Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

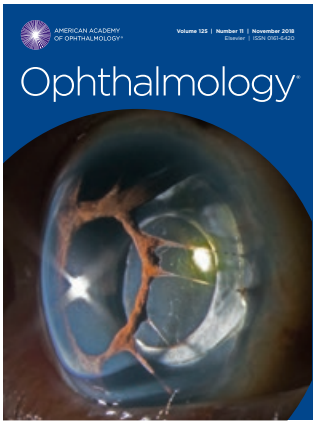
Ophthalmology

Selected by Stephen D. McLeod, MD

Predicting RNFL Thinning in Glaucoma

November 2018

Moghimi et al. investigated potential links between thinning of the retinal nerve fiber layer (RNFL) and baseline vessel density of the macula and optic nerve head (ONH). They hypothesized that the degree of vessel density may predict RNFL thinning of eyes with mild or moderate glaucoma. Their findings suggest that lower macular and ONH vessel density are associated with faster RNFL decline, as measured by spectral-domain optical coherence tomography (SD-OCT).



For this prospective observational study, 83 patients with mild or moderate primary open-angle glaucoma (132 eyes) received follow-up for at least 2 years (average, 27.3 ± 3.36 months). Measurements of macular whole-image vessel density (m-wiVD) and ONH whole-image vessel density (onh-wiVD) were acquired at baseline, using OCT angiography. Measurements of RNFL thickness, minimum rim width, and ganglion cell plus inner plexiform layer thickness were obtained semiannually using SD-OCT. Random-effects models were used to ascertain relationships between vessel density parameters at baseline and the rates of RNFL loss, after adjusting for confounding factors. Outcomes of interest were the effects of m-wiVD and onh-wiVD on rates of RNFL loss.

The average RNFL thickness at baseline was 79.5 ± 14.8 μm, which declined by a mean slope of –1.07 μm per year. In the univariate model, which included just a predictive factor and time plus their interaction, each 1% lower m-wiVD and onh-wiVD was associated with a 0.11-μm per year and 0.06-μm per year faster rate of RNFL decline, respectively. A similar relationship between low m-wiVD/onh-wiVD and faster rates of RNFL loss was observed with other multivariate models. Nevertheless, in this study, the link between vessel density measurements and rate of RNFL loss was weak. In univariate and multivariate analyses, average central corneal thickness predicted faster RNFL decline.

Eyes with advanced glaucoma were not included in the study because their RNFL is unlikely to undergo rapid change. This research offers new insight for glaucoma management and supports the role of OCT parameters in predicting the risk and rate of glaucoma progression. Macular and ONH vessel density may be specific parameters to include in this assessment.

Baseline Influencers of Vision and Edema in Proliferative DR: Ranibizumab Versus PRP

November 2018

In a post hoc analysis of data from randomized multicenter trials, **Bressler et al.** aimed to identify baseline factors associated with change in visual acuity (VA) or development of vision-impairing central-involved diabetic macular edema (DME) occurring after treatment of proliferative diabetic retinopathy (PDR) with ranibizumab or panretinal photocoagulation (PRP).

The study included 328 eyes that received 2 years of follow-up and 302 eyes that did not have vision-impairing central-involved DME at baseline in Protocol S of the Diabetic Retinopathy Clinical Research Network (DRCR.net). The latter eyes were not required to complete the 2-year visit because the analysis incorporated all available and censored data for participants without vision-impairing central-involved DME.

Treatments were intravitreous ranibizumab (0.5 mg/0.05 mL) or PRP. Primary outcome measures were change in VA (area under the curve) and development of vision-impairing (20/32 or worse) central-involved DME during the 2-year period.

After multivariable analysis with adjustment for baseline VA and central subfield thickness, no factors were identified as being relevant to either primary outcome. In the PRP group, worsening VA was more common with higher levels of hemoglobin A_{1c}, greater severity of diabetic retinopathy

(DR), and higher mean arterial pressure. Vision-impairing central-involved DME was more likely to occur in the presence of high hemoglobin A_{1c}, more severe DR, and cystoid defects within 500 µm of the macula center.

