Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Adjuvant Sunitinib for High-Risk Uveal Melanoma

February 2018

Primary uveal melanoma is the most common primary intraocular malignancy in adults, and effective adjuvant treatment is lacking. Despite definitive treatment of the primary tumor, systemic metastases occur in up to 50% of patients. **Valsecchi et al.** performed a retrospective study of patients with high-risk primary uveal melanoma to compare survival rates between those who received adjuvant sunitinib and those who did not (institutional historical controls). The adjuvant treatment produced promising results that warrant investigation in prospective studies.

For their study, the authors utilized records from the uveal melanoma cytogenetic database of the Wills Eye Hospital Oncology Service.

Outcomes for adults who received adjuvant sunitinib for 6 months (n = 54; median age, 56 years) were compared with outcomes for historical controls in the same risk category (n = 74; median age, 62 years). Kaplan-Meier and Cox proportional hazards models were used to assess overall survival, and propensity scores were used to adjust for nonrandom assignment to sunitinib therapy.

Patients in the sunitinib group exhibited worse cytogenetic or molecular features, had smaller tumors, and were younger. There were 51 deaths: 14 (26%) in the sunitinib group and 37 (50%) among controls. According to univariate analysis, patients treated with sunitinib had longer survival (hazard ratio, 0.53; p = .041). Multivariate Cox regression analysis showed a significant relationship between sunitinib use and age as a dichotomous variable (p = .003).

Factors that were significant in predicting overall survival were cytogenetic/molecular status (p = .015), T-size category (p = .022), gender (p = .040), and adjuvant sunitinib in patients under 60 years of age (p = .004). These findings were confirmed by propensity score analysis.

Although adjuvant sunitinib was associated with longer survival in this study, the findings are limited by the retrospective nature of the research. As a follow-up to this work, the authors are conducting a randomized noncomparative trial of sunitinib and valproic acid. Data obtained from that trial will dictate whether a placebo-controlled study of adjuvant sunitinib should be considered.

Challenges of Type I Boston Keratoprosthesis in Children

February 2018

The Boston type 1 keratoprosthesis (KPro) has become a viable alternative to traditional penetrating keratoplasty (PKP) to treat severe corneal pathology in adults, but little data exist on its use in children.

In a multicenter study, **Fung et al.** documented outcomes and complications of Boston type 1 KPro implantation in children and noted that the procedure is associated with multiple challenges and poor outcomes.

Their study involved reviewing records of patients younger than 17 years of age who underwent KPro surgery at 1 of 3 ophthalmology centers in Canada between January 2010 and November 2014. All procedures were performed by an experienced cornea surgeon. Data were collected and analyzed, including preoperative characteristics, intraoperative complications, postoperative complications, device retention, and best-corrected visual acuity (BCVA).

Before surgery, BCVA ranged from 20/600 to light perception. All of the patients had been diagnosed as having glaucoma, and glaucoma drainage devices (GDDs) had been inserted in 6 eyes before KPro implantation.

The KPro device was implanted in 11 patients (11 eyes) and was the primary corneal procedure in 6 of them. At the most recent exam (mean follow-up, 41.8 months; range, 6.5-85.0 months), 2 eyes had retained their preoperative

BCVA, and 5 eyes lost light perception. Postoperative complications included retroprosthetic membrane (9 eyes), corneal melt (5 eyes), retinal detachment (5 eyes), infectious keratitis (3 eyes), endophthalmitis (3 eyes), and GDD erosion (2 eyes). The initial KPro device was retained in only 4 eyes (36.4%).

This study shows that KPro surgery in children is a major undertaking that can produce permanent and irreversible changes to ocular anatomic features. The authors do not advocate using it in the pediatric population, and all 3 centers involved in this study have stopped offering KPro surgery for children with corneal opacification.

Because the distance between the lens and cornea is short in children, the procedure routinely requires lensectomy and anterior vitrectomy and may warrant subtotal iridectomy and GDDs. Therefore, KPro implantation could subject children to lifelong follow-up, long-term use of topical antibiotics, and perpetual risk of sight-threatening complications.

