Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

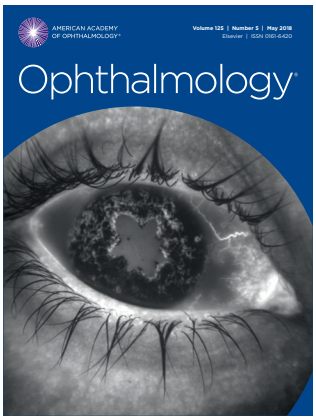
Primary Tube or Trabeculectomy for Glaucoma: 1-Year Outcomes

May 2018

Gedde et al. reviewed 1-year treatment outcomes of the primary tube versus trabeculectomy (PTVT) study and found that trabeculectomy plus mitomycin C (MMC) achieved greater success than did tube-shunt surgery.

This multicenter randomized study included 242 patients (242 eyes) with medically uncontrolled glaucoma and no previous incisional ocular surgery. Patients were enrolled at 1 of 16 centers and were assigned randomly to receive a tube shunt (350-mm^2 Baerveldt glaucoma implant; n = 125) or trabeculectomy and MMC (0.4 mg/mL for 2 minutes; n = 117). Outcome measures were intraocular pressure (IOP), number of glaucoma medications, visual acuity, visual field findings, surgical complications, and treatment failure. Failure was defined as any of the following: IOP > 21 mm Hg or reduced by 20% or less from baseline on 2 consecutive follow-up visits after 3 months, IOP ≤ 5 mm Hg on 2 consecutive follow-up visits after 3 months, reoperation for glaucoma, or loss of light-perception vision.

The cumulative probability of failure in the year of follow-up was 17.3% for the tube group and 7.9% for the trabeculectomy group. At 1 year, the mean (± standard deviation [SD]) IOP was 13.8 (4.1) mm Hg for those with a tube shunt and 12.4 (4.4) mm Hg for those with trabeculectomy. The number of glaucoma medications (± SD) at 1 year was 2.1 (1.4) in the tube group and 0.9 (1.4) in the trabeculectomy group.



Postoperative complications occurred in 29% of tube recipients and 41% of trabeculectomy cases. Serious complications resulting in reoperation or a loss of at least 2 Snellen lines occurred in 1 patient (< 1%) in the tube group and 8 (7%) in the trabeculectomy group.

In general, the minimally invasive glaucoma procedures introduced in recent years have been less effective than tubes or trabeculectomy for lowering IOP. The authors stressed that selecting a suitable glaucoma operation involves considering risk/benefit profiles on a case-by-case basis, and they noted that they plan to report 3- and 5-year outcomes of the PTVT study.

Real-World Effect of Anti-VEGF Drugs on IOP

May 2018

In a review of IRIS Registry data, **Atchison et al.** looked at intraocular pressure (IOP) in eyes treated with an anti–vascular endothelial growth factor (anti-VEGF) agent and compared that with IOP levels in untreated fellow eyes. They found that treatment generally resulted in a small but significant decrease in IOP; however, some treated eyes had substantial elevation of IOP.

For their study, the authors identified 23,776 patients who received at least 12 injections of a single anti-VEGF drug (aflibercept, bevacizumab, or ranibizumab) in their right eye. Left eyes were not treated. Diagnoses were neovascular age-related macular degeneration (AMD) only (73%), diabetic macular edema only (12%), vein occlusion with macular edema (11%), and a combination of these conditions (4%). The minimum follow-up period was 1 year.

Primary outcome measures were IOP change from baseline and the proportion of eyes with a clinically significant increase in IOP, defined as a sustained increase of at least 6 mm Hg resulting in IOP > 21 mm Hg. Subgroup analyses were conducted among patients with AMD only and patients who did not have anti-VEGF treatment in the year before study entry.

Mean IOP declined from baseline to ≥ 1 year in all treatment arms, including subsets. Overall, the mean decrease was 0.9 mm Hg for treated eyes and 0.2 mm Hg for untreated eyes. A generalized linear model accounting for confounders showed that, in most groups, the degree of IOP lowering was less with bevacizumab than with aflibercept or ranibizumab.

Clinically significant increases in IOP were sustained in 2.6% of treated eyes and 1.5% of untreated eyes; the rates by treatment were 1.9% for aflibercept, 2.8% for bevacizumab, and 2.8% for ranibizumab. The increases in untreated eyes were significantly lower than in eyes treated with bevacizumab and ranibizumab, but not with aflibercept. The reason for this difference is unclear and requires further investigation. Aflibercept is the only drug in this study with affinity for placental growth factor, which could affect the trabecular meshwork in a manner that is not yet known.