Overall, VA improved and vision-impairing central DME was rare with ranibizumab in Protocol S. The analysis suggests that these favorable outcomes occur regardless of baseline factors. However, when PRP is the main treatment for PDR, patients with poor glycemic control or severe DR may be more susceptible to vision-impairing central-involved DME and VA loss than are those with better glycemic control or milder DR, even if the DME is treated with ranibizumab.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Vascular Safety Profile of Ranibizumab

November 2018

Intravitreal anti–vascular endothelial growth factor (VEGF) drugs carry an increased risk of systemic events, including those of a cardiovascular and cerebrovascular nature. **Zarbin et al.** set out to evaluate the vascular safety profile of ranibizumab 0.5 mg relative to sham treatment, with or without verteporfin, in patients with neovascular age-related macular degeneration (AMD). In addition, they compared ranibizumab 0.3 mg to sham and 0.3 mg to 0.5 mg of ranibizumab. They found low rates of vascular events in these patients overall and no clinically meaningful differences between patients treated with ranibizumab and those treated with sham or verteporfin.

For this study, researchers evaluated data from 7 randomized trials (phases 2-4). The pooled dataset comprised 4,080 patients with wet AMD. Of these, 1,764 patients were treated with ranibizumab 0.3 mg, and 1,854 were treated with ranibizumab 0.5 mg. Relevant safety endpoints included arterial thromboembolic events (ATEs), myocardial infarction (MI), stroke, transient ischemic attacks (TIAs), and vascular deaths. Pairwise comparisons for ranibizumab 0.5 mg (the globally approved dosage for wet AMD) and sham or verteporfin were performed using Cox proportional hazard regression and rates per 100 patient-years.

Hazard ratios (95% confidence intervals) included 1, indicating no significant treatment differences, for all endpoints, between ranibizumab 0.5 mg and sham or verteporfin. Although this supports the established risk-benefit profile of ranibizumab in patients with neovascular AMD, the authors noted that extrapolating these findings to the real-world population is limited by the enrollment criteria of the selected studies—and that more data are needed on the systemic safety of anti-VEGF drugs in clinical practice.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Cataract Surgery Alters Corneal Biomechanics and IOP

November 2018

Using the updated Corvis ST tonometer, **Hirasawa et al.** studied the effects of cataract surgery on corneal biomechanics and intraocular pressure (IOP). They noted a decrease in the stiffness parameter at applanation 1 (SP A1) and increases in deformation amplitude maximum (DA max) and integrated radius, suggesting that the cornea is less stiff following cataract surgery.

This prospective, interventional case series included 39 patients (39 eyes) with cataract. Measurements with the Corvis ST tonometer were obtained before surgery and at 1 week, 1 month, and 3 months postoperatively; parameters included DA max, DA ratio max (1 mm and 2 mm), integrated radius, SP A1, Ambrosio relational thickness to the horizontal profile (ARTh), Corvis biomechanical index, central corneal thickness, noncorrected IOP, and biomechanically corrected IOP. In addition, they measured IOP with Goldmann applanation tonometry and a noncontact tonometer. The linear mixed model was used to compare measurements for each time point, with and without adjustment for biomechanically corrected IOP and central corneal thickness.

All IOP measurements decreased over time. Increased central corneal thickness was noted at 1 week and 3 months. Although the Corvis biomechanical index was elevated at 1 week, it returned to preoperative status by 1 month. A decrease in ARTh was observed at 1 week and 1 month; this parameter returned to its preoperative level by 3 months. DA max and integrated radius had increased by month 3, and SP A1 had decreased by this time.

The authors advise caution when applying these results to clinical practice. They noted that 1 week following surgery may be too soon to use the Corvis biomechanical index to identify keratoconus.