Intravitreal Bevacizumab or Laser for ROP: 4-Year Outcomes

February 2018

As the survival rate for infants with very low birth weight has increased, so have concerns about improving long-term outcomes for retinopathy of prematurity (ROP). Laser ablation is still the standard of care for ROP, but anti–vascular endothelial growth factor (VEGF) drugs, including intravitreal bevacizumab, have generated interest. To compare long-term outcomes of ROP treatment, **Lepore et al.** conducted a follow-up study of infants born prematurely with type 1, zone 1 disease who had received bevacizumab or undergone laser photoablation. They found that serious ocular effects were more likely to remain in bevacizumab-treated eyes.

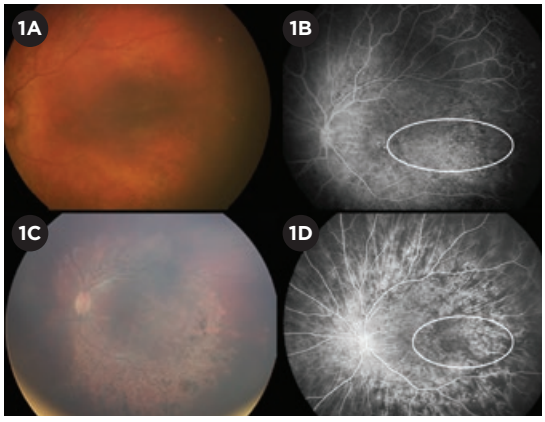
The authors' randomized trial was conducted at Catholic University in Rome from September 2009 through March 2012. Twenty-one infants (42 eyes) received laser photoablation of the peripheral avascular retina in 1 eye and an injection of bevacizumab 0.5 mg in the other. Fluorescein angiography (FA) was performed before and 9 months after treatment. At an average of 4 years after treatment, additional digital retinal and FA images were obtained. Two ROP experts assessed images of 20 eyes in the bevacizumab group and 19 in the laser group for retinal and choroidal features.

At 4 years of age, abnormalities persisted in many bevacizumab-treated eyes, including vessel leakage (13 of 19 eyes), abnormal vessel branching (17 of 20 eyes), vascular tangles (15 of 18 eyes), and shunts (17 of 18 eyes). The authors attributed these problems to ongoing circulation issues. In contrast, fewer laser-treated eyes showed vessel leakage (1 of 18 eyes), abnormal shunts (2 of 19 eyes), or tangles (1 of 18 eyes). No branching abnormalities were observed in this group.

Moreover, at the posterior pole, hyperfluorescent lesions persisted in 55% of bevacizumab-treated eyes and 16% of laser-treated eyes.

The authors noted that many of these outcomes are "worrisome," but they emphasized the importance of FA in identifying unresolved abnormalities. Modalities such as FA and optical coherence tomography could become instrumental in selecting eyes for treatment and determining the timing of interventions. The authors urged clinicians to consider systemic as well as ocular health in their efforts to optimize treatment for infants with serious ROP.

—Summaries by Lynda Seminara



ROP. *Color fundus (1A) and FA (1B) 9 months after bevacizumab injection, with an area of retinal capillary hypoperfusion evident (white circle). Four years later, significant pigmentary abnormalities are evident at the posterior pole (1C), as is a persistent lesion on FA (1D, white circle).*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Serum VEGF Levels and Anti-VEGF Drugs: Results From IVAN

February 2018

Rogers et al. set out to evaluate the potential impact of serum vascular endothelial growth factor (sVEGF) in patients who have neovascular age-related macular degeneration (AMD) and received intravitreal injections of anti-VEGF drugs. In addition, they sought to determine whether there were any associations between sVEGF levels and systemic serious adverse events (SSAEs), notably those of an arteriothrombotic or immunologically mediated nature.