10-Year Review of Liability Claims in Ophthalmology

May 2018

Thompson et al. assessed closed medical professional liability claims against ophthalmologists in the United States and found that 24% of claims resulted in payment. Two-thirds were dropped, withdrawn, or dismissed. Cataract and corneal surgeries were the most common claims-related procedures. The average cost associated with liability claims was lower for ophthalmology than for the average of all health specialties combined.

For their study, the authors obtained 10-year data from the Physician Insurers Association of America data-sharing project. They gathered details of claims in ophthalmology and claims for all health specialties, including physician demographics, prevalence rates, associated costs, resolutions, and various medical factors. They also compared data for the first 5 years (2006-2010) and latter 5 years of the study (2011-2015).

During the full 10-year period, 90,743 liability claims were closed, and 24,670 were paid. Of these, only 2.6% of closed claims and 2.2% of all paid claims were against ophthalmologists. Among the ophthalmology claims with a verdict, 90% favored the ophthalmologist. Cataract and corneal surgeries were the most common and costly surgeries in this dataset, accounting for 50% of ophthalmology claims and for $47,641,376 and $32,570,148 (respectively) in total paid indemnity. The average indemnity was higher for corneal procedures ($304,476) than for vitreoretinal procedures ($270,141) or oculoplastic procedures of the eyelid ($222,471) or the orbit and eyeball ($183,467). The chief medical factors prompting claims against ophthalmologists were improper performance, error in diagnosis, and failure to recognize a complication of treatment.

Between the first and second 5-year periods, the prevalence and cost of claims related to endophthalmitis declined: from 38 (3.3%) of 1,160 (average indemnity, $516,875) to 26 (2.2%) of 1,165 (average indemnity, $247,083). The average indemnity paid and amount spent on legal defense was lower for ophthalmologists than for all health specialists combined (indemnity: $280,227 vs. $335,578; legal: $41,450 vs. $46,391).

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Ziv-Aflibercept for Diabetic Macular Edema

May 2018

Ziv-aflibercept, a recombinant fusion protein, has a mechanism that is similar in action to that of aflibercept—and is available at a lower cost than the proprietary anti–vascular endothelial growth factor (VEGF) drug. **Bonyadi et al.** set out to evaluate 2 doses of ziv-aflibercept and compare them with intravitreal bevacizumab for the treatment of center-involving diabetic macular edema (DME). They found that patients who received ziv-aflibercept improved more than those who received bevacizumab, with the caveat that the greatest improvement was noted in those eyes that had the worst visual acuity (VA) at baseline.

For this 1-year double-blind study, the researchers randomly assigned 123 eyes with center-involving DME to 1 of 3 arms: 1) 2.5 mg of intravitreal ziv-aflibercept (n = 42); 2) 1.25 mg of intravitreal ziv-aflibercept (n = 42); and 3) 1.25 mg of intravitreal bevacizumab (n = 39). Initially, all patients were treated every 4 weeks for 3 loading injections. After that, patients in the bevacizumab cohort were treated every 4 weeks, while those in the 2 ziv-aflibercept cohorts were treated every 8 weeks. The main outcome measure was change in best-corrected VA (BCVA) at 1 year.

At final follow-up, BCVA was superior in the ziv-aflibercept patients to that of those who received bevacizumab, with mean improvements of 16 and 18 ETDRS letters found for ziv-aflibercept 2.5 mg and 1.25 mg, respectively, versus 14 letters for bevacizumab. This effect was pronounced in those patients who had worse levels of vision at baseline (defined as ≤ 20/50)—improvements of 24, 25, and 14 letters were found for the 2.5-mg ziv-aflibercept, 1.25-mg ziv-aflibercept, and bevacizumab groups, respectively.

With regard to central macular thickness (CMT), the final measurement was less than 250 µm in 64.7% of those who received 2.5 mg of ziv-aflibercept, 53.3% of the 1.25-mg ziv-aflibercept cohort, and 40% of those who received bevacizumab.

All told, those who received 2.5 mg of ziv-aflibercept were given an average of 6.71 injections, versus 6.67 injections in the 1.25-mg ziv-aflibercept arm and 11.56 in the bevacizumab arm. No cases of major ocular or systemic complications were noted.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

POAG Progression and Diabetes

May 2018

Risk factors for glaucoma progression have not been clearly defined, and there is long-standing debate on the role of type 2 diabetes mellitus (DM) in primary open-angle glaucoma (POAG). Elevated intraocular pressure and impaired vascular supply to the optic nerve head have both been implicated in the pathophysiology of POAG—and as type 2 DM has been thought to involve both pathogenic processes, it may be a risk factor for POAG.