Is It Time to Reclassify Large Macular Holes?

November 2018

In the Manchester Large Macular Hole Study, **Ch'ng et al.** looked at anatomic and functional outcomes after vitrectomy for large full-thickness macular holes (FTMH). They found that standard treatment for FTMH is adequate for most holes under 650 µm in diameter.

This retrospective interventional study included 258 eyes with idiopathic large FTMH (diameter >400 µm) treated during a 5-year period. All eyes underwent pars plana vitrectomy (PPV), internal limiting membrane (ILM) peel, gas tamponade, and face-down posturing. The face-down position was maintained for 1-5 days. Anatomic and functional success rates were measured, as was the relationship between the size of the macular holes and their closure.

Anatomic closure was achieved in 90% of eyes. Rates of closure were ≥91% for patients with holes <650 µm. This coincides with the currently accepted success standard of ~90%. Among patients with larger FTMH (650 µm to 1,416 µm), the success rate was only 76%. Maximum sensitivity and specificity were obtained at a cutoff diameter of ≤630 µm (76.7% sensitivity, 69.2%

specificity), yielding a Youden index of 0.46. By 3 months postoperatively, 57% of eyes had improved ≥0.3 LogMAR units from preoperative status.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Five-Year Outcomes of Randomized Trial Comparing Laser with Ranibizumab for PDR

October 2018

Gross et al. compared the efficacy and safety of intravitreous ranibizumab and panretinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR) through 5 years in a randomized clinical trial. They found that visual acuity (VA) was very good for most patients in both study arms, consistent with 2-year outcomes. Rates of vision-impairing diabetic macular edema (DME) were lower in the ranibizumab group.

This study included patients who had enrolled in the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S trial by December 2012. Eyes had been assigned randomly to receive intravitreous ranibizumab (n = 191) or PRP (n = 203). The frequency of ranibizumab treatment was based on a protocol-specified algorithm. The 5-year analysis began in January 2018. The main outcome was the mean change in VA; secondary outcomes included peripheral visual field loss, development of vision-impairing DME, and adverse events.

The 5-year visit was completed for 240 eyes (184 patients), 117 of which received ranibizumab. The mean number of treatments over 5 years was 19.2 in the ranibizumab group (with an average of 3 injections each year in years 2, 3, 4, and 5) and a mean of 5.4 treatments over 5 years in the PRP group. Mean changes in VA letter score were 3.1 and 3.0, respectively, for the ranibizumab and PRP groups. The mean change in cumulative visual field total point score was −330 dB for ranibizumab recipients and −527 dB for patients with PRP. Vision-impairing DME occurred in 27 and 53 eyes, respectively, for a cumulative probability of 22% in the ranibizumab group and 38% in the PRP group (hazard ratio = 0.4; 95% confidence interval [CI]: 0.3-0.7; p < 001).

Despite a mean VA of 20/25 in both groups at 5 years, vitreous hemorrhage occurred in 48% of eyes treated with ranibizumab and in 46% of eyes treated with PRP. Vitrectomy was performed in 11% and 19% of eyes, respectively. Both groups had low rates of iris neovascularization and neovascular glaucoma, although retinal detachment occurred in 6% of the ranibizumab group and 15% of the PRP group. Rates of systemic adverse events were comparable.

The authors note that these findings support either anti–vascular endothelial growth factor therapy or PRP as viable treatments for patients with PDR through at least 5 years and emphasize the importance of considering patient-specific factors when selecting a treatment, including the patient's anticipated likelihood of compliance and overall health status as well as cost issues.

Racial Differences in Long-Term Trabeculectomy Outcomes

October 2018

Evidence indicates that failure after trabeculectomy without antimetabolites is more common among patients of African descent. Although adjunctive use of mitomycin C (MMC) improves the likelihood of success, data are lacking for patients of African descent who have undergone trabeculectomy combined with MMC. To identify prognostic indicators of failure, **Nguyen et al.** compared outcomes of initial trabeculectomy plus MMC between patients of African and European descent and found that those of African descent were more likely to experience failure after trabeculectomy and bleb leak.

