaluated, swabbed, and discharged home within 30 minutes of intake. Results from specimens received by 3 p.m. are available the next morning.

Employees whose swabs are positive for AVC are given a 14-day work furlough, while those whose swabs are negative return to work when free of signs and symptoms (generally 1-3 days after onset). Employees in both groups must be cleared by an Occupational Health nurse practitioner before returning to work.

Between Nov. 22, 2011, and Oct. 31, 2014, 858 of 4,883 initial employee Occupational Health visits (18%) were due to eye-related complaints. The nurse practitioners judged 542 (62%) of the eye complaints as possible AVC cases and submitted swabs for PCR; 44 of these were confirmed positive for AVC, and the employees were given a 14-day furlough. Specific adenoviral serotypes could be determined in 32 of the 44, and 13 of these had serotypes associated with the more serious EKC.

The authors noted that outbreaks reported in hospitals and eye clinics have caused substantial morbidity and lost productivity. However, since implementation of this pilot program at JHH, no health care-associated AVC outbreaks have occurred, and substantially fewer employees were placed on furlough than would have been the case had clinical diagnosis alone been used.

Thus, the authors concluded that implementation of this algorithm, encompassing rapid detection of AVC

and isolation of affected employees, has been successful and cost-effective for their institution. They noted that no PCR test for the detection of adenovirus in conjunctival specimens is commercially available, so clinical laboratories must develop their own tests. They also stated that further study and refinement of serotyping may reveal that shorter furloughs may be appropriate in some cases.

JAMA Ophthalmology

1-Year Efficacy of 3 Anti-VEGF Agents in DME

February 2016

Wells et al., on behalf of the Diabetic Retinopathy Clinical Research Network, reported additional outcomes from a randomized trial comparing aflibercept, bevacizumab, and ranibizumab for diabetic macular edema (DME) within subgroups based on baseline visual acuity (VA) and central subfield thickness (CST). The authors used a post hoc exploratory analysis of data from that trial in a group of 660 adults with DME and decreased VA.

Treatment involved repeated 0.05-mL intravitreal injections of 2.0 mg of aflibercept (224 eyes), 1.25 mg of bevacizumab (218 eyes), or 0.3 mg of ranibizumab (218 eyes) as needed per protocol. Prespecified subgroups were established according to baseline VA and CST. For VA, the thresholds were defined as worse (20/50 or worse) or better (20/32-20/40) VA; for CST, they were defined as thicker (≥ 400 μm) or thinner (250-399 μm).

In the subgroup with worse baseline VA ($n = 305$), irrespective of baseline CST, aflibercept showed greater improvement than bevacizumab or ranibizumab for several VA outcomes. In the subgroup with better VA and thinner CST at baseline (61-73 eyes across 3 treatment groups), VA outcomes were similar between groups; mean change was +7.2, +8.4, and +7.6 letters for aflibercept, bevacizumab, and ranibizumab, respectively.

However, results from the subgroup with better VA and thicker CST at baseline (31-43 eyes) suggested worse

VA outcomes in the bevacizumab group; mean change from baseline to 1 year was +9.5, +5.4, and +9.5 letters in the aflibercept, bevacizumab, and ranibizumab groups, respectively; and VA letter score was greater than 84 (approximately 20/20) in 21 of 33 (64%), 7 of 31 (23%), and 21 of 43 (49%) eyes, respectively. The adjusted differences and 95% CIs were 39% (17%-60%) for aflibercept vs. bevacizumab, 25% (5%-46%) for ranibizumab vs. bevacizumab, and 13% (-8% to 35%) for aflibercept vs. ranibizumab.

These post hoc secondary findings suggest that for eyes with better initial VA and thicker CST, some VA outcomes may be worse in the bevacizumab group than in the aflibercept and ranibizumab groups. Given the exploratory nature of these analyses and the small sample size within subgroups, the authors recommended caution in using the data to guide treatment decisions.

Prior Insulin Therapy and Visual Function Outcomes in Diabetes

February 2016

Interventions to improve glycemic control through early intensive treatment of diabetes have been shown to reduce rates of severe retinopathy and preserve visual acuity (VA). Gubitosi-Klug et al., on behalf of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies, assessed the effects of prior intensive insulin treatment and risk factors on patient-reported visual function in this DCCT/EDIC cohort.

The cohort included 1,184 participants with type 1 diabetes from the DCCT/EDIC studies (randomized clinical trial/observational follow-up study) who completed the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) during EDIC years 17 through 20 (Sept. 1, 2009, through April 30, 2014) at 28 institutions across the United States and Canada. The primary outcome was the composite NEI-VFQ-25 score. Secondary outcomes were VA, retinopathy level (determined from stereoscopic color fundus photographs), and NEI-

VFQ-25 subscale scores. The composite NEI-VFQ-25 scale and its subscales were scored 0 to 100, corresponding to poor to excellent function, respectively.

