Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

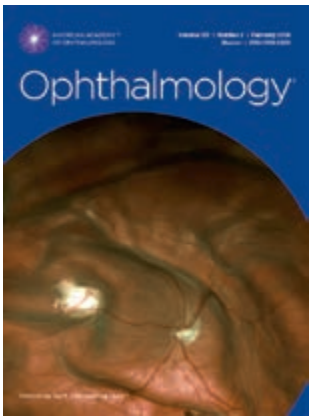
Gene Therapy for LHON

March 2016

Leber hereditary optic neuropathy (LHON) is a disorder characterized by severe, rapidly progressive, and usually bilateral vision loss. **Feuer et al.** present their findings from the first 5 patients who participated in a gene therapy trial to assess the safety and tolerability of escalating doses of an adeno-associated virus (AAV2) vector that expresses normal ND4 complementary DNA in patients with a G to A mutation at nucleotide 11778 of the mitochondrial genome.

The 5 patients were legally blind individuals with LHON. Four had vision loss for more than 12 months, while the fifth had vision loss for less than 12 months. They each received a unilateral injection of the study drug. The first 3 participants received a low dose of the study drug; the fourth patient (loss for more than 12 months) received a medium dose, and the fifth participant (loss for less than 12 months) received a low dose. Treated participants were observed for 90 to 180 days and underwent ocular and systemic safety assessments along with visual structure and function examinations. The main outcome measure was loss of visual acuity (VA), which was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart.

VA remained unchanged from baseline to 3 months in the first 3 participants. In 2 participants (number 4, medium dose; and number 5, low dose), VA increased from hand motions to 7 ETDRS letters and by 15 letters, respectively. No patients lost vision, and no serious adverse events occurred. Minor adverse events included a transient increase in IOP, exposure keratitis, subconjunctival hemorrhage, sore throat, and a transient increase in neutralizing antibodies against AAV2 in 1 study participant. All blood samples were negative for vector DNA. Follow-up will continue on these patients, and the researchers plan to add more participants over the next 4 years.



Precision Pulse Capsulotomy: Preclinical Safety and Performance Assessment

February 2016

Chang et al. described a new method, called precision pulse capsulotomy (PPC), for making anterior capsulotomies using a disposable handheld instrument that is integrated into the conventional phacoemulsification surgical sequence. According to the authors, this device produces a fast, highly focused, multipulse low-energy discharge to create a perfectly round anterior capsulotomy instantaneously and simultaneously along all 360 degrees.

In a preclinical safety and performance study, the researchers used human cadaver eyes and New Zealand white rabbits. Miyake-Apple imaging and scanning electron microscopy (SEM) were performed in the human cadaver eyes. Surgical, postoperative slit-lamp, and histopathologic assessments of PPC were performed in 20 live rabbits and were compared with manual continuous curvilinear capsulorrhexis (CCC) in the fellow eye.

The main outcome measures were capsulotomy edge circularity, SEM morphologic features, and zonular movement with PPC in human cadaver eyes. Additional measures included anterior chamber temperature during PPC and grading of ocular inflammation, corneal endothelial damage, anterior capsular opacification (ACO), and posterior capsular opacification (PCO) in the rabbits.

Miyake-Apple imaging revealed minimal zonular stress, and thermocouple measurements showed negligible anterior chamber temperature changes during PPC. The technique also produced round and complete capsulotomies in all 20 rabbit eyes, allowing successful in-the-bag IOL implantations.

In slit-lamp exams at 3 days and at 1, 2, and 4 weeks after surgery, the researchers found no significant differences between PPC and CCC in corneal edema, anterior chamber inflammatory

reaction, capsular fibrosis, ACO, or PCO. Postmortem studies also revealed no differences in the corneal endothelium. All IOLs were well centered in the PPC eyes, and histopathologic analysis revealed no greater amount of inflammatory infiltrates.

The authors concluded that PPC is a new way to automate the consistent creation of a perfectly circular anterior capsulotomy using an instrument that can be incorporated into standard phacoemulsification surgery.

Antiplatelet/Anticoagulant Drugs and Risk of Retinal or Subretinal Hemorrhage

February 2016

Ying et al. examined the use of antiplatelet and anticoagulant medications among participants in the Comparison of Age-Related Macular Degeneration (AMD) Treatments Trials (CATT). The aim of this study was to assess the risk of retinal and subretinal hemorrhage in participants with untreated neovascular AMD in the CATT population.

In this cohort study, participants were interviewed about their use of antiplatelet or anticoagulant drugs. Trained readers evaluated photographs for the presence and size of retinal or subretinal hemorrhages at baseline, year 1, and year 2.