In their study, 135 eyes from patients of African descent (n = 105) were matched to 135 eyes from patients of European descent (n = 117). Matching criteria included age (within 5 years), surgeon, lens status, and follow-up time (within 1 year).

Three levels of qualified success were defined as follows:

- For criteria A, final intraocular pressure (IOP) of ≤18 mm Hg with either ≥20% reduction in IOP or reduction of at least 2 medications.
- For criteria B, a final IOP of ≤15 mm Hg and either ≥25% reduction in IOP or reduction of at least 2 medications.
- For criteria C, a final IOP of ≤12 mm Hg or less and either ≥30% reduction in IOP or reduction of at least 2 medications.

Complete success was similarly defined with the additional requirement of no need for glaucoma medication(s).

At 5 years, the qualified success rates for patients of African descent and those of European descent were as follows: For criteria A, 61% versus 67% (difference, 7.3%, 95% confidence interval [CI], 4.4-10.4); for criteria B, 43% versus 60% (difference, 17.6%, 95% CI, 15.2-20.0); and for criteria C, 25% versus 40% (difference, 15.8%, 95% CI, 11.1-20.5). On multivariable Cox regression analyses, being of African descent was associated with higher failure rate for criteria B and C for qualified success and with all criteria for complete success. The incidence of bleb leaks was higher in those of African descent (29 vs. 11 eyes); these patients also required additional glaucoma surgeries more often than did those of European descent (47 vs. 26 eyes).

These results suggest new strategies to control wound healing after trabeculectomy are needed, and the role of nonfiltering glaucoma surgery should be explored in this subpopulation. *(Also see related commentary by Paul Palmberg, MD, PhD, in the same issue.)*

Fellow-Eye Treatment of Open-Angle Glaucoma: CIGTS Results

October 2018

Once it's clear that a patient requires unilateral treatment for open-angle glaucoma (OAG), it may help to know which traits portend disease progression and need for eventual treatment in the fellow eye (FE). In a post hoc analysis of data from the Collaborative Initial Glaucoma Treatment Study (CIGTS), **Niziol et al.** estimated the time between initial treatment of

the study eye (SE) and the need for treatment of the FE. They found that by 7 years after OAG treatment of the SE, roughly two-thirds of patients had undergone treatment of the FE.

In CIGTS, 607 participants with newly diagnosed OAG in at least 1 eye were assigned randomly to receive topical medication or trabeculectomy. FEs were treated when eligible or at the physician's discretion. Data were collected for up to 11 years. Survival analysis was used to estimate the probability of FE treatment over time and to test potential baseline and time-dependent predictors of treatment need. Using linear regression, disease trajectory was calculated as the eye-specific slopes of mean deviation (MD) and intraocular pressure (IOP) over time. In addition, correlations between SE and FE trajectories also were calculated. Main outcomes were time to FE treatment and the slopes over time (MD and IOP) for SEs and FEs.

Among the FEs, 291 (47.9%) were treated at baseline along with SEs, 123 (20.3%) were treated eventually, and 193 (31.8%) did not receive treatment. The probability of FE treatment for OAG was 0.57 by year 1 and 0.68 by year 7 after SE randomization. Correlations in IOP slopes were 0.57, 0.24, and 0, respectively. The similarity of slopes observed for SEs and treated FEs implies that SE change is a harbinger of FE change and, therefore, warrants close surveillance. Two variables that predict FE intervention are modifiable: hypertension and IOP. Proper attention to these factors may reduce the need for FE treatment. *(Also see related commentary in the same issue by Rohit Varma, MD, MPH, and Xuejuan Jiang, PhD.)*

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Conjunctivitis Secondary to Dupilumab Treatment of Atopic Dermatitis

JAMA Dermatology
Published online Aug. 29, 2018

Treister et al. set out to pinpoint risk factors for conjunctivitis among patients with dupilumab-treated atopic dermatitis (AD). They found the strongest predictors to be severe AD at baseline and the presence of a concomitant atopic disorder.

