

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Pegcetacoplan May Slow GA Progression

February 2020

Although efforts have been made to determine how complement activation pathways may affect the development and progression of age-related macular degeneration (AMD), there is no treatment for geographic atrophy (GA) caused by AMD. Liao et al. investigated the effects of pegcetacoplan, a pegylated complement C3 inhibitor peptide, in patients with GA secondary to AMD. They found that this treatment significantly reduced the growth rate of GA lesions.

For this prospective phase 2 study, the researchers enrolled 246 adults (≥ 50 years of age) with GA. They were assigned randomly (2:2:1:1) to receive either intravitreal injections of pegcetacoplan (15 mg) or sham injections, on either a monthly or every-other-month basis, for a 12-month period. Follow-up assessment occurred at months 15 and 18. Fundus autofluorescence imaging was used to evaluate GA area and growth. The main efficacy end point was mean change in square root of the lesion area from baseline to month 12. Safety end points included the number and severity of treatment-emergent adverse events.

By 12 months, the lesion growth rate relative to sham injection was 29% slower with monthly pegcetacoplan ($p = .008$) and 20% slower with peg-

cetacoplan every other month (EOM; $p = .067$). The effect of monthly or EOM pegcetacoplan was greater in the second six months of treatment (reductions of 45% and 33%, respectively). The lesions started growing when

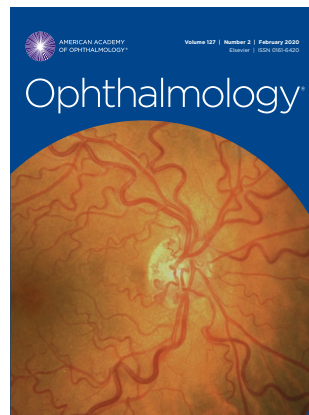
active treatment was stopped, suggesting the need for ongoing injections. Of note, new-onset exudative AMD was found more frequently in pegcetacoplan-treated eyes (21% vs 9%). Otherwise, the drug's safety profile resembled that of other intravitreal agents. The patients most prone to exudative AMD had a history of choroidal neovascularization in the fellow eye. Two cases of culture-positive endophthalmitis and one case of culture-negative endophthalmitis occurred in patients who received pegcetacoplan.

According to the authors, their study shows the effectiveness of C3 inhibition in slowing GA progression. Both efficacy and safety were sufficiently favorable to warrant phase 3 studies.

IRIS Registry: Endophthalmitis After Cataract Surgery

February 2020

Pershing et al. assessed the incidence and visual outcomes of acute-onset endophthalmitis after cataract surgery.



They found that, from 2013 to 2017, the incidence of acute-onset endophthalmitis was 0.04% in the United States. The condition was much more common if cataract surgery was combined with other ophthalmic procedures.

This study involved a review of electronic health records for patients who had acute-onset postoperative endophthalmitis within 30

days of cataract surgery. Diagnosis codes were used to identify relevant cases in the IRIS (Intelligent Research in Sight) Registry database. Annual and aggregate five-year incidences were determined for all cataract surgeries, including standalone cataract procedures and cataract surgeries combined with other ophthalmic surgery. Patient characteristics were collected and compared. Mean and median visual acuity (VA) were calculated for various time points, including one month preoperatively and one week, one month, and three months postoperatively. Main outcomes were the incidence of acute-onset postoperative endophthalmitis and the visual results for affected patients.

The study population included more than 5 million patients who had cataract surgery from 2013 through 2017 in the United States (~8.5 million eyes). Acute-onset endophthalmitis occurred in 3,629 eyes (0.04%). Endophthalmitis was most common in the youngest subset (1-17 years), and it occurred

in 0.20% of patients who underwent a concomitant ophthalmic surgery, versus in 0.04% of standalone cases. Among patients with anterior vitrectomy, the endophthalmitis rate was 0.35%. Three months post-op, mean VA in the endophthalmitis group was 20/100 (median, 20/50), compared with approximately 20/40 (median, 20/30) for patients without endophthalmitis. Four percent of the endophthalmitis group had VA of 20/20 or better by post-op month 3.