The researchers found that patients who received bevacizumab experienced a greater decrease in sVEGF than did those who received ranibizumab but that this difference was eliminated when treatment ceased for ≥ 3 months. In addition, they found that higher sVEGF levels increased the likelihood that a patient would experience an arteriothrombotic SSAE, while bevacizumab was more likely to raise the risk of an immunologically mediated SSAE.

For this study, the researchers performed an exploratory analysis of data from the IVAN trial, which was conducted in the United Kingdom.

IVAN (Inhibit VEGF in Age-related choroidal Neovascularization) enrolled 610 patients with wet AMD, who were randomized to receive either bevacizumab or ranibizumab. At month 3, after receiving 3 treatments, they were further randomized to either continuous (monthly) dosing or discontinuous treatment (given on an as-needed basis, with those who restarted treatment

mandated to receive 3 consecutive monthly injections). Follow-up extended to 2 years.

Average sVEGF levels were higher in women than in men and in participants who had a history of deep vein thrombosis or pulmonary embolism—and lower in those with a history of myocardial infarction or stroke (including transient ischemic attacks). They did not differ at baseline by age, smoking status, history of heart failure, or diabetes.

On average, sVEGF decreased from a geometric mean of 169 picograms (pg)/mL at baseline to 64 pg/mL at month 24. The decrease was greater in those who received bevacizumab and was apparent by month 1. However, at months 12 and 24, sVEGF levels were similar for the 2 drugs for patients who were 3 months out from treatment.

With regard to SSAEs, 161 of the patients experienced at least 1 SSAE during the trial. Of these, 53 had an arteriothrombotic event and 23 had an immunologically mediated event, and the risk of the latter was higher in those who received bevacizumab. The authors noted that this finding needs to be evaluated in future studies.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Phenotype of Uveitis in Children With Psoriatic Arthritis or Psoriasis

February 2018

Salek et al. pooled the experience of 2 university-based referral centers to begin characterizing the uveitis associated with juvenile psoriatic arthritis and psoriasis. Findings of their study suggest that early-onset juvenile psoriatic arthritis may be a distinct condition, one that is especially severe when it starts before the child is 7 years old.

Study data were collected from Oregon Health & Science University in Portland and the University of Bristol in England. Overall, 6 children were identified (4 boys, 2 girls). Of these, 5 had uveitis and psoriatic arthritis, and 1 had uveitis plus psoriasis. Medical records were reviewed for demographics, descriptions of ocular and joint diseases, medical treatments administered, and complications.

The mean age at presentation was 5.7 years (range, 2-12 years). In 5 of the 6 patients, the disease began before 6 years of age. The uveitis was bilateral in 4 patients. Three patients had anterior uveitis only, and 3 had combined anterior and intermediate uveitis. The response to topical corticosteroids was inadequate in all 6 children. Despite the use of systemic corticosteroids for many months in most of the children, all 6 eventually required methotrexate. Inadequate response to methotrexate resulted in treatment with 1 or more biologic agents in every patient. Five patients underwent at least 1 ophthalmic surgery (e.g., vitrectomy, cataract extraction, glaucoma control).

Although the sample size was small, results indicate that children with psoriasis or psoriatic arthritis occurring by age 6 are at risk for bilateral, chronic, severe uveitis that could warrant biologic therapy as well as surgery.

The differential diagnosis of arthritis associated with psoriasis is extensive. It includes ankylosing spondylitis, reactive arthritis, inflammatory bowel disease, Behçet disease, Kawasaki disease, and sarcoidosis. The authors suggest that early-onset juvenile psoriatic arthritis be added to this list as an entity distinct from other types of psoriatic arthritis.

Scleral Lenses Reduce the Need for Corneal Transplant in Severe Keratoconus

February 2018

Koppen et al. looked at success and failure rates of scleral lens correction for severe keratoconus to determine whether this treatment could be a viable alternative to corneal transplantation. Their research showed that these lenses may spare many patients from the surgery.