With this in mind, **Hou et al.** compared rates of visual field (VF) loss

and retinal nerve fiber layer (RNFL) thinning for patients with POAG and found no difference in VF progression between patients without type 2 DM and those who had type 2 DM with undetectable diabetic retinopathy. They also found that treated DM was linked to significantly slower loss of RNFL thickness.

This study included 197 eyes. The POAG/DM group consisted of 55 eyes (32 patients) and the POAG-only group included 142 eyes (111 age-matched patients). Participants had been enrolled in the Diagnostic Innovations in Glaucoma Study; those with type 2 DM were identified by self-reporting a history of DM and use of medication for diabetes. Univariate and multivariable mixed-effects models were applied to compare rates of VF loss and RNFL loss between the study groups. Median follow-up time was 5.7 years.

Results showed that the mean rate of global RNFL loss was 2-fold slower in the POAG/DM group (–0.40 vs. –0.83 µm per year; p = .01). The POAG/DM group also had slower rates of VF mean deviation and pattern standard deviation loss, but the between-group differences were not significant.

The global and sectoral RNFL thinning rates for metformin users and nonusers in the POAG/DM group were compared to determine whether metformin could have a protective effect, but no significant difference was observed. Not surprisingly, most subjects in the POAG/DM group (84.4%) were taking metformin (solo or combined), so the subanalysis is limited by the small sample of nonusers.

If glaucoma is diabetes of the brain, which has been proposed by some investigators, insulin and other diabetes medications might be remedies for glaucoma. Research is needed to address this topic and assess whether such treatments could protect against glaucomatous damage.

Culture Results May Guide Treatment of Severe Fungal Keratitis

May 2018

In a secondary analysis of data from the Mycotic Ulcer Treatment Trial–II (MUTT–II), **Ray et al.** aimed to identify patients with fungal keratitis who are at risk of poor outcomes and thus may benefit from aggressive treatment and additional monitoring. They found that patients with positive (vs. negative) cultures on day 6 had a 2-fold greater risk for corneal perforation or the need for therapeutic penetrating keratoplasty (PK).

For this secondary analysis, the researchers included patients with smear-positive filamentous fungal ulcer and visual acuity (VA) of 20/400 or worse at presentation, at which time medical therapy was started. Using backward stepwise regression with covariates for baseline traits, the authors compared clinical outcomes between patients who had positive cultures and those who had negative cultures on day 6. The primary outcome measure was the rate of corneal perforation and/or need for therapeutic PK. Secondary outcomes included 3-month best spectacle-corrected VA (BSCVA), size of infiltrate/scar at 3 months, and rate of re-epithelialization.

The analyses showed that, even after controlling for baseline ulcer characteristics, patients with positive cultures on day 6 had twice the hazard of experiencing corneal perforation or needing therapeutic penetrating keratoplasty (p = .002) than patients with negative cultures. Moreover, culture positivity correlated with poorer BSCVA at 3 months (average of 0.26 logMAR lines worse than for patients with negative cultures; p = .001). However, a positive culture on day 6 was not predictive of infiltrate/scar size or the time to re-epithelialization.

Hence, 6-day culture results may be a valuable tool for making treatment decisions for patients with severe fungal keratitis. Findings of repeat cultures may be useful for risk stratification and for identifying patients at high risk of poor outcomes. Culture positivity is an objective indicator of response to medical therapy. The authors stated that this research, coupled with their earlier findings for less severe ulcers, represents the advent of a new standard of care for fungal keratitis.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Anti-VEGF for Macular Edema: Monthly or Treat-and-Extend?

April 2018

In a randomized clinical trial, the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) established that, in the first 6 months of treatment, bevacizumab, on average, does not result in inferior visual acuity (VA) outcomes when compared to aflibercept for managing macular edema from central retinal or hemiretinal vein occlusion.

In a subsequent analysis of SCORE2 data among the participants who exhibited a good response to 6 months of monthly injections, **Scott et al.** compared monthly and treat-and-extend (TAE) regimens of aflibercept or bevacizumab. They found that TAE was associated with fewer injections and no meaningful differences in VA between the treatment schedules. Nonetheless, they advised that—because of the wide confidence intervals on VA differences between these 2 retreatment regimens—caution is warranted before concluding that the 2 treatment schedules are associated with similar vision outcomes.

