

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Ranibizumab Port Delivery System for AMD: Phase 2

August 2019

Campochiaro et al. investigated the safety and efficacy of the port delivery system with ranibizumab (PDS) for neovascular age-related macular degeneration (AMD). They found a dose response for multiple end points, and the treatment generally was well tolerated. Visual and anatomic outcomes with PDS 100 mg/mL were comparable to those achieved by monthly intravitreal injection of ranibizumab 0.5 mg.

This study, known as Ladder, was a phase 2 trial conducted among 220 patients with AMD diagnosed in the preceding nine months. Prior to study entry, all participants had received at least two intravitreal anti-VEGF injections and had responded to treatment. Patients were assigned randomly (3:3:3:2) to receive PDS filled with ranibizumab 10 mg/mL ($n = 58$), 40 mg/mL ($n = 62$), or 100 mg/mL ($n = 59$), or monthly intravitreal injection of ranibizumab 0.5 mg ($n = 41$). The primary efficacy end point was the time to initial refill of the implant; this was assessed when the last enrollee completed the month 9 visit. Other outcomes included safety, improvement in best-corrected visual acuity (BCVA), and change in central foveal thickness. BCVA was assessed using the letter chart of the Early Treatment Diabetic Retinopathy Study (ETDRS).

The median time to first refill was 8.7, 13.0, and 15.0 months for recipients of PDS 10, 40, and 100 mg/mL, respectively. At month 9, the adjusted mean changes from baseline in BCVA were -3.2, -0.5, +5.0, and +3.9 ETDRS letters for treatment with PDS 10 mg/mL, PDS 40 mg/mL, PDS 100 mg/mL, and monthly injections, respectively. At month 9, the adjusted mean change from baseline in central foveal thickness was similar for those in the PDS 100 mg/mL group and the monthly injection group, but the implant system involved fewer treatment sessions.

In general, PDS insertions and refills were well tolerated. After optimizing the surgical procedure, the rate of post-operative vitreous hemorrhage was 4.5% (7 of 157); only one event was classified as serious. There was no sign of implant clogging.

The researchers concluded that this system may reduce treatment burden while preserving vision. The findings indicate that VEGF inhibition can be sustained safely for lengthy periods using the PDS, with outcomes similar to those of monthly injections. This may help guide treatment for AMD and other retinal conditions. The Archway phase 3 trial is the next step.

Intrastromal Voriconazole for Filamentous Fungal Keratitis

August 2019

Managing corneal ulcers is challenging because of limited treatment options and poor outcomes. Although topical natamycin is the most common treatment for moderate and severe fungal keratitis, outcomes remain unsatisfactory. Narayana et al. assessed the utility of adjuvant intrastromal injection of voriconazole as primary treatment for filamentous fungal keratitis. They found that, when compared with topical natamycin alone, adding intrastromal voriconazole (ISV) did not result in better outcomes.

This outcome-masked, randomized controlled trial was conducted at Aravind Eye Hospital in India. The study population comprised 151 patients (151 eyes) with moderate vision loss resulting from a fungal ulcer. Study eyes were assigned randomly to receive topical natamycin either alone or combined with ISV. The main outcome measure was microbiological cure according to three-day repeat culture analysis. Secondary outcomes were microbiological cure on seven-day repeat culture analysis; three-week and three-month best spectacle-corrected visual acuity; infiltrate and/or scar size; perforation rate; need for therapeutic penetrating keratoplasty (TPK); and other adverse events.



Culture samples were available for 68 of the patients. After controlling for baseline culture status, the odds of three- and seven-day culture positivity were 1.82 and 1.98 times greater, respectively, for eyes that had combination treatment ($p = .26$ and $p = .20$, respectively, vs. eyes with natamycin monotherapy). Visual acuity decreased further in eyes with combination treatment ($p = .75$), and scar/infiltrate size was greater in these eyes ($p = .11$).