From a cohort of 142 patients who received dupilumab for AD, conjunctivitis occurred in 12 (8.5%). Dupilumab exposure consisted of a 600-mg loading dose, followed by weekly injection of 300 mg. AD severity, as measured by investigator global assessment, was documented at the start of treatment and at the onset of conjunctivitis.

At baseline, 9 (75%) of the 12 patients had severe AD. The mean age at conjunctivitis onset was 30 years. The conjunctivitis occurred at a mean of 15.8 weeks of treatment (range, 8-41 weeks) and was considered severe or moderate-to-severe in 4 patients. Dupilumab was stopped in 3 patients, all of whom had severe conjunctivitis. These 3 patients had severe AD at baseline plus at least 1 other atopic condition. The 2 patients who discontinued the drug permanently also had a history of hay fever. In both of these patients, the conjunctivitis improved after treatment and dupilumab discontinuation, but it did not resolve fully.

Larger, multicenter studies are needed to confirm risk factors and determine effective treatment for conjunctivitis. At-risk patients may benefit from early ophthalmology referral and prophylactic care.

Ophthalmic NSAIDs for Corneal Dystrophy Caused by *SLC4A11* Mutation

Investigative Ophthalmology & Visual Science
2018;59(10):4258-4267

Some mutations of the *SLC4A11* gene cause misfolding of the SLC4A11 protein, which may lead to Fuchs endothelial corneal dystrophy (FECD) or congenital hereditary endothelial dystrophy (CHED). **Alka and Casey** tested 5 ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) for their ability to correct SLC4A11 folding defects. They found that 4 of the 5 NSAIDs provided significant rescue of *SLC4A11* mutants to the cell surface. In addition, 2 of the drugs restored osmotically driven water flux of *SLC4A11* mutants. The 5 drugs studied were bromfenac, diclofenac, flurbiprofen, ketorolac tromethamine, and nepafenac.

HEK293 cells expressing CHED- and FECD-causing *SLC4A11* mutants were grown in 96-well dishes, with or without an NSAID. Except for ketorolac, the tested drug concentrations were twice the EC50. The amount of ketorolac was much lower (0.25 μM) because concentrations >5 μM are toxic to HEK293 cells.

Using bioluminescence resonance energy transfer (BRET) and confocal microscopy, the authors tested each NSAID's ability to correct mutant *SLC4A11* cell-surface trafficking. Upon treatment, they also tested the ability of mutant *SLC4A11*-expressing cells to mediate water flux, which may mimic water flux across the corneal endothelial cell basolateral membrane.

BRET assays showed significant rescue of *SLC4A11* mutants to the cell surface by 4 of the 5 NSAIDs. Diclofenac and nepafenac were the most effective for moving endoplasmic reticulum –retained missense mutant *SLC4A11* to the cell surface. In 20 of 30 intracellular-retained *SLC4A11* mutants, diclofenac significantly restored cell-surface abundance. In some cases, diclofenac restored mutant *SLC4A11* water flux activity to the level of wild-type *SLC4A11*. Ketorolac had no effect on cell-surface abundance. Of the 3 mutants examined for cell-surface abundance (L843P, G709E, and E143K), L843P had the greatest improvement in trafficking.

This research suggests that topical ophthalmic NSAIDs possess sufficient permeability to reach the corneal endothelium. The authors encourage testing of diclofenac eyedrops to treat corneal dystrophy in patients with certain *SLC4A11* missense mutations. Wide use of NSAIDs for FECD or CHED would require robust data from well-designed clinical trials in which appropriate dosing regimens are established.

—Summaries by Lynda Seminara

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