The overall average NEI-VFQ-25 score for the 1,184 participants (mean [SD] age, 52.3 [6.9] years; 48% female) with a 30-year duration of diabetes was high: median, 91.7, with an interquartile range (IQR) of 89.7-96.9. For the intensive treatment group (n = 605), the median score was 94.7, and IQR was 91.0-97.2. The conventional treatment group (n = 579) had a median of 94.0 and an IQR of 88.4-96.1 (p = .006 for intensive vs. conventional).

After adjustment for sex, age, hemoglobin A_{1c} level, and retinopathy level at DCCT baseline, the former intensive treatment group had a significant, albeit modest, improvement in overall NEI-VFQ-25 score compared with the former conventional diabetes treatment group (median difference, -1.0; 95% CI, -1.7 to -0.3; p = .006). This beneficial treatment effect was fully attributed to the prior glycemic control in DCCT.

Those with VA worse than 20/100 reported the largest decline in visual function (median difference, -21.0; 95% CI, -40.5 to -1.6; p = .03). The study suggests that intensive diabetes therapy modestly improved NEI-VFQ-25 scores 30 years after the start of the DCCT. Among all factors contributing to patient-reported visual function, VA had the greatest effect.

OTHER JOURNALS

Choroideremia Is a Systemic Disease

Investigative Ophthalmology & Visual Science

2015;56(13):8158-8165.

Choroideremia (CHM) has long been considered to be an isolated ocular disorder confined to the retina and choroid. But recent findings by **Zhang et al.** propose that CHM is a systemic condition that involves prominent crystals in lymphocytes and significant fatty acid abnormalities.

The researchers identified a Sri Lankan family whose members have severe choroidal degenerations that

appeared to be inherited in an X-linked fashion, and they postulated that these findings represented a new disease entity. When they discovered that the phenotype overlapped that of Bietti's crystalline dystrophy—which was recently found to have systemic features—they suspected that systemic disease might be present in this new entity as well.

For phenotyping, the researchers conducted detailed eye exams via optical coherence tomography. Genotyping entailed whole exome sequencing and Sanger sequencing confirmation. Systemic studies included electron microscopy of peripheral blood cells, as well as detailed fatty acid profiles in both plasma and red blood cell membranes. The fatty acid levels were compared with those of normal controls, and values that were 2 standard deviations above or below normal controls were evaluated further.

A *REPI* mutation was found in the Sri Lankan family, which suggested CHM. The investigators then found crystals in the peripheral blood lymphocytes of family members and discovered significant plasma fatty acid abnormalities and red blood cell abnormalities, including elevated plasmalogens. To replicate their discoveries, the researchers expanded the cohort to 9 unrelated CHM patients. They then genotyped them for *REPI* mutations and found the same abnormalities (crystals and fatty acid abnormalities) in all patients.

The researchers stated that, to their knowledge, this is the first time that CHM has been found to be a systemic disease.

Racial and Socioeconomic Disparities in Retinoblastoma

JAMA Pediatrics

2015;169(12):1096-1104

Truong et al. investigated the effects of socioeconomic status, race, and ethnicity on the extent of children's retinoblastoma and on their ultimate outcomes. The authors reviewed records in 18 Surveillance, Epidemiology, and End Results (SEER) registries across the United States from Jan. 1, 2000, through Dec. 31, 2010, and identified

830 cases of retinoblastoma among children aged 0 to 9 years during that time. They also analyzed race and ethnicity, poverty level, educational attainment, language isolation, crowding, unemployment, and the percentage of immigrants in the community.

Although retinoblastoma has become readily curable in recent years, the authors found significant disparities among children's care and outcomes within specific populations. Focusing primarily on disease extent, ocular outcome, and children's survival, the researchers noted that most studies that have investigated disparities in childhood cancer outcomes in high-income countries have not found significant differences based on socioeconomic or ethnic factors.

However, based on their own analysis of the SEER data, the authors observed significant disparities among patients with retinoblastoma. They found that although survival did not vary significantly among the socioeconomic groups, the extent of disease at presentation and the likelihood of enucleation did. For example, Hispanic children were more likely to present with extraocular disease (33% vs. 20%), and they were 41% more likely to have undergone enucleation than were non-Hispanic white children. Low socioeconomic status may limit access to primary care and cancer-related care and delay diagnosis and treatment. The authors concluded that addressing such disparities in childhood cancer is critical, given the known morbidity and the long-term psychological, financial, and medical burdens faced by these children and their families.

Ophthalmology summaries are written by Marianne Doran and edited by Susan M. MacDonald, MD. *American Journal of Ophthalmology* summaries are written by Peggy Denny and edited by Richard K. Parrish II, MD. *JAMA Ophthalmology* summaries are based on authors' abstracts, as edited by senior editor(s). *Other Journals* summaries are written by Marianne Doran and edited by Deepak P. Edward, MD.



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