The authors' retrospective case series included patients with severe keratoconus (maximal keratometry [Kmax] value ≥ 70 D) who attended the keratoconus clinic at Antwerp University Hospital in Belgium during a 5-year period. Excluded from participation were patients with amblyopia, mental disability, or any concomitant ocular disease that could limit visual potential.

Scleral lens fitting was proposed for 75 eyes; Kmax ranged from 70 to 130 D (mean, 81.70 D). Eight of these eyes underwent corneal transplantation, which was required because of lens intolerance, insufficient visual acuity with the lenses, or problems handling the lenses.

All told, scleral contact lenses were prescribed for 51 of the 75 eyes. The mean gain in visual acuity (scleral lens vs. spectacle-corrected visual acuity) was 0.54 ± 0.18 (decimal fraction, Snellen chart). Seven eyes were lost to follow-up, and lens wear was abandoned in 4 eyes because of the patient's inability to handle the lens. At the most recent follow-up visit, the lens was being worn in 40 eyes (mean follow-up time, 30.15 months).

In summary, 40 (78%) of 51 eyes with severe keratoconus that otherwise would have undergone corneal transplantation were treated successfully with long-term wear of scleral contact lenses.

The authors acknowledge that their keratoconus management strategy, which is focused on specialty contact lenses, may differ from that of other experts. Most importantly, patients should be educated on all treatment options, and the chosen approach should address the unique needs of each person.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Does the Presence of Trainees Have an Effect on the Duration of Patient Appointments?

January 2018

In the current climate of electronic health records (EHR) and value-based reimbursement models, there is constant pressure to improve clinical efficiency. This can be especially challenging for

academic medical centers, where trainees must be educated during the delivery of care. **Goldstein et al.** conducted research at an outpatient ophthalmology clinic and found that the presence of trainees correlated with lengthier appointments.

The single-center cohort study was performed at Oregon Health & Science University in Portland and included 49,448 patient appointments, 33 attending physicians, and 40 trainees. The trainees were residents or clinical fellows in ophthalmology. EHR audit logs were reviewed for time frames of clinical sessions, duration of patient appointments (determined from time stamps), and the presence/absence of a trainee during an appointment or a clinic session. Linear mixed models were devised to address variability among clinicians and patients.

During clinic sessions, patient appointments that involved a trainee were significantly longer than were those without a trainee (mean, 105.0 vs. 80.3 minutes).

Appointments with residents and fellows were 32% and 30% longer, respectively, than appointments without trainees. Presence of a trainee resulted in longer mean appointment times for 29 of the 33 attending physicians, shorter appointment times for 3 physicians, and no change for 1 physician. For all billing levels, trainee presence correlated with longer mean appointment times.

Although the authors acknowledged that study-design limitations can affect data interpretation, their findings highlight the challenge of maintaining efficiency in academic medical centers and raise questions about the suitability of current reimbursement models. The authors hope their work will inspire further research on medical education and clinical workflow, including ways to maximize learning, clinical efficiency, and care quality. They also encourage policy-making discussions of optimal methods to evaluate and reimburse physicians who practice in academic medical centers. *(Also see related commentary by Jennifer L. Lindsey, MD, and Paul Sternberg Jr., MD, in the same issue.)*

Cataract Surgery Reduces Cause-Specific Mortality for Older Women

January 2018

Cataract surgery has been shown to correlate with lower risk of all-cause mortality, potentially because of improved health status and functional independence; however, the association between cataract surgery and cause-specific mortality had not been investigated. To this end, **Tseng et al.** aimed to determine the relationship between cataract surgery and total and cause-specific mortality in older women. Results of their study indicate that this surgery may lower the mortality risk associated with systemic illnesses.

The study included nationwide data of the Women's Health Initiative (WHI), from July 2014 through September 2017, for women ≥ 65 years of age who had cataract. Cataract surgery was determined by Medicare claim codes. Outcomes of interest were all-cause mortality and mortality attributed to cancer, vascular, accidental, neurologic, pulmonary, and infectious causes.