The authors concluded that these findings may inform point-of-care conversations with patients about risk and prognosis and can serve as a foundation for new research. Risk factors for endophthalmitis may include younger age, cataract surgery combined with other ophthalmic surgeries, and anterior vitrectomy.

Rinucumab Plus Aflibercept Versus Aflibercept Alone for Wet AMD

February 2020

Heier et al. compared the efficacy and safety of aflibercept plus rinucumab to that of aflibercept monotherapy in patients with neovascular age-related macular degeneration (AMD). They found that the combination treatment did not significantly improve best-corrected visual acuity (BCVA).

This phase 2 multidose study included 505 patients (≥ 50 years of age) whose BCVA ranged from 73 to 24 letters. Participants were randomly allocated to receive intravitreal low-dose (1 mg) rinucumab + aflibercept 2 mg, high-dose (3 mg) rinucumab + aflibercept 2 mg, or aflibercept 2 mg monotherapy. These treatments were given every four weeks through week 12. Following this, patients on the low-dose combination continued the same treatment through week 28. Patients in the other groups were randomly assigned to continue their treatment or switch to the other treatment. Follow-up occurred every four weeks through week 52.

At week 12, mean BCVA gains were 5.8 letters with both combinations of aflibercept/rinucumab and 7.5 letters with aflibercept alone. By 12 weeks of

treatment, 12%, 19%, and 22% of eyes on the low-dose combo, high-dose combo, and aflibercept monotherapy (respectively) had gained at least 15 letters. The mean reductions in central retinal thickness from baseline were 126.1, 127.1, and 126.9 μm , respectively. The proportions of eyes with complete fluid resolution were 35%, 24%, and 42%, respectively. Vision and anatomic outcomes at week 28 were consistent with week 12 results. Through week 52, intraocular inflammation was infrequent except in the high-dose combination group (incidence of 7.5%). The most common ocular adverse events were conjunctival hemorrhage and retinal hemorrhage. By 52 weeks, more than a third of the study population had experienced at least one ocular adverse event.

This research suggests that adding rinucumab to aflibercept does not produce better visual or anatomic outcomes than aflibercept alone in treatment-naïve patients with neovascular AMD.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Forecasting Retinal Thinning and Visual Field Loss

January/February 2020

Progressive thinning of the circumpapillary retinal nerve fiber layer (cpRNFL) thickness, as measured by optical coherence tomography (OCT), may indicate worsening optic nerve damage. Sedai et al. developed a multimodal model to forecast cpRNFL thickness at future visits.

For this observational study, the researchers enrolled 1,089 participants. Of these, 643 had glaucoma, 405 were glaucoma suspects, and 41 served as healthy controls. All underwent an initial comprehensive ophthalmic examination that included OCT scanning, and they were then monitored for 3.57 ± 1.69 years. The number of visits ranged from three to 30, and the mean interval between visits was 9.7 ± 9.0 months.

The researchers developed four fore-

casting models, based on the number of visits used (one to four); all four models used a combination of clinical, structural, and functional data, including deep learning-derived OCT features. The results were compared to a commonly adopted linear regression model, and the main outcome measure was the mean absolute difference and Pearson correlation coefficient between the true and forecasted values of the cpRNFL in the three cohorts.

Results showed that the most accurate forecasting model used three visits. The mean error was $1.10 \pm 0.60 \mu\text{m}$ in healthy patients, $1.79 \pm 1.73 \mu\text{m}$ in glaucoma suspects, and $1.87 \pm 1.85 \mu\text{m}$ in patients with glaucoma. In contrast, the standard linear regression model showed a mean error of $1.55 \pm 1.16 \mu\text{m}$, $2.40 \pm 2.67 \mu\text{m}$, and $3.02 \pm 3.06 \mu\text{m}$, respectively, in the three groups. The Pearson correlation coefficient between the forecasted value and the measured thickness was $p < 0.01$ for all three groups.

