Journal Highlights

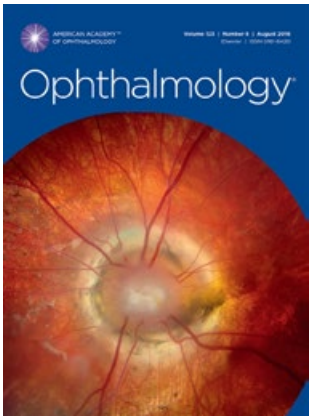
NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Enhanced Benefit in DME From AKB-9778 Tie2 Activation + VEGF Suppression

August 2016

Campochiaro et al. conducted a phase 2a randomized controlled double-masked clinical trial to assess the effect of AKB-9778 (an investigational Tie-2–activating agent that blocks vascular leakage) alone and in combination with ranibizumab in patients with diabetic macular edema (DME). They found that the combined therapy was more effective than monotherapy with either drug.



Study participants (n = 144) had decreased vision from DME and a central subfield thickness (CST) of ≥325 µm, as measured by spectral-domain optical coherence tomography. They were randomized into 3 groups: 1) AKB-9778 monotherapy—subcutaneous AKB-9778 twice-daily (BID) plus monthly sham intraocular injections; 2) combination therapy—subcutaneous AKB-9778 BID plus monthly intravitreal ranibizumab; or 3) ranibizumab monotherapy—subcutaneous placebo injections BID plus monthly intravitreal ranibizumab. AKB-9778 was administered in 15-mg doses, and ranibizumab in 0.3-mg doses. Best-corrected visual acuity (BCVA) and CST were measured at baseline and every 4 weeks. The primary outcome measure was mean change from baseline CST at week 12. Additional outcomes included BCVA and safety.

At week 12, the mean change from baseline CST was significantly greater in the combination group (–164.4 ± 24.2 µm) than in the ranibizumab monotherapy group (–110.4 ± 17.2 µm; p = .008); in the AKB-9778 monotherapy group, the change was 6.2 ± 13.0 µm. At week 12, mean CST and percentage of eyes with resolved edema were 340.0 ± 11.2 µm and 29.2%, respectively, in the combination group versus 392.1 ± 17.1 µm and 17.0%, respectively, in the ranibizumab monotherapy group.

The mean change from baseline BCVA (in letters) was 6.3 ± 1.3 in the combination group; 5.7 ± 1.2 in the ranibizumab monotherapy group; and 1.5 ± 1.2 in the AKB-9778 monotherapy group. Percentages of eyes that gained ≥10 letters and ≥15 letters were 35.4% and 20.8%, respectively, in the combination therapy group; 29.8% and 17.0%, respectively, in the ranibizumab group; and 8.7% and 4.3%, respectively, in the AKB-9778 group.

AKB-9778 was well tolerated, with no clear differences in adverse events between treatment groups.

Overall, this study demonstrates that activation of Tie2 through subcutaneous injections of AKB-9778 in combination with VEGF suppression is more effective than anti-VEGF therapy alone in treating DME.

Risks for Surgical Treatment of Cataracts in Postmenopausal Women

August 2016

Floud et al. used data on 1,312,051 postmenopausal women in the U.K.'s Million Women Study to identify risk factors associated with cataract surgery in that group. The researchers found that diabetes, smoking, and obesity were significant risk factors for undergoing cataract surgery.

In this population-based cohort study, the average age was 56 years (standard deviation [SD], 4.8), and none of the women had previous cataract surgery, hospital admission with cataracts, or cancer at baseline. The women were followed for an average of 11 (SD, 3) years. The main outcome measure was cataract surgery, identified by linkage to central National Health Service records for inpatient and day-patient admissions. The researchers used Cox regression analysis to calculate adjusted relative risks (RRs) for cataract surgery by lifestyle factors, treatment for diabetes, reproductive history, and use of hormonal therapies.

Over the study period, 89,343 participants (6.8%) underwent cataract surgery. Women with diabetes were at the greatest risk (RR, 2.90; 95% CI,

2.82-2.97). Other factors associated with an increased risk of cataract surgery were smoking 15 or more cigarettes daily (RR, 1.26; 95% CI, 1.23-1.30) and obesity (body mass index [BMI] ≥30 vs. BMI <25 kg/m^2: RR, 1.12; 95% CI, 1.10-1.14).

The researchers concluded that diabetes, smoking, and obesity were risk factors for cataract surgery. Among the other factors analyzed, alcohol use, physical activity, reproductive history, and use of hormonal therapies had little, if any, association with cataract surgery risk. Further, the authors commented that because cataracts are a leading cause of visual impairment, and cataract surgery is the most common operation in the U.K., it is important to identify any risk factors that may be modifiable.