The log-rank test and Cox regression models were used to compare mortality data for patients who did and did not undergo cataract surgery, with adjustments made for demographics, smoking status, alcohol use, body mass index, physical activity, and systemic and ocular comorbidities.

Of the 74,044 women with cataract (mean age, 70.5 years), 41,735 underwent cataract surgery. The crude incidence of all-cause mortality was 1.52 per 100 person-years in the cataract surgery group and 2.56 per 100 person-years in the cataract diagnosis group. Covariate-adjusted Cox models showed a link between cataract surgery and reduced all-cause mortality (adjusted hazards ratio [AHR], 0.40) and between cataract surgery and mortality related to cancer (AHR, 0.31), vascular (AHR, 0.42), accidental (AHR, 0.44), neurologic (AHR, 0.43), pulmonary (AHR, 0.63), and infectious (AHR, 0.44) diseases.

It is unclear whether the favorable associations relate directly to cataract surgery. Patients who underwent the surgery had a much lower mortality rate, despite their overall sicker systemic profile. The authors hypothesize that the mechanism of association is multifactorial and can vary by systemic condition. Whether a patient receives cataract surgery depends on demographic, socioeconomic, and other factors, which warrant exploration. Further study of the relationship between cataract surgery, systemic disease, and disease-related mortality may improve patient care and overall health outcomes. *(Also see related commentary by Justine R. Smith, FRANZCO, PhD, in the same issue.)*

Trial of Dexamethasone Plus Ranibizumab for Persistent DME

January 2018

Although anti–vascular endothelial growth factor (anti-VEGF) therapy is often effective for diabetic macular edema (DME), some patients experience persistent edema and decreased visual acuity despite monthly injection. In a phase 2 randomized clinical trial, **Maturi et al.** added dexamethasone (known to reduce retinal thickening) to ongoing ranibizumab treatment to see if visual outcomes could be improved for patients with persistent DME. After 24 weeks of treatment, visual acuity was no better for patients on combination therapy than for those on ranibizumab alone.

The trial was conducted at 40 U.S. sites between February 2014 and December 2016. Adults who had DME despite ≥ 3 anti-VEGF injections in the previous 20 weeks received 3 additional ranibizumab injections during a 12-week run-in phase. Their visual acuity ranged from 20/32 to 20/320. Eligible patients with persistent DME continued ranibizumab injections and were assigned randomly to receive 700 μg of dexamethasone (combination group) or sham treatment (ranibizumab group). Treatments were administered as often as every 4 weeks, with the schedule based on a structured protocol. The main outcome measure was change in visual acuity letter score from randomization to week 24.

Among the 116 patients (median age, 65 years; 129 eyes), 65 eyes underwent combination treatment and 64 had ranibizumab alone. At 24 weeks, mean (standard deviation [SD]) visual acuity had improved by 2.7 (9.8) letters in the combination group and 3.0 (7.1) letters in the ranibizumab group (adjusted group difference, 0.5 letter; $p = .73$). Mean (SD) change in central subfield thickness was 110 (86) and 62 (97) µm, respectively (adjusted group difference, 52; $p < .001$). Increased intraocular pressure or initiation of antihypertensive eyedrops was reported for 29% of eyes in the combination group and for 0 eyes in the ranibizumab group ($p < .001$).

Despite the significantly greater reduction in retinal thickness in the combination group, adding dexamethasone to ranibizumab treatment did not lead to greater improvement in vision in patients with persistent DME compared to ranibizumab with a sham dexamethasone injection.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Do Hyperreflective Dots on SD-OCT Predict Response to Macular Edema Treatment?

Investigative Ophthalmology & Visual Science
2017;58:5958-5967

Methods to predict therapeutic response may prevent unnecessary treatment and improve outcomes for patients with macular edema. **Hwang et al.** aimed to determine whether the quantity of hyperreflective dots (HRDs) on spectral-domain optical coherence tomography (SD-OCT) at baseline could indicate treatment response to intravitreal bevacizumab or dexamethasone injections in eyes with macular edema. They found that correlations exist but are different for the 2 therapies.