The authors concluded that adding ISV injections to topical natamycin does not improve outcomes of moderate or severe filamentous fungal ulcers. Their findings are consistent with those of similar studies.

Risk Factors for Progression of NTG in Japanese Patients

August 2019

Sakata et al. evaluated the history and risk factors associated with progression of normal-tension glaucoma (NTG) in patients who received close follow-up but were not treated. Among their study population, whose mean intraocular pressure (IOP) at baseline was 12.3 mm Hg without treatment, the probability of glaucoma progression within five years was 66%. Significant contributors to progression were long-term fluctuation of IOP, greater vertical cup-to-disc (C/D) ratio, and the presence or history of disc hemorrhage.

For this study, the researchers included 90 Japanese patients with NTG whose IOP had been consistently below 16 mm Hg before study entry, without any glaucoma treatment. During the study, visual fields (VF) were examined at three-month intervals, and disc/peripapillary retinal photographs were obtained every six months. Treatment was not provided during the study. Outcomes of interest were deterioration in VF (defined by established criteria) and the disc/peripapillary retina (judged by three independent observers). Life table analysis was used to estimate the time to disease progression, and risk factors were identified using a Cox proportional hazards model.

The mean age of the study group was 54 years; mean baseline IOP was

12.3 mm Hg; and mean deviation was -2.8 dB. The mean deviation (MD) slope averaged -0.33 dB per year. The probability of glaucoma progression by year 5 was 66% according to VF or disc/peripapillary retinal deterioration (criterion 1), 52% by VF deterioration alone (criterion 2), and 50% by disc/peripapillary retinal deterioration alone (criterion 3).

Significant predictors of progression according to criterion 1 were presence or history of disc hemorrhage ($p < .001$), long-term IOP fluctuation ($p = .020$), and greater vertical C/D ratio ($p = .018$). The latter two factors also were significant predictors of progression according to criterion 2 ($p = .011$ and $.036$, respectively). The significant predictors for criterion 3 progression were long-term IOP fluctuation ($p = .022$) and the presence or history of disc hemorrhage ($p = .0018$).

The common predictor of progression among all three criteria was long-term fluctuation of IOP. The authors emphasized that the apparent link between fluctuating IOP and progression of NTG may have therapeutic implications. (*Also see related commentary by C. Gustavo De Moraes, MD, MPH, in the same issue.*)

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Nonhuman Primates' IOP Rises in Response to Stress

July/August 2019

In an experimental study involving three nonhuman primates, Turner et al. set out to quantify the effect of stress on intraocular pressure (IOP). They found that the animals' IOP increased rapidly and significantly in response to a stress-inducing activity.

The researchers evaluated three male rhesus macaques between 4 and 6 years of age. They used a wireless telemetry system to continuously record bilateral IOP, aortic blood pressure, and heart rate before, during, and after the animals were given an intramuscular injection of an anesthetic. The experiment was

repeated four times at least two weeks apart in each animal.

Data were collected at six points in time: 1) at baseline, before a technician approached the anteroom to the animals' holding room, 2) when the animals could hear, but not see, the technicians entering the anteroom, 3) when the technician entered the holding room, 4) while the animal was restrained in preparation for the injection, 5) immediately after the injection, and 6) 30 seconds after release of the restraint. Baseline IOP was determined by averaging two minutes of continuous IOP data before the technician approached the animals' space.

Results showed that the animals' IOP, mean arterial pressure, and heart rate increased by 27%, 38%, and 34%, respectively, in anticipation of the injection. Within 10 seconds of the animals hearing the technician enter the outer anteroom door, their IOP increased approximately 10%, and it reached its maximum within approximately 1 minute of first anticipating human contact. After release of the restraint, arterial pressure and heart rate remained elevated, while IOP decreased.