For this analysis, participants with a protocol-defined good response to monthly injections in the first 6 months of SCORE2 continued on aflibercept or bevacizumab after random assignment to a monthly or TAE schedule. The primary outcome was difference in best-corrected VA letter score (VALS) from month 6 to month 12.

At month 12 in the aflibercept arm, the mean VALS was 72.7 (approximately 20/40) in the monthly group (n = 79) and 71.6 (approximately 20/40) in the TAE group (n = 80), with a mean improvement of 0.8 letters in the monthly group and a mean decline of 1.2 letters in the TAE group. The between-group difference in VALS change was 1.88 letters (97.5% confidence interval [CI], –1.07 to 4.83). At month 12 in the bevacizumab arm, mean VALS was 75.2 (approximately 20/32) in the monthly group (n = 67) and 74.0 (approximate-

ly 20/32) in the TAE group (n = 67), with mean decreases of 1.6 and 0.4 letters, respectively. The between-group difference in VALS change was 1.98 letters (97.5% CI, –1.08 to 5.03 letters). In both treatment arms, more injections were administered in the monthly group than the TAE group (aflibercept: 5.8 vs. 3.8 injections, respectively; bevacizumab: 5.8 vs. 4.5 injections, respectively). *(Also see related commentary by Jennifer K. Sun, MD, MPH, in the same issue.)*

Unmet Psychosocial Needs of Adults With Uveal Melanoma

April 2018

Williamson et al. researched the type and frequency of medical, psychosocial, and sociodemographic factors associated with unmet needs of patients with uveal melanoma. In their study, nearly all patients had at least 1 unmet need in the week following diagnosis. Although the severity of these unmet needs subsequently declined, they did not vanish altogether, as most patients reported having the same concerns several months later. Psychosocial support represented the greatest domain of unmet needs.

The study included 107 patients (mean age, 59 years) with uveal melanoma diagnosed by an ophthalmologist. Patients used the Cancer Needs Questionnaire to report their unmet needs 1 week after diagnosis and 3 months later. Eighty-six patients completed the questionnaire at 1 week, and 82 patients completed it 3 months later.

One week after diagnosis, 99% of patients noted at least 1 unmet need. Three months later, 86% reported at least 1 unmet need. The most common concerns pertained to health information and psychosocial support. Although the number of unmet needs declined during the 3-month period, the severity of sociodemographic and medical factors remained similar. Prediagnosis factors found to correlate with lower severity of unmet needs 1 week after diagnosis were greater instrumental social support and lower neuroticism.

Although large social networks are often thought to lead to more robust emotional health, the opposite proved true in this study, as having a smaller social network correlated with lower severity of unmet needs at the 3-month assessment and a decline in needs during the 3-month period. Patients with large interactive social networks may be overwhelmed by the magnitude of available information, and smaller social networks may offer support that is better suited to the patient's unique needs, the authors suggested.

Findings of this study suggest that needs assessments may promote early identification of patients in greatest need of supportive care. The authors encouraged testing of interventions that target health information and psychological factors, particularly neuroticism. Ensuring social support, such as transportation to medical appointments, also may be helpful. *(Also see related commentary by Zélia M. Corrêa, MD, PhD, in the same issue.)*

Race and Glaucoma Progression

April 2018

In a multicenter longitudinal study of visual field changes in Europeans and Africans with glaucoma, **Gracitelli et al.** found that African descent is linked to larger variability in standard automated perimetry results and greater time to detect disease progression.

Participants were enrolled from the Diagnostic Innovations in Glaucoma Study and the African Descent and Glaucoma Evaluation Study; 173 patients (236 eyes) were of European descent and 171 (235 eyes) were of African descent. Mean baseline age was similar for the study groups, as was gender distribution. Differences in test-retest variability were investigated, and the simulated time to detect glaucoma progression was estimated. For each eye, standard automated perimetry mean deviation values were regressed over time, and the standard deviation (SD) of residuals was used as a measure of variability. Distributions of residuals were used in computer simulations to reconstruct real-world standard automated perimetry mean deviation trajectories under different assumptions for change rates and testing schedules. The mean follow-up period was 7.5 years.

The mean (SD) of residuals was found to be larger for eyes in the African group: 1.45 (0.83) dB versus 1.12 (0.48) dB in the European group (mean difference, 0.33 dB). As glaucoma progressed, those of African descent were more likely to have a greater increase in visual field variability. Disease progression was detected earlier in the European group, as demonstrated by simulation analyses. For a scenario with baseline mean deviation of –10 dB and a change rate of –0.5 dB/year, progression detection was delayed by 3.1 years in the African group (assuming 80% power and annual testing).