In future work, the researchers plan to include visual functional parameters, which would provide a more complete outlook for individual patients.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Using SD-OCT to Detect Complete PVD

February 2020

Hwang et al. set out to assess whether preoperative spectral-domain optical coherence tomography (SD-OCT) of the macula could accurately detect posterior vitreous detachment (PVD). They found that an accurate determination of attached vitreous can be made if the premacular bursa or posterior vitreous cortex are visualized.

For this retrospective chart review, the researchers evaluated 175 patients (175 eyes) who underwent vitrectomy surgery between Jan. 1, 2009, and Dec. 31, 2017. Two masked ophthalmologists independently graded the patients' preoperative SD-OCT scans, and those results were compared against the treating surgeons' intraoperative notes re-

garding the likelihood of PVD. Attached vitreous was identified on OCT by visualization of the posterior vitreous cortex or the premacular bursa. Complete PVD was identified by the absence of these findings and was considered a positive outcome for the purpose of the analysis.

During the grading process, 38 eyes were confirmed as having complete PVD, and 137 were assessed as attached vitreous. However, at the time of surgery, 20 of the 38 eyes with complete PVD were described as having preexisting PVD (true positives), and 18 were documented as having attached vitreous (false positives). With regard to the 137 eyes graded as attached vitreous on OCT, 129 had attached vitreous at the time of surgery (true negatives), while eight had preexisting PVD at that time (false negatives).

The sensitivity of SD-OCT for detecting complete PVD was 71%, the specificity was 88%, the positive predictive value was 53%, and the negative predictive value was 94%. The most common diagnosis was macular hole (53%); in these eyes, the sensitivity of pre-op OCT in correctly diagnosing PVD was 67%, specificity was 88%, positive predictive value was 38%, and negative predictive value was 96%.

The authors noted that the OCT scans were not obtained with the enhanced vitreous imaging technique, which aids in visualizing vitreous structures. In particular, they said, if neither the premacular bursa nor the posterior vitreous cortex is visualized, SD-OCT has a poor predictive value, and ultrasound is needed to accurately identify complete PVD. (*Also see related commentary by Justis P. Ehlers, MD, in the same issue.*)

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Intraoperative OCT for Tissue Orientation in DMEK

February 2020

In a report on the first 100 cases of the DISCOVER study, which included “learning curve” operations, Patel et

al. noted that intraoperative optical coherence tomography (iOCT) facilitated tissue orientation in Descemet membrane endothelial keratoplasty (DMEK) and eliminated the need for external markings. Even for novice DMEK surgeons, the complication rates and unscrolling times compared favorably with those of other tissue-orientation methods.

DISCOVER was a single-center study of 100 eyes (76 patients) in which iOCT was used for tissue orientation. A questionnaire was completed by attending surgeons to gauge the impact and value of iOCT in this operative setting. Main outcome measures were the perceived utility of iOCT, graft unscrolling efficiency, and the frequency of post-op complications.

Forty-three operations were performed by a staff physician, and the remainder by six novice surgeons (cornea fellows under supervision). Fifty-two eyes received concurrent phacoemulsification with lens implantation. Nine eyes required rebubbling, resulting from poor post-op adherence of the graft. The rebubbling rate was slightly lower for cornea fellows (8.9%) than for the primary surgeon (9.5%). These rates are significantly lower than the average of 17 studies that did not include iOCT (28.8%).

The graft was easily visualized in all 100 eyes, including three in which an S-stamp was present but could not be readily discerned. Primary graft failure occurred in two eyes: In one, the graft was inverted due to iOCT misinterpretation by the surgeon; the other failure was ascribed to poor-quality tissue. The average unscrolling time was 4.4 ± 4.1 minutes (range, 0.7-27.6 minutes), which compares favorably with that of previous reports.

These findings support the potential value of iOCT for DMEK procedures, said the authors. This technology may reduce the DMEK learning curve and help both novice and veteran surgeons to achieve excellent results. The authors noted that a randomized controlled trial of iOCT-assisted surgery versus S-stamp surgery may shed further light on the possible link between S-stamping and postoperative rebubbling.