Previous studies in humans have documented rises in blood pressure and IOP when patients are anxious or stressed. However, as those studies used snapshot measurements that required subject contact, no precontact baseline could be established, and the time course of IOP change could not be assessed. Thus, for a fuller picture of the impact of stress on IOP, measurement technologies that don't require interaction with the patient are needed.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Anti-VEGF Protocols in Current Practice

August 2019

Uhr et al. evaluated current practice patterns and safety protocols used by retina specialists who administer intravitreal injections of anti-VEGF medications. They found that physi-

cians who have been in practice for 16 or more years are more likely to follow outdated protocols, and that physicians who practice in an academic setting are more likely to use protective wear during the procedure.

For this study, the researchers surveyed members of the American Society of Retina Specialists. Of 2,782 members, 399 responded, for a 14.3% response rate. Nearly 80% of those who responded practiced in the United States, and almost 60% had been practicing for more than 16 years.

Overall, the results indicate a growing awareness of the potentially harmful effects of topical antibiotics. For instance, only 10.9% of respondents reported that they “always or often” use preinjection antibiotics, and 16.6% said that they instill topical antibiotics immediately after injection. However, later-career ophthalmologists were more likely to continue using antibiotics: For instance, 13.7% of those who had practiced for 16 or more years used preinjection antibiotics, compared to 6.7% of those who were newer to practice. Postinjection antibiotics were used by 18.4% of those who had practiced for 16 or more years, compared to 14% of those who had 0-15 years in practice.

A similar pattern was noted in the practice of scrubbing a patient’s eyelids or lashes with an antiseptic before administering an injection and the use of povidone-iodine. Later-career physicians were more likely to scrub a patient’s eyelids or lashes with an antiseptic than were younger physicians (43.6% vs. 30.5%). In addition, retina specialists in practice longer were less likely to use povidone-iodine before injection than were their younger counterparts (89.7% vs. 95.7%).

Finally, as for protective wear, a U.S. consensus panel has recommended either the use of a mask or, if one is not used, a no-talking policy during intra-vitreous injections. Academic providers were more likely than those practicing in the community to wear a mask (43% vs. 29.9%)—and of all providers who do not wear a mask, only two-thirds abide by a no-talking policy.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Limited Vitrectomy Is Cost-Effective for Myodesopsia

August 2019

Rostami et al. looked at the cost-effectiveness of limited vitrectomy as treatment for vision-degrading myodesopsia. They found that the procedure is effective both clinically and economically. It improved contrast sensitivity function (CSF) and visual acuity, and its cost-utility ratio (when compared to no treatment) exceeded that of cataract surgery, retinal detachment repair, and treatments for other eye disorders.

This study was a retrospective interventional case series in which third-party payer costs were analyzed. The researchers included 67 patients with unilateral vitreous floaters; of these, 20 were nonmyopes with posterior vitreous detachment (PVD), 17 were myopes without PVD, and 30 were myopes with PVD. Participants completed the NEI Visual Function Questionnaire (NEI VFQ-39). Best-corrected visual acuity (BCVA) and CSF were assessed before and after limited vitrectomy, and a cost-utility analysis was performed.

After vitrectomy, the mean VFQ-39 score increased 19% ($p < .00001$). General vision improved by 27% among the entire group ($p < .00001$) and by 37% in those with nonmyopic PVD ($p < .00001$ for each). NEI VFQ-39 correlations with time trade-off utilities indicated that quality of life improved 14.4%. BCVA improved 13.5% ($p < .00001$), and CSF improved 53% ($p < .00001$). The incremental patient value gain from limited vitrectomy was 2.38 quality adjusted life-years (QALYs), and the average cost-utility ratio in 2018 U.S. dollars was \$1,574 per QALY.

The fact that myopes without PVD had the lowest cost-utility ratio of the subgroups (\$1,338/QALY) should help to guide case selection, the authors said. Larger studies of longer duration are needed to capture adverse events and to draw conclusions about the cost-utility of this procedure relative to that of treatments for other eye conditions.