Among 1,165 study participants with gradable photographs, 724 (62.1%) had a retinal or subretinal hemorrhage at baseline. Of these hemorrhages, 84.4% were 1 disc area (DA) or less, 8.1% were 1 to 2 DA, and 7.5% were larger than 2 DA. At baseline, 608 participants (52.2%) were taking antiplatelet or anticoagulant medications or both.

At baseline, hemorrhage was present in 64.5% of antiplatelet or anticoagulant users and in 59.6% of nonusers. The researchers found no association between the presence or size of baseline hemorrhage and the type, dose, or duration of antiplatelet or anticoagulant use. Among 1,078 participants photographed at year 1 or year 2, 44 additional hemorrhages (occurring in 4.1%) were detected. These hemorrhages were not associated with antiplatelet or anticoagulant use at baseline or during follow-up. However, among participants with hypertension, antiplatelet or anticoagulant use was found to be associated with a higher rate of hemorrhage at baseline (66.8%), but it was not associated with the size of hemorrhage.

The authors commented that various studies have examined the question of association between retinal and subretinal hemorrhages and use of antiplatelet or anticoagulant drugs, and the results have been mixed. In this study, they found no significant associations overall, though the subgroup of patients with hypertension did have a 1.5-fold increased risk of hemorrhage. The authors concluded that nonhypertensive patients with AMD could continue taking needed antiplatelet or anticoagulant drugs without fear of increased risk of visual loss from hemorrhage. However, among AMD patients with hypertension, antiplatelet or anticoagulant use was associated with 1.5-fold increased risk of retinal or subretinal hemorrhage; thus, blood pressure status should be considered when such drugs are prescribed in this population.

American Journal of Ophthalmology

Fine Needle Aspiration Biopsy in Uveal Melanoma

February 2016

Sellam et al. reported the technical aspects, complications, and outcomes of fine needle aspiration biopsy (FNAB) in uveal melanoma by means of a retrospective cohort study.

FNAB was performed at an ocular oncology clinic if the tumor was more than 5 mm in thickness. Array comparative genomic hybridization analysis was conducted on biopsy samples with sufficient tissue. The main outcome measures were success rates (that is, samples that gave a successful result for biomarker analysis), complications, liver metastasis, and overall survival. The study included 217 consecutive patients with a mean age of 57 years; mean tumor thickness was 8.4 mm. The mean follow-up period was 31 months.

The procedure was successful in 169 patients (78%). Thirty-one patients (14%) experienced intravitreal hemorrhage, 9 of whom required vitreal surgery. There were no cases of endophthalmitis, orbital dissemination, local recurrence, or rhegmatogenous retinal detachment. Thirty-two patients (15%) developed metastasis during the study, and 20 of them died. Of the 169 successful samples, 53 patients (31%) were classified as low risk, 41 (24%) as intermediate risk, and 54 (32%) as high risk. Fifteen patients (9%) did not have any detectable chromosomal abnormality, and 6 (4%) could not be classified.

The authors concluded that FNAB is a relatively safe procedure that can be routinely used to obtain tissue biopsy samples for molecular genomic analysis. Further, they noted that such analysis helps determine the frequency of metastases and prognosis in uveal melanoma.

Dry Eye Patients With Chronic Pain Syndromes

February 2016

Vehof et al. conducted a cross-sectional study to investigate clinical characteristics of dry eye disease (DED) patients with a chronic pain syndrome. The study compared ocular signs and symptoms in DED patients with and without a chronic pain syndrome in 2 cohorts. In both cohorts, patients with a chronic pain syndrome had increased severity of all dry eye symptoms, even though the objective signs were similar or less severe compared with those in patients without a chronic pain syndrome.

One cohort included 425 DED patients at a tertiary care center in the Netherlands. Chronic pain syndromes of irritable bowel syndrome, chronic pelvic pain, and fibromyalgia were assessed by questionnaires. Outcome variables were Ocular Surface Disease Index (OSDI) symptom questionnaire, tear osmolarity, Schirmer test, tear breakup time, conjunctival hyperemia, corneal and conjunctival staining, and amount of mucus. Outcomes were cross-sectionally compared between DED patients with or without a chronic

pain syndrome.

Among the 425 DED patients, 74 (17%) reported at least 1 chronic pain syndrome. The total OSDI symptom score was significantly higher in DED patients with a chronic pain syndrome than in those without (46 vs. 34, $p < .0005$). Moreover, patients with a chronic pain syndrome scored higher on every single subscale of the 12-item symptom questionnaire. However, ocular signs were similar or even less severe in these patients than in those without a chronic pain syndrome.

In addition, the researchers looked at a cohort of 64 DED patients from a population-based cohort, the TwinsUK Adult Twin Registry, which had a lower risk of ascertainment bias than the tertiary care clinic population. Similar to the Netherlands cohort, DED patients with a chronic pain syndrome in this UK cohort had higher subscale and total symptom scores.