Amblyopia and Refractive Errors in Young Children

February 2020

Between 2012 and 2017, preschool-aged children were screened with an autorefractor in the Preschool Vision Program at the University of California, Los Angeles. In a summary of the five-year findings, Margines et al. noted that astigmatism was the most common refractive error (present in 53%); the frequency was highest among Latino children, who also had poorer uncorrected and corrected visual acuity. Amblyopia occurred in 1% of the study population. Nearly 8% of screened children received eyeglasses.

Of the 79,451 children who met eligibility criteria, 18% failed the initial screening and were offered another screening on a subsequent day. If specific criteria were met for myopia, hyperopia, astigmatism, or anisometropia, a full cycloplegic exam was conducted.

Only 56% of those who failed the screening returned for examination. Of those who did, 84% (n = 6,779) received the cycloplegic exam. Among these children, nearly 87% (n = 5,883) were found to need eyeglasses; another 7.3% (n = 498) received glasses from being in the care of an optometrist or ophthalmologist. Because exam results were similar for each child's eyes, only the right-eye data were analyzed.

Among children with cycloplegic exams, hyperopia was found in 61%, myopia in 20%, and astigmatism in 93%. Astigmatism rates were highest among Latino children. An astigmatism cutoff of ≥ 1.50 D in either eye predicted the need for glasses in 93%; a cutoff of ≥ 1.50 D in both eyes increased the predictive value to 96%.

Refractive amblyopia was noted in 780 children (1% of those screened; 11.5% of those examined); 211 (27%) of them were bilateral amblyopes. Refractive errors varied significantly by age and ethnicity. The mean spherical equivalent (SE) for 3-year-olds was much lower than that of 4- and 5-year-olds (0.94, 1.2, and 1.2 D, respectively). The mean SE was 0.83 D for Asians, 1.0 D for blacks, 1.1 D for Latinos, and 2.1 D for whites.

According to the authors, this study represents the largest published sample of vision-screening results for pre-schoolers, and it provides further insight into the prevalence of common refractive errors and their link to race/ethnicity. The data can “inform screening criteria to more accurately identify children who need intervention to prevent permanent vision loss,” said the authors.

—*Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Opioids After Corneal Surgery

January 2020

In a study of adults undergoing corneal surgery, **Woodward et al.** looked at the effect of reducing the usual number of prescribed opioid tablets on patients' post-op consumption of the drugs. Cohort 1 received the typical number of tablets; cohort 2 received significantly fewer. On average, the first cohort used twice as many pills as the second cohort.

For this prospective study, the first of two cohorts was surveyed to assess the quantity of opioid tablets used after routine corneal surgery, for which the standard number of pills was prescribed. Subsequently, the number of prescribed tablets was decreased, and patients in cohort 2 received a lesser quantity. Concurrently, a statewide monitoring program began providing patients with additional information on pain control, opioid use, and opioid disposal. The study's main outcome was the difference in tablet use by the two cohorts, determined by the two-sample t test.

The overall study population included 82 patients (51% male). The mean age was 42.5 years. There were 38 patients in the first cohort and 44 in the second. Cohort 1 was prescribed significantly more tablets than cohort 2 (18.8 vs. 6.6; difference, 12.2 [95% confidence interval (CI), 10.4-14.0]; $p < .001$) and consumed more tablets (8.3 vs. 4.0; difference, 4.3 [95% CI, 1.4-7.2]; $p = .005$). Cohort 1 also had significantly more unused tablets (10.3

vs. 2.9; difference, 7.5 [95% CI, 4.7-10.2]; $p < .001$).

Of the patients in cohort 2, pain control reportedly was adequate for 70% and more than needed for 22%. Twenty patients in this cohort had tablets left over—and of these, 17 did not dispose of the remaining tablets, and the remaining three discarded them.