Projection-Resolved OCTA of Plexuses in Retinitis Pigmentosa

August 2019

Hagag et al. used projection-resolved optical coherence tomography angiography (PR-OCTA) to characterize microvascular changes in three retinal plexuses of patients with retinitis pigmentosa (RP). They found that PR-OCTA enabled the detection of changes in the perifoveal regions of the intermediate and deep capillary plexuses. No damage was detected in the superior vascular complex.

This prospective cross-sectional study was performed at a tertiary academic center and included patients with RP and age-matched healthy controls. Spectral-domain OCT was used to obtain 6-mm macular scans, and blood flow was detected with a split-spectrum amplitude decorrelation algorithm. A PR-OCTA algorithm was applied to suppress projection artifacts and resolve microvasculature in the intermediate capillary plexus, deep capillary plexus, and superior vascular complex. Vessel density was calculated from en face OCTA of the parafoveal and perifoveal regions in all three plexuses and the all-plexus inner retinal slab. Inner and outer retinal thickness was measured from structural OCT scans. Statistical measures included generalized estimating equations and Spearman rank-order correlation coefficients.

The study included 44 eyes of 26 patients with RP and 34 eyes of 26 healthy controls. Compared with control eyes, reduction in vessel density was significantly lower in the perifovea of RP eyes but not in the parafovea of the inner retinal slab ($p = .001$ and $.56$, respectively). In RP eyes, the intermediate and deep capillary plexuses had more damage than did the superior vascular complex. Also noted was significant thickening of the inner retina, along with thinning of the outer retina. Vessel density in the perifovea of the deep and intermediate capillary plexuses correlated strongly with outer retinal thickness in patients with RP who had no history of cystoid macular edema.

—Summaries by Lynda Seminara

One-Year Outcomes for Children After Cataract Surgery

July 2019

Repka et al., for the Pediatric Eye Disease Investigator Group (PEDIG), evaluated outcomes in 880 children who underwent lensectomy for cataract surgery in at least one eye. Within the year following surgery, amblyopia occurred in just over half of the study population, and visual acuity (VA) was normal in roughly one-third. Although the rate of unexpected complications was low, subsequent surgery was needed in 17% of study eyes.

This PEDIG study was conducted from June 2012 to July 2015; the children represented 61 pediatric eye care practices (57 in the United States, three in Canada, and one in the United Kingdom). All participants were less than 13 years old at the time of lensectomy (with or without IOL implantation) and had follow-up within 15 months of the surgery. Main outcome measures were VA and the rates of amblyopia, confirmed glaucoma, suspected glaucoma, and other intraocular surgery. The mean age at annual follow-up was 4.9 years. Of the 880 patients, 41.1% (n = 362) had bilateral surgery and 58.9% (n = 518) had unilateral surgery. Of the 1,132 study eyes, 60.2% (n = 654) received an IOL.

According to follow-up data, 51% of participants (n = 449) experienced amblyopia. Among children age 3 or older, mean VA was 0.30 logMAR (~20/40) in 153 bilateral pseudophakic eyes, 0.49 logMAR (~20/63) in 141 unilateral pseudophakic eyes, 0.47 logMAR (~20/63) in 21 bilateral aphakic eyes, and 0.61 logMAR (~20/80) in 17 unilateral aphakic eyes. Improvement in VA correlated with older age at surgery for eyes with bilateral or unilateral pseudophakia.

A new diagnosis of glaucoma or suspected glaucoma was made for 6.3% of eyes that did not have glaucoma before lensectomy (67/1,064), 13.2% of eyes with bilateral aphakia (36/273), 7.9% of

eyes with unilateral aphakia (14/178), 1.6% of eyes with bilateral pseudophakia (5/308), and 3.9% of eyes with unilateral pseudophakia (12/305). Subsequent intraocular surgery (most commonly for visual axis obscuration) was required for 17% of study eyes (189/1,132).

The authors recommend frequent monitoring of pediatric patients in the year following lensectomy to detect visual axis clouding and changes in vision.