In DED patients, chronic pain syndromes seem to be common and are associated with increased severity of DED symptoms across all domains of the OSDI, even though objective ocular surface signs are no worse. Greater awareness of chronic pain syndromes might aid clinicians in understanding the discrepancy between signs and symptoms in DED.

Reoperation and Binocularity After Strabismus Surgery in Children

February 2016

Leffler et al. used a retrospective cross-sectional study to determine the predictors of reoperation and abnormal binocularity outcomes (including amblyopia and diplopia) following pediatric strabismus surgery.

The authors reviewed a national insurance database to identify children under the age of 18 years who had strabismus procedures between 2007 and 2013. Interventions included adjustable- or fixed-suture strabismus surgery and botulinum toxin injection. The main outcome measure was reoperation or diagnosis of abnormal binocularity in the first postoperative year.

Of 11,115 children who had strabismus procedures, 851 (8%) underwent reoperation. The reoperation rate was 7% for fixed-suture surgeries, 10% for adjustable-suture surgeries, and 45% for botulinum injections. Age under 2 years was associated with higher reoperation and abnormal binocularity rates. For horizontal strabismus, the postoperative abnormal binocularity rate was 13% for fixed-suture surgery and 26% for botulinum injection.

Reoperation rates tended to be higher with adjustable sutures or botulinum toxin injection and lower with 3- or 4-muscle surgery. Esotropia, hyperopia, and botulinum injection were independently associated with higher rates of postoperative abnormal binocularity. For vertical surgeries, predictors of reoperation were adjustable suture use and superior oblique surgery.

Although previous studies conducted among adults found a lower rate of reoperation with use of adjustable sutures, our study found that in children, adjustable sutures were not associated with a lower reoperation rate. Younger age, esotropia, hyperopia, and botulinum injection were associated with postoperative abnormal binocularity. Superior oblique surgery and botulinum injection were associated with higher rates of reoperation.

JAMA Ophthalmology

Review of Prolonged Monthly Therapy for DME

February 2016

Although intravitreal (IVT) anti-VEGF therapy is used to treat numerous retinal conditions, controversy remains regarding its systemic safety. Thus, **Avery and Gordon** investigated the safety of IVT anti-VEGF in patients with diabetic macular edema, focusing on the subgroup of patients with the highest level of exposure: monthly injections for 2 years.

A search was conducted through MEDLINE, Cochrane Central Register of Controlled Trials, clinicaltrials.gov, and ophthalmology congress abstracts from Jan. 1, 1947 (the starting date of MEDLINE), to May 19, 2015. The researchers identified randomized clinical trials that evaluated patients who received monthly anti-VEGF injections for DME for 2 years and that included the outcome measures of cerebrovascular accidents (CVA), myocardial infarctions (MI), arteriothrombotic events, and mortality. The primary end points included CVA and all-cause mortality in the highest-dose arms. Secondary outcomes included MI, arteriothrombotic events, and vascular-related death.

Of 1,126 articles reviewed, 598 were removed as duplicate studies and 524 were excluded for lack of monthly treatment data for 2 years. This process left 4 studies that met criteria for the meta-analysis: 2 trials using monthly aflibercept and 2 using monthly ranibizumab, representing 1,328 study participants. The primary evaluation (1,078 subjects) combined the monthly aflibercept and the 0.5-mg ranibizumab arms and yielded an increased risk for death compared with sham and laser treatments (OR, 2.98; $p = .003$). Analysis including monthly aflibercept and 0.5-mg ranibizumab yielded an increased risk for CVA (OR, 2.33; $p = .04$) and vascular death (OR, 2.51; $p = .03$). No definitive increased risk for MI and arteriothrombotic events was seen with any dose combinations.

The authors concluded that for patients with DME, assessment of the highest-level exposure group revealed a possible increased risk for death and CVA. Consideration of total exposure to anti-VEGF agents when treating those at high risk for vascular disease may be important.

Detection of Strabismus by Lay Observers in Ethnically Diverse Images

February 2016

Understanding the way that lay individuals perceive strabismus has implications for setting surgical goals and for counseling patients with strabismus. **Chan et al.** examined the magnitude at which strabismus is detectable by lay observers in an ethnically diverse set of images.

Photographs of 12 models (black, white, and Asian) were altered to simulate strabismus ranging from esotropia

of 21 prism diopters (Δ) to exotropia of 21Δ. These images were presented to 120 individuals aged 21 years or older from the general community in Boston, who were asked whether strabismus was present. The researchers sought to determine the threshold angle at which 70% of lay observers detected the presence of strabismus.