The authors' retrospective study included 82 eyes with diabetic macular edema (DME) and 68 eyes with macular edema from retinal vein occlusion (RVO). Patients with treatment-naïve macular edema initially received 3 consecutive bevacizumab injections, and treatment response was documented. Following these injections, nonresponders received dexamethasone. HRDs were counted manually and independently by 2 masked retina specialists. The authors documented treatment response in relation to best-corrected visual acuity (BCVA), number of HRDs, and incidence of outer plexiform layer (OPL) disruption.

Thirty-six eyes with DME (43.9%) and 22 with RVO (32.4%) did not respond to bevacizumab. The number of baseline HRDs in bevacizumab nonresponders (DME, 16.06 ± 6.60; RVO, 14.23 ± 4.09) was significantly greater than in responders (DME, 11.26 ± 3.64, $p < .001$; RVO, 11.17 ± 4.83, $p = .013$) and did not decline after bevacizumab treatment. Eyes that responded to dexamethasone but not to bevacizumab had significantly more baseline HRDs than eyes that did not respond to either treatment (19.56 ± 6.75 vs. 11.50 ± 3.78; $p = .006$). The OPL disruption rate was significantly higher for bevacizumab nonresponders than responders (DME, $p < .001$; RVO, $p = .001$). BCVA improved in bevacizumab responders but not in bevacizumab nonresponders.

In summary, the number of HRDs on baseline SD-OCT may indicate whether macular edema will improve with intravitreal bevacizumab or dexamethasone. In bevacizumab responders, the number of HRDs was small. The larger number of HRDs in dexamethasone responders may reflect greater inflammation of the retina. Hence, the latter treatment may be most effective in eyes that exhibit many HRDs and OPL disruptions. Large-scale prospective studies that include automated quantification of HRDs are encouraged.

Prospective Trial of Corneal Reconstruction With Biomaterial-Free COMECs

Cornea
2018;37(1):76-83

Conventional therapeutic options for limbal stem cell deficiency (LSCD) are allogenic limbal graft transplantation and autologous conjunctivolimbal graft from the contralateral eye. However, regenerative medicine involving adult stem cells for ocular reconstruction is gaining popularity. **Kim et al.** studied the efficacy and safety of transplanting biomaterial-free cultured oral mucosal epithelial cell sheets (COMECs) for ocular reconstruction in patients with total LSCD. Their findings indicate that the procedure is generally safe and efficacious for this purpose.

For this prospective trial, which was conducted in Seoul, South Korea, the researchers included 8 patients with complete LSCD. COMECs were prepared in a culture system without temperature-sensitive polymers or carriers. The sheets were transplanted but not sutured. After transplant stabilization, 4 patients underwent penetrating keratoplasty. During the subsequent 6 months, the authors documented stability of epithelialization, changes in visual acuity, and postoperative complications. Immunofluorescent staining of corneal cytokeratins (K) was conducted for the patients who underwent penetrating keratoplasty.

The ocular surface was successfully reconstructed in 6 eyes. Complete stable epithelialization was achieved in a mean of 53.6 days. Five eyes had visual improvement of ≥ 2 lines. The procedure failed in 2 eyes, which exhibited full symblepharon in all 4 quadrants. Following keratoplasty, the corneal phenotypic marker (K12) and mucosal phenotypic markers (K4 and K13) were well expressed, suggesting that COMECs acquire part of the corneal phenotype. K1, K8, and K19 showed minimal expression. No ocular infections or noteworthy systemic complications were reported. Finally, local tumor formation was not observed in any patient.

Although these findings indicate that transplantation of biomaterial-free COMECs is generally effective and safe for reconstructing the ocular surface in patients with LSCD, it may be prudent to exclude candidates who have complete symblepharon in all 4 quadrants. Meticulous postoperative care is crucial to maintain stability of the COMECs and to optimize overall outcomes.

—Summaries by Lynda Seminara