Impact of Discrimination on Visually Impaired Older Adults

July 2019

Jackson et al. reviewed data on perceived discrimination against visual impairment for thousands of older adults. They found that people with poor eyesight who perceived discrimination were more likely to be depressed, lonely, and dissatisfied with life than were their counterparts who did not perceive discrimination. Not surprisingly, such discrimination appeared to correlate with poor well-being and reduced quality of life (QoL).

For their study, the authors collected data on 7,677 people age 50 and older who participated in the English Longitudinal Study of Ageing. Experiences of perceived discrimination were reported for a one-year period. The authors assessed participants' depressive symptoms, life satisfaction, QoL, and loneliness. Eyesight, which was not previously validated for study participants, was self-rated and was categorized as poor (fair, poor, or blind) or good (excellent, very good, or good). Logistic regression analysis was used to analyze differences in perceived discrimination between those who reported poor eyesight and those who reported good eyesight and to evaluate potential correlations between perceived discrimination and well-being for those with poor eyesight.

Among the study participants (mean age, 66.71 years), those with poor eyesight were more likely to perceive discrimination (odds ratio, 1.41; p < .001 vs. those with good eyesight). Cross-sectionally, participants with poor eyesight who perceived discrimination

were more likely to have symptoms of depression, to experience loneliness, to have poorer QoL, and to have reduced life satisfaction than were those who did not report discrimination. Perceived discrimination was linked to greater risk of depressive symptoms in participants who reported poor eyesight at the six-year follow-up.

Taking steps to address this discrimination may mitigate the risk of poor well-being in this population, the authors said. Moreover, asking visually impaired patients about their well-being during office visits may help identify those in greatest need of support. (*Also see related commentary by Alan R. Morse, JD, PhD, in the same issue.*)

Quality of Life After DMEK or Ultrathin DSAEK

July 2019

In the primary Descemet Endothelial Thickness Comparison Trial (DETECT), postoperative visual acuity (VA) was better with Descemet membrane endothelial keratoplasty (DMEK) than with ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK). In a preplanned secondary analysis of DETECT, Ang et al. looked at whether this benefit of DMEK translates to enhanced vision-related quality of life (QoL). They found no meaningful differences between the study arms.

The primary study included 38 patients with isolated endothelial dysfunction. Study eyes were assigned randomly to undergo UT-DSAEK or DMEK. The NEI's 39-item Visual Function Questionnaire (NEI VFQ-39) was administered preoperatively and at three and 12 months postoperatively. In the secondary analysis, 38 eyes were involved in the three-month assessment and 26 eyes in the 12-month review. (For patients who had second-eye surgery between months 3 and 12, all subsequent NEI VFQ-39 data were excluded from analysis.) Responses were analyzed using the NEI-defined traditional subscales and composite score, on a 100-point scale and with Rasch-refined analysis.

Mean VA at baseline was 0.35 logMAR (~20/50) in the DMEK arm

and 0.28 logMAR (~20/40) in the UT-DSAEK arm. Each study arm included 19 patients: 18 with Fuchs dystrophy and one with pseudophakic bullous keratopathy. The mean age was 68 years for all participants.

Overall, patients experienced improvement of 9.1 points in the NEI VFQ-39 composite score from baseline to month 3 ($p < .001$) and improvement of 11.6 points from baseline to month 12 ($p < .001$). At three months, improvement was 0.9 points greater for the DMEK group after controlling for baseline NEI VFQ-39 ($p = .80$ vs. UT-DSAEK group).

In summary, even though VA in DETECT was better after DMEK than after UT-DSAEK, there was no significant difference in patient-reported vision-related QoL between the study arms at month 3 or month 12. Although objective measurements such as VA are crucial for improving techniques of corneal transplantation, the authors believe that, regardless of their findings, patients are more concerned about vision-related QoL. (*Also see related commentary by Alan Sugar, MD, in the same issue.*)

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Features of Serous Retinal Detachment in Preeclampsia and Malignant Hypertension

Eye (London)

Published online May 14, 2019

Lee et al. looked at the characteristics of hypertensive choroidopathy with serous retinal detachment (SRD) in preeclampsia and malignant hypertension. They also explored the possibility of choroidal ischemia contributing to the pathogenesis of preeclampsia. Findings of their research suggest that elevated blood pressure affects the choroid earlier than the retina and that choroidal thickness declines after resolution of choroidopathy. Visual prognosis was better for patients with preeclampsia than for those with hypertension. The residual flow defects found in the choriocapillaris confirmed the long-hy-

pothesized notion that ischemia is an underlying mechanism of hypertensive choroidopathy.