In white and black models, the detection threshold was higher for esotropia than for exotropia ($p < .001$ for both). For white models, the threshold was 23.2Δ (95% CI, 21.0-26.5) for esotropia and 13.5Δ (95% CI, 12.5-14.6) for exotropia. For black models, the threshold was 20.8Δ (95% CI, 19.2-22.2) for esotropia and 16.3Δ (95% CI, 15.5-17.2) for exotropia. There was an opposite trend for the Asian models; the threshold for detecting esotropia (14.3Δ; 95% CI, 13.2-15.7) was lower than that for exotropia (20.9Δ; 95% CI, 18.0-24.6).

The authors concluded that esotropia was easier for lay observers to detect than exotropia in Asian models and that exotropia was easier to detect than esotropia in white and black models. This information may be of value when managing patients who have concerns about the social relevance of their strabismus. Future studies should include diverse individuals and make an effort to account for individual factors that may alter the perception of strabismus.

Oral Fluoroquinolones and Uveitis Risk

February 2016

Oral fluoroquinolones are the most commonly prescribed antibiotic class in the outpatient setting, but recent reports have suggested an association between their use and an increased risk of uveitis. **Sandhu et al.** evaluated the hazard of uveitis in fluoroquinolone users by means of a retrospective cohort study conducted using medical claims data from a large national U.S. insurer.

Cohorts from ambulatory care centers across the United States were created including every new user of an oral fluoroquinolone or a β-lactam antibiotic prescription with at least 24 months of data prior to the date of the prescription from Jan. 1, 2000, to Jan. 30, 2013. Patients were excluded for any previous diagnosis of uveitis or a uveitis-associated systemic illness. Participants were censored for a new diagnosis of a uveitis-associated systemic illness, the end of an observation period, use of the other class of antibiotic, or removal from the insurance plan. The hazard of a uveitis diagnosis after a fluoroquinolone prescription was compared with that of a β-lactam prescription by means of multivariate regression with Cox proportional hazards models.

Of the 4,387,651 patients in the database, 843,854 receiving a fluoroquinolone and 3,543,797 receiving a β-lactam were included. After adjustment for age, race, and gender, no hazard was seen for developing uveitis at the 30-, 60-, or 90-day observation windows (hazard ratio [HR] range, 0.96-1.05; $p > .38$ for all comparisons). The 365-day observation period showed a small increase in the HR for the fluoroquinolone cohort (1.11; $p < .001$). Moxifloxacin produced an increased hazard for uveitis at every time point (HR range, 1.47-1.75; $p < .001$ for all comparisons). Secondary analysis demonstrated a similar hazard at 365 days for a later diagnosis of a uveitis-associated systemic illness after fluoroquinolone use (HR range, 1.46-1.96; $p < .001$ for all comparisons).

The authors concluded that these data do not support an association between oral fluoroquinolone use and uveitis. Instead, this study shows an association between oral fluoroquinolone use and the risk for uveitis-associated systemic illnesses, which is a possible source of bias that could explain the findings of previous studies.

OTHER JOURNALS

Traumatic IOP Elevation and Glaucoma After Open-Globe Injury

Eye

Published online September 18, 2015

Bojikian et al. examined the occurrence of traumatic intraocular pressure (IOP) elevation and glaucoma after open-globe injuries. In a retrospective observational case series, they reviewed outcomes among patients who had undergone open-globe repair at one institution between May 1997 and July 2010 and found that almost a quarter of eyes experienced elevated IOP.

The researchers defined traumatic IOP elevation as an IOP of 22 mm Hg at more than 1 office visit. Glaucoma was defined as the need for, and use of, glaucoma medication for at least 3 months, and/or the need for glaucoma surgery.

The study included 515 eyes of 515 patients and had a mean follow-up of 12.6 ± 20.1 months. Of these eyes, 120 (23.3%) developed traumatic IOP elevation at a mean time of 1.5 ± 3.4 months (range, 1 day to 2 years) after the injury. Traumatic glaucoma developed in 32 eyes (6.2%), and 6 eyes (1.2%) required glaucoma surgery. Kaplan-Meier 6- and 12-month estimates for the development of traumatic IOP elevation were 27.2% and 32.4%, respectively, while estimates for the development of traumatic glaucoma were 7.1% and 11.0%, respectively. Multivariate regression analysis also identified associations between traumatic IOP elevation and older age.

The investigators concluded that posttraumatic glaucoma is a serious complication of open-globe injuries and has the potential to blind an already damaged eye. Most cases develop within 6 months, but continuing vigilance is important. The authors noted that penetrating keratoplasty—either before or after eye repair—and vitreous hemorrhage are notable risk factors in this patient population.

Ophthalmology summaries are written by Marianne Doran and edited by Susan M. MacDonald, MD. *American Journal of Ophthalmology* summaries are edited by Thomas J. Liesegang, 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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