Immediate Sequential Bilateral Pediatric Vitreoretinal Surgery

August 2016

Because many infants and young children who require vitreoretinal surgery on both eyes are medically fragile and at risk from general anesthesia, **Yonekawa et al.** assessed the feasibility and safety of immediate sequential bilateral vitreoretinal surgery (ISBVS) in pediatric patients. They found that ISBVS was a feasible and safe treatment paradigm for these young patients when repeated general anesthesia is undesirable or impractical.

This was a multicenter retrospective interventional case series from 24 centers worldwide. The study included 344 surgeries from 172 ISBVS procedures performed in 167 patients aged 17 years or younger (mean age, 1.3 ± 2.6 years). ISBVS is defined as vitrectomy, scleral buckle, or lensectomy using a vitreous cutter in both eyes sequentially during the same anesthesia session. Nonexclusive indications for ISBVS were rapidly progressive disease, 74.6%; systemic morbidity placing the child at high anesthesia risk, 76.0%; and residence remote from surgery location, 30.2%. The most common diagnoses included retinopathy of prematurity (ROP), 72.7%; familial exudative vitreoretinopathy, 7.0%; abusive head trauma, 4.1%; persistent fetal vasculature, 3.5%; and Norrie disease, 2.3%.

Mean surgical time was 143 ± 59 minutes for both eyes. No intraoperative ocular complications were reported, although 2 eyes (from different patients) experienced unilateral vitreous hemorrhage in the immediate postoperative period. There were no cases of endophthalmitis, choroidal hemorrhage, or hypotony.

Mean total anesthesia time was 203 ± 87 minutes. No cases of anesthesia-related death, malignant hyperthermia, anaphylaxis, or cardiac events occurred. One patient required reintubation, and 1 had prolonged oxygen desaturation. Mean follow-up after surgery was 103 weeks, and anatomic success and globe salvage rates were 89.8% and 98.0%, respectively.

The authors gave a number of guidelines for performing ISBVS safely. Among these were rescrubbing, regowning, and regloving between procedures on the 2 eyes, as well as using new drapes, a new set of instruments, and different medication lots for the second eye. In conclusion, they endorsed ISBVS as a treatment option for patients in whom separate staged bilateral surgeries would unduly increase the risk for vision loss, mortality, or both.

American Journal of Ophthalmology

Predictors and Short-term Costs of Laser Trabeculoplasty vs. Medication in OAG

August 2016

Laser trabeculoplasty (LT) has been posited as a way to reduce glaucoma treatment costs and medication nonadherence. **Schultz et al.** examined costs for patients who received LT versus additional medications and found that while the glaucoma-specific (GS) pharmacy costs were lower for LT patients in the 24 months after the procedure, the overall GS treatment costs were comparable between the LT and medication groups.

This was a retrospective administrative claims analysis, based on medical and pharmacy claims data between 2007 and 2012. Records were analyzed to identify open-angle glaucoma (OAG) patients already on prostaglandin analogue monotherapy who had an index-date LT claim (LT cohort) or a second medication class claim (Rx cohort); claims were reviewed for the 12 months before and 24 months after the index date. The study included 4,743 LT patients and 16,484 Rx patients.

The researchers found that over the course of the study, the per-patient GS pharmacy costs were significantly lower in the LT cohort than the Rx cohort ($807 vs. $1,467, respectively; $p < .0001$). At 45 days after LT, 60% of patients did not have a pharmacy claim; this was down to 20% by 24 months. However, the LT cohort had significantly higher GS medical costs ($2,684 vs. $1,980; $p < .0001$), with 28% of those costs specifically related to the LT procedure. The overall GS costs ($3,441 vs. $3,408, respectively, $p = .325$) were not significantly different between groups.

The study also investigated the factors predicting whether a patient on OAG monotherapy would receive LT or an additional drug. Younger age, greater comorbidity (e.g., diabetes), and a history of poor adherence were significant predictors for LT. Regional differences were also found, with highest rates of LT use in the Pacific, west north central, and east north central regions of the United States.

The authors acknowledged some study limitations: The analysis was based only on claims data and did not account for the clinical findings of individual patients; nor did it distinguish between laser treatments (e.g., argon vs. selective laser trabeculoplasty; or 180- vs. 360-degree application). Regardless, the authors concluded that these real-world claims data demonstrate that, overall, LT does not reduce the cost of glaucoma care.

Economic Model of ROP Screening and Treatment: Mexico and the United States

August 2016

Using an economic model they developed (EcROP), **Rothschild et al.** analyzed the impact of ROP screening in the United States and Mexico, which

they selected as examples of high- and middle-income nations, respectively. They found that in both types of economies, well-designed screening programs were highly cost-effective.