This study shows that pain control after corneal surgery generally is adequate or better even if patients are prescribed fewer opioid tablets. However, because the patients did not properly dispose of unneeded tablets, the authors recommend that physicians encourage safe opioid storage and disposal. They emphasized that “ophthalmologists should balance patients' pain control needs with opioid tablet prescribing after ophthalmic surgical procedures.”

Glaucoma After Pediatric Lensectomy

January 2020

Understanding the incidence and risk factors related to glaucoma after cataract surgery in children can help to guide disease management. **Freedman et al.**, for the Pediatric Eye Disease Investigator Group, looked at the frequency of glaucoma in the year following pediatric lensectomy. In their study of children under 13 years of age, the incidence of confirmed or suspected glaucoma was 6.3%. Possible risk factors were aphakia and younger age.

This multicenter study included 702 children (970 eyes) who received unilateral or bilateral lensectomy between June 2012 and July 2015 in the United States (57 sites), Canada (three sites), or the United Kingdom (one site). Glaucoma and suspected glaucoma had been diagnosed using standardized criteria. Patients were required to have at least one follow-up visit between six and 18 months after lensectomy. The primary outcome was the risk of glaucoma.

The mean age of the study group was 3.4 years; 50% were male; and 61% were white. Following cataract surgery, glaucoma was confirmed for 52 eyes and suspected in 14 (adjusted overall risk, 6.3%). The mean age at lensectomy in glaucomatous eyes was 1.9 years

(range, 0.07-11.2 years). Glaucoma surgery was performed in 23 (34.8%) of the 66 affected eyes, at a median of 3.3 months after lensectomy (range, 0.9-14.8 months).

The risk of confirmed or suspected glaucoma was 15.7% for children aged three months or younger at lensectomy, 3.4% for those older than three months, 11.2% among aphakic eyes, and 2.6% for pseudophakic eyes. Variables that did not appear related to glaucoma development were sex, race/ethnicity, laterality of lensectomy, use/nonuse of anterior vitrectomy, anterior segment abnormality before lensectomy, and intraoperative complications.

The authors concluded that only a small number of children are at risk for glaucoma in the year following cataract removal. Frequent monitoring for signs of glaucoma is warranted after pediatric lensectomy, said the authors, especially in young infants and children with post-op aphakia. Monitoring of the study group will continue through five years following lensectomy, which may uncover more cases and show a different risk factor profile. “Such long-term data may help the pediatric cataract surgeon better understand the risk factors and pathogenesis of glaucoma following lensectomy,” said the authors, which may lead to better treatment strategies.

Genetic Data May Predict Myopia in Children

January 2020

Mojarrad et al. focused on whether genetic data may identify children at risk of developing myopia and whether including genetic predisposition to educational attainment may improve the accuracy of myopia prediction. In their study, the area under the curve for predicting myopia by polygenic risk score (PRS) was 0.67 for any myopia and 0.73 for high myopia, the latter being commonly linked to PRS in the top 10%.

This meta-analysis used data from three genome-wide association studies (GWAS). One GWAS pertained to educational attainment and the others to refractive error; all three were from

the UK Biobank. A PRS had been derived from the cohort of mothers in an earlier population-based validation sample, the Avon Longitudinal Study of Parents and Children. The predictive variable was a PRS derived from GWAS data for refractive error ($n = 95,619$), the age a child began wearing spectacles ($n = 287,448$), and educational attainment ($n = 328,917$). The main outcome measure was area under the receiver operating characteristic curve (AUROC) in analyses for predicting myopia, using noncycloplegic autorefractive measurements to denote myopia severity: equal to or less than -0.75 D (any myopia), -3.00 D (moderate myopia), and -5.00 D (high myopia), respectively.

Data for 383,067 adults between the ages of 40 and 69 were entered into the analyses. The PRS was found to have an AUROC of 0.67 for predicting any type of myopia, 0.75 for predicting moderate myopia, and 0.73 for predicting high myopia. Incorporating PRS data on genetic predisposition to educational attainment improved the AUROC marginally for any myopia but not for moderate or high myopia. PRS in the top 10% denoted a 6.1-fold greater risk of high myopia.