For this retrospective case series, the researchers reviewed medical charts for 29 patients with preeclampsia (53 eyes) and 24 patients with hypertension (45 eyes). Clinical characteristics were documented, and multimodal imaging results were evaluated. The two cohorts were comparable in age, follow-up duration, baseline visual acuity, central macular thickness (CMT), and subfoveal choroidal thickness. Blood pressure parameters (including pulse rate and systolic and diastolic blood pressure) were significantly higher in the hypertension group.

After resolution of the SRD, reductions in CMT ($p < .001$) and choroidal thickness ($p = .003$) were found to be greater in patients with preeclampsia ($p < .001$ and $p = .003$, respectively, vs. the hypertension group). Features of hypertensive retinopathy, including hemorrhage, exudates, cotton-wool spots, and optic disc edema, were more common in patients with hypertension ($p = .001$). Final visual acuity was better in those with preeclampsia ($p = .048$). Factors linked to poor vision were the presence of retinopathy features ($p = .005$) and retinal detachment in the macula ($p = .017$).

Although SRD hypertensive choroidopathy presented with choroidal thickening that decreased after resolution, the residual flow defects observed in the choriocapillaris confirmed the long-hypothesized notion that ischemia is a mechanism behind hypertensive choroidopathy. To the authors' knowledge, this study represents the first application of multimodal retinal imaging in the evaluation and comparison of clinical manifestations of SRD in preeclampsia and malignant hypertension.

Using AI to Screen for Diabetic Retinopathy in Africa

Lancet Digital Health

2019;1:e35-e44

Bellemo et al. tested an artificial intelligence (AI) model of deep learning as part of a screening program for diabetic retinopathy (DR) in Zambia.

Their AI system was able to detect referable DR, vision-threatening DR, and diabetic macular edema (DME). Moreover, AI-generated grading was faster than human grading and was equally accurate in identifying systemic risk factors for DR.

For this clinical validation study, the authors adopted an ensemble AI model involving two convolutional neural networks. The model was first trained on 76,370 retinal fundus photographs from 13,099 patients with diabetes who participated in the Singapore Integrated Diabetic Retinopathy Program. The model was then used to evaluate patients with diabetes who attended a mobile screening event at five urban centers in Zambia's Copperbelt Province. Referable DR was defined as non-proliferative DR of moderate or worse severity, DME, or ungradable images.

The authors calculated area under the curve (AUC), sensitivity, and specificity for referable DR, and they compared sensitivities of vision-threatening DR and DME achieved by the AI system and by the grading performed by retina specialists. They also conducted multivariate analysis to compare the two methods of grading.

Among the 4,504 study images from 3,093 eyes (1,574 people with diabetes), the AI system identified referable DR in 697 eyes (22.5%). It detected vision-threatening DR in 171 eyes (5.5%) and DME in 249 eyes (8.1%). The AUC of the AI system for referable DR was 0.973. The corresponding sensitivity and specificity were 92.25% and 89.04%, respectively. The system's sensitivity for detecting vision-threatening DR and DME was 99.42% and 97.19%, respectively. Outcomes for the AI model resembled those of human graders; both models identified major risk factors for referable DR, including longer duration of diabetes, higher systolic blood pressure, and higher levels of glycated hemoglobin.

Additional study is needed to assess the cost-effectiveness of AI models, said the authors. Moreover, it will be crucial to ensure that under-resourced areas have enough specialists to treat referable DR.

—Summaries by Lynda Seminara