Although both the United States and Mexico have recommended ROP screening guidelines for premature infants, blindness from ROP remains a substantial burden, which the authors attribute to incomplete adherence to these guidelines. They estimated an 80% penetrance of screening in the United States and 52% in Mexico. For both countries, they then compared the direct and indirect costs of ROP-related blindness under actual conditions versus an "ideal" model of 100% screening of the targeted population, followed by appropriate treatment.

In addition to findings from published literature, the EcROP model incorporated country-specific economic data based on local standard-of-care clinical protocols, as well as information from in-person interviews with caregivers of 52 children at schools for the blind or pediatric eye clinics in Atlanta, Georgia, and 43 in Mexico City.

In determining the costs of blindness, EcROP included both direct costs (e.g., educational/training fees, specialized equipment such as Braille writers, and government disability payments) and indirect costs (e.g., reduced productivity of the patient and the caregiver). For ROP screening and treatment, direct costs included all equipment, labor, and facilities expenses associated with evidence-based ROP screening, treatment, and follow-up; while indirect costs included caregiver productivity lost to medical appointments. EcROP also included quality-adjusted life years (QALY) in the incremental cost-effectiveness analysis.

The authors found that an ideal national ROP screening and treatment program would yield substantial savings. They estimated that the incremental net benefit of an ideal program over current practice would be $5,556 per child ($206,574,333 annually) in the United States and $3,628 per child ($205,906,959 annually) in Mexico.

They concluded that EcROP data support the cost savings and QALY improvement, as well as societal benefits, from implementation of effective ROP management. Although the time window for ROP identification and treatment is brief, the potential impact is lifelong for the patient and family.

Minimum Standardized Patient-Centered Outcome Measures for Macular Degeneration

August 2016

Various types of outcome measures have been used in studies and in clinical management of macular degeneration. On behalf of the International Consortium for Health Outcomes Measurement (ICHOM), **Rodrigues et al.** sought to define a minimum set of measures for tracking, comparing, and improving care of patients with conditions including neovascular and nonneovascular age-related macular degeneration (AMD), polypoidal choroidal vasculopathy, and neovascular myopic macular degeneration.

The ICHOM working group consisted of 18 experts from 10 countries on 4 continents. They used a modified Delphi technique, incorporating structured teleconferences and survey questionnaires, to arrive at consensus decisions. Potential outcomes were identified through review of outcomes collected in existing registries and reported in major clinical trials and were selected and refined by the group based on impact on patients, relationship to good clinical care, and feasibility of measurement in routine practice.

Noting that increases in objectively measured distance visual acuity are not necessarily consistent with improved visual functioning, the authors recommended including measures of near visual acuity, reading speed, and contrast sensitivity as well. Further, they emphasized the importance of real-life patient-reported outcome measures (PROMs) in disease management. The group established minimum standards in 3 major areas: (1) visual functioning and vision-related quality of life, encompassing distance visual acuity as well as PROMs of mobility, emotional well-being, and ability to read and access information; (2) disutility of care, including treatment burden and complications; and (3) disease control, involving anatomic measures such as presence of fluid, edema, and hemorrhage. In addition, the working group recommended a timeline for scheduling each of these measurements. ICHOM has made the full report freely available at www.ichom.org/medical-conditions/macular-degeneration/.

JAMA Ophthalmology

Visual Impairment and Blindness in U.S. Adults: 2015-2050

July 2016

Shifting demographics and aging populations are increasing the number of individuals with visual impairment (VI) and blindness in the United States. **Varma et al.** sought to determine the demographic and geographic variations in VI and blindness in adults in the U.S. population in 2015 and to estimate the projected prevalence through 2050. They found that despite the high prevalence of VI and blindness in minorities, the largest current and future burden is predicted to be among older non-Hispanic white women.

This was a population-based cross-sectional study in which the researchers pooled data from 6 population-based studies on VI and blindness in the United States that included participants aged 40 years and older. Prevalence of VI and blindness was reported by age, sex, race/ethnicity, and per capita prevalence by state using the U.S. Census projections (Jan. 1, 2015-Dec. 31, 2050).

The results showed that in 2015, a total of 1.02 million people in the United States were blind (defined as best-corrected visual acuity [BCVA] ≤20/200 in the better-seeing eye), and approximately 3.22 million had VI (BCVA <20/40 in the better-seeing eye, excluding blindness); and up to 8.2 million people had VI due to uncorrected refractive error. By 2050, these numbers are projected to double to approximately 2.01 million, 6.95 million, and 16.4 million, respectively. In 2015, the highest numbers of these conditions were among non-Hispanic white individuals (2.28 million), women (1.84

million), and older adults (1.61 million); these groups are predicted to remain the most affected through 2050.