This research adds to previous studies of the high prevalence of glaucoma-related visual impairment among people of African descent. The high variability in visual field test-retest results can prolong detection of progression. To avert this, the authors suggested increasing the frequency of testing, which may yield better estimates of change indices over time; using complementary methods to assess progression; and combining structural and functional testing. *(Also see related commentary by Eve J. Higginbotham, SM, MD, in the same issue.)*

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Clear Lens Extraction for PACG in EAGLE

British Journal of Ophthalmology
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Refractive outcomes for eyes with primary angle-closure glaucoma (PACG) that undergo lens extraction can be unpredictable because of anatomic features such as shallow anterior chamber depth, short axial length, and a thickened lens positioned anteriorly. In the EAGLE study (Effectiveness in Angle-closure Glaucoma of Lens Extraction), patients with PAC/PACG who were treated with clear lens extraction (CLE) had better quality of life and control of intraocular pressure than

their counterparts who received laser peripheral iridotomy (PI).

In a subsequent report, **Day et al.** described the surgical details, visual outcomes, and postoperative refractive errors of EAGLE participants who received CLE. They concluded that CLE is appropriate for some patients with PAC or PACG, but they emphasized the importance of individualized treatment, as CLE may result in suboptimal refractive outcomes in some eyes.

In the original study, eligible patients were assigned randomly to receive CLE or PI. The CLE group underwent phacoemulsification and implantation of a monofocal intraocular lens (IOL) within 60 days of randomization. Synechiolysis was permitted in accordance with local practice.

In this subsequent review, the authors reported postoperative corrected distance visual acuity (CDVA) at 36 months for the CLE group (n = 208). Collected data included the IOL formula and predicted refraction. Laser biometry was used to estimate axial length and IOL power.

Mean baseline CDVA was 77.9 letters (± standard deviation [SD], 12.4) and did not change significantly by month 36 (mean CDVA, 79.9; SD, 10.9). Spherical equivalents were +1.7 D (SD, 2.3) preoperatively and +0.08 D (SD, 0.95) at 36 months.

Overall, by 3 years postoperatively, 59% of eyes were within ± 0.5 D of their predicted refraction, and 85% eyes were within ± 1.0 D of that goal. Axial length < 22 mm correlated with outcomes that varied by > 1 D from predictions.

Although the mean CDVA of patients who underwent clear lens extraction for PACG appeared stable in the ensuing 3 years, and refractive error improved, the predictability of refractive outcomes was less than optimal, the authors said.

—Summary by Lynda Seminara

AI, Transfer Learning, and Retinal Disease

Cell
2018;172(5):1122-1131

Artificial intelligence (AI) systems typically employ a highly specialized deep learning machine and a dataset of millions of images. **Kermany et al.** evaluated a new deep learning framework that uses transfer learning, thus allowing these systems to use a smaller dataset of images. They found that their system effectively classified spectral-domain optical coherence tomography (SD-OCT) images of age-related macular degeneration and diabetic macular edema (DME), matching the proficiency of human experts.

For the study, a dataset of 108,312 SD-OCT images from 4,686 patients was used to train the deep learning framework. The model was then tested with a validation dataset of 1,000 images from 633 patients, with the images evenly drawn from image subsets of choroidal neovascularization (CNV), DME, drusen, and no disease.

The AI system categorized the OCT images as "urgent referrals" (those with CNV or DME); "routine referrals" (those with drusen); and "observation" (those with no disease), achieving an accuracy rate of 96.6%, with a sensitivity of 97.8% and specificity of 97.4%. An independent test set of images was used to compare the network's referral decisions with those made by 6 experienced ophthalmologists; the network's performance was comparable to that of the human experts.

The researchers also performed occlusion testing to identify the areas of greatest importance used by their AI system in assigning a diagnosis. They noted that the greatest benefit of occlusion testing is that it sheds light on how neural networks "think," thus making the process more transparent and bolstering confidence in the results. In this study, the occlusion tests confirmed that the AI system made its decisions using accurate distinguishing features.

In a novel twist, the researchers also used their system to evaluate chest x-ray images for the purposes of diagnosing pediatric pneumonia. They found that the system successfully differentiated between viral and bacterial pneumonia, with an accuracy of 92.8%. This demonstrates that the system can be applied to a wide range of medical imaging techniques across multiple medical specialties, they said.

—Summary by Jean Shaw

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