This research suggests that a personalized medicine approach to myopia may be feasible for predicting myopia risk in very young children. However, the predictive accuracy of PRS would need improvement to merit its use in clinical practice, said the authors, who noted that “cycloplegic autorefractive remains a better indicator of myopia risk” (AUROC of 0.87), particularly in children older than age 6.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

PCR Risk Rises Following Anti-VEGF Treatment

Journal of Cataract & Refractive Surgery

Published online Sept. 10, 2019

In a retrospective review, **Nagar et al.** looked at the relationship between prior intravitreal anti-VEGF therapy and

the risk of posterior capsular rupture (PCR) during phacoemulsification. They found that PCR occurred in more than 9% of eyes with previous anti-VEGF injections, compared with less than 2% of eyes that did not have this treatment. A higher number of injections denoted a greater risk of rupture.

For this study, the authors reviewed electronic health records of patients who underwent phacoemulsification at a single eye care center in London during a two-year period. Collected data included patient demographics, indication for intravitreal therapy, number of intravitreal injections, and surgical complications. The primary outcome measure was PCR during phacoemulsification, as defined by the Royal College of Ophthalmologists' database audit of cataract surgery. Univariate logistic regression was used to explore associations between intravitreal anti-VEGF treatment and the occurrence of PCR.

Data were available for 4,047 eyes; of these, 108 had received injections of an anti-VEGF agent. Three eyes had trauma to the posterior capsule preoperatively and were excluded from final analyses. Logistic regression (after excluding those eyes) confirmed that prior anti-VEGF treatment carries a greater risk of PCR (9.26% vs. 1.88% for eyes that had not received intravitreal injections; $p < .0001$). A dose-dependent relationship was found for the number of anti-VEGF injections and the likelihood of PCR: 8.6% relative risk per injection. Eyes that received more than 10 injections had a higher PCR rate than those with fewer injections (6.1% vs. 14.3%, $p = .18$).

The authors recommend expanding their study to further explore and understand this relationship.

Detecting Visual Field Loss in Patients With Diabetes and Unapparent DR

Investigative Ophthalmology & Visual Science

2019;60(14):4711-4716

Neuroretinopathy has been gaining recognition as an independent cause of vision loss in patients with diabetes. **Bao**

et al. hypothesized that diabetes itself (without diabetic retinopathy [DR]) causes inner retinal visual defects, and that frequency doubling technology (FDT)-based visual perimetry can identify diabetic neuroretinopathy in the absence of clinically detectable microvascular DR. Their analysis showed that patients with diabetes may have substantial inner neuroretinopathy, even if typical microvascular lesions are not present.

For this study, data were gathered for participants of the National Health and Nutrition Examination Survey (NHANES) 2005-2008 who received fundus photography and visual field screening by FDT. Visual fields were screened in accordance with the FDT protocol, which requires a 19-subfield suprathreshold test. Patients were considered to have visual field loss if a defect was found in at least two subfields on the first and second test, and if at least one of those subfields was defective in both tests. The mean number of defective visual fields in each eye of each patient was calculated for three threshold levels: 5% or lesser, 2% or lesser, and 1%.

Of the 5,482 patients who met eligibility criteria and had gradable photos for both eyes, 1,488 were excluded due to unreliable FDT testing or their status as glaucoma suspects or glaucoma patients. The final analysis of 3,994 patients (7,988 eyes) showed that those with diabetes and no apparent DR were more likely than those without diabetes to have at least one subfield defect at the 5%, 2%, and 1% probability levels (41.3% vs. 28.6%; 27.4% vs. 17.5%; 15.9% vs. 9.4%; all $p < .0008$). Multivariable regression showed that each additional percentage of glycated hemoglobin denoted 19% greater odds of at least one visual subfield defect in patients with diabetes and no apparent DR.

The authors acknowledge that it isn't clear whether diabetic neuroretinopathy and classic DR occur in parallel or sequentially. However, the data do show that inner neuroretinopathy occurs with diabetes in the absence of typical microvascular lesions.

—Summaries by Lynda Seminara