Currently, African American individuals have the highest prevalence of VI and blindness. But by 2050, the highest prevalence of VI among minorities will shift from African Americans (15.2% in 2015; 16.3% in 2050) to Hispanics (9.9% in 2015; 20.3% in 2050). For both 2015 and 2050, the states projected to have the highest per capita prevalence of VI are Florida and Hawaii, while those with the highest per capita prevalence of blindness will be Mississippi and Louisiana.

In conclusion, the researchers said, these findings suggest that vision screening for refractive error and early eye disease could reduce the proportion of individuals who experience unnecessary VI and blindness, decrease societal costs, and contribute to better quality of life. Further, they suggested that education and screening programs targeted toward non-Hispanic white women and minorities will become increasingly important because of the projected growth of these populations.

Association of Football Subconcussive Head Impacts With Near Point of Convergence

July 2016

Concern is growing that even low-level (subconcussive) head impacts in sports can cause significant brain injury if they occur repeatedly. **Kawata et al.** investigated whether such repetitive head impacts during preseason football practice cause changes in the ocular near point of convergence (NPC) ocular-motor function. They found that players who had more frequent and stronger subconcussive impacts had greater convergence insufficiency than those with fewer and less severe impacts. However, after 3 weeks of rest, convergence normalized to baseline levels.

This was a prospective observational study that included 29 National Collegiate Athletic Association Division I football players who participated in baseline and preseason practices (1 noncontact and 4 contact). Each participant was fitted with an accelerometer-embedded mouthguard that measured head impact kinematics. Outcome measures, including head impacts, NPC, and a self-reported symptom checklist, were taken at all practices and at postseason follow-up.

A total of 1,193 head impacts were recorded for the whole group of participants. The players were categorized into lower (n = 7) or higher (n = 22) impact groups, based on the sum of head impacts from all 5 practices. The authors found significant differences in head impact kinematics between lower- and higher-impact groups (number of impacts, 6 vs. 41); linear acceleration (99*g* vs. 1,112*g*, respectively); and angular acceleration (7,589 radian/s^2 vs. 65,016 radian/s^2, respectively). The trajectory and cumulative burden of subconcussive impacts on NPC differed significantly between the 2 groups. In the higher-impact group, there was a linear increase in NPC over time (B for linear trend, unstandardized coefficient [SE]: 0.76 [0.12], $p < .001$) that plateaued and resolved by postseason follow-up (B for quadratic trend [SE]: −0.06 [0.008], $p < .001$). In the lower-impact group, there was no change in NPC over time. Group differences were initially observed after the first contact practice and remained until the final full-gear practice. No group differences were observed in postseason follow-up. There were no differences in symptom scores between groups over time.

The authors concluded that even though the participants did not report symptoms, these data suggest that repetitive subconcussive head impacts are associated with changes in NPC, which highlights the vulnerability and slow recovery of the ocular-motor system following such impacts. They further noted that NPC may become a useful clinical tool in deciphering brain injury.

Levels of UV-A Light Protection in Automobile Windshields and Side Windows

July 2016

Given the association between ultraviolet A (UV-A) light and risks of skin cancer and cataract, **Boxer Wachler** assessed the level of UV-A protection afforded by the front windshields and side windows of automobiles. He found that the average UV-A blockage from windshields was 96%, while blockage from side windows averaged 71%.

The author carried out a cross-sectional study that included 29 automobiles from 15 automobile manufacturers, with model years ranging from 1990 to 2014. For all autos, he measured the outside ambient UV-A radiation and UV-A radiation behind the front windshield and behind the driver's side windows. All measurements were taken on the same cloudless day (May 4, 2014) in Los Angeles, using a handheld UV-A light meter.

The average percentage of front-windshield UV-A blockage was 96% (range, 95%-98%) and was higher than the average percentage of side-window blockage, which was 71% (range, 44%-96%). A high level of side-window UV-A blockage (>90%) was found in 4 of 29 automobiles (13.8%). The study did not find any correlation between age of the vehicle and percentage of UV-A blockage.

The author commented that these results may in part explain the reported higher rates of cataract in left eyes and left-sided facial skin cancer, and he suggested that automakers consider increasing the degree of UV-A protection in the side windows. In conclusion, the author noted that this study may have relevance beyond autos in raising awareness of UV-A transmission through other types of windows and developing recommendations for UV protection in glass used in residential, commercial, and school buildings.

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